

# EVIDENCE

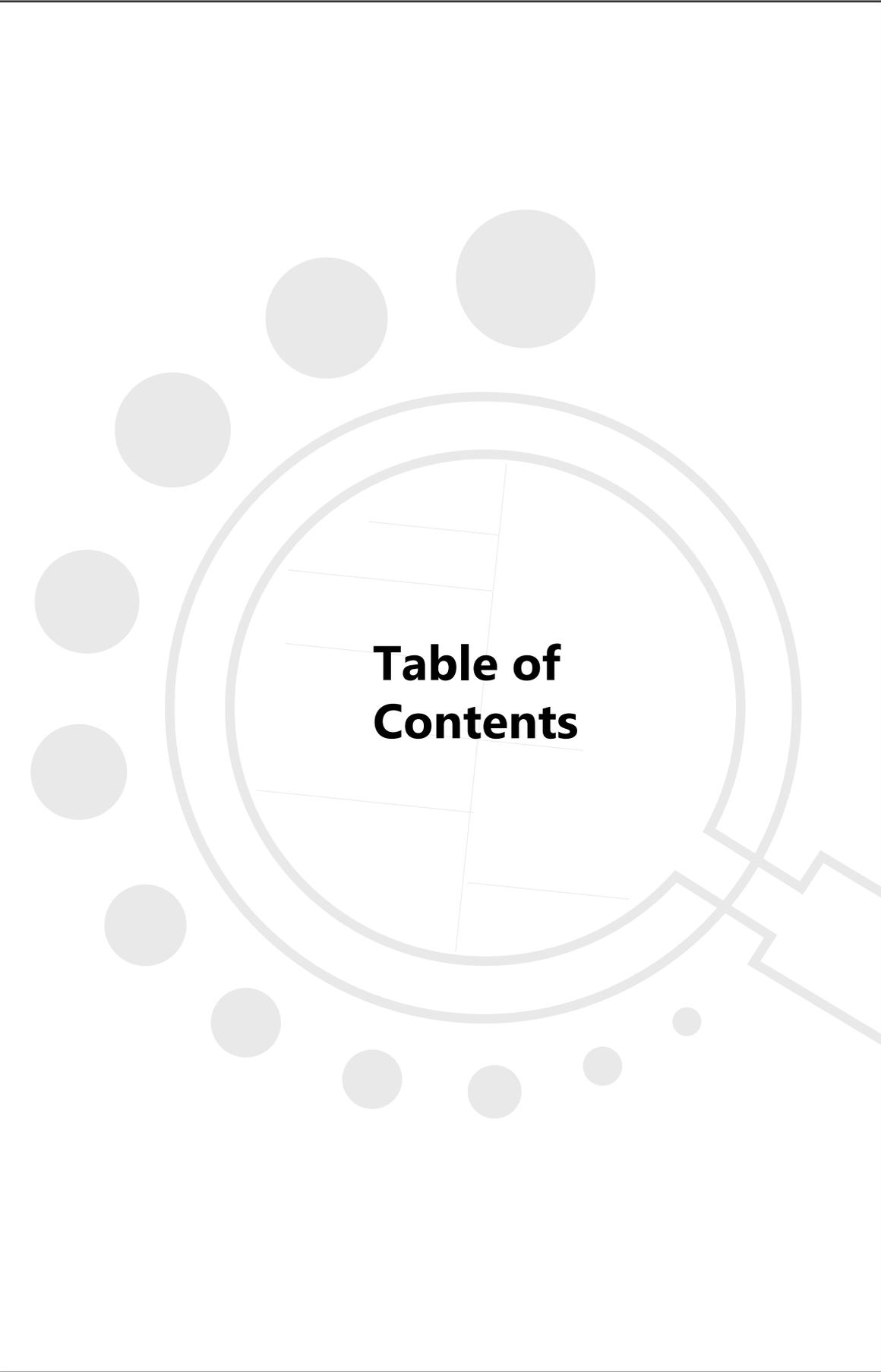


Evidence-Based Medicine

## **The Best Evidence on Family Planning Methods and Practices**







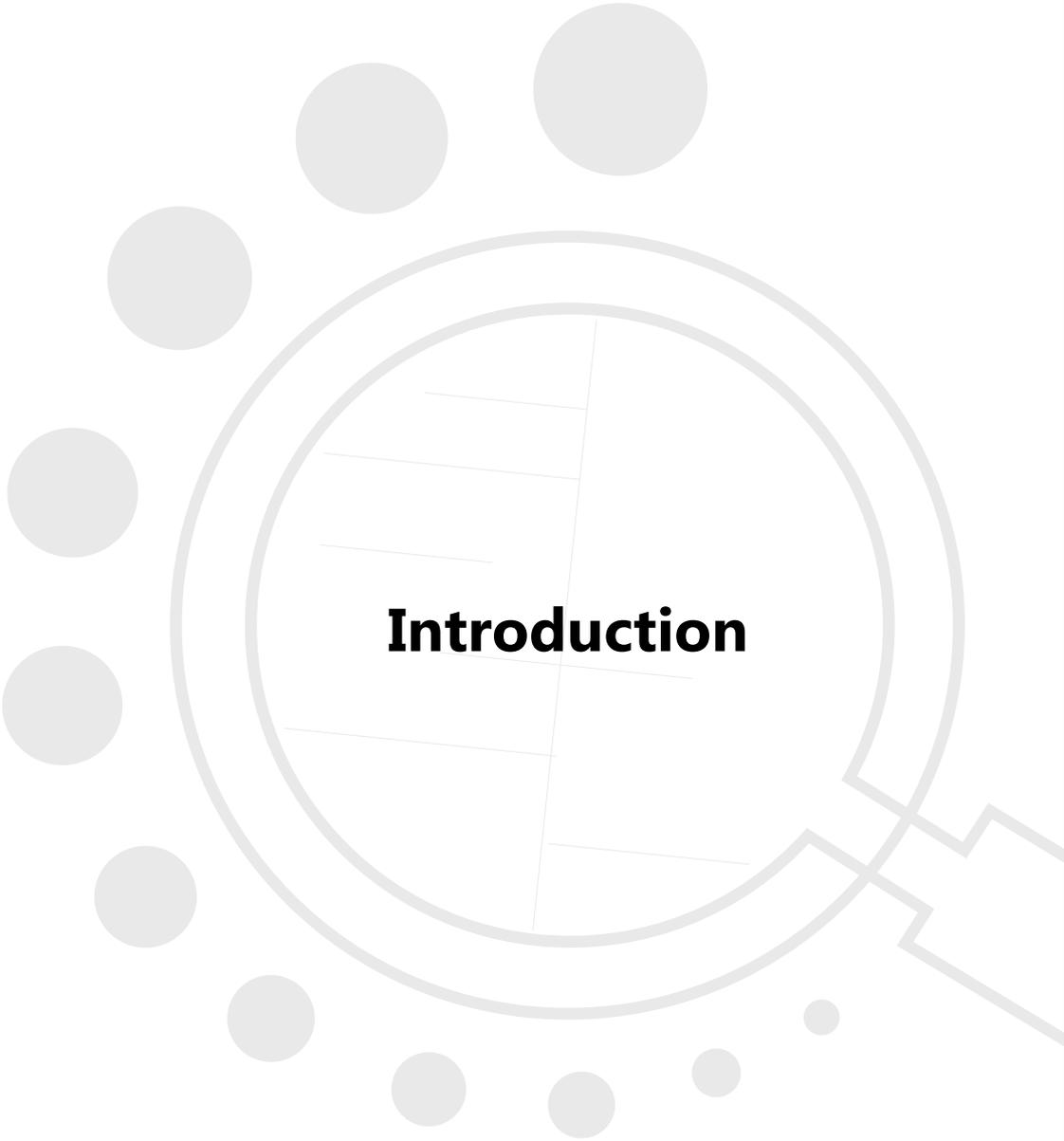
**Table of  
Contents**



# Table of Contents

1. **Introduction**
2. **Background Research:  
Overcoming Barriers to Modern Contraceptive Use**
3. **Evidence Based Medicine:  
An Advanced Paradigm for Medical Practice**
4. **Evidence Based Medicine Tools:  
Critically Appraised Topic (CAT)**
5. **Level of Evidence:  
The Best Research**
6. **Resources**
7. **Critically Appraised Topics (CATs)**
  - a) **Birth Spacing**
  - b) **Combined Oral Contraceptives (COCs)**
  - c) **Depot-Medroxyprogesterone Acetate (DMPA) Injectables**
  - d) **Intrauterine Devices (IUDs)**
  - e) **Progestin-Only Pills (POPs)**
  - f) **Implants**
  - g) **Vaginal Ring**
  - h) **Special Topics**





# Introduction



# Introduction

**Dear Health Colleagues,**

**The Jordan Evidence-Based Medicine/Reproductive Health (JEBM/RH) Group** is pleased to present this first set of Critically Appraised Topics, or “CATs,” on issues related to family planning methods. The evidence-based findings presented in these CATs represent the best and frequently the latest available medical research that address clinical questions regarding contraceptive methods available in Jordan. In line with the evidence-based medicine (EBM) process, we encourage you to interpret these research findings in the context of your experience as a clinician and your patient’s values. This publication of CATs complements the Ministry of Health’s recently released “Evidence-Based Clinical Practice Guidelines for Contraceptive Use (2013).” We also encourage you to visit the Electronic Library of Medicine – Jordan ([www.elm.jo/](http://www.elm.jo/)), where we have posted the CATs.

The JEBM/RH Group was formed in early 2011 to promote the practice of evidence-based medicine in reproductive health. Our group currently consists of 12 obstetrician-gynecologist professors, epidemiologists and practicing clinicians.

The mission of the JEBM/RH Group is to:

- Critically appraise research on issues related to reproductive medicine, initially focusing on contraception
- Disseminate the best evidence on contraceptive methods to health providers, patients and the public
- Promote updates to the Jordanian health provider community identifying the “best evidence” in addressing patient problems related to contraceptive side effects and health concerns as well as on the benefits of modern contraceptive methods, including non-contraceptive benefits

We have conducted a series of roundtable discussions on the evidence concern-

ing contraceptive methods and birth spacing throughout the kingdom. We will keep you informed about these roundtable discussions and invite you to join them if you wish to learn more about the practice of EBM and the evidence concerning contraception in particular. We also invite you to contact us if you would like the JEBM/RH Group to assist you in researching a reproductive health issue that you have encountered in your clinical practice, or if you are interested in joining our group.

**Sincerely,**

**The Jordan Evidence-Based Medicine/Reproductive Health Group**

# Jordan Evidence-Based Medicine Reproductive Health Group Members



**Abdul Malek Abdul Malek, MD, Mb. Bch., DOG,  
JBOG, FICS, FRCOG**

Senior Consultant Obstetrician and Gynecologist  
President (former), Jordanian Society of Obstetrician  
and Gynecologists  
Vice Chairman, Jordan Evidence-Based Medicine Society,  
Jordan Medical Association  
Member of the maternal mortality steering committee, Higher  
Population Council

---



**Abu El Heija Adel, MBBC, FRCOG**

Professor, Obstetrics and Gynecology, Faculty of Medicine,  
Mutah University  
Published 50 papers in international and regional journals  
Chairman (former), Obstetrics & Gynecology Departments,  
Jordan University of Science and Technology and Mutah  
University  
Dean (former), Faculty of Medicine, Mutah University (two  
terms)  
Examiner, Arab and Jordanian Boards for Obstetrics &  
Gynecology  
Reviewer of national, regional, and international journals

---



**Al Daoud Maysoon, MD**

Consultant Obstetrician and Gynecologist

---



**Al Hamaly Sawsan, MD**

Consultant Obstetrician and Gynecologist  
Advisor, Arab Gynecology Board

---



**Al Kuran Oqba, MD, MRCOG**

Consultant Obstetrician and Gynecologist, Feto-Maternal  
medicine  
Associate Professor, Jordan University of Science and  
Technology

---



**Al-Jefout Moamar, MD, PhD Reproductive Health  
Sciences and Human Genetics**

Assistant Professor and Specialist Consultant in  
Reproductive Medicine and Endoscopic Surgery, Mutah  
University  
Ambassador, World Endometriosis Society  
Chair, Endometriosis Special Interest Group, Middle East  
Fertility Society  
Award, Society of Gynecological Investigation  
Author, scientific articles, textbook chapters on  
endometriosis

---



**Al-Mehaisen Lama, MD, MRCOG**

Associate Professor, Jordan University of Science and  
Technology  
Consultant obstetrician and gynecologist - Urogynecology

---



**Al-Musa Abed El Halim, MD, PhD Epidemiology**

Chairman, Evidence-Based Medicine Society, Jordan  
Medical Association  
Community medicine consultant

---



**Amarin Zouhair, MD, MSc (Med Sci), FMGEMS,  
FRCOG, MHPE (Med Edu), FFPH**

Professor, Obstetrician and Gynecologist  
Dean of Faculty of Medicine, Mutah University-karak

---



**Hawa Nather, MD**

Professor, Obstetrics and Gynecology, Faculty of Medicine,  
Mutah University  
Chairman, Obstetrics and Gynecology Department  
Committee member for updating obstetrics and gynecological  
academic educational programs



**Khadra Maysa', MD, MMed, JBOG**

Consultant, Obstetrics and Gynecology  
Assistant Professor, Faculty of Medicine, University of  
Jordan

Reproductive and infertility consultant  
Head of the IVF Unit, Jordan University Hospital  
Fellowship, Reproductive Endocrinology and Infertility,  
Sydney, Australia  
Master of Medicine (Reproductive Health and Human  
Genetics), University of Sydney

---



**Ihsan Nu'eimat**

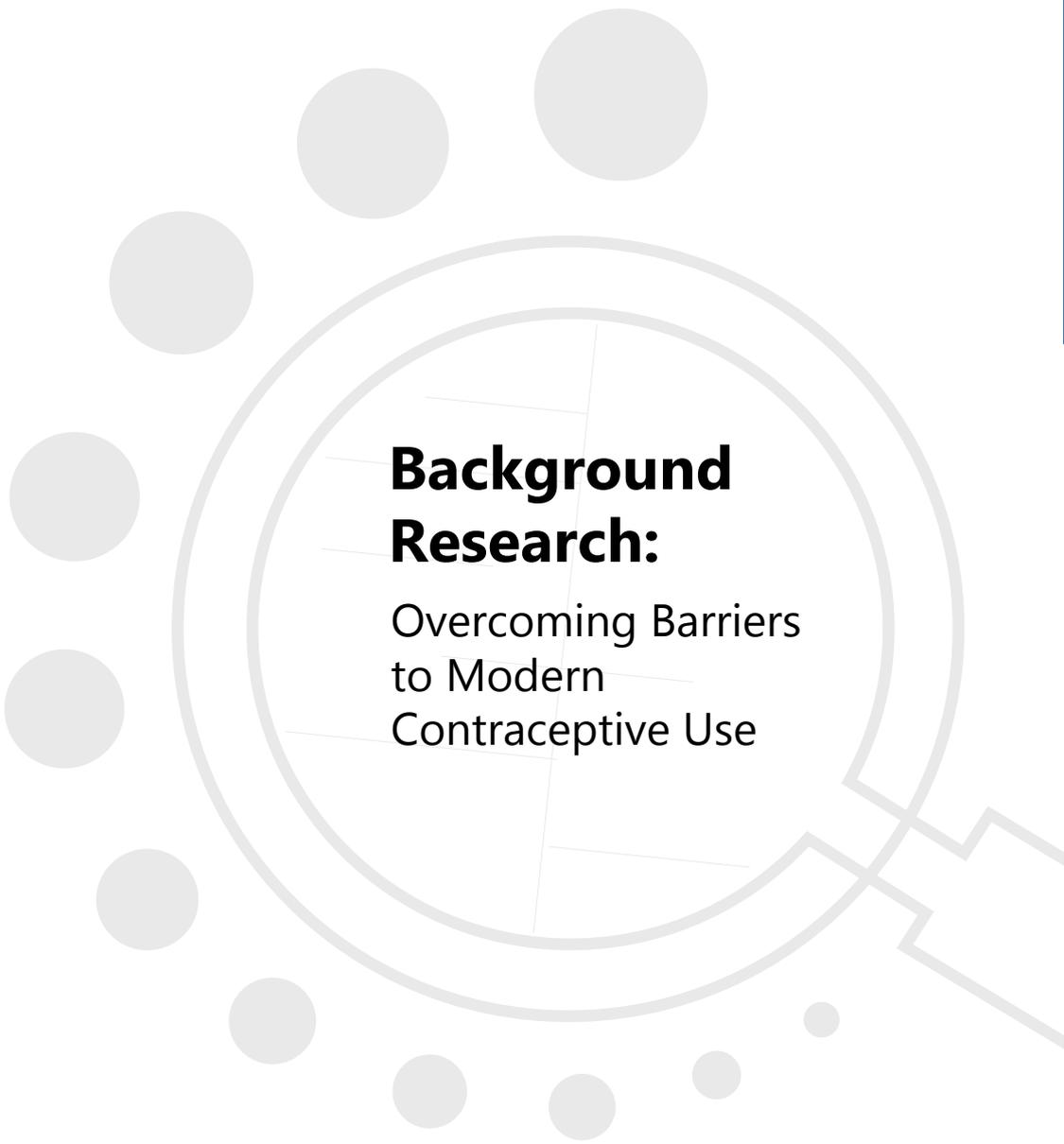
Consultant Obstetrician and Gynecologist

---



**Qatawneh Ayman, MD**

Assistant Professor, Urogynecology, Faculty of Medicine,  
University of Jordan



## **Background Research:**

Overcoming Barriers  
to Modern  
Contraceptive Use



## Background Research

### Overcoming Barriers to Modern Contraceptive Use

The 2012 Jordan Population and Family Health Survey (JPFHS) showed that knowledge of family planning and contraceptive methods is almost universal among Jordanian married women of reproductive age (MWRA). Among MWRA, 61% were practicing some form of contraception – 42% were using a modern contraceptive method (IUD, pills, condoms) – a rate that has essentially been flat over the past 10 years, while 19% were using a less effective traditional method such as withdrawal or periodic abstinence.

The survey revealed that many Jordanian women do not use or they discontinue use of modern contraceptives because of fear of side effects and health repercussions. Among surveyed MWRA who said they do not intend to use contraception in the future, 17% said their reasons were fear of side effects and health concerns. More pronounced however are contraceptive discontinuation rates due to side effect fears and health concerns, as summarized in the table below.

<b>Contraceptive Method</b>	<b>First Year Discontinuation Rate</b>	<b>Discontinuation due to Side Effects/Health Concerns</b>
Oral contraceptive pills	46%	16%
Injectable contraceptives	64%	28%
Intrauterine device (IUD)	15%	6%

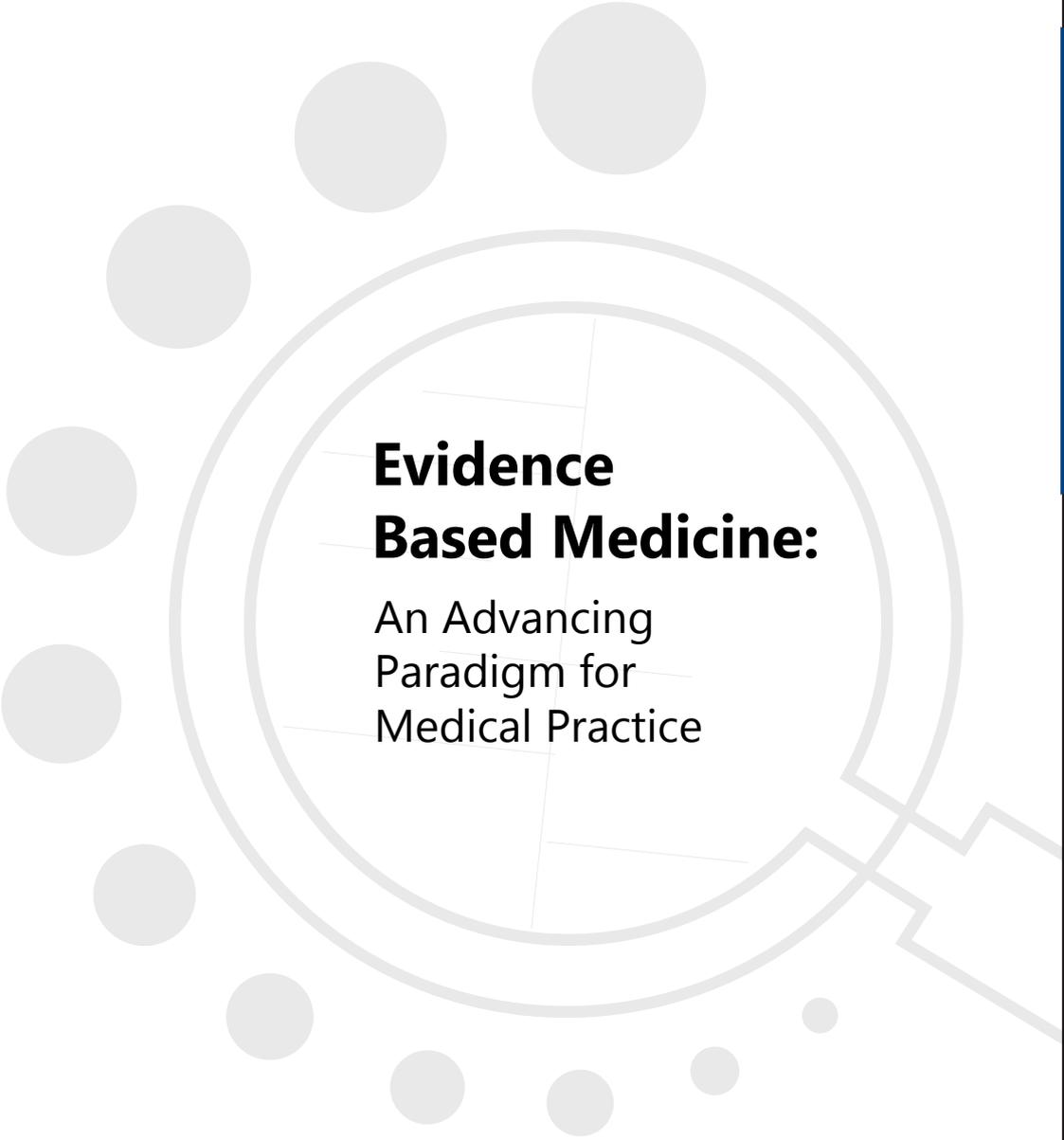
Source: 2012 JPFHS

Meanwhile, among the Jordanian medical community, barriers to prescribing a modern contraceptive method are Multi-dimensional. These barriers include a lack of up-to-date information as well as a range of misconceptions. These misconceptions are most pronounced for hormonal contraceptive methods which include oral contraceptive pills, injectables and implants.

Yet, there is clear demand and need for modern contraception in Jordan. In the 2012 JPFHS, 12% of MWRA said they wanted either to have no more children or to space their next birth yet they were not using any method of contraception.

### **The Need for Evidence-Based Medicine in Family Planning**

Health providers need the most up-to-date information to address the needs of their clients who want an effective family planning method but are worried about contraceptive side effects and health impacts. Moreover, this information must be *credible and based on the best evidence*. Providers need to be armed with the facts, based on solid, documented evidence, and they need that information to be presented in a way that directly and concisely addresses patient concerns and their own misconceptions, specific to the Jordanian context. This is what the **Jordan Evidence-Based Medicine/Reproductive Health Group's** publication, *Evidence on Family Planning Methods*, seeks to address.



**Evidence  
Based Medicine:**

An Advancing  
Paradigm for  
Medical Practice



# **Evidence-Based Medicine: An Advancing Paradigm for Medical Practice**

## **What is EBM?**

**Evidence-Based Medicine (EBM)** is the integration of best research evidence with clinical expertise and patient values.

By **best research evidence**, we mean clinically relevant research, often from the basic sciences of medicine, but especially from patient-centered clinical research focused on the accuracy and precision of diagnostic tests (including clinical examination), the power of prognostic markers, and the efficacy and safety of therapeutic, rehabilitative and preventive regimens. New evidence from clinical research may invalidate previously accepted diagnostic tests and treatments these one often replaced with new ones that are more accurate, more efficacious and safer.

By **clinical expertise**, we mean the ability to use our clinical skills and experience to identify each patient's unique health state and diagnosis, the individual risks and benefits of potential interventions, and their personal values and expectations.

By **patient values**, we mean the unique preferences, concerns and expectations each patient brings to a clinical encounter. This must be integrated into clinical decisions if they are to benefit the patient.

When these three are integrated, clinicians and patients form a diagnostic and therapeutic alliance that optimizes outcomes and quality of life.

— *Evidence-Based Medicine: How to Practice and Teach EBM, 2000*

## **Two Fundamental Principles of EBM**

As a distinctive approach to patient care, EBM involves two fundamental principles. First, evidence alone is never sufficient to make a clinical decision. Decision-makers must always trade the benefits and risks, inconvenience, and costs associated with alternative management strategies, and in doing so consider the patient's values. Second, EBM posits a hierarchy of evidence to guide clinical decision-making.

— *The Users' Guides to the Medical Literature: A Manual for Evidence-Based Clinical Practice, American Medical Association, 2002*

## **Who Practices EBM?**

**EBM is a widely practiced, internationally sanctioned approach to medicine.**

The World Health Organization (WHO) has adopted an EBM framework in developing health policy around the world.

— *WHO Health Report 2000 as reported in the Lancet 5/26/2001*

The Journal of the American Medical Association (JAMA) developed and published 25 "Users' Guides" on EBM to promote the adoption of EBM in clinical practice in the US.

— *JAMA Users' Guides by the EBM Working Group, 1992-2000*

A study found broad support for the principals of EBM among obstetricians and gynecologists, worldwide.

— *International Journal of Gynecology and Obstetrics 72 (2001)*

## **How Do We Practice EBM?**

**The practice of EBM comprises five steps:**

- Step 1**      Converting the need for information (about prevention, diagnosis, prognosis, therapy, causation, etc.) into an answerable question.
- Step 2**      Finding the best evidence to answer that question.

- Step 3** Critically appraising that evidence for its validity (closeness to the truth), impact (size of effect), and applicability (usefulness in our clinical practice).
- Step 4** Integrating the critical appraisal with our clinical expertise and experience and with our patients' unique biology (e.g. their eligibility for contraceptive methods), values (e.g. their beliefs and preferences) and circumstances.
- Step 5** Evaluating our effectiveness and efficiency in executing steps 1-4 seeking always to improve them both for next time.

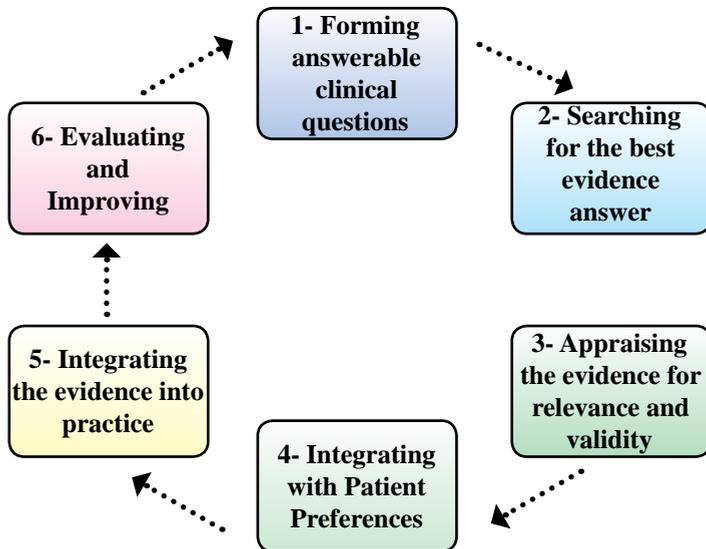
### **What Are the Results of EBM?**

Population-based “outcome research” shows that those who receive evidence-based therapies have better outcomes than those who do not.

— *Evidence-Based Medicine: How to Practice and Teach EBM, 2000*

# How to Apply *Evidence-Based Medicine in Clinical Decision Making*

## An Overview



### The EBM Clinical Question

The EBM Cycle starts with asking a question that you can answer. This question addresses a clinical situation or scenario, which may have been encountered during rounds, a clinic consultation, or while reading. The key element about this question is that it is easily searched and answerable in online medical resources such as PUBMED. The elements of a well-phrased clinical question are:

- 1. Population, Patient or Person (P)** – or what group of people would I want to target in my query. This may include patients, asymptomatic people, a group of people with a certain condition, or others.
- 2. Interventions or Exposures (I)** – may refer to the surgical or medical procedures (drugs, operations, treatments) that would have to be evaluated for comparison, or may refer to condition or factors present in a group of people that would have to be associated with a result.

3. **Comparison (C)** – refers to the other group without the intervention or exposure, which would be compared with the group with the intervention or exposure, if applicable.
4. **Outcome (O)** – refers to the consequences of the exposure or the intervention previously mentioned.

Examples of the Clinical Question are:

- a. Among multiparous women (P), what are the effects on sexual satisfaction (O) between those who had a bilateral tubal ligation (I) and those who used a non-permanent method of contraception (C)?
- b. Among women with Human Papilloma viruses (P), what is the risk of developing sexually transmitted diseases (O) if they used oral contraceptives (I) compared to their use of condoms (C)?

The Clinical Question components (P, I, C, O) would be important because it clarifies the main issues being studied in the literature, which makes it easier to do a search for relevant articles for review.

### **Medical Literature Search**

The number of journals in the medical literature is increasing every day, along with the number of papers and reports. There are millions of papers now catalogued in MEDLINE, which is open for all users via the website at [www.ncbi.nih.gov/pubmed](http://www.ncbi.nih.gov/pubmed).

Before going through MEDLINE, there are important steps that have to be followed sequentially that would save computer time and facilitate an efficient MEDLINE search. These steps include the following:

1. **Phrase** the question as precisely as possible and identify the *P*, *I*, *C*, and *O* of the clinical question.
2. **Rank** these concepts (P, I, O) according to importance.
3. **Expand** the most important concept to account for variations in terminology and spelling.

4. **Conduct** the search using MEDLINE, entering first the concepts that were ranked as most important and intersecting them with the succeeding expanded concepts that were subsequently ranked.<sup>3</sup>

EBM practitioners can type expanded concepts in the MEDLINE search box as “free text” or type “MeSH” (see below). The search will lead to a series of articles that can be narrowed by the intersection of concepts sequentially until a manageable yield is obtained. The practitioner may then assess or appraise the retrieved articles as useful or not. The “Clinical Queries” option of PubMed uses a series of filters that can dramatically improve the focus and reduce the number of ‘hits’, often saving a lot of time). **MeSH** refers to **Medical Subject Headings** that more or less uses standardized medical terms. It is organized into a complex hierarchy called the *MESH Tree*, which starts with the more general conceptual terms and becomes more and more specific as more branches are encountered.

Below is a systematic guide for doing a medical article search.

1. Go to *www.ncbi.nlm.nih.gov* to access PubMed.
2. On the Search bar, choose the PubMed group, or the MeSH group, and type your **P** or **I** (**Population** or **Intervention** of the PICO). What you enter first is determined by how you ranked these concepts.
3. Once you get hits (articles that are important and have been retrieved), you can review the MeSH term so that the search strategy can be refined.
4. Store it in history.
5. If there are too few hits if you use MeSH, try looking for it using free text in PubMed.
6. Choose the term in PubMed or MeSH for your O (outcome) or whatever was ranked next.
7. Do the above term as with number 3 and 4.
8. In the search box, you can mix the history search strategy for the I and the O (#3 and #6, remember?)
9. If you have few hits, you can just scan them and look for the most appropriate article.
10. If there are too many, you can choose to expand subsequent concepts or use method filters that are more stringent (such as blinding, place-

bo-controlled etc.) or you may go to the limits bar on the screen, and choose only Randomized Controlled Trials, or limit the publication year, or language.

- 11.** For each concept, you can intersect this sequentially with the others (as ranked) until you obtain a manageable number of yields for the articles.
- 12.** As noted above, you can also use the Clinical Queries button on PubMed (on the blue margin, left side of screen, 2nd section called “PubMed Services”, 6th one down. This facility contains built-in filters for category, emphasis (sensitivity versus specificity), and systematic reviews.
- 13.** The above steps should limit your search to the best strategy. You can also use guidelines and reviews.

Some journals offer their articles online at no charge. Try also [www.freemedicaljournals.com](http://www.freemedicaljournals.com).

For those with available resources, one may try using the Loansome Doc program. Loansome Doc enables PubMed and NLM Gateway users to order documents found in MEDLINE®. It is available to users worldwide. A user can order articles from a list of citations retrieved from PubMed and the NLM Gateway by sending requests to a library for the full-text documents. The URL for Loansome Doc is: [http://www.nlm.nih.gov/pubs/factsheets/loansome\\_doc.html](http://www.nlm.nih.gov/pubs/factsheets/loansome_doc.html)





# **Evidence Based Medicine Tool:**

Critically Appraised  
Topic (CAT)



# The Critically Appraised Topic (CAT)

A critically appraised topic (or CAT) is a one or two-page summary of a search and critical appraisal of the literature related to a focused clinical question, and it includes a “clinical bottom line” reflecting synthesis of the best available medical research. We recommend that clinicians counseling patients on family planning keep this evidence notebook nearby and refer to the appropriate CATs to answer patient questions and to support clinical decision making regarding contraception. Following illustrates the CAT format that the JEBM/RH Group uses, with a breakdown of its different components.

**Resumption of ovulation after removal of the combined contraceptive vaginal ring (NuvaRing®) is rapid.**



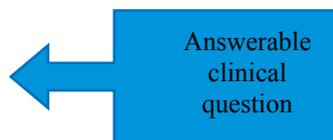
## Conclusion

The combined contraceptive vaginal ring is a highly effective, reversible method of hormonal contraception. The vaginal ring acts similarly to the combined oral contraceptive and return to ovulation for most is rapid occurring for half or more women within 17-19 days after removal.



## Clinical Question

Does the use of combined contraceptive vaginal ring affect return to fertility?



## Search Terms

Combined contraceptive vaginal ring, NuvaRing®, return to fertility

## Citations

Mulder TMT, Dieben TOM, Bennick HJTC. *Ovarian Function with a novel combined contraceptive vaginal ring*. Human Reproduction 2002;17(10):2594-2599

## Object of Research

Combined contraceptive vaginal ring

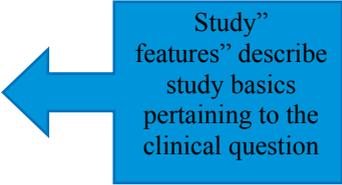
## Research Outcome

Return to fertility

### Study Features

This is an open label, randomized, pharmacodynamic study of the combined contraceptive vaginal ring assessing ovarian function when there are deviations from the recommended usage schedule.

The recommended regimen is one in which the ring is used continuously for three weeks followed by one ring free week. Forty-five combined contraceptive vaginal ring users were enrolled in the study and all used the ring continuously for three weeks. Fifteen women (Group A) had a one-week ring free period followed by another ring use period of three weeks. Another 15 women (Group B) had a ring free week followed by three days of ring use and a third 15 (Group C) had a ring free period until a 13 mm follicle was detected by ultrasound. Group C then used the ring for three weeks followed by a one-week ring free period.



Study” features” describe study basics pertaining to the clinical question

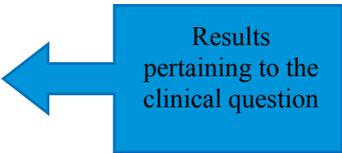
### *Evidence Grade: Level 1*

#### The Evidence

Regardless of the length of the second cycle, 3 weeks (group A) versus 3 days (group B), the time to ovulation after ring removal was similar (19 versus 17 days). The median time needed to develop a follicle up to 13 mm in diameter (group C) was 11 days (range 8–21 days); none of the women ovulated after insertion of the second ring. (Note: Median time is the point in which at least half the women returned to ovulation.)



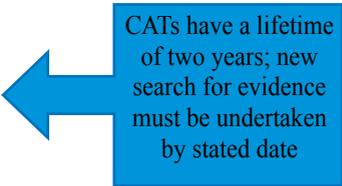
Graded level of evidence (see following section on “levels of evidence”)



Results pertaining to the clinical question

**Appraised by:** The Jordan Evidence-Based Medicine Reproductive Health Group

**Update by:** 5 March 2016



CATs have a lifetime of two years; new search for evidence must be undertaken by stated date

**Level of  
Evidence:**

The Best Research



# Level of Evidence

The Critically Appraised Topics (CATs) are supported by the “best research” available to answer a specific clinical question. Assigning a “level of evidence” places the research in context as multiple studies may be cited in the CAT. The JEBM/RH Group uses the following “evidence grading” system for the medical research appraised in CATs.

- Level I** High quality randomized controlled trial with statistically significant difference or no statistically significant difference but narrow confidence intervals.  
Systematic review of at least two Level I randomized controlled trials (and study results were homogeneous)
- Level II** Less quality randomized controlled trial (e.g. < 80% follow-up, no blinding, or improper randomization)  
Prospective comparative study  
Systematic review of Level II studies or Level I studies with inconsistent results
- Level III** Case control study  
Retrospective comparative study  
Systematic review of Level III studies
- Level IV** Case series
- Level V** Expert opinion or anecdotal reports

Note that the age of the study is not included





# Resources



## Resources

### **Books**

Sackett, David; Straus, Sharon, et al: *Evidence-Based Medicine How to Practice and Teach EBM*, London: Churchill Livingstone, 2000.

Guyatt, Gordon; Rennie, Drummond: *Hayward, Robert, User's Guide to Medical Literature, A Manual for Evidence-Based Clinical Practice*. University of Alberta, Edmonton, Canada and the American Medical Association Press, 2002.

### **Online Medical Information Resources**

Electronic Library of Medicine – Jordan [www.elm.jo/](http://www.elm.jo/)

ACP Journal Club [www.acpjc.org](http://www.acpjc.org)

Cochrane Library <http://www.cochrane.org/>

Up-To-Date [www.uptodate.com](http://www.uptodate.com)

MEDLINE PubMed <http://www.ncbi.nlm.nih.gov/pubmed/>

Medical Matrix [www.medmatrix.org/info/medlinetable.asp](http://www.medmatrix.org/info/medlinetable.asp)

Medscape <http://emedicine.medscape.com/>

Medical World [www.mwsearch.com](http://www.mwsearch.com)

Clinical Practice Guidelines [www.guidelines.gov](http://www.guidelines.gov)

MD Consult [www.mdconsult.com](http://www.mdconsult.com)

Ovid [www.ovid.com](http://www.ovid.com)





**Critically  
Appraised  
Topics (CATs)**





# Birth Spacing

Birth Spacing



## **List of Critically Appraised Topics Birthspacing**

- 1-Premature Births
- 2-Low Birth Weight
- 3-Gestational Age
- 4-Neonatal Mortality
- 5-Child Growth
- 6-Breastfeeding
- 7-Infant Mortality
- 8-Child Mortality
- 9-Maternal Deaths
- 10-Preeclampsia
- 11-Anemia
- 12-High Blood Pressure
- 13-Obstructed Labor
- 14-Congenital Anomalies
- 15-Autism

*Note that the level of evidence accompanying each publication in each of the CATs refers to the study design*

## **Shorter birth intervals are associated with an increased risk of premature births**

### **Conclusion**

Inter-pregnancy intervals shorter than 18 months and longer than 59 months are significantly associated with increased risk of adverse perinatal outcomes including premature births. Spacing pregnancies appropriately may prevent many of these preterm births.

### **Clinical Question**

Are shorter birth intervals associated with an increased risk of premature births?

### **Search Terms**

Premature delivery, inter-pregnancy interval

### **Citation**

Conde-Agudelo A, Rosas-Bermudez A, Kafury-Goeta AC. *Birth Spacing and Risk of Adverse Perinatal Outcomes A Meta-analysis*. JAMA 2006;295:1809-1823.

### **Object of Research**

Birth spacing

### **Research Outcome**

Premature birth

### **Study Features**

This meta-analysis included cohort, cross-sectional, and case-control studies with results adjusted for maternal age and socioeconomic status. Estimates of relative risk of birth spacing and perinatal outcomes were made. Initially, 130 articles were identified in the search with 67 (52%) included.

*(Level 2 Evidence)*

### **The Evidence**

Compared with inter-pregnancy intervals of 18 to 23 months, inter-pregnancy intervals shorter than 6 months, 6 to 11 months and 12-17 months were associated with an increased risks of preterm birth with pooled adjusted odds ratios and 95% confidence intervals of 1.40 [95% CI: 1.24-1.58], 1.14 [95% CI: 1.10-1.17], and 1.07 [95% CI: 1.03- 1.11], respectively. Inter-pregnancy intervals longer than 59 months were also associated with a significantly greater risk for preterm births with an odds ratio=1.20 [1.17-1.24]

**Appraised by:** The Jordan Evidence-Based Medicine Reproductive Health Group

**Update by:** 4 July 2015

## **Short birth intervals are associated with an increased risk of low infant birth weight**

### **Conclusion**

Inter-pregnancy intervals shorter than 18 months are significantly associated with low infant birth weight compared with infants born to women with intervals of 18 to 23 months

### **Clinical Question**

Are shorter birth intervals associated with low infant birth weights?

### **Search Terms**

Birth spacing, inter-pregnancy interval, birth weight, perinatal outcomes

### **Citation**

Conde-Agudelo A, Rosas-Bermundez A, Kafury-Goeta AC. *Birth Spacing and Risk of Adverse Perinatal Outcomes A Meta-analysis*. JAMA 2006;295; 1809-1823.

### **Object of research**

Birth spacing

### **Research Outcome**

Birth weight

### **Study Features**

This is a systematic review, including meta-analysis, of the relationship between birth spacing and the risk of adverse perinatal outcomes. A total of 67 studies, including 11,091,659 pregnancies, met the inclusion criteria. Out of the 67 studies, 26 studies provided data on low birth weight. These studies were either cohort, cross-sectional, or case-control. Thirty percent of these studies were conducted in the United States. The remaining were conducted in, Latin America, Asia, Africa, Europe, and Australia. Out of the studies that provided data on low birth weight for systematic review, 10 provided data for a meta-analyses.

*(Level 2 Evidence)*

## **The Evidence**

- Among the 26 studies that provided data on low birth weight, 20 reported an association with short birth intervals, 7 found an association with long intervals, and 6 found no association with inter-pregnancy intervals.
- The highest risk for low birth weight was for intervals shorter than 20 months and longer than 60 months when compared with infants born to women with intervals of 18 to 23 months
- Comparing the number of women whose inter-pregnancy intervals were between 18 and 23 months to those whose pregnancies were less than 18 months, the following adjusted odds ratios (OR) with corresponding 95% confidence intervals for the association between short inter-pregnancy intervals and low birth weight at less than 6 months, 6-11 months, and 12-17 months were 1.61 (95% CI: 1.39-1.86), 1.14 (95% CI: 1.10-1.18), and 1.05 (95% CI: 1.01-1.09), respectively.

**Appraised by:** The Jordan Evidence Based Medicine Reproductive Health Group

**Update by:** 4 July 2015

## **Short inter-pregnancy intervals are associated with a risk for small for gestational age.**

### **Conclusion**

For infants who were small for gestational age (SGA), a significant risk factor was inter-pregnancy intervals shorter than 18 months. It was also noted that there was also an increased risk of SGA for inter-pregnancy intervals of at least 60 months.

### **Clinical Question**

Is there a relationship between inter-pregnancy intervals and the risk for small for gestational age (SGA) babies?

### **Search Terms**

Inter-pregnancy interval, birth spacing, small for gestational age

### **Citation**

Conde-Agudelo A, Rosas- Bermude A, Kafury-Goeta AC. *Birth Spacing and Risk of Adverse Perinatal Outcomes: A Meta-analysis*. JAMA. 2006;295(15):1809-1823

### **Object of Research**

Birth spacing and gestational age

### **Research Outcome**

Small for gestational age babies

### **Study Features**

This is a systematic review using a prospectively defined process to identify research involving adverse perinatal outcomes and birth spacing. Initially, 130 studies were considered relevant (Cohort, cross sectional, and case control studies) using key word terms for birth spacing and adverse perinatal outcomes. Of these 130 papers, specifically addressed the clinical question as to whether or not there was an association between inter-pregnancy intervals and pregnancies small for gestational age.

*(Level 2 Evidence)*

**The Evidence**

Of the 24 studies, 14 reported an association between SGA and short intervals, 6 between SGA and long intervals, and 10 found no association. Compared with inter-pregnancy intervals of 18 to 23 months, intervals shorter than 6 months were associated with an increased risk of SGA. The adjusted odds ratio was 1.26 [95% CI: 1.18-1.33]. Similarly, a significant association between increased risk and birth interval was found for 6 to 11 and 12 to 17 months. The adjusted odds ratio for these intervals were 1.11 [95% CI: 1.04-1.19] and 1.06 [95% CI: 1.01-1.10], respectively. The adjusted odds ratio for those with an inter-pregnancy interval of more than 59 months was 1.29 [95% CI: 1.20-1.39].

**Appraised by:** The Jordan Evidence-Based Medicine Reproductive Health Group

**Update by:** 4 July 2015

## **Mothers with shorter birth intervals are at increased risk of death of their children before the first month**

### **Conclusion**

Pregnancy intervals less than 36 months are associated with an increased risk of neonatal mortality.

### **Clinical Question**

Are shorter birth intervals associated with an increased risk of neonatal mortality?

### **Search Terms**

Neonatal mortality, birth interval, inter-pregnancy interval

### **Citation**

Rutstein S. *Effects of preceding birth intervals on neonatal, infant and under-five mortality and nutritional status in developing countries: evidence from the demographic and health surveys*. International Journal of Gynecology and Obstetrics; (2005), 89: S7-S24.

### **Object of Research**

Birth spacing

### **Research Outcome**

Neonatal mortality (death of child during first 30 days after birth)

### **Study Features**

This is an analysis of retrospective survey data from the Demographic and Health Surveys (DHS) from 17 developing countries (Bangladesh, Bolivia, Ivory Coast, Egypt, Ghana, Guatemala, India, Indonesia, Kenya, Morocco, Nepal, Nigeria, Peru, Philippines, Tanzania, Uganda, Zambia) collected between 1990 and 1997. The analysis compared under five years of age neonatal mortality rates for preceding monthly birth intervals of < 18, 18-23, 24-29, 30-35, 36-41 42-47, 48-53 54-59 and 60+ months.

*(Level 3 Evidence)*

**The Evidence**

Compared with the birth interval of 36 to 41 months, for most countries, neonatal mortality generally declined from a high for those with a birth interval less than 18 months to a low for those with an interval 48 to 59 months. The only exception to this pattern was in Kenya where neonatal deaths were significantly lower for women with an inter-pregnancy interval less than 18 months.

**Appraised by:** The Jordan Evidence Based Medicine Reproductive Health Group

**Update by:** 4 July 2015

# **Increasing the interval between births results in a decreased risk in stunting and underweight children under age five**

## **Conclusion**

Increased birth intervals in under developed countries were associated with a linear decrease in stunting and underweight children under five. The decrease was less pronounced for those underweight than for stunting. There does not appear to be an association between birth interval and wasting, however.

## **Clinical Question**

Are shorter birth intervals associated with an increased risk of lower growth rates for children under 5 years?

## **Search Terms**

Growth before age 5, stunting, underweight, wasting, birth interval, inter-pregnancy interval

## **Citation**

Rutstein S. *Effects of preceding birth intervals on neonatal, infant and under-five mortality and nutritional status in developing countries: evidence from the demographic and health surveys*. International Journal of Gynecology and Obstetrics; (2005), 89: S7-S24.

## **Object of Research**

Birth spacing

## **Research Outcome**

Child growth

## **Study Features**

This is an analysis of retrospective survey data from the Demographic and Health Surveys (DHS) from 17 developing countries (Bangladesh, Bolivia, Ivory Coast, Egypt, Ghana, Guatemala, India, Indonesia, Kenya, Morocco, Nepal, Nigeria, Peru, Philippines, Tanzania, Uganda, Zambia) collected between 1990 and 1997. Growth was assessed by anthropometric measurements on children under 5. In two countries (India and Uganda), children

under 4 years were weighed and measured. In three other countries (Bolivia, Ivory Coast, and Nepal) measurements were made on children less than 3 years. In three countries (Egypt, the Philippines, Indonesia) anthropometry was not included. The analysis compared stunting, underweight, and wasting for the successive preceding monthly birth intervals of < 18, 18-23, 24-29, 30-35, 36-41 42-47, 48-53 54-59 and 60+ months.

*(Level 3 Evidence)*

### **The Evidence**

Stunted growth among children is a reduced growth rate in their human development and in this study, the unweighted averages showed a statistically significant linear decline with increasing birth intervals ( $p=0.004$ ). That is, as the birth interval increases, stunting decreases. Similarly there is a linear decline with increasing birth interval for those children who are underweight ( $p=0.012$ ). Wasting refers to the process by which a debilitating disease causes muscle and fat tissue to “waste” away and, in this study, there was no apparent relationship between wasting and increasing birth interval ( $p=0.532$ ).

**Appraised by:** The Jordan Evidence Based Medicine Reproductive Health Group

**Update by:** 4 July 2015

## **Shorter birth intervals are associated with less time to breast feed the infant.**

### **Conclusion**

Shorter birth intervals are associated with significantly less time for the infant to breast feed.

### **Clinical Question**

Are shorter birth intervals associated with less time to breast feed the infant?

### **Search Terms**

Birth intervals, breast feeding

### **Citation**

Dim C, Ugwu E, Iloghalu E. *Duration and determinants of inter-birth interval among women in Enugu, south-eastern Nigeria*. Journal of Obstetrics and Gynecology (2013);22:175-170.

### **Object of Research**

Birth spacing

### **Research Outcome**

Length of breast feeding

### **Study Features**

This is a cross-sectional study of 420 consecutive women receiving antenatal care and family planning at clinics of the University of Nigeria Teaching Hospital in Enugu, Nigeria. All women who had two or more live births were eligible for the study. A short inter-birth interval was defined as less than 24 months. Information concerning breast-feeding practices was collected.

*(Level 3 Evidence)*

## **The Evidence**

It was found that women with a short inter-birth interval are more likely to breast feed for ten or fewer months than those experiencing longer inter-birth intervals. [Odds Ratio=3.30 (95% CI 2.16-5.06)]. The differences between the two groups are statistically significant ( $p < 0.001$ )

**Appraised by:** The Jordan Evidence-Based Medicine Reproductive Health Group

**Update by:** 4 July 2015

# **Mothers with shorter birth intervals are at an increased risk for their child to die before age one**

## **Conclusion**

Pregnancy intervals less than 15 months are associated with a significantly increased risk of a child's death before age one or post-neonatal mortality.

## **Clinical Question**

Are shorter birth intervals associated with an increased risk of death between the ages 1 and 12 months?

## **Search Terms**

Death before age 1, post-neonatal mortality, birth interval, inter-pregnancy interval

## **Citation**

DaVanzo J, Hale H, Razzaque A, Rahman M. *The effects of pregnancy spacing on infant and child mortality in Matlab, Bangladesh: How they vary by the type of pregnancy outcome that began the interval.* Population Studies; 2008, Vol. 62(2): 131-154.

Rutstein S. *Effects of preceding birth intervals on neonatal, infant and under-five mortality and nutritional status in developing countries: evidence from the demographic and health surveys.* International Journal of Gynecology and Obstetrics; (2005), 89: S7-S24.

## **Object of Research**

Birth spacing

## **Research Outcome**

Post neonatal mortality (between ages 1 and 12 months)

## **Study Features**

DaVanzo et al

This study used data from Matlab, a typical rural subdistrict of Bangladesh. Data on 119,718 children who survived their first month after birth

were included in the analysis. Of these, 3,684 died before their first birthday. Child mortality rates for birth intervals at less than 15 months, 15-17 months, 18-23 months and 24-35 months were compared to rates for those occurring for birth intervals 36-59 months.

*(Level 3 Evidence)*

#### Rutstein

This is an analysis of retrospective survey data from the Demographic and Health Surveys (DHS) from 17 developing countries (Bangladesh, Bolivia, Ivory Coast, Egypt, Ghana, Guatemala, India, Indonesia, Kenya, Morocco, Nepal, Nigeria, Peru, Philippines, Tanzania, Uganda, Zambia) collected between 1990 and 1997. The analysis included a comparison of mortality rates of infants between 1 and 12 months for preceding monthly birth intervals of less than 18, 18-23, 24-29, 30-35, 36-41 42-47, 48-53 54-59 and 60+ months.

*(Level 3 Evidence)*

#### **The Evidence**

##### DaVanzo et al

When the previous birth outcome is considered, the relative risk (RR) of mortality between the age of one month to a year is highest for the birth interval less than 15 months (previous birth alive: RR=3.14,  $p<0.001$ ). The risk decreased with increasing birth intervals.

#### Rutstein

Results from the 17 selected countries showed a pattern of decreasing post neonatal mortality with increasing birth interval. Compared with a preceding birth interval of 36 to 59 months, infant mortality is higher on average by 230 percent, 100 percent, 60 percent, and 30 percent for intervals less than 18 months, 18 to 23 months, 24 to 29 months, and 30 to 35 months, respectively.

**Appraised by:** The Jordan Evidence Based Medicine Reproductive Health Group

**Update by:** 4 July 2015

## **Mothers with shorter birth intervals are on increased risk of death of their children before the age of five**

### **Conclusion**

Pregnancy intervals less than 36 months are associated with increased risk of a child's death before age five.

### **Clinical Question**

Are shorter birth intervals associated with an increased risk of child's death between the ages of one and five?

### **Search Terms**

Death before age 5, birth interval, inter-pregnancy interval

### **Citation**

DaVanzo J, Hale H, Razzaque A, Rahman M. *The effects of pregnancy spacing on infant and child mortality in Matlab, Bangladesh: How they vary by the type of pregnancy outcome that began the interval.* Population Studies; 2008, Vol. 62(2): 131-154.

Rutstein S. *Effects of preceding birth intervals on neonatal, infant and under-five mortality and nutritional status in developing countries: evidence from the demographic and health surveys.* International Journal of Gynecology and Obstetrics; (2005), 89: S7-S24.

### **Object of Research**

Birth spacing

### **Research Outcome**

Child mortality before age 5

## **Study Features**

### DaVanzo et al

This is a retrospective cohort study using data from Matlab, a typical rural subdistrict of Bangladesh. Data on 110,191 children who survived until their first birthday were included in the analysis. Of these, 3,223 died before their fifth birthday. Child mortality rates for birth intervals at less than 15 months, 15-17 months, 18-23 months and 24-35 months were compared to rates for those occurring for birth intervals 36-59 months.

*(Level 3 Evidence)*

### Rutstein

This is an analysis of retrospective survey data from the Demographic and Health Surveys (DHS) from 17 developing countries (Bangladesh, Bolivia, Ivory Coast, Egypt, Ghana, Guatemala, India, Indonesia, Kenya, Morocco, Nepal, Nigeria, Peru, Philippines, Tanzania, Uganda, Zambia) collected between 1990 and 1997. The analysis include a comparison of under five years of age childhood mortality rates for preceding monthly birth intervals of less than 18, 18-23, 24-29, 30-35, 36-41 42-47, 48-53 54-59 and 60+ months.

*(Level 3 Evidence)*

## **The Evidence**

### DaVanzo et al

When birth parity, mother's age, mother's education, father's presence, religion, household space, month of birth, calendar year period, and whether or not the mother lived in a maternal and child health area were controlled, the relative risk (RR) of mortality at ages 1-4 is highest for birth intervals of 15 to 17 months (RR=1.83,  $p<0.001$ ). Compared with those having intervals of 36 to 59 months, higher relative risks were noted for birth intervals less than 15 months (RR=1.50,  $p<0.10$ ), 18 to 23 months (RR=1.41,  $p<0.001$ ), and 24 to 35 months (RR=1.23,  $p<0.01$ ). Note that the relative risk for less than 15 months is not statistically significant, but this may be the result of a small sample size for that category.

### Rutstein

Under five mortality in the 17 selected countries varies from 42 to 163 deaths per 1000 births. On average, children born after short intervals of less than 18 months between births and 18 to 23 months between births, are respectively 3.0 and 1.9 times more likely to die before their fifth birthday as are children born 36 to 59 months. In addition, those children born after intervals of 24 to 29 months and 30 to 35 months have a 60 percent and 30 percent greater chance of dying than do children born after 36 to 59 months.

**Appraised by:** The Jordan Evidence Based Medicine Reproductive Health Group

**Update by:** 4 July 2015\_

# **Short birth intervals are associated with an increased risk of maternal mortality**

## **Conclusion**

Birth intervals of less than six months are associated with an increased risk of maternal mortality. For birth intervals between 6-12 months there is a suggested increased risk of maternal death, but the risk is not statistically significant.

## **Clinical Question**

Is there an association between short inter-pregnancy intervals and an increased risk of maternal mortality?

## **Search Terms**

Inter-pregnancy interval, birth spacing, maternal death, maternal mortality

## **Citation**

Conde-Agudelo A, Rosas-Bermúdez A, Kafury-Goeta AC.

*Effects of birth spacing on maternal health: a systematic review.* Am J Obstet Gynecol 2007 Apr; 196(4):297-308

## **Object of Research**

Birth spacing, inter-pregnancy interval

## **Research Outcome**

Maternal death, maternal mortality

## **Study Features**

This is a systemic review of observational studies (cohort, case-control or cross-sectional) addressing the association between inter-pregnancy intervals and maternal deaths. In all, five studies were identified, but only two were considered of high quality and are included in this assessment of birth intervals and the risk of maternal death. The other three studies were case-control designs and were not considered to be of high quality. One of the two high quality studies (Conde-Agudelo et al; 2000) is a large, cross-sectional design

of Latin American women who conceived 18 to 23 months after a previous birth compared with women who conceived within six months of the end of their last pregnancy. The other study was of Bangladeshi women (Da Vanzo et al; 2005) and the comparison was of women whose inter-pregnancy interval was less than 12 months to those whose inter-pregnancy interval was less than 6 months.  
*(Level 3 Evidence)*

### **The Evidence**

Conde-Agudelo et al; 2000

This is a large cross-sectional study (456,889 patients included) from 18 Latin American countries. It was found that women with inter-pregnancy intervals of less than 6 months had an increased risk of maternal death (Odds Ratio=2.5, 95% CI 1.2-5.4) when compared with women conceiving at 18-23 months after their last birth.

Da Vanzo et al; 2005

This is longitudinal study spanned a period of more than twenty years (115,872 patients included). For inter-pregnancy intervals 27 to 50 months, there was a non-significant association a risk for maternal death when compared with inter-pregnancy intervals less than 6 months [adjusted Odds Ratio=1.56 (95% CI 0.73-3.33)]. For those with an inter-pregnancy interval of 6 to 11 months, compared to inter-pregnancy intervals of 27 to 50 months, again there was no significant association between the two intervals [adjusted Odds Ratio=1.50, 95% (CI 0.73-3.08)]. There were few maternal deaths in these categories and there may not have been a sufficient number to show a statistically significant difference.

**Appraised by:** The Jordan Evidence-Based Medicine Reproductive Health Group

**Update by:** 23 August 2015

## **Inter-pregnancy intervals less than 6 months and those 48 months or more appear to be associated with an increased risk of preeclampsia**

### **Conclusion**

Short intervals less than 6 months, and long intervals, more than 4 years appear to be associated with an increased risk of pre-eclampsia. Most of the reviewed studies suggested a dose-response relationship between an increasing pregnancy interval and preeclampsia.

### **Clinical Question**

Are shorter birth intervals associated with an increased risk of preeclampsia?

### **Search Terms**

Birth spacing, preeclampsia

### **Object of Research**

Birth spacing

### **Research Outcome**

Preeclampsia

### **Citation**

Conde- Aguidelo A, Rosas-Bermudez AR, Kafury-Goeta AC. *Effect of birth spacing on maternal health: a systematic review*. American Journal of Obstetrics & Gynecology 2007

### **Study Features**

This is a systematic review that includes five cross-sectional studies and one case control study rated of high quality. About one million pregnancies were available to assess the relationship between birth spacing and preeclampsia comparing different birth spacing intervals. These studies all used different categories of intervals and a long inter-pregnancy interval was defined variously as greater than 48 months, 60 months, or 75 months.

*(Level 3 Evidence)*

## **The Evidence**

Although the exact length of interval at which the risk of preeclampsia begins to increase was not clear from reviewed data, inter-pregnancy intervals of 5 years or more appeared to be associated with a 60% to 80% increased risk of preeclampsia. Most studies reported increasing odds ratios with increasing intervals though two studies reported that inter-pregnancy intervals of less than six months were associated with an increased risk of preeclampsia.

**Appraised by:** The Jordan Evidence Based Medicine Reproductive Health Group

**Update by:** 4 July 2015

## **Short inter-pregnancy intervals appear to be associated with an increased risk of anemia for the mother**

### **Conclusion**

Short inter-pregnancy intervals appear to be associated with an increased incidence of anemia in mothers, however further well controlled studies are required.

### **Clinical Question**

Are shorter birth intervals associated with an increased risk of anemia?

### **Search Terms**

Birth spacing, anemia

### **Object of Research**

Birth spacing

### **Research Outcome**

Maternal anemia

### **Citation**

Lazović N, Pocekovac. *The importance of time intervals between childbirth and anemia in pregnancy.* Srp Arh Celok Lek. 1996; 124(11-12):307-10.

Conde-Agudelo, A, Rosas-Bermudez A, Kafrey-Goeta AC. *Effects of birth spacing on maternal health : a systematic review.* American Journal of Obstetrics and Gynecology 2007;

### **Study Features**

Lazović, et al

This is a prospective study of 100 women with one previous live birth. Lab measurements (erythrocytes, hematocrit, hemoglobin, and serum iron) were conducted in each group to assess anemia. The measurements were done in each of the three trimesters of a full term delivery in 100 women with two live births. One group of these pregnant women (68%) were in their second pregnancy two years after the first, while the smaller group (32%) became pregnant after at least four years.

*(Level 2 Evidence)*

### Conde-Agudelo et al

Five studies met the inclusion criteria for this systematic review. Three cross-sectional studies rated as of high quality and two cohort studies rated as “not of high quality” evaluated the association between birth spacing and maternal anemia. All five studies controlled for maternal age and parity, Four controlled for socioeconomic variables, but only one controlled for prophylactic iron supplementation during pregnancy.

*(Level 3 Evidence)*

### **The Evidence**

#### Lazović,et al

In each trimester of pregnancy, anemia was found to be greater in women with inter-pregnancy intervals less than two years as compared to those with intervals greater than four years. The differences in the second and third trimester were statistically significant.

#### Conde-Agudelo et al

The study from Latin America reported a 30% increased risk of anemia among women with inter- pregnancy shorter than 6 months when compared with women with intervals of 18-23 months. Similarly, the study from Nigeria showed that birth intervals shorter than 24 months were associated with increased anemia. It should be noted that the two studies from Bangladesh and Singapore did not result in a significant association between inter pregnancy interval and anemia. However, in the Bangladesh study, the authors reported that anemia was diagnosed on a clinical basis and not on laboratory tests. This is not considered a reliable method of assessing anemia. In the study from Pakistan, the length of birth interval was not associated with a change of hemoglobin levels over consecutive pregnancies

**Appraised by:** The Jordan Evidence Based Medicine Reproductive Health Group

**Update by:** 4 July 2015

## **Women with short inter-pregnancy intervals do not appear to be at an increased risk for elevated mean arterial pressure**

### **Conclusion**

Shorter inter-pregnancy interval does not appear to be associated with an increased risk of elevated mean arterial pressure.

### **Clinical Question**

Is the length of the birth interval associated with pregnancy induced high blood pressure as measured by mean arterial pressure?

### **Search Terms**

Birth spacing, high blood pressure, mean arterial pressure

### **Citation**

Mikolajczyk RT, Zhang J, Ford J, Grewal J. *Effects of interpregnancy interval on blood pressure in consecutive pregnancies.* Am J Epidemiol 2008;168:422-426.

### **Object of Research**

Birth spacing and mean arterial pressure

### **Research Outcome**

Pregnancy induced hypertension

### **Study Features**

This is a study of 533 women who received care at one of 12 large, urban hospitals in the United States. The objective of the study was to assess the effect of the inter-pregnancy interval on mean arterial pressure (MAP defined as  $1/3$  systolic blood pressure +  $2/3$  diastolic blood pressure) for two consecutive pregnancies. All women in the study had a full term first pregnancy

and those with a preexisting chronic hypertension in that first pregnancy were excluded. Paternity in the two pregnancies was unchanged in 81 percent of the women, changed in 4 percent and uncertain in the remainder. Most women had a short inter-pregnancy interval of one year or less and an interval of 3 years was rare (4%).

*(Level 3 Evidence)*

### **The Evidence**

MAP was found to follow a U-shaped trajectory in both pregnancies with an average reading in the corresponding stages of gestation being consistently lower in the second pregnancy. After adjusting for differences in body mass during the two pregnancies, MAP was approximately 2 mmHg lower in the second pregnancy among women with very short inter-pregnancy intervals. This difference diminished linearly as the interval increased. (Note that there are differences of opinion as to whether paternity change contributes to an increased risk of preeclampsia. For this reason, the authors included paternity change in their analysis and found no effect, but this has to be qualified because of the low number of confirmed and unconfirmed paternity changes.

**Appraised by:** The Jordan Evidence-Based Medicine Reproductive Health Group,

**Update by:** 23 August 2015

## **In singleton births to multiparous women the risk of labor dystocia appears to increase with increasing inter-pregnancy interval.**

### **Conclusion**

In this study, the risk of labor dystocia (either functional or mechanical) increased with increasing inter pregnancy interval, in singleton births to multiparous mothers

### **Clinical Question**

Are shorter birth intervals associated with obstructed and prolonged labor?

### **Search Terms**

Birth spacing, birth intervals, obstructed labor, prolonged labor.

### **Citation**

Zhu BP, Grigorescu V, Le T, et al. *Labor dystocia and its association with inter-pregnancy interval*. Am J Obstet Gynecol 2006;195:121-8.

### **Object of Research**

Birth spacing

### **Research Outcome**

Obstructed and prolonged labor

### **Study Features**

This study was conducted to evaluate the prevalence of labor dystocia and its association with inter-pregnancy interval. The birth data for the state of Michigan, USA infants who were born from 1994 to 2002 was linked with the hospital discharge data, 650,000 pregnancies were included in this study. The International Classification of Diseases (9th revision, clinical modifications, ICD-9-CM) codes that indicate labor dystocia were reviewed by a physician panel of an obstetrician, pediatrician and medical epidemiologist. Dystocia was categorized as either functional (included delayed delivery, failed induc-

tion, uterine inertia or abnormal uterine contractions, and prolonged labor) and mechanical (included malposition or mal-presentation of the fetus, obstructed labor and disproportion). The prevalence of labor dystocia was estimated and a stratified analyses to evaluate labor dystocia in relation to inter-pregnancy interval was done. The analysis controlled for other reproductive risk factors. (*Level 3 Evidence*)

### **The Evidence**

Overall, 20.8% of the births involved had labor dystocia (11.1% functional; 12.5% mechanical). Considering singleton births to multiparous mothers, the risk of labor dystocia increased with the inter-pregnancy interval. Compared with an inter-pregnancy interval of less than 2 years, the adjusted odds ratios that were associated with inter-pregnancy intervals of 2 to 3, 4 to 5, 6 to 7, 8 to 9, and 10+ years were 1.06 (95% CI, 1.04-1.08), 1.15 (95% CI, 1.12-1.17), 1.25 (95% CI, 1.21-1.29), 1.31 (95% CI, 1.26-1.37), and 1.50 (95% CI, 1.45-1.56), respectively. Controlling for other reproductive risk factors, dystocia was associated even more strongly with an increasing inter-pregnancy interval.

**Appraised by:** The Jordan Evidence Based Medicine Reproductive Health Group

**Updates by:** 4 July 2015

## **Inter pregnancy intervals of less than six months are associated with an increased risk of congenital anomalies (birth defects)**

### **Conclusion**

Birth intervals of less than six months were found to be associated with increased risk of congenital anomalies

### **Clinical Question**

Are shorter birth intervals associated with congenital anomalies (birth defects)?

### **Search Terms**

Birth intervals, congenital anomalies, birth defects

### **Citation**

Grisaru-Granovsky S, Gordon ES, Haklai Z, Samueloff A, Schimmel MM. *Effect of interpregnancy interval on adverse perinatal outcomes—a national study*. *Contraception*. 2009 Dec;80(6):512-8.

### **Object of Research**

Birth intervals

### **Research Outcome**

Congenital anomalies, birth defects

### **Study Features**

This is a prospective longitudinal cohort study in Israel of birth certificates of siblings born to the same biological mother, with at least one previous birth and a subsequent singleton pregnancy. Adverse pregnancy outcomes included preterm delivery, very preterm birth, small for gestational age, very small for gestational age (SGA), early neonatal death and major congenital malformations as reported to the Ministry of Health according to their guidelines. The study included 440,838 live births reported over 5 years. Primiparas and multiple pregnancies were excluded.

*(Level 2 Evidence)*

**The Evidence**

The reference birth interval was taken as 12-23 months. For inter-pregnancy intervals shorter than 6 months, there was a significantly increased risk of congenital malformations (OR=1.14; 95% CI: 1.04-1.24). In this study, no other significant risks for congenital anomalies were found for inter-pregnancy intervals greater than six months when compared to 12 to 23 months.

**Appraised by:** The Jordan Evidence-Based Medicine Reproductive Health Group

**Update by:** 4 July 2015

## **Shorter birth intervals appear associated with an increased risk of autism**

### **Conclusion**

Children born after shorter intervals from their mother's last pregnancy are at increased risk of developing autism; the highest risk appears associated when pregnancies are spaced less than 1 year apart.

### **Clinical Question**

Are shorter birth intervals associated with an increased risk of autism?

### **Search Terms**

Premature delivery, inter-pregnancy interval, autistic child

### **Citation**

Cheslack-Postava K, Liu K, Bearman P. *Closely Spaced Pregnancies Are Associated With Increased Odds of Autism in California Sibling Births*. *Pediatrics* (2011); 127(2): 246–253

### **Object of Research**

Birth spacing

### **Research Outcome**

Autism in children

### **Study Features**

Pairs of first- and second-born singleton siblings were identified from all California births occurred between 1992 and 2002 using birth records, and autism diagnoses identified through linked records of the California Department of Developmental Services.

**(Level 3 Evidence)**

### **The Evidence**

An inverse relationship between inter-pregnancy interval and the risk of autism among 662,730 second-born children was observed. In particular, inter-pregnancy intervals of less than 12, 12 to 23, and 24 to 35 months were associated with respective odds ratios for autism of 3.39 (95% CI: 3.00-3.82),

1.86 (95% CI: 1.65-2.10), and 1.26 (95% CI: 1.10-1.45) relative to inter-pregnancy intervals of at least 36 months. Second-born children were at increased risk of autism relative to their firstborn siblings only in those with short inter-pregnancy intervals.

**Appraised by:** The Jordan Evidence-Based Medicine Reproductive Health Group

**Update by:** 4 July 2015



# Combined Oral Contraceptives (COCs)

Combined Oral  
Contraceptives



## COMBINED ORAL CONTRACEPTIVE PILLS

In Jordan, for about 8 percent of all married women of reproductive age use combined oral contraceptive pills (COC). Most women can use combined oral contraceptives, but health professionals should be aware of the World Health Organization Medical Eligibility Criteria for Contraceptive Use<sup>2</sup>.

### **Effectiveness**

Combined oral contraceptives are highly effective. Among women who use the COC correctly and consistently, less than 1 percent will experience a method failure in the first year of use. In terms of typical use though, it is estimated that 8 percent become pregnant in the first year<sup>3</sup>. Duration of use is not associated with any decrease in efficacy or safety suggesting no need for a rest period.

### **Mode of Action**

The primary mode of action of a combined oral contraceptive is that it acts to prevent fertilization. The progestins in all COCs provide most of the contraceptive effect though the estrogens also contribute to ovulation suppression. COCs also act by thickening the cervical mucus thus preventing sperm entry into the upper genital tract<sup>4</sup>.

### **Advantages of Combined Oral Contraceptives**

In addition to being highly effective, other advantages to using combined oral contraceptives are:

- the absolute number of ectopic pregnancies are reduced<sup>5,6</sup>
- it is rapidly reversible<sup>7,8</sup>
- it is an option throughout reproductive years
- it decreases menstrual blood loss/regulates menses<sup>9,10,11</sup>

*Cycle control with the use of a combined oral contraceptive is good and there is also a decreased menstrual blood loss.*

- it decreases dysmenorrhea, especially among young users<sup>12,13</sup>

*There is evidence that women treated for dysmenorrhea with low dose COCs show an improvement in symptoms.*

## **Disadvantages of Combined Oral Contraceptives**

- Requires Daily Administration

*Differences in pregnancy rates of those taking their pill daily versus those who are not consistent compliers.*

## **Special Topics**

- Cardiovascular Risks

*Compared to non-use of hormonal contraceptives, COC use does not appear to be associated with an elevated risk of myocardial infarction or hemorrhagic stroke. However, there is small increase in risk of an ischemic stroke and an almost two fold increase in the risk of venous thromboembolism<sup>14</sup>. However, the absolute risk of each of these is low as they are not common in healthy women of reproductive age.*

- Cancer

*The use of combined oral contraceptives provides a protective effect for endometrial<sup>15</sup> and ovarian cancer<sup>15,16</sup>. Recent studies suggest there is no elevated risk for breast cancer<sup>14</sup>, but there does appear to be an increased risk for cervical cancer<sup>15</sup>.*

## REFERENCES

### Combined Oral Contraceptives

1. Department of Statistics [Jordan] and ICF Macro,2010. *Jordan Population and Family Health Curvey 2009*. Calverton, Maryland, USA: Department of Statistics and ICF Macro.
2. World Health Organization. *Medical eligibility criteria for contraceptive use*. Geneva:WHO, 2004.
3. Hatcher RA, Trussell J, Nelson AL, Cates W, Stewart F, Kowal D. *Contraceptive Efficacy*. Contraceptive Technology. New York: Ardent Media Inc, 2008. 747-826.
4. Hatcher RA, Trussell J, Nelson AL, Cates W, Stewart F, Kowal D. *Combined oral contraceptives*. Contraceptive Technology. New York: Ardent Media Inc, 2008. 197-198.
5. Furlong L. *Pregnancy risk when contraception fails*. J Reprod Med 2002;47(11):881-885.
6. Mol BWJ, Ankum WM, Bossuyt PMM, Van der Veen F. *Contraception and the risk of ectopic pregnancy: A meta-analysis*. Contraception 1995;52:337-341.
7. Barnhart K, Schreiber C. *Return to fertility following discontinuation of oral contraceptives*. Fertility and Sterility 2009; 91(3):659-663.
8. Cronin, M, Schellschmidt I, Dinger J. *Previous use of oral contraceptives does not negatively affect initial and 1-year rates of pregnancy after oral-contraceptive cessation*. Obstetrics & Gynecology. September 2009;114(3):616-622.
9. Nelson A, Parke S, Makalova D, Serrani M, Palacios S. *Efficacy and bleeding profile of a combined oral contraceptive containing oestradiol valerate/dienogest: A pooled analysis of three studies conducted in North America and Europe*. Eur J Contracept Reprod Health Care 2013;18:264-273.
10. Huber J, Foidart JM, Wuttke W, Merki-Feld GS, The HS, Gerking C, Schedllschrmidt I, Heithecker R. *Efficacy and tolerability of a monophasic oral contraceptive containing ethinylestradiol and drospirenone*. Eur J Contracept Reprod Health Care 2000;5:25-34.

11. Larsson, G, Milson L, Lindstedt G, Rybo G. *The influence of a low-dose combined oral contraceptive on blood loss and iron status.* Contraception 1992;46(4):327-334.
12. Wong C, Farquhar C, Roberts H, Proctor M. *Oral contraceptive pill as treatment for primary dysmenorrhea.* Cochrane Database of Systematic Reviews 2009, Issue 2. Art. No.: CD002120.DOI: 10.1002/14651858.CD002120.pub2.
13. Lindh I, Ellstrom AA, Milsom I. *The effect of combined oral contraceptives and age on dysmenorrhea: an epidemiological study.* Human Reprod 2012;27(3):676-682.
14. Urrutia RP, Coeytaux RR, McBroom AJ, Gierisch JM, Havrilesky LJ, Moorman PG, Lowrey WJ, Dinan M, Hasselblad V, Sanders GD, Myers ER. *Risk of acute thromboembolic events with oral contraceptive use.* Obstet Gynecol 2013;122:380-389.
15. Vessey M, Yeates D. *Oral contraceptive use and cancer: final report from the Oxford-Family Planning Association contraceptive study.* Contraception 2013;88:678-683.
16. Collaborative Group on Epidemiological Studies of Ovarian Cancer. *“Ovarian cancer and oral contraceptives: collaborative reanalysis of data from 45 epidemiological studies including 23,257 women with ovarian cancer and 87,303 controls.”* Lancet 2008;371:303-314.

## **List of Critically Appraised Topics**

- 1-Ectopic Pregnancy
- 2-Return to Fertility
- 3-Menstrual Blood Loss
- 4-Dysmenorrhea
- 5-Premenstrual Dysphoric Disorder
- 6-Weight Gain
- 7-Acne
- 8-Hirsutism
- 9-Headache
- 10-Depression
- 11-Myocardial Infarction
- 12-Stroke
- 13-Venous Thromboembolism
- 14-Benign Breast Disease
- 15-Endometrial Cancer
- 16-Ovarian Cancer
- 17-Cervical Cancer
- 18-Breast Cancer

*Note that the level of evidence accompanying each publication in each of the CATs refers to the study design.*



## **The use of combined oral contraceptives (COCs) may be associated with a decrease in the risk of an ectopic pregnancy**

### **Conclusion**

Based on the results of selected reviews of studies involving ectopic pregnancy, it appears that the use of combined oral contraceptives may have a protective effect against ectopic pregnancy.

### **Clinical Question**

Is there a decrease in the risk of ectopic pregnancy among women taking combined oral contraceptives?

### **Search Terms**

Combined oral contraceptives, ectopic pregnancy

### **Citation**

Furlong L. *Pregnancy risk when contraception fails.* J Reprod Med 2002;47(11):881-885.

Mol BWJ, Ankum WM, Bossuyt PMM, Van der Veen F. *Contraception and the risk of ectopic pregnancy: A meta-analysis.* Contraception 1995;52:337-341.

### **Object of Research**

Combined oral contraceptives

### **Research Outcome**

Ectopic pregnancy

### **Study Features**

#### Furlong

This is a review of seven contraceptives including combined oral contraceptives. Data were abstracted from a review of clinical trial data submitted to the United States Food and Drug Administration.

*(Level 2 Evidence)*

### Mol et al

The study was a meta-analysis of 12 case control studies and 1 cohort study involving different contraceptive methods. Five of the studies, all case control, involved combined oral contraceptives. Cases in the control studies were women with an ectopic pregnancy. Controls were non-pregnant or pregnant women actively on COCs or with past use. For the cohort study, women who used COCs were compared to a group of women who had not used them.

*(Level 3 Evidence)*

### **The Evidence**

#### Furlong

Among 37,223 28 day cycles, there were 27 pregnancies among the women using a COC and included in clinical studies supporting the submissions for approval of different combined oral contraceptives. No ectopic pregnancies were reported. The estimate for the incidence of ectopic pregnancies among all pregnancies in the United States is about 1 in 50.

### Mol et al

Among pregnant women, current users of COCs, the odds ratio was 0.19 when compared to non-pregnant controls. When compared to pregnant controls the odds ratio was 1.8.

**Appraised by:** The Jordan Evidence Based Medicine Reproductive Health Group

**Update by:** 27 March 2016

## **There may be a small delay in return to fertility after combined oral contraceptive (COC) users stop their method to become pregnant**

### **Conclusion**

Overall, the cumulative rate of pregnancy for fertile women previously using a combined oral contraceptive (COC) did not differ from that observed in fertile women who attempted to become pregnant without prior contraception. However, some studies suggest that time to pregnancy may be longer than other contraceptive methods in the first months after cessation.

### **Clinical Question**

Is there a decrease in conception rate after cessation of a combined oral contraceptive?

### **Search Terms**

Oral contraceptives, ethinyl estradiol, dienogest, fertility return, conception rate

### **Citations**

Barnhart K, Schreiber C. *Return to fertility following discontinuation of oral contraceptives*. *Fertility and Sterility* 2009; 91(3):659-663.

Cronin, M, Schellschmidt I, Dinger J. *Previous use of oral contraceptives does not negatively affect initial and 1-year rates of pregnancy after oral-contraceptive cessation*. *Obstetrics & Gynecology*. September 2009;114(3):616-622.

### **Object of Research**

Combined oral contraceptive

### **Research Outcome**

Cumulative conception rate after discontinuation of a combined oral contraception

## **Study Features**

### Barnhart et al

This is a review of published data including cases from randomized controlled trials, controlled trials, cohort studies and cross-sectional studies of women who discontinue contraceptive use in order to conceive.

*(Level 2 Evidence)*

### Cronin, et al

This was a controlled, prospective cohort study of 59,510 users of combined oral contraceptives recruited from a network of 1,113 existing medical practices in seven European countries. (Austria, Belgium, Denmark, France, Germany, the Netherlands, and the United Kingdom.) Women who requested a new prescription were invited to participate in the study. Of the 59,510 users enrolled, 2,064 stopped use of their COC because they planned to become pregnant. Among this group, 509 used a COC containing drospirenone, 529 used one containing levonorgestrel and 1,026 used a COC containing another of the following progestins; chlormadinone, cyproterone acetate, desogestrel, dienogest, norethisterone, and norgestimate.

The study was sponsored by the manufacturer of a drospirenone-containing combined oral contraceptive.

*(Level 2 Evidence)*

## **The Evidence**

### Barnhart et al

- In a study in the United Kingdom at a Family Planning Association, after discontinuing their COC to become pregnant, the one year pregnancy rate was 29.9% for nulliparous women and 40.1% for parous women. In comparison, the corresponding percentages for women who stopped using a diaphragm to become pregnant were 55.6% and 64.8% respectively. These group differences in the percentage of women who had not given birth decreased over time and were not significantly different.
- In another United Kingdom study involving nulliparous women, conception rate for this group was 32% at one year and 84% at the end of 30 months. The corresponding one year rates of conception for discontinuers of IUDs and barrier methods was 39% and 54%, respectively. For COC discontinuers, the five year conception rate was 95%.
- In a study of former contraceptive users (n=3,214) who stopped various methods of contraception, it was found that the interval from cessation of contraception to conception was 13 months or greater for 24.8% for discontinuers of combined oral contraceptive users as compared to 12.4% and 8.5% for former users of intrauterine devices and diaphragms, respectively. The difference in return to fertility among these methods and combined oral contraceptives was greatest in the first three months following cessation of their COC use. However, conception rates in subsequent months after discontinuation were comparable to those seen in IUD and diaphragm users.
- Two studies reported no association between duration of COC use and time to conception. In a large prospective study of prolonged use (> 5 years) of COCs, 88.1% of the women who planned to conceive did so within 12 months and nearly all (99.5%) did so by the end of three years. When results were analyzed by duration of use, the results were as follows:

Duration of use (Years)	Conception Rate
or more 5	89.5%
to 4 3	88.0%
to 2 1	85.2%
Less than 1	83.5%

Cronin, et al

- Overall, 21.1% of the women who discontinued their COC to become pregnant conceived within one month after cessation. The pregnancy rate was 45.7% at 3 months and 79.4% at 12 months after discontinuation of their oral contraceptive.
- The duration of use was not associated with the time to return to fertility.
- The rate of pregnancy was lower in nulliparous women than in parous women in the initial months, but almost identical after one year.
- The effect of age on the rate of pregnancy had only a minor effect. As expected, women older than 35 had a notably lower rate of pregnancy than those under 35 years of age.
- Progestin type, ethinyl estradiol dose, and duration of use had no major influence on the rate of pregnancy after cessation.
- Rates of pregnancy were significantly reduced when current and nonsmokers were compared.
- Comment: Incidence of conception among women not using a contraceptive was 86% at the end of one year. (Source: Lobo RA et al. Textbook Infertility, Contraception, and Reproductive Endocrinology, 4th Edition. 1997)

**Appraised by:** The Jordan Evidence Based Medicine Reproductive Health Group

**Update by:** 26 March 2016

## **The use of combined oral contraceptives (COCs) is associated with a significant decrease in menstrual blood loss**

### **Conclusion**

Cycle control was found to be good in four representative studies of the use of COCs and their effect on menstrual blood loss.

### **Clinical Question**

Is there a decrease in menstrual blood loss among women using combined oral contraceptives?

### **Search Terms**

Oral contraceptives, menstrual blood loss

### **Citation**

Nelson A, Parke S, Makalova D, Serrani M, Palacios S. *Efficacy and bleeding profile of a combined oral contraceptive containing oestradiol valerate/dienogest: A pooled analysis of three studies conducted in North America and Europe.* Eur J Contracept Reprod Health Care 2013;18:264-273.

Huber J, Foidart JM, Wuttke W, Merki-Feld GS, The HS, Gerking C, Schedltschmidt I, Heithecker R. *Efficacy and tolerability of a monophasic oral contraceptive containing ethinylestradiol and drospirenone.* Eur J Contracept Reprod Health Care 2000;5:25-34.

Larsson, G, Milson L, Lindstedt G, Rybo G. The influence of a low-dose combined oral contraceptive on blood loss and iron status. *Contraception* 1992;46(4):327-334.

### **Object of Research**

Combined oral contraceptive

### **Research Outcome**

Menstrual blood loss

## **Study Features**

### Nelson et al

This is a pooled analysis of two open label, non-comparative trials of estradiol valerate/dienogest and a randomized trial of the same contraceptive compared to a monophasic regimen of 20 mcg ethinyl estradiol/100 mcg levonorgestrel. One open label and the randomized trials were multicenter studies in North America and Europe. The second open label study was a multicenter study conducted in Europe. A total of 2,266 women were included in the analysis.

*(Level 1 Evidence)*

### Huber et al

This was a randomized open-label, 13 cycle study performed at 80 European centers. Cycle control was assessed during 13 cycles of contraception. Of 2,069 women in the study, 1,657 were randomly assigned to the drospirenone group and 412 to the desogestrel group.

*(Level 1 Evidence)*

### Larsson et al

This was an open label study assessing menstrual blood loss in 20 healthy young women using a low-dose combined oral contraceptive (ethinyl estradiol 30 mcg, desogestrel 0.15 mg). Menstrual blood loss was measured by collecting sanitary pads and tampons for each day of menstruation. Menstrual blood loss was also measured during the cycle just prior to initiation of the COC.

*(Level 2 Evidence)*

## **The Evidence**

### Nelson et al

Cycle control was analyzed for all study participants and not adjusted for missed pills or other inconsistent use. The mean number of bleeding/spotting days and episodes as well as the mean duration of these bleeding periods decreased from the first 90 day reference period to the second 90 day reference period for the estradiol valerate/dienogest COC and was generally maintained. The bleeding patterns and overall cycle control of the comparison COC were similar.

### Huber et al

Cycle control with both ethinyl estradiol/drospirenone and ethinyl estradiol desogestrel was found to be good and the incidence of intermenstrual bleeding was low in both groups. In both groups, the majority of women reported withdrawal bleeding lasting between 4 and 7 days. Over time, there was a trend towards a shorter duration of withdrawal bleeding.

Larsson et al

Reduction in blood loss was most evident during the first two days of the menstrual cycle. The amount of the blood loss during the sixth cycle was significantly less than their loss in the cycle just prior to pill initiation for all women in the study. All women had normal hemoglobin concentrations and hematocrit.

**Appraised by:** The Jordan Evidence Based Medicine Reproductive Health Group

**Update by:** 29 March 2016

## **Women who use combined oral contraceptives (COCs) appear to have a lower incidence and severity of dysmenorrhea symptoms than women who take no contraception**

### **Conclusion**

There is some evidence that women treated for dysmenorrhea with low dose COCs show an improvement in symptoms. However, evidence from comparative studies to support this assertion is limited.

### **Clinical Question**

Is the use of combined oral contraceptives associated with a lower incidence of dysmenorrhea symptoms than women taking no contraception?

### **Search Terms**

Oral contraceptives, dysmenorrhea

### **Citations**

Wong C, Farquhar C, Roberts H, Proctor M. *Oral contraceptive pill as treatment for primary dysmenorrhea*. Cochrane Database of Systematic Reviews 2009, Issue 2. Art. No.: CD002120.DOI: 10.1002/14651858.CD002120.pub2.

Lindh I, Ellstrom AA, Milsom I. *The effect of combined oral contraceptives and age on dysmenorrhea: an epidemiological study*. Human Reprod 2012;27(3):676-682.

### **Object of Research**

Combined oral contraceptives

### **Research Outcome**

Dysmenorrhea

## **Study Features**

### Wong et al

This is a systematic review of a combined oral contraceptive as a treatment for primary dysmenorrhea. Ten studies were included in the review. The selected studies included randomized controlled trials comparing different types of combined oral contraceptives with other COCs, placebo, no treatment or treatment with a non-steroidal anti-inflammatory drug assessing their effect on primary dysmenorrhea. Pain was assessed using a visual analogue scale, reported as an adverse event, or the Moos Menstrual Disorder Questionnaires (MMDQ).

(Note: The MMDQ contains six items; muscle stiffness, headache, cramps, backache, fatigue, and general aches and pains. Patients rated each of these on a five point scale from none to severe for their last menstrual cycle.)

*(Level 1 Evidence)*

Study Features (continued)

### Lindh et al

This is a case control study conducted in Sweden in which postal questionnaires regarding weight/height, contraception, pregnancy history and other reproductive health factors were sent to random samples of 19-year old women born in 1962 (n=656), 1972 (n=780), and 1982 (n=666). The responders were assessed again five years later at the age of 24. Current severity of dysmenorrhea was measured on each occasion by a verbal multidimensional scoring system (VMS) and by a visual analogue scale (VAS).

*(Level 3 Evidence)*

## **The Evidence**

### Wong et al

In seven of the randomized controlled trials, the outcome of pain relief across different COCs yielded an Odds Ratio=2.01 (95% CI: 1.32–3.08). The studies were not consistent though by removing those studies with inadequate alloca-

tion concealment suggested a significant treatment benefit [Odds Ratio=2.99 (95% CI: 1.76 – 5.07)] and these studies were consistent, that is, they were homogeneous. The authors concluded that there is limited evidence of pain improvement with the use of a COC (both low and medium dose estrogen) in women with dysmenorrhea.

Lindh et al

The severity of dysmenorrhea was significantly lower for COC users when compared to non-users. This was independent of an age effect in which pain scores also decreased with increasing age.

**Appraised by: The Jordan Evidence Based Medicine Reproductive Health Group**

Update by: 29 March 2016

# **The use of combined oral contraceptives containing drospirenone helps treat women with premenstrual syndrome and premenstrual dysphoric disorder**

## **Conclusion**

The progestin drospirenone plus 20mcg ethinyl estradiol appears to alleviate some of the symptoms for women suffering from premenstrual syndrome (PMS) and its more severe form, premenstrual dysphoric disorder (PMDD).

## **Clinical Question**

Does use of a COCs containing drospirenone alleviate symptoms for women suffering from premenstrual syndrome and its more severe form, premenstrual dysphoric disorder?

## **Search Terms**

Oral contraceptives, premenstrual dysphoric disorder, premenstrual syndrome

## **Citation**

Lopez LM, Kaptein AA, Helmerhorse FM. *Oral contraceptives containing drospirenone for premenstrual syndrome*. Cochrane Database Syst Rev 2009; Jan 21;(1): CD007249

## **Object of Research**

Combined oral contraceptive

## **Research Outcome**

Premenstrual Dysphoric Disorder; Premenstrual Syndrome

## **Study Features**

This is a systematic review which includes 5 randomized control trials (3 were double-blind, 2 were open label). The study included 1600 women of reproductive age with measured premenstrual symptoms, participating in a randomized control trial of the use of a drospirenone containing COC for her symptoms. The trials were conducted in Belgium, the Netherlands, Germany, USA, and Thailand. Treatment duration ranged from 3 to 26 cycles.

*(Level 1 Evidence)*

## **The Evidence**

- Two of the trials showed less severe premenstrual symptoms after 3 months of use of a COC with drospirenone (plus 20 mcg ethinyl estradiol) compared with women taking a placebo
- Women taking drospirenone containing COCs had less impairment in terms of productivity, social activities, and relationship compared to those taking a placebo
- In a study of comparing another COC to a COC containing drospirenone and 30 mcg dose of ethinyl estradiol, the drospirenone containing pill users were less likely to have premenstrual (OR= 0.31, 95% CI: 0.14 - 0.69)

**Appraised by:** The Jordan Evidence Based Medicine Reproductive Health Group

Update by: 9 April 2016

**There is no strong evidence supporting an association between the use of combined oral contraceptives (COCs) and weight gain.**

### **Conclusion**

Available evidence is insufficient to determine the effect of combined oral contraceptives on weight gain. No large effect is evident as trials to evaluate the link between combined oral contraceptives and weight gain require a non-hormonal group to control for other factors including changes in weight over time. Few women discontinued use of their COC because of weight gain.

### **Clinical Question**

Do women taking combination oral contraceptives have greater weight gain than women not taking them?

### **Search Terms**

Contraceptives, oral contraceptives, contraception, weight gain.

### **Citations**

Gallo MF, Lopez LM, Grimes DA, Schulz KF, Helmerhorst FM. *Combination contraceptives: effects on weight*. Cochrane Database of Systematic Reviews 2009, Issue 4. Art. No.: CD003987. DOI: 10.1002/14651858.CD003987.pub3.

Foidart JM, Wuntke W, Bouw GM, Gerlinger C, Heithecker R. A comparative investigation of contraceptive reliability, cycle control and tolerance of two monophasic oral contraceptives containing either drospirenone or desogestrel. *The European Journal of Contraception and Reproductive Health Care*, 2000;5:124-13.

### **Object of Research**

Combined oral contraceptives

### **Research Outcome**

Change in weight

## **Study Features**

Gallo, et al

This systematic review evaluated the association between COCs and weight change. 595 randomized controlled trials comparing COC use to placebo or a second COC were found. After eliminating those studies that failed to follow patients beyond three cycles of therapy and those with insufficient data regarding weight change, a final analysis was performed on 47 studies

- The combined oral contraceptives evaluated in the 47 trials included 18 different progestins and 3 different dosage levels of estrogen. With the exception of two studies (one with 40 mcg EE and one with 50 mcg EE), the estrogen dosage levels ranged from 20 to 35 mcg. Sample sizes ranged from 20 to 5,654 patients (median number 196). The duration of the studies ranged from 3-24 treatment cycles though most were included from 6 to 12 cycles. Measurements at cycles 6 and 12 as well as the last treatment cycle were used as a standard throughout this analysis.
- The eligibility criteria for the participants varied among the trials with most trials recruiting healthy women of reproductive age without contraindications to oral contraceptive use.

***(Level 1 Evidence)***

Foidart et al

This multicenter, open-label, randomized study was carried out in 26 European centers and included 900 women 627 completing 26 cycles plus the follow-up.

- Of these 627 women, 310 were randomly assigned to receive ethinyl-estradiol/drospirenone and 317 to receive ethinylestradiol/desogestrel.
- Women randomly assigned to one of the two contraceptives were between 18 and 35 years of age without contraindications to oral contraceptive use.

***(Level 1 Evidence)***

## **The Evidence**

### Gallo et al

- For the three studies that included a placebo group, there was no evidence supporting a causal association between combination oral contraceptives with weight gain.
- Most comparisons of different combination oral contraceptives showed no substantial difference in weight gain.
- Discontinuation of combination oral contraceptives because of weight gain did not differ among groups where this was reported.
- Many of the studies did not use rigorous methods of measuring weight. Variations in scale calibration or differences in weighing techniques could affect the findings. Similarly, obtaining weights at differing times of the day, whether the subject was fasting or fed, and level of clothing could account for some of the differences.

### Foidart et al

- In the ethinyl estradiol/drospirenone group, the mean body weight per cycle remained slightly below baseline throughout the study except in cycles 25 and 26. In contrast, in the ethinyl estradiol/desogestrel group, mean body weight was slightly below baseline only in cycles 1–5. From cycle 7, the mean body weight was above baseline though not all women showed the same pattern of change. In both groups, the majority of women maintained a stable body weight within 2 kg of their baseline weight.
- There were no reported discontinuations in either group due to weight gain

**Appraised by:** The Jordan Evidence Based Medicine Reproductive Health Group

**Update by:** 26 March 2016

## **Combined oral contraceptives (COCs) are safe and effective in the treatment of moderate facial acne in women**

### **Conclusion**

The COCs evaluated in placebo-controlled trials were effective in reducing inflammatory and non-inflammatory facial acne lesions. Few differences were found between COC types in their effectiveness for treating acne.

### **Clinical Question**

Are combined oral contraceptives safe and effective for use in treating women with acne?

### **Search Terms**

Combined oral contraceptives, acne

### **Citation**

Arowojulu AO, Gallo MF, Lopez LM, Grimes DA, and Garner SE. *Combined oral contraceptive pills for treatment of acne*. Cochrane Database of Systematic Reviews 2009, Issue 3. Art. No.: CD004425. DOI: 10.1002/14651858.CD004425.pub4.

### **Object of Research**

Combined oral contraceptives

### **Research Outcome**

Change in specific types of facial lesions, change in total lesion count, global assessments, and discontinuation.

### **Study Features**

All studies were randomized controlled trials and compared the effectiveness of a COC containing an estrogen and a progestin to placebo or another active therapy for acne in women. Twenty-three studies were included in the analysis.

A total of 8,051 participants were enrolled in the 25 trials. Individual sample sizes varied from 24 to 1,154. The trials varied considerably in the comparison groups and the doses of ethinyl estradiol ranged from 20 µg to 50 µg in combination with eight types of progestin. The duration of the trials varied from 3 to 12 treatment cycles though most were 6 cycles in duration. Only two studies had fewer than six treatment cycles.

*(Level 1 Evidence)*

### **The Evidence**

- Compared to placebo, COCs had a greater reduction in acne lesion counts, severity grades and self-assessed acne.
- In the treatment of acne, differences in the comparative effectiveness of COCs containing varying progestin types and estrogen dosages, no important differences were noted.
- The effectiveness of COCs compared to other acne treatments is less clear.

**Appraised by: The Jordan Evidence Based Medicine Reproductive Health Group**

**Update by: 27 March 2016**

## **The use of low-dose combined oral contraceptives (COCs) reduces manifestations of hirsutism in women.**

### **Conclusion**

Low-dose combination oral contraceptives, especially those containing drospirenone or cyproterone acetate, have an antiandrogenic activity and reduce manifestations of hirsutism after 6 months of use.

### **Clinical Question**

Is there any association between use of low-dose combination oral contraceptives and decreased hirsutism?

### **Search Terms**

Hirsutism, combination oral contraceptives, low-dose oral contraceptives

### **Citations**

Oner G, Muderris II. *A prospective randomized trial comparing low-dose ethinyl estradiol and drospirenone 24/4 combined oral contraceptive versus 21/7 combined oral contraceptive in the treatment of hirsutism.* Contraception 2011;84:508-511.

Batukan C, Muderris II. *Efficacy of a new oral contraceptive containing drospirenone and ethinyl in the long-term treatment of hirsutism.* Gynecological Endocrinology 2007;23:38-44.

### **Object of Research**

Combination oral contraceptives (COCs), low-dose oral contraceptives

### **Research Outcome**

Improvement in hirsutism

### **Study Features**

Oner et al

This is a prospective randomized trial conducted to compare the clinical efficacy of two oral contraceptives containing drospirenone in the treatment of hirsutism. Fifty women with moderate to severe hirsutism were recruited from an outpatient hirsutism clinic in Kayseri, Turkey. Twenty five women each were randomly assigned to either a 0.03 mg ethinyl estradiol and 3 mg

drospirenone 21/7 combined oral contraceptive (Group 1) or a 0.02 mg ethinyl estradiol and 3 mg drospirenone 24/4 combined oral contraceptive (Group 2). Hirsutism was assessed using the Ferriman-Gallway (F-G) scoring system. F-G baseline scores for both groups were similar at baseline.

*(Level 1 Evidence)*

#### Batukan et al

This is a prospective randomized study of 100 female outpatients from a hirsutism clinic in Kayseri, Turkey. Eligible participants were non-pregnant, premenopausal women with moderate and severe hirsutism measured by the Ferriman-Gallway (F-G) scale. They were randomly assigned to receive either 3 mg drospirenone/30 mcg ethinyl estradiol or 2 mg cyproterone acetate and 35 mcg ethinyl estradiol for 12 months. Their hirsutism status was evaluated at months 6 and 12 after baseline.

*(Level 1 Evidence)*

### **The Evidence**

#### Oner et al

Three women were lost to follow-up and their results are not presented. An improvement in F-G scores was observed in both groups at six months. For Group 1, the decrease in scores was 17.3 to 8.7 and for Group 2 the corresponding decrease was 17.5 to 7.9. Both changes were statistically significant ( $p < 0.001$ ), but not statistically different. The treatment of hirsutism with both combined oral contraceptives containing drospirenone offered comparable effects.

#### Batukan et al

Both groups achieved a similar effect in terms of decreasing clinical hirsutism scores. There were no significant differences between the two groups at the end of 12 months. However, reductions for the drospirenone group were significantly greater than for the cyproterone acetate at 6 months suggesting that drospirenone group may have a faster resolution of hirsutism.

**Appraised by:** The Jordan Evidence Based Medicine Reproductive Health Group

**Update by:** 27 March 2016

**There is some indication that combined oral contraceptives (COCs) are associated with the occurrence of headache, but the effect is usually transient.**

### **Conclusion**

There is little evidence that combined oral contraceptives are associated with persistent headaches. Headaches that occur during early cycles of contraceptive use tend to improve or disappear with continued use. No evidence supports the clinical practice of switching combined oral contraceptives to treat headache.

### **Clinical Question**

Is the use of combined oral contraceptives associated with the increased risk of headache?

### **Search Terms**

Low-dose oral contraceptives, headache.

### **Citation**

Loder EW, Buse DC, Golub JR. *Headache as a side effect of combination estrogen progestin oral contraceptives: A systematic review.* American Journal of Obstetrics and Gynecology 2005;193:636–49

### **Object of Research**

Combined oral contraceptives.

### **Research Outcome**

Headache as reported by patient.

### **Study Features**

This is a review of prospective controlled trials conducted in the USA, Europe and Australia. Studies were available for inclusion if the use of combined estrogen-progestogen COCs for 21 days was followed by 7 days of placebo or no placebo pill was involved and they had elicited information about changes in headache or migraine.

Out of 121 identified articles seven were included: 4 prospective placebo controlled trials, 2 studies with a non-hormonal method control, and 1 study with a non-contraceptive control. The sample sizes in these studies ranged from 40 to 3,179 women and the total number of patients was 5,026. All but 1 study were conducted and published in the 1960s or 1970s and studied COCs with higher estrogen content than current COCs.

***(Level 1 Evidence)***

Study	Results of Study
Cullberg	No significant difference between COC and placebo No significant differences among preparations with different progestins
Goldzieher	Complaints of headache significantly higher in COC group only for first cycle
Ryan	Migraine population and migraine worse in 70% of COC users, but improved in 30% over two month duration of study
Coney	No significant difference between COC and placebo group over 6 month duration of study
Herzberg[1]	No significant difference in headache complaints between COC users and control group using a barrier method over 11 month study.
Herzberg[2]	Slightly more women in the COC group reported moderate to severe headaches than in the IUD group at 3 of 4 follow-up visits. Thirty percent of discontinuers among COC users were for headache compared with none in the IUD group.
Diddle	No significant difference in headache complaints between COC users and untreated control subjects

Other findings are:

- Headaches related to COC use generally are precipitated by estrogen withdrawal during the pill-free or placebo pill week of treatment.
- The dose and type of progesterone do not appear to influence the incidence rate of headache
- Regardless of cause, when a headache begins or worsens in conjunction with COC use, it tends to improve or disappear despite continued use

**Appraised by:** The Jordan Evidence Based Medicine Reproductive Health Group

**Update by:** 29 March 2016

## **There is no apparent association between use of combined oral contraceptives (COCs) and an increased risk of depression.**

### **Conclusion**

No association between COCs use and depressive symptoms in young women who use COCs for contraceptive reasons was found. Physicians prescribing COCs for contraception need not be concerned about their use and effect on depression.

### **Clinical Question**

Is the use of combined oral contraceptives associated with the increased risk of depression?

### **Search Terms**

Combined oral contraceptives, depression.

### **Citation**

Butcher B, Radenbach K, Wildt L. *Hormonal contraception and depression: a survey of the present state of knowledge.* Arch Gynecol Obstet 2012;286:251-236.

### **Object of Research**

Combined oral contraceptive

### **Research Outcome**

Depression

### **Study Features**

This is a review of studies examining the relationship between depressive disorders and hormonal contraception. Only reviewed studies that relate directly to depression or depressive symptoms are presented here. Study designs included prospective cohort studies and a one randomized study comparing combined oral contraceptives to non-hormonal methods.

*(Level 2 Evidence)*

## **The Evidence**

- In a United States based study, 232 women using a combined oral contraceptive were compared to 948 non hormonal contraception users. Women on combined oral contraceptives showed lower severity of depression, better physical function and fewer anxiety disorders.
- In a large scale Australian study, nearly 20,000 women were surveyed between the years 2000 and 2003. Using a standardized depression scale, no differences in depressive symptoms in users and non-users of oral contraceptives were shown.
- In a study of 76 women who were randomly assigned to either a combined oral contraceptive or a placebo for three months as therapy for dysmenorrhea. Depressive symptoms were also assessed by a standardized test for depression. No differences between the two groups were found.

**Appraised by:** The Jordan Evidence Based Medicine Reproductive Health Group

**Update by:** 28 March 2016

**For low dose combined oral contraceptives (COCs), there is no strong evidence linking their use and an increased risk of a myocardial infarction.**

### **Conclusion**

The risk of myocardial infarction (MI) with current or past users of the lowest dose (20 mcg estrogen) was not increased though the strength of evidence for this is low. For low dose oral contraceptives (30-35 mcg estrogen), there is no increased risk.

### **Clinical Question**

Is the use of combined oral contraceptives associated with an increased risk of a myocardial infarction?

### **Search Terms**

Low-dose oral contraceptives, myocardial infarction

### **Citation**

Urrutia RP, Coeytaux RR, McBroom AJ, Gierisch JM, Havrilesky LJ, Moorman PG, Lowrey WJ, Dinan M, Hasselblad V, Sanders GD, Myers ER. *Risk of acute thromboembolic events with oral contraceptive use.* *Obstet Gynecol* 2013;122:380-389.

### **Object of Research**

Low-dose oral contraceptives.

### **Research Outcome**

Myocardial infarction

### **Study Features**

This is a systematic review of 11 studies involving myocardial infarction; 7 case control studies, 4 cohort studies and 1 pooled analysis. Studies involved patients from Europe, Africa, Asia, Latin America, and the United States. Odds ratios were calculated comparing current to non-current combined oral contraceptive use.

*(Level 2 Evidence)*

## The Evidence

For myocardial infarction, there was no suggested increased risk associated with the use of a combined oral contraceptive (Odds Ratio=1.34; 95% CI: 0.87 – 2.08). Not all studies were consistent, however as shown in the table below.

Study	Odds Ratio	Confidence 95% Interval
WHO Collaboration, 1997	5.640	12.787 – 2.488
Sidney, 1998	0.940	2.204 – 0.401
Mant, 1998	1.500	3.725 – 0.604
Dunn, 1999	0.790	1.163 – 0.537
Rosenberg, 2001	1.300	2.156 – 0.784
Tanis, 2001	2.000	2.683 – 1.491
Margolis, 2007	0.700	1.400 – 0.350
Heinemann, 1999	0.940	2.880 – 0.307
Summary	1.342	2.080 – 0.865

There was insufficient data to assess the risk of myocardial infarction associated with different estrogen doses though one study evaluated low compared with high estrogen dose and reported no difference. Assessing the risk associated with different generation progestins, comparing current to non-current pill users yielded the following results; that is, no significant risk with third generation progestins was found.

Study	Odds Ratio	Confidence 95% Interval
First generation progestin	3.37	5.54 – 2.04
Second generation progestin	1.79	2.75 – 1.16
Third generation progestin	1.34	1.98 – 0.91

Comment: Clinicians making decisions about prescribing combined oral contraceptives should consider that the absolute risk of a myocardial infarction is very low among women of this age even when there are other risk factors.

**Appraised by:** The Jordan Evidence Based Medicine Reproductive Health Group

**Updates by:** 28 March 2016

**Among users of low dose combined oral contraceptives (COCs), there is a small, increased risk of ischemic stroke though not of hemorrhagic stroke.**

### **Conclusion**

Women who use a low dose oral contraceptive are, in the aggregate, at a slightly increased risk for ischemic stroke. Similar findings were not found for hemorrhagic stroke. Women who have risk factors for stroke and who use an oral contraceptive should be monitored. However, since stroke is rare in this age group (approximately 1 in 12,000), the absolute increase in risk is small.

### **Clinical Question**

Is there an association between use of a low dose (< 35 mcg EE) oral contraceptive and stroke?

### **Search Terms**

Low-dose oral contraceptives, ischemic and hemorrhagic stroke.

### **Citations**

Urrutia RP, Coeytaux RR, McBroom AJ, Gierisch JM, Havrilesky LJ, Moorman PG, Lowrey WJ, Dinan M, Hasselblad V, Sanders GD, Myers ER. *Risk of acute thromboembolic events with oral contraceptive use.* *Obstet Gynecol* 2013;122:380-389.

### **Object of Research**

Low-dose oral contraceptives

### **Research Outcome**

Ischemic and hemorrhagic stroke.

### **Study Features**

This is a systematic review of 15 studies involving stroke; 10 case control studies, 4 cohort studies and 1 pooled analysis. Studies involved patients from Europe, the United Kingdom and the United States. Odds ratios were calculated comparing current to non-current combined oral contraceptive use. (*Level 2 Evidence*)

## The Evidence

For ischemic stroke, there was a suggested increased risk associated with the use of a combined oral contraceptive (Odds Ratio=1.90; 95% CI 1.24 – 2.91). Not all studies were consistent, however as shown in the table below.

Study	Odds Ratio	Confidence 95% Interval
Petitti, 1996	1.180	2.584 - 0.539
Chang, 1996	4.200	10.120 - 1.743
Yang, 2009	1.100	2.009 - 0.602
Siritho, 2003	1.620	3.816 - 0.688
Lewis, 1999	2.860	4.045 - 2.022
Mant, 1998	2.900	6.585 - 1.277
Schwartz, 1997	0.900	2.969 - 0.273
Summary	1.902	2.912 - 1.243

Four studies were used to evaluate the risk of hemorrhagic stroke. There was no suggested increased risk for hemorrhagic stroke among combined oral contraceptive users (Odds ratio=1.03; 95% CI 0.71 – 1.49). The four studies were generally consistent.

Study	Odds Ratio	Confidence 95% Interval
Petitti, 1996	1.140	2.163 – 0.601
Chang, 1999	1.100	1.930 – 0.627
Yang, 2009	0.400	2.050 – 0.078
Schwartz, 1997	0.930	2.324 – 0.372
Summary	1.027	1.492 – 0.707

**Appraised by:** The Jordan Evidence Based Medicine Group

**Update by:** 27 March 2016

## **There is an increased risk of venous thromboembolism associated with the use of combined oral contraceptives (COCs)**

### **Conclusion**

There is an increase in the risk of venous thromboembolism (VTE) among women who use COCs. However, the absolute risk is very small. No statistically significant differences among the different generations of progestins were noted.

### **Clinical Question**

Is the use of combined oral contraceptives associated with an increased risk of venous thromboembolism?

### **Search Terms**

Low-dose oral contraceptives, venous thromboembolism

### **Citation**

Urrutia RP, Coeytaux RR, McBroom AJ, Gierisch JM, Havrilesky LJ, Moorman PG, Lowrey WJ, Dinan M, Hasselblad V, Sanders GD, Myers ER. *Risk of acute thromboembolic events with oral contraceptive use.* *Obstet Gynecol* 2013;122:380-389.

Object of Research

Low-dose oral contraceptives.

### **Research Outcome**

Venous thromboembolism

### **Study Features**

This is a systematic review of studies involving the incidence of venous thromboembolism among combined oral contraceptive users; 20 case control studies and 14 cohort studies. Studies involved patients from Europe, the United Kingdom and the United States. Odds ratios were calculated comparing current to non-current combined oral contraceptive use.

*(Level 2 Evidence)*

## The Evidence

For venous thromboembolism, there was a suggested increased risk associated with the use of a combined oral contraceptive (Odds Ratio=2.97; 95% CI 2.46 – 3.59). Not all studies were consistent, however as shown in the table below. A sensitivity analysis was performed eliminating the Andersen 2 study in which their calculated odds ratios were the highest reported. Results were essentially unchanged whether this study was included or excluded.

Study	Odds Ratio	Confidence 95% Interval
WHO Collaboration, 1997	4.100	5.226 – 3.216
Grodstein, 1996	2.200	5.975 – 0.810
Andersen, 1998	5.200	16.648 – 1.624
Andersen 2, 1998	48.600	422.389 – 5.592
Hannafor, 1998	1.600	2.044 – 1.252
Bloemenkamp, 1999	3.900	5.775 – 2.634
Lewis, 1999	2.900	4.086 – 2.058
Spannagi, 2000	3.000	5.000 – 1.800
Sidney, 2004	2.990	4.808 – 1.859
Huerta, 2007	1.850	2.480 – 1.380
Austin, 2009	2.800	5.650 – 1.388
Van Hylckama, 2009	4.388	5.089 – 3.784
Lidegaard, 2009	2.830	3.016 – 2.655
Barsoum, 2010	4.030	8.882 – 1.828
Dinger, 2010	2.400	3.200 – 1.800
Summary	2.970	3.591 – 2.456

Three studies allowed for the calculation of the risk of VTE comparing estrogen levels. No significant differences were between estrogen levels (high 50 mcg versus low less than 50 mcg).

Six case control studies were available to assess differences among the different generations. No significant differences were found among first, second, third and fourth generation progestins (Odds ratios=4.06, 3.28, 4.06, and 5.36, respectively). That is, all generations had elevated risks for venous thromboembolism.

**Appraised by:** The Jordan Evidence Based Medicine Reproductive Health Group

**Update by:** 28 March 2016

## **Users of combined oral contraceptives (COCs) have a reduced risk of hospitalization due to benign breast disease.**

### **Conclusion**

Combined oral contraceptives appear to reduce the risk of benign breast disease as measured by the hospitalization rate for this condition. For those diagnosed with fibroadenoma and chronic cystic disease, there is an apparent protective effect present for women using COCs regardless of the level of estrogen.

### **Clinical Question**

Are women who are taking or have taken oral contraceptives at an increased risk for hospitalization due to benign breast disease?

### **Search Terms**

Oral contraceptives, benign breast disease, chronic cystic disease, fibroadenoma, breast lump

### **Citations**

Vessey M and Yeates D. *Oral contraceptives and benign breast disease: an update of findings in a large cohort study.* Contraception 2007;76:418-424.

### **Object of Research**

Combined oral contraceptives

### **Research Outcome**

Hospitalization due to benign breast disease (fibroadenoma, confirmed cystic disease, breast lumps)

### **Study Features**

The Oxford-Family Planning Association contraceptive study is a cohort design begun in the early years (1968) of oral contraceptive use. From 1968 to 1974 women were recruited at 17 family planning clinics in England and Scotland. Women were aged 25 to 39 years, married, Caucasian, British, and current COC users of at least five months. At aged 45, women were classified as never users, used for more than 8 years or more, or used for less than 8

years. The study includes 17,032 women using different methods of contraception. The analysis in this study included 185 women with histologically confirmed fibroadenoma, 1,361 with histologically confirmed cystic disease, and 650 with breast lumps not subjected to biopsy. Women with a history of benign breast disease or breast cancer on entry into the study were excluded. Because benign breast disease is a variable and imprecise diagnosis, in this study, the relative risk of hospitalization for benign breast disease was calculated separately for fibroadenoma, confirmed cystic disease, and breast lumps.

**(Level 2 Evidence)**

### **The Evidence**

The relative risk of hospitalization for benign breast disease was calculated separately for fibroadenoma, confirmed cystic disease, and breast lumps. Note that relative risk in this context is essentially a ratio of the risk hospitalization due to benign breast disease among COC users to non-users. A ratio of less than 1 means that the risk for COC users is less than non-COC users. Results were as follows:

- The relative risk for hospitalization due to fibroadenoma was less than 1 for all durations of COC use and hospital referral rates declined with increasing duration of use of a COC.
- The relative risk for confirmed cystic disease decreased with increasing duration of COC use. The relative risk was less than 1 in all time intervals (2 years or less up to more than 10 years), but was significantly less than 1 only for durations of more than six years. As with fibroadenoma, hospital referral rates for confirmed cystic disease declined with increasing duration of use of a COC.
- For breast lumps, the relative risk for COC users was not significantly increased relative to never users regardless of duration of use.

**Appraised by:** The Jordan Evidence Based Medicine Reproductive Health Group

**Update by:** 29 March 2016

**Among users of combined oral contraceptives (COCs), there appears to be a protective effect against uterine body or endometrial cancer.**

### **Conclusion**

This prospective study provides the best information to date on the relationship between COC use and endometrial cancer. It appears that combined oral contraceptives offer long-term protection against endometrial cancer.

### **Clinical Question**

Are women who are taking or have taken oral contraceptives at an increased risk for endometrial cancer?

### **Search Terms**

Oral contraceptives, uterine body cancer, endometrial cancer

### **Citation**

Vessey M, Yeates D. *Oral contraceptive use and cancer: final report from the Oxford-Family Planning Association contraceptive study*. *Contraception* 2013;88:678-683.

### **Object of Research**

Low-dose oral contraceptives

### **Research Outcome**

Endometrial cancer

### **Study Features**

The Oxford-Family Planning Association contraceptive study is a cohort design begun in the early years (1968) of oral contraceptive use. Between the years 1968 to 1974, 17,032 women were recruited at 17 family planning clinics in England and Scotland. Women were aged 25 to 39 years, married, Caucasian, British, and a current COC user for at least five months. At aged 45, each women was classified as never users of COCs, used a COC for more

than 8 years or more, or used for less than 8 years. Two-thirds of all women in this study had used a COC containing 50 mg of estrogen. Almost all women who had uterine body cancer were diagnosed as endometrial cancer.

*(Level 2 Evidence)*

### **The Evidence**

The rate ratio was calculated using never users as the reference group. The findings were that

- the rate ratio for endometrial cancer among COC users regardless of duration was 0.5 with a 95% confidence interval of (0.3 – 0.7).
- there was no apparent association with duration of COC use; the rate ratios were essentially unchanged from 0.7 (95% CI: 0.4 – 1.2) for 48 or fewer months of use to 0.3 (95% CI: 0.2 – 0.6) for 97 or more month of user.
- women who stopped using a combined oral contraceptive ten or more years had no increased risk for endometrial cancer when compared to never users of COCs.

**Appraised by:** The Jordan Evidence Based Medicine Reproductive Health Group

**Update by:** 29 March 2016

**Among users of combined oral contraceptives, there appears to be long term protection against ovarian cancer.**

### **Conclusion**

Virtually every study in the world literature of COC use has shown a protective effect from acquiring ovarian cancer that lasts for more than 30 years after the cessation of COC use.

### **Clinical Question**

Are women who are taking or have taken oral contraceptives at an increased risk for ovarian cancer?

### **Search Terms**

Oral contraceptives, ovarian cancer

### **Citations**

Vessey M and Painter R. *Oral contraceptive use and cancer: final report from the Oxford Family Planning Association contraceptive study.* Contraception 2013;88:678-683.

Collaborative Group on Epidemiological Studies of Ovarian Cancer. “*Ovarian cancer and oral contraceptives: collaborative reanalysis of data from 45 epidemiological studies including 23,257 women with ovarian cancer and 87,303 controls.*” Lancet 2008;371:303-314.

### **Object of Research**

Low-dose oral contraceptives

### **Research Outcome**

Ovarian cancer

## **Study Features**

### Vessey and Yeates

The Oxford-Family Planning Association contraceptive study is a cohort design begun in the early years (1968) of oral contraceptive use. Between the years 1968 to 1974, 17,032 women were recruited at 17 family planning clinics in England and Scotland. Women were aged 25 to 39 years, married, Caucasian, British, and a current COC user of at least five months. At aged 45, each women was classified as never users of COCs, used a COC for more than 8 years or more, or used for less than 8 years. Two-thirds of all women in this study had used a COC containing 50 mg of estrogen.

**(Level 2 Evidence)**

### Collaborative Study

This is a reanalysis of worldwide epidemiologic studies on the relationship between ovarian cancer and the use of hormonal contraceptives. Each selected study (45 in number) was drawn from 21 different countries. Thirteen of the studies are prospective, 19 are case control with population controls, and 13 are case control with hospital controls. In total, the studies include individual data for 23,257 women with ovarian cancer. 7,308 (31%) had used an oral contraceptive. For the controls there were 87,303 without ovarian cancer of whom 32,717 (37%) had used an oral contraceptive.

**(Level 2 Evidence)**

## **The Evidence**

### Vessey and Yeates

In this study, the rate ratio is calculated using never users as the reference group. The findings were that the rate ratio for ovarian cancer among COC for all durations was 0.5 (95% CI: 0.4 – 0.7). No significant changes were noted with duration of use.

### Collaborative Study

In this study, the findings are that:

- in all of the studies, the relative risk was less than one suggesting a protective effect for ovarian cancer among users of combined oral contraceptives. The relative risk associated with ever use of COCs was 0.73 (95% CI: 0.70 – 0.76).
- the reduction in risk persisted for more than 30 years after oral contraceptive use had ceased.
- the reduction in risk did not vary on use in the 1960s, 1970s, or 1980s though estrogen dosing in commonly used formulations changed over these decades.

**Appraised by:** The Jordan Evidence Based Medicine Reproductive Health Group

Update by: 9 April 2016

**Among users of combined oral contraceptives (COCs), there appears to be an increased risk for cervical cancer and this risk increases with duration of use.**

### **Conclusion**

The relative risk of cervical cancer is increased in current users of oral contraceptives and declines after cessation of use. While duration of use is also positively associated with an increasing cervical cancer risk, similar to ever use, there is a gradual decrease in risk with time elapsed since last use.

### **Clinical Question**

Are women who are taking or have taken oral contraceptives at an increased risk for cervical cancer?

### **Search Terms**

Oral contraceptives, cervical cancer

### **Citation**

Vessey M, Yeates D. *Oral contraceptive use and cancer: final report from the Oxford-Family Planning Association contraceptive study*. *Contraception* 2013;88:678-683.

### **Object of Research**

Combined oral contraceptives

### **Research Outcome**

Cervical cancer

### **Study Features**

The Oxford-Family Planning Association contraceptive study is a cohort design begun in the early years (1968) of oral contraceptive use. Between the years 1968 to 1974, 17,032 women were recruited at 17 family planning clinics in England and Scotland. Women were aged 25 to 39 years, married,

Caucasian, British, and a current COC user of at least five months. At aged 45, each women was classified as never users of COCs, used a COC for more than 8 years or more, or used for less than 8 years.

*(Level 2 Evidence)*

### **The Evidence**

The rate ratio was calculated using never users as the reference group. The findings were that

- the rate ratio for cervical cancer among COC users regardless of duration was 3.4 (95% CI: 1.6 – 8.9).
- there was a strong positive association with duration of COC use; the rate ratios increased from 2.3 (95% CI: 0.9 – 1.2) for 48 or fewer months of use up to 4.8 (95% CI: 2.0 – 12.9) for those using COCs for 97 or more months.
- women who had stopped using a combined oral contraceptive ten or more years had no increased risk for cervical cancer when compared to never users of COCs.

**Appraised by:** The Jordan Evidence Based Medicine Reproductive Health Group

**Update by:** 28 March 2014

**Among users of combined oral contraceptives (COCs), there does not appear to be an increased risk of breast cancer.**

### **Conclusion**

There have been many studies, both retrospective and prospective, exploring the link between COC use and breast cancer. This prospective study provides the best information to date on this relationship and it appears that there is a complete absence of any relationship between COC use and breast cancer.

### **Clinical Question**

Are women who are taking or have taken oral contraceptives at an increased risk for breast cancer?

### **Search Terms**

Oral contraceptives, breast cancer

### **Citations:**

Vessey M, Yeates D. *Oral contraceptive use and cancer: final report from the Oxford-Family Planning Association contraceptive study*. *Contraception* 2013;88:678-683.

### **Object of Research**

Combined oral contraceptives

### **Research Outcome**

Breast cancer

### **Study Features**

The Oxford-Family Planning Association contraceptive study is a cohort design begun in the early years (1968) of oral contraceptive use. Between the years 1968 to 1974, 17,032 women were recruited at 17 family planning clinics in England and Scotland. Women were aged 25 to 39 years, married, Caucasian, British, and a current COC user of at least five months. At aged 45, each women was classified as never users of COCs, used a COC for more than 8 years or more, or used for less than 8 years.

*(Level 2 Evidence)*

## **The Evidence**

The rate ratio was calculated using never users as the reference group. The findings were that

- the rate ratio for breast cancer among COC users regardless of duration was 1.0 (95% CI: 0.9 – 1.1).
- there was no apparent association with duration of COC use; the rate ratios were essentially unchanged from 1.0 (95% CI: 0.9 – 1.4) for 48 or fewer months of use to 1.0 (95% CI: (0.9 – 1.2) for those using 97 or more month.
- women who had stopped using a combined oral contraceptive ten or more years had no increased risk for breast cancer when compared to never users of COCs.

**Appraised by:** The Jordan Evidence Based Medicine Reproductive Health Group

**Update by:** 29 March 2016





**Depot  
Medroxyprogesterone  
Acetate (DMPA)  
Injectables**

**DMPA**



## **DEPOT MEDROXPROGESTERONE ACETATE**

In Jordan, the proportion of married women of reproductive age using depot medroxyprogesterone acetate (DMPA) is less than 1 percent<sup>1</sup>. Most women can use DMPA, but health professionals should be aware of the World Health Organization Medical Eligibility Criteria for Contraceptive Use<sup>2</sup>.

### **Effectiveness**

Depot medroxyprogesterone acetate (Depo Provera<sup>®</sup>) is highly effective if taken every three months as directed. With correct and consistent use, less than 1 percent will experience a method failure in the first year of use. Typical users though have failure rates about 3 percent in the first year<sup>3</sup>. For women who prefer an injectable contraceptive method, duration of use is not associated with any decrease in efficacy or safety. Thus, the use of DMPA does not require a rest period.

### **Mode of Action**

There are several modes of action of DMPA in preventing pregnancy. It acts primarily by inhibiting ovulation. Other ways that DMPA may prevent pregnancy are by a thickening of the cervical mucus thus preventing sperm entry into the upper genital tract, or by altering the endometrium thus inhibiting implantation of a fertilized egg<sup>4</sup>.

### **Advantages of Depot Medroxyprogesterone Acetate**

In addition to being effective, other advantages to using DMPA are:

- the absolute number of ectopic pregnancies are reduced<sup>5</sup>
- it is reversible<sup>6,7,8</sup>
- it is an option throughout reproductive years
- a suggested decrease in menstrual bleeding<sup>9</sup>
- a reduced risk of anemia<sup>10</sup>
- less pain from endometriosis<sup>11,12</sup>
- no apparent increased cardiovascular risks<sup>13</sup>
- is safe for the infant of a breastfeeding woman<sup>14</sup>

### **Disadvantages of Depot Medroxyprogesterone Acetate**

- menstrual cycle disturbances<sup>9</sup>
- return visits are required every three months
- not possible to discontinue immediately
- return to fertility is likely to be delayed<sup>6,7,8</sup>

### **Special Topics**

- Cancer

*No apparent elevation of cancer risk though studies of association with breast cancer are not consistent<sup>15-20</sup>.*

- Bone Mineral Density Loss

*Some loss of bone mineral density which may be associated with a risk of fractures in some women<sup>21,22</sup>.*

## REFERENCES

### Depot Medroxyprogesterone Acetate

1. Department of Statistics [Jordan] and ICF Macro,2010. *Jordan Population and Family Health Curvey 2009*. Calverton, Maryland, USA: Department of Statistics and ICF Macro.
2. World Health Organization. *Medical eligibility criteria for contraceptive use*. Geneva:WHO, 2004.
3. Hatcher RA, Trussell J, Nelson AL, Cates W, Stewart F, Kowal D. *Contraceptive Efficacy*. Contraceptive Technology. New York: Ardent Media Inc, 2008. 747-826.
4. Hatcher RA, Trussell J, Nelson AL, Cates W, Stewart F, Kowal D. *Injectable contraceptives*. Contraceptive Technology. New York: Ardent Media Inc, 2008. 158-159.
5. Borgatta L, Murthy A, Chuang C, et al. *Pregnancies diagnosed during Depo-Provera use*. Contraception 2001;66:169-172.
6. Schwallie PC, Assenzo JR. *The effect of depot medroxyprogesterone acetate on pituitary and ovarian function, and the return of fertility following its discontinuation: A review*. Contraception 1974;10(2):181-202.
7. Pardthaisong T. *Return of fertility after use of the injectable contraceptive Depo Provera: updated data analysis*. J Biosoc Sci 1984;16:23-34.
8. Affandi B, Santoso SS, Djajadilaga, Hadisaputra W, Moeloek FA, Prihartono J, Lubis F, Samil RS. *Pregnancy after removal of Norplant implants contraceptive*. Contraception 1987;36:203-209.
9. Westhoff C. *Depot-medroxyprogesterone acetate injection (Depo-Provera): a highly effective contraceptive option with proven long-term safety*. Contraception. 2003;68:75–87.
10. Task Force for Epidemiological Research on Reproductive Health, United Nations Development Programme/United Nations Population Fund/World Health Organization/World Bank Special Programme of Research, Development and Research Training in Human Reproduction, World Health Organization, Geneva, Switzerland. *Effects*

- of contraceptives on hemoglobin and ferritin. Contraception* 1998 Nov;58(5):262-73.
11. Vercellini P, De Giori O, Oldani S, et al. *Depot medroxyprogesterone acetate versus an oral contraceptive combine with a very-low-dose danazol for long term treatment of pelvic pain associated with endometriosis. Am J Obstet Gynecol* 401-170:396;1996.
  12. Walch K, Unfried G, Huber J, Kurz C, et al. *Implanon versus medroxyprogesterone acetate: effects on pain scores in patients with symptomatic endometriosis – a pilot study. Contraception* 2009; 79:29-34.
  13. The WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. *Cardiovascular disease and use of oral and injectable progestogen-only contraceptives and combined injectable contraceptives. Results of an international, multicenter, case-control study. Contraception* 1998;57:315-324.
  14. World Health Organization (WHO) Task Force on Oral Contraceptives. *Effects of hormonal contraceptives on breast milk composition and infant growth. Stud Fam Plann.* 1988 Nov-Dec;19(6 Pt 1):361-9.
  15. Lumbiganon P. Depo-medroxyprogesterone acetate (DMPA) and cancer of the endometrium and ovary. *Contraception* March 1994;49;203-209.
  16. The WHO Collaborative Study of Neoplasia and Steroid Contraception. *Depot-medroxyprogesterone acetate (DMPA) and risk of invasive squamous cell cervical cancer. Contraception* 1992;45:299-312.
  17. Thomas DB, Ray RM. *Depot-medroxyprogesterone acetate (DMPA) and risk of invasive adenocarcinomas and adenosquamous carcinomas of the uterine cervix. The WHO Collaborative Study of Neoplasia and Steroid Contraception. Contraception* 1995;52:307-312.
  18. Strom, BL, et al. *Absence of Injectable and Implantable Progestin-only Contraceptives on Subsequent Risk of Breast Cancer. Contraception*, 2004. (69); 353-360.
  19. Li C, Beaber E, Tang M, Porter, P, Daling H, Malone K. *Effect of depo-medroxyprogesterone acetate on breast cancer risk among women 20-44 years of age. Cancer Res* 2012;72(8):2028-2035.
  20. Mati JG et al. *Depot-medroxyprogesterone acetate (DMPA) and risk*

- of liver cancer*. Int J Cancer 1991;49:182-185.
21. Lanza L, McQuay L, Rothman K, Bone H, Kaunitz A, Harel Z, Ataher Q, Ross D, Arena P, Wolter K. *Use of depot medroxyprogesterone acetate contraception and incidence of bone fracture*. Obstet Gynec 2013;121(3):593-600.
  22. Lopez L, Chen M, Mullins S, Curtis K, Helmerhorst F. *Steroidal contraceptives and bone fractures in women: evidence from observational studies (Review)*. Cochrane Database of Systematic Reviews 2012, Issue 8. Art. No.: CD009849, DOI:10.1002/14651858.CD009849.pub 2.

## **List of Critically Appraised Topics**

- 1-Efficacy
- 2-Ectopic Pregnancy
- 3-Return to Fertility
- 4-Menstrual Blood Loss
- 5-Amenorrhea
- 6-Anemia
- 7-Counseling
- 8-Endometriosis
- 9-Fibroids
- 10-Pelvic Inflammatory Disease
- 11-Weight Gain
- 12-Acne
- 13-Depression
- 14-Hypertension
- 15-Myocardial Infarction
- 16-Stroke
- 17--Venous Thromboembolism
- 18-Endometrial Cancer
- 19-Ovarian Cancer
- 20-Cervical Cancer
- 21-Breast Cancer
- 22-Liver Cancer
- 23-Fractures
- 24-Breastfeeding

*Note that the level of evidence accompanying each publication in each of the CATs refers to the study design.*

**Depot medroxyprogesterone acetate is an effective contraceptive for both breastfeeding and non-breastfeeding women when used correctly and consistently.**

**Conclusion**

Studies show depot medroxyprogesterone acetate 150 mg IM (DMPA) is a highly effective contraceptive method for both breastfeeding and non-breastfeeding women when used correctly and consistently.

**Clinical Question**

Is depot medroxyprogesterone an effective contraceptive for women?

**Search Terms**

Depot medroxyprogesterone, DMPA, Depo Provera, effectiveness

**Citation**

Hatcher RA, Trussell J, Nelson AL, Cates W, Stewart F, Kowal D. *Contraceptive Efficacy*. Contraceptive Technology. New York: Ardent Media Inc., 2008. 747-826.

**Object of Research**

Depot medroxyprogesterone

**Research Outcome**

Pregnancy in breastfeeding and non-breastfeeding women

**Study Features**

This is a review of nine studies assessing the efficacy of depot medroxyprogesterone 150 mg IM as a contraceptive. The sample size for one study was not available, but the other seven included 8,292 women ranging from 209 to 3,857. The median sample size was 650. Trial locations included European countries, the United Kingdom, the United States, as well as those from Africa, Latin America, and Asia. One study in Bangladesh was of 100 women who received their injection immediately postpartum.

*(Level 1 Evidence)*

## **The Evidence**

The one-year results for these studies were:

- No pregnancies in the immediate postpartum study though 100 cases is insufficient to assess a pregnancy rate.
- One-year pregnancy rates ranged from a low of zero to a high of 3.2. The highest rate was based on 209 cases whereas the two studies with over a thousand women reported one-year pregnancy rates of 0.1 and 0.3.

**Appraised by:** The Jordan Evidence-Based Medicine Reproductive Health Group

**Update by:** 26 April 2016

## **Among current users of depot medroxyprogesterone, there is no increased risk of ectopic pregnancy**

### **Conclusion**

Based on the results of a review of series reports of ectopic pregnancy, use of depot medroxyprogesterone (DMPA) as a contraceptive method decreases the overall incidence of ectopic pregnancy since there are few pregnancies among women who use an effective contraceptive method. Similarly there is no increased proportion of ectopic pregnancies among women who conceive while using depot medroxyprogesterone acetate though the possibility of ectopic pregnancy should be ruled out.

### **Clinical Question**

Is there an increased risk of ectopic pregnancy among women using depot medroxyprogesterone acetate?

### **Search Terms**

Depo Provera, DMPA, depot medroxyprogesterone, ectopic pregnancy

### **Citation**

Borgatta L, Murthy A, Chuang C, et al. *Pregnancies diagnosed during Depo-Provera use.* Contraception 2001;66:169-172.

### **Object of Research**

Depot medroxyprogesterone acetate

### **Research Outcome**

Ectopic pregnancy

### **Study Features**

This is a retrospective study based on a series of reports of pregnancies to the Insurance Division of Planned Parenthood Federation of America during the years 1994 to 1998 inclusive. Cases were included only if a pregnancy was reported after depot medroxyprogesterone acetate had been administered at a

Planned Parenthood site.  
(*Level 2 Evidence*)

**The Evidence**

A total of 949,182 users of DMPA users were identified among which there were 402 reported pregnancies with a rate of 0.42 pregnancies/1000 users. Of these, there were 4 identified ectopic pregnancies or 1.5% of all pregnancies.

Comment: Based on data from the US Center for Disease Control as well as the WHO, the current estimated ectopic pregnancy rate without contraceptive use is approximately 2%. The current rate for DMPA based on these data is not significantly different from these estimates.

**Appraised by:** The Jordan Evidence Based Medicine-Reproductive Health Group

**Update by:** 11 March 2016

## **Among users of depot medroxyprogesterone acetate, there is no apparent association between use and failure to return to fertility though return is often delayed**

### **Conclusion**

While there is no apparent association between use of depot medroxyprogesterone (DMPA) as a contraceptive and a return to fertility, users tend to experience some delay relative to other contraceptive users such as those using an IUD. That is, DMPA normally causes amenorrhea in the majority of users; however it is very rare for this to lead to infertility. Note that though the studies cited are old (1974, 1984, 1987), the return to fertility rates are consistent in the three studies and thus convincing.

### **Clinical Question**

Is there an association between return to fertility and the use of DMPA as a contraceptive?

### **Search Terms**

Depo Provera, DMPA, return to fertility

### **Citations**

Schwallie PC, Assenzo JR. *The effect of depot medroxyprogesterone acetate on pituitary and ovarian function, and the return of fertility following its discontinuation: A review.* Contraception 1974;10(2):181-202.

Pardthaisong T. *Return of fertility after use of the injectable contraceptive Depo Provera: updated data analysis.* J Biosoc Sci 1984;16:23-34.

Affandi B, Santoso SS, Djajadilaga, Hadisaputra W, Moeloek FA, Prihartono J, Lubis F, Samil RS. *Pregnancy after removal of Norplant implants contraceptive.* Contraception 1987;36:203-209.

### **Object of Research**

Depo Provera

## **Research Outcome**

Return to fertility after discontinuation of method

### **Study Features**

#### Schwallie

This is data taken from published and unpublished sources. 188 women who dropped from the Upjohn collaborative DMPA clinical study to become pregnant were included. Of these 74 (39.4%) were lost to follow-up, changed their mind or moved away.

*(Level 2 Evidence)*

#### Pardthaisong

This is a study of Thai contraceptive users who discontinued their method for a planned pregnancy. In all there were 796 former DMPA users, 437 former oral contraceptive users, and 125 former IUD users. The patients' demographic characteristics were not described in this paper.

*(Level 2 Evidence)*

### **Study Features (continued)**

#### Affandi

This is a study of Indonesian contraceptive users who discontinued their method for a planned pregnancy. In all there were 47 former DMPA users, 75 former IUD users and 51 former Norplant users. Mean ages (26 years) and parity (1.7 live births) were similar across the 3 groups.

*(Level 2 Evidence)*

### **The Evidence**

#### Schwallie

Of the 114 DMPA users followed in this study, all became pregnant. The median time to pregnancy was 10 months. Of the 74 classified as lost to follow-up, 44 (59.5%) were true lost to follow-up, 5 (6.8%) returned to menses and then were lost to follow, 6 (8.1%) moved away, 18 (24.3%), changed their mind about becoming pregnant, and one other was removed because of

treatment for infertility prior to initiation of the study.

Pardthaisong

747 (94%) DMPA users returned to fertility at 36 months as compared to 117 (94%) IUD users. There was no apparent association between the length of use and a return to fertility.

Affandi

42 (89%) of all DMPA discontinuers returned to fertility at 24 months as compared to 65 (87%) IUD discontinuers.

**Appraised by:** The Jordan Evidence Based Medicine-Reproductive Health Group

**Update By:** 15 March 2016

## **The use of depot medroxyprogesterone acetate is associated with a significant decrease in menstrual blood loss**

### **Conclusion**

Depot medroxyprogesterone acetate (DMPA) is associated with a significant decrease in menstrual blood loss. If women are counseled about this possibility, continuation rates may be improved.

### **Clinical Question**

Is the use of depot medroxyprogesterone acetate contraceptive associated with an increased risk of menorrhagia?

### **Search Terms**

Depot medroxyprogesterone acetate, DMPA, Depo Provera, menorrhagia.

### **Citations**

Westhoff C. *Depot-medroxyprogesterone acetate injection (Depo-Provera): a highly effective contraceptive option with proven long-term safety*. *Contraception*. 2003;68:75–87.

### **Object of Research**

Depot medroxyprogesterone acetate

### **Research Outcome**

Menorrhagia

### **Study Features**

This is a comprehensive review of 17 relevant studies of long-term data regarding the menstrual patterns among users of DMPA. The studies range from controlled clinical trials to retrospective chart reviews and follow-up surveys.

*(Level 1 Evidence)*

**The Evidence**

Based on these data, menstrual changes, such as spotting/irregular bleeding and longer durations of menses, are relatively common in the initial 3 months, but these tend to decrease over time. Bleeding associated with DMPA was more frequently characterized by spotting or light bleeding rather than heavy menstrual flow. Although the irregular bleeding with DMPA declines substantially with time, menstrual cycle changes are a major reason for patient discontinuation.

**Appraised by:** The Jordan Evidence Based Medicine-Reproductive Health Group

**Update by:** 15 March 2016

## **The use of depot medroxyprogesterone acetate is associated with a significant increase in amenorrhea**

### **Conclusion**

Depot medroxyprogesterone acetate (DMPA) is associated with an increase amenorrhea. The likelihood of a user experiencing amenorrhea increases with usage.

### **Clinical Question**

Is the use of depot medroxyprogesterone acetate contraceptive associated with an increased risk of amenorrhea?

### **Search Terms**

Depot medroxyprogesterone acetate, DMPA, Depo-Provera, amenorrhea.

### **Citation**

Hubacher D, Lopez L, Steiner MJ, Dorflinger L. *Menstrual pattern changes from levonorgestrel subdermal implants and DMPA: systematic review and evidence-based comparisons*. Contraception 2009;80:113-8.

### **Object of Research**

Depot medroxyprogesterone acetate.

### **Research Outcome**

Amenorrhea

### **Study Features**

This a systematic review of 16 published articles including 5 studies of DMPA. The studies involved diaries and standard World Health Organization definitions for menstrual pattern changes for bleeding or spotting days, amenorrhea, or a normal pattern in four consecutive 90 day reference periods. Amenorrhea was defined as no bleeding in the 90 days reference period. The studies documenting amenorrhea included 1600 DMPA users from Vietnam, the United States, and ten WHO centers from Africa, Asia, Europe and North America.

*(Level 1 Evidence)*

**The Evidence**

For DMPA use, the prevalence of amenorrhea at successive 90-day periods was 12%, 25%, 37% and 46%. At 12 months, normal menstrual patterns were experienced by only 11% of DMPA users.

Comment: There is some suggestion that counseling women about likely menstrual pattern changes with DMPA use may decrease discontinuation due to amenorrhea with this method.

**Appraised by: The Jordan Evidence Based Medicine Reproductive Health Group**

**Update by:** 11 March 2016

# **The use of depot medroxyprogesterone acetate decreases the incidence of anemia**

## **Conclusion**

Depot medroxyprogesterone acetate (DMPA) is associated with a decrease in anemia incidence as measured by hemoglobin and ferritin levels.

## **Clinical Question**

Is the use of depot medroxyprogesterone acetate contraceptive associated with a decrease in the incidence of anemia?

## **Search Terms**

Depot medroxyprogesterone acetate, Depo-Provera, DMPA, hemoglobin, anemia.

## **Citation**

Task Force for Epidemiological Research on Reproductive Health, United Nations Development Programme/United Nations Population Fund/World Health Organization/World Bank Special Programme of Research, Development and Research Training in Human Reproduction, World Health Organization, Geneva, Switzerland. *Effects of contraceptives on hemoglobin and ferritin*. Contraception 1998 Nov;58(5):262-73.

## **Object of Research**

Depot medroxyprogesterone acetate.

## **Research Outcome**

Hemoglobin levels, anemia.

## **Study Features**

This is a cross sectional study of current contraceptive users including DMPA. Women were non-pregnant and non-lactating. Countries with DMPA users were Bangladesh (n=51), Pakistan (n=25), and Thailand (two sites n=95 and n=50). The objective was to assess the effects of depot medroxyprogesterone

acetate contraceptive on hemoglobin and ferritin levels. Current users of other contraceptive methods (e.g. combined oral contraceptives, intrauterine devices) were compared with users of DMPA. Women with normal hemoglobin at the time of initiation of their contraceptive were asked to participate in a longitudinal component of the study in which hemoglobin and ferritin levels were assessed at a 3, 6, 9 and 12 months follow-up.

*(Level 2 Evidence)*

### **The Evidence**

Current users of hormonal contraceptive methods generally had higher hemoglobin and ferritin levels than nonusers. The differences between women using a hormonal contraceptive and nonusers in mean values for hemoglobin varied between 3 and 6 g/L and for ferritin between 2 and 18 g/L. Significant mean increases of hemoglobin and ferritin levels at 12 months were observed among the users of oral contraceptives and DMPA, but not among users of copper or stainless steel ring IUDs.

**Appraised by:** The Jordan Evidence Based Medicine-Reproductive Health Group

**Update by:** 15 March 2016

## **Users of depot medroxyprogesterone acetate who receive structured pretreatment counseling experience less rates of discontinuation than those with routine counseling**

### **Conclusion**

For women using depot medroxyprogesterone (DMPA), discontinuation can be decreased if they are given structured counseling designed to inform them of common use-related adverse effects (e.g. menstrual cycle disruptions).

### **Clinical Question**

Does the provision of structured counseling on expected side effects of DMPA use affect continuation rates for this contraceptive?

### **Search Terms**

Depot medroxyprogesterone acetate, DMPA, Depo-Provera, pretreatment counseling

### **Citation**

Lei ZW, Wu SC, Garceau R, et al. *Effect of pretreatment counseling on discontinuation rates in Chinese women given depo-medroxyprogesterone acetate for contraception.* Contraception 1996;53(6):357-361.

### **Object of Research**

Depot medroxyprogesterone acetate

### **Research Outcome**

Discontinuation rates after pretreatment counseling on side effects associated with the use of DMPA

### **Study Features**

This was a prospective, comparative study in four clinical sites conducted in China. The objective was to assess the effect of an intensive, detailed, structured pretreatment counseling as compared to routine counseling. Women (n=204) at two of the clinics received the intensive counseling while those

(n=217) at the other two had routine counseling. Women between the ages of 18 and 40 were enrolled at the four different clinics. The structured counseling included information on the mode of action of DMPA as well as common hormonal and possible side effects.

*(Level 2 Evidence)*

### **The Evidence**

Within 3 months after receiving one DMPA dose, 3% of those who received structured counseling dropped out as compared to 25% who had received routine counseling. At 12 months, the corresponding rates for the two groups were 11% and 42%, respectively. For the structured counseling group, 5% dropped out for irregular bleeding and none left the study because of amenorrhea. For the routine counseling group, the corresponding dropout rates were 19% and 2%, respectively.

**Appraised by:** The Jordan Evidence Based Medicine-Reproductive Health Group

**Update by:** 15 March 2016

## **The use of depot medroxyprogesterone acetate is effective in decreasing pain associated with endometriosis**

### **Conclusion**

Depot medroxyprogesterone acetate (DMPA) is an effective treatment for pain associated with endometriosis.

### **Clinical Question**

Is the use of depot medroxyprogesterone acetate contraceptive associated with a decrease in pain associated with endometriosis?

### **Search Terms**

Depot medroxyprogesterone acetate, DMPA, Depo Provera, pain associated with endometriosis

### **Citations**

Vercellini P, De Giori O, Oldani S, et al. *Depot medroxyprogesterone acetate versus an oral contraceptive combine with a very-low-dose danazol for long term treatment of pelvic pain associated with endometriosis.* Am J Obstet Gynecol 1996;175:396-401.

Walch K, Unfried G, Huber J, Kurz C, et al. *Implanon versus medroxyprogesterone acetate: effects on pain scores in patients with symptomatic endometriosis – a pilot study.* Contraception 2009; 79:29-34.

### **Object of Research**

Depot medroxyprogesterone acetate.

### **Research Outcome**

Pain associated with endometriosis

## **Study Features**

### Vercellini

Eighty patients with laparoscopic confirmed endometriosis and moderate or severe pelvic pain (dysmenorrhea, deep dyspareunia, and nonmenstrual pelvic pain) were randomly assigned to one of two treatments for 1 year in an open label, prospective clinical study. Treatments were either intramuscular depot medroxyprogesterone acetate 150 mg every 3 months or a cyclic monophasic oral contraceptive (ethinyl estradiol 0.02 mg, desogestrel 0.15 mg) combined with oral danazol 50 mg a day for 21 days of each 28-day cycle. The women were asked to grade the degree of their satisfaction at the end of therapy. Variations in severity of symptoms during treatment were determined by a 10 cm visual analog and a 0- to 3-point verbal rating scale.

*(Level 1 Evidence)*

### Walch

In an open label, one year, prospective clinical study of women with histologically confirmed endometriosis, 21 were randomly assigned to receive Implanon and 20 to receive depot medroxyprogesterone. They were evaluated for pain improvement according to a visual analog scale as well as overall degree of satisfaction.

*(Level 1 Evidence)*

## **The Evidence**

### Vercellini

A significant decrease in symptom scores was observed in both groups. Twenty nine (72.5%) of 40 subjects in the depot medroxyprogesterone acetate group were satisfied after 1 year of therapy compared with 23 (57.5%) of 40 in the oral contraceptive plus danazol group (Odds Ratio=1.95, 95% confidence interval 0.76-4.97). Numerically, the DMPA group had better symptom scores, but the relative risk was not statistically significant.

### Walch

During the follow-up period at one year, an improvement in pain intensity was observed in both treatment groups. The average decrease in pain was 68 percent in the implant group and 53 percent in the DMPA group. Numerically, at each quarterly evaluation, the decreases were greater in the Implanon group though the differences with the DMPA group were not statistically significant. However, the overall degree of users satisfied or very satisfied among those using Implanon and those using DMPA was similar (Implanon: 57%; DMPA:58%).

**Appraised by:** The Jordan Evidence Based Medicine-Reproductive Health Group

**Update by:** 15 March 2016

# **Depot medroxyprogesterone acetate is associated with a decrease in the incidence of uterine fibroids**

## **Conclusion**

Depot medroxyprogesterone acetate (DMPA) is associated with a decrease in the incidence of uterine fibroids when compared to non-users of contraceptives. When compared with current use of combined oral contraceptives (COCs) this decrease is significantly better.

## **Clinical Question**

Is the use of depot medroxyprogesterone acetate contraceptive associated with a decrease incidence of uterine fibroids?

## **Search Terms**

Depot medroxyprogesterone acetate, DMPA, Depo -Provera, myomas, uterine fibroids

## **Citation**

Wise LA, Palmer JR, Harlow BL, Spiegelman D, Stewart EA, et al. *Reproductive factors, hormonal contraception and risk of uterine leiomyomata in African American women: a prospective study.* Amer J Epidemiology 2004;159:113-123.

## **Object of Research**

Depot medroxyprogesterone acetate

## **Research Outcome**

Uterine fibroids, leiomyomata

## **Study Features**

This is a prospective cohort study conducted in the United States as part of the Black Women's Health Study. Through a questionnaire, women were recruited in 1995 if they subscribed to Essence magazine, were a member of a Black professional organization, or were a friend or relative of a respon-

dent. The baseline questionnaire elicited information on demographic and behavioral characteristics, reproductive and contraceptive histories, health care utilization, and medical conditions. After exclusions, 22,895 premenopausal women with intact uteri and no previous self-reported diagnosis of uterine leiomyomata were subsequently identified and included in the study. Updated information was obtained from the sample every two years. Of these women, 3 percent were depot medroxyprogesterone users.

*(Level 2 Evidence)*

### **The Evidence**

Among those using DMPA, there appeared to be a significant decrease in the risk of uterine leiomyomata when compared to non-users of a hormonal contraceptive (Rate Ratio=0.5; 95% confidence interval 0.4 - 0.9).

**Appraised by: The Jordan Evidence Based Medicine-Reproductive Health Group**

**Update by: 15 March 2016**

## **Use of depot medroxyprogesterone acetate does not appear to be associated with an increased risk of pelvic inflammatory disease.**

### **Conclusion**

The use of depot medroxyprogesterone acetate (DMPA) does not appear to result in an increased risk of pelvic inflammatory disease, and it may actually protect women from acute pelvic inflammatory disease. The mechanism of this potentially protective effect is not well understood, but is possibly due to the increase of the viscosity of cervical mucus.

### **Clinical Question**

Is the use of DMPA associated with an increased risk of pelvic inflammatory disease?

### **Search Terms**

Depo-Provera, DMPA, depot medroxyprogesterone acetate, PID, pelvic inflammatory disease

### **Citations**

WHO Task force on Intrauterine Devices. *PID associated with fertility regulating agents*. *Contraception* 1984;30:1-21.

Gray RH. *Letter to the editor: Reduced risk of pelvic inflammatory disease with injectable contraceptives*. *The Lancet* 1985;1(8436):1046.

### **Object of Research**

Depot medroxyprogesterone acetate

### **Research Outcome**

Pelvic inflammatory disease

### **Study Features**

This is a report of a multinational case control study which was conducted in Africa, Asia, South America and Europe by the World Health Organization between March, 1978 and December, 1979. The diagnosis of pelvic inflammatory disease was based on an oral temperature of 38C, suprapubic tenderness with guarding, and cervical or adnexal tenderness, or a pelvic mass

on vaginal examination. 319 acute PID cases were identified. Two controls for each PID case were selected from non-gynecological, non-obstetric patients identified within six months of initial case presentation. Thus, 638 controls were matched with the 319 acute PID cases for parity, age, marital status and inpatients/ outpatients status. (Note that the WHO publication is used to define the study design and population. No DMPA results are provided in this publication.)

*(Level 3 Evidence)*

### **The Evidence**

Of the PID cases, 10 (3.1%) reported current use of injectable contraceptive as compared to 38 (6.0%) controls. The odds ratio of acute pelvic inflammatory disease associated with current injectable contraceptive use was 0.5 (95% CI:0.25-1.0). Though not statistically significant, this suggests that injectable progestin may protect women from acute pelvic inflammatory disease, possibly by increasing the viscosity of cervical mucus.

**Comment:** The reduced risk of PID in users of injectable contraceptives is of similar magnitude to the risks reported for users of combined oral contraceptives, barrier methods and female sterilization in developed and developing countries.

**Developed by:** The Jordan Evidence Based Medicine and Reproductive Health Group

**Update By:** 16 March 2016

# **The association between the use of depot medroxyprogesterone acetate (DMPA) and with weight gain is not clear**

## **Conclusion**

Results from this systematic study of weight gain including depot medroxyprogesterone acetate users are not consistent. For most studies, weight gain among DMPA users was less than 2 kg. Designs without a placebo control make it difficult to assess causality.

## **Clinical Question**

Are women who take DMPA for contraception at an increased risk for weight gain?

## **Search Terms**

DMPA, Depo-Provera depot-medroxyprogesterone acetate, weight gain

## **Citations**

Lopez Lm, Edelman A, Chen-Mok M, Trussell J, Helmerhorst FM. *Progestin-only contraceptives: effects on weight*. Cochrane Database of Systematic Reviews 2011; Issue 4. Art. No.: CD008815. DOI:10.1002/14651858.CD008815.pub2.

## **Object of Research**

Depot medroxyprogesterone acetate

## **Research Outcome**

Weight gain

## **Study Features**

This is a systematic review of different progestin only contraceptives and their effect on weight gain. Ten studies involving DMPA were identified though one is not presented here as it compares interval and postpartum users of DMPA. The primary outcome in these studies was mean change in body

weight. The studies were as follows:

- USA (2009):
- Rhodesia(1976): Two groups, each of 500 women, received DMPA 150 mg every three months or DMPA 450 mg every six months. Weight was measured at each visit.

*(Level 1 Evidence)*

### **The Evidence**

Mean gain among DMPA users was less than 2 kg for most studies up to one year.

**Appraised by:** The Jordan Evidence Based Medicine-Reproductive Health Group

**Update by:** 15 March 2016

## **The use of depot medroxyprogesterone as a contraceptive is not associated with any changes in the incidence of acne.**

### **Conclusion**

When compared with women who were not using a hormonal contraceptive method, there does not appear to be any evidence that depot medroxyprogesterone acetate (DMPA) either increases or decreases acne.

### **Clinical Question**

Is the use of depot medroxyprogesterone acetate contraceptive associated with a decrease in acne?

### **Search Terms**

Depot medroxyprogesterone acetate, acne vulgaris.

### **Citation**

Berenson AB, Odom SD, Breitkopf CR, Rahman M. *Physiologic and psychologic symptoms associated with use of injectable contraception and 20 microg oral contraceptive pills*. Am J Obstet Gynecol. 2008;199:351

### **Object of Research**

Depot medroxyprogesterone acetate

### **Research Outcome**

Acne

### **Study Features**

This a prospective, cohort study of 608 women in which 17 symptoms (including acne) were assessed prior to their initiation of contraception and every 6 months thereafter for 24 months. Of the total of 608 women included in the study, 218 selected oral contraceptive pills, 219 DMPA, and 171 non-hormonal contraception. The 3 groups were similar at baseline with regard to race/ethnicity, age, or income but did differ regarding marital status, education, and parity.

*(Level 2 Evidence)*

**The Evidence**

Relative to women using a non-hormonal method of contraception, those using depot medroxyprogesterone showed neither a decrease nor an increase in the risk of acne [odds ratio=0.99 (95% confidence interval: 0.65-1.51)]. Consistent with other studies, women who had selected an oral contraceptive showed an improvement in their acne symptoms.

**Appraised by:** The Jordan Evidence Based Medicine Reproductive Health Group

**Update by:** 15 March 2016

# **The relationship between depressive symptoms and the use of depot medroxyprogesterone acetate is not clear**

## **Conclusion**

Individual women may experience an increase in depression when they use depot medroxyprogesterone acetate (DMPA). However, data evaluating the impact of DMPA on mood are limited and conflicting. A history of depression is not a contraindication to DMPA user.

## **Clinical Question**

Is the use of depot medroxyprogesterone acetate associated with increased risk of depression?

## **Search Terms**

Depot medroxyprogesterone acetate, DMPA, Depo Provera, depression.

## **Citations**

Westhoff C, Truman C, Kaness D, Cushman L, Davidson A, Rulin M, Heartwell S. *Depressive Symptoms and Depo -Provera*. *Contraception* 1998,57:237-240.

Civic D, Scholes D, Ichikawa L, et al. *Depressive symptoms in users and non- users of Depot Medroxy progesterone acetate*. *Contraception* 2000, 61: 385-390

Gupta N, O'Brien R, et al. *Mood changes in adolescents using Depot-Medroxy progesterone acetate for contraception: A prospective study*. *J. PediatricAdoles Gynecol* (2001) 14: 71-76

## **Object of Research:**

Depot medroxyprogesterone acetate

## **Research Outcome**

Depressive Symptoms.

## **Study Features**

### Westhoff, Truman et al

Women in a prospective multicenter study were evaluated to identify a possible relationship between depressive symptoms and the use of contraceptives. Baseline depressive symptom scores were assessed for users of DMPA, Norplant implants, sterilization and pills. All women were interviewed at 6 month intervals using a closed ended questionnaire. Of the 2,007 women seen at baseline, 495 (24.8%) selected DMPA. Of these 393 (79.4%) completed follow-up whether or not they continued use of their injectable method. They were interviewed at 12 months after study initiation. Overall, 172 (43.8%) continued to use DMPA and 221 (56.2%) discontinued.

*(Level 2 Evidence)*

### Civic et al

This is a prospective, population based study in the United States of 183 women using DMPA and a control group of 274 non-users. The age range was between 18-39 years. Data on depressive symptoms was collected at 6 month intervals for up to three years. The questionnaire included an assessment of the level of depressive symptoms during the last two weeks prior to their evaluation using the Community Epidemiology Survey Depression Scale (CSE-D).

*(Level 2 Evidence)*

### Gupta et al

This a prospective study set in urban hospital, adolescent clinic. Thirty-nine young women who chose DMPA as contraceptive method and 24 who chose not to use any hormonal contraception were enrolled as subjects and controls. Two standard questionnaires were used; the Beck Depression Inventory (BDI) and the Multiple Affect Adjective Checklist –Revised (MAACL-R). These questionnaires were administered at baseline to all participants and at 3, 6, 12 months after the initiation of the study.

*(Level 2 Evidence)*

## **The Evidence**

Westhoff, Truman et al :

Among those who discontinued DMPA, there was no change in depressive symptoms at the 12 month follow-up. Among continuing users, there was a decrease in depressive symptoms from 7.4 at baseline to 6.7 at one year. Among those women who entered the study with depressive symptoms and scored in the highest quintile, there was no increase in these symptoms. In fact, the reverse was true in that they experienced a decrease in scores by several points during the study. That is, the use of DMPA did not exacerbate symptoms in women with pre existing symptoms.

Civic et al:

Relative to non-users, women who discontinued DMPA had elevated depressive symptoms prior to discontinuation (Odds Ratio=1.6; 95% CI = 1.03-2.48). Continuing users also experienced an elevated, though not statistically significant, risk compared to non-users (Odds Ratio=1.44; 95% CI= 1.00-2.07). It should be noted that discontinuers had higher depressive symptoms before they started their contraceptive.

Gupta et al:

Adolescents using DMPA did not show depressive symptoms when over a period of 12 months as measured by two standardized questionnaires (Beck Depressive inventory) and the (Multiple Affect Checklist-revised).

**Appraised by:** The Jordan Evidence Based Medicine-Reproductive Health Group.

**Updated by:** 26 April 2016

# **Use of depot medroxyprogesterone acetate does not appear to be associated with an increased risk of hypertension**

## **Conclusion**

Depot medroxyprogesterone acetate (DMPA) does not appear to be associated with an increased risk of hypertension. Further, DMPA may be the choice of contraception in hypertensive patients as long term use of this injectable should not have any unfavorable effects on blood pressure.

## **Clinical question**

Is the use of depot medroxyprogesterone acetate associated with an increased risk of hypertension?

## **Search Terms**

Depo-Provera, DMPA, depot medroxyprogesterone acetate, hypertension, blood pressure

## **Citations**

Cuong DT, Huong M. *Comparative Phase III clinical trial of two injectable contraceptive preparations, depot-medroxyprogesterone acetate and Cyclofem, in Vietnamese women.* Contraception 1996;54:169-179.

Taneeapanichskul S, Reinorayoon D, Jaisamrarn U. *Effects of DMPA on weight and blood pressure in long term users.* Contraception 1999;59:301-303.

## **Object of Research**

Depot medroxyprogesterone acetate

## **Research Outcome**

Hypertension

## **Study Features**

### Cuong and Huong

This is a comparative study of Vietnamese women randomly assigned to either the one month combined injectable, Cyclofem, or the three month inject-

able, DMPA. Four study centers were involved at which 150 women in each received one of the two injectables.

*(Level 1 Evidence)*

#### Taneepanichskul

This is a case control study conducted in Thailand. The two groups were comprised of 50 DMPA users and 50 non-hormonal IUD users. All had been using their contraceptive for at least 10 years. They were matched for selected sociodemographic characteristics (age, parity, income and life style). All of the users were normotensive at the beginning of the study period. WHO/British Hypertension Society guidelines were used for classifications of blood pressure.

*(Level 3 Evidence)*

#### **The Evidence**

##### Coung and Huong

Both groups experienced a mean drop in blood pressure. In the DMPA group, there was a 1.6 mmHG drop in the systolic blood pressure and 0.5 mmHG drop in the diastolic blood pressure. There were no discontinuations from the study due to changes in blood pressure.

##### Taneepanichskul

Five (10%) users of DMPA developed hypertension compared to 7 (14%) of the IUD users. This difference is not statistically significant. No cases of hypotension were reported. There were no differences in blood pressure changes with long term DMPA or IUD use.

**Developed by:** The Jordan Evidence Based Medicine-Reproductive Health Group

**Update By:** 25 April 2016

# **The use of depot medroxyprogesterone acetate does not increase the risk of myocardial infarction**

## **Conclusion**

The use of depot medroxyprogesterone acetate (DMPA) as a contraceptive does not appear to be associated with significant increase in risk of myocardial infarction.

## **Clinical Question**

Is the use of DMPA as a contraceptive associated with an increased risk of myocardial infarction?

## **Search Terms**

Depot medroxyprogesterone acetate, Depo-Provera, DMPA, myocardial infarction

## **Citation**

The WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. *Cardiovascular disease and use of oral and injectable progestogen-only contraceptives and combined injectable contraceptives. Results of an international, multicenter, case-control study.* Contraception 1998;57:315-324.

## **Object of Research**

Depot medroxyprogesterone acetate.

## **Research Outcome**

Myocardial infarction

## **Study Features**

This is a hospital-based, case-control study which was undertaken in 21 centers in 17 countries subdivided into 4 regions (Africa, Asia, Europe, and Latin America). Eligible cases were women aged 15 – 49 years, who had been admitted to collaborating hospitals between 1 February 1989 and 31 January

1995. The medical history and the findings of examinations and investigations were used to classify acute myocardial infarction cases as definite or possible. Up to 3 control subjects were matched for each case.

Of the 3,697 cases included in the analyses, 364 had suffered a myocardial infarction, of which one case was a current user of DMPA. Cases and controls had similar mean ages, body mass indices, and numbers of live births. The prevalence of DMPA use was highest in Asia (2.6%) and lowest in Europe (0.3%). Crude and adjusted odds ratios associated with the current use of DMPA compared with nonusers were estimated. The odds ratios were adjusted for high blood pressure and smoking categories.

*(Level 3 Evidence)*

### **The Evidence**

Crude and adjusted odds ratios for myocardial infarction in relation to current the use of DMPA were 0.52 (95% CI: 0.06 – 4.38) and 0.66 (95% CI: 0.07 – 6.00) respectively. Based on these findings, there is no apparent risk of myocardial infarction among users of DMPA.

### **Comment**

Though the number of cases included in this study is small, the results provide reassurance that the use of DMPA was not associated with any significant increase in the risk of myocardial infarction. The small number of cases and control subjects in this study may be attributed to low incidence of myocardial infarction in women of childbearing years and in part because of the limited use of DMPA as contraceptive during the years of the study.

**Appraised by:** The Jordan Evidence Based Medicine-Reproductive Health Group

**Update by:** 15 March 2016

## **The use of depot medroxyprogesterone acetate does not increase the risk of stroke**

### **Conclusion**

The use of depot medroxyprogesterone acetate (DMPA) as a contraceptive does not appear to be associated with significant increase in risk of stroke. The results of studies to date provide reassurance that the use of DMPA is not associated with any significant increase in the risk of stroke.

### **Clinical Question**

Is the use of DMPA associated with an increased risk of stroke?

### **Search Terms**

DMPA, Depo-Provera, depot medroxyprogesterone acetate, stroke

### **Citation**

The WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. *Cardiovascular disease and use of oral and injectable progestogen-only contraceptives and combined injectable contraceptives. Results of an international, multicenter, case-control study.* Contraception 1998;57:315-324.

### **Object of Research**

Depot medroxyprogesterone acetate

### **Research Outcome**

Stroke

### **Study Features**

This is multicenter, hospital-based case-control study which was undertaken in 21 centers in 17 countries subdivided into 4 regions (Africa, Asia, Europe, and Latin America). Eligible cases were women within the age 15 – 49 years who had been admitted to a collaborating hospital between 1 February 1989 and 31 January 1993. Cases included hemorrhagic, ischemic, and unspecified types of stroke. For each case, an average of 3 control subjects were found as matches.

Of the 3,697 cases included in the analyses, 2196 had suffered a stroke. Twenty five cases were current users of DMPA. These 25 cases were matched to 81 controls. Cases and controls had similar mean ages, body mass indices, and numbers of live births. The prevalence of DMPA use was highest in Asia (2.6%) and lowest in Europe (0.3%).

*(Level 3 Evidence)*

### **The Evidence**

Crude and adjusted odds ratios for stroke in relation to current use of DMPA were 0.93 (95% CI: 0.58 – 1.48) and 0.89 (95% CI: 0.53 – 1.49), respectively. Based on these results, there is no apparent increased risk of stroke among users of DMPA.

**Comment:** The small number of cases and control subject in this study may be attributed to low incidence of stroke event in women of childbearing years and in part because of the limited use of DMPA as contraceptive during the years of the study.

**Appraised by:** The Jordan Evidence Based Medicine-Reproductive Health Group

**Update by:** 15 March 2016

## **The use of depot medroxyprogesterone acetate as a contraceptive does not appear to be associated with an increased risk of venous thromboembolism.**

### **Conclusion**

The use of depot medroxyprogesterone acetate (DMPA) does not increase the risk of venous thromboembolism. The results of this study provide some reassurance that the use of DMPA is not associated with an increased risk of venous thromboembolism.

### **Clinical Question**

Is the use of DMPA associated with an increased risk of venous thromboembolism?

### **Search Terms**

DMPA, depot medroxyprogesterone, Depo-Provera, venous thromboembolism

### **Citation**

The WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. *Cardiovascular disease and use of oral and injectable progestogen-only contraceptives and combined injectable contraceptives. Results of an international, multicenter, case-control study.* Contraception 1998;57:315-324.

### **Object of Research**

Depot medroxyprogesterone acetate

### **Research Outcome**

Venous thromboembolism

### **Study Features**

This is multicenter, hospital-based case-control study which was undertaken in 21 centers in 17 countries subdivided into 4 regions (Africa, Asia, Europe, and Latin America). Eligible cases were women within the age 15 – 49 years

who had been admitted to a collaborating hospital between 1 February 1989 and 31 January 1993. Cases included those with venous thromboembolism. For each case, an average of 3 control subjects were found as matches.

Of the 3,697 cases included in the analyses, 1137 had suffered venous thromboembolism. Eleven cases were current users of DMPA. These 11 cases were matched to 34 controls. Cases and controls had similar mean ages, body mass indices, and numbers of live births. The prevalence of DMPA use was highest in Asia (2.6%) and lowest in Europe (0.3%).

*(Level 3 Evidence)*

### **The Evidence**

Crude and adjusted odds ratios for venous thromboembolism in relation to current use of DMPA were 1.27 (95% CI: 0.63 – 2.57) and 2.19 (95% CI: 0.66 – 7.26), respectively. Based on these results, there is does not appear to be any increased risk of venous thromboembolism among users of DMPA.

### **Comment**

The small number of cases and control subject in this study may be attributed to low incidence of venous thromboembolism in women of childbearing years and in part because of the limited use of DMPA as contraceptive during the years of the study.

**Appraised by:** The Jordan Evidence Based Medicine-Reproductive Health Group

**Update by:** 15 March 2016

# **There is no association between the use of depot medroxyprogesterone acetate as a contraceptive and the incidence in endometrial cancer**

## **Conclusion**

In this small study, there is not apparent increased risk of endometrial cancer among women using depot medroxyprogesterone acetate (DMPA) for contraception. Suggestions of a possible protective effect require larger studies.

## **Clinical Question**

Is the use of depot medroxyprogesterone acetate associated with an increased risk of endometrial cancer?

## **Search Terms**

DMPA, depot medroxyprogesterone acetate, Depo Provera, endometrial cancer

## **Citation**

Lumbiganon P. *Depo-medroxyprogesterone acetate (DMPA) and cancer of the endometrium and ovary.* Contraception March 1994;49:203-209.

## **Object of Research:**

Depot medroxyprogesterone acetate

## **Research Outcome**

Endometrial cancer

## **Study Features**

This is a review of two studies of the association between DMPA use and endometrial cancer. The first study was conducted in the United States, the second is WHO collaborative study of neoplasia and steroid hormone contraceptives.

US Study/Atlanta, Georgia: This is a record linkage study of 5000 black women receiving DMPA during a period from 1967 to 1976. These women were followed for four to thirteen years after their initial DMPA injection.

WHO Collaborative Study: This is a hospital-based case-control study carried out in 14 centers in 11 countries. However, there were too few cases to assess the association between DMPA and endometrial cancer outside the three studies in Thailand and results are based only on these three. Controls were selected from among women admitted to the same three hospitals other than the obstetric and gynecologic wards.

*(Level 2 Evidence)*

### **The Evidence**

US Study/Atlanta, Georgia: The number of cases found in this study linking hospital records (DMPA users and cancer cases) was too small to make any definitive statement about risk. However, the relative risk for all types of uterine cancer in DMPA users was 1.2 (95% CI: 0.1-6.7). Note that this relative risk was calculated comparing the actual incidence in the 5000 DMPA users with the expected number of uterine cancers in this group (0.83) based on National Cancer Institute estimates.

### WHO Collaborative Study

In this hospital-based, case control study, 122 women with pathologically confirmed endometrial cancer were identified and matched with 939 controls. The adjusted relative risk was 0.21 (95% CI: 0.06-0.79) suggesting a protective effect of DMPA against endometrial cancer among users.

**Appraised by:** The Jordan Evidence Based Medicine Reproductive Health Group

**Update by:** 16 March 2016

## **There is no association between the use of depot medroxyprogesterone acetate (DMPA) as a contraceptive and the incidence in ovarian cancer.**

### **Conclusion**

While there is a suggestion of a protective effect of DMPA for ovarian cancer, there is clearly no increased risk among women using this injectable contraceptive.

### **Clinical Question**

Is the use of depot medroxyprogesterone acetate associated with an increased risk of ovarian cancer?

### **Search Terms**

DMPA, depot medroxyprogesterone acetate, Depo Provera, ovarian cancer

### **Citation**

Lumbiganon P. *Depo-medroxyprogesterone acetate (DMPA) and cancer of the endometrium and ovary.* Contraception March 1994;49;203-209.

### **Object of Research:**

Depot medroxyprogesterone acetate

### **Research Outcome**

Ovarian cancer

### **Study Features**

This is a review of two studies assessing the potential association between DMPA use and ovarian cancer. One study was conducted in the United States while the other was a WHO collaborative study of neoplasia and steroid hormone contraceptives.

US Study/Atlanta, Georgia: This study was based on linking hospital records of 5000 women receiving DMPA during the period 1967 o 1976. These women were followed for four to thirteen years.

WHO Collaborative Study: This was also hospital-based and used a case-control approach. Hospitals were in fourteen different centers and eleven countries. However, there were too few cases to assess the association between DMPA and ovarian cancer outside the three studies in Thailand and one in Mexico. Accordingly the study is based only on these four hospitals. Controls were selected from among women admitted to the same four hospitals other than the obstetric and gynecologic wards.

*(Level 2 Evidence)*

### **The Evidence**

US Study/Atlanta, Georgia: The number of cases found in this study linking hospital records (DMPA users and cancer cases) was too small to make any definitive statement about risk. However, the relative risk for ovarian cancer in DMPA users was 0.8 (95% CI: 0.1-4.6). Note that this relative risk was calculated comparing the actual incidence in the 5000 DMPA users with the expected number of ovarian cancers in this group (1.16) based on National Cancer Institute estimates.

WHO Collaborative Study: In this hospital-based, case control study, 224 women with histologically confirmed epithelial ovarian cancer were found with 1,781 controls. The adjusted relative risk was 1.07 (95% CI: 0.06-1.8) suggesting no increased risk of ovarian cancer among DMPA users.

**Appraised by:** The Jordan Evidence Based Medicine Reproductive Health Group

**Update by:** 16 March 2016

## **The use of depot medroxyprogesterone acetate does not increase the risk of invasive cervical cancer**

### **Conclusion**

Based on the results of these studies, the use of depot medroxyprogesterone acetate (DMPA) as a contraceptive does not appear to be associated with an increase in the risk of invasive carcinoma of the cervix, nor with use of over 12 years. Importantly, the results of these two studies provide reassurance that prolonged use of DMPA does not increase the risk of invasive cervical carcinomas, even after a potential period of non-use over a decade after initiation of DMPA.

### **Clinical Question**

Is the use of depot medroxyprogesterone acetate associated with an increased risk of invasive cervical cancer?

### **Search Terms**

DMPA, depot medroxyprogesterone acetate, Depo-Provera, cervical cancer

### **Citations**

The WHO Collaborative Study of Neoplasia and Steroid Contraception. *Depot medroxyprogesterone acetate (DMPA) and risk of invasive squamous cell cervical cancer*. *Contraception* 1992;45:299-312.

Thomas DB, Ray RM. *Depot-medroxyprogesterone acetate (DMPA) and risk of invasive adenocarcinomas and adenosquamous carcinomas of the uterine cervix*. *The WHO Collaborative Study of Neoplasia and Steroid Contraception*. *Contraception* 1995;52:307-312.

### **Object of Research**

DMPA

### **Research Outcome**

Invasive cervical cancer

## **Study Features**

### WHO Collaborative Group

This is hospital-based case-control study. Cases were 2,009 women with invasive squamous cell cervical cancer and 9,583 controls from Thailand, Mexico and Kenya. Risk factors, such as age, center, total number of pregnancies, number of prior Pap smears, and any use of oral contraceptives were controlled for in the analysis. The relative risk estimates of invasive cervical cancer in relation to months of use, months since first initiation, and months since last use of DMPA were estimated.

*(Level 3 Evidence)*

### Thomas and Ray

This is hospital-based, case control study conducted from October 1979 to September 1988 and included cases and controls from Thailand, Mexico and Kenya. Cases were collected from interviews of 239 women with adenocarcinoma and 85 women with adenosquamous carcinomas, as well as 2,534 controls. The two groups were matched for age, center, parity, year of entry as well as ever use of oral contraception or premenopausal estrogens. The relative risk of adenomatous cervical cancer in women who ever used DMPA was estimated adjusting for known risk factors including sexual behaviors, smoking, genital warts, and months of DMPA use, and months since first and last use of DMPA.

*(Level 3 Evidence)*

## **The Evidence**

### WHO Collaborative Group

- The relative risk of invasive squamous cell cervical carcinoma in women who ever used DMPA was 1.11 (95% CI: 0.96 – 1.29). This is not statistically significant.
- No trends in risk with duration of use or times since initial or most recent exposure were observed.

Thomas and Ray

Calculation of relative risks for adeno- and adenosquamous carcinomas yielded similar results, and accordingly, the two groups were combined.

- The combined relative risk of adeno- and adenosquamous cervical carcinomas in women who ever used DMPA was 0.75 (95% CI: 0.51 – 1.1).
- No trends in risk were observed with duration of DMPA use, time since first or last use, or age at first use.

**Appraised by:** The Jordan Evidence Based Medicine-Reproductive Health Group

**Update by:** 16 March 2016

## **Depot medroxyprogesterone acetate does not appear to increase the risk of breast cancer.**

### **Conclusion**

There was no increase in breast cancer risk in women who had ever been exposed to depot medroxyprogesterone acetate (DMPA). Risk was not increased among current users, in those who had used in the previous 5 years, in those whose first use was before age 25 or 35, and in those used for 24 months. However, one study found that recent users aged 20 to 44 who used DMPA for more than one year had a two-fold increased risk for breast cancer though this finding was not supported in other similar studies.

### **Clinical Question**

Are women who are current or previous users of depot medroxyprogesterone acetate at increased risk for the development of breast cancer?

### **Search Terms**

DMPA, depot medroxyprogesterone acetate, Depo Provera, breast cancer; breast neoplasm

### **Citations**

Strom, BL, et al. *Absence of Injectable and Implantable Progestin-only Contraceptives on Subsequent Risk of Breast Cancer*. *Contraception*, 2004. (69); 353-360.

Li C, Beaber E, Tang M, Porter, P, Daling H, Malone K. *Effect of depo-medroxyprogesterone acetate on breast cancer risk among women 20-44 years of age*. *Cancer Res* 2012;72(8):2028-2035.

### **Object of Study**

Depot medroxyprogesterone acetate

### **Research Outcome**

Breast cancer

### **Study Features**

Strom et al

This is a population-based, multicenter case control study of 4,575 US women who had histologically confirmed breast cancer. Controls were randomly selected from the same geographic area as the cases and were 4,682 in number. Controls had no previous cancer diagnosis and were matched with the cases by age, race and geographic location.

*Evidence Grade: Level 3*

### **Li et al**

This is a population-based case control study of breast cancer among women 20 to 44 years of age in the United States. Cases were women 20 to 44 years of age diagnosed with a primary invasive breast cancer between June 2004 and June 2010 with no previous history of *in situ* or invasive breast cancer. Controls were identified through the Cancer Surveillance System that serves 13 counties of western Washington State. Controls were ascertained via random digit dialing of landline home telephone numbers. Of the 1,359 eligible controls identified, 1,056 (78%) were interviewed. Controls were matched to cases within 5-year age groups to cases with approximately one control for each case. Three groups of controls were defined; never used hormonal contraception (n=91), ever used DMPA (n=100), and ever used hormonal contraception but never used DMPA (n=728).

*Evidence Grade: Level 3*

### **The Evidence**

#### **Strom et al**

A total of 127 subjects were exposed to DMPA (58 cases/69 controls). There was no significant increase in risk for women who had ever been exposed to DMPA. Risk was not increased among current users, defined as women who used DMPA within 1 year of the reference date [Odds Ratio=0.7, 95% CI: 0.4- 1.3], those who initiated use in the 5 years immediately preceding the reference date [Odds Ratio=0.9, 95% CI: 0.5- 1.4], those whose first use was before age 25 [Odds Ratio=1.3, 95% CI: 0.7- 2.3], or those whose use began before age 35 [Odds Ratio=0.9, 95% CI:0.6-1.3]. Risk was significantly reduced among women whose first use was within 1 year of the reference date [Odds Ratio=0.3, 95% CI: 0.07-0.94]. Short-term users ( $\leq 6$  months duration) were at decreased risk relative to never users [Odds Ratio=0.6, 95% CI: 0.4- 1.0]. Among women with at least 24 months of use, risk was not statistically significantly increased relative to never users [Odds Ratio=1.4, 95% CI: 0.8- 2.5].

**Li et al**

A total of 221 subjects were exposed to DMPA (121 cases/100 controls). There was no significant increase in risk for women who had ever been exposed to DMPA [Odds Ratio=1.2, 95% CI: 0.9–1.6], nor in women when the last use was <5years ago [Odds Ratio=1.5, 95% CI: 0.9-2.7]. However, recent users of DMPA for 12 months or longer had a 2.2-fold increased risk of breast cancer (95% CI: 1.2–4.2).

**Appraised by:** The Jordan Evidence Based Medicine-Reproductive Health Group

**Update by:** 16 March 2016

# **The use of depot medroxyprogesterone acetate for contraception does not have any effect on the risk of liver cancer in women**

## **Conclusion**

Exposure to DMPA does not appear to increase a woman's risk of contracting liver cancer.

## **Clinical Question**

Are women who take depot medroxyprogesterone acetate for contraception more likely to get liver cancer than those who do not use it?

## **Search Terms**

Depo medroxyprogesterone acetate, liver cancer

## **Citation**

Mati JG et al. *Depot-medroxyprogesterone acetate (DMPA) and risk of liver cancer*. Int J Cancer 1991;49:182-185.

## **Object of Research**

Depot medroxyprogesterone acetate

## **Research Outcome**

Liver cancer

## **Study Features**

This is a hospital-based, case-control study conducted at three centers in Thailand and one in Kenya. Women more than 15 years of age and who had used a steroid contraceptive during their fertile years were identified through hospital admission records. All women in Thailand with diagnosed liver cancer were histologically confirmed though this was not always the case in Kenya. In all, 71 liver cancer cases were identified and interviewed. Controls from the same hospital were identified though they were not matched individually. In total, there were 530 controls. The data from Thailand and Kenya were analyzed separately because the estimates of the relative risk in ever-users in these countries were so dissimilar. Thus data from these two sites were not combined.

*(Level 3 Evidence)*

**The Evidence**

In Kenya, 18.2% of the cases and 8.5% of the controls had ever used DMPA. In contrast, 8.2% of the cases and 16.8% of the controls in Thailand had used DMPA. Because of this dissimilarity, the relative risk (RR) was calculated separately for each country (Kenya: RR=1.64 95% CI 0.4-6.6, Thailand: RR=0.33 95% CI 0.1-1.0). Neither risk was statistically significant suggesting that there is no likely association between the use of DMPA and liver cancer.

**Appraised by:** The Jordan Evidence Based Medicine-Reproductive Health Group

**Update By:** 16 March 2016

## **For long term use of depot medroxyprogesterone acetate, there may be an increased risk of fracture though the studies are not confirming**

### **Conclusion**

In a study comparing depot medroxyprogesterone acetate (DMPA) users and users of other contraceptives, non-users had lower fracture rates though there is a suggestion that there may be inherent differences in the groups. Further, fracture rates among DMPA users remained similar over time suggesting that no causal effect between loss of bone mass density and the incidence of fractures can be assumed. In a second review of studies assessing the relationship of fractures and DMPA use, there was a consistent pattern showing an increased risk for fractures.

### **Clinical Question**

In a healthy woman of childbearing age, does long term depot medroxyprogesterone acetate (DMPA) use result in significantly increased risk of fractures?

### **Search Terms**

Depot medroxyprogesterone, Depo Provera, DMPA, fractures, bone health

### **Citation**

Lanza L, McQuay L, Rothman K, Bone H, Kaunitz A, Harel Z, Ataher Q, Ross D, Arena P, Wolter K. *Use of depot medroxyprogesterone acetate contraception and incidence of bone fracture*. *Obstet Gynecol* 2013;121(3):593-600.

Lopez L, Chen M, Mullins S, Curtis K, Helmerhorst F. *Steroidal contraceptives and bone fractures in women: evidence from observational studies (Review)*. *Cochrane Database of Systematic Reviews* 2012, Issue 8. Art. No.: CD009849, DOI:10.1002/14651858.CD009849.pub2.

### **Object of Research**

Depot medroxyprogesterone acetate (DMPA)

### **Research Outcome**

Bone mineral density and fracture

## **Study Features**

### Lanza et al

Two cohorts of women, DMPA users and women using non-prescription contraceptives, were selected from the General Practice Research Database. The objective was to compare the incidence of fractures in these two cohorts. Cumulative DMPA exposure for each woman was categorized as low (1 to 7 injections) or high (more than 7 injections). The full cohort included 312,395 women and the subcohort with at least six months of baseline history included 166,637 (53%). The incidence of fracture after initiation of contraception in the sub-cohort was similar to that in the full cohort.

*Evidence Grade: Level 3*

### Lopez et al

This is a review of cohort and case control studies involving steroidal contraceptives and the risk of fracture. Four studies involving depot medroxyprogesterone acetate were identified; two cohort studies and two case control studies though one of the cohort studies did not have a comparable cohort and is not referenced here. The studies were as follows:

- *Kaunitz 2010*: This is a cohort study which included women using DMPA before age 50 and using the UK based General Practice Research Database. Interventions were users of DMPA versus other hormonal contraceptives. The primary outcome was incident fractures.
- *Meir 2010*: This is a case control study using the UK based General Practice Research Database. Interventions were users of DMPA versus other hormonal contraceptives. The primary outcome was incident first time fractures.
- *Vestergaard 2006*: This is a case control study in Demark using the National Hospital Discharge Register. The study includes DMPA users and nonusers of DMPA. The primary outcome was fractures sustained in the year 2000.

*(Level 2 Evidence)*

## **The Evidence**

### Lanza et al

Before starting their contraceptive, the crude fracture rate for DMPA users was 8.4 per 1000 person-years as compared to non-DMPA users of 6.6 per 1000 person years. The difference was statistically significant. After starting their contraceptive, the crude fracture rate was 7.3 per 1000 person-years for non-use of DMPA and 9.1 per 1000 person-years during DMPA use. The crude

incidence rate ratio was 1.37 (95% CI: 1.29-1.45) and the crude incidence rate difference was 2.42 per 1000 person-years (95% CI: 1.94-2.91). Although DMPA users had a higher fracture risk than nonusers, the risk did not increase after DMPA was initiated nor did the fractures in the DMPA group correlate with bone mass density loss.

Lopez et al

- Kaunitz 2010: Overall, DMPA users had a greater risk of fractures with an incident rate ratio of 1.44 (95% CI: 1.38 – 1.50).
- Meier 2010: Current and past users of DMPA were more likely to have a fracture than non users. The odds increased slightly with the number of prescriptions.
- Vestergaard 2006: DMPA ever users were slightly more likely to have a fracture than non users.

**Appraised by:** The Jordan Evidence Based Medicine-Reproductive Health Group

**Update by:** 16 March 2016

## **Among breast feeding women using depot-medroxyprogesterone acetate as a contraceptive, there is no decrease in milk volume nor is the growth of the infant affected**

### **Conclusion**

DMPA is safe as a method of contraception for the infants of breast feeding women as it does not adversely affect milk secretion or infant growth.

### **Clinical Question**

For breastfeeding women, does DMPA affect the volume of breast milk and infant growth?

### **Search Terms**

Depo Provera, depot medroxyprogesterone acetate, DMPA, breast milk composition, infant growth

### **Citation**

World Health Organization (WHO) Task Force on Oral Contraceptives. *Effects of hormonal contraceptives on breast milk composition and infant growth*. Stud Fam Plann. 1988 Nov-Dec;19(6 Pt 1):361-9

### **Object of Research**

Depot medroxyprogesterone acetate

### **Research Outcome**

Infant safety measured by breast milk changes and growth

### **Study Features**

This is a WHO study of breastfeeding women assessing the effect of four contraceptive groups on breast milk volume and composition as well as infant growth. Measurements were taken at three and four week intervals up to six months after delivery. The four groups included two in which the women were randomly assigned to receive either a combined oral contraceptive (COC) or a progestin only pill (POP). A non-random group using non-hor-

monal methods was also studied in three centers (one in Hungary and two in Thailand) and a fourth group at two Thai centers that elected to use depot medroxyprogesterone acetate (DMPA) were also included. Altogether 341 women entered the study and in the two Thai centers, 59 were DMPA users and 83 were non-hormonal controls. Only the DMPA and non-hormonal contraceptive group outcomes are presented here.

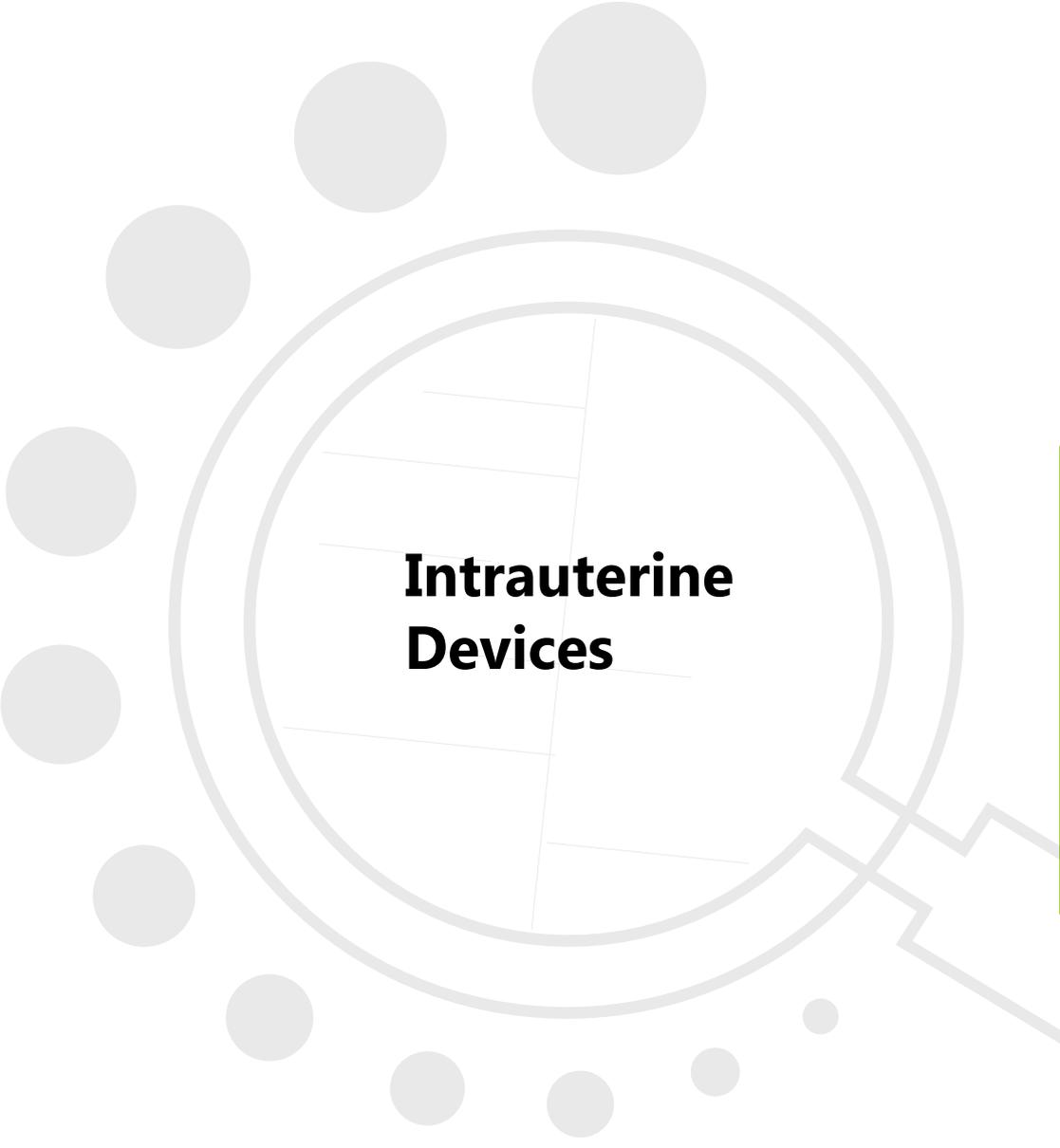
*(Level 2 Evidence)*

### **The Evidence**

Comparing DMPA users and the non-hormonal control group, no significant differences in changes from baseline were noted in milk volume at any of the follow-up visits. At one center, numerical changes from baseline were smaller for the DMPA group while at the other, corresponding changes were smaller for the control group. Only minor shifts occurred in milk composition when compared to controls. Finally, relative to the controls no significant differences in infant weight were noted for DMPA users.

**Appraised by:** The Jordan Evidence Based Medicine and Reproductive Health Group

**Update By:** 16 March 2016



**Intrauterine  
Devices**





## **Intrauterine Contraception**

In Jordan, the primary intrauterine devices available are the Copper T 380A (Cu-IUD) and the levonorgestrel intrauterine system (LNG-IUS) marketed under the commercial name Mirena<sup>®</sup>. Most women can use either of these methods, but health professionals should be aware of the World Health Organization Medical Eligibility Criteria for Contraceptive Use.

### **Effectiveness**

Both the Cu-IUD and LNG-IUS are highly effective in the prevention of pregnancy and continuation rates are high compared to other methods of reversible contraception. The approved life span of the Copper T 380A is ten years and that of the levonorgestrel intrauterine system five years. Duration within this approved use is not associated with any decrease in efficacy.

### **Mode of Action**

The primary mode of action for intrauterine contraception is the prevention of fertilization. It promotes thinning of the endometrium to prevent implantation, inhibits sperm from reaching or fertilizing the egg, and the effect of thickening the cervical mucus prevents sperm from entering the uterus.

### **Advantages of Intrauterine Contraception**

In addition to being highly effective, there are other advantages to the use of intrauterine contraception.

- Reduces the absolute number of ectopic pregnancies
- Easily reversible
- Long lasting
- Convenient
- Cost-effective

## **Disadvantages of Intrauterine Contraception**

- Menstrual cycle disturbances

*Menstrual cycle disturbances are one of the main reasons for discontinuation of the*

*Cu-IUD. Spotting and increased menstrual blood loss are common among those using this method. The LNG-IUS is not associated with the increased menstrual blood loss.*

- Cramping and pain

*Along with bleeding, pain and cramping are also common reasons for discontinuation of the Cu-IUD. Use of ibuprofen does not result in better outcomes as measured by removals.*

- Upper genital tract infections

*During the first 20 days after insertion, there appears to be an increased risk of upper genital tract infections. Antibiotics at the time of insertion have not been found to decrease infections. Over time, the increased risk of infection disappears.*

## REFERENCES

### Intrauterine Devices

1. Department of Statistics [Jordan] and ICF Macro, 2010. *Jordan Population and Family Health Survey 2009*. Calverton, Maryland, USA: Department of Statistics and ICF Macro.
  - World Health Organization. *Medical eligibility criteria for contraceptive use*. Geneva: WHO, 2004.
  - Hatcher RA, Trussell J, Nelson AL, Cates W, Stewart F, Kowal D. *Contraceptive Efficacy*. Contraceptive Technology. New York: Ardent Media Inc, 2008. 747-826.
  - United Nations Development Programme/United Nations Population Fund/World Health Organization/World Bank. *Special Programme of Research, Development and Research Training in Human Reproduction Long-Term Reversible Contraception Twelve Years of Experience With the TCU380A and TCU220C*. Contraception 1997;56:341-362.
  - Hatcher RA, Trussell J, Nelson AL, Cates W, Stewart F, Kowal D. *Combined oral contraceptives*. Contraceptive Technology. New York: Ardent Media Inc, 2008. 197-198.
  - Furlong L. *Pregnancy risk when contraception fails*. J Reprod Med 2002;47(11):881-885.
  - Skjeldestad FE. *The impact of intrauterine devices on subsequent fertility*. Curr Opin Obstet Gynecol 2008;20:275-280.
  - Hubacher D, Lara-Ricalde R, Taylor DJ, Guerra-Infante F, Fuzman-Rodriguez R. *Use of copper intrauterine devices and the risk of tubal infertility among nulligravid women*. N Engl J Med 2001;345:561-567.
  - Doll H, Vessey M, Painter R. *Return of fertility in nulliparous women after discontinuation of the intrauterine device: comparison with women discontinuing other methods of contraception*. Brit J Obstet Gynecol 2001;108:304-314.
  - Hubacher D, Chen P, Park S. *Side effects from the Copper IUD: do they decrease over time?* Contraception 2009;79:356-362.
  - Luukkainen T, Toivonen J. *Levonorgestrel-releasing IUD as a*

*method of contraception with therapeutic properties.* Contraception 1995;52:269-278.

- Hubacher D, Reyes V, Lillo S, et al. *Preventing copper intrauterine device removals due to side effects among first-time users: randomized trial to study the effect of prophylactic ibuprofen.* Human Reproduction 2006;21:1467-1472.
- Grimes D. *Intrauterine device and upper-genital-tract infection.* Lancet 2000; 356:1013-19.
- Grimes DA, Schulz KF. *Antibiotic prophylaxis for intrauterine contraceptive device insertion.* Cochrane Database of Systematic Reviews 1999, Issue 3. Art. No.: CD001327. DOI: 10.1002/14651858.CD001327. Edited/Substantively amended: 13 April 2008

## **List of Critically Appraised Topics**

1. Comparative Efficacy
2. Long Term Use of IUDs
3. Return of Fertility
4. Ectopic Pregnancy
5. Birth Outcomes in Case of IUD Failure
6. Menstrual Cycle Disturbances/Cu-IUD
7. Menstrual Cycle/LNG-IUS
8. Amenorrhea/LNG-IUS
9. Cramping and Pain
10. Prophylactic Use of Ibuprofen
11. Upper Genital Tract Infections
12. Antibiotic Use at Insertion
13. Fibroids
14. Weight Gain/Cu-IUD
15. Weight Gain/LNG-IUS
16. Cervical Cancer
17. Endometrial Cancer
18. Nulliparous Women
19. Postpartum Women
20. Diabetic Women

*Note that the level of evidence accompanying each publication in each of the CATs refers to the study design.*



## **The intrauterine device is one of the most effective contraceptive methods available across different geographic settings**

### **Conclusion**

The intrauterine device (IUD) is an extremely effective method of contraception, especially when compared with other methods, modern or traditional.

### **Clinical Question**

What is the efficacy of the IUD in comparison to other methods?\_

### **Citations**

Trussell J. *Contraceptive failure in the United States* Contraception 2004; 70:89-96.

Department of Statistics (Jordan) and ICF Macro International Inc. *Jordan Population and Family Health Survey 2009*.

El-Zanaty F, Way A. *Egypt Demographic and Health Survey 2008*. El-Zanaty and Associates ,and Macro International. 2009.

### **Object of Research**

IUD, contraceptive efficacy, contraceptive failure

### **Research Outcome**

Contraceptive failure relative to IUD

### **Study Features**

#### Trussell

This is a summary of typical use failure rates of contraceptive users in the United States and is based on the National Surveys of Family Growth conducted by the National Center for Health Statistics in which women aged 15 to 44 were interviewed about topics that included contraceptive use and experience.

*(Level 2 Evidence)*

### Jordan Population and Health Survey

This is a summary of typical use failure rates of contraceptive users in Jordan and is based on a survey conducted in 2009 in which currently women aged 15 to 49 were interviewed about topics that included contraceptive use and experience. Approximately 10,000 women in Jordan were interviewed.

*(Level 2 Evidence)*

### Egypt Demographic and Health Survey

This is a summary of typical use failure rates of contraceptive users in Egypt and is based on a survey conducted in 2008 in which currently women aged 15 to 49 were interviewed about topics that included contraceptive use and experience. Approximately 16,500 women in Egypt were interviewed.

*(Level 2 Evidence)*

### **The Evidence**

The IUD has one of the lowest typical use failure rates of any method with a less than 1 per 100 women users at the end of one year. The failure rate was consistent across the three countries, Jordan, Egypt, and the USA,

Method	Percent of women experiencing an unintended pregnancy during the first year of typical use		
	(Jordan (2009	(Egypt (2008	(USA (1995
Pill	8.1	6.2	8
IUD	1.1	0.9	0.8 <sup>1</sup>
Injectables	1.6	0.9	3
Male Condom	10.1	8.2	15
Lactation Amenorrhea	6.7	Not reported	Not reported
Periodic Abstinence	20.6	Not reported	25
Withdrawal	12.8	Not reported	27

Reported as Copper T. Corresponding percent for the levonorgestrel containing intrauterine system is 0.1.

**Appraised by:** The Jordan Evidence Based Medicine and Reproductive Health Group

**Update by:** 17 March 2016

## **The Copper T-380A IUD is safe and effective for use up to 12 years**

### **Conclusion**

Although Copper T-380A is approved for use in the United States for 10 years and is licensed for use in the United Kingdom for 8 years, it has been shown to maintain its efficacy for 12 years.

### **Clinical Question**

For an IUD user, does the risk of pregnancy increase if she has had the device inserted for more than five years (and it has not been replaced)?

### **Search Terms**

IUD, long-term use

### **Citation**

United Nations Development Programme/United Nations Population Fund/World Health Organization/World Bank. Special Programme of Research, Development and Research Training in Human Reproduction *Long-Term Reversible Contraception Twelve Years of Experience With the TCU380A and TCU220C*. Contraception 1997;56:341-362.

### **Object of Research**

IUD, long-term use

### **Research Outcome**

Long term pregnancy risk

### **Study Features**

This is a study of 12-years of experience with the TCU220C and TCU380A devices from two randomized, multicenter trials conducted in 24 centers. Totals of 3,277 and 1,396 women, respectively, were recruited for use of each device between 1981 and 1986 and followed at 3, 6 and 12 months after insertion and yearly thereafter.

*(Level 1 Evidence)*

**The Evidence**

At the end of 12 years, 17,098 women-years of experience had been accumulated for the TCU220C and 7,159 women-years for the TCU380A. The cumulative 12-year intrauterine pregnancy rates were 7.0 (standard error [SE] 0.6) per 100 women for the TCU220C and 1.9 (SE 0.5) for the TCU380A. The difference was statistically significant ( $p < 0.001$ ). Pregnancy rates were highest in the first year after insertion and the TCU220C had a consistently higher annual pregnancy rate than the TCU380A at all intervals after insertion. No pregnancies were reported with the TCU380A after 8 years of use.

**Appraised by:** The Jordan Evidence Based Medicine Reproductive Health Group

**Update by:** 17 March 2016

# **Copper-T IUD users have no decreased risk of return to fertility**

## **Conclusion**

Studies of women desiring to become pregnant after using an IUD found no increased risk of an inability to become pregnant. However, when compared to those who had used a barrier method, there may be some delay in return. Short-term (less than 3.5 years) IUD use by nulliparous women was not associated with decreased fertility. However, there is a suggestion from one study not corroborated in a second that long term use of more than 78 months may decrease a woman's ability to become pregnant. The WHO listed nulliparity as category 2; that is the benefits outweigh the risks.

## **Clinical Question**

Is there an increase in the risk of infertility among women using an intrauterine device?

## **Search Terms**

Intrauterine device, IUD, infertility, fertility return

## **Citations**

Skjeldestad FE. *The impact of intrauterine devices on subsequent fertility.* Curr Opin Obstet Gynecol 2008;20:275-280.

Hubacher D, Lara-Ricalde R, Taylor DJ, Guerra-Infante F, Fuzman-Rodriguez R. *Use of copper intrauterine devices and the risk of tubal infertility among nulligravid women.* N Engl J Med 2001;345:561-567.

Doll H, Vessey M, Painter R. *Return of fertility in nulliparous women after discontinuation of the intrauterine device: comparison with women discontinuing other methods of contraception.* Brit J Obstet Gynecol 2001;108:304-314.

## **Object of Research**

Intrauterine devices

## **Research Outcome**

Fertility rate, infertility

## **Study Features**

### Skjedestad

This is a systematic review of subsequent fertility among women whose intra-uterine device was removed due to their desire to become pregnant. Women were included if they had either participated in a randomized clinical trials assessing effectiveness of different devices, in a large case series with their device removed in a physician's office, or in large clinic driven studies of contraceptive practice.

*(Level 2 Evidence)*

### Hubacher et al

This is a case-control study of infertile women from three public hospitals in Mexico City. All consecutive nulligravid, infertile women scheduled for diagnostic hystero-salpingography were invited to participate in the study. Infertility was defined as failure to conceive after one or more years of unprotected intercourse. Women with a previous pregnancy, tubal sterilization or previous diagnostic laparoscopy were excluded from the study. In all, 358 women with primary infertility who had tubal occlusion, 953 women with primary infertility who did not have tubal occlusion, and 584 primigravid women (pregnant controls) were enrolled.

*(Level 3 Evidence)*

### Doll et al

This was a prospective cohort study of nulliparous women from 17 family planning clinics in England and Scotland. Three groups of women were studied; 162 using IUDs, 158 oral contraceptive pills, and 238 natural planning and barrier methods.

*(Level 2 Evidence)*

## **The Evidence**

### Skjeldestad

For women recruited from the randomized controlled trials who stopped using an IUD to get pregnant became pregnant, 77 to 87 percent became preg-

nant within 12 months. The corresponding range of rates of those recruited from case series studies was 71 to 86. For those from randomized controlled trials, the three year range of pregnancy rates was 92 to 97. Only one of the case series studies reported a three year pregnancy rate, 94 percent. There was no evidence from these studies that time to conception was influenced duration of use, type of device, parity or age at time of removal.

#### Hubacher et al

Previous use of a copper IUD was not associated with an increased risk of tubal occlusion when compared with either infertile controls [Odds Ratio=1.0; (95% CI 0.6-1.7)] or the pregnant controls [Odds Ratio=0.9; (95% CI 0.5-1.6)]. Additionally, duration of use, removal for side effects, or a history of gynecologic symptoms during the use of the IUD were not associated with an increased risk of tubal occlusion.

#### Doll et al

- After 12 months, 39% of the nulliparous women who had been using an IUD became pregnant and delivered compared to 32% of those who used combined oral contraceptives (COCs), and 54% of those who used natural or barrier methods.
- After 18 months, 67% of the nulliparous women who had been using an IUD had given birth compared to 70% of those using COCs, and 76% of those who used natural or barrier methods.
- Nulliparous women who had used their IUD for 78 or more months (long term users) were less likely to deliver in the first 12 months after removal than nulliparous women who had used their IUD less than 42 months (28% versus 46%). At 36 months after removal, 79 percent of long term users delivered as compared to 91 percent of those using their device for less than 42 months.

**Appraised by:** The Jordan Evidence-Based Medicine Reproductive Health Group

**Update by:** 22 March 2016

**Among current users of intrauterine devices there is an increased risk of an ectopic pregnancy if there is a pregnancy**

### **Conclusion**

Since fewer pregnancies occur for users of contraception, the absolute number of ectopic pregnancies are reduced because there are fewer pregnancies. However, if a pregnancy occurs with either a copper IUD or a levonorgestrel intrauterine system, it is important to rule out the occurrence of an ectopic pregnancy as it appears that the ratio of ectopic pregnancies to intrauterine pregnancies may be increased.

### **Clinical Question**

Is there an increased risk of ectopic pregnancy among women using an IUD?

### **Search Terms**

Intrauterine device, IUD, levonorgestrel intrauterine system, ectopic pregnancy

### **Citation**

Furlong L. *Ectopic pregnancy risk when contraception fails.* J Reprod Med 2002;47:881-885.

### **Object of Research**

Intrauterine devices

### **Research Outcome**

Ectopic pregnancy rate

### **Study Features**

This is a review of data submissions by pharmaceutical companies to the US Food and Drug Administration in support of the applications for approval of their contraceptives. Data were obtained from clinical trials conducted by the companies. The US population rate for ectopic pregnancy was obtained from the Center for Disease Control.

*(Level 2 Evidence)*

## **The Evidence**

For the Copper T IUD, the ratio of ectopic pregnancies to total pregnancies was 1:16 compared to 1:50, the estimate for all pregnancies in the United States. In a large postmarketing study in Finland, 18 ectopic pregnancies out of 232 pregnancies were identified though the copper device brands were not provided. This ratio is 1:13 similar to that found in the original FDA submission.

For the levonorgestrel IUD, the ratio of ectopic pregnancies to total pregnancies is 1:2, but this ratio is based on only 10 pregnancies from their clinical trial studies. Still, from the large Finnish postmarketing study, 44 out of 108 pregnancies yielding a ratio of 1:2.3 consistent with the data submitted to the US Food and Drug Administration.

**Appraised by:** The Jordan EBM Reproductive Health Group

**Update by:** 22 March 2016

# **Pregnancies complicated by an intrauterine device in situ are associated with a greater risk of adverse outcomes**

## **Conclusion**

Women conceiving with an intrauterine device are at increased risk for adverse obstetric outcomes. The risk is higher with a retained intrauterine device compared with early intrauterine device removal. Pregnancies continuing with the IUD retained are more likely to result in a spontaneous abortion than those for who the device was removed or expelled. Thus, early removal reduces the risk of an adverse pregnancy outcome. Even with an early removal, however, the risk of a spontaneous is higher than pregnancies not a result of an IUD failure.

## **Clinical Question**

Does a pregnancy with an intrauterine device in situ increase the risk of adverse pregnancy outcomes?

## **Search Terms**

IUD, pregnancy outcome, birth defects.

## **Citations**

Brahmi D, Steenland MW, Renner RM, et al. *Pregnancy outcomes with an IUD in situ: a systematic review*. Contraception 2012;85:131-139.

## **Object of Research**

Intrauterine device

## **Research Outcome**

Birth defects

## **Study Features**

This is a review article which includes information from studies comparing the IUD retained versus removed, three studies comparing the IUD retained versus removed versus pregnancies conceived without an IUD, and one of the

IUD retained versus pregnancies conceived without an IUD. The studies are: Canada, Puerto Rico, USA: This is a retrospective cohort study from 1970 – 1976. Of 918 pregnancies with an IUD in situ at conception, 275 continued their pregnancies with 157 retaining their IUD and 118 having it removed or it was expelled.

Turkey[1]: This is a retrospective cohort study from 1994-1999. Of 618 pregnancies with an IUD in situ at conception, 89 continued their pregnancies with 26 retaining their IUDs and 56 having it removed or it was expelled.

Turkey[2]: This is a retrospective cohort study from 2009-2010. Of 48 pregnancies with an IUD in situ at conception, 30 retained their IUDs and 18 had it removed or it was expelled.

France[1]: This is a retrospective cohort study from 1979 -1985. Of 157 pregnancies with an IUD in situ at conception, 29 retained their IUDs and 38 had it removed or it was expelled.

France[2]: This is a retrospective cohort study from 1985 -1988. Of pregnancies with an IUD in situ at conception, 12 retained their IUDs and 41 had it removed or it was expelled.

Israel[1]: This is a retrospective cohort study from 1988 -2007. Of pregnancies with an IUD in situ at conception, 98 retained their IUDs and 191 had it removed or it was expelled.

Israel[2]: This is a retrospective cohort study. Of pregnancies with an IUD in situ at conception, 16 had their IUDs removed. These outcomes were compared with 48 pregnancies without an IUD matched for age, parity and gravidity.

Chile: This is a retrospective cohort study from 1997-2007. Of pregnancies with an IUD in situ at conception, 196 retained their IUDs and these were compared to 121,101 pregnant women with no IUD.

***(Level 3 Evidence)***

## The Evidence

The following is a summary of outcomes from these studies.

### Canada, Puerto Rico, USA

IUD retained (n=157)	IUD removed/expelled	(n=118)
Spontaneous Abortion	54%	20%
Preterm Delivery	17%	4%
Live birth	44%	79%
Still birth/neonatal death	2%	1%

### Turkey[1]

IUD retained (n=26)	IUD removed/expelled	(n=56)
Spontaneous Abortion	77%	27%
Preterm Delivery	23%	7%
Still birth/neonatal death	-	-

### Turkey[2]

IUD retained (n=30)	IUD removed/expelled	(n=18)
Spontaneous Abortion	53%	17%
Preterm Delivery	23%	6%
Live birth	-	-
Still birth/neonatal death	-	-
Vaginal bleeding	40%	28%
Placental abruption	7%	0%
Premature rupture (PROM)	40%	0%
Small for gestational age	7%	11%

Chile

	IUD retained (n=196)	No IUD (n=121,101)
Spontaneous abortion	16%	< 1%
Preterm Delivery	56%	< 1%
Premature rupture (PROM)	35%	< 1%
Placental previa	2%	< 1%
Placental abruption	8%	< 1%
Chorioamnionitis	8%	< 1%
Malformations	8%	< 1%
Small for gestational age	5%	< 1%

France[1]

IUD retained (n=29)	IUD removed/expelled (n=38)
Spontaneous Abortion	48% 8%
Septic abortion	7% 0%
Preterm Delivery	* *
Live birth	* *
Vaginal bleeding	* *
Premature rupture (PROM)	* *
*Combined categories	90% 34%

Note: A comparison group of pregnancies with no IUD reported vaginal bleeding in 10% of all cases. 13 percent of all pregnancies conceived with an IUD in situ resulted in a congenital malformation.

France[2]

	IUD retained (n=12)	IUD removed/ expelled (n=41)	No IUD (n=14,442)
Preterm Delivery	25%	17%	7%
Vaginal bleeding	16%	8%	10%
Premature rupture (PROM)	9%	12%	3%
Malformations	9%	2%	7

Israel[1]

	IUD retained (n=98)	IUD removed/ expelled (n=194)	No IUD (n=141,191)
Preterm Delivery	18%	14%	7%
Birth weight < 2.5 kg	11%	13%	7%
Premature rupture (PROM)	10%	8%	6%
Placental previa	4%	4%	4%
Placental abruption	4%	2%	1%
Chorioamnionitis	7%	4%	1%
Malformations	10%	6%	5%

Israel[2]

	IUD retained (n=16)	No IUD (n=48)
Preterm Delivery	19%	2%

**Appraised by:** The Jordan Evidence Based Medicine Reproductive Health Group

**Update by:** 25 March 2016

## **Use of the Copper intrauterine device is associated with an increase in menstrual bleeding.**

### **Conclusion**

The side effect menstrual bleeding and intermenstrual spotting were found to be fairly constant over time. Removal for bleeding and/or pain is a major reason for discontinuation of IUD use.

### **Clinical Question**

Is the use of a Copper IUD associated with an increase in menstrual bleeding and intermenstrual spotting?

### **Search Terms**

Copper IUD, abdominal, cramps and pain.

### **Citation**

Hubacher D, Chen P, Park S. *Side effects from the Copper IUD: do they decrease over time?* Contraception 2009;79:356-362.

### **Object of Research**

Copper IUD

### **Research Outcome**

Menstrual bleeding amount, number days of menstrual bleeding and intermenstrual spotting

### **Study Features**

This is a reanalysis of a prospective study of first-time IUD users. In the original study, 1,962 Chilean women acceptors were randomly assigned to take ibuprofen or a placebo during menses for the first six months of IUD use. In the original analysis, no differences between the two groups were found and consequently this reanalysis is based on the combined groups (ibuprofen

and placebo). In all 1,947 (99%) women, aged 18-49 years of age, provided follow-up information. Five percent of the women were nulliparous. This information consisted of each woman's assessment of the amount of menstrual blood lost during their last menses as compared to that they experienced before IUD use. The number of days of bleeding as well as of spotting was also recorded.

*(Level 2 Evidence)*

### **The Evidence**

In the first 9-week period, 68% of the women reported more menstrual blood loss than the period before insertion. Nearly half of the women reported increased menstrual blood loss at the follow-up visits at 9-19 months, 19-39 months and after 39 months. The average length of their menses remained constant at about 6 over the same period. Almost one quarter of the women noted spotting on at least one day during the same follow-up period.

**Appraised by:** The Jordan Evidence Based Medicine Reproductive Health Group

**Update by:** 17 March 2016

## **Use of the levonorgestrel releasing IUS was associated with a decrease in menstrual bleeding relative to copper intrauterine devices**

### **Conclusion**

The side effect of menstrual bleeding and intermenstrual spotting were found to be less for the levonorgestrel intrauterine system (LNG-IUS) than the Copper T intrauterine device (IUD). Quantitative measurements of menstrual blood loss confirmed this find.

### **Clinical Question**

Is the use of a levonorgestrel IUS associated with a decrease in menstrual bleeding and intermenstrual spotting relative to the Copper T IUD?

### **Search Terms**

LNG-IUS, menstrual bleeding, intermenstrual bleeding.

### **Citation**

Luukkainen T, Toivonen J. *Levonorgestrel-releasing IUD as a method of contraception with therapeutic properties*. Contraception 1995;52:269-278.

### **Object of Research**

LNG-IUS

### **Research Outcome**

Menstrual bleeding amount, number days of menstrual bleeding and intermenstrual spotting, quantitative menstrual blood loss

### **Study Features**

This is a review of seven comparative clinical studies of the LNG-IUS compared with a Cu IUD. Two of these studies included quantitative measurement of menstrual blood loss. The number of days of bleeding and spotting was recorded.

*(Level 2 Evidence)*

**The Evidence**

In early comparative multicenter studies, rates of removal for bleeding in short-term use were similar for the LNG-IUS and the Cu T IUD. However, in a Latin American trial, a lower one year removal rate for bleeding was observed for the LNG-IUS relative to the CU IUD; 0.8 and 7.3, respectively. Other multicenter studies also demonstrated a significant reduction in removal for bleeding for the LNG-IUS compared to the copper IUD control. Quantitative measurement of menstrual blood loss showed a significant reduction in the first year of use for the first year of use and an increase for the other CU IUDs.

**Appraised by:** The Jordan Evidence Based Medicine Reproductive Health Group

**Update by:** 17 March 2016

## **Among users of the levonorgestrel intrauterine system, there an increased risk of amenorrhea relative to non-hormonal IUDs**

### **Conclusion**

Compared to the Copper T 380 Ag intrauterine device (IUD), there is an increased risk of amenorrhea with the use of the levonorgestrel intrauterine system (LNG-IUS). Consideration may be given to counseling potential users that this side effect may be expected.

### **Clinical Question**

Is there an increased risk of amenorrhea with the use of the levonorgestrel IUS?

### **Search Terms**

Levonorgestrel IUS, Mirena<sup>®</sup>, amenorrhea

### **Citation**

French R, Sorhaindo AM, Van Vliet HAAM, Mansour DD, Robinson AA, Logan S, Helmerhorst FM, Guillebaud J, Cowan FM. *Progestogen-releasing intrauterine systems versus other forms of reversible contraceptives for contraception (Review)*. Cochrane Database of Systematic Reviews 2004, Issue 3. Art. No.: CD001776. DOI:10.1002/14651858.CD001776.pub2.

### **Object of Research**

Levonorgestrel IUS

### **Research Outcome**

Incidence of amenorrhea

### **Study Features**

This is a systematic review of randomized controlled trials comparing LNG-20 IUSs (Mirena<sup>®</sup>) with other reversible contraceptive methods. Relative to the occurrence of amenorrhea, only one study comparing non-hormonal IUDs was identified.

*(Level 1 Evidence)*

**The Evidence**

LNG-20 IUS users were more likely to experience a lack of menstrual bleeding than the Copper T380 Ag at three months [Risk Ratio=2.35; (95% CI 1.37-4.04)] and at three years [Risk Ratio=11.08; (95% CI 6.61-18.57)].

**Appraised by:** The Jordan Evidence Based Medicine Reproductive Health Group

**Update by:** 17 March 2016

## **Use of the Copper T IUD is associated with an increase in pelvic pain.**

### **Conclusion**

The side effects of pain and cramping during menses decreases over time including among those of greatest severity. However, removal for pain remains a major reason for discontinuation of IUD use.

### **Clinical Question**

Is the use of a Copper T IUD associated with an increased risk of cramping and pain?

### **Search Terms**

Copper T IUD, abdominal, cramps and pain.

### **Citation**

Hubacher D, Chen P, Park S. *Side effects from the Copper IUD: do they decrease over time?* Contraception 2009;79:356-362.

### **Object of Research**

Copper T IUD

### **Research Outcome**

Abdominal cramping and pain

### **Study Features**

This is a reanalysis of a prospective study of first-time IUD users. In the original study, 1,962 Chilean women acceptors were randomly assigned to take ibuprofen or a placebo during menses for the first six months of IUD use. In the original analysis, no differences between the two groups were found and consequently this reanalysis is based on the combined groups (ibuprofen and placebo). In all, 1,947 (99%) women, aged 18-49 years of age, provided follow-up information. Five percent of the women were nulliparous. Included is a comparison of menstrual pain during their last menses as compared to that they experienced before IUD use.

*(Level 2 Evidence)*

## **The Evidence**

In the first 9-week period, 38% of the women reported more menstrual pain with their IUD compared to the period prior to insertion. At the same time 25% reported less pain. At weeks 9-19, 19-39, and 39 or more, lower percentages of women reported more severe pain (31%, 33%, and 33%, respectively). Over this time period, the number of pain events decreased from 1.1 to 0.3. In all, approximately 9% of all women users had their IUD removed for either pain and/or menstrual bleeding.<sup>1</sup>

<sup>1</sup> Removal rates taken from original study. Hubacher et al. *Preventing copper uterine device removals due to side effects among first time users: randomized trial to study the effect of prophylactic ibuprofen.* Human Reproduction 2006; 21(6): 1467-1472.

**Appraised by:** The Jordan Evidence Based Medicine Reproductive Health Group

**Update by:** 17 March 2016

## **Use of ibuprofen prophylactically to reduce pelvic pain among Copper IUD users does not appear to provide improve removal rates related to pain and/or menstrual bleeding**

### **Conclusion**

The use of ibuprofen to decrease intrauterine device (IUD) removals due to side effects of pain and cramping during menses was not found to have the desired effect. Removal for pain was a major reason for discontinuation of IUD use for both those receiving ibuprofen or a placebo.

### **Clinical Question**

Is the use of prophylactic ibuprofen associated with a reduction of copper IUD removals for side effects associated with pain?

### **Search Terms**

Copper IUD, abdominal, cramps and pain.

### **Citation**

Hubacher D, Reyes V, Lillo S, et al. *Preventing copper intrauterine device removals due to side effects among first-time users: randomized trial to study the effect of prophylactic ibuprofen.* Human Reproduction 2006;21:1467-1472.

### **Object of Research**

Copper IUD

### **Research Outcome**

Removal of IUD due to abdominal cramping and/or pain

### **Study Features**

This is a prospective study of first-time IUD users. In this study, Chilean women acceptors were randomly assigned to take either ibuprofen or a placebo during menses for the first six months of IUD use. In all 2,019 women, aged 18-49 years of age were enrolled in the study with 1,011 randomly as-

signed to receive ibuprofen and 1,008 randomly assigned to receive placebo. Five percent of the women were nulliparous. Follow-up was scheduled for 6, 13, 26, and 52 weeks after insertion. During this time, collected information consisted of menstrual pain during their last menses as compared to that they experienced before IUD insertion.

*(Level 1 Evidence)*

### **The Evidence**

At the end of 6 and 12 months after insertion, removals for all reasons including pain were similar for both groups. In all, approximately 10% of all women users had their IUD removed for either pain and/or menstrual bleeding.

**Appraised by:** The Jordan Evidence Based Medicine Reproductive Health Group

**Update by:** 17 March 2016

## **The use of intrauterine devices is associated with a small increase in the risk of pelvic inflammatory disease with most cases occurring within 20 days after insertion**

### **Conclusion**

Findings suggest that pelvic inflammatory disease (PID) among intrauterine device (IUD) users is most strongly related to the insertion process and to background risks of sexually transmissible disease such as multiple partners. PID is an infrequent event beyond the first 20 days after insertion.

### **Clinical Question**

Is there an increase in the risk of PID among women using an IUD?

### **Search Terms**

Intrauterine device, IUD, pelvic inflammatory disease, PID

### **Citation**

Grimes D. *Intrauterine device and upper-genital-tract infection*. *Lancet* 2000; 356:1013-19.

### **Object of Research**

Intrauterine devices

### **Research Outcome**

Pelvic inflammatory disease

### **Study Features**

This is a systematic review of published evidence concerning IUD-associated infection. Studies included in the review are randomized trials, cohort and case control studies. Because randomization did not include a non-contracepting group, these studies are equivalent to cohort studies.

*(Level 2 Evidence)*

**The Evidence**

In the 1960's a large case control study in the United States showed an inverse relationship between risk and time since insertion; that is as time after insertion increased, the risk of infection decreased. Since that time, another large case control study in the United States found that the risk was restricted to the first 4 months after IUD insertion. By month 5 after insertion, risk was not significantly increased. Finally, in a WHO study, the increased risk was found to be confined to the first 20 days after insertion.

**Appraised by:** The Jordan Evidence-Based Medicine Reproductive Health Group

**Update by:** 23 March 2016

# **The use of antibiotics at the time of insertion of intrauterine devices is not associated with a decrease in the risk of infection**

## **Conclusion**

Based on the results of a systematic review of studies involving the routine use of antibiotics at the time of insertion of an IUD, it appears there is no benefit with regard to a reduced incidence of infection. This finding goes along with the fact that the risk of infection from IUD insertion is minimal.

## **Clinical Question**

Is there a decrease in the risk of infection with the routine use of antibiotics at the time of IUD insertion?

## **Search Terms**

Intrauterine device, pelvic infection, endometritis

## **Citation**

Grimes DA, Schulz KF. *Antibiotic prophylaxis for intrauterine contraceptive device insertion*. Cochrane Database of Systematic Reviews 1999, Issue 3. Art. No.: CD001327. DOI: 10.1002/14651858.CD001327. Edited/Substantively amended: 13 April 2008

## **Object of Research**

Intrauterine devices

## **Research Outcome**

Pelvic and intrauterine infection rates; also unscheduled visits to a clinic

## **Study Features**

The study was a meta-analysis which included only randomized control trials; 4 trials were selected for analysis. Combined, they included almost 5800 women.

*(Level 1 Evidence)*

## **The Evidence**

- There was no significant decrease in the rate of pelvic inflammatory disease (PID) in the 4 studies. (Odds Ratio=0.89, CI 0.53-1.51)
- There was no difference in the rate of IUD removal within 90 days after insertion. (Odds Ratio=1.05, CI 0.68-1.63)
- There was a small decrease in unscheduled clinic visit among those treated with an antibiotic for any reason. (Odds Ratio= 0.82, CI 0.70-0.98).

**Appraised by:** The Jordan Evidence-Based Medicine Reproductive Health Group

**Update by:** 23 March 2016

## **Most women with uterine fibroids without distortion of the uterine cavity can safely use the levonorgestrel releasing intra-uterine system**

### **Conclusion**

The levonorgestrel releasing IUS (LNG-IUS) may be used by women with fibroids that do not have a severely distorted uterine cavity in such a way that insertion is not safely possible. Fibroid and uterine volume, as well as vaginal bleeding, often decline after insertion of the LNG- IUS though women with fibroids may have a higher rate of expulsion than women without fibroids. While no copper device studies were identified in this review, the WHO medical eligibility criteria for insertion of either a copper bearing or levonorgestrel releasing device are the same; that is, use either method under any circumstances when there is no distortion of the uterine cavity. For women with distortion of the uterine cavity, the method is not recommended.

### **Clinical Question**

Does the insertion of an intrauterine device increase the risk of menstrual bleeding or expulsion among women with fibroids?

### **Search Terms**

IUD, LNG-IUS, fibroids

### **Citation**

Zapata LB, Whiteman MK, Tepper NK, Jamieson DJ, Marchbanks PA, Curtis KM. *Intrauterine device use among women with uterine fibroids: a systematic review*. Contraception 2010;82:41-55.

### **Object of Research**

Insertion of the levonorgestrel releasing intrauterine system in women with fibroids

### **Research Outcome**

Increased menstrual bleeding, expulsion rates of a contraceptive device in women with fibroids

## **Study Features**

This is a systematic review of IUD use to evaluate the risk of an IUD insertion in women with uterine fibroids. Eleven studies that met the inclusion criteria were identified, all of which examined outcomes of users of the levonorgestrel-releasing intrauterine system (LNG-IUS). No studies included information on a copper bearing IUD nor were there any studies sufficiently large to assess efficacy of the LNG-IUS in this patient population. All the 11 non-comparative studies (10 prospective, 1 retrospective) included an assessment of uterine bleeding outcomes and eight were identified. Eight of the studies (7 non-comparative prospective and 1 comparative, retrospective study) reported expulsion rates.

*(Level 1 Evidence)*

## **The Evidence**

Evidence from 10 of 11 non comparative studies suggests that LNG-IUD use among women with fibroids does not increase menstrual bleeding. Results from all studies of women who continued use of the device through the entire study period showed that the women had decreased menstrual bleeding. Two cohort studies (1 prospective and 1 retrospective) reported higher rates of LNG-IUD expulsion among women with uterine fibroids (11% in each) than among women without uterine fibroids (0% and 3%). One of the cohort studies also reported a significantly higher rate of expulsion among women with greater uterine volumes (13%) than among women with smaller uterine volumes (0%). Volume size may be a possible proxy for fibroid size.

## **Reviewer's Comment**

After treatment of fibroids by uterine artery embolization, it usually takes the uterus three to six months to reach its new reduced size. As a result, some suggest waiting until there is no evidence of ongoing fibroid necrosis (as evidenced by passage of necrotic tissue or watery discharge), and until the uterus has completed its shrinking process before inserting an IUD after embolization for fibroids.

**Appraised by:** The Jordan Evidence Based Medicine Reproductive Health Group

**Update by:** 24 March 2016

## **The use of a copper intrauterine device may be associated with weight gain**

### **Conclusion**

Users of a copper intrauterine device (IUD) experience a small weight increase over time though whether this is due to device use or aging is not clear. Older women gained more weight than younger women. Parity, decade of IUD insertion and hypertension were not found to be significant determinants of weight variation.

### **Clinical Question**

Is the use of a Copper IUD associated with weight gain?

### **Search Terms**

Copper IUD, weight gain.

### **Citation**

Hassan DF, Petta CA, Aldrighi JM, Bahamondes L, Perrotti M. *Weight variation in a cohort of women using copper IUD for contraception*. *Contraception*. 2003;68(1):27-30.

### **Object of Research**

Copper IUD

### **Research Outcome**

Weight gain

### **Study Features**

This was a retrospective cohort study of 1,697 IUD Brazilian women who had used the Copper T IUD for at least five years and were followed for 7 years of use. Weight measurements were taken at the time of IUD insertion and every year thereafter.

*(Level 3 Evidence)*

**The Evidence**

The mean age of the women at the beginning of follow-up was 27.6 years and the mean height was 150 cm. The mean weight at the time of IUD insertion was 58.5 kg. After 5 and 7 years of follow-up, the mean weight was 61.2 kg and 62.4 kg, respectively. The changes were statistically significant. During the 7 years of follow-up, older women gained more weight than younger women. Parity, decade of IUD insertion and hypertension were not noted to be significant determinants of weight variation.

**Appraised by:** The Jordan Evidence Based Medicine Reproductive Health Group

**Update by:** 23 March 2016

# **Use of the levonorgestrel-releasing intrauterine system does not appear to be associated with a significant increase in body weight**

## **Conclusion**

Though weight gain occurs for users of the levonorgestrel releasing intrauterine system (LNG-IUS) gains are minimal over a five year period.

## **Clinical question**

Is there an association between levonorgestrel-releasing intrauterine system and body weight?

## **Search Terms**

Levonorgestrel-releasing intrauterine system. Body weight

## **Citation**

Yela DA, Monteiro IM, Bahamondes LG, Del Castillo S, Bahamondes MV, Fernandes A. *Weight variation in users of the levonorgestrel-releasing intrauterine system, of the copper IUD and of medroxyprogesterone acetate in Brazil.* Rev Assoc Med Bras, 2006 Jan- Feb: 52(1):32-6.Epub 2006 Apr 10.

## **Object of Research**

Levonorgestrel–releasing intrauterine system (LNG-IUS)

## **Research Outcome**

Body weight changes.

## **Study Features**

This is a prospective cohort study of 163 women users of the LNG- IUS admitted to the study in 1998. Comparisons with the TCU 380A IUD and with depot medroxyprogesterone acetate (DMPA) users were made by matching weight and age to those woman using LNG-IUS. All women were followed for up to five years. Each year weight was measured and their BMI was calculated.

*(Level 2 Evidence)*

**The Evidence**

Weight recorded at the onset of the study was: 62.9 kg, 62.8 kg and 62.5 for the users of the LNG-IUS, the copper IUD and DMPA respectively. Weight increases of 3.1 kg, 4.9, and 8.2 kg were observed at the end of the fifth year among users of the LNG-IUS, the Copper IUD and DMPA, respectively (p=0.009).

**Appraised by:** The Jordan Evidence Based Medicine Reproductive Health Group

**Update by:** 24 March 2016

**Among users of intrauterine devices, there appears to be no increased risk of cervical cancer.**

### **Conclusion**

The data from these studies suggests that IUD use might act as a protective cofactor in cervical carcinogenesis.

### **Clinical Question**

Are women who are using an intrauterine device at an increased risk for cervical cancer?

### **Search Terms**

Intrauterine devices, cervical cancer

### **Citation**

Castellsague X, Diaz M, Vaccarella S et al. *Intrauterine device use, cervical infection with human papillomavirus, and risk of cervical cancer: a pooled analysis of 26 epidemiological studies.* Lancet 2011;12:1023-1031.

### **Object of Research**

Intrauterine devices

### **Research Outcome**

Cervical cancer

### **Study Features**

This is a review of 10 case control studies of cervical cancer done in 8 countries and 16 human papillomavirus (HPV) prevalence studies in 14 countries. In all, 2,205 women with cervical cancer and 2,214 matched controls without cervical cancer were included in the case control studies. In the HPV prevalence studies, 15,272 women were included. Information on intrauterine device use was obtained from personal interviews though the types of IUDs were not identified in the analysis.

*(Level 3 Evidence)*

## **The Evidence**

After adjusting for relevant confounding variables, the following was noted:

- a strong inverse relationship suggesting a protective effect of IUD use was found between ever use of an IUD and cervical cancer (OR=0.55; 95% CI: 0.42 - 0.70)
- a protective association was suggested for IUD use with
  - squamous-cell carcinoma (OR=0.56; 95% CI: 0.43 - 0.72)
  - adenocarcinoma and adenosquamos carcinoma (OR=0.46; 95% CI: 0.22 – 0.97)
- no association among HPV-positive women (OR=0.68; 95% CI: 0.44 – 1.06). This means that no association was found between IUD use and detection of cervical HPV DNA among women without cervical cancer.

Odds ratios (OR) adjusted for potential confounders.

CI=Confidence interval.

**Appraised by:** The Jordan Evidence Based Medicine Reproductive Health Group

**Update by:** 24 March 2016

**Among users of intrauterine devices, there appears to be a protective effect against endometrial cancer.**

### **Conclusion**

In this review of studies involving the use of an IUD, there appears to be a protective effect against endometrial cancer. Data were not sufficient to differentiate between medicated and non-medicated IUDs.

### **Clinical Question**

Are women who are using an intrauterine device at an increased risk for endometrial cancer?

### **Search Terms**

Intrauterine devices, endometrial cancer

### **Citation**

Hubacher D, Grimes DA. *Noncontraceptive health benefits of intrauterine devices: a systematic review.* Obstet Gynecol Surv 2002;57:120-128.

### **Object of Research**

Intrauterine devices

### **Research Outcome**

Endometrial cancer

### **Study Features**

In this review of non-contraceptive benefits of intrauterine devices and the risk of endometrial cancer, six case control studies were identified. One, the steel ring from China is not included here. Both medicated and non-medicated devices were included though sample sizes for the medicated device were too small to draw any definitive conclusions.

*(Level 3 Evidence)*

## The Evidence

Results from the case control studies on endometrial cancer are shown below. Note that all but one of the studies show a suggested or statistically significant protective effect.

Study	Publication Year	Odds Ratio* [95% CI]
Salazar-Martinez et al.	1999	0.4 [0.2–1.0]
Sturgeon et al.	1997	0.6 [0.3–1.0]
Hill et al.	1997	0.6 [0.4–0.9]
Rosenblatt and Thomas	1996	0.7 [0.4–1.3]
Parazzini et al.	1994	0.4 [0.1–1.0]
Castellsague et al.	1993	0.5 [0.3–0.8].

\* Odds ratios adjusted for potential confounders.

CI=Confidence interval.

Based on a sub analysis focusing on the duration and timing of use of the IUD, no consistent pattern emerged to suggest that either of these factors was associated with either an increase or decrease in the risk of endometrial cancer.

**Appraised by:** The Jordan Evidence Based Medicine Reproductive Health Group

**Update by:** 24 March 2016

# **The use of the levonorgestrel releasing intrauterine system and the Copper T380A intrauterine device are safe and effective for nulliparous women seeking intrauterine contraception**

## **Conclusion**

All available copper intrauterine devices (IUD) as well as the levonorgestrel releasing intrauterine system (LNG-IUS) are suitable for nulliparous women though they are more likely to have higher rates of expulsion and removals due to bleeding and pain than women users who have previously been pregnant. Note thought that the results of these studies must be interpreted cautiously as information in the published results is incomplete and sample sizes are small or indeterminate.

## **Clinical Question**

Is the use of a Copper IUD or the LNG-IUS (Mirena®) associated with increased expulsion and removals for bleeding and pain among nulliparous women?

## **Search Terms**

Copper IUD, LNG-IUS, nulliparous women, complication rates.

## **Citations**

Hubacher D. *Copper intrauterine device use by nulliparous women: review of side effects*. *Contraception* 2007; 75:S8-S11.

Suhonen S, Haukkamaa M, Jakobsson T, Rauramo I. *Clinical performance of a levonorgestrel intrauterine system and oral contraceptives in young nulliparous women: a comparative study*. *Contraception* 2004; 69:407-412.

## **Object of Research**

Copper IUD, LNG-20 in nulliparous women

## **Research Outcome**

Expulsion rate, rate of removal for pain and/or bleeding

## **Study Features**

### Hubacher

This is a review of 20 studies comparing insertions of:

- copper devices in parous and nulliparous women and
- different devices in nulliparous women.

All these studies contained information on expulsions and IUD removals for bleeding and pain. The number of women included in each study was not always provided nor was there information on effectiveness in preventing pregnancy.

*(Level 2 Evidence)*

### Suhonen et al

This is a one-year randomized controlled study designed to compare the safety and acceptability of a levonorgestrel intrauterine system and oral contraceptives in young, nulliparous women. The median age of the participants was 21 years in both groups. Women who participated were randomly assigned to receive either an LNG-IUS (n=94) or Marvelon<sup>®</sup>, a combined oral contraceptive (n=99). No pregnancies in either group were reported for either group.

*(Level 1 Evidence)*

## **The Evidence**

### Hubacher

In 13 of the 20 different comparisons, nulliparous women had higher rates of expulsion compared with parous women. Similarly, in 15 of the 20 different comparisons, nulliparous women also had higher rates of removal for bleeding and pain.

### Suhonen et al

During the first year of use, 19 (20%) women discontinued the LNG-IUS and 27 (27%) discontinued their COC. The primary reason for discontinuation among all users of the LNG-IUS users was for bleeding and/or pain (9%) as compared to none for the COC users. There was 1 (1%) expulsion in the

LNG-IUS group of users. Hormonal related adverse effects were responsible for 9 (10%) COC discontinuations and other personal reasons were particularly significant with 14 (15%) discontinuation for this reason.

**Appraised by:** The Jordan Evidence-Based Medicine/Reproductive Health Group

**Update by:** 25 March 2016

## **The Copper T intrauterine device can be inserted safely and effectively immediate postpartum though expulsion rates tend to be higher than when inserted six weeks or more later**

### **Conclusion**

An intrauterine device (IUD) can be inserted immediately after delivery (within 10 minutes) without significantly increasing the risk of adverse effects such as perforation, bleeding, pain and infection. During the postpartum period, it appears that immediate postplacental IUD insertion within 10 minutes has the lowest risk of expulsion among postpartum insertions but remains higher than interval insertion.

### **Clinical Question**

Can an intrauterine device be inserted immediate postpartum?

### **Search Terms**

IUD, postpartum, after delivery

### **Citation**

Kapp N. and K. M. Curtis. *Intrauterine device insertion during the postpartum period: a systematic review*. Contraception 2009. 80(4): 327-336.

### **Object of Research**

IUD

### **Research Outcome**

Complication rates as measured by expulsions and removals.

### **Study Features**

This is a systemic review of studies of IUD insertion during the postpartum period. A total of 10 studies comparing postpartum early or delayed postpartum insertion and 4 comparing postpartum insertion versus interval insertion were selected for review.

*(Level 1 Evidence)*

## **The Evidence**

Results from the six studies are included in this review of postpartum IUD insertion comparing the safety and effectiveness of immediate post partum insertion (within 10 min of placental delivery) with later postpartum insertion.

Eroglu K et al. A prospective cohort study in Turkey compared outcomes among women where insertion of a CuT380A IUD took place within 10 minutes of placental delivery (n=84) with outcomes among those with later insertions (>10 min <72 h, n=46) or with interval insertions (>6 weeks, n=138). After 1 year, the IUD expulsion rate was 36.9% among women with IUDs placed immediately after delivery, 69.8% among those with IUDs placed in the later postpartum period and 6.9% among those with IUDs placed more than 6 weeks postpartum (p<.003). Pregnancy rates among the groups were not different. Nor did the rate of complications differ significantly among the groups. Uterine perforation occurred in 3 (2.3%) of the interval group.

Ricalde et al: A study in Mexico followed 157 women randomly selected to receive the CuT380A or the multiload Cu375 either immediately (within 10 min, n=64) or between 10 min and 48 h after delivery (delayed, n=93). At the one year follow-up, expulsion rates for immediate insertion after cesarean and vaginal delivery (9% and 13%, respectively) did not differ statistically from delayed postpartum insertion (4% and 12%, respectively). No statistical difference was found between the rates of women who removed their IUDs for medical reasons. There were no perforations or pregnancies in any group.

El-Shafei et al: A prospective cohort study in Egypt examined 1,132 women after postpartum insertion of a CuT380A IUD over 3 years: 1,016 insertions occurred within 10 min of placental delivery (immediate) and 116 were placed between 10 min and 48 h after placental delivery (delayed). Follow-up was conducted 4 times during the first year, and 90% of participants returned for at least two follow-up visits. Expulsion rates were 2.4 and 2.6 per 100 women years for the immediate and delayed groups, respectively. The rates were not statistically significant. There were no perforations in either group. Rates of various measures of pain and bleeding were low overall and did not differ between the two groups.

Morrison et al: A prospective cohort study in Kenya and Mali compared infection and expulsion rates among 204 women with immediate postpartum insertion compared to 113 women with later postpartum insertion (>10 min to 72 h after delivery). Expulsions rates were not statistically different between the two groups in both countries. Infections during 6 months were rare overall and did not differ significantly by insertion timing.

Brenner et al: A prospective study of 100 US women received the modified CuT220C (Delta-T IUD) shortly after delivery: 65 insertions were within 10 min, 22 insertions were between 11 and 60 min and 13 women had insertions between 1 h and 55 h following vaginal delivery. Expulsion rates were 8.5% among women who had insertions within 30 min of placental delivery compared with 55.6% among women who had insertions between 31 min to 55 h. No perforations or cervical lacerations occurred.

Chi et al: This is a pooled analysis which examined data from nine sites around the world (one each in Australia, Bangladesh, Brazil, Costa Rica, Panama, Taiwan and Turkey and two sites in Egypt) where IUD insertion occurred less than 10 min after placental delivery compared with data from two sites (Chile and Thailand) where IUD insertion occurred after 2 hours to 23 hours, 24 to 47 hours, and 48 to 72 hours after placental delivery. Different types of IUDs were used. After adjustments for age and parity, the estimated expulsion rate was 9.5% among women with IUD placement less than 10 min after placental delivery compared with 28.8% and 37.3% among those in the later insertion groups ( $p < .001$ ).

The following are expulsion rates of the studies comparing postpartum versus interval insertions

Expulsion rates for interval insertions are significantly lower than for postpartum insertions.

Study Country	Postpart n	.Inter n	Three months		One Year		Greater than one year	
			PP	Int	PP	Int	PP	Int
Mexico	125	125	16%	3%	-	-	-	-
Belgium	562	1,394	-	-	-	-	11% <sup>1</sup>	2%
Belgium/ Netherlands	556	4412	-	-	-	-	9% <sup>2</sup>	3%
Turkey	84	138	-	-	37% <sup>3</sup> 70% <sup>4</sup>	7%	-	-

<sup>1</sup> One year expulsion rates

<sup>2</sup> Four year expulsion rates

<sup>3</sup> Immediate postpartum

<sup>4</sup> Delayed postpartum

**Appraised by:** Jordan Evidence Based Medicine Reproductive Health Group

**Update by:** 27 April 2016

## **Use of an intrauterine device, whether levonorgestrel releasing or a Copper T380A, appears to be safe in women with diabetes mellitus types 1 and 2**

### **Conclusion**

As hormonal contraceptives might influence carbohydrate and lipid metabolism and increases micro-and macro vascular complications, an intrauterine device appears effective, reversible and safe as a method in women with diabetes mellitus types 1 and 2. Note that the WHO recommendations are that the Copper T380A can be inserted in women with diabetes in any circumstance. The recommendation for the levonorgestrel releasing device is the same for women with a history of gestational disease and a recommendation that women can generally use the method in all other cases.

### **Clinical Question**

Can a woman with diabetes safely use an IUD?

### **Search Terms**

IUD, diabetes mellitus.

### **Citations**

Visser J, Snel M, Van Vliet HA. *Hormonal versus non- hormonal contraceptives in women with diabetes mellitus type 1 and 2*. Cochrane Data Base Syst Rev 2006 Oct 18 ;( 4); CD003990.

Kjos SL, Ballagh SA, La Cour M, Xiang A, Mishell DR Jr. *The copper T 380A intrauterine device in women with type II diabetes mellitus*. Obstet Gynecol. 1994 Dec; 84(6); 1006-9.

### **Object of Research**

Intrauterine device

### **Research Outcome**

Worsening of diabetes mellitus condition.

## **Study Features**

### Visser J et al

This is a systematic review of randomized control trials. Only one study involving IUDs was deemed of good methodological quality. It compared the influence of levonorgestrel releasing IUD versus copper-IUD on carbohydrate metabolism with type I diabetes mellitus.

*(Level 1 Evidence)*

### Kjos SL et al

This is prospective study of 176 women with type II or non-insulin dependent diabetes and in whom the copper T380A IUD was inserted. They were followed for five years.

*(Level 2 Evidence)*

## **The Evidence**

### Visser J et al

This study compared the influence of levonorgestrel releasing IUD versus copper-IUD on carbohydrate metabolism with type I diabetes mellitus. No differences were found in daily insulin requirement, glycosylated hemoglobin (HbA1c) or fasting blood sugar after twelve months.

### Kjos SL et al

Sixteen women never returned after their initial insertion so the remaining 160 women comprised the study cohort. Over half the women had the device inserted within three months after giving birth. The continuation rate at the end of three years after insertion was 70% (117). None of the users developed acute salpingitis and the overall removal rates per 100 women-years were as follows: pregnancy (1.57), expulsion (1.96), medical reasons (4.31) and for personal reasons (3.91). The copper T380A IUD appears to be safe and effective in women with type II diabetes when standard criteria for IUD insertion are followed.

**Appraised by:** The Jordan Evidence Based Medicine and Reproductive Health Group

**Update by:** 24 March 2016





# Progestin-Only Pills (POPs)

Progestin-Only Pills



## **PROGESTIN ONLY PILLS**

In Jordan, the proportion of those using the progestin only pill (POP) is not specifically available, but is likely to be less than 1 percent. Most women can use progestin only pills, but health professionals should be aware of the World Health Organization Medical Eligibility Criteria for Contraceptive Use<sup>1</sup>.

### **Effectiveness**

Progestin only pills are highly effective if taken as directed though they are less effective in typical use. Among women who use the POP correctly and consistently, approximately 1 percent will experience a method failure in the first year of use. Typical users though have failure rates as high as 14 percent in the first year<sup>2</sup>. For women who prefer an oral contraceptive, the use of a progestin only pill does not require a rest period. Duration of use is not associated with any decrease in efficacy or safety.

### **Mode of Action**

There are several modes of action of the progestin only pill in preventing pregnancy. It may inhibit ovulation, cause thickening of the cervical mucus thus preventing sperm entry into the upper genital tract, reduce the activity of the cilia in the fallopian tube and perhaps preventing the sperm and egg from meeting, or it may alter the endometrium thus inhibiting implantation of a fertilized egg<sup>3</sup>

### **Advantages of Progestin Only Pills**

In addition to being effective, other advantages to using progestin only pills are:

- there are few contraindications<sup>1</sup>
- the absolute number of ectopic pregnancies are reduced<sup>4</sup>
- it is rapidly reversible<sup>5</sup>
- it is an option throughout reproductive years
- it is a simple, daily fixed regimen.

### **Disadvantages of Progestin Only Pills**

- Requires Daily Administration

*Differences in pregnancy rates of those taking their pill daily versus those who are not consistent users<sup>2</sup> .*

- Menstrual cycle disruption

*Often causes irregular bleeding and spotting during the menstrual cycle<sup>6</sup>*

### **Special Topics**

- Cardiovascular Risks

*POP use is not associated with an elevated risk of any cardiovascular event<sup>7-9</sup>.*

- Cancer

*There is limited information on the use of progestin only pills and any form of cancer.*

- Postpartum Use/Effect on Breastfeeding

*No evidence that use of the POP during breastfeeding affects the health of the infant<sup>10</sup>.*

## REFERENCES

### Progestin Only Pills

- World Health Organization. *Medical eligibility criteria for contraceptive use*. Geneva:WHO, 2004.
- Hatcher RA, Trussell J, Nelson AL, Cates W, Stewart F, Kowal D. *Contraceptive Efficacy*. Contraceptive Technology. New York: Ardent Media Inc, 2008. 747-826.
- Hatcher RA, Trussell J, Nelson AL, Cates W, Stewart F, Kowal D. *Progestin-only pills*. Contraceptive Technology. New York: Ardent Media Inc, 2008. 182-183.
- Furlong L. *Pregnancy risk when contraception fails*. J Reprod Med 2002;47(11):881-885.
- McCann MF, Potter LS. *Progestin-only oral contraception: A comprehensive review*. Contraception 1994;50(Supplement 1), S9-S195.
- Grimes DA, Lopez LM, O'Brien PA, Raymond EG. *Progestin-only pills for contraception*. Cochrane Database of Systematic Reviews 2010, Issue 1. Art.No.:CD007541.DOI: 10.1002/14651858.Cd007541.pub2.
- Chakhtoura Z, Canonico M, Gompel A, Scarabin P, Plu-reau G. *Progestogen-only contraceptives and the risk of myocardial infarction: a meta-analysis*. J Clin Endocrinol Metab 2011; 96:1169-1174.
- Heinemann LA, Assman A, DoMinh T, Garbe E, et al. *Oral progestogen-only contraceptives and cardiovascular risk: results from the Transnational Study on Oral Contraceptives and the Health of Women*. Eur J Contracept Reprod Health Care 1999; 4(2):67-73.
- Heinemann LA, Assman A, DoMinh T, Garbe E, et al. *Oral progestogen-only contraceptives and cardiovascular risk: results from the Transnational Study on Oral Contraceptives and the Health of Women*. Eur J Contracept Reprod Health Care 1999; 4(2):67-73.
- Kapp N, Curtis K, Nanda K. *Progestogen-only contraceptive use among breastfeeding women: a systematic review*. Contraception 2010;82:17-37.

## **List of Critically Appraised Topics**

- 1-Efficacy
- 2-Ectopic Pregnancy
- 3-Return to Fertility
- 4-Menstrual Blood Loss
- 5-Amenorrhea
- 6-Weight Gain
- 7-Nausea
- 8-Acne
- 9- Breast Tenderness
- 10-Ovarian Cysts
- 11-Headache
- 12-Hypertension
- 13-Myocardial Infarction
- 14-Stroke
- 15--Venous Thromboembolism
- 16-Breastfeeding

*Note that the level of evidence accompanying each publication in each of the CATs refers to the study design.*

## **Progestin only pills (POPs) are effective contraceptives in both breastfeeding and non-breastfeeding women when used correctly and consistently.**

### **Conclusion**

Among studies of progestin-only pills, no significant differences among the different progestins were found with respect to contraceptive effectiveness. However, it should be noted that none of the studies comparing one progestin with another were sufficient in sample size to differentiate between different progestins. Despite these limitations, it appears that when used correctly, progestin-only pills are effective in preventing pregnancy.

### **Clinical Question**

Is the progestin-only pill effective contraception for women?

### **Search Terms**

Progestogen-only pill, effectiveness

### **Citations**

Grimes DA, Lopez LM, O'Brien PA, Raymond EG. *Progestin-only pills for contraception (Review)*. Cochrane Database of Systematic Reviews 2011, Issue 7. Art. No.: CD007541. DOI: 10.1002/14651858.Cd007541.pub2.

### **Object of Research**

Progestin-only pills

### **Research Outcome**

Pregnancy in breastfeeding and non-breastfeeding women

### **Study Features**

This is a review of six randomized controlled trials designed to assess the efficacy of progestin-only pills as a contraceptive. These studies included 2,738 participants both breastfeeding and non-breastfeeding, and their sample sizes ranged from 86 to 1,320 women. Approximately 1 in 5 of these women were

breastfeeding and had not returned to menses. Trial locations included European countries, the United Kingdom, the United States, India, China, South Africa, Nigeria, and Kenya. Comparisons were made between progestin-only pills, between progestin-only pills and combined oral contraceptives, as well as the timing of pill start (six weeks or six months postpartum). It should be noted that none of the studies were of sufficient size to differentiate between any of the contraceptive methods in terms of accidental pregnancy rates.

*(Level 1 Evidence)*

### **The Evidence**

The results for the pill comparisons were:

- no differences were found between the progestin-only pills containing desogestrel and levonorgestrel (rate ratio=0.27; 95% CI: 0.06-1.19). The Pearl Index excluding gross non-compliance was 0.14 for the desogestrel group and 1.17 for the levonorgestrel group.<sup>1</sup>
- no differences were found between progestin-only pills with mifepristone or those containing levonorgestrel (odds ratio=0.71; 95% CI: 0.07-6.95).
- in a WHO four-pill comparison, one year pregnancy rates were numerically highest with the progestin-only pill norethisterone 350 µg and lowest with the combination pill containing levonorgestrel 150 µg and ethinyl estradiol 30µg. At 360 days, the cumulative discontinuation rate for accidental pregnancy was lower with combined levonorgestrel and ethinyl estradiol (2.7%) than with the other pills: levonorgestrel alone (9.5%), combined norethisterone and mestranol (8.3%), and norethisterone alone (13.2%). No statistically significant differences were noted among the four regimens though the study was not planned with sufficient sample size to detect expected small differences.
- in a small study of the progestin-only pill containing ethynodiol versus a combined oral contraceptive, no pregnancies were reported.

In one study in which the comparison was of a progestin-only pill taken at 6 weeks postpartum versus the same pill taken 6 months, postpartum, no differences in pregnancy rates were noted.

Collaborative Study Group on the Desogestrel-containing progesterone- only pill. *A double- blind study comparing the contraceptive efficacy, acceptability and safety of two progesterone-only pills containing desogestrel 75 mcg/day and levonorgestrel 30 mcg/day.*

Eur Jour of Contracep and Reprod Health Care 1998;3:169-178

**Appraised by:** The Jordan Evidence-Based Medicine Reproductive Health Group

**Update by:** 30 March 2016

## **Use of progestin-only pills (POPs) does not increase absolute number of ectopic pregnancies, but if there is a method failure, an ectopic pregnancy should be ruled out.**

### **Conclusion**

Among women using a progestin-only pill, there does not appear to be an increase in the ectopic pregnancy rate. While precise rates are difficult to estimate given the small number of POP users worldwide and the subsequent decrease in pregnancies, like all contraceptives, the absolute number of ectopic pregnancies does not increase as a result of the overall reduction of pregnancies. Note however though the absolute numbers of ectopic pregnancies is decreased, should a pregnancy occur while using a POP, there is a greater likelihood that it is ectopic than with other contraceptive methods. However, a history of ectopic pregnancy need not be considered a contraindication to POP use.

### **Clinical Question**

Is there an increase in the risk of ectopic pregnancies among women taking progestin only pills?

### **Search Terms**

Progestin-only pills, progestin-only oral contraceptives, ectopic pregnancy

### **Citations**

Furlong L. “*Ectopic Pregnancy Risk When Contraception Fails: A Review*”  
The Journal of Reproductive Medicine 2002;11(47):881-885.

### **Object of Research**

Progestin-only pills

### **Research Outcome**

Ectopic pregnancy

### **Study Features**

This is a review of seven contraceptives including combined oral contraceptives. Data were abstracted from reviews of clinical trials submitted to the United States Food and Drug Administration.

*(Level 2 Evidence)*

### **The Evidence**

The proportion of ectopic pregnancies among all pregnancies is 1:20 for users of progestin-only pills as compared to an estimate of 1:50 in women in the United States not using a contraceptive method.

**Appraised by:** The Jordan Evidence Based Medicine Reproductive Health Group

**Update by:** 22 April 2016

## **There is no apparent association between use of progestin only pills (POPs) and delays in return to fertility after their cessation**

### **Conclusion**

Data on return to fertility for progestin only pills is sparse. However, available studies suggest that the cumulative rate of pregnancy for fertile women previously using a progestin only pill did not differ from that observed in fertile women who attempted to become pregnant without prior contraception.

### **Clinical Question**

Is there a decrease in conception rate after cessation of a progestin only pill for contraception?

### **Search Terms**

Progestin only pill, POP, return to fertility, conception rate.

### **Citation**

McCann MF, Potter LS. *Progestin-only oral contraception: A comprehensive review*. Contraception 1994;50(Supplement 1), S9-S195.

### **Object of Research**

Progestin only pills

### **Research Outcome**

Conception after termination of progestin-only pills

### **Study Features**

This is a literature review of earlier use of POPs (pre-1994) and return to fertility. The review includes

- 6 women in a study in the United Kingdom stopped use of their POP (norgestrel) in order to become pregnant, two within one cycle of use and the others after a period ranging from two to six months.

- 43 women in a study in the United Kingdom stopped use of their POP (norethisterone 0.35 mg)
- 83 women using a progestin-only pill in a study in the United Kingdom stopped use of their POP.

*(Level 2 Evidence)*

### **The Evidence**

From the results of these studies, there does not appear to be any significant delay in return to fertility among women stopping their POP to become pregnant.

- In the study of 6 women, all these women became pregnant within six months, two of them within the first month
- In the study of 43 women using norethisterone 0.35 mg/day, the majority became pregnant within three months and 10 took longer than six months. The remainder of these women became pregnant between three and six months.
- In a study of 83 POP users, return to fertility was similar to those who stopped using a diaphragm to become pregnant.

**Appraised by:** The Jordan Evidence Based Medicine Reproductive Health Group

**Update by:** 30 March 2016

## **Use of a progestin only pill (POP) often results in menstrual cycle changes primarily in irregular bleeding or spotting.**

### **Conclusion**

Progestin-only pills are associated with more bleeding disturbances than combined oral contraceptives and discontinuation for this reason can be as high as 10 percent in the first year of use. Among the different progestins, desogestrel was associated with more bleeding problems than the pill containing levonorgestrel.

### **Clinical Question**

Do women who are not breastfeeding, but using progestin only pills, at higher risk of menstrual bleeding disturbances?

### **Search Terms**

Progestin-only pill, vaginal bleeding

### **Citations**

Grimes DA, Lopez LM, O'Brien PA, Raymond EG. *Progestin-only pills for contraception*. Cochrane Database of Systematic Reviews 2010, Issue 1. Art. No.:CD007541.DOI: 10.1002/14651858.Cd007541.pub2.

### **Object of Research**

Progestin-only pills

### **Research Outcome**

Bleeding disturbances

### **Study Features**

This systematic review examined six randomized controlled trials of progestin-only pills for differences in efficacy, acceptability, continuation rates, and bleeding disturbances. The POPs included in these studies contained one of the following progestins; levonorgestrel 35 mcg and 30 mcg, desogestrel 75

mcg, mifepristone 5 mg, ethynodiol diacetate 0.25 mg, norethisterone 350 mcg, norethisterone acetate 300 mcg and megestrol acetate 700 mcg. The trials enrolled 2738 participants, and sample sizes in the six studies ranged from 86 to 1306 women. Trial locations included European countries, United Kingdom, United States, India, China, South Africa, Nigeria, and Kenya. (*Level 1 Evidence*)

### **The Evidence**

In the trial comparing the desogestrel versus levonorgestrel progestin-only pill, desogestrel was associated with more bleeding disturbances than levonorgestrel. Discontinuation because of irregular bleeding was somewhat more common (rate ratio=1.32; 95% CI: 0.99-1.78) though the difference was not statistically significant.

The trial comparing low-dose mifepristone versus a levonorgestrel progestin-only pill resulted in a higher prevalence of amenorrhea in the former group; about half of women assigned to mifepristone had no bleeding while taking the drug.

In the trial which included a progestin-only pill at a dosage level not currently available, bleeding irregularities were more common with the progestin-only pill than with the combined oral contraceptive. Irregular cycles occurred significantly more often in women assigned to the progestin-only pill in contrast to those assigned to the COC (odds ratio 135.96; 95% CI: 7.63 - 2421.02). Bleeding between menstrual periods was also significantly more common with the progestin-only pill (odds ratio= 6.20; 95% CI: 2.11-18.22)

In the WHO four-pill comparison study, the four pills (two progestin-only, two combined oral contraceptives) included norethisterone 350 µg, levonorgestrel 30 µg, norethisterone 1mg plus mestranol 50 µg, and levonorgestrel 150 µg plus ethinyl estradiol 30 µg). At 360 days, the cumulative discontinuation rate for bleeding disturbances was lower with combined levonorgestrel and ethinyl estradiol (9.7%) than with the other pills: combined norethisterone

and mestranol (23.2%), norethisterone alone (24.2%), and levonorgestrel alone (26.0%).

In the fourth trial, discontinuation related to menstrual disturbances was significantly less common with norethisterone acetate (rate ratio=0.30; 95% CI: 0.15-0.62), than with norgestrel.

**Appraised by:** The Jordan Evidence Based Medicine Reproductive Health Group

**Update by:** 7 April 2016

## **Use of a progestin-only pill among non-breastfeeding women may be associated with amenorrhea.**

### **Conclusion**

Among progestin only pill users, complaints and reasons for discontinuation of their contraceptive include amenorrhea.

### **Clinical Question**

Is there an increase in amenorrhea among women taking progestin only pills?

### **Search Terms**

Progestin-only pills, progestin-only oral contraceptives, amenorrhea

### **Citations**

Broome M, Fotherby K. *Clinical experience with the progesterone-only pill.* Contraception 1990;42(5): 498-495.

Collaborative Study Group on the Desogestrel-containing Progestogen-only Pill. "A double-blind study comparing the contraceptive efficacy, acceptability and safety of two progestogen-only pills containing desogestrel 75 micrograms/day or levonorgestrel 30 micrograms/day" Eur J Contracept Reprod Health Care 1998 Dec;3(4):169-78.

### **Object of Research**

Progestin-only pills

### **Research Outcome**

Amenorrhea

### **Study Features**

#### Broome et al

This was a study of 358 progestogen-only pills users at a clinic in England. Data were abstracted from clinic records. The POPs used contained either ethynodiol diacetate 500 mcg, norethisterone 350 mcg or levonorgestrel 30 mcg. The women in this study used their selected POP for up to 150 months with 34 (9.5%) using theirs for less than 6 months.

*(Level 3 Evidence)*

### Collaborative Group

This was a randomized, double-blind study of progestin-only pills in which 989 women were assigned to the desogestrel 75 mcg group and 331 to the levonorgestrel 30 mcg group. Women were observed for thirteen 28-day cycles. Bleeding patterns for non-breastfeeding and those for breastfeeding women were analyzed separately as lactation may affect the bleeding pattern. (*Level 1 Evidence*)

### **The Evidence**

#### Broome et al

Of those women using their POP for more than six months, 25 (7.7%) reported mostly amenorrhea, 29 (9.0%) reported a mixture of regular cycles and amenorrhea, and 20 (6.2%) reported a mixture of irregular cycles and amenorrhea. And 3 (0.9%) others reported a mixture of regular or irregular cycles and amenorrhea.

### Collaborative Group

The incidence of amenorrhea was 3.4 times higher with the desogestrel group as compared to those using the levonorgestrel pill. Within this group, women who switched from another contraceptive to a progestin-only pill experienced a higher incidence of amenorrhea than those who were starting this regimen without an immediate prior contraceptive. Note that among the 28 desogestrel users who experienced amenorrhea during the period of 29 to 118 days, 70 percent would also report amenorrhea in the period from 299 to 388 days.

**Appraised by:** The Jordan Evidence Based Medicine Reproductive Health Group

**Update by:** 7 April 2016

**There is no apparent association between the use of a progestin only pill contraceptive and weight gain though there is insufficient information on which to make a definitive statement.**

### **Conclusion**

Significant changes in weight were not a factor in discontinuation of the use of the progestin only pill. Nor were significant weight gains noted in these randomized controlled trials. However, small sample sizes and lack of a placebo control in these studies make it difficult to make any definitive statement about association of the use of progestin only pills and weight gain.

### **Clinical Question**

Is there a use of a progestin only pill for contraception associated with weight gain?

### **Search Terms**

Progestin only pill, POP, weight gain

### **Citations**

Collaborative Study Group on the Desogestrel-containing progesterone-only pill. *A double-blind study comparing the contraceptive efficacy, acceptability and safety of two progesterone-only pills containing desogestrel 75 mcg/day and levonorgestrel 30 mcg/day.*

Eur J Contracept Reprod Health Care 1998;3:169-178

Lopez LM, Edelman a, Chen M, Otterness C, Trussel J, Helmerhorst FM. *Progestin-only contraceptives effects on weight.* Cochrane Database of Systematic Reviews 2013, Issue 7. Art. No.: CD008815.DOI: 10.1002/14651858.CD00815.pub3.

### **Object of Research**

Progestin only pills

### **Research Outcome**

Weight gain

## **Study Features**

### Collaborative Group

This is a double-blind comparison of two progestin-only pills, one containing desogestrel 75 mcg/day (n=979) and the other levonorgestrel 30 mcg/day (n=329). Weight measurements were routinely recorded at each visit during the study.

*(Level 1 Evidence)*

### Lopez et al

This is a systematic review of the association between progestin-only contraceptives and weight gain. Only one study involving a progestin-only pill was identified, this of a comparison of norethisterone 350 mcg and levonorgestrel 30 mcg. The study was a randomized controlled trial involving 51 women in England, 17 to 41 years of age.

*(Level 1 Evidence)*

## **The Evidence**

### Collaborative Group

With respect to weight changes, no differences between treatment groups nor significant changes from baseline body weight were noted during the study. Less than 3% of all women in the study reported weight gain as an adverse event.

### Lopez et al

Weight change from baseline was small and, at six months, there were no significant differences between the two groups. The small sample sizes of the two groups are a significant weakness of the study.

**Appraised by:** The Jordan Evidence Based medicine Reproductive Health Group

**Update by:** 7 April 2016

**While women using a progestin-only pill for contraception experience some nausea, current study designs do not allow an assessment of causality.**

### **Conclusion**

Among progestin only pill users, complaints and reasons for discontinuation of their contraceptive include nausea. The proportion of users of POPs who reported nausea is less than 5 percent. The extent to which nausea is caused by their pill use cannot be determined from the available data.

### **Clinical Question**

Is there an increase in nausea among women taking progestin only pills?

### **Search Terms**

Progestin-only pills, progestin-only oral contraceptives, nausea, gastrointestinal distress

### **Citations**

Collaborative Study Group on the Desogestrel-containing Progestogen-only Pill. *A double-blind study comparing the contraceptive efficacy, acceptability and safety of two progestogen-only pills containing desogestrel 75 micrograms/day or levonorgestrel 30 micrograms/day.* Eur J Contracept Reprod Health Care 1988 Dec;3(4):169-78.

McCann MF, Potter LS. *Progestin-only oral contraception: A comprehensive review.* Contraception 1994;50(Supplement 1), S9-S195.

### **Object of research**

Progestin-only pills

### **Research Outcome**

Nausea

## **Study Features**

### Collaborative Group

This is a randomized, double-blind study of progestin-only pills in which 989 women were assigned to the desorgestrel 75 mcg group and 331 to the levonorgestrel 30 mcg group. Women were observed for 13 28-day cycles.

*(Level 1 Evidence)*

### McCann and Potter

This is a review of 8 selected studies that included information about discontinuation of a progestin only pill due to a non-menstrual side effect. Of these, six were prospective and contained discontinuation rates for either nausea or gastrointestinal distress. Two of these reported discontinuation for non-menstrual side effects as a group and were also excluded from this assessment.

The four studies included are as follows:

- England (1977): This is a prospective study with one year follow-up of three progestins; norethisterone 0.35 mg (n=200), chlormadinone acetate 0.5 mg (n=182), and mesgestrol acetate 0.5 mg (n=174). Most users were less than six months postpartum though reports about breastfeeding were not included.
- United States (1974): This was an open label study of 2,202 women using norgestrel 0.075 mg studied from 1 to 67 cycles.
- UK, Jamaica, New Zealand (1982): This is multicenter study of norethisterone 0.35 mg of 913 women. The median age of these women was 27 and ranged from 16 to 54 years of age.
- England (1972): These data were obtained as part of the continuing follow-up of contraceptive users in the Oxford Family Planning Association. Only data from the norethisterone users (1746 women years of use) are provided in the publication. The study included other contraceptive users of both hormonal and non-hormonal methods.

*(Level 1 Evidence)*

## **The Evidence**

### Collaborative Group

3.3 percent of the women in the desogestrel group reported nausea as an adverse event as compared to 1.5% in the levonorgestrel group.

### McCann and Potter

In the five studies, results were:

- England: Less than 1 percent of the norethisterone and megestrol acetate users discontinued for nausea. 1 percent of the chlormadinone acetate users discontinued for nausea.
- United States: Less than 1 percent of the users of norgestrel discontinued because of gastrointestinal distress.
- UK, Jamaica, New Zealand: No discontinuations were reported for nausea or gastrointestinal distress.
- England/Oxford follow-up study: Approximately 3 percent of all norethisterone users discontinued because of gastrointestinal distress as compared to 1 percent of those using all other contraceptives included in the follow-up. Note that these included both hormonal and non-hormonal contraceptives.

**Appraised by:** The Jordan Evidence Based Medicine Reproductive Health Group

**Update by:** 9 April 2016

## **Women using a progestin-only pill for contraception experience acne infrequently.**

### **Conclusion**

Among progestin only pill users, complaints and reasons for their discontinuation infrequently includes an increase in acne. But, unlike use of the combined oral contraceptive, the effect of a progestin only pill in decreasing acne is not clear.

### **Clinical Question**

Is there an increase in acne episodes among women taking progestin only pills?

### **Search Terms**

Progestin-only pills, progestin-only oral contraceptives, acne

### **Citations**

Collaborative Study Group on the Desogestrel-containing Progestogen-only Pill. *A double-blind study comparing the contraceptive efficacy, acceptability and safety of two progestogen-only pills containing desogestrel 75 micrograms/day or levonorgestrel 30 micrograms/day.* *Eur J Contracept Reprod Health Care* 1988 Dec;3(4):169-78.

McCann MF, Potter LS. *Progestin-only oral contraception: A comprehensive review* *Contraception* 1994;50(Supplement 1), S9-S195.

### **Object of Research**

Progestin-only pills

### **Research Outcome**

Acne

### **Study Features**

#### Collaborative Group

This is a randomized, double-blind study of progestin-only pills in which 989 women were assigned to the desogestrel 75 mcg group and 331 to the levonorgestrel 30 mcg group. Women were observed for 13 28-day cycles. (*Level 1 Evidence*)

## **Study Features (continued)**

### McCann and Potter

This is a review of 8 selected studies that included information about discontinuation of a progestin only pill due to a non-menstrual side effect. Of these, six were prospective and contained discontinuation rates for side effects. Two of these reported discontinuation for non-menstrual side effects as a group and were excluded from this assessment. The four remaining studies are:

- England (1977): This is a prospective study with one year follow-up of three progestins; norethisterone 0.35 mg (n=200), chlormadinone acetate 0.5 mg (n=182), and mesgestrol acetate 0.5 mg (n=174). Most users were less than six months postpartum though reports about breastfeeding were not included.
- United States (1974): This was an open label study of 2,202 women using norgestrel 0.075 mg studied from 1 to 67 cycles.
- UK, Jamaica, New Zealand (1982): This is multicenter study of norethisterone 0.35 mg of 913 women. The median age of these women was 27 and ranged from 16 to 54 years of age.
- England (1972): These data were obtained as part of the continuing follow-up of contraceptive users in the Oxford Family Planning Association. Only data from the norethisterone users (1746 women years of use) were provided. The study included other contraceptive users of both hormonal and non-hormonal methods though these were combined.

### *(Level 1 Evidence)*

## **The Evidence**

### Collaborative Group

3.1 percent of the women in the desogestrel group reported acne as an adverse event as compared to 4.0% in the levonorgestrel group.

### McCann and Potter

In the four studies, results were:

- England: There were no reports of discontinuation as a result of an acne episode in any of the progestin only pill user groups.

- United States: Less than ½ of a percent of the users of norgestrel discontinued because of an acne episode.
- UK, Jamaica, New Zealand: No discontinuations were reported for acne though there was one discontinuation for an unspecified skin complaint.
- England/Oxford follow-up study: There were no reports of discontinuation as a result of an acne episode in any of the progestin only pill user groups.

**Appraised by:** The Jordan Based Evidence Based Medicine Reproductive Health Group

**Update by:** 4 April 2016

## **Women using a progestin-only pill for contraception do not appear to experience elevated levels of breast tenderness.**

### **Conclusion**

Among progestin only pill (POP) users, complaints and reasons for discontinuation of their contraceptive include breast tenderness. However, the effect of a progestin only pill on increasing breast tenderness is not clear based on available data.

### **Clinical Question**

Is there an increase in breast tenderness among women taking progestin only pills?

### **Search Terms**

Progestin-only pills, progestin-only oral contraceptives, breast tenderness, breast pain

### **Citation**

McCann MF, Potter LS. *Progestin-only oral contraception: A comprehensive review*. Contraception 1994;50(Supplement 1), S9-S195.

### **Object of research**

Progestin-only pills

### **Research Outcome**

Breast tenderness, breast pain

### **Study Features**

This is a review of studies that include information about discontinuation of a progestin only pill due to non-menstrual side effects. Only four of these studies provide detailed information as to discontinuations for non-menstrual side effects. Results from these four studies are as follows:

- England (1977): This was a prospective study with one year follow-up of the experience of 556 women using one of three progestins: norethisterone 0.35 mg (n=200), chlormadinone acetate 0.5 mg (n=182), and megestrol acetate 0.5 mg (n=174). Most were less than six months postpartum though reports about breastfeeding were not

included.

- United States (1974): This was an open label study of 2,202 women using norgestrel 0.075 mg studied from 1 to 67 cycles.
- UK, Jamaica, New Zealand (1982): This was a multicenter study of 913 women using norethisterone 0.35 mg of 913 women. The median age of these women was 27 and ranged from 16 to 54 years of age.
- England (1972): These data were obtained as part of the continuing follow-up of contraceptive users in the Oxford Family Planning Association. Only data from the norethisterone users (1746 women) and non-hormonal contraceptive users (138 women).

*Evidence Grade: Level 2*

### **The Evidence**

In the four studies, results were:

- England: There were no reports of discontinuation because of breast tenderness in any of the progestin only pill user groups.
- United States: Less than ½ of a percent of the users of norgestrel discontinued because of a breast discomfort.
- UK, Jamaica, and New Zealand: No discontinuations were reported for breast discomfort.
- England/Oxford follow-up study: In the norethisterone group, 5.1% of the women in the study discontinued because of breast discomfort as compared to 5.3% of those using an IUD or diaphragm.

**Appraised by:** The Evidence Based Medicine Reproductive Health Group

**Update by:** 9 April 2016

## **The use of a progestin only pill for contraception is associated with an increase in the risk of functional ovarian cysts.**

### **Conclusion**

Based on the results of this study, use of the progestin only pill (POP) is associated with an increase in symptomatic cyst formation.

### **Clinical Question**

Is there an increase in the risk of functional ovarian cysts among women taking progestin only pills?

### **Search Terms**

Progestin only pills, functional ovarian cysts

### **Citation**

Taylor Y, Adams J, Jacobs HS, Guillebaud J. *Ultrasound demonstration of increased frequency of functional ovarian cysts in women using progestogen-only oral contraception.* Br J Obstetrics and Gynaecology 1985;92:1003-1009.

### **Object of Research**

Progestin only pills

### **Research Outcome**

Functional ovarian cysts

### **Study Features**

This is a prospective comparative study of 21 progestin-only pill users with 21 controls. Progestin-only pill users had been using their method of at least six months. Six used a progestin-only pill containing 30 mcg of levonorgestrel, 8 used one containing 350 mcg of norethisterone, and the remaining 7 used a pill containing 500 mcg of ethynodiol diacetate. All progestin-only pill users were symptom free at the time of study initiation. Controls consisted of healthy volunteers aged between 24 and 37 years who reported regular menstrual cycles and who were not exposed to any artificial hormones or any other medications. The majority of the controls used the diaphragm for contraception and none had a history of ovarian cyst formation. Controls were similar to the progestin only pill users in terms of age, body weight and previous fertility.

*Evidence Grade: Level 2*

**The Evidence**

Among the progestin only pills users, 8 (38%) had a functional cyst identified by an ultrasound scan at the end of the first bleeding episode, as compared to 4 (19%) of the control group. For the progestin only pill group, three of the cysts regressed during the next cycle. Eleven of the 14 pill users who failed to ovulate also had a function cyst. In the control group, ovulation occurred in 16 of the 21 women. In a sub study of 7 of the pill users, all cysts disappeared by the end of the second pill-free cycle.

**Appraised by:** The Evidence Based Medicine Reproductive Health Group

**Update by:** 9 April 2016

## **The association between progestin only pill use and the incidence of headache is not clear.**

### **Conclusion**

There is some evidence available that use of progestin only pills (POPs) is associated with the occurrence of headache, though the precise extent to which these common symptoms are actually caused by the pills cannot be determined from available data.

### **Clinical Question**

Is the use of progestin-only pills associated with an increased risk of a headache?

### **Search Terms**

Progestin-only pills, progestin-only oral contraceptives, headache

### **Citation**

McCann MF, Potter LS. *Progestin-only oral contraception: A comprehensive review.*

Contraception 1994;50(Supplement 1), S9-S195.

### **Object of Research**

Progestin-only pills

### **Research Outcome**

Headache

### **Study Features**

This is a literature review of earlier use of POPs (pre-1994) and reports of headache. Studies reporting discontinuation for and/or reports of headache include the following:

- A prospective study of 556 English women using a progestin-only pill containing norethisterone 0.35 mg, chlormadinone acetate 0.5 mg, or megestrol acetate 0.05 mg,
- A prospective, open label study of 2,202 women from eight clinical investigations in the United States and Puerto Rico who used a pro-

gestin-only pill containing 0.075 mg norgestrel continuously for 1 to 69 consecutive cycles,

- A multi-center study of 913 women in the United Kingdom, Jamaica, and New Zealand using a progestin-only pill containing norethisterone 0.35 mg,
- Data from the continuing follow-up study of the Oxford, England Family Planning Association, reporting the experience of 3,165 women using either norethisterone 0.35 mg, norgestrel 0.075 mg, ethynodiol diacetate 0.5 mg, or levonorgestrel 0.03 mg. One hundred thirty-eight others used either an intrauterine device (IUD) or diaphragm.

*(Level 2 Evidence)*

### **The Evidence**

Selected results relating to the incidence of headaches with the use of a progestin-only pill from these studies are as follows:

- In the prospective study of 556 English women using a progestin-only pill, discontinuations due to a headache ranged from 1% for the norethisterone group to 2.2% for the chlormadinone group.
- In the prospective, open label, non-comparative study of 2,202 women from eight clinical investigations of norgestrel in the United States and Puerto Rico 1.2% discontinued due to headache.
- In the multi-center study of 913 women in the United Kingdom, Jamaica, and New Zealand 3% discontinued due to either headache or migraine,
- From the data of the continuing follow-up study of the Oxford, England Family Planning Association, 7.4% of the norethisterone users discontinued due to headache as compared to 6.1% for the IUD and diaphragm users.

**Appraised by:** The Jordan Evidence Based Medicine Reproductive Health Group

**Update by:** 9 April 2016

**Available studies consistently report no association between the use of progestin only pills (POPs) for contraception and hypertension.**

### **Conclusion**

The risk of hypertension associated with the use of progestin only pills appears to be low or non-existent. However, data that support this conclusion are limited and should be interpreted with caution.

### **Clinical Question**

Is there an increase in the risk of hypertension among women using progestin only pills for contraception?

### **Search Terms**

Progestin only pills, hypertension

### **Citation**

Hussain SF. *Progestogen-only pills and high blood pressure. Is there an association? A literature review.* Contraception 2004;69:89-97.

### **Object of Research**

Progestin only pills

### **Research Outcome**

Blood pressure

### **Study Features**

Four studies were identified, two conducted in the United States and one each in Scotland and the United Kingdom. Three of the studies were prospective controlled and one was cross-sectional. Women were normotensive at the start of the studies. Sample sizes of progestin only pill users were 143, 119, 77, and 94 for the four studies.

*(Level 2 Evidence)*

**The Evidence**

In the United Kingdom the blood pressure was lower in the POP user group than in nonusers. In one United States study, progestin-only pill users had a significant fall in diastolic blood pressure. In the other two studies there was no association between POP use and change in blood pressure.

**Appraised by:** The Jordan Evidence Based Medicine Reproductive Health Group

**Update by:** 9 April 2016

# **The use of progestin only pills (POPs) for contraception does not appear to be associated with an increase in the risk of a myocardial infarction**

## **Conclusion**

There is no convincing evidence that progestin only pills for contraception increases the risk of a myocardial infarction. However, data that support this conclusion are limited by the small number of exposed cases and should be interpreted cautiously.

## **Clinical Question**

Is there an increase in the risk of a myocardial infarction among women using progestin only pills for contraception?

## **Search Terms**

Progestin only pills, myocardial infarction

## **Citation**

Chakhtoura Z, Canonico M, Gompel A, Scarabin P, Plu-reau G. *Progestogen-only contraceptives and the risk of myocardial infarction: a meta-analysis.* J Clin Endocrinol Metab 2011;96:1169-1174.

## **Object of Research**

Progestin only pills

## **Research Outcome**

Myocardial infarction including fatal myocardial infarction

## **Study Features**

Six case control studies involving 1,817 cases and 6,822 controls were identified. Women aged 16-45<sup>+</sup> were matched for age and other risk factors for a myocardial infarction (e.g. diabetes, high blood pressure). Studies were carried out in the United Kingdom (2), the United States (2), Europe (1) and worldwide (1).

*(Level 3 Evidence)*

## The Evidence

There were no significant differences between the controls and those with a cardiovascular event. Odds ratios with the corresponding 95% confidence intervals are shown in the following table:

Source	Odds Ratio	Confidence Interval 95%
Thorogood, 1991	0.50	1.83 – 0.14
Petitti, 1998	3.50	56.50 – 0.20
WHO, 1998	0.78	3.13 – 0.20
Heinemann, 1999	0.94	2,91 – 0.31
Dunn, 1999	1.48	3.65 – 0.60
Rosenberg, 2001	4.58	73.42 – 0.29

**Appraised by:** The Jordan Evidence Based Medicine Reproductive Health Group

**Update by:** 31 March 2016

## **The use of a progestin only pill (POP) for contraception is not associated with an increase in the risk of a stroke**

### **Conclusion**

There is no convincing evidence that the use of progestin only pills for contraception increase the risk of a cardiovascular event of stroke. However, data that support this conclusion are limited by the small number of exposed cases and should be interpreted cautiously.

### **Clinical Question**

Is there an increase in the risk of a stroke among women using progestin only pills for contraception?

### **Search Terms**

Progestin only pills, stroke

### **Citation**

Heinemann LA, Assman A, DoMinh T, Garbe E, et al. *Oral progestogen-only contraceptives and cardiovascular risk: results from the Transnational Study on Oral Contraceptives and the Health of Women*. Eur J Contracept Reprod Health Care 1999; 4(2):67-73.

### **Object of Research**

Progestin only pills

### **Research Outcome**

Stroke

### **Study Features**

This is a case control study of 1,058 women aged 16-44 in 16 centers across five countries. Cases included in the study were women with a myocardial infarction, thromboembolic a cerebrovascular accident or a venous thromboembolism. Two control groups with a total of 3,808 women unaffected

by these diseases were also enrolled. One control group was hospitalized women with other diagnoses while the other control group was comprised of women from the community. All controls were matched to the same 5-year age group as the cases.

*(Level 3 Evidence)*

### **The Evidence**

There were no significant differences between the controls and those with a cardiovascular event. Odds ratios with the corresponding 95% confidence intervals (CI) are as follows:

- all cardiovascular events odds ratio=0.84 (95% CI: 0.45 – 1.58)
- stroke odds ratio=1.60 (95% CI: 0.24 – 10.72)

The odds ratio for stroke suggests there is no significant increase in the risk of stroke for progestin only pill users.

**Appraised by:** The Jordan Evidence Based Medicine Reproductive Health Group

**Update by:** 23 November 2012

# **The use of progestin only pill (POPs) for contraception is not associated with an increase in the risk venous thromboembolism**

## **Conclusion**

The risk of venous thromboembolic disease (VTE) associated with the use of progestin only pills appears to be low or non-existent. However, data that support this conclusion are limited and should be interpreted with caution.

## **Clinical Question**

Is there an increase in the risk of venous thromboembolism among women using progestin only pills for contraception?

## **Search Terms**

Progestin only pills, venous thromboembolism, VTE

## **Citation**

Gomes PV, Deitcher SR. *“Risk of venous thromboembolic disease associated with hormonal contraceptives and hormone replacement therapy”* Arch Intern 2004; 164:1965-1976.

## **Object of Research**

Progestin only pills

## **Research Outcome**

Venous thromboembolism

## **Study Features**

Data on progestin-only pill VTE risk were derived from 8 case control studies. Two of these studies included women using the POP for therapeutic reasons (e.g. menstrual bleeding) though seven involved women using it for contraception. These may have contained higher progestin doses or different progestins altogether. Women were matched for selected demographic factors including no previous history of cardiovascular diseases.

*(Level 3 Evidence)*

## The Evidence

In the 7 case control studies which included only use of progestin only pills for contraception, there were no significant increases in the risk of venous thromboembolism for users of progestin only pills for contraception.

Source	Odds Ratio	Confidence Interval 95%
Lewis, 1996	1.28	2.5 – 0.66
Farmer, 1997	0.84/10,000 <sup>1</sup>	Not available
Lidegaard, 1998	2.61	9.8 – 0.69
WHO, 1998	1.74	3.99 – 0.8
Vasilakis, 1999	1.3	6.8 – 0.3
Heinemann, 1999	0.68	2.6 – 0.3
Lidegaard, 2002	2.0	5.1 - 0.8

<sup>1</sup> Risk is expressed as crude rate from the cohort analysis

**Appraised by:** JEBM Group

**Update by:** 14 December 2012

## **Progestin-only pills (POPs) do not appear to decrease milk volume for women who are breast feeding and are safe for the breastfed infants.**

### **Conclusion**

Progestin-only pills are safe as a method of contraception for breast feeding women. Among users of POPs, no significant changes were observed in terms of infant growth, health or development when compared to non-hormonal method users or to the use of the lactation amenorrhea method.

### **Clinical question**

Does the use of a progestin only pill by breastfeeding women adversely affect development of the infant?

### **Search terms**

Progestin-only pills, POP, breast feeding

### **Citation**

Kapp N, Curtis K, Nanda K. *Progestogen-only contraceptive use among breastfeeding women: a systematic review.* Contraception 2010;82:17-37.

### **Object of Research**

Progestin-only pills.

### **Research Outcome**

Infant growth

### **Study Features**

This is a systematic review to assess whether the use of progestin only pills during breastfeeding has any adverse effect on infant growth or health. Five studies involving a progestin-only pill and lactating women were identified. These studies were:

- a randomized study in Mexico included 12 norethisterone 350 mcg pills users and 10 women using a placebo.

- a non-randomized clinical study in Egypt which included 10 lynestrenol 500 mcg pill users, 10 on ethinyl estradiol users, 10 combine oral contraceptives, and 10 on a placebo,
- a cohort study in Argentina in which 150 used a progestin only pill containing levonorgestrel 30 mcg pills and were compared with 150 women on non-hormonal methods,
- a cross sectional survey in Scotland in which 100 women received a progestin only pill containing chlormadione acetate (0.6 mg) and were compared to 173 historical controls,
- a cohort study in Iceland of 42 women using desogestrel 75 mg, and 41 using a copper intrauterine device,
- a WHO, prospective, cohort study, with a nested randomized pill trial in Hungary and Thailand included 85 POP and 86 combined oral contraceptive (COC) users, and 111 non hormonal barrier contraceptive users and 59 three month injectable users (DMPA).
- a prospective cohort study in Chile included 109 IUD, 228 DMPA, 185 POP and 143 lactation amenorrhea method (LAM).
- a WHO cohort study included participants from Egypt, Thailand, Kenya, Chile and Hungary. One other cohort study in Iran was reported, but results of three month injectable and POP users were combined. These data are not presented here.

*(Level 1 Evidence)*

**The Evidence**

Results from these studies were as follows:

- Mexico: No significant differences between POP users and the placebo group in milk volume or composition or infant growth.
- Egypt: Milk yield as assessed by infant weight increased in all contraceptive groups relative to placebo, but was greatest among the POP exposed infants. Similarly, the greatest growth was also in the POP exposed infants. Results are to be reviewed cautiously because of small sample size of POP users (n=10).
- Argentina: Women in the non-hormonal group were more likely to use supplementation and to report decreased milk volume than those

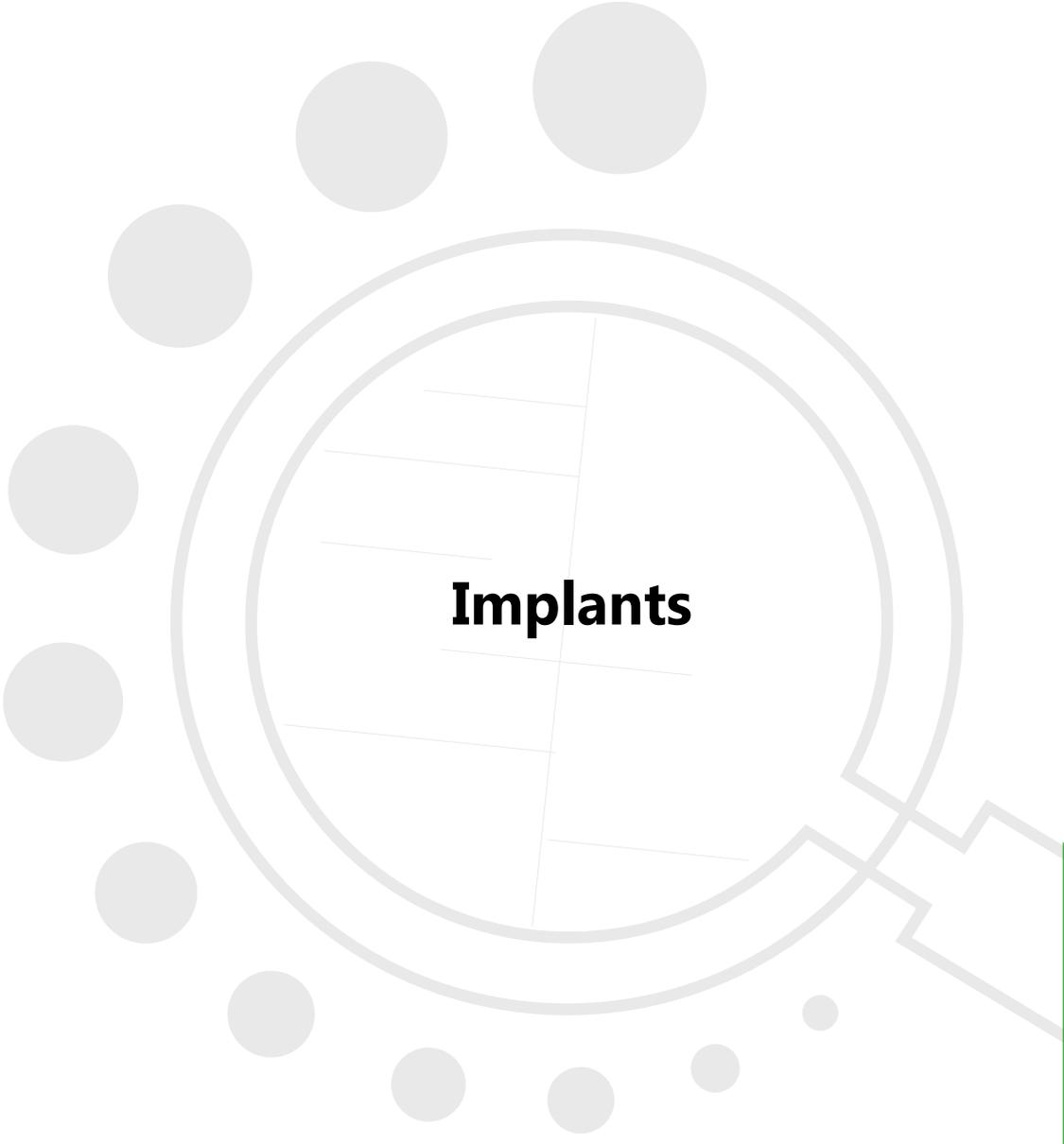
using a POP. No group differences in infant growth were found.

- Scotland: Among women who initiated their POP before 42 days, equal proportions of pill users and those using hormonal methods were still breastfeeding after three months.
- Iceland: At cycle 7, 78% of the desogestrel users compared with 59% of IUD users were still breastfeeding. No differences in milk volume or chemistry were noted.
- In the Hungarian and Thai WHO randomized controlled trial, no differences among the groups of POP, COC, the three month injectable or users of non-hormonal barrier methods were found in terms of infant growth or weight. Nor were there any differences in health of the infant. Milk volume decreased over time in all groups, but the greatest decrease was in the COC group.
- Chile: No differences among the LAM, progestin only contraceptives or Copper IUD groups were noted in terms duration of breastfeeding, infant growth or development.

**Appraised by:** The Jordan Evidence Based Medicine Reproductive Health Group

**Update by:** 9 April 2016





**Implants**



## **PROGESTIN ONLY IMPLANT**

In Jordan, the proportion of married women of reproductive age using an implant is less than half a percent<sup>1</sup>. The primary implant used in Jordan is the single rod etonogestrel (ENG) implant, commercially known as Implanon®. Most women can use this progestin only implant, but health professionals should be aware of the World Health Organization Medical Eligibility Criteria for Contraceptive Use<sup>2</sup>.

### **Effectiveness**

Implanon® is highly effective if used as directed. It is approved for three years of use and with correct placement, less than 1 percent will experience a method failure in the first year of use<sup>3,4</sup>. For women who prefer an implant, duration of use is not associated with any decrease in efficacy or safety<sup>5</sup>.

### **Mode of Action**

There are several modes of action of Implanon® in preventing pregnancy. It acts primarily by suppressing ovulation. Other ways Implanon® may act to prevent pregnancy is to alter the endometrial structure and to impede sperm penetration by thickening cervical mucus<sup>6</sup>.

### **Advantages of Implanon®**

In addition to being highly effective, other advantages to using Implanon® are:

- the absolute number of ectopic pregnancies are reduced<sup>7-11</sup>
- it is reversible<sup>12-14</sup>
- ease of use
- relief of dysmenorrhea<sup>14</sup>
- it is an option throughout reproductive years

### **Disadvantages of Implanon®**

- Menstrual cycle disturbances<sup>15</sup>
- Increased risk of ovarian cysts<sup>16</sup>

## **Special Topics**

- Amenorrhea

*There is an increased risk of amenorrhea<sup>17-19</sup>.*

- Cancer

*No data available to appropriately assess cancer risks.*

- Postpartum Use/Effect on Breastfeeding

*Among breast feeding women using Implanon®, there is no decrease in milk volume nor is the growth of the infant affected<sup>20</sup>*

## REFERENCES

### Single Rod Etonogestrel (ENG) Implant

1. Department of Statistics [Jordan] and ICF Macro,2010. *Jordan Population and Family Health Curvey 2009*. Calverton, Maryland, USA: Department of Statistics and ICF Macro.
2. World Health Organization. *Medical eligibility criteria for contraceptive use*. Geneva:WHO, 2004.
3. Darney P, Patel A, Rosen K, Shapiro LS, Kauntiz AM, *Safety and efficacy of a single-rod etonogestrel implant (Implanon): results from 11 international clinical trials*. Fertil Steril; 91(5):1646-53, 2008.
4. Power J, French R, Cowan FM. *Subdermal implantable contraceptives versus other forms of reversible contraceptives or other implants as effective methods for preventing pregnancy*. Cochrane Database of Systematic Reviews (2012) Issue 2, Art. No.: CD001326. DOI:10.1002/14651858.CD001326.pub2.
5. Graesslin O, Korver T. *The contraceptive efficacy of Implanon® a review of clinical trials and marketing experience*. Eur J Contracept Reprod Health Care. 2008; 13 Suppl 1: 4-12.
6. Hatcher RA, Trussell J, Nelson AL, Cates W, Stewart F, Kowal D. *Contraceptive implants*. Contraceptive Technology. New York: Ardent Media Inc, 2008. 147-148.
7. Mansour M, Louis-Sylvestre C, Paniel BJ. *Ectopic pregnancy with etonogestrel contraceptive implant (Implanon): first case*. J Gynecol Obstet Biol reprod (Paris) 2005 Oct;34(34):608-9.
8. Panti S, Ebdan P, Kavelighan K, Bibby J. *Ectopic pregnancy with Implanon*. J Fam plan Reprod Health Care 2006; 32(2): 115
9. Henderson P, Gillespie MD. *Ectopic pregnancy with Implanon*. J Fam plan Reprod Health Care 2007; 33(2):125-6
10. Olowu O, Karunaratne J, Odejinmi F. *Ectopic pregnancy with Implanon as a method of contraception in a woman with a previous ectopic pregnancy-case report*. Eur J contracept Reprod Health Care 2011;16(3):229-231
11. Bouquier J, Fulda V, Bats A, Lecuru F, Huchon C. *A life-threatening*

- ectopic pregnancy with etonogestrel implant. Contraception 2012; 85(2):215-217.*
12. Affandi B, Korvert T, Geurts TB, Bennick H. *A pilot study with a single-rod contraceptive implant (Implanon®) in 200 Indonesian women treated for ≤ 4 years. Contraception 1999;59:167-174.*
  13. Croxatto HB, Urbancsek J, Massai R et al. *A multicenter efficacy and safety study of the single contraceptive implant Implanon®. Human Reproduction 1999;14(4):976-981.*
  14. Funk S, Miller MM, Mishell D, et al. *Safety and efficacy of Implanon™. A single-rod implantable contraceptive containing etonogestrel. Contraception 2005;71:319-326.*
  15. Mansour D, Korver T, Fraser IM. *The effects of Implanon® on menstrual bleeding. Eur J Contracept Reprod Health 2008;13:13-28.*
  16. Hidalgo MM, Lisondo C, Juliato CT, Espejo-Arce X, Monteiro I, Bahamondes L. *Ovarian cysts in users of Implanon® and Jadelle® subdermal contraceptive implants. Contraception 2006; 73:532-536.*
  17. Gezginc K, Balci O, Karatayli R., Colakoglu MC. *Contraceptive efficacy and side effects of Implanon®. Eur J Contracept Reprod Health Care 2007; Vol. 12, No. 4: 362-365.*
  18. Bitzer J, Tschudin S, Alder J, Swiss Implanon Study Group. *Acceptability and side effects of Implanon Switzerland: a retrospective study by the Implanon Swiss Study Group. Eur J Contracept Reprod Health Care 2004; Dec;9(4):278-284.*
  19. Bhatia P, Sangita N, Shivani A, Chitra T. *Implanon: Subdermal Single Rod Contraceptive Implant. Journal of Obstetrics and Gynecology of India 2011; 61(4):422-425.*
  20. Gurtcheff SE, Turok DK, Stoddard G, Murphy PA, Gibson M, Jones KP. *Lactogenesis after early postpartum use of the contraceptive implant: a randomized controlled trial. Obstet Gynecol. 2011;117:1114-21.*

## **List of Critically Appraised Topics**

- 1-Efficacy
- 2-Long Term Use
- 3-Liver Enzymes Use
- 4-Ectopic Pregnancy
- 5-Return to Fertility
- 6-Menstrual Blood Loss
- 7-Amenorrhea
- 8-Dysmenorrhea
- 9-Endometriosis
- 10-Weight Gain
- 11-Acne
- 12-Libido
- 13-Vision Changes
- 14-Bone Mass Density
- 15-Ovarian Cysts
- 16-Headache
- 17-Hypertension
- 18-Stroke
- 19-Breastfeeding

*Note that the level of evidence accompanying each publication in each of the CATs refers to the study design.*



# **The single rod etonogestrel implant is highly efficacious and comparable to other contraceptive methods containing hormone as well as intrauterine devices**

## **Conclusion**

The single rod etonogestrel implant is highly effective contraceptive for up to three years after insertion.

## **Clinical Question**

What is the efficacy of the single rod etonogestrel implant in comparison to other methods?

## **Search Terms**

Implanon<sup>®</sup>, single rod etonogestrel implant, contraceptive efficacy

## **Citations**

Darney P, Patel A, Rosen K, Shapiro LS, Kaunitz AM, *Safety and efficacy of a single-rod etonogestrel implant (Implanon): results from 11 international clinical trials*. Fertil Steril; 91(5):1646-53, 2008.

Power J, French R, Cowan FM. *Subdermal implantable contraceptives versus other forms of reversible contraceptives or other implants as effective methods for preventing pregnancy*. Cochrane Database of Systematic Reviews (2012) Issue 2, Art. No.: CD001326. DOI:10.1002/14651858.CD001326.pub2.

## **Object of Research**

Single rod etonogestrel implant

## **Research Outcome**

Efficacy

## **Study Features**

### Darney et al

This report is based on an integrated analysis of the clinical data from 11 international studies. Studies were conducted in the United States., Chile, Europe, and Asia. A total of 923 subjects were enrolled in the clinical studies designed to assess efficacy. Failure was said to have occurred if a pregnancy occurred while the implant was in place or if it occurred within 14 days after its removal.

*(Level 1 Evidence)*

### Power et al

This is a review of all randomized and controlled trials comparing subdermal implants with other forms of reversible contraceptives. Primary outcomes of these studies were pregnancy and continuation. All nine identified trials compared different types of contraceptive implant. Eight, involving 1578 women, compared the single rod etonogestrel implant with Norplant®, and one, involving 1198 women, compared Jadelle® with Norplant.

*(Level 1 Evidence)*

## **The Evidence**

### Darney P, et al

No pregnancies were reported while the ENG implants were in place. There were six pregnancies reported with a conception date within 14 days after the removal of the single rod etonogestrel implant. The cumulative Pearl Index of the implant was 0.38 (year 1 and 2 Pearl Indexes were 0.27 and 0.30, respectively).

### Power et al

There was no difference between the single rod etonogestrel implant and Norplant® for contraceptive effectiveness rates or continuation over 4 years. Both were highly effective methods of contraception with no pregnancies occurring in any of the trials during 26,972 and 28,108 women months of follow up respectively. The authors failed to find any randomized clinical trials that compared subdermal implants with either IUDs, oral contraceptives, barrier-

methods or injectable contraceptives.

Note: Based on data from studies of other contraceptives, these rates are compare favorably with the efficacy of other contraceptives.

**Appraised by:** The Jordan Evidence-Based Medicine Reproductive Health Group

**Update by:** 3 March 2016

## **There is no decrease in the efficacy of the single rod etonogestrel implant over time**

### **Conclusion**

The single rod etonogestrel implant is a highly effective and quickly reversible sub dermal long- acting hormonal method of contraception for women. Typical use of this implant achieves a contraceptive effectiveness exceeding 99%. There is no evidence that use up to three years increases the risk of pregnancy.

### **Clinical question:**

Is there a decrease in the efficacy of the single rod etonogestrel implant (Implanon®) over time?

### **Search Terms**

Implanon®, single rod etonogestrel implant, increased risk of pregnancy

### **Citation**

Graesslin O, Korver T. *The contraceptive efficacy of Implanon® a review of clinical trials and marketing experience.* Eur J Contracept Reprod Health Care. 2008; 13 Suppl 1: 4-12.

### **Object of Research**

Single rod etonogestrel implant

### **Research outcome**

Increased risk of pregnancy

### **Study Features:**

This analysis included 11 international studies and data collected during 9 years of marketing experience (1998-2007). Seven of these studies were noncomparative; the four other studies included the 6-rod levonorgestrel

implant system or an intrauterine device as a comparator. All studies except one were of at least two years in duration, and all had contraceptive efficacy as an objective. The integrated efficacy analysis included 923 non-breastfeeding women.

***(Level 1 Evidence)***

**The Evidence:**

The 923 non-breastfeeding women were exposed to the implant for 24,100 cycles. No in-treatment or pretreatment pregnancies were reported. Fifty post treatment pregnancies were reported six of which occurred within 14 days of implant removal, indicating that fertility had quickly returned. Over 9 years of recorded experience, an overall pregnancy rate of 0.049 per 100 implants sold (estimated Pearl index =0.031 based on all pregnancies reported). When only counting contraceptive method failure the pregnancy rate was 0.010 per 100 implants sold (estimated Pearl index= 0.006). Considering the pregnancy distribution over the three-year period, the Pearl Index was 0.021 for year 1, 0.034 for year 2, and 0.054 for year 3.

Note: One Australian postmarketing study (Harrison-Woolrych and Hill Contraception 2005; 71:306-308) reports an approximate failure rate of 1 per 1000 insertions (218 pregnancies out of 204,486 insertions) though 130 of these pregnancies were either because of non-insertion or prior conception. No information was given as to the timing of these pregnancies so that a statement about long term use could not be made.

**Appraised by:** The Jordan Evidence Based Medicine Reproductive Health Group

**Update By:** 26 February 2016

## **Women using the single rod etonogestrel implant may have higher rates of contraceptive method failure with concomitant use of liver enzymes inducers**

### **Conclusion**

The efficacy of the single rod etonogestrel implant may be reduced in women taking liver enzymes inducers drugs such as antiepileptic. For women using this implant for contraception, the product information advises an additional barrier method when using a hepatic-enzyme inducing drug and for at least 7 days after discontinuation.

### **Clinical Question**

Is the use of the single rod etonogestrel implant in women taking liver enzymes inducers drugs associated with increased contraception failure rate?

### **Search Terms**

Implanon<sup>®</sup>, the single rod etonogestrel implant, liver enzymes inducers, contraception, failure rates

### **Citation**

Harrison-Woolrych M, Hill R. *Unintended pregnancies with the etonogestrel implant (Implanon): a case series from post marketing experience in Australia*. Contraception, 2005; 71(4):306-8.

### **Object of Research**

Single rod etonogestrel implant

### **Research Outcome**

Liver enzymes inducers

### **Study Features**

This post marketing surveillance study describes a case series of 218 unintended pregnancies associated with the etonogestrel implant, from May 1, 2001, to April 30, 2004 (the first 3 years following licensing in Australia).

These cases were reported to the Australian Adverse Drug Reactions Advisory Committee. Each case of confirmed pregnancy associated with the implant was assessed to determine possible reasons for contraceptive failure. The information taken into account included the estimated date of conception from ultrasound scans or other information (to determine if the woman was already pregnant at the time of insertion), the timing of insertion (with respect to the menstrual cycle or whether postpartum insertion), any concomitant medicine use (for possible drug interactions) and evidence that the implant was actually inserted (including blood etonogestrel levels and/or location by palpation or ultrasound scanning).

*(Level 4 Evidence)*

### **The Evidence**

Of 218 cases included, 8 (4%) were determined to have resulted from interactions with concomitant medications. All drug interactions identified in this case series involved antiepileptic drugs; with 7 of these 8 women taking carbamazepine (which is liver enzymes inducer) while using the single rod etonogestrel implant.

**Appraised by:** The Jordan Evidence Based Medicine Reproductive Health Group

**Updates by:** 2 March 2016

## **The use of the single rod etonogestrel implant is associated with a very rare, but possible risk of ectopic pregnancy.**

### **Conclusion**

The single rod etonogestrel implant is associated with very low failure rate which means the possibility of having ectopic pregnancy is very rare. However, based on reported case studies, the possibility of an ectopic pregnancy should be considered in any women using the single rod etonogestrel implant as contraception and who presents with missed period and abdominal pain.

### **Clinical Question**

Is there an increased risk of ectopic pregnancy among women using the single rod etonogestrel implant?

### **Search Terms**

Implanon<sup>®</sup>, single rod etonogestrel implant, ectopic pregnancy

### **Citations**

Mansour M, Louis-Sylvestre C, Paniel BJ. *Ectopic pregnancy with etonogestrel contraceptive implant (Implanon): first case.* J Gynecol Obstet Biol reprod (Paris) 2005 Oct;34(34):608-9.

Panti S, Ebdan P, Kavelighan K, Bibby J. *Ectopic pregnancy with Implanon.* J Fam plan Reprod Health Care 2006; 32(2): 115

Henderson P, Gillespie MD. *Ectopic pregnancy with Implanon.* J Fam plan Reprod Health Care 2007; 33(2):125-6

Olowu O, Karunaratne J, Odejinmi F. *Ectopic pregnancy with Implanon as a method of contraception in a woman with a previous ectopic pregnancy-case report.* Eur J contracept Reprod Health Care 2011;16(3):229-231

Bouquier J, Fulda V, Bats A, Lecuru F, Huchon C. *A life-threatening ectopic pregnancy with etonogestrel implant.* Contraception 2012; 85(2):215-217

### **Object of Research**

Single rod etonogestrel implant

## **Subject of Research**

Ectopic pregnancy

## **Study Features**

All the 5 reported studies were case reports published during the period 2005 to 2012 (3 reports from UK and 2 from France). Due to the high efficacy of the single rod etonogestrel implant as contraception, a given pregnancy is very rare, so is ectopic gestation. No large scale study that deals with the incidence of ectopic pregnancy and Implanon® was found in our search.

**(Level 4 Evidence)**

## **The Evidence**

Mansour, Louis-Sylvestre and Paniel

The first published case report study of ectopic pregnancy occurring in a patient with Implanon® who had no obvious risk factor predisposing to a failure of technique (implant in place for less than 2 years and normal body mass index). In addition there was no risk factor for an ectopic pregnancy. This case was considered as primary failure of the contraceptive effect.

Panti, Ebdan, et al

A 27-year-old woman, who had no history of any risk factor for ectopic pregnancy. Implant in place for 6 months duration. This patient was on Rifampicin treatment for tuberculosis. This drug is known to have a reducing effect on the contraceptive efficacy of Implanon®.

Henderson and Gillespie

A 25-year-old woman, who had had a single rod etonogestrel implant inserted 28 months prior to the occurrence of ectopic pregnancy. Neither obvious risk factor predisposing to a failure of technique nor any risk factors for an ectopic pregnancy were reported in this case. This case was considered as primary failure of the contraceptive effect.

Olowu, Karunaratne and Odejinmi

A 26-year-old woman presented with an ectopic pregnancy conceived while having a single rod etonogestrel implant in situ. The only risk factor which was reported here was a previous history of treated contralateral ectopic pregnancy 2 years before this pregnancy, following which the implant was inserted.

Bouquier, Fulda, et al

A case of ruptured ectopic pregnancy reported in a patient with the single rod etonogestrel implant. The implant was in place for less than 2 years. The only factor predisposing to a failure in this case was a moderately elevated body mass index (BMI=29).

**Comment**

Despite the lack of any large scale studies, the results of these 5 case reports suggest that physicians should be alert to the possibility of an ectopic pregnancy among women using Implanon.

**Appraised by:** The Jordan Evidence Based Medicine – Reproductive Health Group

**Update by:** 3 March 2016

## **The use of the single rod etonogestrel implant is not associated with a decrease in the ability to become pregnant after removal.**

### **Conclusion**

The ability to become pregnant after removal of the single rod etonogestrel implant as determined by a return to normal menstrual cycles or ovulation is rapid. Most women who did not use another method of contraception after removal became pregnant within twelve months.

### **Clinical Question**

Is the use of the single rod etonogestrel implant associated with a decrease in ability to become pregnant after removal?

### **Search Terms**

Implanon<sup>®</sup>, single rod etonogestrel implant, return to fertility

### **Citation**

Affandi B, Korvert T, Geurts TB, Bennick H. *A pilot study with a single-rod contraceptive implant (Implanon<sup>®</sup>) in 200 Indonesian women treated for  $\leq 4$  years.* Contraception 1999;59:167-174.

Croxatto HB, Urbancsek J, Massai R et al. *A multicenter efficacy and safety study of the single contraceptive implant Implanon<sup>®</sup>.* Human Reproduction 1999;14(4):976-981.

Funk S, Miller MM, Mishell D, et al. *Safety and efficacy of Implanon<sup>™</sup>. A single-rod implantable contraceptive containing etonogestrel.* Contraception 2005;71:319-326.

### **Object of Research**

Implanon<sup>®</sup>

### **Research Outcome**

Return to fertility determined by return to menses

## **Study Features**

### Affandi et al

This is an open-label, non-comparative, single center study conducted in Jakarta, Indonesia. Two hundred women were enrolled in the study for a period of two years with a possible extension of three to four years. Women included in the study were 18-40 years, sexually active, with a normal menstrual cycle of 24-35 days. A post-treatment evaluation was performed on those women using no method of contraception after removal of their implant.

*(Level 2 Evidence)*

### Croxatto et al

This is an open-label, multicenter study designed to assess the efficacy, safety, and acceptability of the single-rod contraceptive implant Implanon®. The study involved 635 healthy women who were sexually active and of childbearing potential and 21 centers in 11 countries in Europe and South America. Return to fertility was determined by a reported return to menses.

*(Level 2 Evidence)*

### Funk et al

This is an open-label multicenter study conducted in the United States and designed to assess the safety and efficacy of Implanon®. The study involved 330 sexually active women between the ages of 18 and 4 and with apparently normal menstrual cycles. Return to fertility was determined by a reported return to menses.

*(Level 2 Evidence)*

## **The Evidence**

### Affandi et al

Sixty-nine women who discontinued and were found not to be using another form of contraception, all experienced a return to normal menstruation. The number of women who became pregnant during this period was not reported.

*Evidence grade: Level*

Croxatto et al

Posttreatment information three months after removal of their implant was obtained. Of those who chose a non-hormonal method of contraception 91 percent returned to normal menses within tthree months. This was not influenced by the length of use of their implant use. Of the posttreatment pregnancies that were reported, the estimated date of conception was within 90 days in 20 (14%) of the 145 who “no contraceptive method.”

*Evidence grade: Level*

Funk et al

Post treatment information three months after removal of their implant was available for 282 (85%) of the 330 women in the study. Of these, 248 (88%) reported their menses had returned to normal. Forty-six of these women did not use any contraceptive after removal and 11(24%) became pregnant between 7 and 131 days later.

*Evidence grade: Level*

**Appraised by:** The Jordan Evidence-Based Medicine Reproductive Health Group

**Update by:** 6 January 2016

## **The use of the single rod etonogestrel implant is associated with abnormal uterine bleeding patterns**

### **Conclusion**

The use of the single rod etonogestrel implant is associated with an unpredictable bleeding pattern, which includes infrequent, frequent, and/or prolonged bleeding. The bleeding pattern experienced during the first three months is broadly predictive of future bleeding patterns for many women. Effective pre-insertion counseling on the possible changes in bleeding patterns may improve continuation rates.

### **Clinical Question**

Is the use of single rod etonogestrel implant associated with abnormal uterine bleeding?

### **Search Terms**

Implanon<sup>®</sup>, single rod etonogestrel implant, abnormal uterine bleeding

### **Citation**

Mansour D, Korver T, Fraser IM. *The effects of Implanon<sup>®</sup> on menstrual bleeding patterns*. Eur J Contracept Reprod Health 2008; Vol. 13: 13-28.

### **Object of Research**

Single rod etonogestrel implant

### **Research Outcome**

Abnormal uterine bleeding patterns

### **Studies Features**

Data from 11 clinical trials including 923 women were reviewed. These studies were conducted in the United States, Southeast Asia, Europe, Chile, and Russia. The women were between 18 and 40 years of age, were sexually active, and had previously reported regular menstrual cycles. Breast feeding subjects and those without post baseline efficacy data were excluded. Assess-

ments included bleeding-spotting records and patient-perceived reasons for discontinuation. In addition, to assess whether blood loss associated with the use of the implant resulted in anemia, hemoglobin blood levels were measured at baseline and at the end of treatment in several studies.

Data were analyzed by dividing each subject's bleeding information into 90-day segments. Each segment represented on "reference period." Reference period information was considered invalid and thus excluded if bleeding information was missing for three or more consecutive days. The authors used WHO recommended definitions. For each of the 90-day reference periods, amenorrhea was defined as no bleeding or spotting days, infrequent bleeding as less than three bleeding/spotting episodes excluding amenorrhea, frequent bleeding as 3 to 5 bleeding/spotting days, and prolonged bleeding as any uninterrupted bleeding/spotting lasting more than 14 days.

*(Level 1 Evidence)*

### **The Evidence**

Single rod etonogestrel implant use was found to be associated with the following bleeding irregularities; infrequent bleeding (33.6%), amenorrhea (22.2%), prolonged bleeding (17.7%), and frequent bleeding (6.7%). In 75% of the reference periods, bleeding-spotting days were fewer than or comparable to those observed during the natural cycle, but they occurred at unpredictable intervals. The bleeding pattern experienced during the initial phase predicted future patterns for the majority of women. The group of women with favorable bleeding patterns during the first three months tended to continue with this pattern throughout the first two years of use, whereas the group with unfavorable initial patterns had at least a 50% chance that the pattern would improve. Some 11.3% of patients discontinued due to bleeding irregularities, mainly because of prolonged flow and frequent irregular bleeding.

**Appraised by:** The Jordan Evidence-Based Medicine Reproductive Health Group

**Update by:** 2 March 2016

## **Use of the single rod etonogestrel implant is associated with an increase the risk of amenorrhea**

### **Conclusion**

The single rod etonogestrel implant is an effective contraceptive device though the risk of amenorrhea is increased. .

### **Clinical Question**

Does the single rod etonogestrel implant increase the incidence of amenorrhea?

### **Search Terms**

Single rod etonogestrel implant, amenorrhea

### **Object of Research**

Implanon<sup>®</sup>, single rod etonogestrel implant

### **Research Outcome**

Amenorrhea.

### **Citations**

Gezginc K, Balci O, Karatayli R., Colakoglu MC. *Contraceptive efficacy and side effects of Implanon<sup>®</sup>*. Eur J Contracept Reprod Health Care 2007; Vol. 12, No. 4: 362-365.

Bitzer J, Tschudin S, Alder J, Swiss Implanon Study Group. *Acceptability and side-effects of Implanon Switerland: a retropectie study by the Implanon Swiss Study Group*. Eur J Contracept Reprod Health Care 2004; Dec;9(4):278-284.

Bhatia P, Sangita N, Shivani A, Chitra T. *Implanon: Subdermal Single Rod Contraceptive Implant*. Journal of Obstetrics and Gynecology of India 2011; 61(4):422-425.

## **Study Features**

### Gezgine et al

This is a prospective cohort study of 80 patients who received the single rod etonogestrel implant as a contraceptive. The study was conducted in Konya, Turkey starting in 2004 and completed in 2006. Amenorrhea was defined as the absence of menstruation for three months.

*(Level 2 Evidence)*

### Bitzer et al

This is a multicenter, retrospective study of the single-rod etonogestrel contraceptive implant in which 1,183 women users were identified. A total of 991 (84%) women had at least one follow-up visit and 306 (26%) had two visits with a mean duration between insertion and follow-up of 224 days and 347 days, respectively.

*(Level 2 Evidence)*

## **Study Features (con't)**

### Bhatia et al

This is a prospective study of 200 Indian women users of the single rod etonogestrel implant enrolled over a period of one year in 2004 and 2005. The plan was for women to use the implant for up to three years.

*(Level 2 Evidence)*

## **The Evidence**

### Gezgine et al

Amenorrhea was reported by 33 (41%) of the 80 patients. The time of these events post-insertion was not reported. None of the women in this study had their implant removed because of amenorrhea.

### Bitzer et al

Amenorrhea was reported by one-third of all women. The time of these events post-insertion was not reported. Importantly, none of these women in this study had their implant removed because of amenorrhea.

Bhatia et al

Nine (4.5%) of the 200 women had their device removed because of amenorrhea. Overall, almost one-quarter of all users reported the occurrence of amenorrhea.

**Appraised by:** The Jordan Evidence Based Medicine Reproductive Health Group

**Update by:** 3 March 2016

## **The use of the single rod etonogestrel is associated with relief of dysmenorrhea**

### **Conclusion**

In a sub-study of a large multicentre study in the United States, there is evidence that the single rod etonogestrel implant is associated with relief of dysmenorrhea. Almost half of the women in this study reported decreased dysmenorrhea.

### **Clinical question:**

Is the use of Implanon® associated with any changes in dysmenorrhea?

### **Search Terms**

Implanon®, Single rod etonogestrel implants, dysmenorrhea

### **Object of Research**

Single rod etonogestrel implant

### **Research Outcome**

Changes in dysmenorrhea

### **Citations**

Funk S, Miller M, Mishel D, et al. *Safety and efficacy of Implanon™, a single-rod implantable contraceptive containing etonogestrel*. *Contraception* 2005; 71: 319-326.

### **Study Features:**

This is a multicenter cohort study of 330 sexually active female volunteers in the United States. Of these 330 women, 315 (95.5%) provided baseline and post baseline information on dysmenorrhea. Single rod etonogestrel implant contraceptive acceptors were assessed over a two year period at 3 month intervals.

*(Level 2 Evidence)*

**The Evidence**

The percentage of women with dysmenorrhea at baseline was almost three times that observed at post baseline; 59 percent compared to 21 percent. The shifts from baseline to the end of the study showed that 151 (48%) women reported decreased dysmenorrhea, 139 (44%) reported no change, and 25 (8%) reported an increase. Of the 187 women who had dysmenorrhea at baseline, 151 (81%) reported decreased dysmenorrhea, 26 (14%) reported no change, and 10 (5%) reported increased dysmenorrhea.

**Appraised by:** The Jordan Evidence Based Medicine Reproductive Health Group

**Update By:** 2 March 2016

# **The use of the single rod etonogestrel implant is associated with an improvement of symptoms of endometriosis**

## **Conclusion**

The therapeutic effect of the single rod etonogestrel implant is similar to depot medroxyprogesterone acetate (DMPA) for the treatment of symptomatic endometriosis. Improvement in the symptoms associated with endometriosis was general associated with the implant.

## **Clinical question:**

Is the use of the single rod etonogestrel implant associated with an improvement in the symptoms of endometriosis?

## **Search Terms**

Single rod etonogestrel implant, Implanon<sup>®</sup>, endometriosis

## **Object of Research**

Single rod etonogestrel implant

## **Research Outcome**

Improvement of endometriosis symptoms

## **Citations**

Walsh K, Unfried G, et al. *Implanon<sup>®</sup> versus medroxy progesterone acetate: effects on pain scores in patients with symptomatic endometriosis. a pilot study.* Contraception 2009; 79(1):29-34.

Funk S, Miller M, Mishel D, et al. *Safety and efficacy of Implanon<sup>™</sup>, a single-rod implantable contraceptive containing etonogestrel.* Contraception 2005; 71: 319-326.

Croxatto H, Urbancsel, Massai R, et al. *A multicentre efficacy and safety study of the single contraceptive implant Implanon<sup>®</sup>.* European Soc Human Reprod and Embryology 1999; 14: 976-981.

## **Study Features**

### Walsh K, et al.

This clinical research was conducted in the university hospital , 41 patients with dysmenorrhea, non menstrual pelvic pain and dyspareunia associated with histologically proven endometriosis were included in an open, prospective, randomized, controlled trials .Twenty- one women were assigned by computer- generated randomization to receive Implanon® and 20 to receive DMPA. Prior to inclusion in the study, women were requested to grade the severity of dysmenorrhea, non-menstrual pelvic pain, and dyspareunia on a 100-mm visual analog scale (AS).

*(Level 1 Evidence)*

### Funk et al

This is a multicenter cohort study of 330 sexually active women in the United States. Acceptors of the single rod etonogestrel implant contraceptive method were assessed over a two year period at 3 month intervals. Dysmenorrhea, a symptom of endometriosis was assessed at the time of insertion of the device and at each of the follow-up visits. At baseline, 136 (41.2%) of the acceptors had no dysmenorrhea, 120 (36.4%) mild, 73 (22.1%) severe and 1 (0.3%) very severe.

*(Level 2 Evidence)*

### Croxatto et al

This is a multicenter cohort study of 635 sexually active women in Europe. Acceptors of the single rod etonogestrel implant contraceptive method were to be assessed over a two year period at 3 month intervals, but the period of observation was extended to 3 years in a group of 137 women in two centres. Dysmenorrhea, a symptom of endometriosis was assessed at the time of insertion of the device and at each of the follow-up visits. At study initiation, 35 percent of the women reported a history of dysmenorrhea.

*(Level 2 Evidence)*

## **The Evidence**

### Walsh K, et al

During a follow-up period of 1 year, there were clear improvements in pain intensity for both treatment options. After 6 months, the average decrease in pain was 68% in the single rod etonogestrel implant group and 53% in the DMPA group. The side-effects profile and the overall degree of satisfaction after study termination were comparable for both treatment options.

### Funk et al

Three hundred fifteen implant users provided baseline and post baseline dysmenorrhea information. Of these, 151 (48%) reported decreased dysmenorrhea, 139 (44%) reported no change and 25 (8%) an increase in dysmenorrhea.

### Croxatto et al

At the end of the study, dysmenorrhea had improved in 87 percent of the women using implants and who had a history of dysmenorrhea. In 4 percent, this symptom was reported as a new occurrence or a worsening of existing dysmenorrhea.

**Appraised by:** The Jordan Evidence Based Medicine Reproductive Health Group

**Update By:** 3 March 2016

## **The use of a single rod progesterone is not associated with significant weight gain**

### **Conclusion**

Weight change was variable among women using progestin-only contraceptives. However, adjusting for other weight risk factors, when compared to a copper IUD, no significant weight gain among the single rod etonogestrel implant users was observed.

### **Clinical Question**

Is the use of a single rod etonogestrel implant associated with weight gain?

### **Search Terms**

Single rod etonogestrel implant, Implanon<sup>®</sup>, weight gain.

### **Citations**

Vickery Z, Madden T, Zhao Q, Secura GM, Allsworth JE, Peipert JF. *Weight change at 12 months in users of three progestin-only contraceptive methods.* Contraception 2013; 88(4):503-8.

### **Object of Research**

Single rod etonogestrel implant

### **Research Outcome**

Weight gain

### **Study Features**

This was a sub-study of the Contraceptive CHOICE Project, a prospective cohort study of 9,256 women provided no-cost contraception. Women who had been using the single rod etonogestrel implant, LNG-IUS a three months injectable DMPA or a copper IUD continuously for at least 11 months were eligible for participation. The study obtained body weight at enrollment and at 12 months and compared the weight change for each progestin-only method to the copper IUD. A total of 427 women were enrolled: 130 ENG implant users, 130 LNG-IUS users, 67 DMPA users and 100 copper IUD users. (*Level 2 Evidence*)

**The Evidence**

The mean weight change (in kilograms) over 12 months was 2.1 for the single rod etonogestrel implant users; 1.0 for LNG-IUS users ; 2.2 for DMPA users and 0.2 for copper IUD users. The range of weight change was broad across all contraceptive methods. When adjusting for baseline factors, compared to the copper IUD, no difference in weight gain with the single rod etonogestrel implant, LNG-IUS or DMPA was observed.

**Appraised by:** The Jordan Evidence Based Medicine Reproductive Health Group

**Update by:** 2 March 2016

# **The use of the single rod etonogestrel implant does not have an overall effect on severity of acne**

## **Conclusion**

In a sub-study of a large multicentre study in the United States, there was no evidence that the single rod etonogestrel implant is associated with any negative effects on acne. However, among those with acne at the start of the study, more than half experienced an improvement of their acne condition.

## **Clinical question:**

Is the use of the single rod etonogestrel implant associated with any changes in acne?

## **Search Terms**

Implanon<sup>®</sup>, single rod etonogestrel, acne

## **Object of Research**

Single rod etonogestrel implant

## **Research Outcome**

Perceived changes in acne

## **Citations**

Funk S, Miller M, Mishel D, et al. *Safety and efficacy of Implanon<sup>™</sup>, a single-rod implantable contraceptive containing etonogestrel*. *Contraception* 2005; 71: 319-326.

## **Study Features:**

This is a multicenter cohort study of 330 sexually active women in the United States. Of these 330 women, 315 (95.5%) provided baseline and post baseline information on their acne condition. These Implanon<sup>®</sup> contraceptive acceptors were assessed over a two year period at 3 month intervals.

*(Level 2 Evidence)*

**The Evidence**

There were no observed changes in the proportion of those with acne at baseline (26.7%) and at post baseline (23.8%). The shifts from baseline to the end of the study showed that 51 (16%) women reported decreased acne, 221 (70%) reported no change, and 43 (14%) reported increased acne. Of the 231 women who did not have acne at baseline, 195 (84%) reported no change whereas 36 (16%) reported increased incidence of acne. Of the 84 women who had acne at baseline, 51 (61%) reported a decrease, 26 (31%) reported no change and 7 (8%) reported increased acne.

**Appraised by:** The Jordan Evidence Based Medicine Reproductive Health Group

**Update By:** 2 March 2016

## **Women using the single rod etonogestrel implant had a small reduction in libido after one year of use.**

### **Conclusion**

The single rod etonogestrel implant used as a contraceptive had little effect on women sexuality and the reduction in libido was observed in less than 10% of users. It should be noted that no large scale studies are available to assess decreases in libido.

### **Clinical Question**

Is the use of the single rod etonogestrel implant associated with a decrease in libido?

### **Search Terms**

Single rod etonogestrel implant, Implanon<sup>®</sup>, sexuality, libido

### **Citation**

Aisien AO, Enosolease ME. *Safety, efficacy and acceptability of implanon a single rod implantable contraceptive (etonogestrel) in University of Benin Teaching Hospital.* Niger J Clin Pract. 2010;13(3):331-5.

Gezginc K, Balci O, Karatayli R, Colakoglu MC. *Contraceptive efficacy and side effects of Implanon<sup>®</sup>.* Eur J Contracept Reprod Health Care 2007;12(4):362-365.

### **Object of Research**

Single rod etonogestrel implant

### **Research Outcome**

Libido

## **Study Features**

### Aisien et al

This study was part of an on-going prospective longitudinal study that involved 32 women out of 46 sexually active healthy volunteers aged between 24-45 years. They were recruited from a family planning clinic between February and March 2007. All the subjects received the single rod etonogestrel implant etonogestrel. The 32 women had completed records after 12 months of the single rod etonogestrel implant. Data on socio-demographic characteristics, menstrual pattern, haematological indices, weight, blood pressure, side effects and user's satisfaction were collected and analyzed.

*(Level 2 Evidence)*

### Gezginc et al

This is a prospective study of 80 Turkish women who used the single rod etonogestrel implant for contraception. All women were followed up at three months intervals for at least a year.

*(Level 2 Evidence)*

## **The Evidence**

### Aisien et al

Only 3 (7.3%) women reported a reduction in libido. There were no discontinuations were reported for this reason.

### Gezginc et al

Loss of libido was reported by 2 (2.5%) women. Both of these women had the device removed.

**Appraised by:** The Jordan Evidence Based Medicine Reproductive Health Group

**Updates by:** 3 March 2016

## **The use of the single rod progesterone is not associated with any vision disturbances**

### **Conclusion**

In small sub-study of a large multicenter investigation, the single rod etonogestrel implant was not found to be not associated with any negative effects on vision.

### **Clinical question:**

Is the use of the single rod etonogestrel implant associated with any vision disturbances?

### **Search Terms**

Single rod etonogestrel implant, Implanon<sup>®</sup>, vision disturbances

### **Object of Research**

Single rod etonogestrel implant

### **Research Outcome**

Changes in vision

### **Citation**

Funk S, Miller M, Mishel D, et al. *Safety and efficacy of Implanon™, a single-rod implantable contraceptive containing etonogestrel*. *Contraception* 2005; 71: 319-326.

### **Study Features:**

This is a multicenter cohort study of 330 sexually active women in the United States. Acceptors of the single rod etonogestrel implant were assessed over a two year period at 3 month intervals. A small sub-group of 20 women were assessed for vision changes using gross external examinations, slit lamp examinations and ophthalmoscopy.

*(Level 2 Evidence)*

**The Evidence**

Ophthalmologic examinations revealed no clinically significant findings in the subset of 20 women.

**Appraised by:** The Jordan Evidence Based Medicine Reproductive Health Group

**Update By:** 2 March 2016

## **The use of the single rod etonogestrel implant may have an effect on loss of bone mineral density (BMD)**

### **Conclusion**

Use of the single rod etonogestrel implant for up to 3 years resulted in lower bone mass density relative to pre-insertion measurements. The clinical significance of these changes are unclear. In a comparative study with IUD users, no significant differences with single rod etonogestrel implant users were found in bone mass density changes.

### **Clinical Question**

Is the use of a single rod etonogestrel implant associated with a significant decrease in bone mineral density?

### **Search Terms**

Implanon®, single rod etonogestrel implant, bone mineral density

### **Citations**

Monteriro-Dantas C, Espejo-Arce X, Lui-Filho JF, Fernandes AM, Monteiro I, and Bahamondes L. *A three-year longitudinal evaluation of the forearm bone density of users of etonogestrel- and levonogestrel-releasing contraceptive implants*. Reproductive Health 2007;12(4):11.

Beerthuisen R, van Beck A, Massai R, MäKäräinen L, in't Hout J, and Bennink HC. *Bone mineral density during long-term use of the progestagen contraceptive implant Implanon® compared to a non-hormonal method of contraception*. Human Reproduction 2000;15(1):118-122.

### **Object of Research**

Single rod etonogestrel implant

### **Subject of Research**

Bone mineral density

## **Study Features**

### Monteriro-Dantas et al.

This was a prospective study conducted in Brazil between August 2003 and July 2004. Initially it included 111 women, 19-43 years of age. Patients were randomly allocated to two groups: 56 to a single rod etonogestrel implant and 55 to a two-rod levonorgestrel contraceptive (Jadelle®) implant. Bone mineral density (BMD) was evaluated at the mid shaft of the distal radius and at the ultra-distal radius. Measurements were taken using dual-energy X-ray absorptiometry before insertion and at 18 and 36 months of use.

*(Level 2 Evidence)*

### Beerthuisen et al.

This was open, prospective, comparative multi-centre study (Finland, Chile, and Netherlands) for healthy women between the ages of 18 and 40 years. The study was designed to study the effect of the single rod etonogestrel implant on BMD. The control group used a non-hormone-medicated IUD. BMD measurements included the lumbar spine ( $L_2 - L_4$ ), the proximal femur, Ward's triangle, and distal radius. These were taken at baseline and at 6, 12 and 24 months post-insertion using dual-energy, X-ray absorptiometry. Data was collected from 44 women using the implant and 29 using a non-hormonal IUD.

*(Level 2 Evidence)*

## **The Evidence**

### Monteriro-Dantas et al

At the 18 month evaluation, the BMD of the distal radius in the single rod etonogestrel group dropped from pre-insertion level of 0.475 g/cm<sup>2</sup> to 0.454 g/cm<sup>2</sup> after 18 months of usage ( $p < 0.0001$ ). The ultra-distal radius dropped from 0.406 g/cm<sup>2</sup> to 0.390 g/cm<sup>2</sup> ( $p=0.104$ ). The difference at the mid shaft ulna was statistically significant

At 36 months, 36 (64%) of the original 56 single rod etonogestrel patients continued to use the method. For this group, the BMD of the distal radius dropped from pre-insertion level of 0.475 g/cm<sup>2</sup> to 0.447 g/cm<sup>2</sup> at 36 months

of usage ( $p < 0.0001$ ). The ultra-distal radius changed from baseline figure of  $0.406 \text{ g/cm}^2$  to  $0.396 \text{ g/cm}^2$  at 36 months ( $p=0.249$ ).

The authors comment that though BMD was decreased relative to baseline at 18 and 36 months, it is not possible to conclude that the losses are of clinical significance.

Beerthuisen et al.

This study did not show any significant differences in BMD between the single rod etonogestrel implant and the non-hormone IUD groups in the initial assessments nor in the follow-up measurements for all the different sites evaluated.

**Appraised by:** The Jordan Evidence Based Medicine-Reproductive Health Group,

**Update by:** 3 March 2016

## **The use of the single rod etonogestrel implant is associated with an increased risk of simple ovarian cysts**

### **Conclusion**

The finding of ovarian cysts or enlarged ovarian follicles during the first year of use of the single rod etonogestrel implant is common and transient. Nevertheless, close follow-up is recommended to exclude other underlying pathological causes.

### **Clinical Question**

Is the use of the single rod etonogestrel implant associated with an increased risk of ovarian cysts?

### **Search Terms**

Ovarian cysts, single rod etonogestrel implant, Implanon®

### **Citation**

Hidalgo MM, Lisondo C, Juliato CT, Espejo-Arce X, Monteiro I, Bahamondes L. *Ovarian cysts in users of Implanon® and Jadelle® subdermal contraceptive implants*. *Contraception* 2006; 73:532-536.

### **Object of Research**

Single rod etonogestrel implant

### **Research Outcome**

Ovarian cysts

## **Study Features**

This is a prospective Brazilian study of the three contraceptive methods; the single rod etonogestrel implant, Jadelle® and a TCU380. Women were recruited at insertion and consecutively followed up for one year at three month intervals. In total, 116 single rod etonogestrel implant users, 123 users of Jadelle® and 105 users of the TCU380 IUD were enrolled in the study. The presence of an ovarian cyst or ovarian follicle was assessed at the three, six, and twelve month period after insertion of their implant/device.

*(Level 2 Evidence)*

## **The Evidence**

Ovarian cysts were detected in 6 (5.2%), 16 (13.0%), and 2 (1.9%) users of the single rod etonogestrel implant, Jadelle® and the TCU3800, respectively at the third month of use. The differences among the groups was statistically significant ( $p < 0.005$ ). At six months, the presence of ovarian cysts in these three groups was detected in 8 (7.2%), 9 (8.0%) and 1 (2.1%), respectively. This difference among the three groups was not statistically significant ( $p = .168$ ) while at 12 months, 27 (26.7%), 15 (14.6%) and 1 (1.2%) ovarian cysts, respectively, were detected. At this follow-up visit, ovarian cysts were detected in almost twice the number of single rod etonogestrel implant users as compared to those who were Jadelle® users. Both types of implants had a significantly higher prevalence than the IUD users. The presence of these ovarian cysts was transient with disappearance occurring 7 to 72 days for the single rod implant, 7 to 62 days for Jadelle®, and 7 to 53 days for the TCU380 IUD.

**Appraised by:** The Jordan Evidence Based Medicine-Reproductive Health Group

**Update by:** 3 March 2016

**The use of the single rod etonogestrel implant appears to be associated with an increased risk of headache.**

### **Conclusion**

Headache as an adverse event appears to be associated with the use of the Implanon®.

### **Clinical Question**

Is the use of Implanon® associated with an increased risk of headache?

### **Search Terms**

Single rod etonogestrel implant, Implanon®, headache

### **Citation**

Darney, P., A. Patel, et al. (2009). *Safety and efficacy of a single-rod etonogestrel implant (Implanon): results from 11 international clinical trials.* Fertil Steril 91(5): 1646-1653.

### **Object of Research**

Single rod etonogestrel implant

### **Research Outcome**

Headache

### **Study Features**

This report is based on an integrated analysis of the clinical data from 11 international Good Clinical Practice compliant studies. Studies were conducted in the U.S, Chile, Europe and Asia. Study participants were healthy, sexually active women, 18-40 years of age with normal menstrual cycles. After exclusion of women who used other hormonal contraception in the last 2-6 months, or who had recent delivery or abortion, a total of 946 subjects using Implanon® were enrolled in the clinical studies.

*(Level 1 Evidence)*

**The Evidence**

All adverse events experienced by subjects throughout the duration of the 11 clinical trials are presented. Of those adverse events headache was observed in 15.5% and headache was the primary reason for discontinuation in 1.6 percent of the users.

**Appraised by:** The Jordan Evidence-Based Medicine Reproductive Health Group

**Update by:** 3 March 2016

## **The use of the single rod etonogestrel implant is not associated with increased risk of hypertension.**

### **Conclusion**

Some women using the single rod etonogestrel implant experience slight increases in blood pressure while others have a decrease. Overall, most women stay within normal limits with respect to systolic and the diastolic blood pressure

### **Clinical question**

Is the use of the single rod etonogestrel implant associated with an increased risk of hypertension?

### **Search Terms**

Implanon<sup>®</sup>, the single rod etonogestrel implant, hypertension

### **Citations**

Aisien AO.et al. *Safety, efficacy and acceptability of Implanon a single rod implantable contraceptive (Etonogestril) in University of Benin Teaching Hospital.*

Nigerian Journal of Clinical Practice 2010; Vol. 13(3):331-335.

Croxatto HB, Urbancsek J, Massai R, Bennink HC, et al. *A multicenter efficacy and safety study of the single contraceptive implnt Implanon<sup>®</sup>.* Human Reproduction 1999; 14(4): 976-981.

### **Object of Research**

Single rod etonogestrel implant

### **Research outcome**

Hypertension

### **Study Features**

Aisien et al

This was part of an ongoing prospective longitudinal study that involved 32 women out of 46 sexually active healthy informed volunteers recruited

from a Nigerian family planning clinic between February and March 2007. All the subjects received the single rod etonogestrel implant containing 68 mg etonogestrel. Data on socio-demographic characteristics, menstrual pattern, hematological indices, weight, blood pressure, side effects and user's satisfaction were collected and analyzed.

*(Level 2 Evidence)*

Croxatto et al

This is an open label, multicenter study to assess efficacy and safety of the single-rod etonogestrel contraceptive implant. The study drew patients from 21 centers in nine different countries and involved 635 young healthy women who were sexually active and of child bearing potential. Women were followed up every three months for three years. A systolic blood pressure reading greater than 140 mmHG with an increase of 20 mmHg and a diastolic greater than 90 mmHg with an increase greater than 10 mmHg each at two assessments or at the last assessment was considered clinically significant.

*(Level 2 Evidence)*

**The Evidence:**

Aisien et al

The mean systolic and diastolic blood pressures did not show any significantly significant changes from baseline at the 6 months follow up (systolic:  $p=0.17$ ; diastolic  $p=0.64$ ). However at 12 months there were statistically significant changes from baseline though the changes were within normal range (systolic:  $p=0.003$ ; diastolic  $p=0.05$ ).

Croxatto et al

Ten (1.6%) had women clinically significant blood pressure readings. Overall though, the mean systolic and diastolic blood pressure showed a small decrease over time.

**Appraised by:** The Jordan Evidence Based Medicine Reproductive Health Group

**Update By:** 2 March 2016

## **There is no evidence that the use of the single rod etonogestrel is associated with an increase in stroke**

### **Conclusion**

Data on the use of the single rod etonogestrel implant with respect to stroke is sparse. But WHO Guidelines consider this progestin only method as a contraceptive option for women with a history of stroke.

### **Clinical Question**

Does the use of the single rod etonogestrel implant increase the risk of stroke?

### **Search Terms**

Implanon<sup>®</sup>, the single rod etonogestrel implant, stroke

### **Citation**

Darney P, Patel A, Rosen K, Shapiro LS, Kaunitz AM, *Safety and efficacy of a single-rod etonogestrel implant (Implanon): results from 11 international clinical trials.* Fertil Steril; 91(5):1646-53, 2008.

Department of Reproductive Health, World Health Organization. *Medical Eligibility Criteria for Contraceptive Use. 4<sup>th</sup> ed.* 2009.

### **Object of Research**

Progestin only contraceptives, the single rod etonogestrel implant. Implanon<sup>®</sup>

### **Research Outcome**

Stroke

### **Study Features**

This report is based on an integrated analysis of the clinical data from 11 international studies. Studies were conducted in the United States., Chile, Europe, and Asia. A total of 923 subjects were enrolled in the clinical studies designed to assess safety.

*(Level 1 Evidence)*

**The Evidence**

Fifty-six (5.9%) of 942 women using the single rod etonogestrel implant experienced a total of 77 serious adverse events. None of these women experienced an event involving deep vein thrombosis, stroke or myocardial infarction.

**Appraised by:** The Jordan Evidence-Based Medicine Reproductive Health Group

**Update by:** 3 March 2016

# **The use of the single rod etonogestrel implant used by breastfeeding woman does not affect breast milk production**

## **Conclusion**

When early insertion of the single rod etonogestrel implant was compared to standard insertion time, there were not significant differences in breastfeeding outcomes. That is, early postpartum insertion does not appear to affect breast milk production in breastfeeding women.

## **Clinical Question**

Will the use of the single rod etonogestrel implant in a breastfeeding woman affect breast milk production?

## **Search Terms**

Single rod etonogestrel implant, Implanon<sup>®</sup>, breastfeeding, breast milk production, lactogenesis.

## **Citation**

Gurtcheff SE, Turok DK, Stoddard G, Murphy PA, Gibson M, Jones KP. *Lactogenesis after early postpartum use of the contraceptive implant: a randomized controlled trial*. *Obstet Gynecol*. 2011;117:1114-21.

## **Object of Research**

Single rod etonogestrel implant

## **Subject of Research**

Breast milk production

## **Study Features**

This was a randomized controlled trial. Sixty-nine women who desired the etonogestrel implant for contraception were enrolled. They were healthy peripartum women with healthy, term newborns were randomly assigned to early (1–3 days) or standard (4–8 weeks) postpartum insertion. Thirty-five were randomly assigned to early insertion and 34 to standard insertion. There

were no statistically significant differences between the groups in age, race, parity, mode of delivery, use of anesthesia, or prior breastfeeding experience.

The primary outcomes, time to lactogenesis stage II and lactation failure, were documented by a validated measure. The margin for the mean difference in time to lactogenesis stage II was defined as 8 additional hours. Secondary data (device continuation and contraceptive use, breast milk analysis, supplementation rates, side effects, and bleeding patterns) were collected at periodic intervals for 6 months.

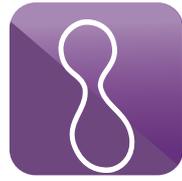
*(Level 1 Evidence)*

### **The Evidence**

Early insertion was found to be similar to standard insertion in time to lactogenesis stage II [early: mean=64.3±19.6 hours; standard: 65.2±18.5 hours]. Early insertion was also found to be similar to standard insertion in incidence of lactation failure [early: 0/35; standard: 1/34]. Nor was use of formula supplementation significantly different between the two groups. Finally, analysis of milk composition at 6 weeks revealed no significant differences.

**Appraised by:** The Jordan Evidence Based Medicine-Reproductive Health Group

**Update by:** 3 March 2016



**Vaginal Ring**

**Vaginal Ring**



## **VAGINAL CONTRACEPTIVE RING**

In Jordan, the combined vaginal ring contraceptive is likely used by less than half a percent of all women of reproductive age and was not even quantified in the 2009 Jordan Demographic Health Survey<sup>1</sup>. In Jordan it is marketed under the commercial name NuvaRing®. Most women can use the vaginal ring, but health professionals should be aware of the World Health Organization Medical Eligibility Criteria for Contraceptive Use<sup>2</sup>.

### **Effectiveness**

The vaginal ring is highly effective. Among women who use the method correctly and consistently, less than 1 percent will experience a method failure in the first year of use. In terms of typical use though, no reliable estimates are available<sup>3</sup>. Duration of use is not associated with any decrease in efficacy or safety suggesting that there is no need for a rest period.

### **Mode of Action**

The primary mode of action of the vaginal ring is ovulation suppression. Other possible mechanisms include effects on cervical viscosity and endometrial thinning<sup>4</sup>.

### **Advantages of the Vaginal Ring**

In addition to being highly effective, other advantages to using the vaginal ring are:

- that it acts like a combined oral contraceptive and thus the absolute number of ectopic pregnancies are reduced<sup>5</sup>
- it is rapidly reversible<sup>6</sup>
- it is an option throughout reproductive years
- it decreases menstrual blood loss/regulates menses<sup>7</sup>

*Cycle control with the use of a vaginal ring is comparable to a combined oral contraceptive; that is, it is good and there is also a decreased menstrual blood loss.*

### **Disadvantages of the Vaginal Ring**

- Requires Weekly Administration

*Differences in pregnancy rates of those taking their pill daily versus those who are not consistent compliers .*

- Increased risk of vaginitis<sup>8-10</sup>

## **Special Topics**

- Cardiovascular Risks<sup>11</sup>

*The use of the combined contraceptive vaginal ring (NuvaRing®) appears to have a similar risk of thromboembolism as women using standard combined low dose oral contraceptive pills. However, current data are insufficient to detect a significant increase in such a rare event.*

- Breastfeeding<sup>2</sup>

*Data are not available to assess the effect of the combined contraceptive vaginal ring as used by breastfeeding women. However, based on indirect evidence drawn from studies addressing combined oral contraceptive pills and their use by breastfeeding women, the WHO does not recommend the ring for use during the first six months postpartum*

- Cancer

*There is not sufficient data to assess any association of the vaginal ring and any cancer of the reproductive system or breast cancer. Because it acts similarly to the combined oral contraceptive, it may provide similar protective effects though this is speculative.*

## REFERENCES

### Vaginal Contraceptive Rings

1. Department of Statistics [Jordan] and ICF Macro,2010. *Jordan Population and Family Health Curvey 2009*. Calverton, Maryland, USA: Department of Statistics and ICF Macro.
2. World Health Organization. *Medical eligibility criteria for contraceptive use*. Geneva:WHO, 2004.
3. Hatcher RA, Trussell J, Nelson AL, Cates W, Stewart F, Kowal D. *Contraceptive Efficacy*. Contraceptive Technology. New York: Ardent Media Inc, 2008. 747-826.
4. Hatcher RA, Trussell J, Nelson AL, Cates W, Stewart F, Kowal D. *Contraceptive patch and vaginal contraceptive ring*. Contraceptive Technology. New York: Ardent Media Inc, 2008. 283.
5. Mol BWJ, Ankum WM, Bossuyt PMM, Van der Veen F. *Contraception and the risk of ectopic pregnancy: A meta-analysis*. Contraception 1995;52:337-341.
6. Mulder TMT, Dieben TOM, Bennick HJTC. *Ovarian Function with a novel combined contraceptive vaginal ring*. Human Reproduction 2002;17(10):2594-2599
7. Lopez LM, Grimes DA, Gallo MF, et al, *Skin patch and vaginal ring versus combined oral contraceptives*. Cochrane Database of Systemic Reviews 2013, Issue 3. Art. No.: CD003552. DOL:10.1002/14651858. CD003552.pub4.
8. Mohamed AM, El-Sherbiny WS, Mostafa WA. *Combined contraceptive ring versus combined oral contraceptive (30- $\mu$ g ethinylestradiol and 3-mg drospirenone)*. Int J Gynaecol Obstet 2011; 114(2): 145-146.
9. Oddsson K, Leifels-Fischer B, Reoberto de Mel N, et al. *Efficacy and safety of a contraceptive vaginal ring (NuvaRing) compared with a combined oral contraceptive: a 1-year randomized trial*. Contraception 2005; 71:176-182.
10. Camacho DP, et al. *Vaginal yeast adherence to the combined contraceptive vaginal ring (CCVR)*. Contraception. 2007; 76(6):439-43.
11. Dinger J, Mohner S, Heinemann K. *Cardiovascular risk associated with the use of an etonogestrel-containing vaginal ring*. Obset Gynecol 2013;122(4): 800-808.

## **List of Critically Appraised Topics**

- 1-Efficacy
- 2-Acceptability
- 3-Return to Fertility
- 4-Ectopic Pregnancy
- 5-Menstrual Blood Loss
- 6-Venous Thromboembolism
- 7-Blood Pressure
- 8-Headache
- 9-Migraine
- 10-Vaginitis
- 11-Antimycotics
- 12-Tampons
- 13-Weight Gain
- 14-Bone Mass Density
- 15-Breastfeeding

*Note that the level evidence accompanying each publication in each of the CATs refers to the study design.*

# **The combined contraceptive vaginal ring (NuvaRing®) is an effective contraceptive method for women preferring to use short acting hormonal contraception**

## **Conclusion**

The efficacy of contraceptive methods in descending order are: (1) long-acting hormonal contraceptives (LNG-IUS and single rod etonogestrel implant); (2) Cu-IUDs with at least 300 mm<sup>2</sup> surface area; (3) Cu-IUDs with less than 300 mm<sup>2</sup> surface area; (4) short-acting hormonal contraceptives (injectables, oral contraceptives, the patch and the combined contraceptive vaginal ring), and (5) barrier and natural methods.

## **Clinical Question**

What is the efficacy of combined contraceptive vaginal ring in comparison to other methods?

## **Search Terms**

Contraceptives, combined contraceptive vaginal ring, NuvaRing®, efficacy, effectiveness

## **Citation**

Mansour D, Inki P, Gemzell-Danielsson K. *Efficacy of contraceptive methods: A review of the literature*. Eur J Contracept Reprod Health Care. 2010;15(1):4-16

## **Object of Research**

Combined contraceptive vaginal ring

## **Research Outcome**

Efficacy

## **Study Features**

Standard medical databases were searched for published articles with objective to identify studies reporting contraceptive efficacy which included the Pearl Index. Reports that recruited less than 400 subjects per study group

and those covering less than six cycles/six months were excluded. In addition, unlicensed products or those not internationally available, (e.g. emergency contraception), and male or female sterilization studies were excluded. Information was identified and extracted from 139 studies.

*(Level 2 Evidence)*

### **The Evidence**

One-year Pearl Indices (# pregnancies per 100 women years of use) reported for combined contraceptive vaginal ring ranged from 0.25 to 1.23 under typical use. Short-acting user-dependent hormonal methods were generally less than 2.5 (combined oral contraceptives: 0-1.26, progesterone only pill: 0.14). Pearl indices for long-acting hormonal methods (single rod etonogestrel implant and the levonorgestrel releasing-intrauterine system [LNG-IUS]) generally ranged between 0–0.6 per 100 at one year, but wider ranges (0.1–1.5 per 100) were observed for the copper intrauterine devices (0.1–1.4 per 100 for Cu-IUDs with surface area  $\geq 300\text{mm}^2$  and 0.6–1.5 per 100 for those with surface area  $< 300\text{mm}^2$ ). Pearl indices for the male condom ranged between 2.5-5.9, natural methods ranged between 3.8-20.4.

**Appraised by:** The Jordan Evidence Based Medicine Reproductive Health Group

**Update by:** 4 March 2016

## **There is a high level of user and partner acceptability for the combined contraceptive vaginal ring**

### **Conclusion**

There is a high level of user and partner acceptability for the combined contraceptive vaginal ring. The majority of women found the instructions for use to be clear, felt comfortable with the ring during intercourse, were very satisfied with the ring, and would recommend it to others.

### **Clinical Question**

What is the level of user and partner acceptability of the combined contraceptive vaginal ring?

### **Search Terms**

Combined contraceptive vaginal ring, NuvaRing<sup>®</sup>, contraceptive, acceptability.

### **Citations**

Novak A, de la Loge C, Abetz L, van der Meulen E.A. *The combined contraceptive vaginal ring, NuvaRing: an international study of user acceptability.* Contraception 67 (2003) 187–194

### **Object of Research**

Combined contraceptive vaginal ring

### **Research Outcome**

User and partner acceptability.

### **Study Features**

Two large-scale open-label, non-comparative, multi-center studies of the combined contraceptive vaginal ring's efficacy, cycle control, tolerability and acceptability were included in this review

One study was in the United States and Canada, and the other was carried out in 12 European countries. The participants were asked to assess their acceptability of the combined contraceptive vaginal ring by completing a 21-item questionnaire after cycles 3, 6 and 13 or on early withdrawal from the studies. The women were also asked to indicate what, in their opinion, was the best method of contraception at baseline and again as part of the questionnaire assessments.

The questionnaire contained 21 questions (items) in total, of which 17 related to the following six domains: clarity of instructions, ease of use, sexual comfort, satisfaction, cycle-related characteristics and compliance. Cross-cultural differences were compared between countries.

*(Level 2 Evidence)*

### **The Evidence**

A total of 1950 women (82% of those recruited) completed a questionnaire at cycle 3. At baseline, 66% of participants preferred oral contraceptives, but after three cycles of ring use 81% preferred the ring. On study completion, 97% agreed that the instructions for use were clear; 85% of women and 71% of their partners never/rarely felt the ring during intercourse and 94% of their partners never/rarely minded that the woman was using the ring. Overall acceptance was high, 96% were satisfied with the ring and 97% would recommend the ring to others. Similar responses were seen for women who prematurely discontinued from the studies, except that slightly fewer women were satisfied (60%) and would recommend the ring (75%) for use by others. Reasons for liking the ring included “not having to remember anything” (45%) and “ease of use” (27%).

**Appraised by:** The Jordan Evidence Based Medicine-Reproductive Health Group

**Update by:** 4 March 2016

## **Resumption of ovulation after removal of the combined contraceptive vaginal ring (NuvaRing®) is rapid.**

### **Conclusion**

The combined contraceptive vaginal ring is a highly effective, reversible method of hormonal contraception. The vaginal ring acts similarly to the combined oral contraceptive and return to ovulation for most is rapid occurring for half or more women within 17-19 days after removal.

### **Clinical Question**

Does the use of combined contraceptive vaginal ring affect return to fertility?

### **Search Terms**

Combined contraceptive vaginal ring, NuvaRing®, return to fertility

### **Citations**

Mulder TMT, Dieben TOM, Bennick HJTC. *Ovarian Function with a novel combined contraceptive vaginal ring.* Human Reproduction 2002;17(10):2594-2599

### **Object of Research**

Combined contraceptive vaginal ring

### **Research Outcome**

Return to fertility

### **Study Features**

This is an open label, randomized, pharmacodynamic study of the combined contraceptive vaginal ring assessing ovarian function when there are deviations from the recommended usage schedule. The recommended regimen is one in which the ring is used continuously for three weeks followed by one ring free week. Forty-five combined contraceptive vaginal ring users were enrolled in the study and all used the ring continuously for three weeks. Fifteen women (Group A) had a one week ring free period followed by another ring use period of three weeks. Another 15 women (Group B) had a ring free week followed by three days of ring use and a third 15 (Group C) had a ring

free period until a 13 mm follicle was detected by ultrasound. Group C then used the ring for three weeks followed by a one week ring free period.

***(Level 1 Evidence)***

### **The Evidence**

Regardless of the length of the second cycle, 3 weeks (group A) versus 3 days (group B), the time to ovulation after ring removal was similar (19 versus 17 days). The median time needed to develop a follicle up to 13 mm in diameter (group C) was 11 days (range 8–21 days); none of the women ovulated after insertion of the second ring. (Note: Median time is the point in which at least half the women returned to ovulation.)

Comment: As there were no research regarding return to fertility after vaginal ring use, and as this current study has limitations regarding the duration of the method, we expect what applies to combined contraceptive pills is the same as combined contraceptive vaginal ring in terms of return to fertility.

**Appraised by:** The Jordan Evidence-Based Medicine Reproductive Health Group

**Update by:** 5 March 2016

**Assuming that the combined vaginal contraceptive ring is similar to a combined oral contraceptive pill in terms of prevention of pregnancy, there is indirect evidence that the use of the ring may be associated with a significant decrease in the risk of an ectopic pregnancy**

### **Conclusion**

There is not enough patient information to determine whether or not the combined vaginal contraceptive ring is associated with a decrease in ectopic pregnancy should there be a method failure. However, combination hormonal contraceptives including the combined contraceptive vaginal ring decrease the number of ectopic pregnancies since fewer pregnancies of any type occur. Based on the results of a review of studies involving combined oral contraceptives and their effect in reducing ectopic pregnancy risk, even if a pregnancy occurs, the combined vaginal contraceptive ring may also have a protective effect against ectopic pregnancy.

### **Clinical Question**

Is there a decrease in the risk of ectopic pregnancy among women using the combined vaginal contraceptive ring?

### **Search Terms**

Oral contraceptives, combined vaginal contraceptive ring, NuvaRing®, ectopic pregnancy

### **Citation**

Mol BWJ, Ankum WM, Bossuyt PMM, Van der Veen F. *Contraception and the risk of ectopic pregnancy: A meta-analysis*. *Contraception* 1995;52:337-341.

### **Object of Research**

Combined vaginal contraceptive ring

## **Subject of Research**

Ectopic pregnancy

## **Study Features**

The study was a meta-analysis of 12 case control studies and 1 cohort study though only 5 of the case control studies involved combined oral contraceptives. Cases in the control studies were women with an ectopic pregnancy. Controls were non-pregnant or pregnant women actively on COCs or with past use. For the cohort study, women who used COCs were compared to a group of women who had not used them. Note that data for the vaginal ring is not available, but this method is part of the class of combined hormonal contraceptive methods.

*(Level 3 Evidence)*

## **The Evidence**

Among pregnant women, current users of COCs had a 0.19 odds ratio when compared to non-pregnant controls. This suggests that women users of COCs have less risk of an ectopic pregnancy than those who do not. The chance of past COC users having an ectopic pregnancy showed the risk for an ectopic was no different from non-pregnant or pregnant non-users.

**Appraised by:** The Jordan Evidence Based Medicine Reproductive Health Group State University

**Update by:** 5 March 2016

**Users of the combined contraceptive vaginal ring were found to have better cycle control than users of combined oral contraceptives.**

**Conclusion**

Compared to users of combined oral contraceptives, there is some evidence that users of the combined contraceptive vaginal ring had better cycle control as measured by the number of bleeding episodes and length of menstrual periods.

**Clinical Question**

Is the use of the combined contraceptive vaginal ring associated with abnormal uterine bleeding?

**Search Terms**

Combined contraceptive vaginal ring, NuvaRing<sup>®</sup>, abnormal uterine bleeding

**Citation**

Lopez LM, Grimes DA, Gallo MF, et al, *Skin patch and vaginal ring versus combined oral contraceptives*. Cochrane Database of Systemic Reviews 2013, Issue 3. Art. No.: CD003552. DOL:10.1002/14651858.CD003552.pub4.

**Object of Research**

Combined contraceptive vaginal ring

**Research Outcome**

Cycle control, bleeding, spotting

## **Study Features**

This is a systematic review of randomized controlled trials which includes studies involving the combined contraceptive vaginal ring. Eleven studies involving the ring were found comparing this method to different combined oral contraceptives (COCs). Of these, seven studies reported bleeding data. Five of these obtained bleeding data from diaries, one from reported adverse events, and one from a questionnaire about bleeding. Included in the analysis are studies conducted in European, North and South America, and Egypt.

*(Level 1 Evidence)*

## **The Evidence**

The significant differences found in these studies include the following:

- European multicenter: The mean number of breakthrough bleeding or spotting days was higher for the ring group at cycle 6.
- European/South American multicenter: Breakthrough bleeding was less likely for ring users at cycle 6, but not at cycle 13.
- USA Single Center: Prolonged bleeding (bleeding or spotting lasting at least 10 days was less likely for ring users than COC users. Frequent bleeding (4 or more episodes of bleeding or spotting) was also less likely for the ring users.
- European study: Spotting and breakthrough bleeding were less common among ring users. Also early or late withdrawal bleeding was less likely among ring users than COC users.

**Appraised by:** The Jordan Evidence Based Medicine Reproductive Health Group

**Update by:** 5 March 2016

# **The use of combined contraceptive vaginal ring (NuvaRing®) is associated with an increased risk of thromboembolism**

## **Conclusion**

The use of the combined contraceptive vaginal ring (NuvaRing®) is not associated with an increased risk of thromboembolism compared with women using standard combined low dose oral contraceptive pills.

## **Clinical Question**

Is the use of the combined contraceptive vaginal ring associated with increased risk of venous thromboembolism?

## **Search Terms**

Combined contraceptive vaginal ring, etonogestrel/estradiol vaginal ring, NuvaRing®, thromboembolic disorders, cardiovascular disorders.

## **Citations**

Dinger J, Mohner S, Heinemann K. *Cardiovascular risk associated with the use of an etonogestrel-containing vaginal ring*. *Obstet Gynecol* 2013;122(4): 800-808.

## **Object of Research**

Combined contraceptive vaginal ring

## **Subject of Research**

Thromboembolic disorders

## **Study Features**

This was a prospective, controlled, cohort study performed in the United States and five European countries with two cohorts; new users of the vaginal ring and new users of combined oral contraceptives (COCs). The study included 33,295 users of the vaginal ring or a COC recruited by 1,661 study centers. Follow-up for study participants occurred for 2 to 4 years. The primary clinical outcomes of interest were cardiovascular outcomes, particularly venous and arterial thromboembolism. Outcomes were validated by attending physicians and further adjudicated by an independent board.

**The Evidence**

Follow up for the study participants included 66,489 women-years of use and loss to follow-up was 2.9 percent. Only 34 occurrences of venous thromboembolism (VTE) were found during the four years of follow-up and the rate of VTE was similar in users of the vaginal ring and uses of combined oral contraceptives. The rates of VTE for the ring and COC groups were 8.8 and 9.9 per 100,000 women years, respectively.

**Appraised by:** The Jordan Evidence Based Medicine Reproductive Health Group

**Update by:** 8 March 2016

## **Women using the combined contraceptive vaginal ring (NuvaRing®) as contraceptive showed no significant changes in either systolic or diastolic blood pressure after 12 months of usage**

### **Conclusion**

Blood pressure is not altered by the usage of a combined contraceptive vaginal ring.

### **Clinical Question**

Is the use of the combined contraceptive vaginal ring associated with an increase in blood pressure?

### **Search Terms**

Combined contraceptive vaginal ring, NuvaRing®, blood pressure

### **Citation**

Mohamed AM, El-Sherbiny WS, Mostafa WA. *Combined contraceptive ring versus combined oral contraceptive (30- $\mu$ g ethinylestradiol and 3-mg drospirenone)*. Int J Gynaecol Obstet. 2011; 114(2):145-8.

### **Object of Research**

Combined contraceptive vaginal ring

### **Research Outcome**

Blood pressure

### **Study Features**

This is randomized, open-label study which included 600 women who attended the contraception clinic at Kasr El-Aini Hospital in Cairo, Egypt, between May 1, 2008, and July 31, 2010. The women were 17–42 years of age, had regular menstrual cycles and were randomly divided into 2 groups, with 300 women per group at the beginning of treatment. The women were randomized to receive the combined contraceptive vaginal ring or a combined oral contraceptive (COC) containing 30  $\mu$ g of ethinyl estradiol and

3 mg of drospirenone. Only 239 women in the ring group completed the study compared with 251 women in the combined oral contraceptive.

All participants received treatment for 12 consecutive cycles. Each treatment cycle consisted of 3 weeks of ring/pill treatment followed by a 1-week ring-free/pill-free period. Blood pressure, height, and weight were recorded at each clinic visit 3, 6, 9, and 12 months.

*(Level 1 Evidence)*

### **The Evidence**

In the combined contraceptive vaginal ring group, baseline systolic blood pressure was  $114.6 \pm 10.7$ , at 3 months it was  $114.3 \pm 10.7$ , at 6 months it was  $113.9 \pm 10.4$  and at 12 months it was  $114.4 \pm 10.6$  mmHg. In women received combined oral contraceptive, baseline systolic blood pressure in was  $117.3 \pm 10.9$ , at 3 months it was  $125.4 \pm 13.1$ , at 6 months it was  $125.6 \pm 12.9$  and at 12 months it was  $126.2 \pm 13.2$ mmHg.

In the combined contraceptive vaginal ring group, baseline diastolic blood pressure was  $72.4 \pm 9.1$ , at 3 months it was  $71.7 \pm 8.4$ , at 6 months it was  $73.2 \pm 8.2$  and at 12 months it was  $71.8 \pm 8.4$ mmHg. In women received combined oral contraceptive, baseline diastolic blood pressure in was  $71.5 \pm 8.1$ , at 3 months it was  $78.5 \pm 9.9$ , at 6 months it was  $81.5 \pm 10.1$  and at 12 months it  $79.7 \pm 10.3$  mmHg.

The differences in systolic or diastolic blood pressure, either at baseline or 3, 6 and 12 months for either method were not statistically significant. Women who used combined oral contraceptives tended to have higher systolic and diastolic blood pressure compared with women who used the combined contraceptive vaginal ring at 3, 6 and 12 months, but the differences were not statistically significant.

**Appraised by:** The Jordan Evidence-Based Medicine Reproductive Health Group

**Update by:** 7 March 2016

## **The use of the combined contraceptive vaginal ring (NuvaRing®) is associated with increased incidence of headache**

### **Conclusion**

Occurrence of headaches is often associated with the use of hormonal contraceptives including combined oral contraceptives as well as the combined contraceptive vaginal ring. The occurrence of these headaches may lead to discontinuation of the method.

### **Clinical Question**

Is the use of the combined contraceptive vaginal ring associated with increased incidence of headache?

### **Search Terms**

Combined contraceptive vaginal ring, NuvaRing®, headache, tolerability

### **Citation**

Oddsson K, Leifels-Fischer B, Roberto de Melo N et al. *Efficacy and safety of a combined vaginal ring (NuvaRing) compared with a combine oral contraceptive: a 1-year randomized trial.* Contraception 2005;(71):176-182.

### **Object of Research**

Combined contraceptive vaginal ring

### **Research Outcome**

Headache

### **Study Features**

This is an open-label, randomized, multicenter trial study comparing the tolerability of combined contraceptive vaginal ring with a low dose, combined oral contraceptive (COC). The study was conducted in 11 countries in Europe and South America with 512 women randomly assigned to use the ring and 518 to the COC.

*(Level 1 Evidence)*

**The Evidence**

Headache was the most commonly reported adverse effect in both groups. In the combined contraceptive vaginal ring group there were 37 (7.2%) who reported a headache which was classified by the investigators as drug-related. The corresponding number for the COC group was 30 (5.8%). Overall, 97 (18.9%) combined vaginal contraceptive ring users and 77 (14.8%) of the COC users reported a headache during the study. Four (0.8%) of the ring users and 8 (1.5%) of the COC users discontinued their method because of a headache.

**Appraised by:** The Jordan Evidence Based Medicine-Reproductive Health Group

**Update by:** 7 March 2016

## **The use of combined contraceptive vaginal ring is not associated with increased risk of migraine headaches.**

### **Conclusion:**

Use of an extended-cycle combined contraceptive vaginal ring was associated with a reduced frequency of migraine aura and with resolution of menstrual related migraine. Given the small sample size of the study and the use of the extended use of the ring, generalization of results to all ring users should be made with caution.

### **Clinical Question**

Is the use of the combined contraceptive vaginal ring associated with a decreased risk of migraine headaches?

### **Search Terms**

Combined contraceptive vaginal ring, NuvaRing<sup>®</sup>, migraine.

### **Citations**

Calhoun A. et al. *The impact of extended – cycle vaginal ring contraception on migraine aura: a retrospective case series.* Headache. 2012; 52(8):1246-53.

### **Object of Research**

Combined contraceptive vaginal ring

### **Research outcome**

Migraine

### **Study Features**

This is a pilot study based on a retrospective review of a data base of 830 women seen in a menstrual related migraine clinic to identify women who met the inclusion criteria of current history of migraine with aura, a confirmed diagnosis of migraine related menstruation and extended use of a combined vaginal contraceptive ring. Standardized calendars that specifically docu-

mented bleeding patterns, headache details, and occurrence of aura were required of all patients in this clinic. Twenty-eight (3.4%) of the 830 identified women met the study criteria, none of whom were smokers.

*(Level 3 Evidence)*

**The Evidence**

Of the 28 women, 5 (18%) discontinued use of etonogestrel/ethinyl estradiol within the first month, leaving 23 evaluable subjects. At baseline, subjects averaged 3.23 migraine auras/month (range: 0.1-12). With extended dosing of the vaginal ring contraceptive, median frequency was reduced to 0.23 auras per month following treatment after a mean observation of 7.8 months ( $P < 0.0005$ ). No subject reported an increase in aura frequency. Using the ring continuously, migraine related menstruation was eliminated in 91.3% of the evaluable subjects. No comparison group (e.g. non users of the ring) was available

**Appraised by:** The Jordan Evidence Based Medicine Reproductive Health Group

**Update By:** 7 March 2016

## **The use of combined vaginal contraceptive ring is associated with an increased risk of vaginitis and vaginal discharge.**

### **Conclusion**

Vaginitis appears to be associated with the use of the combined contraceptive vaginal ring. In two separate randomized studies, the occurrence of vaginitis thought to be associated with vaginal ring use were less than 5 percent.

### **Clinical Question**

Does the use of the combined contraceptive vaginal ring increase the risk of vaginitis?

### **Search Terms**

Combined contraceptive vaginal ring, NuvaRing®, vaginal infection, vaginitis

### **Citations**

Mohamed AM, El-Sherbiny WS, Mostafa WA. *Combined contraceptive ring versus combined oral contraceptive (30- $\mu$ g ethinylestradiol and 3-mg drospirenone)*. Int J Gynaecol Obstet 2011; 114(2): 145-146.

Oddsson K, Leifels-Fischer B, Reoberto de Mel N, et al. *Efficacy and safety of a contraceptive vaginal ring (NuvaRing) compared with a combined oral contraceptive: a 1-year randomized trial*. Contraception 2005; 71:176-182.

Camacho DP, et al. *Vaginal yeast adherence to the combined contraceptive vaginal ring (CCVR)*. Contraception. 2007; 76(6):439-43.

### **Object of Research**

Combined contraceptive vaginal ring

### **Research Outcome**

Vaginal infection

## **Study Features**

### Mohamed et al

This is a study of women seeking contraception at a family planning clinic in Cairo, Egypt. Three hundred women each were randomly assigned to receive either the combined contraceptive vaginal ring or a combined oral contraceptive (COC) for 12 cycles in this one year, open-label study  
*(Level 1 Evidence)*

### Oddsson et al

This is an open-label, one year, randomized study to compare the efficacy and tolerability of the combined contraceptive vaginal ring to a combined oral contraceptive (COC). A total of 512 ring and 518 COC users received and started their contraceptive method.

*(Level 1 Evidence)*

### Camacho DP et al.

Yeast infections are known to be a source of vaginitis. The purpose of this study was to evaluate the in vitro adherence of different yeasts, isolated from vaginal exudates of patients with vulvovaginal candidiasis to the combined contraceptive vaginal ring. Four isolates of *Candida* sp. and one of *Saccharomyces cerevisiae* were used.

*(Level 1 Evidence)*

## **The Evidence**

### Mohamed et al

Vaginitis was present in 11 (4.6%) ring users and in 3 (1.2%) COC users. This difference was statistically significant ( $p < 0.05$ ). [Note that the authors use as the denominator all women who completed the study. Assuming that all 300 women in each group had an opportunity to report an adverse effect, 1 percent of the COC users and 3.7 percent of the ring users had vaginitis).

Oddsson et al

For the vaginal ring group, 54 (10.5%) women reported or were diagnosed as having vaginitis. Of these diagnoses, 20 (3.9%) were thought to be definitely, possibly or probably related to the ring use. For the COC users, the corresponding numbers were 24 (4.6%) and 5 (1.0%), respectively.

Camacho et al

All yeast were capable of adhering to the vaginal ring. The adherence of the tested yeasts to the ring could potentially facilitate the development and/or recurrence of vulvovaginal candidiasis in susceptible patients using the contraceptive method.

**Appraised by:** The Jordan Evidence Based Medicine Reproductive Health Group

**Update By:** 8 March 2016

## **The use of antimycotic co-medication is not expected to compromise NuvaRing's contraceptive efficacy or tolerability.**

### **Conclusion**

Antimycotic co-medication slightly increases the amount of hormones released from the combined contraceptive vaginal ring. However, the increases in serum levels observed with different antimycotic formulations are not expected to compromise NuvaRing's contraceptive efficacy or tolerability.

### **Clinical question**

Does the use of antimycotic co-medications affect the NuvaRing contraceptive efficacy and tolerability?

### **Search Terms**

Combined contraceptive vaginal ring, NuvaRing<sup>®</sup>. antimycotic co-medications

### **Citations**

C.H.J. Verhoevena, M.W. van den Heuvelb, T.M.T. Muldersa, Th.O.M. Diebena,\*

*The contraceptive vaginal ring, NuvaRing, and antimycotic co-medication.* Contraception 69(2004)129-132.

### **Object of Research:**

Combined contraceptive vaginal ring

### **Research Outcome**

Effect of antimycotic co-medications

### **Study Features.**

The effect of antimycotic co-medication on the systemic exposure to etonogestrel (ENG) and ethinylestradiol (EE) released from the contraceptive vaginal ring, NuvaRing was investigated. Different formulations of miconazole nitrate and single as well as multiple dosing were investigated

during two separate randomized, open-labels, crossover studies. The first study recruited 12 women to compare the effects of co-use of NuvaRing and a single dose of antimycotic to NuvaRing alone. The second study recruited 14 women to compare the effects of multiple doses of an antimycotic vaginal suppository to an antimycotic vaginal cream equivalent.

### **The Evidence.**

Co-administration of all three antimycotic formulation resulted in a slight increase in systemic exposure to ENG and EE over time, with suppositories having a more pronounced effect than a cream formulation in the multiple – dosing study.

Over 24 and 48 hours no significant effects of co- medication with a single dose of anti mycotic on the systemic exposure to ENG and EE released from vaginal ring were observed. However , over 312 hours, there was significant increase in the systemic exposure to ENG (17%)and EE(16%)released from the ring relative to the control cycle.

The mean ENG and EE serum concentrations showed an increase during treatment with both antimycotic suppositories and cream . After treatment the average concentration of ENG and EE remained elevated compared with the first day of interaction treatment .

In addition, ENG and EE content remaining in the rings after use was determined ex vivo. Less steroids remained in rings from subjects treated with antimycotics plus Nuva-Ring than with NuvaRing alone, indicating that ENG and EE release rates were higher in the presence of the antimycotic. (Miconazole nitrate is lipophilic in nature, which may facilitate the release of the (lipophilic) hormones from the ring). The increase in serum level observed with the different antimycotic formulations are not expected to compromise NuvaRing contraceptive efficacy and tolerability.

**Appraised by:**

The Jordan Evidence Based Medicine Reproductive Health Group

**Update By:** 10 March 2016

**The use of tampons is not expected to compromise the combined contraceptive vaginal ring's (NuvaRing®) contraceptive efficacy or tolerability.**

**Conclusion**

Tampon co- usage did not result in any changes in serum etonogestrel or ethinyl estrodial concentrations and is thus not expected to compromise the combined contraceptive vaginal ring's contraceptive efficacy.

**Clinical Question**

Does the use of tampons affect the NuvaRing contraceptive efficacy?

**Search Terms**

Combined contraceptive vaginal ring, NuvaRing®, tampon use

**Citations:**

Carole H.J Verhoeven, Th,M Dieben.

The combined contraceptive vaginal ring, NuvaRing and tampon co-usage. *Contraception* 69(2004) 197-199.

**Object of Research:**

NuvaRing

**Subject of Research:**

Tampon co-usage.

**Study Features.**

This open-label, randomized, cross-over study assessed systemic exposure to the contraceptive hormones released from the combined contraceptive vaginal ring, NuvaRing with tampon co-usage. One cycle of ring use consists of 3 weeks of ring use followed by a 1-week ring-free period.

*(Level 1 Evidence)*

Fourteen healthy women were randomized to use both NuvaRing and tampons (Kotex regular) or NuvaRing alone for one cycle; participants then switched to the alternate treatment regimen for a second cycle of ring use. The first tampon was self-administered on day 8 of the interaction cycle; 4 tampons a day were used for 3 consecutive days.

**The Evidence.**

The mean serum ENG and EE concentrations in the ring–tampon interaction cycle were similar to those observed in the control cycle. There were no statistically significant effects of tampon co-usage on the systemic exposure to ENG released from NuvaRing over the two time periods (24 and 72 h) analyzed .

Appraised by:

Dr. A.M.ABDUL MALEK, Senior Consultant Ob&Gyn.

Reviewed by: Dr. Abdul-Halim Al-Musa Consultant Epidemiologist

Update By: March 10, 2016

# **The use of the combined contraceptive vaginal ring is not associated with greater weight gain than the combined oral contraceptive**

## **Conclusion**

Small weight increases for users of the vaginal ring were noted though reports of this as an adverse event were less than two percent of all users.

## **Clinical Question**

Is the use of the combined contraceptive vaginal ring associated with weight gain?

## **Search Terms**

vaginal ringweight gain

## **Citations**

Mohamed AM, El-Sherbiny WS, Mostafa WA. *Combined contraceptive ring versus combined oral contraceptive (30- $\mu$ g ethinylestradiol and 3-mg drospirenone)*. Int J Gynaecol Obstet 2011; 114(2): 145-146,

O'Connell KJ, Osborn LM, Westoff C. *Measured and reported weight change for women using a vaginal contraceptive ring vs. a low-dose oral contraceptive*. Contraception 2005; 72: 323-327.

## **Object of Research**

Combined contraceptive vaginal ring

## **Research Outcome**

Weight gain, measured and reported.

## **Study Features**

Mohamed et al

This is a study of women seeking contraception seeking contraception at a family planning clinic in Cairo, Egypt. Three hundred women each were

randomly assigned to receive either the combined contraceptive vaginal ring or a combined oral contraceptive (COC) for 12 cycles in this one year, randomized, open-label study

*(Level 1 Evidence)*

O'Connell et al

This is a randomized, open label study in which 100 women received a combined oral contraceptive (COC) and 101 received the combined contraceptive vaginal ring. The study was designed to assess acceptability and satisfaction. Study coordinators were blinded to the contraceptive assignment. Ninety-eight ring and 96 pill acceptors were weighed at the time of the initiation of their contraceptive method. The main outcome variable was the mean difference between their measured and perceived weight at entrance though differences in the two groups were also estimated.

*(Level 1 Evidence)*

### **The Evidence**

Mohamed et al

Weight increases were reported by 4 (1.7%) of the combined contraceptive vaginal ring users and in 11 (4.5%) of those using a COC. This difference was statistically significant ( $p < 0.05$ ).

O'Connell et al

Eight-two of the vaginal ring acceptors were weighed at the time of study initiation and exit compared to 79 COC users. The gains between the COC and ring groups were similar (COC: 3.1 lbs; ring 2.5 lbs). These weight gains were not significantly different though the combined group change from baseline of 2.8 lbs was found to be so.

**Appraised by:** The Jordan Evidence Based Medicine Reproductive Health Group

**Update by:** 8 March 2016

# **Long-term use of combined contraceptive vaginal ring (NuvaRing®) produces no changes in bone mineral density (BMD) in healthy women**

## **Conclusion**

Long use (up to 2 year) of the combined contraceptive vaginal ring in healthy young and pre-menopausal women did not result in any changes in BMD.

## **Clinical Question**

Does the combined contraceptive vaginal ring affect bone mineral density in healthy women?

## **Search Terms**

Combined contraceptive vaginal ring, NuvaRing® and bone mineral density

## **Citations**

Massai R, MäKäräinen L, Kuukankorpi A, Klipping C, Duijkers I and Dieben T. *The combined contraceptive vaginal ring and bone mineral density in healthy pre-menopausal women*. Human Reproduction 2005;20(10):2764-2768.

Massaro M, Di Cario C, Gargano V, Formisano C, Bifulco G, Nappi C. *Effects of the contraceptive patch and the vaginal ring on bone metabolism and bone mineral density: a prospective, controlled, randomized study*. Contraception 2010;81:209-214

## **Object of Research**

Combined contraceptive vaginal ring

## **Research Outcome**

Changes in bone mineral density

## **Study Features**

Massai R, MäKäräinen L, et al.

This was an open-label, multicenter study conducted at 2 centers in Finland and single centers in Chile and The Netherlands. It included 144 healthy women aged 18-35 years followed for two years. The women included combined contraceptive vaginal ring users (n=103) and a control/comparison group (n=39) in a ratio 3:1 respectively. The control group was comprised of women who used a non-hormonal IUD or other non-hormonal methods of contraception. Measurements of bone mineral density were made at the lumbar spine (L2-L4) and the proximal femur using dual-energy X-ray absorptiometry at screening and at months 12 and 24 of the study.

*(Level 2 Evidence)*

Massaro M, Di Cario C, et al.

This was a prospective, randomized controlled study, conducted in Naples, Italy from May to October 2008. It included 40 healthy women aged 23-34 years, randomly assigned equally to one of two methods of combined contraceptives (patch or vaginal ring). Twenty other women not seeking contraception were used as healthy controls. All studied women had measurements of BMD at the lumbar spine (L1-L4) using dual-energy X-ray absorptiometry at screening and after 12 months from initiation of the study.

*(Level 1 Evidence)*

## **The Evidence**

Massai R, MäKäräinen L, et al.

Out of 144 women, 76 combined contraceptive vaginal ring users completed the study compared to 31 women in the control group. The BMD of the proximal femur and the lumbar spine showed no change from baseline in the contraceptive ring users at either the 12 or 24 months follow-up. However, the BMD at 24 months in the control group showed a slight but clinically insignificant increase from the baseline.

Massaro M, Di Carlo C, et al.

The BMD values in the three groups at baseline and after 12 months are shown in the following table:

Spinal BMD (g/cm <sup>2</sup> )	NuvaRing <sup>®</sup> user	Patch user	Control group
Baseline	1.040 ± 0.12	1.042 ± 0.15	1.041 ± 0.08
After 12 months	1.041 ± 0.09	1.041 ± 0.18	1.042 ± 0.02

There were no significant differences in mean spinal BMD values among the three groups nor in comparison with base line values.

**Appraised by:** The Jordan Evidence Based Medicine – Reproductive Health Group

**Update by:** 8 March 2016

## **Use of the combined contraceptive vaginal ring (NuvaRing®) as a contraceptive method is not recommended for breastfeeding women less than six months postpartum.**

### **Conclusion**

Data are not available to assess the effect of the combined contraceptive vaginal ring as used by breastfeeding women. However, based on indirect evidence drawn from studies addressing combined oral contraceptive pills, use by breastfeeding women, the WHO does not recommend the ring for use during the first six months postpartum.

### **Clinical Question**

Does the use of combined contraceptive vaginal ring affect milk production while breastfeeding?

### **Search Terms**

NuvaRing®, combined contraceptive vaginal ring, combined oral contraceptive, breastfeeding

### **Citations**

Truitt ST, Fraser AB, Grimes DA, et al. *Hormonal contraception during lactation: systematic review of randomized controlled trials*. *Contraception* 2003; 68:233-238.

WORLD HEALTH ORGANIZATION. REPRODUCTIVE, H. *WHO Medical Eligibility Criteria for Contraceptive Use*, World Health Organization. 2010.

### **Object of Research**

Combined contraceptive vaginal ring

### **Research Outcome**

Lactation, breast milk production

## Study Features

This is a systematic review of randomized controlled trials. Three studies involving combined oral contraceptives (COCs) were found; a WHO sponsored trial comparing COCs to a progestin-only pill (POP), and two other studies comparing COCs to placebo. For the two placebo-comparator studies, one study used the subjective need for supplemental infant feeds and infant weight as a proxy for milk adequacy while the other was not specified. In the study using a progestin-only pill as a comparator, breast milk volume was determined by pump expression using a standardized process.

(Level of indirect evidence not assessed)

## The Evidence

In the WHO trial, at six weeks, the volume of the expressed milk in the COC and POP groups were similar. However, most women in both groups had declines in milk volume over time though the amount for the COC group was greater than that for those using a POP.

In the other two studies, one found inhibitory effects on milk volume in the COC. On the other hand, in the second study, no differences were found between the COC and placebo groups with respect to milk volume, lactation initiation, or infant growth.

## Comment

The WHO “Medical eligibility criteria for contraceptive use” makes the following recommendation with respect to the combined contraceptive vaginal ring for breastfeeding women.

<6 weeks postpartum	Method not to be used
≥6 weeks and < 6 months	Use of method not recommended unless other more
postpartum (primarily appropriate methods are not available or not breastfeeding)	Acceptable
≥6 months postpartum	Generally use method

**Appraised by:** The Jordan Evidence-Based Medicine Reproductive Health Group

**Update by:** 8 March 2016





**Special Topics**



**Contraceptive continuation can be enhanced when health care professionals support the stated desires of their clients by giving them the requested method.**

### **Conclusion**

Based on the results of this study in which the client's desire for a particular contraceptive method is explored as a determinate of continuation, it was found that when their choice was not denied, continuation was higher regardless of the method selected.

### **Clinical Question**

Does agreement with the client's contraceptive choice make a difference in method compliance and continuation?

### **Search Terms**

Contraceptive discontinuation, client/family planning worker interactions

### **Citation**

Pariani S, Heer DM, Arsdol MD. *Does choice make a difference to contraceptive use? Evidence from East Java.* Studies in Family Planning 1992;22,6:384-390.

### **Object of Research**

Contraceptive choice

### **Research Outcome**

Contraceptive continuation rates

### **Study Features**

This is a prospective study of family planning program clients attending a government family planning clinic in East Java. Before receiving a family planning method, clients were interviewed regarding their socio-demographic characteristics and their preferred method of contraception. Immediately after being introduced to a method, they were again interviewed about the methods suggested and the method they intended to use. Of the 2,501 initial respondents, 1,945 (77.8%) were re-interviewed at their homes a year later. (*Level 2 Evidence*)

## **The Evidence**

- The odds of discontinuation were 0.13 when choice was not denied and husbands and wives concurred when compared to when choice was denied and husbands and wives disagreed.
- The odds of discontinuation were 6.58 when there was concurrence between the husband and wife and choice was denied compared to when choice was not denied and the husband and wife did not agree.

**Appraised by:** The Jordan Evidence Based Medicine Reproductive Health Group

**Update by:** 7 April 2016

