

EVIDENCE BASED MEDICINE CATS

On Family Planning & Reproductive Health

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CATALYST
consortium



In this issue:

- 1- COCs and breast cancer.
- 2- DMPA and cervical cancer.
- 3- COCs and cervical cancer.
- 4- DMPA and Breastfeeding

للمزيد من المعلومات
يمكنك الإتصال بأسرة تحرير النشرة

كاتاليسست كونسورشيام

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This is an evidence-based series that is intended to provide you with a concise up to date series of Critically Appraised Topics (CATs) on family planning (FP) and reproductive health (RH) issues. Each issue will include a summary of the latest information available on a particular topic and is followed by a critical appraisal drawn from the most recently available literature.

The 'EBM' series of CATs is intended to be interactive. Our team members have already a number of ready-made interesting topics that will be made available to you on regular basis. However they are here to help providing you with any information related to the field of FP/RH.

Furthermore, any question that might arise during your day-to-day practice should be properly answered. We may help you formulating this clinical question and find the best available answer.

Tahseen project is very concerned of using EBM in supplying service providers with the most up to date medical knowledge in FP/RH, to achieve the quality service by the end of the project's years.

This is the first issue of our series... Read it and enjoy the evidence.

Appraised by: MEDTEC EBM Team

To be updated by :Dec. 2004

**The use of combined oral
contraceptive pills does not cause
breast cancer**



استخدام أقراص منع الحمل المركبة
لا يسبب سرطان الثدي

The absolute risk of developing breast cancer increases very slightly in women using combined oral contraceptives, and a detection bias cannot be ruled out, there is no sufficient evidence to assume a cause-effect relationship between the development of breast cancer and oral contraceptive use.

أظهرت الدراسة أن الزيادة النسبية في احتمال الإصابة بسرطان الثدي بين مستخدمات أقراص منع الحمل قد تكون نتيجة لزيادة اكتشاف المرض بين المستخدمات اللاتي يتعرضن للكشف الدوري على الثدي بشكل أكثر انتظاماً من غير المستخدمات ، كما أظهرت الدراسة أن الزيادة الحقيقية في عدد حالات سرطان الثدي بين المستخدمات لأقراص منع الحمل المركبة مقارنة بغير المستخدمات تعتبر طفيفة للغاية وهذه الزيادة الطفيفة لا يمكن أن تفسر حدوث سرطان الثدي كنتيجة لاستخدام هذه الأقراص ، مما يجعلنا نأخذ في الاعتبار الفوائد الصحية والاجتماعية لاستخدام الأقراص عند تقييم مخاطرها.

Background Knowledge :

There have been some beliefs for many years that use of hormonal contraception is linked to an increased risk of breast cancer. These beliefs have been fueled by the fact that widespread use of hormonal contraceptives, particularly combined oral contraceptives (COCs), has paralleled an increased incidence of breast cancer in many countries.

Increasing evidence that breast cancer is hormonally mediated has heightened concern about a possible link. Yet numerous investigations of possible COCs/breast cancer associations have been carried out around the world, and to date have not provided conclusive answers. In general, weak, and sometimes conflicting associations have characterized these studies. Some studies have shown an increased risk of breast cancer with COCs use before first pregnancy and with long duration of use, but other studies have not shown these increased risks. These inconsistent results have been linked to a variety of factors, including the changing regimens and patterns of COCs use and dose of hormones in the pill over the past 30 years, different methodologies and subject populations among various studies, and other factors.

Three-part Clinical Question:

Are women using Combined oral contraceptives at a greater risk of developing breast cancer?

Search Terms:

Combined oral contraceptives AND breast cancer.

Citation:

The WHO Collaborative Group on Hormonal Factors in Breast Cancer, 1996.(Meta-analysis). The WHO Technical Report Series. Geneva: World Health Organization, 1996

Study Patients:

The collaborative study involved a compilation of individual data on 16345 women with breast cancer and 106826 controls from 54 studies in 25 countries. Most of the studies were from Europe and North America, but Asia, Africa, and Latin America also were represented.

Exposure of Interest:

Use of oral contraceptives.

The Outcome:

Detection of breast cancer



Comments:

- Breast cancer may be more frequently diagnosed in COCs users due to more physician contact and subsequent screening (detection bias). Among women who use COCs from age 25 to 29, the incidence of breast cancer is very similar to that of non-users through age 40
- Even among women who use COCs throughout their 20s, there was minimal difference in breast cancer incidence compared with non-users after 10 years of stopping use (Maximum of 4.7 case / 100000 users /year).
- The only group with a significant, those small increase in breast cancer incidence in COCs users, was those who began using COCs before the age of 20 detection bias may be a factor in this slight increase in incidence.
- Up to 20 years after cessation of COCs use the difference between ever-users and never-users is not so much in the total number of breast cancers diagnosed, but in their clinical presentation, with the breast cancers diagnosed in ever-users being less advanced clinically than those diagnosed in never-users.

Study features
There were clearly defined groups of people similar in all important ways other than the exposure to COCs
Exposures and outcomes were objective
Follow-up was long enough.
Follow-up was complete.

The Evidence:		Breast cancer	
		Present	Absent
Oral contraceptive Use	Yes	8448	53468
	No	7897	53358
NNH		960	

NNH: Number Needed to Harm

(The number of patients who if they received experimental treatment, would lead to one patient being harmed)

There is no association between carcinoma in situ of the cervix and the use of DMPA



لا توجد علاقة بين حدوث سرطان عنق الرحم واستخدام حقن ديبويروفيرا لمنع الحمل

Women using DMPA do not have an increased risk of developing cervical cancer. Detection of various cervical lesions, including CIS, was increased in women using DMPA, but no evidence of a cause-effect relationship could be concluded.

استخدام حقن ديبويروفيرا لمنع الحمل لا يزيد من نسبة حدوث سرطان عنق الرحم. كما أن هناك زيادة في معدل اكتشاف تغيرات في خلايا عنق الرحم والتي تحدث قبل ظهور السرطان في السيدات مستخدمات الحقن ولكن ليس هناك دليل بحثي علي أن حقن ديبويروفيرا تسبب سرطان عنق الرحم.

Background Knowledge:

Cervical cancer is the leading cause of death from cancer among women in developing countries. The disease generally progresses slowly, starting with mild cervical dysplasia (a precancerous condition that regresses in about 60 percent of cases). In some cases, it advances to severe dysplasia or carcinoma in situ (CIS) which are treatable precursors of invasive disease and eventually to invasive carcinoma. The primary underlying cause of cervical cancer is human papilloma virus (HPV), a sexually transmitted infection. Other factors that may influence whether a woman is likely to develop cervical cancer, include tobacco use, nutritional status, parity and some hormonal factors. Most other factors identified as associated with cervical cancer for example, age at first intercourse and number of sexual partners are most likely indicators of risk of HPV exposure rather than independent risk factors. Periodic pap smear screening and treatment of precancerous lesions can largely prevent cervical cancer.

In conclusion, evaluating results of research on the relationship between the use of DMPA and cervical cancer is challenging, because numerous factors may influence development of cervical cancer, and the disease develops over a long time period. Furthermore, in some settings, hormonal contraceptive users are more likely to have pap smears, resulting in detection bias.

Three-part Clinical Question:

Are women using DMPA for contraception at a greater risk of developing cervical cancer?

Search Terms:

DMPA AND cervical cancer.

Citation

The WHO Collaborative Study of Neoplasia and Steroid Contraceptives. 1992 (Meta-analysis).

The WHO Technical Report Series, No. 817. Geneva: World Health Organization, 1992

Study Patients:

The WHO Collaborative Study of Neoplasia and Steroid Contraceptives analyzed data gathered between 1979 and 1988 on two types of cervical cancer from three hospitals, one in Thailand, one in Mexico, and one in Kenya. The study involved 1258 CIS cases detected and 17014 controls.

A separate analysis of data from the study, found that DMPA users appear to have a slightly increased risk of CIS, the precursor to invasive cancer. However the researchers concluded that the increased risk of CIS found in this analysis is likely to be an artifact due to uncontrolled confounding or unidentified sources of bias or could represent the induction of a condition that is reversible or does not proceed to invasive disease. Nevertheless, they recommend that DMPA users are subjected to periodic pap smears, when available.



Exposure of Interest: Use of DMPA

The Outcome: Detection of CIS

Comments:

- DMPA use does not impose an increased risk of development of cervical cancer
- Cervical cancer tends to be associated with a sexually transmitted disease with incidence rates related to sexual behaviors and values rather than drug exposure.
- Detection of CIS in women using DMPA may be a health benefit rather than a risk, allows earlier treatment and follow up to prevent the condition from proceeding into cervical cancer
- The increased detection of CIS does not indicate a cause-effect relationship, as many confounding factors interfere with the study results. Rather, the increased detection points to a "detection bias".

Study features
There were clearly defined groups of people similar in all important ways other than the exposure to DMPA
Exposures and outcomes were objective
Follow-up was long enough.
Follow-up was complete.

The Evidence:

		Carcinoma In Situ	
		Present	Absent
DMPA Use	Yes	735	8507
	No	513	8507
NNH		3800	

No evidence on a cause effect relationship between cervical cancer and the use of combined oral contraceptive pills.



لم يثبت بالدليل البحثي علاقة بين استخدام أقراص منع الحمل المركبة و حدوث سرطان عنق الرحم

There is no evidence indicating a cause effect relationship between COCs use and cervical cancer. On the other hand, a definite relationship exist between HPV infection and cancer cervix

لا توجد أدلة بحثية على ارتباط حدوث سرطان عنق الرحم باستخدام أقراص منع الحمل المركبة . وفى المقابل فإن العلاقة وطيدة بين العدوى بفيروس HPV و حدوث سرطان عنق الرحم

Background Knowledge :

Cervical cancer is the leading cause of death from cancer among women in developing countries.

The disease generally progresses slowly, starting with mild cervical dysplasia (a precancerous condition that regresses in about 60 percent of cases). In some cases, it advances to severe dysplasia or carcinoma in situ (CIS) which are treatable precursors of invasive disease and eventually to invasive carcinoma. The primary underlying cause of cervical cancer is human papilloma virus (HPV), a sexually transmitted infection. Other factors that may increase the risk of developing cervical cancer include tobacco use, nutritional status, parity and some hormonal factors. Most other factors identified as associated with cervical cancer for example, age at first intercourse and number of sexual partners are most likely indicators of risk of HPV exposure rather than independent risk factors.

Periodic pap smear screening and treatment of precancerous lesions can largely prevent cervical cancer.

In conclusion evaluating results of research on the relationship between the use of COCs and cervical cancer is challenging, because numerous factors may influence development of cervical cancer, and the disease develops over a long time period. Furthermore, in some settings, hormonal contraceptive users are more likely to have pap smears, resulting in detection bias.

Three-part Clinical Question:

Are women using combined oral contraceptives at a greater risk of developing cervical cancer ?

Search Terms:

Combined oral contraceptives AND cervical cancer

Citation:

The WHO Collaborative Study of Neoplasia and Steroid Contraceptives.1992 (Meta-analysis). The WHO Technical Report Series, No. 817. Geneva: World Health Organization, 1992

Study Patients:

The WHO Collaborative Study of Neoplasia and Steroid Contraceptives analyzed data gathered between 1979 and 1988 on two types of cervical cancer from 11 hospitals in 9 countries. The analysis of squamous cell cervical carcinoma, the most common form of cervical cancer, involved 850 cases and 13644 controls and was adjusted for various confounding variables. The study found a statistically significant increased relative risk of invasive squamous cell cervical cancer of 1.31 among ever-users of COCs. Risk was highest among women who had used COCs for four or more years and declined in the eight years after last use to that of non-users. This pattern cannot explain a cause-effect relationship between COCs use and cervical cancer .

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A second analysis evaluated possible links between COCs use and adenomatous cervical cancer a rare cancer of the glandular epithelial cells; the relative risk among ever-users of COCs was 1.5. Risk increased with duration of COCs use and young age (< age 25) at first use.

Risk was highest in recent and current users, and declined with time since last use. This is consistent with a detection bias effect rather than a cause-effect relationship.

Another analysis of the WHO study data evaluated the link between COCs use and carcinoma in situ the precursor of invasive cancer. The analysis found an increased risk of CIS among COCs users, but again could not rule out detection bias as a factor in the result.

Study features
There were No clearly defined groups of people similar in all important ways other than the exposure to Combined oral contraceptives
Exposures and outcomes were objective
Follow-up was long enough.
Follow-up was complete.

The Evidence:		Cervical Cancer	
		Present	Absent
COCs Use	Yes	482	6813
	No	368	6831
NNH		6250	

Exposure of Interest: Use of combined oral contraceptives

The Outcome: Detection of cervical cancer

Comments:

- Three large, well-controlled studies failed to find a significant association between the risks of invasive cervical cancer and ever use of COCs.
- Cervical cancer appears to be a sexually transmitted disease.
- The lifetime number of male sexual partners and incidence of human papilloma virus (HPV) infection are positively associated with cervical cancer, while use of barrier contraception (e.g., condom, diaphragm) and spermicidals-containing nonoxynol-9 protects against this disease.
- The unique epidemiology of cervical cancer makes assessment of any association with COCs use difficult.
- Women who use COCs often have more sexual partners and are less likely to use barrier contraception than other women, thus they are of higher risk for cervical cancer.
- In addition, because of examinations associated with prescription renewals, women using COCs undergo cytologic screening more frequently than do others
- The results show that COCs users had enhanced cervical cancer detection. The possibility of an interaction between HPV infection, cervical cancer development, and COCs use could not be ruled out.

DMPA has no detrimental effect on the duration or frequency of breastfeeding in mothers



استخدام حقن ديبويروفيرا لمنع الحمل لا يؤثر على مدة أو معدل الرضاعة الطبيعية

There was no significant difference in the frequency or duration of lactation, nor in the timing of 1st introduction of formula feeding in two cohort groups one taking injectable DMPA, the other taking non-hormonal contraceptives. DMPA when given to mothers in an American urban community immediately postpartum, has no detrimental effect on the duration of lactation, frequency of lactation, or timing of introduction of formula. Within the 1st 16 weeks postpartum.

أظهرت الدراسة المقارنة التي أجريت على مجموعتين من السيدات المرضعات لأطفالهن خلال الستة عشر أسبوعاً الأولى بعد الولادة ، استخدمت فيها المجموعة الأولى حقن ديبويروفيرا لمنع الحمل ، واستخدمت الثانية وسائل غير هرمونية لمنع الحمل، أن استخدام هذه الحقن ليس له تأثير يذكر على مدة أو معدل الرضاعة الطبيعية أو حتى على تركيب لبن الأم .

Background Knowledge:

"Breastfeeding is the normal completion of the reproductive cycle, and is recommended for all infants. The quality of breast milk has all the nutrients a baby needs even if the mother's diet is inadequate. It is an excellent source of carbohydrates, easily digested proteins, fats and minerals. Breast feeding delivers Anti-infective and immunologic advantages to the baby, supports "bonding" which is the emotional tie between the mother and the infant and it enhances the intellectual development of the baby.

A number of studies show "a possible protective effect of human milk feeding" agents upon:

- 1- Sudden infant death syndrome.
- 2- Risk of allergic diseases.
- 3- Diabetes mellitus.
- 4- Crohn's disease and ulcerative colitis.
- 5- Lymphoma.

On the other hand breastfeeding is important to the lactating mother:

The release of oxytocin while breastfeeding speeds uterine involution, bonding and psychosocial effects between the mother and the baby. Breastfeeding has been found to delay the return of menses after childbirth, but it is not a reliable method of birth control. Accordingly, women who do not want to become pregnant and are breastfeeding even in the first months postpartum should use some form of birth control.

Early postpartum contraception can protect the mother against another pregnancy because her return of fertility is often unpredictable. Optimal solutions combine the introduction of breast-feeding and contraception immediately postpartum. However there is some concern about the potentially negative influence on lactation of hormonal contraception immediately postpartum. For this reason, hormonal methods such as Depo-Provera (DMPA) are recommended at 40 days postpartum for breastfeeding women. For the past 30 year,

DMPA has been used widely in more than 90 countries Its efficacy and safety are well established.

For breastfeeding women, DMPA may increase prolactin levels, either directly by acting on anterior pituitary to stimulate the release of prolactin or indirectly by inhibiting the hypothalamic secretion of the prolactin inhibitory factor. The effect of DMPA on lactation was evaluated in several developing countries. Most studies suggest that there is no effect or a slight increase in measured milk volumes and duration of lactation. Importantly none of these studies reported any negative effect on infant growth.

Three-part Clinical Question

Is there any harmful effect of DMPA (taken for contraception) compared to non-hormonal contraceptives on lactation when it is given immediately postpartum?

Search Terms

DMPA AND lactation

Citation:

Hannon PR, Duggan AK, Serwint JR, Vogelhut JW, Witter F, DeAngelis C. The influence of DMPA on the duration of breast-feeding in mothers in an urban community. Arch Ped 1997;151:490-496. Lead author's name and fax: Hannon, PR



Study Patients:

The study was a prospective cohort study.

Patients were 103 postpartum mothers enrolled at the full-term newborn nursery at the Johns Hopkins Hospital, Baltimore, MD between 4/94 - 1/95. Eligibility criteria included:

- 1) had delivered a healthy neonate (gestational age >=36 weeks).
- 2) was breast feeding at the time of neonate discharge and intended to continue at home.
- 3) intended to receive primary care at the same hospital, or at an affiliated HMO.
- 4) chose either DMPA or nonhormonal contraception at discharge and frequency) and timing of 1st formula.
- 5) had a telephone at home.

Exclusion criteria included:

- 1) maternal history of reduction mammoplasty.
- 2) intention to use an IUD, Norplant, or OCPs within the 1st 4 weeks post partum.
- 3) congenital defect or disease in the infant that could affect oralfeeding. Final numbers were 43 women were in the DMPA group, 52 in the nonhormonal contraceptive group. Mean age was 24 years, 90% were African American, 63 were multiparous, 47% had more than high school education, 43% had 1st trimester care.

Exposure of interests: injectable DMPA used as a contraceptive versus a nonhormonal contraceptive (NHC)

The Outcome: Primary outcomes were lactation (duration and frequency) and timing of 1st formula.

Lactation was assessed through weekly interviews by non-blinded nurses beginning at 1 week through 8 weeks; then at 12 and 16 weeks post

partum. Interviewers asked about duration of breast feeding until the infant received no more milk; frequency of lactation at the time of interview; timing of introduction of formula; reasons for termination of lactation; current contraceptive method. Maternal responses to the frequency of lactation questions were blindly and independently reviewed by 2 pediatricians.

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Study features:

- Subjects were clearly defined and are similar in all other important ways.
- Exposures and outcomes were objective and measured non-blindly for the mothers and blindly for the infants responses.
- Follow-up was long enough.
- Follow-up was almost complete.

The Evidence:

	Non-Hormonal Use	Depo-Provera Use
Median Duration of Breastfeeding	6.57 weeks	10.14 weeks
Status at 16 weeks	n =48	n =38
Exclusively breastfeeding	6 (13%)	8 (21%)
Mostly breastfeeding	3 (6%)	1 (3%)
Half breastfeeding	1 (2%)	4 (10%)
Mostly formula feeding	4 (8%)	3 (8%)
Stopped breastfeeding	34 (71%)	22 (58%)

Comments:

The median duration of breastfeeding of the DMPA group was numerically higher than those in the non-hormonal group. However, the difference was not statistically significant.

There were no differences between the two groups in the frequency of lactation.

There were no differences between the two groups in the timing of first introduction of formula.

Though the study results are convincing and study participants in each group were similar relative to important variables affecting lactation, it was a cohort study (non- randomized). Also, the initial assessors were not blinded to the contraceptive status of the subjects.



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