

EVIDENCE

Evidence-Based Medicine

**The Best Evidence
on Family Planning
Methods**

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Introduction

Dear Health Colleagues,

The **Philippine Evidence-Based Reproductive Medicine Network** (PEBRMNet) 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.

The PEBRMNet formed in early 2003 to promote the practice of evidence-based medicine in reproductive health. Our network currently consists of 17 obstetrician-gynecologist professors and practicing clinicians located throughout the country but with the growing interest in evidence-based medicine in the Philippines, we anticipate our membership will grow. (See Annex A for a list of our current members.)

The mission of the PEBRMNet is to: critically appraise research on issues related to reproductive medicine, initially focusing on contraception; disseminate best evidence on contraceptive methods to health providers, patients and the public; expose the health provider community to the value of "best evidence" in addressing patient problems related to contraceptive side effects and health concerns; train other health providers in evidence-based medicine (EBM) skills; and develop evidenced-based guidelines and policies for reproductive medicine and contraception.

We will be conducting a series of workshops on evidence-based medicine and its application towards reproductive health in cooperation with professional associations, the Department of Health, and local government health systems. We will keep you informed about these workshops and invite you to join them if you wish to learn more about the practice of EBM. We also invite you to contact us if you would like the PEBRMNet 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 network!

Sincerely,

Mario R. Festin, MD, MHPEd, FPOGS

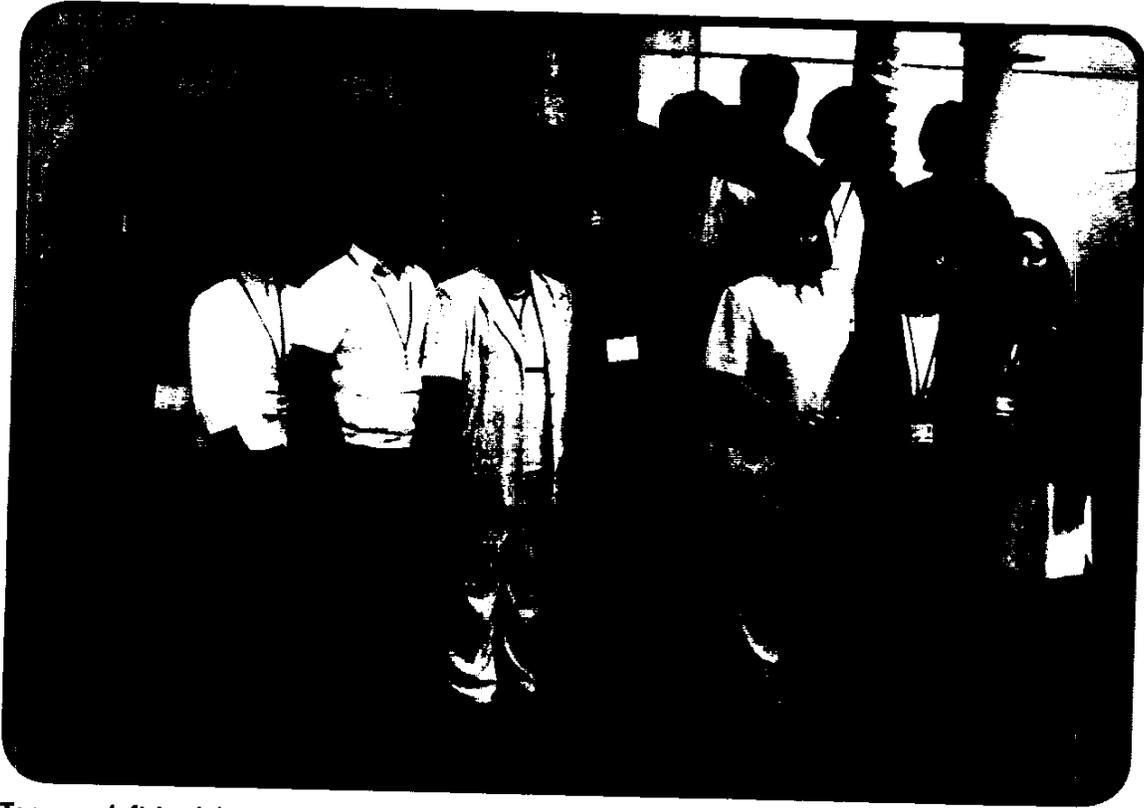
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Evidence-Based Medicine:

A New 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 into 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 both invalidates previously accepted diagnostic tests and treatments and replaces them with new ones that are more powerful, more efficacious and safer.

By **clinical expertise**, we mean the ability to use our clinical skills and past experience to rapidly identify each patient's unique health state and diagnosis, their 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 which must all be integrated into clinical decisions if they are to serve the patient.

- When these three are integrated, clinicians and patients form a diagnostic and therapeutic alliance which 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*

x

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 recent 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 Actually Practice EBM?

The full-blown practice of EBM is composed of five steps:

- Step 1** Converting the need for information (about prevention, diagnosis, prognosis, therapy, causation, etc.) into an answerable question.
- Step 2** Tracking down the best evidence with which 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 with our patients' unique biology, values 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 don't.

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



**Background
Research**



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Overcoming Barriers To Modern Contraceptive Use

In the 2000 Pulse Survey, 94% of Filipinos agreed with the statement that it is important to have the ability to control one's fertility and to plan one's family. The 2002 Family Planning Survey (FPS) however showed that only 35 percent of Filipino couples are using modern contraceptive methods, albeit modern contraceptive use is showing moderate annual growth on a national scale (6% growth registered over 2001). The 2002 FPS showed that another 14% of couples are using less reliable traditional methods of family planning (calendar/rhythm methods or withdrawal). The data shows that traditional method use is on the decline (down from 16% in 2001 and 18% in 1998).

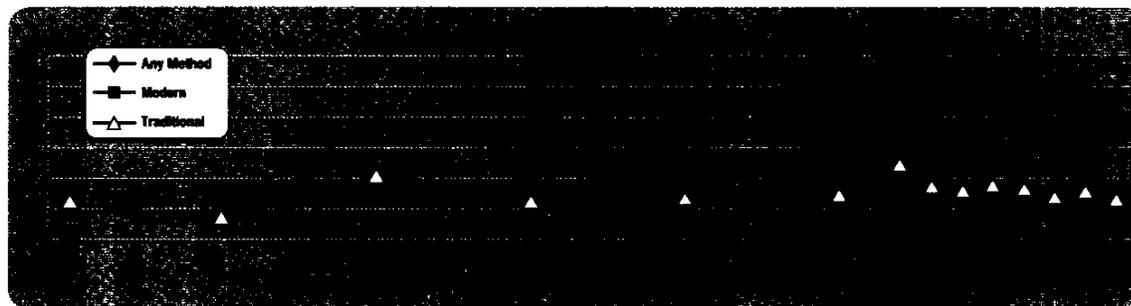


Figure 1. Contraceptive Prevalence Rate, Philippines, 1968-2002

In spite of moderately rising modern contraceptive use, fertility levels still have not dropped to the expressed desires of married women. According to the 1998 Demographic and Health Survey (DHS), Filipino women are having one more child than they would like to have (on average, about four children instead of three). It will not be possible for the fertility rate to drop to women's preferred levels until more couples use modern methods of contraception. Yet there remain major barriers to a more rapid uptake of modern methods. The most significant barrier is not the Catholic religion, as it is frequently believed, but fear of side effects and health concerns. Nearly 27% of non-users cited side effects, health concerns or amenorrhea as reasons they do not use modern contraceptive methods, while only two percent said religion was the main factor. These findings have been consistent over the years.

A secondary review¹ identified some of the key barriers to modern contraceptive use among women and to a lesser extent, identified some barriers and biases among medical providers. As the 2002 FPS continued to confirm, Filipino women are very concerned about menstrual changes, particularly the amenorrhea that is caused by the

¹Ramlow, Reed, *Secondary Review - Barriers to Modern Contraceptive Use Among Women and Medical Providers in the Philippines* (Manila, Philippines: The Social Acceptance Project on Family Planning [TSAP-FP], January 2003).

use of DMPA (commonly known as the injectable). Other frequently cited side effects/health concerns attributed to modern contraceptive use were local interpretations of "high blood" (not limited to hypertension) and "low blood" (not limited to anemia), mood changes, headache/migraine, blood clots, cancers/tumors, (hormone) "accumulation", and sexual dysfunction.

Percent distribution of married women not using contraceptive methods, by reason for non-use, Philippines: 2002

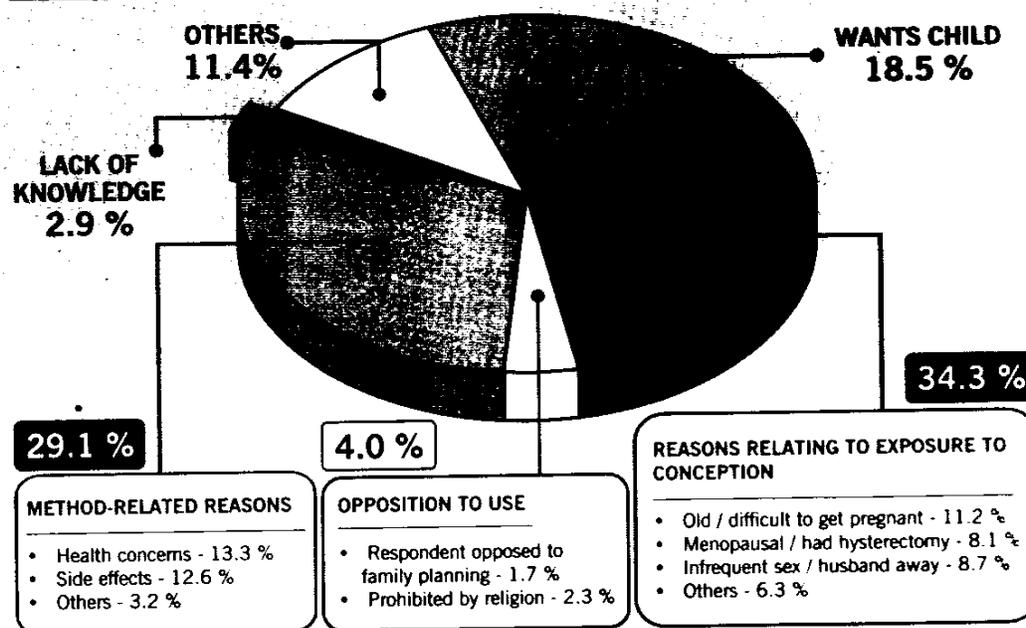


Figure 2. Percent Distribution of Married Women not using contraceptive methods, by reason for non-use, Philippines, 2002

Focus group research has shown that men/husbands can be a negative influence on modern contraceptive use. Apparently, many husbands fuel their wives' side effect fears or health concerns, or ask them outright to stop using contraceptives, without offering to take up a male method of contraception, in part due to their own misconception of vasectomy (fearing sexual dysfunction) or disdain of condoms (loss of pleasure).

Health Providers Share Misconceptions

The secondary review found that many health providers shared their clients' misconceptions, particularly with respect to injectables, IUDs and amenorrhea. Moreover, the review found that providers' personal or religious values frequently influence their behavior. For example, the secondary review showed that over half of 500 providers surveyed in 1995 felt it was inappropriate to prescribe contraceptives to nulliparous women and nearly half conceded their religious beliefs influence their attitudes toward prescribing contraceptives. In addition, one out of five providers agreed with the statement that IUDs are an abortifacient.

PERCENTAGE OF PROVIDERS WHO STRONGLY AGREE WITH THE FOLLOWING UNFAVORABLE STATEMENTS				
Issues	Total	OB/GYNs	GPs	Midwives
If husband doesn't approve of FP, the woman should not use it	51	53	52	48
Reluctant to recommend contraceptives to an unmarried woman	44	43	44	44
Health providers should decide on the method for client	34	25	34	43
IUD is an abortifacient	20	28	23	16

Figure 3. Medical Providers' Unfavorable Attitudes Toward Family Planning, 1995

The Need for Evidence-Based Medicine in Family Planning

Clearly, health providers need more and better information to address their own misconceptions as well as those 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* since there are powerful influences that are frequently guilty of propagating misinformation about contraceptive harms.

Providers need to be armed with the facts, based on solid, documented evidence, and they need that information to be packaged in a way that directly and concisely addresses patient concerns and providers' own misconceptions, specific to the Philippine context. This is what the **PEBRMNet's Critically Appraised Topics** seeks to address. ■

Oral Contraceptives

EVIDENCE

EVIDENCE

The Clinical Scenario

A 30-year-old G2P2 woman consults you because she wants to use oral contraceptives. Her mother was recently diagnosed with breast cancer. She would like to ask you if she can develop breast cancer if she uses oral contraceptives.

Clinical Bottom Line

In women between the ages of 35-64, there is no significant increase in the risk of breast cancer among women who currently or previously used oral contraceptives. The odds ratio did not increase consistently with longer periods of use or with higher doses of estrogen. Use of oral contraceptives by women with a family history of breast cancer was not associated with an increased risk of breast cancer, nor was the initiation of oral contraceptive use at a young age.

Citations

Marchbanks PA, et al. Oral contraceptives and the risk of breast cancer. The New England Journal of Medicine 2002 June; 346(26):2025-2032.

The Study Patients

Cases - 4,575 women 35-64 years of age with breast cancer initially diagnosed from 1994 to 1998 in 5 sites in the US. Controls - 4,682 women in same age group without a diagnosis of breast cancer in the same geographic locations as case subjects.

Exposure of Interest

Oral contraceptive pills (combined or progestin only pills)

The Outcome

Breast cancer (invasive)

Methodological Issues

The subjects were not defined and similar in other important ways. The exposures and outcomes were neither objective nor measured blindly. Follow-up was long and was complete.

The Evidence



Comments:

1. The odds ratio of 0.90 suggests that there may be a protective effect of any previous use of oral contraceptives against breast cancer, but since the confidence interval of the odds ratio crosses 1.0, this value is not significant.
2. When the odds ratios reported in the article were adjusted for the various factors, these still show no significant difference between case and control group, taking into account confounders such as duration and initial age of exposure, duration since last use and type of hormone used. OR = 1.0 (95% CI 0.8 to 1.3) among current users and OR = 0.9 (95% CI 0.8 to 1.0) among previous users.

Answer to Clinical Scenario

Among women who have had breast cancer, they were no more likely to have used oral contraceptives, compared to women who had no breast cancer. This absence of risk was consistently found among all sub-groups of the sample studied. Based on this study, the woman can be advised that there would be no increase in the risk of developing breast cancer if she uses oral contraceptives.

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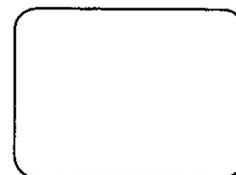
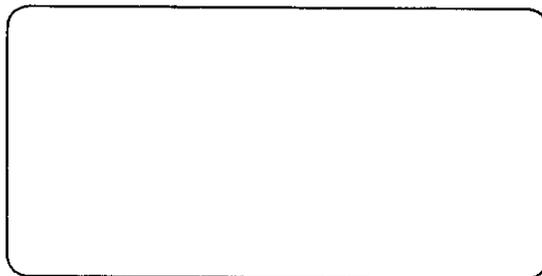
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EVIDENCE

**Use of oral
contraceptive pills
does not lead to an
increased risk of
breast cancer.**



• EVIDENCE

The Clinical Scenario

A 28-year-old woman has been suffering from migraine for many years. She has just delivered a baby and would like to use pills to space her pregnancies. She asks you about the risks of using pills for a patient with migraine like herself.

Clinical Bottom Line

The use of oral contraceptives among women of childbearing age with migraine significantly increases their risk of stroke. The risk for stroke has a multiplicative effect if the patient is a smoker and/or also has high blood pressure.

Citations

Chang CL, Donaghy M, Poulter N, and World Health Organisation Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. Migraine and stroke in young women: case-control study. *BMJ* 1999; 318:13-18.

Lead Author's Name and Contact Information

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The Study Patients

Cases: 291 women aged 20-44 years from five European centers participating in the WHO collaborative study of cardiovascular disease and steroid hormone contraceptives. Subjects have had strokes, acute myocardial infarction, or venous thrombo-embolic disease. Controls: 736 women, up to three hospital-based controls, matched by 5-year age bands and time of admission.

Exposure of Interest

Oral contraceptives and migraine

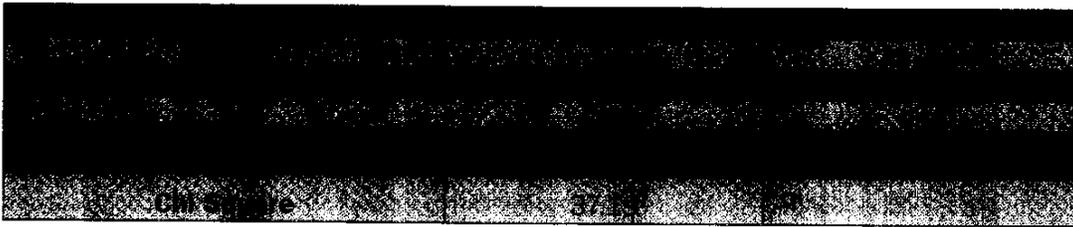
The Outcome

Stroke

Methodological Issues

There were dissimilarities between the case group and the control group. Those cases and controls with a history of migraine were significantly more likely to report having hypertension during pregnancy, or a family history of migraine. There were separate procedures for cases from strokes, which may bias the observations. Follow up is relatively long and complete enough because of the case-control nature of the study.

The Evidence



Comments

1. The summary odds ratio above shows that women with migraine who had stroke had higher odds of having used oral contraceptives.
2. The adjusted odds ratio for association of oral contraceptive use and stroke was not statistically significant for the low dose pills (<50 ug) compared to the high dose pills.
3. Adjusted odds ratios for all stroke, ischaemic stroke and hemorrhagic stroke associated with personal history of migraine were also computed. Migraine alone is already a significant risk factor for ischaemic but not hemorrhagic stroke.

4. The use of oral contraceptives and coexistence of hypertension or smoking seems to exert a greater than multiplicative effect on the risk of ischaemic stroke associated with migraine.
5. This effect was statistically significant especially for smokers, and women should be advised accordingly.
6. More than 80% of migrainous women who used oral contraceptives had not experienced any change in frequency of headache or type of migraine in relation to using the contraceptive. Compared to controls, there was no excess of conversion from simple to classical migraine after starting oral contraceptives in the women who had had a stroke.

Answer to Clinical Scenario

Current recommendation is not to prescribe combined oral contraceptives (COCs) to women with migraine with aura in view of additional stroke risk. Although the incidence of ischaemic stroke is very low in women of reproductive age, it is increased in women with migraine particularly if they also take COCs.

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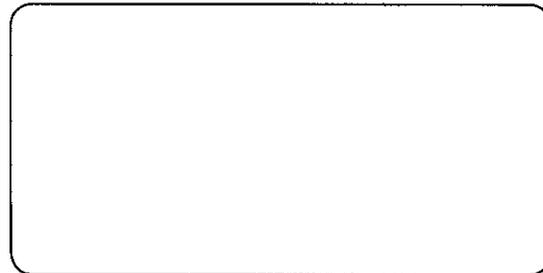
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EVIDENCE

**Women with
migraine who use
oral contraceptives
have an increased
risk of stroke.**



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The Clinical Scenario

A 30-year-old G2P2 woman consults you because she wants to use oral contraceptives. She has a neighbor who recently was diagnosed with cancer of the cervix. She would like to ask you if she could develop cancer of the cervix if she uses oral contraceptives. She is planning to use the method only for a few years.

Clinical Bottom Line

The analysis suggests that risk of invasive squamous cervical cancer and in-situ cancer for women who tested positive for HPV infection is not increased among short term users of oral contraceptives (< 5 years) (OR= .73). However, among women who are tested for HPV DNA the risk is increased three- to four-fold if they have used oral contraceptives for 5 years or longer.

Citations

Moreno VM, Bosch FX, Munoz N, Meijer CJL, Shah KV, Walbommers JMM, Herrero R, and Francheschi S; for the IARC Multicentric Cervical Cancer Study Group. Effect of oral contraceptives on risk of cervical cancer in women with human papilloma virus infection: The IARC multicentric case-control study. Lancet Vol 359 1985 to 1092, March 2002.

Corresponding Author's Name and Contact Information

Dr. Victor Moreno, Epidemiology and Cancer Registry Service, Catalan Institute of Oncology, Hospital Duran y Reynals (E-mail: v.moreno@ico.scs.es)

Level of Evidence

3e Pooled Case-Control

The Study Patients

Histologically diagnosed Carcinoma in Situ and Invasive Cervical Cancer (of the squamous cell type) patients with Human Papilloma Virus Infection were included. Controls were taken from the same country sites. One of the country sites was the Philippines.

Exposure of Interest

Ever use of oral contraceptives, length of use of Oral Contraceptives. This was ascertained using questionnaires.

The Outcome

Cervical Neoplasia (CIS and Invasive Cancer)

Methodological Issues

Subjects were defined and similar in other important ways. The exposures and outcomes were either objective or measured blind. Follow-up was long enough; follow-up was complete enough.

The Evidence

	No	%	163
Chi Square		0.00	

	No	%	163
Chi Square	28	7.21	

Comments

1. The Human Papilloma Virus (HPV) has been established to have an important role in the causation of cervical cancer, and is probably a prerequisite for the development of the disease, among other factors.
2. The prevalence of HPV in cases of cancer of the cervix was 94% and in Carcinoma in situ was 72%. Overall prevalence for cases was 90% while it was 13% in controls.
3. In the Philippine sample in the article, HPV prevalence in cases of cancer was 96% and in controls was 9%.
4. Exogenous female hormones such as those used in oral contraceptives have been proposed as co-factors in the development of cancer of the cervix.
5. Previous case-control studies of the association of oral contraceptives and cervical cancer did not have accurate information about the HPV status of the controls, and thus were not considered as susceptible to cancer of the cervix. Absence of such information could have biased estimates of the association to unity.
6. The article did not mention in detail how the case and control populations were chosen, because these have been described elsewhere.

The paper recommends that extra effort should be made for women who are long-term users of oral contraceptives to be included in cervical screening programs. The article did not mention how the case and control population were chosen, because these have been described elsewhere.

Answer to Clinical Scenario

There is no increased risk for women who use oral contraceptives if they use them for less than five years when they are HPV positive. For those who plan to use pills longer and for those who do not know their HPV status, they should be included in cervical cancer screening programs.

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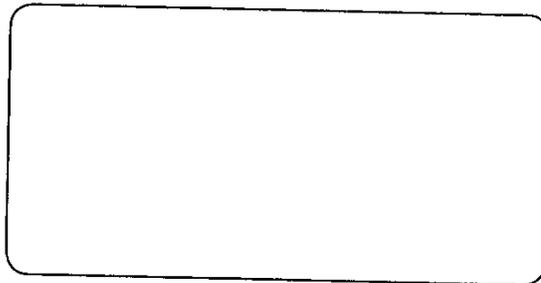
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EVIDENCE

**Short-term oral
contraceptive use (< 5 years)
does not increase the risk
of cervical cancer in women
with human papilloma virus
infection, but long term use
(> 5 years) does increase the
risk.**



• EVIDENCE

The Clinical Scenario

A 30-year-old woman on pills wishes to get pregnant. She is worried, however, that because she has been taking pills for more than 5 years, the pills might cause abnormalities like Down syndrome in future children. She comes to you for advice.

Clinical Bottom Line

There is no increased risk of Down syndrome in a pregnancy that follows cessation of oral contraceptive pill even for pregnancies that occur within the next cycle. This lack of relationship was demonstrated for groups of mothers who were 34 and 35 years old.

Citations

Martinez-Frias, ML et al. Periconceptional Exposure to Contraceptive Pills and Risk for Down Syndrome. *Journal of Perinatology* 2001; 21:288-292.

The Study Patients

This is a case-control study using the data from the Spanish Collaborative Study of Congenital Malformation (ECEMC) between April 1976 and June 1998. For each malformed infant (case), the next non-malformed infant of the same sex born in the same hospital was selected as a control subject. A total of 1,527,579 liveborn infants were surveyed; 27,278 selected as cases; 2,056 were diagnosed as Down syndrome; 1,506 mothers used OCs.

Next page >>

Level of Evidence 3b: Individual Case-Control Study

The population studied comprised 1277 women where OC was the last contraceptive used.

There were two approaches used. First was the pair matching analysis and the second was the case-control using the rest of the total 17,183 controls of the ECEMC database with specified data on maternal use of OCs and maternal age. The possible relationship between Down syndrome with the use of OC was analyzed by studying the cases whose mothers became pregnant during the use of oral contraceptive pills and those whose mothers stopped the contraceptive treatment at the following intervals before becoming pregnant: one month, two months, and three months or more.

Exposure of Interest

OC use before a pregnancy

The Outcome

Down syndrome

Methodological Issues

The subjects were defined and similar in other important ways. The exposures (intake of oral contraceptive pills) and outcomes (presence or absence of Down syndrome) were either objective or measured blind. The collaborating physician collected the same data for both malformed and non-malformed infant.

Follow-up was considered long and complete enough in this case control study. The possible relationship between Down syndrome with the use of OC was analyzed by studying the cases whose mothers became pregnant during the use of oral contraceptive pills and those whose mothers stopped the contraceptive treatment at the following intervals before becoming pregnant: one month, two months, and three months or more.

The Evidence

	Present	Absent
No	994	13131
Chi Square	6.82	

Comments:

1. This is a specific study that analyzed only the relationship between prior use of OC's and Down syndrome.
2. The Odds Ratio of 0.87 seems to show a trend of protection against Down syndrome, but this is not significant.
3. All other groups of women and timing of stopping of oral contraceptive pills did not differ significantly.
4. The authors attempted to further stratify the groups as to the time when OCPs were stopped. The OR that women less than 34 years old who had children with Down syndrome took pills and stopped their intake after conception was 2.71 (CI 1.48, 4.89). The numbers in the subgroup analysis, however, are small, and there would not be enough power to detect actual differences.
5. The OR that women over 35 who had children with Down syndrome took pills and stopped their intake about 1 month before conception was 0.26 (CI 0.08, 0.75). The numbers in the subgroup analysis, however, are small, and there would not be enough power to detect actual differences.
6. All other groups of women and timing of stopping intake of contraceptive pills did not differ significantly.

Answer to Clinical Scenario

OC pill users do not have an increased risk of bearing children with Down syndrome.

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AED

Academy for Evidence-Based Research



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EVIDENCE

**There is no
increased risk of
Down syndrome in
pregnancies that
follow previous use of
oral contraceptives.**

• EVIDENCE

The Clinical Scenario

A 33-year-old woman is thinking of having her IUD removed only a year after insertion because she has heard stories that she could have problems getting pregnant post-removal. She comes to you for advice, and you want to convince her not to have it removed due to this fertility concern.

Clinical Bottom Line

Users of intrauterine devices for less than 42 months have comparable fertility rates to users of oral contraceptives and barrier methods. Long term IUD users (more than 78 months), however, may have an increased risk of fertility impairment.

Citations

Doll H, Vessey M, and Painter M. Return of fertility in nulliparous women after discontinuation of the Intrauterine Device: Comparison with women discontinuing other methods of contraception. Br J Obstet Gynecol 108: 304-314. March 2001.

Lead Author's Name and Contact Information

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Level of Evidence 2b: Individual Cohort Study

The Study Patients

This is a prospective cohort of 558 nulliparous women, aged 18 to 40 years old in two groups, one group with intrauterine devices and the other on contraceptive pills, from 17 family planning clinics in England and Scotland, who completed information to this study for about 14 years.

Prognostic Factor

Use of contraceptive pills and of intrauterine devices, and other methods of family planning (such as the barrier method).

The Outcome and Methodological Issues

Number of nulliparous women giving birth at term after stopping contraception (OCP, IUD or any other method) in order to conceive. There was a well-defined sample at a uniform (early) stage of illness. Follow-up was long enough; follow-up was not complete. There were no blind, objective outcome criteria. Adjustment was made for other prognostic factors. There was validation in an independent test-set of patients.

The Evidence

Prognostic Factor	Outcome	Risk	Measure	Independence
Stopping Use of Barrier Method	Undelivered after 12 months	45.9%	Percent of Users undelivered	yes
Stopping Use of Oral Contraceptives	Undelivered after 12 months	67.6%	Percent of Users undelivered	yes

Prognostic Factor	Outcome	Risk	Measure	Independence
Ever Use of IUDs	Undelivered after 12 months	57.9%	Percent of Users undelivered	yes
IUD Used 42-78 Months	Undelivered after 12 months	54.7%	Percent of Users undelivered	yes
Never Used IUDs	Undelivered after 12 months	54.7%	Percent of Users undelivered	yes

Comments

1. From an initial group of 1,071 recruited women, only 558 (52%) were able to complete follow up, which may still be considered respectable, considering the long duration of follow up (14 years).
2. Duration of infertility after the study was not completely assessed to see if some users became completely infertile.
3. Proper adjustments in the analysis for other factors were incorporated, such as maternal age, husband's social class, and history of gynecologic illness.
4. Users of barrier methods who stopped this method to achieve a planned pregnancy conceived most quickly and delivered after one year.
5. Short term intrauterine device users (<42 months) showed a fertility pattern more favorable than those seen in discontinuing oral contraceptives (60.7% versus 67.6%).
6. An increasing duration of intrauterine device use was associated with decreasing fertility, with those who used it for more than 78 months being the most impaired (64.3% undelivered).
7. Compared to those using the barrier methods, the NNT for being undelivered after stopping IUDs is 7.

Answer to Clinical Scenario

The use of the IUD for a short time (about less than four years) has comparable return to fertility rates to those who discontinue oral contraceptives. IUD use of more than 6 years may be associated with an increased risk of infertility impairment.

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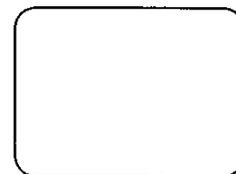
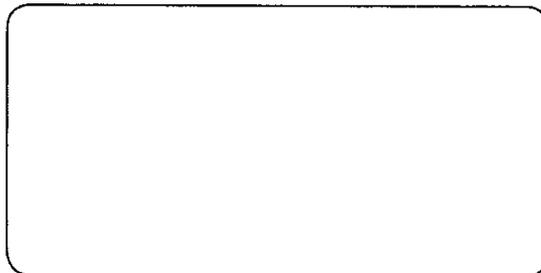
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EVIDENCE

OC pills and short-term IUD use offer quicker return to fertility for nulliparous women compared to long-term IUD use.



EVIDENCE

The Clinical Scenario

A 35-year-old woman wants to use a new oral contraceptive on the market. She has a family history of myocardial infarction as her mother and older sister had it in their early 40's. She is asking if using the new generation OCPs would put her at higher risk for MI.

Clinical Bottom Line

Compared to second generation oral contraceptive users and current non-users, the use of third generation oral contraceptives is not associated with an increased risk of myocardial infarction, according to findings from a multicenter case-control study.

Citations

Lewis, MA et al. Third generation oral contraceptives and risk of myocardial infarction: an international case-control study. *BMJ* 1996; 312: 88-90.

Lead Author's Name and Contact Information

Michael A Lewis, Dept of Epidemiology and Biostatistics, McGill University, Montreal, Canada

Level of Evidence 3b: Individual Case-Control Study

The Study Patients

This was a multinational, multicenter case-control study that included 651 women in the reproductive age group (16-44 years). There were 153 cases with a myocardial infarction event and 498 controls unaffected by myocardial infarction with a 1:3 case-control ratio. The subjects were matched by age (in 5 year age bands), BMI, smoking status, alcohol intake, duration of contraceptive use before current contraceptive, hospital, and community. Controls were identified and interviewed within four months of the myocardial infarction of the index case.

Exposure of Interest

The putative risk factor was the current use of third generation oral contraceptives which contained low dose ethinyl estradiol (20-30 mcg) and one of two progestogens, gestodene or desogestrel. Current use was defined as oral contraceptive use within three months before MI event for a case. The main reference group consisted of second generation combined oral contraceptive pills containing low dose ethinyl estradiol (<50 mcg) and other early progestogens.

The Outcome

Cases were identified by their first myocardial infarction event as defined by ICD code 410. Controls were hospital and community controls with no history of MI.

Methodological Issues

Subjects were defined and similar in other important ways. Because of the nature of study design, it is difficult to tell if the risk factors of interest, exposures, and outcomes were either objective or measured blind; can't tell if follow-up was long enough; can't tell if follow-up was complete enough.

Comments (*Please refer to Table of Evidence on facing page*)

Logistic regression analysis showed that:

1. There was an overall trend towards protection from MI among third generation OC users compared to the main reference group.
2. However, there was also a trend towards slight increase in risk for MI for third generation users compared to current non-users.
3. Smoking as a confounder was found to be significantly associated with MI in all three groups of OC status.

The Evidence

Third generation vs no current use	1.1 (0.4-3.4)	0.9
Hospital controls (n=210)		
Third generation vs no current use	1.9 (0.4-8.7)	0.4
Second generation		
Community controls (n=288)		
Third generation		
Third generation vs no current use	0.9 (0.3-3.0)	0.8
Second generation		

Adjusted for center, age, BMI, smoking, alcohol intake, and duration of contraceptive use before current third generation use

Answer to Clinical Scenario

Compared to second generation oral contraceptive users and current non-users, the use of third generation oral contraceptives is not associated with an increased risk of myocardial infarction.

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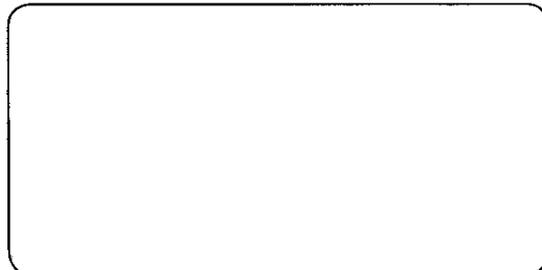
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A Core Issue of the Network Studies of Women

EVIDENCE

The use of third generation oral contraceptives is not associated with myocardial infarction.



• EVIDENCE

The Clinical Scenario

A 20-year-old woman wishes to start using oral combination contraceptives. She is worried about gaining weight because of the pills.

Clinical Bottom Line

Forty-two trials including three placebo-controlled, randomized trials did not find evidence supporting a causal association between combination oral contraceptives and weight gain. Also, most comparisons of different combination contraceptives showed no substantial difference in weight or difference in discontinuation rates due to weight gain.

Available evidence is insufficient to determine the effect of combination contraceptives on weight, but no large effect is evident. *In general, health care providers prescribing combination contraceptives do not need to weigh women.*

Citations

Gallo MF, Grimes DA, Schulz KF, Helmerhorst FM. Combination Contraceptives: Effects on Weight (Cochrane Review). In: The Cochrane Library. Issue 2. 2003. Oxford: Update Software.

Lead Author's Name and Contact Information

Gallo MF Fax: +1 919 544 9190

Level of Evidence [None indicated]

The Review

Data Sources: Cochrane Library

Study Selection: All English language, randomized controlled trials at least three treatment cycles in duration that compared a combination contraceptive to a placebo or with a combination oral contraceptive that differed in drug, dosage, regimen, and/or study length were eligible. 42 trials were selected, 3 of which had a comparison control group.

Data Extraction

Types of Participants: Women of reproductive age without medical contraindications to combination contraceptives.

Types of Intervention: Any combination contraceptives compared to either a placebo or with another combination contraceptive. Trial drug interventions must have included a minimum of three consecutive cycles to be eligible.

Types of Outcome Measures: Trials must have collected data on change in body weight to be eligible for inclusion. Weight change could have been measured as either the change in the study group's mean weight or as the proportion of the study group who lost or gained more than a specified amount.

Methodological Issues

The studies were multiple independent reviews of individual reports. They were tested for heterogeneity. The four comparisons between an oral contraceptive and placebo (Coney 2001; Goldzieher 1971a) found no differences in weight with statistical significance or interval estimation considerations.

Comments

1. **Potential Conflict of Interest:** Dr. Grimes has consulted with or served on a speaker bureau for ALZA, Berlex Laboratories, Gynetics, GynoPharma, Mead Johnson, Organon, Ortho-McNeil, Parke-Davis, Pharmacia-Upjohn, Schering, Schmid, Searle and Wyeth-Ayerst. Dr. Helmerhost has supervised studies sponsored or assigned by various pharmaceutical companies that manufacture oral contraceptives.

Answer to Clinical Scenario

There is no evidence that taking oral contraceptives would lead to weight gain.

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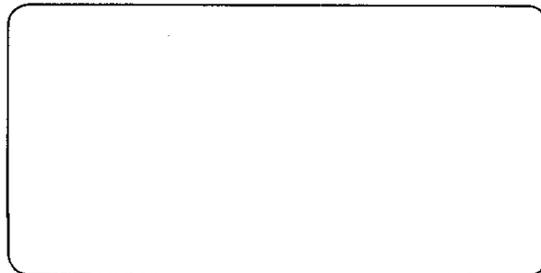
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EVIDENCE

**The use of
combined oral
contraceptives is
not associated with
weight changes in
users.**



EVIDENCE

The Clinical Scenario

A 34-year-old woman is interested in taking oral contraceptive pills but is worried that she may get ovarian cancer.

Clinical Bottom Line

Women exposed to oral contraceptives have a lower incidence of epithelial ovarian cancer than women never exposed to oral contraceptives. This protective effect increases with longer use of OCs (over 5 years).

Citations

Bosetti C et al. Long Term Effects of Oral Contraceptives on Ovarian Cancer Risk. *Int J Cancer*. 2002; 102 (3): 262-5.

Lead Author's Name and Contact Information

Cristina Bosetti; Email: bosetti@marionegri.it

The Study Patients

Cases: 2,768 patients < 70 years of age with histologically confirmed epithelial ovarian cancer

Controls: 6,274 patients < 70 years of age admitted in the same hospital for non-gynecologic conditions within the same time period

Level of Evidence 3a: Systematic review of 6 case-control studies.



Exposure of Interest

Oral contraceptives

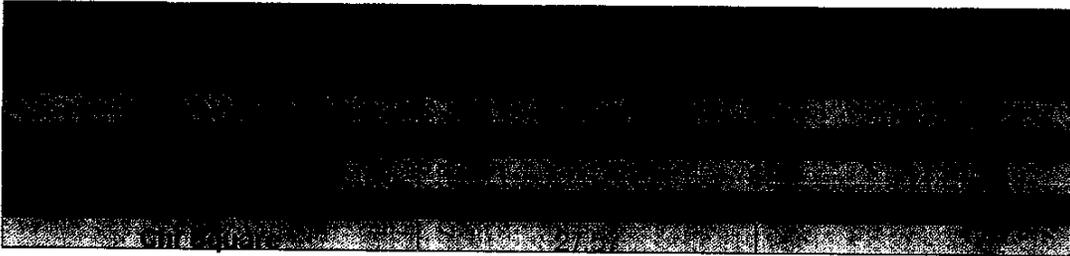
The Outcome

Epithelial ovarian cancer

Methodological Issues

Subjects were defined and similar in other important ways. The exposures and outcomes were either objective or measured blind. Follow-up was long enough; follow-up was complete enough.

The Evidence



Comments

1. This is a systematic review of 6 case-control studies conducted in Europe.
2. The odds ratio in the table above of 0.68 is for ever use of oral contraceptives. This may mean that women who are diagnosed to have epithelial ovarian cancer have less odds ever having been users of oral contraceptives.
3. The odds ratio was 0.42 (CI 0.30-0.59) for duration of use greater or equal to 5 years. The odds of women with epithelial ovarian cancer to have been ever-users of oral contraceptives more than 5 years is even less than in the previous statement.
3. This protective effect of oral contraceptive use lasted for at least 20 years after stopping its usage. An apparent leveling off of this effect after 20 years since last use was more evident after taking into account duration of use.

Answer to Clinical Scenario

Women who have been diagnosed to have epithelial ovarian cancer were less likely to have been users of oral contraceptives. The likelihood is even less if the duration of OCP use is longer.

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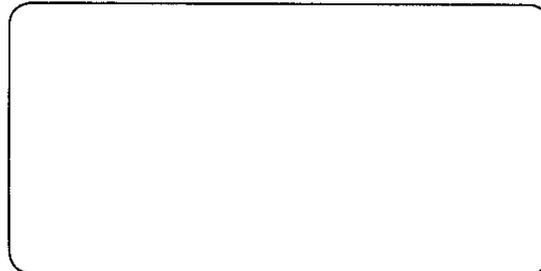
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EVIDENCE

Women who have taken oral contraceptives have a lower risk of epithelial ovarian cancer than those who have never taken oral contraceptives.



EVIDENCE

The Clinical Scenario

A 35-year-old housewife is using oral contraceptives. Her husband notices that she has been irritable lately. She consults you because she thinks the oral contraceptive pills (OCPs) affect her mood.

Clinical Bottom Line

Compared to non-users, oral contraceptive users experience less variability in affect in the different phases of the menstrual cycle, and less negative affect during menstruation.

Citations

Oinonen KA, and Mazmanian D. To what extent do oral contraceptives influence mood and affect? *J Affective Disorders*. 70 (2002) 229-240.

Lead Author's Name and Contact Information

Fax +1-807 3467734

The Review

Data Sources: Medline

Study Selection: Comparative Studies of OCP users and non-users with outcomes on mood and affect using daily rating scales.

Data Extraction: Comparative studies were searched, and retrospective studies were excluded. The studies were not multiple independent reviews of individual reports. They were not tested for heterogeneity.



Level of Evidence [None indicated]



v3

The Results

The majority of the studies found no significant differences in negative affect across the entire menstrual cycle (Paige, 1971; Wilcoxon et al., 1976; Marriott and Faragher, 1986; Almagor and Ben-Porath, 1991) among OC users. While one study found that OC users feel less negative affect across the menstrual cycle (Boyle and Grant, 1992), one study found that monophasic OC users experienced higher negative affect throughout the cycle (Walker and Bancroft, 1990). In terms of positive affect, Almagor and Ben-Porath (1991) found that OC users experienced higher positive affect. Two other studies, however, did not find group differences in positive affect (Silbergeld et al., 1971; Boyle and Grant, 1992).

Comments

1. This was not a systematic review which summarized data using meta-analysis, rather it was a review article on various previously conducted studies evaluating OCP use and its relation to mood and affect.
2. No summary odds ratios were presented, rather summary recommendatory statements were given.
3. In women with OC-related negative mood and affect change, the potential mediators include a history of depression, psychiatric symptoms, dysmenorrhea, and premenstrual mood symptoms prior to OC use, a history of mood symptoms while pregnant, a family history of OC-related mood complaints, being in a postpartum state, and age.
4. More negative mood changes are found in OCs with a lower ratio of progesterone to estrogen.

Answer to Clinical Scenario

It is not likely the patient's mood and affect changes are due to her OCP use. In fact, most OC users experience a beneficial mood effect during their menstrual cycle. There is however a small group of women who can experience negative mood change. For these women, another contraceptive method could be considered, carefully weighing the pluses and minuses of the various alternative methods. For a woman desiring a short-term method of fertility control, oral contraceptives remain one of the best alternatives available.

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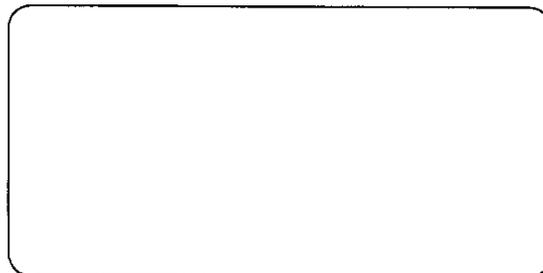
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EVIDENCE

**Oral contraceptive
users experience
less mood changes
and negative
affect during the
menstrual cycle.**



• EVIDENCE

The Clinical Scenario

A 28-year-old woman is asking if her use of oral contraceptives will put her at risk of liver cancer.

Clinical Bottom Line

There is no evidence for an increased risk of liver cancer (hepatocellular cancer) associated with oral contraceptive use. There no increased risk for liver cancer with increasing duration of oral contraceptive (OC) use among the different groups of OCs. The most important risk factors for liver cancer are a prior history of hepatitis B and C.

Citations

The Collaborative MILTS Project Team. Oral Contraceptives and Liver Cancer Results of the Multicentre International Liver Tumor. Contraception 1997; 56:275-284.

The Study Patients

The study is a hospital based case-control study undertaken in 5 European countries from July 1994- June 1996. Women under the age of 65 with and without HCC were recruited. Cases were classified as having a probable or definite diagnosis of HCC. On the average, 4 controls were obtained for each HCC case: 2 hospital controls without malignancy, one hospital control with a tumor diagnosis, and one population control. Frequency matching was done in the same 5 year age groups as the cases; living controls were obtained for cases in which patients were deceased. Cases were identified in specified liver centers and of 368 eligible cases identified, 317 (86.1%) were included. A total of 1060 hospital controls were selected from new admissions with pre-specified diagnoses and 719 population controls were randomly selected from a complete population register.

Level of Evidence Case-Control Study

Exposure of Interest

Oral contraceptive use

The Outcome

Hepatocellular cancer

Methodological Issues

The subjects were defined and similar in other important ways. The exposures and outcomes were either objective or measured blind. Follow-up was considered long and complete enough.

The Evidence

	Present	Absent
No	145	623
Chi Square	12.03	

Comments:

1. There is no significant increase in risk for developing HCC in women who ever used OCs containing cyproterone acetate (CPA), or for women ever using any other type of OC. The results of the unconditional (OR 0.75 [0.54, 1.03]) and conditional logistic regression analysis (OR 1.05 [0.80, 1.37]) are not significantly different for either of the OC subgroups.
2. There was no increased risk of HCC with increased duration of use for all OCs.
3. However, in 51 cases of women with no evidence of hepatitis B or C infection or liver cirrhosis, there was evidence of an association with duration of use. No such trend was observed for the CPA group of OCs.
4. Limitations of the study are: different prevalence of OC use among the different control groups, the different time periods when cases were recruited, and the different sources of information on exposures.

Answer to Clinical Scenario

There are no increased odds that patients with liver cancer (hepatocellular carcinoma) were oral contraceptive pill OCP users compared to those who did not use OCPs.

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A Study Group of The National Institutes of Health
EVIDENCE

**Oral contraceptives
do not increase the
risk of liver cancer.**

• EVIDENCE

The Clinical Scenario

An 18-year-old female client who is sexually active has moderate acne. She wishes to use oral contraceptive pills but was told that OCPs may be harmful for her complexion. Since she already has moderate acne, she is asking if OCPs would not be advisable for her to use.

Clinical Bottom Line

The use of low dose combined oral contraceptive pills is effective and safe for the treatment of moderate acne.

Citations

Leyden J, Shalita A, Hordinsky M, Swinyer L, Stanczyk FZ and Weber ME. Efficacy of a low dose oral contraceptive containing 20 ug of ethinyl estradiol and 100 ug of levonorgestrel for the treatment of moderate acne: A randomized placebo controlled trial. J Am Acad Dermatol. September 2002 Vol. 47 (3) 399-409.

Lead Author's Name and Contact Information

James Leyden, Department of Dermatology of the University of Pennsylvania, and Margaret Weber, Wyeth Pharmaceuticals, St. Davids, PA

Level of Evidence [None indicated]

The Study

Double-blinded concealed randomized controlled trial with intention-to-treat.

The Study Patients

371 patients, at least 14 years old, non-pregnant, with normal Pap smears from 18 investigational sites with moderate facial acne (judged as a total facial count of 6 to 200 non-inflammatory comedones, 10 to 75 inflammatory lesions (papules and pustules) and 5 or fewer nodules.

Control Group

(N=186; unable to tell final number analyzed): Placebo similar in appearance and packaging to the active oral contraceptives were taken for 6 cycles.

Experimental Group

(N=185; unable to tell final number analyzed): Active treatment consisted of tables containing 20 ug of ethinyl estradiol and 100 ug of levonorgestrel in a 28 blister pack with 21 days of active medication followed by 7 days of placebo.

The Evidence

	Mean	SD	Mean	SD		
Change in the number of inflammatory lesions	-5.75	14.00	-8.13	13.14	2.380, P= 0.0437	-0.413 to 5.173

Comments:

1. The reader could not determine the exact number of treatment and control subjects who completed the study. Authors stated that of the 371 patients enrolled at baseline, 246 completed the study (66.3%), with a similar number completing in each arm.
2. Aside from the clinical manifestations of acne, the study also evaluated the biochemical markers of androgenicity which were decreased during EE/LNG treatment compared with placebo and baseline values.
3. The patients in the EE-LNG group also had significantly better scores for clinical global and patient self-assessments than those in the placebo group.
4. The oral contraceptive combination used had the more common components of hormones.
5. Of the patients who took medications, the rate of adverse events which were all minor, were not statistically different between groups (83.4% OCP group versus 73.1% in placebo group.) The most common events were allergic reactions, sinusitis, and metrorrhagia, which were noted to decrease with time.
6. The paper was supported by a grant from Wyeth Pharmaceuticals.

Answer to Clinical Scenario

Low dose oral contraceptives are safe for women with moderate acne and may even treat the condition.

EVIDENCE

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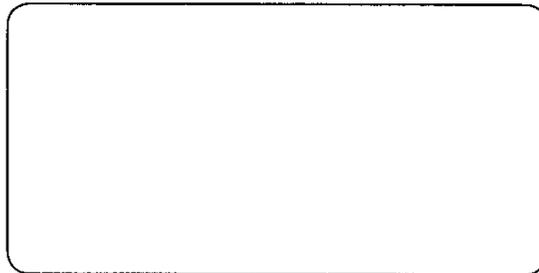
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EVIDENCE

**Low dose oral
contraceptive
use can improve
moderate acne.**



Injectable Contraceptives

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EVIDENCE

EVIDENCE

Women who use DMPA are not at increased risk of cervical cancer.

The Clinical Scenario

A 30-year-old G2P2 woman consults you because she wants to use DMPA for contraception. She has a neighbor who was recently diagnosed with cancer of the cervix. She would like to ask you if she can develop cancer of the cervix if she uses DMPA.

Clinical Bottom Line

Women exposed to DMPA are not at increased risk of developing cervical adenomatous carcinoma.

Citations

Thomas DB et al. Depot-Medroxyprogesterone Acetate (DMPA) and risk of invasive adenocarcinomas and adenosquamous carcinomas of the uterine cervix. *Contraception* Vol. 52: pp 307-312, 1995.

Lead Author's Name and Contact Information

David B. Thomas, Fax No.: 206-667-4787

The Study Patients

CASES: 324 women in Thailand, Mexico & Kenya born after 1930 (except for Chiang Mai, women born after 1925) who had been diagnosed with cervical adenomatous carcinoma from 5 hospitals.

Next page >>

Level of Evidence 3b: Individual Case-Control Study

CONTROLS: 9,583 women hospitalized for conditions other than obstetrical or gynecological, and generally considered as not being associated with the use of steroid contraceptives, who met the same birth and residential criteria as the cases.

Controls were not matched to individual cases. However, the investigators did control for several known risk factors including age, center, year of entry into the study, use of oral contraceptives or premenopausal estrogens, numbers of pregnancies, smoking status, history of genital warts, and male partner sexual behavior.

Exposure of Interest

Use of DMPA

The Outcome

Cervical adenomatous carcinomas

Methodological Issues

The subjects were defined and were similar in other important ways. The appraiser could not tell if the accounting of exposures and outcomes were either objective or measured blindly. It cannot be determined if follow-up was long enough or complete enough.

The Evidence

		Cervical Adenomatous Carcinoma	
		Present	Absent
DMPA Use	Yes	51	395
	No	273	2139
Odds Ratio		1.01	95% CI: 1.01 to 1.02
Chi Square		0.00	

Comments

1. This is a case-control study that relied on subjects' recall of DMPA use over a period of 5-10 years.
2. The odds ratio of 1.01 of developing cervical adenomatous carcinoma when exposed to DMPA means that the odds of having used DMPA is practically the same whether the patient was with cancer or not.
3. The odds for having used DMPA in patients with cancer was unaltered by the months of DMPA use, time since initial or most recent exposure, or age at first use.

Answer to Clinical Scenario

Among women who have had adenomatous cancer of the cervix, they were no more likely to have used DMPA, compared to women who had no such cancer. This absence of risk was consistently found among all sub-groups of the sample studied. Based on this study, the woman can be advised that there would be no increase in the risk of developing adenomatous cancer of the cervix if she uses DMPA.

EVIDENCE

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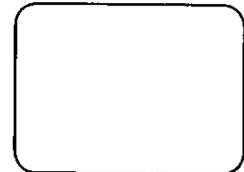
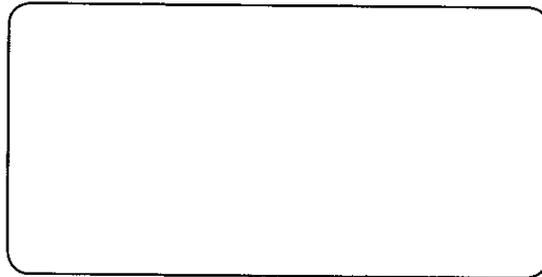
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EVIDENCE

**Women who use
DMPA are not at
increased risk of
cervical cancer.**



• EVIDENCE

Compared to non-lactating women, breastfeeding women on DMPA are more likely to continue using the method for fertility control, and their side effects are less frequent.

The Clinical Scenario

A 23-year-old new mother would be asking about using DMPA as a family planning method. She is also interested in breastfeeding. She is asking about side effects.

Clinical Bottom Line

In lactating women who use Depo Provera for contraception, the discontinuation rate was lower because the occurrence of side-effects was lower, compared to non-lactating women who use Depo Provera. It is therefore desirable to start postpartum women on DMPA while breastfeeding due to lower side effects and resultant higher compliance.

Citations

Sun Danli, Shao Qingxiang, Sang Guowei. A multi-centered trial of the long-acting injectable contraceptive Depo Provera in Chinese women. *Contraception* 62 (2000): 15-18.

Lead Author's Name and Contact Information

Sun Danli, +86-0571-8076765; Fax +86-0571-8075447; Email address: imm.zj@mail.hz.zj.cn

The Study Patients

	Contraceptive, injectable, long-acting
Level of Evidence	2b: Individual Cohort Study
	Depo Provera

A total of 1,994 healthy, fertile, non-pregnant women aged 18 to 40 years received a total of four (4) Depo-Provera injections for contraception at intervals of 90 +/- 7 days. 26% were breastfeeding women who were enrolled within 1 year after parturition with injections started 6 weeks after delivery. These women were followed-up at 3, 6, 9, and 12 months for side effects and discontinuation. Excluded were women with diabetes, abnormal pap smear, confirmed hypertension, history of thromboembolism (cerebrovascular accident or incapacitating migraine), vaginal bleeding of unknown etiology, pregnancy, recent or once severe liver disease, diagnosed or suspected malignancy, abnormal nipple discharge.

Exposure of Interest

Breastfeeding

The Outcome

Discontinuation due to side effects

Methodological Issues

The non-lactating women were older (almost 50% were GE 30 years), versus only 9.8% of lactating women. Also, the previous contraception profiles were very different between them. For example, the prior IUD rate was 21% for non-lactating versus 4.5% for lactating women. The exposures and outcomes were neither objective nor measured blind. Follow-up was long enough; follow-up was complete enough.

The Evidence

		Discontinuation due to			
		Present		Absent	
		Number	Proportion	Number	Proportion
Breastfeeding	Yes	116	0.22	402	0.78
	No	1051	0.29	1051	0.71
Relative Risk:		0.78			
Number Needed to Harm:		1		95% CI: 0.76 to 0.80	
Chi Square		8.27			

Particular to my patient:

Number	1	95% CI: 0.76 to 0.80
---------------	----------	-----------------------------

• EVIDENCE

There is no overall increased risk of getting breast cancer from the use of DMPA for contraception, including long term use (>5 years use).

The Clinical Scenario

A 30-year-old woman is interested in using DMPA but is worried about the risk of developing breast cancer. Her neighbor has breast cancer and she is concerned she may develop it as well.

Clinical Bottom Line

There is no overall association between breast carcinoma and medroxyprogesterone acetate. In addition, the risk of breast cancer among women who took DMPA for long periods (over 5 years) was no different than from those women who never took DMPA (relative risk was 1.0 in both groups).

Citations

Depot Medroxyprogesterone Acetate and Breast Cancer: A Pooled Analysis of the World Health Organization and New Zealand Studies

Lead Author's Name and Contact Information

Skegg, David C.

Level of Evidence 3b: Two Individual Case-Control Studies

The Review

- Data Sources : Medline
- MESH - DMPA (medroxy-progesterone 17-acetate)
- MESH - breast neoplasms
- 67 articles if limited to RCTs (but no relevant articles)
- 15 articles if mixed with Case Control Studies, but the Skegg article chosen because most recent.

The Study Patients

1,768 women with breast cancer ("Cases"), and 13,905 controls. Most were younger than 55 years. Patients were pooled from two studies: a New Zealand study and the WHO study.

Study Selection

The article is a pooled analysis of two studies which were selected because they have similar designs, similar but inconclusive results, and inadequate sample sizes. It was hoped that combining the results will provide a stronger conclusion regarding medroxyprogesterone acetate and breast carcinoma. There is no statement in the article which indicates the method of literature search done, and the criteria for study selection aside from the aforementioned.

Data Extraction

In both case control studies (WHO and New Zealand), the data on contraceptive histories for cases and controls were collected in a standardized questionnaire by trained interviewees. It is stated in the article that the New Zealand questionnaire was partly based on the one developed for the WHO study. In the statistical analyses, the data from New Zealand were converted into a format compatible with the WHO data set. The data from the two studies were then analyzed in the same manner as in the WHO study.

Methodological Issues

One cannot determine if the studies were multiple independent reviews of individual reports. They were tested, however, for heterogeneity and found not to be significant at p-value of 0.23.

The Evidence

Breast Cancer (Overall)	1.1 (1.97, 1.4)	NS
Breast Cancer (New Zealand)	3.1 (1.8, 5.2)	Sig.

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EVIDENCE

There is no overall increased risk of getting breast cancer from the use of DMPA for contraception, including long term use (>5 years use).

Comments:

1. Despite the absence of a systematic review of literature, this article provides the largest available dataset that gives one a better understanding of the relationship between breast carcinoma and medroxyprogesterone acetate.
2. There is no apparent overall increased risk of breast cancer from (ever) use of DMPA. This appears true for women 35 years and older. Further, there is similarly no increased risk from DMPA use relative to duration of use.
3. However, there is a 2.1 odds relative risk (RR) of breast cancer for women under age 35. Current users of DMPA who were younger than 35 had an RR of 2.1 (95% C.I. 1.1 to 3.8). Furthermore, the RR for women who had started using DMPA in the previous 5 years was 2.0 (C.I. 1.5 to 2.8).
4. The RR's for women whose last use was in the more distant past were not elevated. These findings may be somewhat confusing to clinicians; however, most researchers suggest that the increased rates of cancer in young DMPA users for less than 5 years is likely due to the stimulation of an existing cancer rather than the creation of a new cancer in these women.
5. To reassure clinicians, the investigators analyzed risk of breast cancer and length of use of DMPA. They found the risk of breast cancer among women who took DMPA for long periods (over 5 years) was no different than from those women who never took DMPA (relative risk was 1.0 in both groups).
6. The article is highly relevant and uses valid methodology.

Answer to Clinical Scenario

There is no increased risk of developing breast cancer from DMPA.

• EVIDENCE

DMPA reduces the number of hot flashes in menopausal women.

The Clinical Scenario

A 38-year-old woman who has been using DMPA for contraception recently had a total hysterectomy and bilateral salpingo-oophorectomy for endometriosis. She would like to know if she could continue using DMPA safely to prevent the signs and symptoms related to menopause.

Clinical Bottom Line

The use of DMPA decreases the number of episodes of hot flashes per day among menopausal women.

Citations

Barton D, Loprinzi C, et al. Depomedroxyprogesterone Acetate for Hot Flashes. *J Pain Sympt Mgt* 24: 6, 603-607, Dec. 2002.

Lead Author's Name and Contact Information

Debra Barton, 200 First St. SW, Mayo Clinic, Rochester MI, 55905



Level of Evidence

2c: Non-blinded, non-randomized pre-post design with no control group



The Study Patients

Menopausal women being treated for breast cancer but who were no longer on chemotherapy and were complaining of symptoms such as hot flashes were asked to make a diary of episodes of hot flashes while they were being given DMPA. Of the 15 women recruited, one did not complete the study and was excluded.

Single cohort treatment group (N=15; 14 analyzed): DMPA 500 mg IM given every two weeks for a total of 3 doses. There was no control group, just a single cohort in a pre-post design.

The Evidence

Comments

1. This was not a comparative study against women who did not receive DMPA or who received other drugs, just a pre-post design or before-after study without a control group.
2. The study also included a small group of old men.
3. All the female subjects were breast cancer survivors, half of whom were on tamoxifen, possibly limiting the generalizability of the results to menopausal women with no breast cancer.
4. Other minor side effects were reported. Two patients stated they experienced weight gain, two reported muscular spasms, and there was one reported instance of vaginal spotting and weak fingernails.

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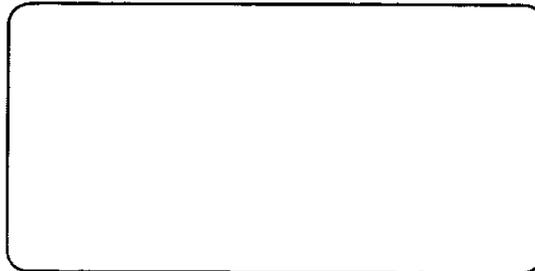
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EVIDENCE

**DMPA reduces
the number of
hot flashes in
menopausal
women.**



5. The favorable effect of decrease in hot flashes persisted six weeks after the DMPA was discontinued.
6. The study did not use a standardized side-effect questionnaire given to the patients; rather it used a diary method.
7. The study is consistent with the findings of an older study which showed that DMPA reduces the frequency and severity of postmenopausal hot flashes. Of 57 postmenopausal women treated with 150 mg DMPA monthly, 51 had significant improvement in hot flashes (Relative risk reduction 2.58, NNT=2) compared to women receiving placebo. (*From Bullock J, Massey F, Gambrell D. Use of medroxyprogesterone acetate to prevent menopausal symptoms. Obstetrics and Gynecology 1975; 46:165-168.*)

Answer to Clinical Scenario

DMPA may be continued for the symptoms of menopause such as hot flashes.

EVIDENCE

DMPA causes a reversible decrease in bone mineral density.

The Clinical Scenario

A 35-year-old female client is on DMPA and is beginning to worry about osteoporosis. She is asking if her contraceptive will cause bone thinning or loss.

Clinical Bottom Line

A population-based cohort study among women enrollees of a Washington state health maintenance organization (HMO) followed 183 DMPA users and 274 non-users for 3 years. Bone mineral density (BMD) decreased significantly among DMPA users, although the authors did not mention the incidence of fractures. The decrease in BMD was reversible. After 30 months discontinuers (N=100) showed a mean BMD similar to that of non-users.

Citations

Scholes, D; LaCroix, A, Ichikawa, L, Barlow WE, Ott SM. Injectable Hormone Contraception and Bone Density: Results from a Prospective Study. *Epidemiology* 2002; 13:581-587.

Lead Author's Name and Contact Information

Delia Scholes, Center for Health Studies, Group Health Cooperative, 1730 Minor Avenue, 16th Floor, Seattle, WA 98101; scholes.d@ghc.org

Level of Evidence [None indicated]

Hits

- Cochrane data base of reviews/DARE/CCTR/ACP Journal Club: 1 hit
 - o 1 non-relevant study
- MEDLINE 1966-April 30, 2003: 33 English language hits
 - o 6 non-relevant studies
 - o 11 level 5 papers: expert opinion, non-systematic review papers
 - o 6 level 4: case series and/or cross sectional studies
 - o 3 level 3b: individual case control
 - o 3 level 2c: "outcomes research" (single cohort)
 - o 4 level 2b: individual cohort studies with control groups:
 - § 3 with short follow-up and/or small cohorts
 - § 1 with large cohorts, 3 year follow-up and monitoring of discontinuers (the study for this CAT)

The Study

Cohort Study

The Study Patients

182 women who received injectable DMPA over a median period of 11 months and a control group of 258 who did not use DMPA who were followed up for three years.

Exposure of Interest

Use of DMPA

The Outcome

BMD level change

Methodological Issues

Subjects were defined and similar in other important ways. The exposures and outcomes were either objective or measured blind. Follow-up was long enough; follow-up was complete enough.

The Evidence and Comments

1. Bone density decreased notably among DMPA-exposed women at the spine (adjusted mean bone density was 0.0053 gm/cm² for DMPA users compared with 0.0023 gm/cm² for non-users for each 6-month interval) and total hip (0.0060 compared with 0.0002 gm/cm²).
2. This represents an annualized mean rate of change at the spine of 0.87% compared with 0.40% and, at the hip, 1.12% compared with 0.05%.
3. Discontinuers of this method (N=110) showed sizable increases in bone density over comparison women (for each 6-month interval, adjusted mean spine bone density was 0.0067 gm/cm² compared with 0.0023 gm/cm², respectively; adjusted mean hip bone density was 0.0035 compared with 0.0002 gm/cm²).
4. Estimated annualized mean rates of change were 1.41% compared with 1.03% at the spine and 0.40% compared with 0.05% at the hip. After 30 months, mean bone density for discontinuers was similar to that of non-users.
5. In this study, DMPA use was strongly associated with bone density loss. Substantial post-discontinuation recovery of bone provides evidence that the effects may be largely reversible.

Answer to Clinical Scenario

There is some decrease in BMD among DMPA users for 12 months, but the decrease is not clinically significant and is easily reversible after discontinuing or stopping use of DMPA.

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EVIDENCE

**DMPA causes
a reversible
decrease in bone
mineral density.**

**Intrauterine
Devices**

EVIDENCE

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The Clinical Scenario

A 30-year-old woman has two children and is interested in using an intrauterine device to prevent pregnancies over the next several years. She consults you because she has heard stories about how it prevents pregnancy. What will you advise her?

Clinical Bottom Line

Both pre-fertilization and post-fertilization effects are significant contributors to the clinical efficacy of all types of IUDs. The pre-fertilization effects are more prominent, especially for the copper IUD. Fertilization occurs relatively infrequently, but the potent post-fertilization effect contributes to achieve the observed low rates of clinical pregnancy.

Citations

Mechanisms of action of intrauterine devices: Update and estimation of post-fertilization effects. Am J Obstet Gynecol December 2002; 187:1699-708.

Data Sources

Medline, Popline

Study Selection

All articles published in peer-reviewed medical literature that provided data or reviews of the mechanism of action of the IUD. Additional articles were taken from the references section of these articles.

Level of Evidence 2c: Outcomes Research

Data Extraction

Women using IUDs were compared to a comparable group without any form of contraception. The outcome data extracted from the numerous studies were recovery of spermatozoa from fallopian tubes, evidence of fertilization (direct observation of fertilization of recovered ova and measurement of early pregnancy factor by rosette inhibition test -- very sensitive test -- during use of various IUDs and in control subjects). Model parameters and estimates of contributions of pre-fertilization and post-fertilization effects during the use of various IUDs were computed using mathematical modeling.

The studies were not multiple independent reviews of individual reports. They were not tested for heterogeneity. The review was not systematically done; instead it was a review of the various mechanisms of action with an attempt for estimating effects using mathematical modeling.

The Evidence

Recovery of spermatozoa from fallopian tubes during use of various IUDs	> 2 hours after insemination	0.33	0.32	49%	31%	3.2	0.25	0.12
Measurement of early pregnancy factor by rosette inhibition test	Secretory phase	0.57	0.30	47%	27%	3.7	0.32	0.32

Model parameters and estimates of post-fertilization loss during use of various IUDs

				Total No.	No. attributable to IUD, low estimate	No. attributable to IUD, high estimate
	19	156	26.10	200	0.72	1.97
		6.1	26.50	105	0.38	1.0
				185	0.6	

Comments

1. The control event rate (CER) refers to how often the outcome takes place in the group without the IUD. These rates are stated in Column 3 of Table 1. The experimental event rate (EER) refers to how often the outcome takes place in the group with the IUD and are shown in Column 4 of Table 1.
2. The relative risk reduction (RRR) in Column 5 shows how much is the effect of the experimental factor (IUD) compared to the control rate. The absolute risk reduction (ARR) in Column 6 shows the difference between the two rates. The number needed to treat (NNT) in Column 7 refers to how many patients should have the IUD so that an additional outcome is achieved. For example, one would have to have 1.6 additional patients with IUDs so that one can have one less directly observed fertilization of a recovered egg or ovum.
3. The IUD thus has a very high efficacy rate. This is reflected by the low NNT. One has to treat very few patients (1.6 to 3.7) to successfully block sperm transport to the fallopian tubes to prevent fertilization of the ova and to prevent pregnancy as measured by the early pregnancy factor (EPF). Likewise, the odds that a patient on IUD will have these pregnancy-related events is low (0.054 to 0.32). Patients with IUDs have a lower EER than the controls (CER).
4. Although a comprehensive search was done, the authors did not specify if they limited their search to randomized control trials. This may affect the review's validity as it may compound the problems of individual trials. There was no mention of how the investigators assessed the validity of the individual studies, and if there were independent reviews by at least two investigators.
5. The authors did not test for heterogeneity in the fertility of couples and just assumed that the underlying potential for pregnancy is the same among couples.
6. The EPF is the earliest available biochemical marker of fertilization of humans in vivo. It can be detected as early as 1 to 2 days after fertilization and is present for the remainder of pregnancy. The use of EPF as evidence of fertilization is not highly acceptable. Although the EPF is very specific, its sensitivity is less clear. Not all studies are able to use this method of detecting fertilization.
7. There are insufficient data to elucidate the exact contribution of the individual mechanisms for the various IUDs. Most estimates were based on known data from the inert IUD which, as the authors explained, are conservative estimates.
8. The authors have emphasized that their mathematics model is limited by the paucity of direct data for the occurrence of fertilization in the presence of the IUD. In particular, there are no direct data for the Copper-380 IUD or the Levonorgestrel-20 IUD. Therefore, the estimates must not be regarded as precise.
9. Fertilization and implantation can occur with IUDs leading to unintended pregnancies, as is true with other modern methods of contraception. However, the IUD's dominant mode of action for preventing pregnancy occurs pre-fertilization of ova.

Answer to Clinical Scenario

The main mechanism of action of the IUD takes place during the pre-fertilization period. The clinical pregnancy rate is low (at most 1% in the inert IUD method) and the fertilization rate is also low especially in the copper IUD method (4 to 8%). The estimated number of post-fertilization losses per woman per year is at most 2 in the inert IUD.

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EVIDENCE

**The primary
mechanisms of action
of various intrauterine
devices (IUDs) are due
to pre-fertilization
effects.**

EVIDENCE

THE EVIDENCE-BASED MEDICINE JOURNAL
USC PRESS, 1999, 1(1), 1-16

The Clinical Scenario

A 28-year-old woman wants to find out if she will be at risk for anemia if she uses IUDs versus oral contraceptive pills (OCPs).

Clinical Bottom Line

There is bigger decrease in Hemoglobin in Cu IUD users compared to OCP users after 12 months of use. Iron supplements should therefore be considered for IUD users in the Philippines, where anemia is common among women.

Citations

Hassan EO, El Hussein M, El-Hahal N. The Effect of 1-year Use of the CuT 380A and Oral Contraceptive Pills on Hemoglobin and Ferritin Levels. *Contraception* 1999; 60: 101-105.

Lead Author's Name and Contact Information

EO Hassan, The Egyptian Fertility Care Society POB 126 Orman. Giza. Cairo. Egypt Fax (202) 346 -8782.

The Study Patients

Egyptian women, 18-40 years old, planning to use either IUD or OCPs, more than 3 months post-partum, not breastfeeding and not taking oral iron supplements. IUD users were similar to OCP users except parity was higher among OCPs users (4.2 versus 3.7).

Level of Evidence 2b: Non-blinded, non-randomized individual cohort study, without intention-to-treat

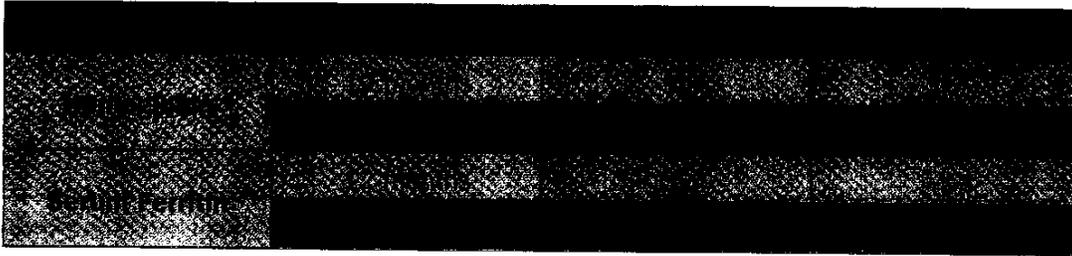
Control Group

(N = 202; 40% analysed at 12 months (N=81)): Oral Contraceptives

Experimental Group

(N = 246; 43.5% analysed at 12 months (N=107)): Copper IUD : CuT380A

The Evidence



Comments

1. There are higher rates of iron loss and depletion of iron stores in women using IUDs, which seems to be dependent on level of hemoglobin at the time of initiation of method use, and duration of method use.
2. A greater drop of Hb levels occurred with initially higher levels of Hb and with duration of IUD use, which may be due to the menstrual changes associated with IUD use.
3. High drop-out rates – about 40% at 12 months.

Answer to Clinical Scenario

There are more cases of anemia among IUD users compared to OCP users, probably due to associated menstrual changes. The IUD is a safe, long-term family planning method, however, and may be preferred by some women versus OCP use.

Iron supplements may be necessary for women in the Philippines, however, since anemia is common among Filipino women.

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EVIDENCE

There are higher rates of anemia among IUD users compared to OCP users.

Barrier Methods

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EVIDENCE

The condom remains the only contraceptive method that offers an overall decreased risk of acquiring a sexually transmitted disease (STD). The use of OCPs or DMPA is associated with a decrease in the risk of some STDs.

The Clinical Scenario

An 18-year-old university student asks about the use of oral contraceptives. She is sexually active, and has had a few boyfriends in school. She asks if there is a chance that she might get infections if she just uses oral contraceptives and her partner does not use condoms.

Clinical Bottom Line

STD protection is mixed with respect to hormonal contraceptive use. In a recently published cohort study conducted among sex workers in Kenya, the use of hormonal contraceptives (oral contraceptive pills and DMPA) has been found to be associated with a decreased incidence in some sexually transmitted diseases (STDs), such as Bacterial Vaginosis among OCP and DMPA users, and Trichomonas and PID among DMPA users. However, the study found an increased incidence of Candida, Cervical Mucopus and Cervicitis among OCP users and an increased incidence in Chlamydia and Cervicitis among DMPA users.

Citations

Baeten JM, Nyange PM, Richardoson BA, Lavreys L, Choban B, Martin HL, Mandaliya K, Ndinya-Achola JO, Bwayo JJ, and Kreiss JK. Hormonal Contraception and risk of sexually transmitted disease acquisition: Results from a prospective study. *Am J Obstet Gynecol* 2001;185:2. 380-385.

Lead Author's Name and Contact Information

Jared M. Baetan, University of Washington, E-mail: jbaetan@u.washington.edu

Search Terms	Hormonal contraception, oral contraceptive pill, medroxyprogesterone acetate, and sexually transmitted diseases
Level of Evidence	2b: Individual Cohort Study
Three Part Clinical Question	Does the use of hormonal contraception affect the risk of acquiring a sexually transmitted disease?

The Study Patients

Female sex workers in Kenya using hormonal contraception. Analyses were corrected for sexual behavior and demographic factors.

Exposure of Interest

Oral contraceptive use and depo-medroxyprogesterone (DMPA) use

The Outcome

Presence of sexually transmitted diseases including chlamydia, vaginal candidiasis, bacterial vaginosis, trichomoniasis, gonorrhea, syphilis, muco-purulent cervicitis, pelvic inflammatory disease.

Methodological Issues

The subjects who used the various methods were defined and were found to be similar in other important ways. The exposures and outcomes were neither measured objective nor measured blind, because of the varied nature of the methods being studied. Follow-up was long and complete enough.

The Evidence

Sexually Transmitted Disease	Incidence Rate per 100 women years of follow up Number of cases	OR	P value	DMPA Use (Hazard Ratio)	P value
Chlamydia	11.10	1.80	0.03	1.60	0.02
Gonorrhea	16.30	1.40	0.10	1.10	0.70
Trichomonas	26.40	0.90	0.60	0.60	0.04
Bacterial vaginosis	-	1.50	0.002	1.10	0.70
Cervical Mucopus	2.90	0.40	0.20	0.60	0.20
Genital Ulcer Disease	6.10	0.90	0.80	1.50	0.20
Syphilis	72.20	1.10	0.40	0.80	0.60
Pelvic Inflammatory Disease	24.00	1.20	<0.004	1.50	0.05
Pelvic Inflammatory Disease	13.00	0.70	0.30	0.40	0.001

Comments

1. A ratio which has a p-value of less than 0.05 suggests that the association of the infection with the method is statistically significant.
2. Consistent condom use was associated with significantly decreased risk of gonorrhea, chlamydia, genital ulcer disease, bacterial vaginosis, and pelvic inflammatory disease.
3. Compared to women who use no contraception, OCP users had an increased risk for chlamydia and vaginal candidiasis, and decreased risk for bacterial vaginosis, and an increased risk for cervical mucopus, and cervicitis.
4. Compared to women who use no contraception, women using DMPA had significantly increased risk for Chlamydia and cervicitis, and decreased risk for bacterial vaginosis, trichomoniasis, and PID.
5. An important caveat—the study was conducted in a high risk population for STDs. Further studies should be designed for a higher number of participants in low-risk group of women.

Answer to Clinical Scenario

The student can have many alternatives for protection against unplanned pregnancy and against STDs. However, some methods are more effective and more practical than others.

The use of hormonal contraceptives (oral contraceptive pills and DMPA) has been found to be associated with a decreased incidence in some sexually transmitted diseases (STDs), such as Bacterial Vaginosis among OCP and DMPA users, and Trichomonas and PID among DMPA users.

However, the study found an increased incidence of Candida, Cervical Mucopus and Cervicitis among OCP users and an increased incidence in Chlamydia and Cervicitis among DMPA users. The condom would be a better alternative if one wishes to prevent or reduce infections.

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EVIDENCE

The condom remains the only contraceptive method that offers an overall decreased risk of acquiring a sexually transmitted disease (STD). The use of OCPs or DMPA is associated with a decrease in the risk of some STDs.

Natural Family Planning

A Publication of the Population Emergency Ethics Project • www.ethicsproject.org

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The probability of pregnancy using the Standard Days Method is 5% with perfect use and 12% with typical use.

The Clinical Scenario

Clinical Bottom Line

With the Standard Days Method, the couples modify their sexual behavior when the woman is fertile and it provides significant protection from unplanned pregnancy *if it is used correctly*. The probability of pregnancy with this method is 5% if correctly used, but with typical use the rate is 12%. The typical use rate must be seriously considered before recommending this method of family planning to couples. There is more than a one out of ten chance of pregnancy with typical use of the Standard Days Method.

Citations

Marcos Arevalo, Victoria Jennings, Iris Sinai. Efficacy of a new method of family planning: the Standard Days Method, *Contraception* 65 (2002) pp. 333-338.

Corresponding Author's Name and Contact Information

Victoria Jennings, E-mail: jenningsv@georgetown.edu (V. Jennings). Fax: -1-202-687-6846

Search Terms

Standard Days Method, Contraceptive Efficacy, Pregnancy Rate

Level of Evidence

2b: Individual Cohort Study of Harm

Three-Part Clinical Question

Do women using the Standard Days Method have the same pregnancy rate or probability of pregnancy as compared to other user-controlled methods currently available (such as cap, condoms, diaphragms, and spermicides)?

The Study Patients

A total of 478 women (married or living with a stable partner) from 5 sites in Bolivia (Trinidad), Peru (Juliaca and Lima) and Philippines (La Trinidad and Tuba) between 18 and 39 years old who had regular cycles of 26 and 32 days long desiring to delay pregnancy at least 1 year were admitted to the study.

Exposure of Interest: Standard Days Method

The Institute of Reproductive Health at Georgetown University proposed a fixed formula among women who typically have menstrual cycles of 26 to 32 days and consider themselves fertile during days 8 to 19 days of their cycles. To prevent unplanned pregnancy, they avoid unprotected intercourse on those days.

The Outcome: Pregnancy rate

Methodological Issues

Subjects in the Standard Days group and the comparison groups were defined and found similar in other important ways. The exposures and outcomes were not measured objectively nor measured blind because of the nature of the methods. Follow-up was adequate and complete.

The Evidence

		Number of Pregnancies			
		Present		Absent	
		Number	Proportion	Number	Proportion
Correct Use of...	Yes	15	0.07	203	0.93
	No	28	0.11	232	0.89
Relative Risk:		0.64			
Number Needed to Harm:		-26	95% CI:	0.60 to 0.68	
Chi Square		2.69			

Comments:

1. In the table, the "No" group in the method used (not SDM) includes all those study participants who did not use the SDM correctly, those who used protective devices during fertile dates, and those who had unprotected sex.
2. This trial showed the Standard Days Method (SDM) is an effective method of family planning, when used correctly. With a pregnancy rate of 5% with correct use, it is comparable to male condoms (5%) and even better compared to other user-controlled barrier methods (spermicides - 6%, cap- 9%, diaphragm- 6%). The SDM is simple to teach, learn and use.

3. The chance of pregnancy using the Standard Days Method is 12% with typical use and therefore the method shares the handicap of all user-controlled methods in that their effective use depends on user (the couple's) behavior. The typical use rate should be acknowledged when reviewing this family planning method option with couples. Most pregnancies occurred during the first cycles of the method use (42% of pregnancies occurred in the first three cycles) and very few in the latter cycles (only three pregnancies in the last five cycles).

One has to make 26 couples use methods other than SDM for a year, to save one pregnancy.

Answer to Clinical Scenario

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EVIDENCE

The probability of pregnancy using the Standard Days Method is 5% with perfect use and 12% with typical use.

Surgical Methods

Journal of the American College of Surgeons
EVIDENCE

EVIDENCE

The risk of ectopic pregnancy after tubal sterilization is lowest when using bipolar salpingectomy and methods other than bipolar coagulation.

The Clinical Scenario

A 30-year-old patient with four children is requesting a tubal ligation. However, she is worried that she might have an ectopic pregnancy, like her neighbor. She comes to you for your opinion.

Clinical Bottom Line

There is only a slightly increased risk of ectopic pregnancy after tubal sterilization. There are various methods of tubal ligation with corresponding probabilities of ectopic pregnancy. The highest 10-year probability is with bipolar coagulation (17.1 per 1000 procedures) while the others have probabilities less than half of this rate. The lowest probability is with post-partum partial salpingectomy (1.5 per 1000 procedures).

Citations

Peterson HB, Xia Z, Hughes JM, Wilcox LS, Tylor LR and Trussell J for the U.S. Collaborative Review of Sterilization Working Group. The risk of ectopic pregnancy after tubal sterilization. *New Engl J Med* 336: 762-767, March 1997.

Lead Author's Name and Contact Information

Herbert B. Peterson, M.D. - National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Mailstop K-34, 4770 Buford Highway, N.E., Atlanta, GA 30341-3724.

Level of Evidence 2b: Individual Cohort Study

The Study Patients

CASES: 9,048 women in 9 USA cities, age 18-44 years, who had undergone tubal sterilization. Names were selected from 9 medical centers.

CONTROLS: 1,637 women in 9 USA cities, age 18-44 years, who had undergone postpartum partial salpingectomy. Names were selected from 9 medical centers.

Exposure of Interest

Tubal sterilization, other than postpartum partial salpingectomy

The Outcome

Ectopic pregnancy

Methodological Issues

The subjects were defined and similar in other important ways. The exposures and outcomes were either objective or measured blind. Follow-up was long enough; follow-up was complete enough.

The Evidence

Method of tubal sterilization	Present	Absent
Other methods	23	8395
Chi Square	23.40	

Particular to my patient:

007	51
-----	----

Comments

1. This is a multi-center, prospective cohort study that had clear and definite measurements of exposure (type of tubal ligation method) and outcome (ectopic pregnancy) variables. The relative risk of ectopic pregnancy after tubal sterilization ranged from 1.2 to 10.0, depending on the method of tubal sterilization.
2. Although there were many methods of tubal sterilization that were used, these should not be evaluated in isolation, but rather considered in the context of the overall risk and benefits of the methods.
3. The cumulative probability of ectopic pregnancy is still significant even after 10 years from tubal sterilization. There were 47 ectopic pregnancies in 10,685 women; the 10-year cumulative probability of ectopic pregnancy for all methods of tubal sterilization combined was 7.3 per 1000 procedures.
4. The cumulative probability varied substantially according to the method of sterilization and the woman's age at the time of sterilization. Women sterilized by bipolar tubal coagulation before the age of 30 years had a probability of ectopic pregnancy that was 27 times as high as that among women of similar age who underwent postpartum partial salpingectomy (31.9 vs. 1.2 ectopic pregnancies per 1000 procedures).
5. The annual rate of ectopic pregnancy for all methods combined in the 4th through 10th years after sterilization was no lower than that in the first 3 years.
6. One would have to perform tubal ligations on 51 women using bipolar coagulation methods instead of the other methods and follow them up for up to 10 years in order to cause one ectopic pregnancy.

Answer to Clinical Scenario

There is a small increase in the possibility that ectopic pregnancy may take place after a tubal ligation, but this is highest only if bipolar coagulation methods are used rather than partial salpingectomy or other techniques. These latter methods are preferred to keep the risk low.

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EVIDENCE

The risk of ectopic pregnancy after tubal sterilization is lowest when using bipolar salpingectomy and methods other than bipolar coagulation.

EVIDENCE

Vasectomy does not affect sexual and marital satisfaction among married men.

The Clinical Scenario

A couple consults you because they are considering vasectomy for the husband because they are happy with three children. However, the couple is worried because they have heard stories that sexual drive decreases after the procedure, and they would like to know your opinion about this.

Clinical Bottom Line

Vasectomy has no effect on the marital and sexual satisfaction of the married male. There was no significant difference between before and after measurements regarding sexual and marital satisfaction, communication and frequency of sexual intercourse in two groups of men (experimental and control) who underwent vasectomy. In an experimental design study, married men from Cape Town, South Africa with completed families voluntarily underwent vasectomy and were followed up until 5 months after the procedure. Data comparing baseline measurements to 5 months post vasectomy showed that vasectomy did not negatively affect a man's sexual and marital satisfaction, communication within marriage and frequency of sexual intercourse.

Citations

Hofmeyr DG and Greef AP. "The Influence of a Vasectomy on the Marital Relationship and Sexual Satisfaction of the Married Man." *J Sex Marital Therapy*. 2002; 28:339-51

Level of Evidence 2b: Individual Cohort Study

The Study Patients

33 men who underwent free vasectomy at the Family Planning Unit (FPU) of the Tygerberg Hospital. Eligibility included the following factors: 1) The man had to be married; 2) the family had to be complete; and 3) the vasectomy had to be voluntary.

Control Group

(N = 31; 31 analyzed): The two control groups were recruited from employees of the Tygerberg Hospital (n=13) and from men who had made inquiries about the vasectomy at the FPU (n=18). Eligibility criteria included: 1) man had to be married; 2) the family had to be complete and 3) neither the man nor the woman could have undergone sterilization previously.

Experimental Group

(N = 33; 32 analyzed): Men who actually underwent vasectomy.

The Outcome and Methodological Issues

The groups were asked to respond to the Index of Sexual Satisfaction (Hudson, Harrison, and Grosscup, 1981) which consists of 25 items and measures behavior, attitudes, occurrences, and affection associates with sexual relationships in marriage and long term relationships. The groups were also asked to respond to three subscales of the Enriching and Nurturing Relationship Issues Communication and Happiness (ENRICH) questionnaire (Olsen 1985). There was also a biographical questionnaire which included background information on the choice of method (motivation for vasectomy, length of time that the vasectomy had been considered). During the after-measurement process, the participants in the experimental group had to provide information regarding their experience and opinions regarding vasectomy. Questions dealt with whether the vasectomy influenced their sexual satisfaction and frequency of sexual intercourse and whether it affected their experience of masculinity. The questionnaire completed by the control and the vasectomy groups measured their sexual satisfaction and frequency of sexual intercourse over the preceding months.

The Evidence

For survey scores change from initial measurement to that taken five months later
Decrease in marital satisfaction – each group had an ACTUAL increase of one point in marital satisfaction score.
Communication – the control groups had a 0.4 point increase while the vasectomy group had a 0.5 point decrease out of a 50 point scale (not significantly different)
Sexual satisfaction (ISS) – the control groups had a decrease of 0.8 to 2.4 points decrease while the vasectomy group had a 1.9 point increase (not statistically different)
Sexual satisfaction (ENRICH) – all groups had an increase, with a range of 0.2 points (vasectomy) to 1.1 (control group1)
Frequency of sex per month – there was an increase of 0.3 times for control group 1, a decrease of 0.3 points for control group 2, and no change for the vasectomy group.

Comments:

The majority of participants experienced no change or increased interest in sexual intercourse.

1. Most participants also indicated that the vasectomy either had no influence on their relationship with their partner or had a positive effect on their relationship.
 2. The participants further indicated that the vasectomy had no negative influence on their marital satisfaction or communication with their partner.
 3. Majority of the participants (91%) indicated that the vasectomy did not negatively influence their feeling of masculinity.
 4. None of the participants after 5 months indicated that they regretted having undergone a vasectomy.
 5. The study used perceptions of men and did not evaluate actual sexual performance.
-

Answer to Clinical Scenario

There is no expected problem with regards to marital and sexual relationships after undergoing a vasectomy. It could even have a positive effect on a couple's sexual relationship.

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EVIDENCE

**Vasectomy does
not affect sexual
and marital
satisfaction among
married men.**

• EVIDENCE

Tubal ligation reduces the risk of abnormal menstrual bleeding.

The Clinical Scenario

A woman is attending an antenatal clinic for her fifth pregnancy. She is being offered a tubal ligation after she delivers her baby. She is worried that because of the tubal ligation, she might have problems with her menstruation.

Clinical Bottom Line

There was a slight decrease in the number of days of menstruation and amount of bleeding during menses among women who had a tubal ligation, but these are not harmful and are even considered beneficial. There were no differences in the amount of pain during menses, in having irregular cycles, and in intermenstrual bleeding among women who had interval tubal ligation. Women who have had tubal ligations will have fewer menstrual abnormalities compared to women who have not undergone the procedure.

Citations

Peterson H et.al. The Risk of Menstrual Abnormalities After Tubal Sterilization. *The New England Journal of Medicine*, Dec. 7, 2000, vol. 343 # 23: 1681-7.

Level of Evidence 2b: Individual Cohort Study

The Study Patients

A total of 9,514 women who underwent tubal sterilization and 573 women whose partners underwent vasectomy were followed in a multicenter study from 1978 to 1987 and from 1985 to 1987, respectively. The study population included women aged 18-44 years, non-Hispanic white and black, Hispanic, American Indian, Alaskan native, and Asian or Pacific islander with gravidity of <2, 2, and >2. They were followed up in a multicenter, prospective cohort study for five years by means of annual follow-up telephone interviews. All women were asked the same questions about six characteristics of their menstrual cycles in the pre-sterilization and follow up interviews.

Exposure of Interest

Bilateral (interval) tubal sterilization/ligation

The Outcome

Abnormal uterine bleeding or persistent menstrual abnormalities, particularly increased menstrual bleeding and inter-menstrual bleeding.

Methodological Issues

Subjects were defined and similar in other important ways. The exposures and outcomes were either objective or measured blindly. The follow-up was long and complete.

The Evidence

(From Table 3 in the article:)

Among the women who had a tubal ligation, there were some favorable effects on menstruation.
1. There was a significant but slight decrease in the number of days of bleeding OR, 2.4 (1.1 – 5.2)
2. There was a significant decrease in the Amount of Menstrual Bleeding after Tubal Ligation OR=1.5 (1.1 – 2.0)
Among the women who had a tubal ligation, there were no significant differences in the occurrence of other menstrual abnormalities.
1. There was no significant decrease in the amount of menstrual pain OR, 1.3 (1.0 – 1.8) (NS)
2. There was no significant increase in the Presence of Cycle Irregularity after Tubal Ligation OR = 1.3 (1.0 – 1.8) (NS)*
3. There was no significant decrease in Inter-menstrual Bleeding after Tubal Ligation OR = 0.6 (0.2 – 1.7) (NS)*
*(NS - no significant difference noted between groups)

Comments

1. The changes in menstruation that took place after tubal ligation were more "favorable" because the women were more likely to have less days of bleeding (OR, 2.4) and less amount of bleeding (OR, 1.5).
2. There were no significant changes in the amount of menstrual pain (OR, 1.3), cycle irregularity (OR, 1.6), and intermenstrual bleeding (OR 0.6).
3. Among women who had had very heavy bleeding, those who had undergone the procedure were more likely to report decreased bleeding (45% vs 33%, $P = 0.03$).
4. The methods of tubal ligation / sterilization used in the study were bipolar coagulation, unipolar coagulation, silicone rubber band application, spring clip application, thermocoagulation, and interval salpingectomy. In the Philippines, the first five techniques mentioned are not readily used or available. Most practitioners use the Modified Pomeroy technique.

Answer to Clinical Scenario

There would be some changes in the menstruation after tubal ligation, but these are not problematic, and may even be considered as favorable or beneficial by women. The changes would include less blood during menses and less days of menstruation. There would be no changes in the degree or amount of pain during menses, in the presence of irregular cycles, and in bleeding in between menses.

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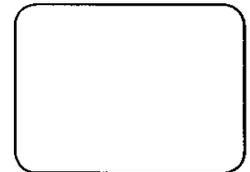
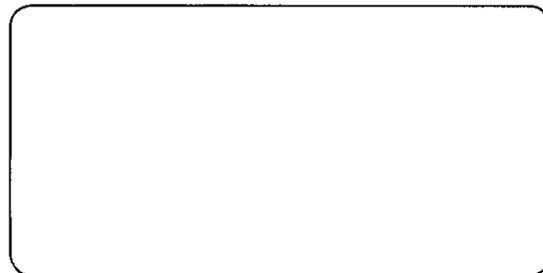
Advancing Evidence and Practice



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EVIDENCE

**Tubal ligation
reduces the risk
of abnormal
menstrual
bleeding.**



• EVIDENCE

Interval tubal sterilization has no effect on sexual interest and pleasure.

The Clinical Scenario

A couple consults you because they are considering a tubal ligation (for the wife) because they are happy with the three children they have. The woman had her last delivery 3 years ago. However, the couple is worried because they heard stories that sexual drive decreases after the procedure, and they would like to know your opinion about this.

Clinical Bottom Line

4,576 women who underwent tubal sterilization had an 80% chance of having no change in sexual interest and an 81.7 % chance of having no change in sexual pleasure. When demographic, clinical, and surgical factors that could affect the overall pattern of sexual outcome were considered, the subgroup analysis likewise showed that the majority showed no change in sexual interest and pleasure after tubal sterilization. Among those with change in their sexual pattern, most experienced positive sexual effects. Negative changes in sexual interest, pleasure occurred mostly among women with post-sterilization regret.

Citations

Costello C, Hillis S, et al for the US Collaborative Review of Sterilization Working Group: The Effect of Interval Tubal Sterilization on Sexual Interest and Pleasure. *Obstetrics and Gynecology* 2002; 100(3):511-517.

The Study Patients

4,576 women (aged 18-44) who underwent interval tubal sterilization, and answered follow-up forms that contained questions related to sexual interest and pleasure, and completed follow-up for two years.

Level of Evidence 2c: Outcomes Research (cohort study with only one cohort)

Prognostic Factors

Age, race, education, marital status, and number of children were chosen as demographic characteristics that could affect the overall pattern of sexual outcome. History of gynecologic conditions (endometriosis, pelvic inflammatory disease, uterine leiomyomata, or ovarian cysts), history of abortion, history of pelvic or abdominal surgery, chronic illness (asthma, diabetes, cancer, thrombotic disease, sickle cell disease, chronic obstructive pulmonary disease, or cardiac, thyroid, or renal disease), type of birth control used in the month before the sterilization procedure, laparotomy versus laparoscopy as the surgical approach, intended method of tubal occlusion, and post-sterilization regret were chosen as potential clinical or surgical influences on post-sterilization sexual interest or pleasure.

The Outcome

The pattern of no change, increased, and decreased post-sterilization sexual interest and pleasure at first and second year of follow-up was evaluated for all women and each subgroup of potential predictor.

Methodological Issues

There was a well-defined sample population. Follow-up was not long enough though follow-up was complete. There were blind, objective outcome criteria. Adjustment was made for different prognostic factors. There was validation in an independent test-set of patients (postpartum and post-abortion sterilization patients). There was no comparable cohort who had not undergone sterilization.

Comments on Evidence (Please refer to Table of Evidence on facing page)

1. When demographic, clinical, and surgical factors that could affect the overall pattern of sexual outcome were considered, the subgroup analysis consistently showed that the majority showed no change in sexual interest and pleasure after tubal sterilization.
2. A large cohort of women had been used for this study, but unfortunately there was no control group to compare them.
3. Also, although a two year follow up seems to be acceptable, a longer follow-up period like five years might be needed to fully assess impact of tubal sterilization on sexual functions.
4. If changes were to occur in sexual interest and in sexual pleasure, the change would most likely be an increase (in 10 to 20% of cases) versus a decrease (0.7 to 4% of cases).
5. The only group in which interval tubal sterilization did not have any group which had a net increase or decrease in sexual interest and pleasure (6.8% and 5.6%, respectively in both groups) were those who manifested some post-sterilization regret.

The Evidence

	No change in sexual interest and pleasure (2 yrs)	80.4 & 81.7 respectively	%
Education	No change in sexual interest and pleasure (2 yrs)	89.2 & 89.3 respectively	%
Number of children	No change in sexual interest and pleasure	80.4 & 81.7 respectively	%
History of abortion	No change in sexual interest and pleasure (2 yrs)	80.3 & 82.4 respectively	%
History of chronic illness	No change in sexual interest and pleasure (2 yrs)	80.0 & 81.3 respectively	%
Birth control method used most often in current pregnancy	No change in sexual interest and pleasure (2 yrs)	82.4 & 84.1 respectively	%
Surgical approach to fallopian tube	No change in sexual interest and pleasure (2 yrs)	81.1 & 83.4 respectively	%
Sterilization method	No change in sexual interest and pleasure (2 yrs)	79.9 & 82.2 respectively	%
Post-sterilization regret	No change in sexual interest and pleasure (2 yrs)	83.1 & 85.2 respectively	%

Answer to Clinical Scenario

In the majority of women who would undergo a tubal ligation, most of the women would have no change in sexual interest or pleasure. In fact, about 10% to 20% of women would actually experience an increase in sexual interest and pleasure. Negative effects would only occur in less than 4% of cases, and these would be among the few who experience post-sterilization regret.

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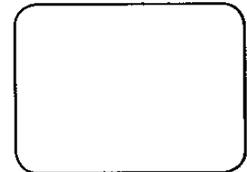
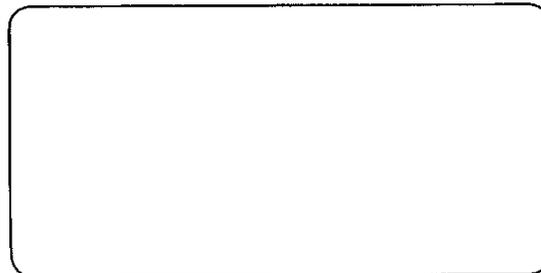
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EVIDENCE

Interval tubal sterilization has no effect on sexual interest and pleasure.



The Review

Data Sources: Medline, Cancerlit

Study Selection: Cohort and case-control studies

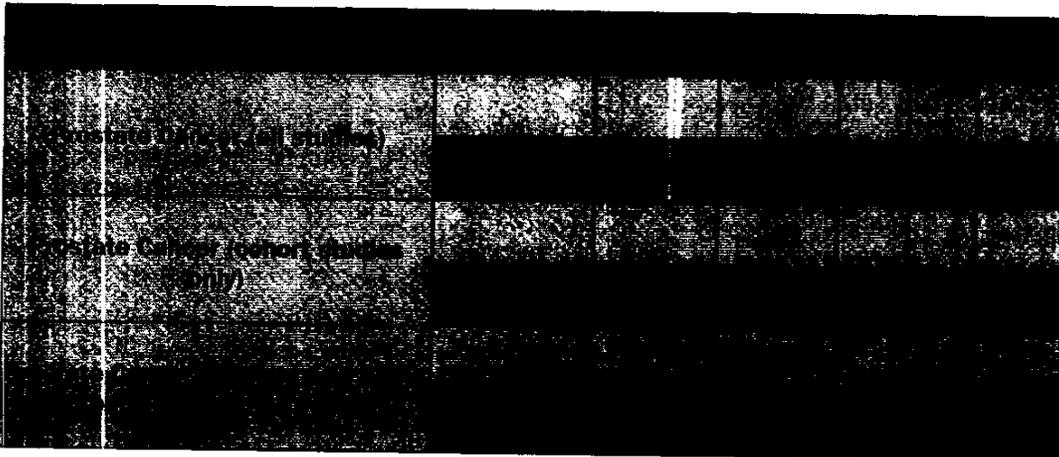
Data Extraction

Extracted information by two of three independent reviewers.

Methodological Issues

The studies were multiple independent reviews of individual reports. They were tested for heterogeneity. There was no assessment for quality of individual studies.

The Evidence



EVIDENCE

There is no likely increased risk for prostate cancer among patients who have had vasectomies.

The Clinical Scenario

A 35-year-old male who wants a vasectomy asks whether he will expose himself to an increased risk for developing prostate cancer after undergoing the procedure.

Clinical Bottom Line

The odds of having had a vasectomy among patients who have prostate cancer are very slightly higher, but the very small difference could be accounted for by bias. With limited evidence, there is no support for a biological mechanism supporting a relationship between vasectomy and prostate cancer.

Citations

Dennis LK, Dawson DV, and Resnick MI, Vasectomy and the Risk of prostate cancer: a Meta-analysis examining vasectomy status, age at vasectomy and time since vasectomy. *Prostate Cancer and Prostatic Diseases* (2002) 5: 193-203.

Lead Author's Name and Contact Information

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Level of Evidence [None indicated]

Comments

1. The main effects included those from case control and cohort studies and there was a high level of heterogeneity, so a random effects model was used in the analysis.
2. The highest odds were shown in a biased sample which were in hospital sampled cases.
3. There seems to be an increase in the risk of prostate cancer with the number of years since vasectomy, which the authors thought to be an effect of sampling bias.
4. With this limited evidence, the authors concluded that there is no support for a biological mechanism supporting a relationship between vasectomy and prostate cancer.

Answer to Clinical Scenario

Based on cohort or follow-up studies, there is likely no increased risk or association with prostate cancer among men who have had a vasectomy.

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EVIDENCE

There is no likely increased risk for prostate cancer among patients who have had vasectomies.

How to Apply Evidence-Based Medicine in Clinical Decision Making

An Overview

The EBM Cycle

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 if they used 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 everyday, along with the number of papers and reports. Since 1966, when the Index Medicus was started, there have been 12 million papers included in the present Index. Reading or even browsing or searching through these would not be humanly possible, so a useful and efficient search strategy is planned.

The Index Medicus has been largely replaced by Medline which is open for use to all via the website at 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 which were ranked as most important and intersecting them with the succeeding expanded concepts that were subsequently ranked.

EBM practitioners can type expanded concepts in the Medline search box either as "free text" or "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. Once the practitioner is happy with the number of articles retrieved he/she may then assess or appraise them 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 **M**edical **S**ubject **H**eadings that more or less uses standardized medical terms. It now includes almost 17,000 concepts. 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 step-by-step guide to do 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. Then, 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 more stringent method filters (such as blinding, placebo-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. Hopefully that can limit your search to the best strategy.

You may also use guidelines or reviews.

Once an appropriate article has been chosen, a request for retrieval of the article may be coursed through the medical libraries, the MSD Resource Center (www.msd.com.ph/javaapp-ph/Merck/resource-center/resource_center.jsp), and the Pfizer virtual libraries (www.pfizer.com.ph/corporate/community/cyber.html) in the different hospitals. Some journals offer their articles online for free. Try also www.freemedicaljournals.com.

For those with available resources, one may try using the Lonesome Doc program. (A word of advice to users: this program is referred to as "Loansome Doc" in some online resources, even on the NLM Gateway itself.) Lonesome 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 Lonesome Doc is www.nlm.nih.gov/pubs/factsheets/loansome_doc.html.

Claims of Evidence

There are so many articles that come out daily (4,000 each day), there should be tools to provide information to assist the reader in selecting which would be useful or not. To do this, there are some rules of evidence that are used.

There are some types of articles that would best address certain types of clinical questions mentioned above.

- For claims of effectiveness, the best type of study is the *Randomized Controlled Trial*. Randomized Controlled Trials (RCTs) are experiments in which individuals are randomly allocated to receive or not receive an experimental preventative, therapeutic or diagnostic procedure and are then followed up to determine the effect of the intervention.
- For claims of accuracy, the best studies are *Standard Criterion Validity Studies* wherein the main focus is to search for validity where the results represent an unbiased estimate of the underlying reality.
- For claims of causation, in the absence of experimental studies, the most appropriate studies are *Cohort Studies*. In the absence of cohort studies *Case-Control Studies* may be resorted to. Case-Control Studies are retrospective investigations designed to determine the association between an exposure and outcome in which patients are chosen or sampled based on the presence (case) or absence (control) of outcome (that is, some patients with the outcome of interest are selected, and compared to a group of patients who have not had the outcome) and the investigator examines the proportion of patients with the exposure in the two groups. Cohort Studies are prospective investigations of the factors that might cause a disorder in which a group (the "cohort") of individuals who do not have evidence of an outcome of interest in the beginning but who are exposed to the putative cause are compared with a concurrent cohort who are also free of the outcome but not exposed to the putative cause. Both cohorts are then followed to compare the incidence of the outcome of interest.
- For claims on prognosis, the most appropriate studies are Cohort Studies, which have been described above.

The main issues in Family Planning deal mostly with claims on effective treatment and with claims on causation. Treatment studies as described briefly above should ideally deal with an experimental design, which can look at a good effect (treatment or cure) or a bad effect (harm or adverse outcome).

There have been a series of guide questions prepared by various centers to assist the reader of articles. Included in this chapter are examples of guides for therapy and harm.

Before an article is even considered, one should assess its relevance to the clinical questions at hand and the setting the reader is working in. Relevance as to the nature and severity of the problem (burden of disease, access to available interventions, important outcomes, and need to change practice) is taken into consideration. This also looks at whether the article is worth taking the time to read? If the answer to any of these questions is "No", it may be better to read other articles first.

There are thirteen guide questions for the appraisal of an article on therapy. To illustrate the importance of critical appraisal, three of the guide questions will be discussed below.

1. Insist or prefer randomized controlled trial when feasible.

When an experimental design compares similar groups except for the intervention of interest, this would best allow a direct association between the outcomes of the experiment with the specific intervention.

In doing these RCTs, the following should be considered in the design.

a. Randomization (or Random Allocation): Allocation of individuals to groups by chance, usually done with the aid of a table of random numbers. This should not be confused with systematic allocation (e.g., on even and odd days of the month) or allocation at the convenience or discretion of the investigator. Randomization optimizes the chance that the treatment groups are equal for known and unknown determinants of outcome. If these groups are equal for baseline prognostic factors, the only difference between the two groups is the treatment. Thus, any difference in the outcome among the two groups can more likely be attributed to the treatment. Random allocation refers to the process of assigning patients to treatment groups in a clinical

trial while random selection is a sampling method used in selecting respondents or subjects in a cross sectional study or survey.

- b. Concealment:** Randomization is concealed if the person who is making the decision about enrolling a patient is unaware of whether the next patient enrolled will be entered in the treatment or control group. If randomization wasn't concealed, there may be conscious or unconscious attempts to allocate patients with better prognoses to the groups with the active treatment arm resulting in exaggeration of the apparent benefit of therapy (or even falsely concluding that treatment is efficacious). Synonymous with Allocation Concealment.
- c. Co-interventions:** Interventions other than treatment under study that may be differentially applied to experimental and control groups and, thus, affect the results of a study, creating a potential bias.
- d. Contamination:** Contamination occurs when participants in either the experimental or control group receive the intervention intended for the other arm of the study, or any intervention that may affect the outcome under study.
- e. Blind (or Blinded or Masked):** The participant of interest is unaware of whether patients have been assigned to the experimental or control group. There are many levels or types of blinding - patients, clinicians, those monitoring outcomes, judicial assessors of outcomes, data analysts, and those writing the paper can all be blinded or masked. Double blinding usually means the subjects (patients) and the investigators are blinded
- f. Bias:** A systematic tendency or trend to produce an outcome that differs from the underlying truth because of some reason or factor that influences this tendency or trend.
- g. Drop-outs** refer to subjects who failed to complete the study due to non compliance, development of adverse event, or got lost to follow-up. **Lost to follow-up** are patients whose status is unknown at the end of the study; therefore endpoints cannot be assessed. However, those who dropped out due to AE (adverse events) or non-compliance can still be followed-up and assessed regarding the outcomes using the intention to treat principle.

All these issues are corrected or minimized if the randomization process is properly done among the subjects of a study.

2. All clinically relevant endpoints must be considered. Many studies usually report laboratory outcomes, such as blood or urine tests. The main reason for this is that these are objective measurements of the results of the intervention. However, the changes in the laboratory outcomes (which are intermediate outcomes) may not necessarily translate to other outcomes that may be clinically important – in particular, final outcomes that are particularly important to the patient.

Among patients with high cholesterol or abnormal lipid profile, an improvement in these laboratory parameters (intermediate outcomes relevant to providers) does not necessarily mean an improvement in the rates of the development of cardiovascular disease or in mortality rates due to heart disease (final outcomes relevant to patients).

Among patients using IUDs, a culture of the vaginal area, which shows growth of organisms does not necessarily mean that there is a clinical infection.

All clinically relevant endpoints must be considered. In family planning studies, aside from effectiveness in preventing pregnancy, other clinical relevant endpoints such as deaths, allergic reactions, pregnancy loss, tumor growth and mortality, depending on the biological characteristics of the method under investigation should be considered.

Also to be considered is the fact that all patients who entered in the study must be accounted for at the end of the study. Dropouts are subjects who decide not to continue participating, or who may be lost to follow-up. Being lost to follow up may be due to many things, such as lack of interest. However, dropping out may also occur as a result of a bad outcome from the study wherein patients can no longer follow-up due to an adverse drug reaction or even death. This is why an active method of monitoring study subjects must be built-in to the study design.

Some of the patients may also intentionally or unintentionally fail to follow the protocol of the study, so that they may end up taking the intervention in the other arm (contamination) or they end up

taking other possible interventions (aside from the study factors) that can affect the outcome significantly (co-intervention). These may seriously influence study outcomes.

To prevent biases from occurring as a result from patients being lost to follow up, contamination and co-intervention, the analysis may be done using the **Intention-to-Treat Principle** (or **Intention-to-Treat Analysis**). This involves analyzing patient outcomes based on which group to which subjects were originally randomized or assigned regardless of whether they actually received the planned intervention in the course of the trial. This analysis preserves the power of randomization, thus maintaining that important unknown factors that influence outcome are likely to be equally distributed in each comparison group.

These two issues on the use of randomization and the presentation of all clinically relevant outcomes are directly related to the VALIDITY questions on the claims of therapy. If there are unanswered questions on how valid the article methods are, or if these are unsatisfactorily answered, the article is judged to be invalid, and the reader is then advised not to proceed with the next steps.

3. When looking at the results of the paper (after being satisfied with its validity and relevance), there should be an **assessment of the magnitude of the clinical benefit**. When evaluating the results of a trial, one should assess the outcome in the experimental arm and compare it with that of the standard or control arm. This magnitude of the effect may be expressed as a single number (point estimate) or as a range of numbers (confidence interval). For example, the risk associated with cigarette smoking and lung cancer is expressed as an Odds Ratio (OR) of 3.0 (point estimate) with an interval estimate or confidence interval of 1.8 – 4.2.

There are many ways of expressing a change between two situations. For example, when we express a change in weight of a person from 80 kg to 60 kg, any of the following statements are applicable, and would thus relate to a clinical term in experimental studies.

- “I lost 25% of my weight.”
 - My relative weight reduction or the **percent that I lost**
 - This would be similar to a **relative risk reduction (RRR)**
- “I am 75% of what I used to weigh.”
 - My relative weight or the **percent that is remaining**
 - This would be similar to the **relative risk (RR)**
- “I lost 20 kg.”
 - My absolute weight difference or the **exact number that I lost**
 - This would be similar to the **absolute risk reduction (ARR)**

The terms **RRR**, **RR**, and **ARR** may be used to describe the change between the two risks that are found in the intervention group and in the control group. Most studies still use RRR and RR, as the numbers are usually higher and more dramatic than ARR. However the ARR and the NNT described below offer measures of effects that are more relevant and easily applicable to patient care.

Another way of describing the change but more relevant to the effect on the use of the intervention is the **Number Needed to Treat (NNT)** which refers to the number of patients who need to be given the intervention or exposure over a specific period of time to incur one good outcome, or prevent one bad outcome. When discussing NNT, it is important to specify the treatment, its duration, and the outcome. It is the inverse of the absolute risk reduction (ARR).

If the main outcome of interest is that of a harmful event, the **Number Needed to Harm (NNH)** is instead used. This refers to the number of patients who would need to be given the intervention or exposure of interest over a specific period of time before one adverse side effect of the treatment will occur. It is the inverse of the absolute risk increase.

One may find the numbers for these terms within the paper itself, or may compute for them using the formulas for these terms.

4. Once the results of the rules of evidence of the RCT are presented, the next step is data integration, which refers reporting the results of the process to allow the others to benefit from the new information provided by your investigation.

Claims of Causation

An important consideration in claims of causation is that of bias. Because of the design in sampling and in implementation, there would inevitably be some bias in the studies associated with claims of causation.

The sampling of the cohort is based on having an exposed group and an unexposed group. There would be some difficulty in treating both groups fairly and equally. Baseline characteristics may not be similar between the two groups. Considering that these patients have to followed-up over a long period of time, the comparison group may not be that motivated to participate in the study and may be lost to follow up. There is also a tendency to favor procedures and inquiry into the exposed group leading to an increased and possibly earlier measurement of the outcome in this group (detection bias).

In case-control studies, the outcomes have already been identified, and are actually the basis for recruitment into the inquiry. There would be better recall of what has happened in the past among the study subjects in the exposed (cases) group (recall bias). There can also be a deeper or more extensive inquiry into the possible factors in the exposed (cases) group (detection bias). The comparison group thus may be under-detected in terms of the outcome because of the fewer and less aggressive measurement.

After Validity and the Results

After evaluating the issues of validity and what the results are, the next step is to answer the questions on generalizability.

Can the results of the article be used in my setting refers to whether the main issues of methodology, sample population characteristics, and effect of the intervention would be major concerns when the article is considered as basis for a local practice.

Part of this includes the consideration that the likely treatment benefits outweigh the potential harm and costs. Many of the new interventions may be effective and innovative, but would cost many

times over compared to the comparison drug or condition. This becomes a major issue in deciding whether the article eventually becomes useful or not.

Because of the effect of the intervention on society or the specific population sample, there would now be a new clinical question that may be brought out, thus restarting the EBM cycle all over again.

Data Integration

Once we have applied the rules of evidence on an article and have written down this assessment, we have made a CRITICALLY APPRAISED TOPIC or a CAT. A CAT provides an EVIDENCE-BASED answer to a question that emerges in clinical practice, in patient encounters/ meetings, or in everyday situations. It is based on the appraisal of an article that was chosen after an extensive literature search because of its relevance in addressing the question or problem that we have. A CAT contains a concise summary of the article, a summary of the results of the critical appraisal, and recommendations for clinicians for a particular clinical scenario and clinical question – all in a page or so.

The CAT provides an answer to the question that was raised earlier in a clinical scenario. This CAT is a written piece of evidence, which answers the question or at least provides the basis for decisions related to that question. A general statement which is based on the CAT and which directly answers the clinical scenario question is presented.

To further describe to the reader some background of the article used for the CAT, the levels of evidence are presented. What are we to do when the irresistible force of the need to offer clinical advice meets with the immovable object of flawed evidence? All we can do is our best: give the advice, but alert the advisees to the flaws in the evidence on which it is based.

Oxford Centre for Evidence-based Medicine Levels of Evidence (May 2001)



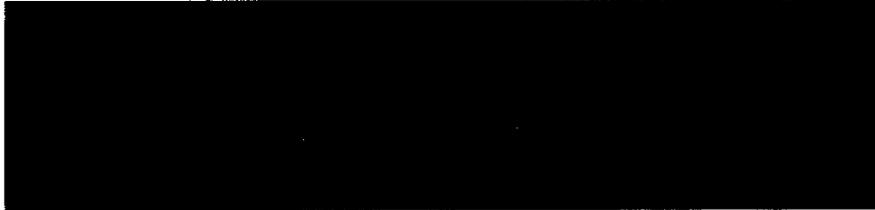
Produced by Bob Phillips, Chris Ball, Dave Sackett, Doug Badenoch, Sharon Straus, Brian Haynes, Martin Dawes since November 1998.

(From www.cebm.net/levels_of_evidence.asp)

Systematic reviews with homogeneity refer to those articles reviewed and subjected to meta-analysis with more or less similar characteristics in terms of study subjects, procedures and outcomes measurement. Not all systematic reviews with statistically significant heterogeneity need be worrisome, and not all worrisome heterogeneity need be statistically significant.

All or none studies are met when all patients died before the treatment became available, but some now survive on it; or when some patients died before the treatment became available, but no one now dies from it.

A CAT maker may make an actual recommendation on what to do on the basis of the level of evidence, taking into account the results of the article being appraised. One type of grading recommendations is presented below.



From www.cebm.net/levels_of_evidence.asp

“Extrapolations” are where data is used in a situation which has potentially clinically important differences than the original study situation.

These critically appraised topics can stand on their own as specific topics of interest, or these may become part of a clinical practice guideline which is a systematically developed statement designed to assist practitioner and patient make decisions about appropriate health care for specific clinical circumstances.

Decision Making

After the problem has been identified, the literature has been searched, a critical appraisal has been done, and the data has been integrated, the next step is to make a clinical decision. The evidence is not the only basis for making decisions. Clinical judgment and patient's preference should also be considered. Other influences (heuristics) are also considered in decision making. Available resources, access to expertise, laboratory, treatment and other phases in the management of a patient or a clinical problem are evaluated in relation to what has been reviewed in the EBM cycle. Once this is applied, a reassessment of the problem at the beginning of the cycle development is made. ■

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Glossary

This glossary is intended to provide guidance as to the meanings of commonly used terms in Evidence Based Medicine.

Absolute Risk Reduction (ARR) or Absolute Risk Increase (ARI):

Difference in the absolute risk (percentage or proportion of patients with an outcome) in the exposed (experimental event rate or EER) versus the unexposed (control event rate or CER). Use ARR when restricted to a beneficial exposure or intervention and ARI when used with a harmful exposure.

Example: $CER - EER = ARR$ or ARI

The use of an experimental drug with the control drug leads to event rates as below. The ARR or ARI is the difference between the two event rates. A new drug for cases of chronic pelvic pain is used in the example.

$$\begin{aligned}ARR &= CER - EER \\ &= 6 \text{ cases}/100 \text{ women (6\%)} - 4 \text{ cases}/100 \text{ women (4\%)} \\ &= 2 \text{ cases}/100 \text{ women (2\%)}\end{aligned}$$

Therefore the Absolute Risk Reduction (ARR) is 2 cases of pelvic pain/100 women treated using the experimental drug.

The (number needed to treat) NNT is defined as:

$$\begin{aligned}NNT &= \frac{1}{ARR} = \frac{1}{CER - EER} \\ &= \frac{1}{2 \text{ cases}/100 \text{ women}} \\ &= \frac{100 \text{ women}}{2 \text{ cases}} \\ &= 50 \text{ women/cases of pelvic pain.}\end{aligned}$$

Therefore the number needed to treat (NNT) is: 50 women must receive this drug for two years in order to prevent one event (treat one (1) case of chronic pelvic pain).

Adjusted Analysis: An adjusted analysis considers differences in prognostic factors between groups that may influence the outcome. For example, in comparison between an experimental treatment and control, if the experimental group is on average of an older age group, and thus at higher risk of an adverse outcome, than the control group, the adjusted analysis will show a larger treatment effect than the unadjusted analysis.

Algorithm: An explicit illustration using boxes and arrows of ordered sequence of steps to be taken in patient care under specified circumstances.

Baseline Risk: The risk of an adverse outcome in the control group of an experiment. May be used interchangeably with control event rate (CER).

Bayesian Analysis: An analysis that starts with a particular probability of an event (the prior or initial or baseline probability) and incorporates new information to calculate or generate a newer or revised probability (a posterior probability).

Before-After Trial: Investigation of an intervention in which the investigators compare the status of patients before and after the intervention.

Bias: A systematic tendency or trend to produce an outcome that differs from the underlying truth because of some reason or factor that influences this tendency or trend.

There are many types of biases, the more common of which include the following:

a) Detection bias or surveillance bias: The tendency to look more carefully or more often for an outcome or an event in one of two groups being compared.

b) Interviewer bias: Greater or better probing by an interviewer in one of two groups being compared, usually in the experimental group

c) Publication bias: Publication bias occurs when the publication of research depends on the direction of the study results (such as positive or favorable results) and whether they are statistically significant (non-significant results usually do not get published).

d) Recall bias: Recall bias occurs when patients who experience an adverse outcome have a different likelihood of recalling an exposure than the patients who do not have an adverse outcome, independent of what is the true extent of exposure. (Ex. Mothers of children with congenital anomalies have a tendency to remember more events in the past compared to mothers with children with no problems.)

Blind (or Blinded or Masked): The participant of interest is unaware of whether patients have been assigned to the experimental or control group. There are many levels or types of blinding -

patients, clinicians, those monitoring outcomes, judicial assessors of outcomes, data analysts, and those writing the paper can all be blinded or masked.

Case Series: A study reporting on a consecutive collection of patients managed or treated in a similar manner, without a control group. For example, a gynecologist-surgeon might describe the characteristics of an outcome for 100 consecutive patients with myoma uteri who were operated using the laparoscopic approach.

Case-Control Study: A study designed to determine the association between an exposure and outcome in which patients were chosen or sampled by outcome (that is, some patients with the outcome of interest are selected, and compared to a group of patients who have not had the outcome) and the investigator examines the proportion of patients with the exposure in the two groups.

Chi-Square Test: A statistical test that examines the distribution of categorical outcomes in two groups, the null hypothesis of which is that the underlying distributions are identical.

Clinical Practice Guideline is a systematically developed statement designed to assist practitioner and patient make decisions about appropriate health care for specific clinical circumstances.

Cohort Study (or Cohort Analytic Study): Prospective investigation of the factors that might cause a disorder in which a group (the "cohort") of individuals who do not have evidence of an outcome of interest in the beginning but who are exposed to the putative cause are compared with a concurrent cohort who are also free of the outcome but not exposed to the putative cause. Both cohorts are then followed to compare the incidence of the outcome of interest.

Co-interventions: Interventions other than treatment under study that may be differentially applied to experimental and control groups and, thus, affect the results of a study, creating a potential bias.

Concealment: Randomization is concealed if the person who is making the decision about enrolling a patient is unaware of whether the next patient enrolled will be entered in the treatment or control group. If randomization wasn't concealed, patients with better prognoses may tend to be preferentially enrolled in the active treatment arm resulting in exaggeration of the apparent benefit of therapy (or even falsely concluding that treatment is efficacious). Synonymous with Allocation Concealment.

Confidence Interval (CI): Range of values within which it is probable or more likely that the true value lies for the whole population of patients from whom the study patients were selected.

Confounder or Confounding Variable: A factor that distorts the true relationship of the study variable of interest by virtue of also being related to the outcome of interest. Confounders are often unequally distributed among the groups being compared. Randomized studies are less likely to have their results distorted by confounders than are observational studies.

Consecutive Sample: A sample in which all potentially eligible patients seen over a period of time are enrolled in the order in which they arrived or were seen in the clinic or place of study.

Contamination: Contamination occurs when participants in either the experimental or control group receive the intervention intended for the other arm of the study.

Continuous Variables: A variable that can theoretically take any value and in practice can take a large number of values with small differences between them. The numerical values in a laboratory examination and the counts of a large number of items (cigarettes) are examples.

Control Event Rate: The risk of an outcome in the control or unexposed group of an experiment. Synonymous with Baseline Risk.

Controlled Trial: Experiment in which individuals are randomly allocated to receive or not receive an experimental procedure for prevention, therapy or diagnosis and then followed to determine the effect of the intervention.

Cost Analysis: If two strategies are analyzed but only costs are compared and not including the expected outcome is termed a cost analysis.

Cost Benefit Analysis: A form of economic analysis in which both the costs and the consequences (including increases in the length and quality of life) are expressed in monetary terms.

Cost Minimization Analysis: An economic analysis conducted in situations where the consequences of the alternatives are identical, and so the only issue is their relative costs.

Cost-Effectiveness Analysis: An economic analysis in which the consequences are expressed in natural units, usually some benefit in health gained. Some examples would include cost per life saved, or cost per unit of blood pressure lowered.

- Cost-Utility Analysis:* A type of cost-effectiveness analysis in which the consequences are expressed in terms of life-years adjusted by peoples' preferences (or utilities). Typically, one considers the incremental cost per incremental gain in quality adjusted life-years or QALYs.
- Crossover Trial:* A study design in which all patients receive both experimental and control treatments in sequence, or one after the other, usually with a washout or treatment free period in between. The outcome in this study must be reversible after discontinuation of the intervention.
- Cross-Sectional Survey:* The observation of a defined population at a single point in time or during a specific time interval. Exposure and outcome are determined simultaneously.
- Decision Analysis:* A systematic approach applying explicit quantitative methods to analyze decision-making under conditions of uncertainty. It involves identifying all available alternatives and estimating the probabilities of potential outcomes associated with each alternative, valuing each outcome, and, on the basis of the probabilities and values, arriving at a quantitative estimate of the relative merit of the alternatives.
- Dependent Variable:* In a regression analysis we identify predictor or independent variables and the target or dependent variable. The factor that changes based on independent variables.
- Disability-Adjusted Life-Years (DALY):* The number of years of life after downward adjustment for disabilities that patients experience.
- Economic Analysis:* A set of formal, quantitative methods used to compare two or more treatments, programs, or strategies with respect to their resource use and their expected outcomes.
- Ecological Survey:* Based on aggregated data for some population as it exists at some point in time; this is used to investigate the relationship for an exposure to a known or presumed risk factor for a specified outcome.
- Economic Evaluation:* Comparative analysis of alternative courses of action in terms of both their costs and consequences.
- Efficiency:* refers to the amount of resources used or input for a certain output or outcome. Technical efficiency is the relationship between inputs (costs) and outputs (in health, quality-adjusted life-years [QALYs]). Treatments that provide more QALYs for the

same or fewer resources are more efficient. Technical efficiency is assessed using cost minimization, cost-effectiveness, and cost-utility analysis.

Event Rate: The proportion of patients in a group in whom the event is observed. Thus, if out of 100 patients, the event is observed in 27, the event rate is 0.27. Control Event Rate (CER) and Experimental Event Rate (EER) are used to refer to this in control and experimental groups of patients respectively.

Evidence Based Health Care: Extends the application of the principles of Evidence-Based Medicine (see below) to all professions associated with health care, including purchasing and management.

Evidence-Based Medicine (EBM): The conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients. The practice of evidence-based medicine requires integration of individual clinical expertise and patient preferences with the best available external clinical evidence from systematic research.

Experimental Event Rate (EER): Proportion of patients in a group in whom an event is observed. Controlled event rate (CER) and experimental event rate (EER) are used to refer to this in control and experimental groups of patients, respectively.

False-Negative: In a treatment study, treatment is considered ineffective when it actually is effective. In a diagnosis study, the patient suffers from the target condition, but the test suggests the patient does not.

False-Positive: In a treatment study, the treatment is deemed effective when it actually is ineffective. In a diagnosis study, the patient does not suffer from the target condition, but the test suggests the patient does.

Focus Groups: Investigators use focus groups, typically gatherings of 4 to 8 people with similar background or experience, to understand their attitudes or their response to a particular situation or experience.

Generalizability: The ability to generalize the findings of a study to a larger group of similar people. Refers to the applicability of results of a trial or study.

Gold Standard: A method having established or widely accepted accuracy for determining a diagnosis or presence or absence of a disease, providing a standard to which a new screening or diagnostic test can be compared. The method need not be a

single or simple procedure but could include follow-up of patients to observe the evolution of their conditions or the consensus of an expert panel of clinicians, as is frequently used in the study of psychiatric conditions. Examples of gold standards in diagnostic tests include coronary angiogram for coronary artery disease and histopathology report for cancer. Synonymous with Criterion Standard and Reference Standard.

Hazard Ratio: Investigators may compute the relative risk (RR) over a period of time, as in a survival analysis, and call it a hazard ratio, the weighted relative risk over the entire study.

Health-Related Quality of Life: Type of Outcome Measurements of how people are feeling, or the value they place on their health state.

Incidence: Number of new cases of disease occurring during a specified period of time; expressed as a percentage of the number of people at risk or who are exposed to a certain factor.

Independent Variables: Explanatory or predictor variables that may be associated with a particular outcome. The term is usually used in the context of a regression analysis.

Intention-to-Treat Principle (or Intention-to-Treat Analysis): Analyzing patient outcomes based on which group into which they were randomized or assigned regardless of whether they actually received the planned intervention in the course of the trial. This analysis preserves the power of randomization, thus maintaining that important unknown factors that influence outcome are likely equally distributed in each comparison group.

Kaplan-Meier Curve: A curve that starts at 100% of the study population and shows the percentage of the population still surviving (or free of disease or some other outcome) at successive times for as long as information is available. Synonymous with Survival Curve.

Kappa Statistic (or Weighted Kappa): A measure of the extent to which observers of an event achieve the possible agreement or similar reading beyond any agreement expected to occur by chance alone. Kappa can take values from -1.0 to 1.0 .

Likelihood Ratio: For a screening or diagnostic test (including clinical signs or symptoms), expresses the relative likelihood that a given test result would be expected in a patient with (as opposed to one without) a disorder of interest. Synonymous with Likelihood.

Logistic Regression: A term used for a regression analysis in which the dependent or target variable is dichotomous (or placed into either of two groups) and which uses a model that relies on logarithms.

Matching: A deliberate process to make the study group and comparison group comparable with respect to factors (or confounders) that are extraneous to the purpose of the investigation but may however interfere with the interpretation of the studies' findings. For example, in case control studies, individual cases may be matched with specific controls on the basis of comparable age, gender, and/or other clinical features. Once you match on something, you cannot use that factor as a possible risk item for analysis.

Meta-Analysis: A systematic overview that incorporates a quantitative strategy for combining the results of several studies into a single pooled or summary estimate.

Multivariate Analysis: An analysis that simultaneously considers a number of predictor variables.

Null Hypothesis: In the hypothesis-testing framework, the starting hypothesis the statistical test is designed to consider and, possibly, reject.

Number Needed to Treat (NNT): The number of patients who need to be treated over a specific period of time to prevent one bad outcome. When discussing NNT, it is important to specify the treatment, its duration, and the bad outcome being prevented. It is the inverse of the absolute risk reduction (ARR).

Number Needed to Harm (NNH): The number of patients who would need to be treated over a specific period of time before one adverse side effect of the treatment will occur. It is the inverse of the absolute risk increase.

Observational Studies (or Observational Study Design): Studies in which patient or physician preference determines whether a patient receives treatment or control.

Odds: A ratio of probability of occurrence to nonoccurrence of an event. If the event rate for a disease is 0.1 (10 percent), its nonevent rate is 0.9 and therefore its odds are 1:9. Comparing it to a piece of pie, the other number is the number of pieces of the rest of the pie.

- Odds Ratio*: A ratio of the odds of an event in an exposed group to the odds of the same event in a group that is not exposed or the control group. Synonymous with Cross-Product Ratio and Relative Odds.
- Outcomes*: Changes in health status that may occur in following subjects or that may stem from exposure to a causal factor or to a therapeutic intervention.
- Overview*: A type of review in which primary research relevant to a question is examined and summarized, and an effort is made to identify all available literature (published or unpublished) that pertains to that question.
- Phase I Studies*: Studies that investigate a drug's physiological effect or ensure that it does not manifest unacceptable early toxicity, often conducted in normal volunteers.
- Phase II Studies*: Initial studies on patients, which provide preliminary evidence of possible drug effectiveness.
- Phase III Studies*: Randomized control trials designed to definitively establish the magnitude of drug benefit.
- Phase IV Studies*: Studies conducted after the effectiveness of a drug has been established and the drug marketed, typically to establish the frequency of unusual toxic effects. Synonymous with Post-Marketing Surveillance Studies.
- Placebo Effect*: The impact of a treatment independent of its biological effect. Interventions (typically a pill or capsule) without biologically active ingredients.
- Predictive Value (PPV or NPV)*: Two categories: Positive Predictive Value -- the proportion of people with a positive test who have the disease; Negative Predictive Value -- proportion of people with a negative test and who are free of disease.
- Pretest Odds*: The odds of the target condition being present before the results of a diagnostic test are available.
- Pretest Probability*: The probability of the target condition being present before the results of a diagnostic test is available.
- Prevalence*: Proportion of persons affected with a particular disease at a specified time. Prevalence rates obtained from high quality studies can inform clinician-efforts to set anchoring pretest probabilities for their patients.
- Prognosis*: The possible outcomes of a disease and the frequency with which they can be expected to occur.

P-value: The probability that results that are more extreme than those actually observed would occur if the null hypothesis was true and the experiment was repeated over and over. Usually this is set at 0.05 as a cut-off point for stating that anything less than this figure would be acceptable for an actual difference to exist.

Qualitative Research: Qualitative research offers insight into social, emotional, and experiential phenomena in health care.

Quality of Care: The extent to which health care meets technical and humanistic standards of optimal care.

Quality-Adjusted Life-Year (QALY): A unit of measure for survival that accounts for the effects of suboptimal health status and the resulting limitations in quality of life. For example, if a patient lives for 10 years and her quality of life is decreased by 50% because of chronic lung disease, her survival would be equivalent to 5 quality-adjusted life-years.

Quantitative Research: Aims to test well-specified hypotheses concerning predetermined variables that yield numbers suitable for statistical analysis.

Randomization (or Random Allocation): Allocation of individuals to groups by chance, usually done with the aid of table of random numbers. Not to be confused with systematic allocation (e.g., on even and odd days of the month) or allocation at the convenience or discretion of the investigator.

Randomized Controlled Trial: Experiment in which individuals are randomly allocated to receive or not receive an experimental preventative, therapeutic or diagnostic procedure and then followed to determine the effect of the intervention. Synonymous with Randomized Trial.

Relative Risk: Ratio of the risk of an event among an exposed population to the risk among the unexposed.

Relative Risk Reduction (RRR): An estimate of the proportion of baseline risk that is removed by the therapy, it is calculated by dividing the absolute risk reduction by the absolute risk in the control group. It is the percent reduction in events in the treated group event rate (EER) compared to the control group event rate (CER):

$$RRR = (CER - EER) / CER * 100$$

In the example for ARR/ARI, the RRR is 33% (2 / 6).

Risk Ratio: A synonym for relative risk: ratio of the risk of an event among an exposed population to the risk among the unexposed. It is the ratio of risk in the treated group (EER) to the risk in the control group (CER): $RR = EER / CER$. RR is used in randomized trials and cohort studies.

Screening: Services, designed to detect people at high risk of suffering from a condition associated with a modifiable adverse outcome, to be offered to persons who have neither symptoms of, nor risk factors (other than age or gender) for a target condition.

Sensitivity Analysis: Any test of the stability of the conclusions of a health care evaluation over a range of probability estimates, value judgments, and assumptions about the structure of the decisions to be made. This may involve the repeated evaluation of a decision model in which one or more of the parameters of interest are varied.

Sensitivity: The proportion of people who truly have a designated disorder who are so identified by the test. The test may consist of, or include, clinical observations.

Specificity: The proportion of people who are truly free of a designated disorder who are so identified by the test. The test may consist of, or include, clinical observations.

“SpPin and SnNout”

SpPin: When a sign/test has a high specificity, a positive result rules in the diagnosis; e.g. the specificity of fluid wave for diagnosing ascites is 92 percent. Therefore, if a person has a fluid wave, it is highly likely that the person has ascites.

SnNout: When a test with a high sensitivity is negative, it effectively rules out the diagnosis of disease, e.g. the sensitivity of a history of ankle swelling for diagnosing ascites is 92 percent, therefore if a person does not have a history of ankle swelling, it is highly unlikely that the person has ascites.

Statistical Significance: A result is statistically significant if the null hypothesis is rejected. That is, the probability of the observed results, given the null hypothesis, falls below an arbitrary threshold (most often .05).

Survey: Observational or descriptive non-experimental study in which individuals are systematically examined for the absence or presence (or degree of presence) of characteristics of interest.

Survival Analysis: An analysis that considers not only the proportion of patients who experience an outcome or endpoint, but also the time pattern of the occurrence of outcomes or endpoints.

Systematic Review: A critical assessment and evaluation of research (not simply a summary) that attempts to address a focused clinical question using methods designed to reduce the likelihood of bias.

Test Threshold: Probability of a disease below which a clinician dismisses a diagnosis and orders no further tests. Above this threshold, additional tests or other management steps may be done until the treatment threshold is met (see below). Also referred to as diagnostic threshold.

Treatment Effect: The results of comparative clinical studies can be expressed using various treatment effect measures. Examples are absolute risk reduction (ARR), relative risk reduction (RRR), odds ratio, number needed to treat (NNT) and effect size. The appropriateness of using these to express a treatment effect, and whether probabilities, means, or medians are used to calculate them depends upon the type of outcome variable used to measure health outcomes. For example, ARR, RRR and NNT are used for dichotomous variables and effect sizes are normally used for continuous variables.

Treatment Threshold: Probability of a disease above which a clinician would consider a diagnosis confirmed and would stop testing and initiate treatment.

Validity: In relation to studies of diagnosis or therapy, a study is valid when the results represent an unbiased estimate of the underlying truth. In relation to health-related quality of life measures, validity represents the extent to which an instrument is measuring what is intended to measure.

Adapted from: Evidence-Based Medicine Working Group, Users Guide to the Medical Literature (G. Guyatt and D. Rennie, eds), JAMA Press, 2002.

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Online Medical Information Resources

Resource	Internet Address
ACP Journal Club	www.acponline.org/catalog/journals/acpic/jcmenu.htm
Best Evidence	www.acponline.org/catalog/electronic/best_evidence.htm
Cochrane Library	www.update-software.com/cochrane/cochrane-frame.htm
Up-To-Date	www.uptodate.com
MEDLINE PubMed	www.ncbi.nlm.nih.gov
Internet Grateful Med	www.igm.nlm.nih.gov
Other sources	www.medmatrix.org/info/medlinetable.asp
Scientific American Medicine	www.samed.com
Clinical Evidence	www.evidence.org
Harrison's Online emedicine	www.harrisonline.com www.emedicine.com
Medscape	www.medscape.com/Home/Topics/homepages.html
Medical Matrix	www.medmatrix.org/index.asp
ScHARR Netting	www.shf.ac.uk
Medical World	www.mwsearch.com
Journal Listings	www.nthames-health.tpmde.ac.uk/connect/journals.html www.pslgroup.com/dg/medjournals.htm
Clinical Practice Guidelines	www.guidelines.gov
MD Consult	www.mdconsult.com
Evidence-based Medicine Reviews (OVID)	www.ovid.com/products/clinical/ebmr.cfm