COLLECTION OF CRITICALLY APPRAISED TOPICS ON CONTRACEPTION

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Introduction

Critically Appraised Topics (CATs) were originally developed by doctors at Oxford University to provide health professionals with concise, practical information about the best evidence on clinical topics, helping them provide their clients with quality information and services without devoting hours to searching and evaluating the evidence. They follow a standard format and provide a brief summary of the clinical evidence from reliable studies. The format of a CAT is as follows:

Title: This is a summary of the results of the "best clinical evidence" in an easy to understand and easy to communicate format. The title contains "the key message."

Conclusion: This is a summary of the overall conclusions of the studies used to develop the CAT.

Clinical Question: The question coming from health professionals.

Search Terms: These are the words used to search the literature to find the best clinical research. Of course, this is only the first step in determining the best research.

Citation: Location of the identified studies in the literature. The cited studies are those chosen as the best clinical evidence and were used for development of the answer to the clinical question.

Object of research: The object is the intervention being studies. In our case the object is usually a contraceptive method.

Subject of research: The subject contains the measurements used to assess the clinical question.

Study Features: Brief description of each study's characteristics.

The Evidence: Brief presentation of each study's conclusion.

Appraised by: Authors.

Update by: The date by which the CAT should be assessed to determine if there are any new clinical findings.

The set of CATs compiled in this document were developed by the Together for Health (TfH) project in Ukraine in order to update health professionals' contraceptive knowledge, using the latest available evidence. They are intended to help dispel widespread myths and misinformation about contraception and to support doctors, pharmacists and other health professionals in providing up-to-date evidence-based family planning information and services. They answer the most frequently-asked questions collected from doctors and pharmacists in Ukraine.

This collection of CATs addresses the perceived negative associations between contraceptive use (oral contraceptives, intrauterine devices etc.) and various medical conditions, as well as non-contraceptive benefits, such as the mitigation of acne or hirsutism. They will be used during detailing visits, medical roundtables, and seminars for health professionals conducted by the PSPs' medical trainers and "key opinion leaders", who have been oriented by

the project to Evidence-Based Medicine and use of the CATs; as well as being distributed by oblast health departments to their networks of service providers. The expectation is that the CATs will reinforce key messages in TfH's training courses for doctors, midlevel health professionals and pharmacists and that they will bring accurate, up-to-date information to the numerous health professionals never reached by the project's training.

The CATs were developed by project-trained Evidence-Based Medicine methodologists associated with the Evidence Based Medicine Center at the Department of Obstetrics, Gynecology and Reproductology in the Ukraine National Medical Academy of Postgraduate Education, with technical assistance from the International Center for Evidence Based Medicine at East Tennessee State University and M. Thomas and Associates through The Academy for Educational Development.

TfH is made possible with the support of the American people through the United States Agency for International Development (USAID). It is implemented by JSI Research & Training Institute, Inc. in collaboration with The Academy for Educational Development and Harvard School of Public Health.

Combined oral contraceptives are safe and effective in the treatment of moderate facial acne in women

Conclusion

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

Clinical Question

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

Search Terms

Combined oral contraceptives, acne

Citation

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

Object of research

Combined oral contraceptives

Subject of research

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

Study Features

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

A total of 8051 participants were enrolled in the 25 trials. Individual sample sizes varied from 24 to 1154. The trials varied considerably in the comparison groups and the doses of ethinyl estradiol ranged from 20 µg to 50 µg in combination with eight types of progestin. The duration of the trials varied from 3 to 12 treatment cycles (mode=6 cycles). Only two studies had fewer than six treatment cycles.

The Evidence

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

Appraised by:

1. The International Center for Evidence Based Medicine, East Tennessee State University;
2. The Evidence Based Medicine Center, Department of Obstetrics, Gynecology and Reproductology, Ukraine National Medical Academy of Postgraduate Education;
3. Together for Health project.

Update by: 4 November 2011

The use of low-dose combination oral contraceptives reduces manifestations of hirsutism in women

Conclusion

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

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

Search Terms:

Hirsutism, combination oral contraceptives, low-dose oral contraceptives

Citations

Batukan C, Muderris II. Efficacy of a new oral contraceptive containing drospirenone and ethinyl in the long-term treatment of hirsutism. Erciyes University, School of Medicine of Obstetrics and Gynecology, Kayseri, Turkey. Fertility and Sterility. Vol.85,No 2, February 2006.

Object of Research

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

Subject of Research

Hirsute women

Study Features

This was an open-label randomized trial that involved 50 female outpatients from the Outpatient Hirsutism Clinic of Erciyes University, School of Medicine of Obstetrics and Gynecology, in Kayseri, Turkey. The trial involved women with moderate and severe hirsutism measured by the Ferriman-Gallwey (F-G) scale who were not pregnant, as well as premenopausal women with no evidence of androgen-producing adrenal or ovarian tumours, Cushing's syndrome, or congenital adrenal hyperplasia - except for polycystic ovaries. Women received 3 mg drospirenone and 30 mcg ethinyl estradiol or 2 mg cyproterone acetate and 35 mcg ethinyl estradiol for 12 months. Their hirsutism status was evaluated in the 6th and the 12th month of treatment.

The Evidence

Evaluation showed a significant reduction of total Ferriman-Gallwey score for both groups after 6 and 12 months. The most significant improvement was observed in breast and abdominal areas, as well as in the areas of the upper lip and the chin. The least significant effect occurred in the areas of the back and arms. Serum levels of total and free testosterone and androstendione decreased whereas serum SHBG level increased. FSH, LH, estradiol and DHEAS levels did not change. There were no significant differences between the two groups at the end of 12 months. However, reductions for the drospirenone group were sig-

nificantly greater than for the cyproterone acetate at 6 months suggesting that drospirenone group had a faster resolution of hirsutism.

Appraised by:

1. The International Center for Evidence Based Medicine, East Tennessee State University;
2. The Evidence Based Medicine Center, Department of Obstetrics, Gynecology and Reproductology, Ukraine National Medical Academy of Postgraduate Education;
3. Together for Health project.

Update by: 6 December 2011

There is no strong evidence supporting an association between COCs and weight gain

Conclusion

A systematic review of randomized controlled trials indicates that there is insufficient evidence to suggest an association between weight gain in women and use of combined oral contraceptives. Few women discontinued use of their COC because of weight gain.

Clinical Question

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

Search Terms

Contraceptives, oral contraceptives, contraception, weight gain.

Citation

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

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

Object of research

Use of combined oral contraceptives compared to another combined oral contraceptive or a placebo.

Subject of research

Change in weight

Study Features

Gallo, et al.

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

- The combined oral contraceptives evaluated in the 47 trials included 18 progestins and 3 estrogens. With the exception of two studies (one with 40 mcg EE and one with 50 mcg EE), the estrogen dosage levels ranged from 20 to 35 mcg. Sample sizes ranged from 20 to 5654 patients (median number 196). The duration of the studies ranged from 3-24 treatment cycles though most were included between 6 and 12 cycles. Measurements at cycles 6 and 12 as well as the last treatment cycle were used as a standard throughout this analysis.

- The eligibility criteria for the participants varied among the trials with most trials recruiting healthy women of reproductive age without contraindications to oral contraceptive use.

Foidart, et al.

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

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

The Evidence

Gallo, et al.

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

Foidart, et al.

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

Appraised by:

1. The International Center for Evidence Based Medicine, East Tennessee State University;
2. The Evidence Based Medicine Center, Department of Obstetrics, Gynecology and Reproductology, Ukraine National Medical Academy of Postgraduate Education;
3. Together for Health project.

Update by: 4 November 2011

There is no strong evidence supporting an association between the vaginal ring and weight gain

Conclusion

There is insufficient evidence to suggest an association between weight gain in women and use of the vaginal ring. Few women discontinued use of their vaginal ring because of weight gain.

Clinical Question

Do women using a vaginal ring have greater weight gain than women not taking them?

Search Terms : Contraceptives, vaginal rings, weight gain.

Citation

Milsom I, Lete I, Bjertnaes A, Rokstad K, Lindh I, Gruber CJ, et al. Effects on cycle control and body weight of the combined contraceptive ring, NuvaRing, versus an oral contraceptive 30 mcg ethinyl estradiol and 3 mg drospirenone. Human Reproduction 2006 Vol.21, No.9 2304–2311,

Object of research

Use of a vaginal ring compared to another combined oral contraceptive.

Subject of research: Change in weight

Study Features

This multicenter, randomized open label study was carried out in 10 European countries and included 923 women, 499 assigned to a vaginal ring (NuvaRing) and 484 to a COC. All women were at least 18 years of age. Body weight measurements were performed at the screening visit as well as each follow-up visit. To standardize individual body weights, measurements were taken at the same time of day and in their underwear. Weight neutrality was assumed if change from baseline was less than 1.5 kg.

The Evidence

The mean change in weight for the vaginal ring was 0.37 kg (95% CI: 0.10-0.64). The corresponding change for the COC group was -0.03 kg (95% CI: -0.29 – 0.23). In both cases, 1.5 kg was outside the confidence interval and the two contraceptives were weight neutral.

Appraised by:

1. The International Center for Evidence Based Medicine, East Tennessee State University;
2. The Evidence Based Medicine Center, Department of Obstetrics, Gynecology and Reproductology, Ukraine National Medical Academy of Postgraduate Education;
3. Together for Health project.

Update by: 18 March 2012

There is no association between use of a combined oral contraceptive and infertility

Conclusion

These studies revealed that the cumulative rate of pregnancy for fertile women previously using a combined oral contraceptive did not differ from that observed in fertile women who attempted to become pregnant without prior contraception.

Clinical Question

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

Search Terms

Oral contraceptives, ethinyl estradiol, dienogest, fertility regain, conception rate.

Citations

Wiegratz I, Mittman K, Dietrich H, Zimmermann T, and Kuhl, H. Fertility after discontinuation of treatment with an oral contraceptive containing 30 mcg of ethinyl estradiol and 2 mg of dienogest. Fertility and Sterility 2006; 85:1812-1819.

Barnhart K, Mirkin S, Grubb G, Constantine G. Return to fertility after cessation of a continuous oral contraceptive. Fertility and Sterility 2009; 91:1664-1666.

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

Object of research

Combined oral contraceptive

Subject of research

Cumulative conception rate within 1 year after termination of EE/DNG, time to pregnancy.

Study Features

Wiegratz et al.

Study participants were 706 in number and between 16 and 41 years of age with the mean age 27 years. The duration of use of their oral contraceptive was between one and 90 cycles. Approximately one-third took their oral contraceptive for more than two years.

Barnhart et al.

In a multicenter study of a continuous regimen of levonorgestrel 90 mcg and ethinyl estradiol 20 mcg, 34 of 2,134 subjects cited a desire to become pregnant as a reason for discontinuing use. Subjects were contacted at 3 and 12 months after their discontinuation to determine if they had conceived. Four were already pregnant before stopping treatment, 4 initiated other contraception, and 5 were lost to follow-up. Results for the remaining 21 women were available for analysis

Study Features (continued)

Cronin, et al.

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

The Evidence

Wiegratz et al.

- When all 706 women are included in the data analysis, a least 87% had become pregnant within one year after stopping their oral contraceptive
- When only the 652 women, for whom there was complete data, were included in the data analysis, 94% had become pregnant within one year after stopping their oral contraceptive.
- 50% of the women had conceived within three months after cessation.
- There was no apparent association between age and conception.
- For women using their oral contraceptive for one year or less time to pregnancy was 3.3 cycles (3.3 months), while for those using their oral contraceptive for more than two years, the average time to pregnancy was 4 cycles (4 months).

Barnhart et al.

- The pregnancy rate was 57% at 3 months, 81% at 12 months, and 86% (18 of 21) at 13 months after discontinuation of treatment.
- There were 6 nulliparous women in the study. Five (83%) of these women had conceived by the end of 9 months. The sixth woman had used an oral contraceptive for 27 days on the study and had not conceived by the time 12 month observation was completed.

Cronin, et al.

- The pregnancy rate was 46% at 3 months and 79% at 12 months after discontinuation of their oral contraceptive.
- The rate of pregnancy was lower in nulliparous women than in parous women in the initial months, but almost identical after one year.
- The effect of age on the rate of pregnancy had only a minor effect. As expected, women older than 35 had a notably lower rate of pregnancy than those under 35 years of age.
- Progestin type, ethinyl estradiol dose, and duration of use had no major influence on the rate of pregnancy after cessation.
- Rates of pregnancy were reduced in current smokers.

Comment: Incidence of spontaneous conception among women not using a contraceptive was 86% at the end of one year. (Source: Lobo RA et al. Textbook infertility, contraception, and reproductive endocrinology, 4th Edition. 1997)

Appraised by:

1. The International Center for Evidence Based Medicine, East Tennessee State University;
2. The Evidence Based Medicine Center, Department of Obstetrics, Gynecology and Reproductology, Ukraine National Medical Academy of Postgraduate Education;
3. Together for Health project.

Update by: 4 November 2011

The vaginal ring and combined oral contraceptive both have high and comparable effectiveness in preventing pregnancy

Conclusion

In two multicenter open label studies revealed that the cumulative rate of pregnancy among combined oral contraceptive and vaginal ring users was similar.

Clinical Question

Is there a comparable conception rate between vaginal ring and combined oral contraceptive users?

Search Terms

Oral contraceptives, vaginal ring, conception rate.

Citations

Oddsen k, Leifels-Fischer B, Weil-Masson D, et al. Efficacy and safety of a contraceptive vaginal ring (NuvaRing) compared with a combined oral contraceptive. Contraception 2005, 71: 176-182.

Ahrendt HJ, Nisand I, Bastianelli C, et al. Efficacy, acceptability and tolerability of the combined contraceptive ring, NuvaRing compared with an oral contraceptive containing 30 mcg ethinyl estradiol and 3 mg drospirenone. Contraception 2006, 74:451-457.

Object of research

Vaginal ring

Subject of research

Conception rate (Pearl index) within 1 year after initiation of the vaginal ring.

Study Features

Oddsson K et al.

This was an open label, multicenter trial conducted in 9 European and 2 South American countries. 1030 women at least 18 years of age and at risk for pregnancy were randomly assigned to 13 cycles of the vaginal ring (NuvaRing) or a COC containing 30 mcg of ethinyl estradiol and 150 mcg of levonorgestrel. 512 women used the vaginal ring and 518 used their assigned COC.

Ahrendt HJ et al.

This was an open-label, comparative, multicenter trial conducted in 10 European countries. In this study, 983 women at least 18 years of age and at risk for pregnancy were randomly assigned to 13 cycles of the vaginal ring (NuvaRing) or a COC containing 3 mg drospirenone and 30 mcg ethinyl estradiol. 499 women used the vaginal ring and 484 used their assigned COC.

The Evidence

Oddsson K et al.

The two groups had approximately the same amount of women-years of exposure. The Pearl Index for the vaginal ring group was 1.23 per women-years of use (95% CI: 0.40-2.86). The corresponding index for the COC group was 1.19 per 100 women-years of use (95% CI: 0.39-2.79). There were no statistically significant differences between the two contraceptive groups.

Ahrendt HJ et al.

The two groups had approximately the same amount of women-years of exposure. The Pearl Index for the vaginal ring group was 0.25 (95% CI: 0.1-1.36) and 0.99 (95% CI: 0.29-2.53) per 100 women-years of use for the vaginal ring and COC groups, respectively. There were no statistically significant differences between the two contraceptive groups.

Appraised by:

1. The International Center for Evidence Based Medicine, East Tennessee State University;
2. The Evidence Based Medicine Center, Department of Obstetrics, Gynecology and Reproductology, Ukraine National Medical Academy of Postgraduate Education;
3. Together for Health project.

Update by: 20 March 2012

Women who use combined oral contraceptives have a lower incidence of dysmenorrhea symptoms than women who take no contraception

Conclusion

Two different studies of women treated for dysmenorrhea with low dose COCs showed a significant improvement in symptoms.

Clinical Question

Does the taking of COCs have a beneficial effect on menstrual problems like dysmenorrhea?

Search Terms

Oral contraceptives, dysmenorrhea

Citations

Davis AR, Westhoff C, O'Connell K, Gallagher N. Oral contraceptives for dysmenorrhea in adolescent girls: A randomized trial. Obstetrics Gynecol 2005;106:97-104.

Hendrix SL, Alexander NJ. Primary dysmenorrhea treatment with a desogestrel-containing low-dose oral contraceptive. Contraception 2002;66:393-399.

Object of research

Combined oral contraceptives

Subject of research

Dysmenorrhea

Study Features

Davis, et al.

This study was a randomized, double-blind, placebo controlled study of 76 otherwise healthy adolescents aged 19 years or less. They reported moderate to severe dysmenorrhea. The main outcome measure was their score on the Moos Menstrual Distress Questionnaire. Patients received either a COC containing 20 mcg ethinyl estradiol with 100 mcg of levonorgestrel or a matching placebo for three months.

Hendrix and Alexander:

This study was a randomized, double-blind, placebo controlled study of 77 women aged 32 years or less. All were diagnosed as having primary dysmenorrhea using the Andersch and Milson dysmenorrhea assessment tool. Participants were also given the Menstrual Distress Questionnaire (MDQ) for four cycles in order to measure the intensity of their dysmenorrhea. They received either a COC containing 20 mcg ethinyl estradiol with 150 mcg of desogestrel or a matching placebo for four months.

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

The Evidence

Davis, et al.

The mean Moos (MDQ) score was significantly less (p=0.004) for the COC group than that for the placebo control group at three months. By Cycle 3, COC users rated their worst pain as less (p=0.02) and used significantly fewer pain medications than placebo users. Also, by Cycle 3, COC users reported fewer days of any pain, fewer days of severe pain, and fewer hours of pain on the worst pain day than placebo users.

Hendrix and Alexander:

During treatment and at the final menses, patients receiving the COC had a greater reduction for all distress measures than the placebo group. Of the four studied measures, the most improvement was found for the symptom of painful cramping.

Appraised by:

1. The International Center for Evidence Based Medicine, East Tennessee State University;
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3. Together for Health project.

Update by: 9 November 2011

The use of a combined oral contraceptive is associated with a significant decrease in menstrual blood loss

Conclusion

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

Clinical Question

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

Search Terms

Oral contraceptives, menstrual blood loss

Citation

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

Runnebaum B, Grunwald K, Rabe T. The efficacy and tolerability of norgestimate/ethinyl estradiol (250 mcg norgestimate/35 mcg ethinyl estradiol): results of an open, multicenter study of 59,701 women. Am J Obstet Gynecol 1992;166 (6 Pt 2):1963-1968.

Huber J, Foidart JM, Wuttke W, Merki-Feld GS, The HS, Gerkinger C, Schedllschrmdt I, Heithecker R. Efficacy and tolerability of a monophasic oral contraceptive containing ethinylestradiol and drospirenone. The European Journal of Contraception and Reproductive Health Care, 2000,5:1,25-34.

Object of research

Combined oral contraceptive

Subject of research

Menstrual blood loss

Study Features

Larsson et al.

In this open label study. 20 healthy young women using a low-dose combined oral contraceptive (ethinyl estridiol 30 mcg,desogestrel 0.15 mg) were investigated. Menstrual blood loss was measured prior to initiation of the COC.

Runnebaum et al.

The efficacy and tolerability of a combined oral contraceptive containing 250 mcg norgestimate and 35 mcg ethinyl estradiol was evaluated in an open-label study of 59,701 women. Tolerability was assessed for all women (n=42,022) who completed six contraceptive cycles.

Huber et al.

This was a randomized open-label, 13 cycle study performed at 80 European centers. Cycle control was assessed during 13 cycles of contraception. Of 2069 women in the study, 1657 were randomized to the drospirenone group and 412 to the desogestrel group.

The Evidence

Larsson et al.

The reduction in blood loss was most evident during the first two days of the menstrual cycle. The amount of the blood loss during the sixth cycle was significantly less for all women in the study. All women had normal hemoglobin concentrations and hematocrit.

Runnebaum et al.

After six cycles of use, reductions in duration of bleeding were noted and 32% of all women experienced a decrease in the intensity of their bleeding.

Huber et al.

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

Appraised by:

1. The International Center for Evidence Based Medicine, East Tennessee State University;
2. The Evidence Based Medicine Center, Department of Obstetrics, Gynecology and Reproductology, Ukraine National Medical Academy of Postgraduate Education;
3. Together for Health project.

Update by: 1 May 2011

Compared to a combined oral contraceptive use of a vaginal ring is associated with better cycle control

Conclusion

When cycle control is assessed in terms of length of withdrawal bleeding and break through bleeding/spotting those using a vaginal ring were found to have fewer days of withdrawal bleeding and less bleeding/spotting than COC users.

Clinical Question

Is there a difference between vaginal ring and COC users in terms of cycle control?

Search Terms: Vaginal ring contraceptives, cycle control

Citation

Milsom I, Lete I, Bjertnaes A, Rokstad K, Lindh I, Gruber CJ, et al. Effects on cycle control and bodyweight of the combined contraceptive ring, NuvaRing, versus an oral contraceptive containing 30 µg ethinyl estradiol and 3 mg drospirenone. Human Reproduction 2006;21:2304–11.

Oddsson K, Leifels-Fischer B, Wiel-Masson D, de Melo NR, Benedetto C, Verhoeven CHJ, et al. Superior cycle control with a contraceptive vaginal ring compared with an oral contraceptive containing 30 µg ethinylestradiol and 150 µg levonorgestrel: a randomized trial. Human Reproduction 2005;20:557–62.

Sabatini R, Cagiano R. Comparison profiles of cycle control, side effects and sexual satisfaction of three hormonal contraceptives. Contraception 2006;74:220–3.

Westhoff C, Osborne LM, Schafer JE, Morroni C. Bleeding patterns after immediate initiation of an oral compared with a vaginal hormonal contraceptive. Obstetrics & Gynecology 2005;106: 89–96.

Object of research: Vaginal ring contraceptive

Subject of research: Menstrual pattern control

Study Features

Milsom et al.

This trial was an open label, randomized, multi-center study designed to compare cycle control of a vaginal ring (n=499) with a COC (n=484) delivering 30 mcg ethinyl estradiol and 3 mg drospirenone.

Oddsson et al.

This trial was an open label, randomized, multi-center, Phase III study designed to compare cycle control of a vaginal ring (n=512) with a COC (n=518) delivering 30 mcg ethinyl estradiol and 150 mcg levonorgestrel.

Sabatini et al.

In this prospective randomized study, the effects of two combined oral contraceptives [20 mcg of ethinylestradiol (EE)/100 mcg of levonorgestrel and 15 mcg of EE/60 mcg of

gestodene] were compared with those of the vaginal ring (15 mcg of EE/120 mcg of etonogestrel). One-year data from 280 women were obtained. Menstrual patterns were evaluated by length of menstrual cycle, length of menstrual flow, early/late withdrawal bleeding, and irregular bleeding.

Westoff et al.

This was an open-label study of 201 women randomly assigned to either a combined oral contraceptive or a vaginal ring. The primary outcome was difference in mean bleeding/spotting days per woman according to treatment assignment. Secondary outcomes were differences in World Health Organization defined menstrual indices, differences in perceived bleeding changes, and differences in bleeding relative to the cycle day at the start of method.

The Evidence

Milsom et al.

The incidence of breakthrough bleeding/spotting was lower for the vaginal ring than with the COC in the majority of cycles. The mean number of withdrawal bleeding days tended to be lower for the vaginal ring group though not statistically so.

Oddsson et al.

For all cycles, the incidence of breakthrough bleeding and spotting was lower for the vaginal ring group than for those using the COC. Withdrawal bleeding occurred in the majority of both vaginal ring and COC users. There was no significant difference between the two groups in early withdrawal bleeding though the incidence of continued withdrawal bleeding was lower in the vaginal ring group for cycles 1 – 12.

Sabatini et al.

During the study, the mean length of menstrual cycles did not significantly change, whereas the mean length of menstrual flow showed a statistically significant decrease among COC 20 mcg EE users in comparison with the other groups. No amenorrhea or unintended pregnancy was recorded throughout this investigation. With respect to cycle control, early and/or late withdrawal bleeding occurred more frequently in COC 15 mcg EE users as compared with the COC 20 mcg EE and vaginal ring groups at cycle 3 ($p < 0.05$ and $p < 0.005$). However, the final data showed a general improvement in all cases. The incidence of irregular bleeding was significantly higher in the COC groups as compared with the vaginal ring group in all cycles at Cycle 3 and at Cycle 12.

Westoff et al.

The mean number of bleeding/spotting days in the 84-day reference period for all subjects was 17.0 days for ring users and 21.4 days for pill users or a mean difference 4.4 days. Using the World Health Organization menstrual indices, the ring users experienced fewer days or episodes of bleeding/spotting and shorter intervals. Significantly more ring users reported a decrease in duration of bleeding relative to the cycle day at study enrollment. This study shows advantageous bleeding patterns for subjects using the contraceptive vaginal ring.

Appraised by:

1. The International Center for Evidence Based Medicine, East Tennessee State University;
2. The Evidence Based Medicine Center, Department of Obstetrics, Gynecology and Reproductology, Ukraine National Medical Academy of Postgraduate Education;
3. Together for Health project.

Update by: 28 March 2012

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

Conclusion

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

Clinical Question

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

Search Terms

Oral contraceptives, premenstrual dysphoric disorder, premenstrual syndrome

Citation

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

Object of research

Combined oral contraceptive

Subject of research

Premenstrual Dysphoric Disorder; Premenstrual Syndrome

Study Features

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

The Evidence

- Two of the trials showed less severe premenstrual symptoms after 3 months of COCs with drospirenone (plus 20 mcg ethinyl estradiol) compared with women taking a placebo
- The women taking drospirenone containing COCs had greater decreases in impairment in productivity, social activities, and relationship compared to those taking a placebo

- One of the studies compared the effect of a COC containing drospirenone to another COC containing 150 mcg levonorgestrel (with the same 30 mcg dose of ethinyl estradiol). At cycle 6 the women taking the COC with drosperinone were less likely to have premenstrual symptoms than those taking the COC with levonorgestrel (OR= 0.31, CI 0.14 to 0.69)

Appraised by:

1. The International Center for Evidence Based Medicine, East Tennessee State University;
2. The Evidence Based Medicine Center, Department of Obstetrics, Gynecology and Reproductology, Ukraine National Medical Academy of Postgraduate Education;
3. Together for Health project.

Update by: 14 December 2011

The use of a combined oral contraceptive is associated with a significant decrease in the risk of an ectopic pregnancy

Conclusion

Based on the results of a review of studies involving ectopic pregnancy, it appears that the use of combined oral contraceptives has a protective effect against ectopic pregnancy.

Clinical Question

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

Search Terms

Oral contraceptives, ectopic pregnancy

Citation

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

Object of research: Combined oral contraceptive

Subject of research: Ectopic pregnancy rate

Study Features

The study was a meta-analysis of 12 case control studies and 1 cohort study though only 5 of the case control studies involved combined oral contraceptives. Cases in the case control studies were women with an ectopic pregnancy. Controls were non-pregnant or pregnant women actively on COCs or with past use. For the cohort study, women who used COCs (study women) were compared to a group of women who had not used them (controls).

The Evidence

- Among pregnant women, current users of COCs had a 0.19 odds ratio when compared to non-pregnant controls. This suggests that women users of COCs have less risk of an ectopic pregnancy than those who do not.
- The odds of past COC users having an ectopic pregnancy showed the risk for an ectopic pregnancy was no different from non-pregnant or pregnant non-users.

Appraised by:

1. The International Center for Evidence Based Medicine, East Tennessee State University;
2. The Evidence Based Medicine Center, Department of Obstetrics, Gynecology and Reproductology, Ukraine National Medical Academy of Postgraduate Education;
3. Together for Health project.

Update by: 30 April 2011

Among users of combined oral contraceptives, there appears to be a protective effect against endometrial cancer

Conclusion

Combined oral contraceptives may confer a long-term protection against endometrial cancer.

Clinical Question

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

Search Terms

Oral contraceptives, endometrial cancer

Citations

Vessey M and Painter R. Oral contraceptive use and cancer. Findings in a large cohort study, 1968 – 2004. British Journal of Cancer 2006;95:385-389.

Tao MH, Xu WH, Zheng W, Zhang Z, Gao Y, Ruan Z, Cheng JR, Gao J, Shu Xo. Oral contraceptive and IUD use and endometrial cancer: a population-based case-control study in Shanghai, China. Int J Cancer 2006:119,2142-2147.

Object of Research

Low-dose oral contraceptives

Subject of Research

Endometrial cancer

Study Features

Vessey and Painter:

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

Tao et al.

This is a population based case control study of Chinese women in Shanghai, China. The study involved 1,204 newly diagnosed endometrial cancer cases (between January 1997 and December 2003 inclusive). All women were between 30 and 69 years of age at the time of diagnosis. The 1,212 age matched health controls were randomly selected from the Shanghai Resident Registry which registers all permanent residents of urban Shanghai.

The Evidence

In the Vessey study, the rate ratio is calculated using never users as the reference group. The findings were that

- the rate ratio for endometrial cancer among COC users regardless of duration was 0.3 with a 95% confidence interval of (0.2 – 0.6).
- there was a strong association with duration of COC use; the rate ratios decreased from 0.6 with a 95% CI (0.3 – 1.1) for 48 and fewer months of use down to 0.1 and a 95% CI (0.0 – 0.4) for the 97 or more month users.

In the Tao et al. study, the findings are that

- the odds ratio for endometrial cancer was 0.75 with a 95% CI of (0.60 – 0.93).
- the odds ratio for women who used a COC for more than 72 months was 0.5 with a 95% CI (0.3 – 0.85).

Comment: Note that a rate ratio or relative risk is a comparison of the risk of endometrial cancer among COC users to never users. A rate ratio or relative risk less than one suggests a protective effect against endometrial cancer among those who used COCs. This protection continues well after stopping use of the COC. (Reference: Family Planning: A Global Handbook for Providers)

Appraised by:

1. The International Center for Evidence Based Medicine, East Tennessee State University;
2. The Evidence Based Medicine Center, Department of Obstetrics, Gynecology and Reproductology, Ukraine National Medical Academy of Postgraduate Education;
3. Together for Health project.

Update by: 7 December 2011

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

Conclusion

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

Clinical Question

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

Search Terms

Oral contraceptives, ovarian cancer

Citations

Vessey M and Painter R. Oral contraceptive use and cancer. Findings in a large cohort study, 1968 – 2004. British Journal of Cancer 2006;95:385-389.

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

Object of Research

Low-dose oral contraceptives

Subject of Research

Ovarian cancer

Study Features

Vessey and Painter

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

Collaborative Study

This is a reanalysis of worldwide epidemiologic studies on the relationship between ovarian cancer and the use of hormonal contraceptives. Each selected study (45 in number) was drawn from 21 different countries. Thirteen of the studies are prospective, 19 are case control with population controls, and 13 are case control with hospital controls. In total, the studies include individual data for 23,257 women with ovarian cancer. 7308 (31%) had used an oral contraceptive. For the controls there were 87,303 without ovarian cancer of whom 32,717 (37%) had used an oral contraceptive.

The Evidence

Vessey and Painter:

In this study, the rate ratio is calculated using never users as the reference group. The findings were that

- the rate ratio for ovarian cancer among COC users regardless of duration was 0.5 with a 95% confidence interval of (0.3 – 0.7).

Collaborative Study:

In this study, the findings are that

- in all of the studies, the relative risk was less than one suggesting a protective effect for ovarian cancer among users of combined oral contraceptives. The aggregate relative risk associated with current use of COCs was 0.73 with a corresponding 99% CI of (0.69 – 0.77).
- the reduction in risk persisted for more than 30 years after oral contraceptive use had ceased.
- the reduction in risk did not vary on use in the 1960s, 1970s, or 1980s though estrogen dosing in commonly used formulations changed over these decades.

Comment: Note that a rate ratio or relative risk is a comparison of the risk of ovarian cancer among COC users to never users. A rate ratio or relative risk less than one suggests a protective effect against ovarian cancer among those who used COCs. This protection continues well after stopping use of the COC. (Reference: Family Planning: A Global Handbook for Providers)

Appraised by:

1. The International Center for Evidence Based Medicine, East Tennessee State University;
2. The Evidence Based Medicine Center, Department of Obstetrics, Gynecology and Reproductology, Ukraine National Medical Academy of Postgraduate Education;
3. Together for Health project.

Update by: 6 December 2011

Among users of combined oral contraceptives, there may be an association with an increased risk of breast cancer though the finding is not consistent among all studies

Conclusion

There have been many studies, both retrospective and prospective, of the link between COC use and breast cancer, but there is no consistent, clear evidence that ever use of COCs increases the risk of breast cancer to users. The effect of family history of breast cancer is not yet fully understood.

Clinical Question

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

Search Terms: Oral contraceptives, breast cancer

Citations:

Hannaford PC, Selveraj S, Elliott AM, Angus V, Iversen L, Lee AJ. Cancer risk among users of oral contraceptives: cohort data from the Royal College of General Practitioner's oral contraceptive study. Brit Med J 2007;335:651.

Vessey M and Painter R. Oral contraceptive use and cancer. Findings in a large cohort study, 1968 – 2004. British Journal of Cancer 2006;95:385-389.

Marchbanks PA, McDonald, JA, Wilson HG, Folger SG, Madel MG, Daling JR, Berstein L, Malone KE, Ursin G, Strom BL, Norman SA, Weiss LK. Oral contraceptives and the risk of breast cancer. N Engl J Med 2002;346(26):2025-2032..

Kahlenborn C, Modugno F, Potter DM, Severs WB. Oral contraceptives use as a risk factor for premenopausal breast cancer: a meta-analysis. Mayo Clin Proc 2006; 81(10):1290-1302

Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormonal contraceptives: collaborative reanalysis of individual data on 53,297 women with breast cancer and 100,239 women without breast cancer from 54 epidemiological studies. Lancet 1996;347:1713-1727.

Object of Research: Low-dose oral contraceptives

Subject of Research: Breast cancer

Study Features

Hannaford et al.

This is a very large prospective cohort study conducted by the UK-based Royal College of General Practitioners. The study recruited 46,000 women from 1400 general practitioners throughout the UK in 1968-69. This report is based on all the health related data collected through late 2004. Half the women were using COCs at the time of recruitment and half were not. Cancer rates were standardized for age, smoking status, social class. Most (75%)

of the pills used in this study were combined oral contraceptives containing more than 50 mcg estrogen. Over time, the majority of women used preparations from more than one estrogen dose category. As a consequence, no analysis by dose formulation was done.

Vessey and Painter:

The Oxford-Family Planning Association contraceptive study is a cohort design begun in the early years (1968) of oral contraceptive use. From 1968 to 1974 women were recruited at 17 family planning clinics in England and Scotland. Women were aged 25 to 39 years, married, Caucasian, British, and a current COC user of at least five months. At aged 45, women were classified as never users, used for more than 8 years or more, or used for less than 8 years. Most (67%) of the pills used in this study were combined oral contraceptives containing more than 50 mcg estrogen. Given the small numbers of women using pills containing less estrogen, no analysis by dose formulation was done.

Marchbanks et al.

This is a population based case control study in five US centers of 4575 women between the ages of 35 and 64 years with breast cancer diagnosed between 1994 and 1998. Controls were comprised of 4,682 women without breast cancer drawn from the same geographic areas matched for age and race. Women who used pills containing more than 50 mcg of estrogen were classified as high dose users. All others using a combination pill were classified as low dose users.

Kahlenborn et al.

This is a review of case control studies of the association of combined oral contraceptive use with the occurrence of premenopausal breast cancer. Thirty-four studies were analyzed in this review and all were published after 1980 and included premenopausal women or those aged 50 or less. Of these 34 studies, 14 were hospital based, 19 were population based and 1 was a combination of the two. The studies were from several countries: Australia, Brazil, Canada, China, Costa Rica, Denmark, England, France, Italy, New Zealand, Singapore, Slovenia, South Africa, Sweden, Taiwan, the Netherlands, and the United States.

Collaborative Group:

This is a reanalysis of worldwide epidemiologic studies on the relationship between breast cancer and the use of hormonal contraceptives. Each selected study (52 in number) included at least 100 women with breast cancer and information on their use of hormonal contraception as well as their reproductive history. Ten of the studies were prospective, 26 were case control with population controls, and 16 were case control with hospital controls.

The Evidence

Hannaford et al.

Cancer rates were calculated for never versus ever COC users.

- The overall standardized rate of breast cancer per 100,000 women years for ever users was 121.53, and 124.20 for never users.
- This means that ever users of COCs had slightly lower risk of having breast cancer than never users of COCs (relative risk 0.98, 95% C.I. 0.87 – 1.10). This lower risk was not statistically significant.
- When analyzed for duration of COC use, the relative risk for having breast cancer was less than 1.0 for ever users compared to never users until the use was for 8 years or longer (relative risk 1.22, 95% C.I. 0.97 – 1.52)

Vessey and Painter:

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

- the overall rate ratio for COC users regardless of duration was 1.0 (95% C.I. 0.8 – 1.1).
- there was no apparent increased risk related to duration.
- there was no apparent increased risk related to time since last use.

Marchbanks et al.

In this study, there was a comparison of the incidence of COC use in those with breast cancer and those without. It was found that

- there was no increase in the risk of breast cancer for current or former users regardless of whether they had used a COC with more than 50 mcg estrogen or one with less.
- for low dose users, the odds ratio for current users was found to be 1.0 with a 95% confidence interval of (0.8 – 1.3).
- for low dose users, the odds ratio (OR) for past users was found to be 0.9 with a 95% confidence interval (CI) of (0.8 – 1.0).
- regardless of whether they had used a low dose oral contraceptive or one with more than 50 mcg estrogen, there was no apparent link between time of use and breast cancer.

Kahlenborn et al.

In this study, it was found that

- overall COC use was associated with an increase in breast cancer risk and an OR of 1.19 and a corresponding 95% CI of (1.09 – 1.29) but only six of the studies resulted in a p-value < 0.05.
- there was a considerable lack of homogeneity and the authors cite as reasons, the differences in the genetic pool of individual study populations as well as various cultural and environmental factors.

Collaborative Group:

It was found that

- in the aggregate, the relative risk associated with current use of COCs was 1.24 with a corresponding 95% CI of (1.15 – 1.33).
- the risk disappeared ten years after cessation of use.
- when the different pill doses were divided into high, median and low estrogen dose, there was an apparent inverse relationship between dose and risk.

Comment: The association between combined oral contraceptive use and breast cancer is not consistent. However, the WHO recommends that women who have certain preexisting conditions such as current breast cancer, benign liver tumors, liver cancer or active viral hepatitis should not use them.

Appraised by:

1. The International Center for Evidence Based Medicine, East Tennessee State University;
2. The Evidence Based Medicine Center, Department of Obstetrics, Gynecology and Reproductology, Ukraine National Medical Academy of Postgraduate Education;
3. Together for Health project.

Update by: 14 February 2012

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

Conclusion

The relative risk of cervical cancer is increased in current users of oral contraceptives and declines after cessation of use. However, ten years after cessation of use, the risk of cervical cancer is similar to that of never users.

Clinical Question

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

Search Terms

Oral contraceptives, cervical cancer

Citations

Hannaford PC, Selveraj S, Elliott AM, Angus V, Iversen L, Lee AJ. Cancer risk among users of oral contraceptives: cohort data from the Royal College of General Practitioner's oral contraceptive study. Brit Med J 2007;335:651.

Vessey M and Painter R. Oral contraceptive use and cancer. Findings in a large cohort study, 1968 – 2004. British Journal of Cancer 2006;95:385-389.

Smith SS, Green J, Berrington de Gonzalez A, Appleby P, Peto J, Plummer M, Franceschi S, Beral V. Cervical cancer and use of hormonal contraceptives: a systematic review. Lancet 2003;361:1159-67.

International Collaboration of Epidemiological Studies of Cervical Cancer. Cervical cancer and hormonal contraceptives: collaborative reanalysis of individual data for 16,573 women with cancer and 35,509 women without cervical cancer from 24 epidemiological studies. Lancet 2007; 370:1609-1621.

Object of Research

Low-dose oral contraceptives

Subject of Research

Cervical cancer

Study Features

Hannaford et al.

This is a very large prospective cohort study conducted by the UK-based Royal College of General Practitioners. The study recruited 46,000 women from 1400 general practitioners throughout the UK in 1968-69. This report is based on all the health related data collected through late 2004. Half the women were using COCs at the time of recruitment and half were not. Cancer rates were standardized for age, smoking status, social class. Most (75%)

of the pills used in this study were combined oral contraceptives containing more than 50 mcg estrogen. Over time, the majority of women used preparations from more than one estrogen dose category. As a consequence, no analysis by dose formulation was done.

Vessey and Painter:

The Oxford-Family Planning Association contraceptive study is a cohort design begun in the early years (1968) of oral contraceptive use. From 1968 to 1974 women were recruited at 17 family planning clinics in England and Scotland. Women were aged 25 to 39 years, married, Caucasian, British, and a current OC user of at least five months. At aged 45, women were classified as never users, used for more than 8 years or more, or used for less than 8 years. Most (67%) of the pills used in this study were combined oral contraceptives containing more than 50 mcg estrogen. Given the small numbers of women using pills containing less estrogen, no analysis by dose formulation was done.

Smith et al.

This is a systematic review involving 28 studies of cervical cancer involving 12,531 women with cervical cancer. There were four cohort studies and 24 case control studies including those with population and/or hospital controls.

International Collaboration:

This is a reanalysis of 24 epidemiological studies of cervical cancer. The study includes 16,573 women with cancer and 35,509 women without cervical cancer. The reanalysis included adjustments for age, number of sexual partners, age at first intercourse, and smoking.

The Evidence

Hannaford et al.

Cancer rates were calculated for never versus ever COC users.

- The overall adjusted rates of cervical cancer per 100,000 women years for ever users was 14.9, and 11.2 for never users.
- This means that ever users of COCs had a numerically, but not statistically significant higher odds of having cervical cancer than never users of COCs (relative risk 1.33, 95% C.I. 0.92 – 1.94)
- When analyzed for duration of COC use, the relative risk for having cervical cancer was statistically significant only for those in which use was 8 years or longer (relative risk 2.73, 95% C.I. 1.61 – 4.61)

Vessey and Painter:

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

- the rate ratio for cervical cancer among COC users regardless of duration was 4.2 with a 95% confidence interval of (1.8 – 12.0).
- there was a strong positive association with duration of COC use; the rate ratios increased from 2.9 with a 95% CI (0.9 – 9.9) for 48 and fewer months of use up to 6.1 and a 95% CI (2.5 – 17.9) for the 97 or more month users.

Smith et al.

The findings were that

- the relative risk for cervical cancer was 2.2 with a 95% CI of (1.9 – 2.4).

- the relative risk increased with increasing use with 1.1 (95% CI: 1.1 – 1.2) for those using COCs less than five years, 1.6 (95% CI: 1.4 – 1,7) for those using COCs 5 to 9 years and 2.2 (95% CI: 1.9 -2.4) for those using COCs 10 years or longer.

International Collaboration:

Among current users of COCs, the risk of invasive cervical cancer increased with increasing duration of use. The risk declined after use ceased and by ten or more years the risk was similar to that of never users.

- the relative risk for five or more years of use was 1.9 with a 95% CI of (1.69 - 2.13).
- a similar pattern was seen for women who tested positive for high risk human papillomavirus.

Comment: In other studies, the human papillomavirus (HPV) has been implicated as the primary causative factor in cervical cancer. However, it is likely that COC use acts as a co-factor. Note, however that for women using the COC for less than five years, there does not appear to be an increased risk. Weighing the various risks and benefits, the World Health Organization does not recommend any changes in oral contraceptive use or practice.

Appraised by:

1. The International Center for Evidence Based Medicine, East Tennessee State University;
2. The Evidence Based Medicine Center, Department of Obstetrics, Gynecology and Reproductology, Ukraine National Medical Academy of Postgraduate Education;
3. Together for Health project.

Update by: 14 February 2012

Users of combined oral contraceptives appear to have a reduced risk of hospitalization due to benign breast disease

Conclusion

Combined oral contraceptives may reduce the risk of benign breast disease, as measured by the hospitalization rate for this condition. For those diagnosed with fibroadenoma and chronic cystic disease, there is an apparent protective effect present for women using OCs containing >50 mcg, 50 mcg and <50 mcg estrogen.

Clinical Question

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

Search Terms

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

Citations

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

Object of Research

Low-dose oral contraceptives

Subject of Research

Hospitalization due to benign breast disease based on one of three diagnoses; fibroadenoma, confirmed cystic disease, and breast lumps.

Study Features

Vessey and Yeates:

The Oxford-Family Planning Association contraceptive study is a cohort design begun in the early years (1968) of oral contraceptive use. From 1968 to 1974 women were recruited at 17 family planning clinics in England and Scotland. Women were aged 25 to 39 years, married, Caucasian, British, and a current COC user of at least five months. At aged 45, women were classified as never users, used for more than 8 years or more, or used for less than 8 years. The study includes 17,032 women using different methods of contraception. The analysis in this study included 185 women with histologically confirmed fibroadenoma, 1361 with histologically confirmed cystic disease, and 650 with breast lumps not subjected to biopsy. Women with a history of benign breast disease or breast cancer on entry into the study were excluded.

The Evidence

Because benign breast disease is a variable and imprecise diagnosis, in this study, the relative risk of hospitalization for benign breast disease was calculated separately for fibroadenoma, confirmed cystic disease, and breast lumps. The findings were that:

- The relative risk for hospitalization due to fibroadenoma was less than 1 for all durations of COC use; that is, hospital referral rates declined with increasing duration of use of a COC.
- The relative risk for confirmed cystic disease decreased with increasing duration of COC use. The relative risk was less than 1 in all time intervals (2 years or less up to more than 10 years), but was significantly less than 1 only for durations of more than six years. As with fibroadenoma, hospital referral rates for confirmed cystic disease declined with increasing duration of use of a COC.
- For breast lumps, the relative risk for COC users was not significantly increased relative to never users at any time interval, with the exception of those using for more than eight years.
- The apparent protective effect was for COCs of > 50 mcg, 50 mcg, and < 50 mcg of estrogen.
- For progestogen only pills, there is no apparent protective effect though there is no increased risk either.

Appraised by:

1. The International Center for Evidence Based Medicine, East Tennessee State University;
2. The Evidence Based Medicine Center, Department of Obstetrics, Gynecology and Reproductology, Ukraine National Medical Academy of Postgraduate Education;
3. Together for Health project.

Update by: 10 December 2011

There does not appear to be any association between long-term use of combination oral contraceptives and the emergence of ovarian cysts in women of reproductive age

Conclusion

Long-term COC use does not provide any apparent risk or benefit in the treatment of functional ovarian cysts in women of reproductive age.

Clinical Question

Is there any association between long-term use of combination oral contraceptives and emergence of ovarian cysts in women of reproductive age?

Search Terms

Combination oral contraceptives (COCs), emergence of ovarian cysts.

Citation

Holt VL, Cushing-Haugen KL, and Daling JR. Oral Contraceptives, Tubal Sterilization, and Functional Ovarian Cyst Risk. Obset Gynec 2003;102(2): 252-258.

Grimes DA, Jones LB, Lopez LM, Schulz KF. Oral contraceptives for functional ovarian cysts. *Cochrane Database of Systematic Review*s 2009, Issue 2. Art. No.: CD006134. DOI: 10.1002/14651858.CD006134.pub3.

Object of Research

Combined oral contraceptives

Subject of Research

Emergence of ovarian cysts in the course of long-term COC use (detection by ultrasound scan).

Study Features

Holt et al.

- Case control study conducted in the USA with women between 18-39 whom ultrasound scan revealed a functional ovarian cyst of 2 cm and more in diameter.
- 392 women were using a COC (monophasic as well as multiphasic ones) with a control group comprised of 623 women who were using other, non-hormonal contraception methods including sterilization.

Grimes et al.

This review included seven randomized controlled studies from four countries (Turkey, Israel, United States, Thailand). The studies included a total of 500 women treated for functional ovarian cysts.

The Evidence

Holt et al.

- The overall odds ratio (OR) was 0.72 [95% C.I. 1.05 - 2.75] for current COC use compared with nonsurgical nonhormonal or no contraception.
- The risk of ovarian cyst emergence was found to be lower in women who were using monophasic COCs containing 35 mcg ethinyl estradiol (OR 0.69; 95% C.I. 0.44 - 1.10) compared to those using monophasic COCs containing less than 35 mcg ethinyl estradiol (OR 0.79; 95% C.I. 0.43, 1.47) or multiphasic COCs (OR 0.76; 95% C.I. 0.49, 1.19).
- Compared to COC use, other contraception methods (e.g., sterilization) were associated with a higher risk of ovarian cyst emergence with an odds ratio of 1.70; 95% C.I. 1.05, 2.75).

Grimes et al.

- Treatment with combined oral contraceptives did not hasten resolution of functional ovarian cysts in any trial whether or not the cysts occurred spontaneously or developed after ovulation induction.
- Most cysts resolved without treatment within a few cycles; persistent cysts tended to be pathological (e.g., endometrioma or para-ovarian cyst) and not physiological.

Comment: Despite the results from the Holt case control study, based on prospective randomized studies, it appears that low-dose COC use has little or no effect on functional ovarian cyst likelihood.

Appraised by:

1. The International Center for Evidence Based Medicine, East Tennessee State University;
2. The Evidence Based Medicine Center, Department of Obstetrics, Gynecology and Reproductology, Ukraine National Medical Academy of Postgraduate Education;
3. Together for Health project.

Update by: 04 January 2012

There is no increased risk of benign liver tumors among users of low dose combined oral contraceptives

Conclusion

Two large case control studies included data from 15 German liver centers for women 15-64 years. The odds ratio for hepato-cellular adenoma and focal nodular hyperplasia among low-dose OC users was low (risk estimates were 0.4 and 0.69 respectively). The results were the same no matter how long COC use was.

Clinical Question

Are women who are taking low dose oral contraceptives at an increased risk for benign liver tumors (hepato-cellular adenoma or focal nodular hyperplasia)?

Search Terms

Oral contraceptives, benign liver tumors

Citations

Heinemann LAJ, Weimann A, Gerken G, et al. Modern oral contraceptive use and benign liver tumors: the German Benign Liver Tumor Case-Control Study. European Journal of Contraception and Reproductive Health Care 1998;3:194-200.

Object of Research

Low-dose oral contraceptives

Subject of Research

Benign liver tumors

Study Features

Heinemann

The German Benign Liver Tumor Case-Control Study is really a set of two case-control studies from a Collaborative study of 15 German liver centers. The study collected data from these centers from 1990-1997 and found 51 cases of hepato-cellular adenoma and 143 cases of focal nodular hyperplasia. The data from these women was compared to 240 age-matched women who had recent abdominal imaging studies.

The Evidence

The odds ratios were calculated using never users as the reference group. Analyses were divided between high dose (≥50mcg estrogen containing COCs) and low dose pill users (<50 mcg). The findings for the low dose users were:

- The odds ratio for hepato-cellular adenoma among ever COC users was 1.25 with a 95% confidence interval of 0.37 – 4.22. This means that there was no significant increased risk of hepato-cellular adenoma among women using an oral contraceptive.

- The odds ratio for focal nodular hyperplasia among ever COC users was 1,96 with a 95% confidence interval of 0.85 – 4.57. This means that there was no significant increased risk of focal nodular hyperplasia among women using an oral contraceptive.
- There were no significant increased trends of risk for either tumor for long-term users (10+years)

Comment: The researchers found a modest increase in risk for both benign tumors among women who took high dose COCs (≥50mcg estrogen containing COCs), but this information is not relevant today.

Appraised by:

1. The International Center for Evidence Based Medicine, East Tennessee State University;
2. The Evidence Based Medicine Center, Department of Obstetrics, Gynecology and Reproductology, Ukraine National Medical Academy of Postgraduate Education;
3. Together for Health project.

Update by: 4 January 2012

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

Conclusion

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

Clinical Question

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

Search Terms

Low-dose oral contraceptives, headache.

Citations

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

Object of Research

Combined oral contraceptives.

Subject of Research

Headache as reported by patient.

Study Features

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

Out of 121 identified articles seven were included: 4 prospective placebo controlled trials, 2 studies with a non-hormonal method control, and 1 study with a non-contraceptive control. The sample sizes in these studies ranged from 40 to 3179 women and the total number of patients was 5026. All but 1 study were conducted and published in the 1960s or 1970s and studied COCs with higher estrogen contents than COCs that are now in common use.

The Evidence

Study	Results of Study
Cullberg	No significant difference between COC and placebo No significant differences among preparations with different progestins
Goldzieher	Complaints of headache significantly higher in COC group only for first cycle
Ryan	Migraine worse in 70% of COC users, but improved in 30% over two month duration of study
Coney	No significant difference between COC and placebo group over 6 month duration of study
Herzberg[1]	No significant difference in headache complaints between COC users and control group over 11 month study.
Herzberg[2]	Slightly more women in the COC group reported moderate to severe headaches than in the IUD group at 3 of 4 follow-up visits.
Diddle	No significant difference in headache complaints between COC users and untreated control subjects

Other findings are:

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

Appraised by:

1. The International Center for Evidence Based Medicine, East Tennessee State University;
2. The Evidence Based Medicine Center, Department of Obstetrics, Gynecology and Reproductology, Ukraine National Medical Academy of Postgraduate Education;
3. Together for Health project.

Update by: 5 January 2012

For oral contraceptives with 20 mcg ethinyl estradiol, there is no apparent association between use and an increased risk of a myocardial infarction

Conclusion

The risk of myocardial infarction (MI) with current or past users of the lowest dose (20 mcg estrogen) was not increased. For low dose oral contraceptives (30-35 mcg estrogen), there appears to be a slightly higher risk.

Clinical Question

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

Search Terms

Low-dose oral contraceptives, myocardial infarction

Citation

Khader YS, Rice J, John L, and Abueita O. Oral contraceptive use and the risk of myocardial infarction: a meta-analysis. Contraception 2003;68(1):11-17.

Object of Research

Low-dose oral contraceptives.

Subject of Research

Myocardial infarction (fatal or nonfatal)

Study Features

This is a review of four cohort studies (7,076 women) and 19 case control studies (4,599 cases and 18,838 controls) were included. The studies were conducted in the USA, Europe, Asia, and Africa. Studies were available for inclusion if:

- there was an adequate definition of a myocardial infarction (most of the studies used symptoms, cardiac enzymes and electrocardiogram),
- women were 15 to 55 years of age,
- the study contained at least 20 MI cases, and
- comparison groups were controlled for age.

The Evidence

- For current users of COCs, there was a statistically significant increased risk of a myocardial infarction in 7 (54%) of the 13 studies. Combining these studies yielded an odds ratio of 2.5.

- For past users of COCs, there was no statistically significant increased risk of a myocardial infarction (odds ratio=1.15). No individual study (n=12) demonstrated an elevated risk for past users of COCs.
- For women under 35 years of age and those 35 years of age and older, the odds ratio is 2.69 and 2.15, respectively suggesting a elevated risk of MI among COC users.
- When the combined effect of COC use and another cardiovascular risk factor (e.g., smoking, hypertension) were combined, there was an even greater risk of myocardial infarction
- For users of COCs containing 20 mcg of ethinyl estradiol, there was no elevated risk of a myocardial infarction.

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

Appraised by:

1. The International Center for Evidence Based Medicine, East Tennessee State University;
2. The Evidence Based Medicine Center, Department of Obstetrics, Gynecology and Reproductology, Ukraine National Medical Academy of Postgraduate Education;
3. Together for Health project.

Updates by: 12 November 2011

Among users of low dose combined oral contraceptives, there is a small, but increased risk of ischemic or hemorrhagic stroke

Conclusion

Women who use a low dose oral contraceptive are, in the aggregate, at a slightly increased risk for stroke. Women who have risk factors for stroke and who use an oral contraceptive should be monitored. However, since stroke is rare in this age group (approximately 1 in 12,000), the absolute increase in risk is small.

Clinical Question

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

Search Terms

Low-dose oral contraceptives, ischemic and hemorrhagic stroke.

Citations

Heinemann LAJ, Lewis MA, Thorogood M, Spitzer WO, Geuggenmoos-Holzman I, Brup-pacher R. Case control study of oral contraceptives and risk of thromboembolic stroke : results from international study on oral contraceptives and health of young women. Brit Med Journal 1997 ;315 :1502-1504 (6 December).

Lidegaard O, Kreiner S. Contraceptives and cerebral thrombosis: a five year national case Case-control study. Contraception 2002;65(3):197-205.

Schwartz SM, Petitti DB, Siscovick DS, Longstreth WT, Sidney S, Raghunathan TE, Quesen-berry CP, Kelaghan J. Stroke and low-dose oral contraceptives in young women: a pooled analysis of two US Studies. Stroke 1998;29:2277-2284.

Siritho S, Thrift AG, McNeill JJ, You RX, Davis SM, Donnan GA; Melbourne Risk Factor Study (MERFS) Group. Risk of ischemic stroke among users of the oral Contraceptive pill: the Melbourne Risk Factor (MERFS) Group. Stroke 2003;34(7):1575-1580.

Jick SS, Myers MW, Jick H. Risk of idiopathic cerebral haemorrhage in women on oral con-traceptives with differing progestagen components. Lancet 1999;354:302-303.

Object of Research

Low-dose oral contraceptives

Subject of Research

Ischemic and hemorrhagic stroke.

Study Features

Heinemann et al.

16 centres in the United Kingdom, Germany, France, Switzerland, and Austria were includ-ed in this study of 220 women aged 16-44 who had an incident ischaemic stroke. Controls

were 775 women unaffected by stroke who were matched with the corresponding case by age (within 5 years) and at the same hospital or community setting.

Lidegaard and Kreiner:

This is a national case control study of Danish women between the ages of 15 and 44 years suffering from a first cerebral ischemic attack during the years 1994 through 1998. Cases (n=626) were drawn from the Danish National Patient Register and controls (n=4054) were drawn from the Central Person Register. Cases and controls were matched according to age as well as the time of year in which they were identified.

Schwartz et al.

Two US population based, case-control studies were combined in this analysis. Data from 175 ischemic stroke cases and 1191 controls were included in this analysis of women 18 to 44 years of age. In one study (California), each case had three controls matched for age and facility of usual care. In the other study (Washington state), women were matched only on age.

Siritho et al.

This is a case control study which included 234 cases and equal number of controls from four major city hospitals in Melbourne, Australia. All women were between the ages of 15 and 55 years of age. Cases were matched with their controls by age and geography.

Jick et al.

This US study was based on the General Practice Research Database which included clinical records from approximately 430 practices of otherwise healthy women below the age of 50. The purpose of the study was to compare the risk of idiopathic cerebral hemorrhage in women who had received oral contraceptives containing either levonorgestrel, desogestrel, or gestodene combined with less than 35 mcg ethinyl estradiol.

The Evidence

Heinemann et al.

Adjusted odds ratios (95% confidence intervals) for ischaemic stroke were 4.4 (2.0-9.9), 3.4 (2.1-5.5) and 3.9 (2.3-6.6) for current use of first, second and third generation oral contraceptives, respectively. The risk estimates were lower if blood pressure was checked before prescription.

Lidegaard and Kreiner:

Comparing the incidence of stroke in current users to non-users for COCs, it was found that the risk of cerebral thrombosis (including thrombotic stroke and transitory ischemic attacks) decreased significantly with decreasing estrogen dose. The results were

- for COCs with 50 mcg of estrogen the odds ratio was found to be 4.5 with a 95% confidence interval of (2.6 – 7.7),
- for COCs with 30 – 40 mcg of estrogen the odds ratio was found to be 1.6 with a 95% confidence interval of (1.3 – 2.0),
- for COCs with 20 mcg of estrogen the odds ratio was found to be 1.7 with a 95% confidence interval of (1.0 – 3.1), and
- for COCs with no estrogen (progestin only pill) the odds ratio was found to be 1.0 with a 95% confidence interval of (0.3 – 3.0).

Schwartz et al.

The odds ratio was calculated for the pooled data and adjusted for stroke risk factors. The results were

- there was no increase in the risk of ischemic stroke for current low dose oral contraceptive users compared with women who had never used an oral contraceptive. The odds ratio (OR) was found to be 0.66 with a 95% confidence interval (CI) of (0.29 – 1.47).
- there was no increase in the risk of hemorrhagic stroke for current low dose oral contraceptive users compared with women who had never used an oral contraceptive. The odds ratio (OR) was found to be 0.95 with a 95% confidence interval (CI) of (0.46 – 1.93).
- that for either stroke type, the odds ratios for current low dose oral contraceptive users were not elevated for women who were 35 years of age and older, cigarette smokers, obese, or not receiving medical therapy for hypertension.

Siritho et al.

Comparing the incidence of stroke in current users to non-current users for COCs with < 50 mcg estrogen, it was found that

- there was no increase in the risk of stroke for current users. The odds ratio (OR) was found to be 1.76 with a 95% confidence interval (CI) of (0.86 – 3.61) and a corresponding p-value of 0.124.
- that factors leading to an increased risk of ischemic stroke were previous history of hypertension (OR=2.18; 95% CI: 1.22 – 3.91), transient ischemic attack (OR=8.17; 95% CI: 1.69 – 39.6), previous myocardial infarction (OR=5.64; 95% CI: 1.04 – 30.61), diabetes mellitus (OR=5.42; 95% CI: 1.42 – 20.75), family history of stroke (OR=2.22; 95% CI: 1.12 – 4.43) and smoking more than 20 cigarettes per day (OR=3.68; 95% CI: 1.22 – 11.09).

Jick et al.

No increased risk of stroke among users of third generation oral contraceptives containing desogestrel or gestodene. The age adjusted risks relative to the levonorgestrel group was 2.3 (0.7-7.4) and 1.4 (95% CI: 0.4-4.8) for the desogestrel and gestodene groups, respectively. Note that since each set of confidence intervals contain 1, it is assumed that there is no difference among the groups.

Appraised by:

1. The International Center for Evidence Based Medicine, East Tennessee State University;
2. The Evidence Based Medicine Center, Department of Obstetrics, Gynecology and Reproductology, Ukraine National Medical Academy of Postgraduate Education;
3. Together for Health project.

Update by: 7 December 2011

There is a very small increased risk for venous thromboembolism from taking oral contraceptives

Conclusion

There is an increased risk in the incidence of venous thromboembolism (VTE) among women who use COCs. However, the absolute risk is very small. In addition, the risk of VTE decreases with increasing duration and decreasing estrogen dose.

Clinical Question

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

Search Terms

Low-dose oral contraceptives, venous thromboembolism

Citation

Gomes MP, Deitcher SR. Risk of venous thromboembolic disease associated with hormonal contraceptives and hormone replacement therapy: a clinical review. Arch Intern Med 2004;164:1965-76.

Dinger JC, Heinemann LJ, Kuhl-Habich D. The safety of drospirenone-containing oral contraceptive: final results from the European Active Surveillance study on oral contraceptives based on 142,475 women-years of observation. Contraception 2007;75:344-354.

van Hylckama Vlieg A, Helmerhorst FM, Vandenbroucke JP, Doggen CJM, Rosendaal FR. The venous thrombotic risk of oral contraceptives, effects of oestrogen dose and progestogen type. Results of the MEGA case-control study. BMJ 2009;339:b2921.

Lidegaard O, Lokkegaard E, Svendsen AL, Agger C. Hormonal contraception and risk of venous thromboembolism: national follow-up study. BMJ 2009;339:b2890.

Seeger JD, Loughlin J, Eng PM, Clifford CR, Cutone J, Walker AM. Risk of thromboembolism in women taking ethynylestradiol/drospirenone and other oral contraceptives. Am J Obstet Gyn 2007:110(3), 587-593.

Object of Research

Low-dose oral contraceptives.

Subject of Research

Venous thromboembolism

Study Features

Gomes et al.

This was a review of 46 available published studies of a 35 year span, and includes one randomized control trial, 3 cohort studies, and 42 case control studies. The study quality varied in that only 1/3 of the studies had any objectively confirmed diagnosis of VTE. Ages in these studies ranged from 15 to less than 50 years.

Dinger et al.

The study was a multinational cohort study of 58,674 women who were new users of drospirenone, levonorgestrel and other progestin-containing COCs. This study was designed to compare risks of adverse cardiovascular and other events associated with the use of drospirenone (DRSP)-containing oral contraceptives and other COCs. Proportions of women in the age groups of under 20, 20–29, 30–39 and over 40 years, namely, 30%, 42%, 21% and 7%, respectively, reflected the typical age profile of COC users in Europe.

van Hylckama Vlieg et al.

This was a large case control study in the Netherlands that analyzed the data of 1524 patients with VTE and 1760 controls. The ages in the COC use group and the controls were similar (mean=37 years of age).

Lidegaard et al.

This was a national cohort study using four Danish registries for prescriptions. Danish women aged 15-49 years between January 1, 1995 and December 31, 2005 were included if they were not pregnant and had no previous history of cancer or cardiovascular diseases. The analysis included 3.4 million women years of use among current users of combined oral contraceptives, 2.3 million women years of former users, and 4.8 million women years of never users.

Seeger et al.

In this study involving a US health insurer database, 22,429 ethinylestradiol/drospirenone initiators and 44,858 other combined oral contraceptive initiators were identified. The study was designed to compare risks of adverse cardiovascular and other events associated with the use of drospirenone (DRSP)-containing oral contraceptives with other COCs. The average age of the women in this study was 28 years and they were followed for an average of 7.6 months.

The Evidence

Gomes et al.

The overall findings consistently indicated a 2-to 6-fold increased risk of VTEs among all COC users compared with nonusers.

- There is a small, increased VTE risk with the use of desogestrel- or gestodene-containing COCs, compared with COCs containing levonorgestrel. Note that the relative risk increase appears large, but the absolute increase in risk is very small, and translates to between 1 to 3 cases per 10,000 woman years.
- The risk of VTE is higher in the first six months to one year of COC use.
- Combination OCs containing 35 µg or less of ethinyl estradiol and a second-generation progestin are associated with the lowest risk of VTEs.
- The true risk associated with COCs containing less than 20 µg of ethinyl estradiol is unknown.
- The incidence rates of VTEs are higher in COC users aged 40 to 49 years as compared to younger users.
- As the absolute risk associated with the use of third generation COCs is not high, the benefits of using third-generation COCs far outweigh the risk.

Dinger et al.

Serious adverse events were rare.

- Rate ratios comparing the incidence of VTE in COCs containing drospirenone to other COCs was 1.
- The VTE incidence for COC users was highest during the first 3 months of use (14.3 VTE/10,000 WY) but subsequently declined with continued use (7.3, 6.3 and 4.5 VTE/10,000 WY) in the second, third and fourth/fifth year of use, respectively).
- Review of the no-use cohort in this study showed that nearly half (45.5%) of all SAEs are linked to pregnancy, delivery and puerperium. As a result, total SAE incidence for no use is considerably higher than that for COC use (rate ratio, approximately 1.5).

van Hylckama Vlieg et al.

- The relative risk of having VTE was increased among COC users (overall odds ratio 5.0 95%CI: 4.2-5.8).
- Among COC users, both the relative risk and absolute risk for VTE increased with age.
- Compared with non-users of COCs, use of COCs containing
  - levonorgestrel increased almost 4 fold (95% CI: 2.9-4.6)
  - gestodene increased 5.6 fold (95% CI: 3.7-8.4)
  - cyprotenene acetate increased 6.8 fold (95% CI: 4.7-10.0)
  - desogestrel increased 7.3 fold (95% CI: 5.3-10.0)
  - drospirenone increased 6.3 fold (95% CI: 2.9-13.6)

Note: Actual rates of VTE were very rare for all the groups of women studied.

Lidegaard et al.

During the period of observation, 4,213 venous thrombotic events were observed with 2,045 of these among current users of combined oral contraceptives. Findings were as follows:

- The absolute risk of venous thromboembolism in non-users was 3.01 per 10,000 women compared to 6.29 in current users.
- The risk of venous thrombosis in current users of combined oral contraceptives decreases with duration of use and decreasing estrogen dose.
- Among COC users, the incidence of VTE decreased with length of use.
- For the same dose of estrogen and the same duration of use, combined oral contraceptives with desogestrel, gestodene, or drospirenone were associated with a higher risk of venous thrombosis than those among users of one containing levonorgestrel.
- Among former users of combined oral contraceptives, there was no increased risk of venous thromboembolism when compared to never users.

Note that based on the data from this study, among current users of COCs, one additional case of VTE would be observed in every 33,000 women-years of use.

Seeger et al.

Using claims data involving oral contraceptive initiators from a US health care insurer, 18 cases of thromboembolism among ethinylestradiol/drospirenone and 39 in the comparators were found. The rate ratio was 0.9 (95% confidence interval: 0.5-1.6) suggesting there was no difference in the risk of thromboembolism among oral contraceptives.

Comments

- Other studies have found that among users of low dose COCs, the risk of cardiovascular death exceeds the risk of death due to pregnancy only among women who smoke 25 or more cigarettes a day and who are over 30 years of age. In any event, relative to non-users, the absolute increase in risk among COC users is very small.
- Note that VTE among women is not linked to occurrence of varicose veins.

Appraised by:

1. The International Center for Evidence Based Medicine, East Tennessee State University;
2. The Evidence Based Medicine Center, Department of Obstetrics, Gynecology and Reproductology, Ukraine National Medical Academy of Postgraduate Education;
3. Together for Health project.

Update by: 4 January 2012

There is no association between use of a combined oral contraceptive and risk of depression

Conclusion

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

Clinical Question

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

Search Terms

Combined oral contraceptives, depression.

Citation

Duke JM, Sibbritt DW, Young AF. Is there an association between the use of oral contraception and depressive symptoms in young Australian women?
Contraception 75 (2007);27– 31

Object of Research

Combined oral contraceptive

Subject of Research

Depression based on the 10 item Center for Epidemiologic Studies Depression scale (CESD-10)

Study Features

This is a large population-based longitudinal study, which is a part of the Australian Longitudinal Study on Women's Health (ALSWH). This review includes results from one study of young women.

This study was conducted in 2003 and included 9,081 women aged between 25 and 30 years. In each study, women were classified as depressed if their CESD-10 score was >10 and as not depressed if their score was <10. They were also asked if they were currently using COCs and, if so, their reason for using COCs as well as how many years in total they had ever taken COCs. When estimating the results adjustment for stressful life events and perceived stress score, body mass index, back pain, allergy, painful periods, smoking, alcohol, illicit drugs and coexisting medical conditions was done.

The Evidence

- Almost one quarter (23.3%) of COC users reported depression as compared to 30.3% of the non-users. The OR adjusted for other risk factors is 1.05 (95% CI=0.90–1.21).

- Of the women who used COCs 39% used it for reasons other than contraception. These women were significantly more likely to report depressive symptoms (30.2%) than women who used COCs for contraception (18.9%). The adjusted OR is 1.32 (95% CI=1.07–1.62).
- There is a statistically significant inverse relationship between the number of years of using COCs and prevalence of depressive symptoms, with the percentage of women reporting depressive symptoms declining as the number of years of COC use increases (p=.009). However, based on these data there may be a plateau effect after 5 years.

Appraised by:

1. The International Center for Evidence Based Medicine, East Tennessee State University;
2. The Evidence Based Medicine Center, Department of Obstetrics, Gynecology and Reproductology, Ukraine National Medical Academy of Postgraduate Education;
3. Together for Health project.

Update by: 7 December 2011

The use of low dose combined oral contraceptives is not associated with an increase in the risk of recurrent vulvovaginal candidiasis in the absence of other risk factors

Conclusion

Use of low dose combined oral contraceptives (COCs) alone does not increase the risk of onset of sporadic vulvovaginal candidiasis. However, they may promote a relapse especially in the presence of other risk factors such as antibiotic therapy, pregnancy and the use of synthetic underwear.

Clinical Question

Is there association between use of low dose combination oral contraceptives and vulvovaginal candidiasis?

Search Terms

Vulvovaginal candidiasis, combination oral contraceptives, oral contraceptives

Citation

Corsello S, Spinillo A, and Penna C. An epidemiological survey of vulvovaginal candidiasis in Italy. European Journal of Obstetrics and Gynaecology and Reproductive Biology 110 (2003)66-72.

Spinillo S, Cappuzzo E, Nicola S, Baltaro F, Ferrari A, and Monaco A. The Impact of Oral Contraception on Vulvovaginal Candidiasis. Contraception 1995;51:293-297.

Object of Research

Combination oral contraceptives (COCs)

Subject of Research

Vulvovaginal candidiasis (VVC)

Study Features

Corsello:

This is a prospective study of 924 women with confirmed vulvovaginal candidiasis conducted at eight Italian clinics between October 1999 and March 2001. 76 women were found to have four or more episodes. The control group was of 463 women with no recent history of vulvovaginal candidiasis.

Spinillo:

This is a case control study of 153 female patients with recurrent vulvovaginal candidiasis seen at the Vaginitis Clinic at the Department of Obstetrics and Gynecology of Pavia University from January 1989 to September 1994. Examination revealed the presence of one or another type of Candida along with other infections. Two control groups of twice the size of the case study group were selected. The first control was of women who were asympto-

matic and vaginal culture negative. The second control was of women with a non-recurrent vulvovaginal candidiasis and no history of vaginitis in the year preceding their visit.

The Evidence

Corsello:

In the vulvovaginal candidiasis group, 20.8 percent of the women used a combined oral contraceptive as compared to 19.9 percent in the control group with no recent history of vulvovaginal candidiasis. For those with four or more episodes, 22.4 percent used an oral contraceptive.

Spinillo:

Cases were more likely than their controls to use oral contraceptives with an odds ratio of 2.15 [95% CI: 1.34 - 3.45] relative to the asymptomatic control group and 1.67 [95% CI: 1.04 – 2.68] relative to the second control of women with vaginal culture positive and no history of vaginitis in the year preceding their visit. This suggests that the use of combined oral contraceptives may influence the recurrence of symptomatic vulvovaginal candidiasis.

Appraised by:

1. The International Center for Evidence Based Medicine, East Tennessee State University;
2. The Evidence Based Medicine Center, Department of Obstetrics, Gynecology and Reproductology, Ukraine National Medical Academy of Postgraduate Education;
3. Together for Health project.

Update by: 24 December 2011

The initiation of COCs immediately after an abortion is safe and effective

Conclusion

Conclusions: Evidence shows that COCs can be safely initiated immediately following surgical and medical abortion in the first-trimester

Clinical Question

Is the initiation of COCs immediately following an abortion safe?

Search Terms

Post abortion, COCs

Citations

Gaffield ME, Kapp N, Ravi A. Use of combined oral contraceptives post abortion. Contraception 2009;80:355–362

Object of research

Post-abortion COC initiation – immediately after versus delayed start

Subject of research

Repeat abortion rate; unplanned pregnancy rate

Study Features

This is a systematic review of studies of COC use following spontaneous, induced (medical or surgical) or septic abortion, from 1966 through June 2008. Seven articles were identified. Three cohort studies examined differences in bleeding patterns after surgical or spontaneous abortion among women using differing COC formulations and two of these studies compared these events with non COC users. In one other cohort study, changes in coagulation parameters were assessed following first-trimester surgical abortion in women electing to initiate a COC immediately after surgically induced abortion for three cycles compared with women who chose copper bearing IUD insertion at the end of the operative procedure. Three randomized controlled trials (RCTs) studied the effect of immediate COC initiation on bleeding patterns after first-trimester induced medical abortion.

The Evidence

Immediate COC initiation after first-trimester medical or surgical induced abortion

- did not increase side effects or prolong vaginal bleeding compared with use of a placebo, copper-bearing intrauterine device (IUD), nonhormonal contraceptive method or COC initiated at a later time.
- after first-trimester surgical abortion produced small increases in coagulation parameters compared with IUD use. These changes were statistically significant, but their clinical relevance is unlikely.
- was not assessed after a second-trimester induced or spontaneous abortion, or septic abortion.

Appraised by:

1. The International Center for Evidence Based Medicine, East Tennessee State University;
2. The Evidence Based Medicine Center, Department of Obstetrics, Gynecology and Reproductology, Ukraine National Medical Academy of Postgraduate Education;
3. Together for Health project.

Update by: 30 March 2012

The initiation of a vaginal ring within one week of a first trimester abortion is safe for and acceptable to the user

Conclusion

The CVR is potentially safe and has high acceptability when used in the proximate postabortion period following a first-trimester abortion.

Clinical Question

Is initiation of a vaginal ring in the proximate post abortion period following a first trimester abortion safe?

Search Terms: Post abortion, vaginal ring

Citations

Fine PM, Tryggestad J, Meyers NJ, Sangi-Haghpeykar H. Safety and acceptability with the use of a contraceptive vaginal ring after surgical or medical abortion. 2007;75(5):367-371.

Object of research: Post-abortion vaginal ring use

Subject of research: Safety

Study Features

This study was conducted in Houston, Texas USA to determine if a contraceptive vaginal ring (CVR) is a safe and acceptable method of contraception when used in the proximate post abortion period following first-trimester surgical or medical abortion. A CVR was inserted within 1 week following a medical or surgical abortion. Participants were followed up for 3 months to determine safety and acceptability. Safety was measured by the absence of signs of infection or serious adverse events. Acceptability was assessed by the CVR satisfaction survey, completed at the 3-month follow-up visit.

The Evidence

Of 81 participants enrolled in the study, 69 (85%) completed the first-month follow-up visit, and 54 (67%) completed the final 3-month follow-up visit. There were no serious adverse events and no signs of infection on physical exam. Most adverse events were mild and not specifically related to the CVR. Related adverse events were those commonly associated with hormonal contraception use. Eighty-nine percent of participants chose to continue the CVR as their birth control method.

Appraised by:

1. The International Center for Evidence Based Medicine, East Tennessee State University;
2. The Evidence Based Medicine Center, Department of Obstetrics, Gynecology and Reproductology, Ukraine National Medical Academy of Postgraduate Education;
3. Together for Health project.

Update by: 28 March 2012

The use of post abortion contraceptive counseling results in a significantly lower unplanned pregnancy rate

Conclusion

In this study of women who had an abortion and had indicated they wished to delay their next pregnancy for at least two years, women who received contraceptive counseling (plus free access to contraceptive methods) were more likely to have accepted a modern contraceptives than those who received usual care, but with no counseling. In addition, they were less likely to have had an unwanted pregnancy after one year.

Clinical Question

Is post abortion counseling effective in reducing the pregnancy rate?

Search Terms

Post abortion counseling and efficacy/effectiveness

Citations

Johnson BR, Ndhlovu S, Farr SL, Chipato T. Reduced unplanned pregnancy and abortion in Zimbabwe through post abortion counseling. Family Planning 2002;33:195-202.

Solo J, Billings DL, Aloo-Obunga C, Ominde A, Makumi M. Creating linkages between incomplete abortion treatment and family planning services in Kenya. Studies in Family Planning 1999;30[1]:17-27.

Savelieva, I., Pile JM, Gorodnichava Z, Ottolenghi E. *Increasing Effective Postabortion Contraceptive Use and Reducing Repeat Abortions in Perm, Russia.* Presentation at APHA, Philadelphia, Pennsylvania, November 9–13, 2002.

Object of research

Post-abortion contraceptive counseling

Subject of research

Unplanned pregnancy rate, contraceptive counseling, contraceptive acceptance

Study Features

Johnson et al.

The study was of two groups of women who had a very recent abortion at one of two Zimbabwe hospitals. Both groups were comprised of women who wished to delay their next pregnancy for at least 2 years. During their hospital stay, 316 women at one hospital received contraceptive counseling regarding all modern methods of family planning. In addition, they were provided access to free contraception. The control group of 320 women (at the other hospital) were given usual care with no emphasis on family planning. They were interviewed regarding contraceptive use and tested for pregnancy once every 3 months for one year.

Solo et al.

This study tested three models for care following treatment of an incomplete abortion in Ministry of Health hospitals in different geographical areas in Kenya. In Model 1, family planning services were offered on the gynecological ward by ward staff whereas Model 2 assessed the effect of offering family planning services on a gynecological ward by Maternal and Child Health-Family Planning (MCH-FP) staff. A third model assessed the effect offering family planning services in the MCH-FP clinic by MCH-FP staff. In each model, the there were two primary measures to determine effectiveness; the proportion of women receiving family planning counseling before discharge from the hospital and the proportion of women leaving the hospital with a method.

Savelieva et al.

This study was conducted at two hospitals and three outpatient facilities in Perm, Russia. Two models were tested. Both models consisted of training providers in family planning counseling and services. The second model was one in which women were offered a free initial three month supply of condoms, pills, DMPA or an IUD for any postabortion client requesting a contraceptive method. The intervention models were compared to a control group of women attending the same facilities prior to the intervention. Researchers interviewed 1,516 women prior to their discharge and conducted 1,079 follow-up interviews.

The Evidence

Johnson et al.

- Soon after the intervention 95% of those receiving counseling were using modern, effective birth control methods compared with only 5% of the controls. At the end of one year after their abortion, 84% of those receiving counseling versus 64% of those who did not were using a modern method ($p<.0001$).
- At the end of one year study 42 (15%) of those receiving counseling versus 98 (34%) of those who did not had an unplanned pregnancy.

Solo et al.

All three models resulted in more than 50 percent of the women receiving some form of family planning counseling before discharge from the hospital. Model 1 in which the ward staff did the counseling resulted in the greatest proportion of those accepting a method prior to discharge.

Model	Proportion Counseled Before Discharge	Proportion Leaving Hospital with a Family Planning Method
1	92%	82%
2	62%	63%
3	54%	75%

Note: Data on decreasing repeat abortions was not a focus of this study though it is assumed that an increase in the acceptance of a contraceptive leads to a decrease in abortions.

Savelieva et al.

- The availability of commodities increased the likelihood that providers would discuss family planning with postabortion clients, but did not result in a significant increase in the use of family planning one year postabortion.

- After the intervention, use of a modern contraceptive method was significantly higher among clients in the intervention groups (Model 1: 62%; Model 2: 67%; Control: 53%)
- At the 13 month follow-up interview, repeat abortion rates had declined in all three groups.

Appraised by:

1. The International Center for Evidence Based Medicine, East Tennessee State University;
2. The Evidence Based Medicine Center, Department of Obstetrics, Gynecology and Reproductology, Ukraine National Medical Academy of Postgraduate Education;
3. Together for Health project.

Update by: 21 December 2011

Contraceptive continuation can be enhanced when health care professionals listen to the stated desires of their clients

Conclusion

Based on the results of this study in which the client's desire for a particular contraceptive method is explored as a determinate of continuation, it was found that when their choice was considered, continuation was higher regardless of the method selected.

Clinical Question: Does choice make a difference to contraceptive use?

Search Terms

Contraceptive discontinuation, client/family planning worker interactions

Citation

Pariani S, Heer DM, Arsdol MD. Does choice make a difference to contraceptive use? Evidence from East Java. Studies in family Planning. 1992;22,6:384-390.

Object of research: Contraceptive choice

Subject of research: Contraceptive continuation rates

Study Features

This was a prospective study of family planning program clients attending a government family planning clinic in East Java. Before receiving a family planning method, clients were interviewed regarding their socio-demographic characteristics and their preferred method of contraception. Immediately after being introduced to a method, they were again interviewed about the methods suggested and the method they intended to use. Of the 2,501 initial respondents, 1,945 (77.8%) were re-interviewed at their homes a year later.

The Evidence

- The odds of discontinuation were 0.13 when choice was granted and husbands and wives concurred when compared to when choice was denied and husbands and wives disagreed.
- The odds of discontinuation were 6.58 when there was concurrence between the husband and wife and choice was denied compared to when choice was denied and the husband and wife did not agree.

Appraised by:

1. The International Center for Evidence Based Medicine, East Tennessee State University;
2. The Evidence Based Medicine Center, Department of Obstetrics, Gynecology and Reproductology, Ukraine National Medical Academy of Postgraduate Education;
3. Together for Health project.

Update by: 14 December 2011

There is no available evidence to support an association between the use of emergency contraception containing mifepristone or levonorgestrel and ectopic pregnancy

Conclusion

The rate of ectopic pregnancy when treatment with emergency contraceptive pills fails does not exceed the rate observed in the general population. Because emergency contraceptive pills are effective in lowering the risk of pregnancy, their use will reduce the chance that an act of intercourse will result in ectopic pregnancy.

Clinical Question: Is there an increased risk of ectopic pregnancy among women using emergency contraception?

Search Terms: Emergency contraception, ectopic pregnancy

Citations

Cleland, Kelly MPA, MPH; Raymond, Elizabeth MD, MPH; Trussell, James PhD; Cheng, Linan MD; Zhu, Haoping MD. Ectopic Pregnancy and Emergency Contraceptive Pills: A Systematic Review. Obstetrics & Gynecology: June 2010 - Volume 115 - Issue 6 - pp 1263-1266

Object of research: Emergency contraception

Subject of research: Ectopic pregnancy

Study Features

This study included data from 136 studies, which followed a defined population of women treated one time with emergency contraceptive pills (either mifepristone or levonorgestrel) and in which the number and location of pregnancies were known. In these studies, 494 pregnancies resulting from a failure mifepristone were followed. The corresponding number of failures in the levonorgestrel studies was 307.

The Evidence

In the studies of mifepristone, 3 of 494 (0.6%) pregnancies were ectopic; in the levonorgestrel studies, 3 of 307 (1%) were ectopic.

Comment: Available ectopic pregnancy rates range from 0.8% to 2% of all reported pregnancies. This study detected a range of 0.6% to 1.1%, depending on the medication used.

Appraised by:

1. The International Center for Evidence Based Medicine, East Tennessee State University;
2. The Evidence Based Medicine Center, Department of Obstetrics, Gynecology and Reproductology, Ukraine National Medical Academy of Postgraduate Education;
3. Together for Health project.

Update by: 2 August 2012

For long term users of Depo-Provera, there is no apparent association between use and failure to return to fertility, though return to fertility is often delayed

Conclusion

When comparing women who discontinued an IUD or DMPA to become pregnant, return to fertility was similar in both groups. However, return to fertility for DMPA users tended to be delayed relative to IUD users. There was no apparent association between length of use and return to fertility as measured by a confirmed pregnancy.

Clinical Question

What is the return to fertility rate of women who have taken DMPA?

Search Terms

DMPA or Depo-Provera and Fertility

Citations

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

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

Object of Research

DMPA, IUDs, or oral contraceptives.

Subject of Research

Confirmed pregnancy. A secondary variable of interest was length of exposure to DMPA and return to fertility.

Study Features

Pardthaisong

All patients were Thai women: 796 former DMPA users; 437 former oral contraceptive users; 125 former IUD users. The patients' demographic characteristics were not described in this paper.

Affandi et al.

All patients were Indonesian: 47 former DMPA users, 75 former IUD users and 51 former Norplant users. Mean ages (26 years) and parity (1.7 live births) were similar across the 3 groups.

The Evidence

Pardthaisong

In this study, 747 (94%) DMPA patients returned to fertility at 36 months as compared to 117 (94%) IUD users. There was no apparent association between the length of use and a return to fertility (See Table below).

Duration of DMPA Use (in months)	Percent conceiving
1 – 12	5.3%
13-24	4.7%
24+	4.7%

Affandi et al.

In this study 42 (89%) of all DMPA patients returned to fertility at 24 months as compared to 65 (87%) IUD users.

Comment

- DMPA normally causes amenorrhea in the majority of users; however it is very rare for this to lead to infertility.
- Though these studies are old (1984, 1987), the return to fertility rates are consistent in the two studies and thus convincing.
- The rates of return to fertility were similar for the IUD and DMPA groups though time to return to fertility has been shown to be more than a year in some cases. Further, the reasons for those in either study whose fertility did not return (Pardthaisong: 6% for both groups; Affandi: IUD, 13% and DMPA, 11%) is unlikely to be related to the contraceptive method.

Appraised by:

1. The International Center for Evidence Based Medicine, East Tennessee State University;
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3. Together for Health project.

Update by: 26 July 2012

The association between the use of depo-medroxyprogesterone acetate (DMPA) and bone fractures is not clear

Conclusion

Bone density in some users of depot-medroxyprogesterone acetate (DMPA) may decrease, but whether this is clinical significant is not clear. Among users of DMPA, substantial post-discontinuation recovery of bone suggests that the effects may be largely reversible.

Clinical Question

In a healthy woman of childbearing age, does long term depot-medroxyprogesterone acetate (DMPA) use result in significantly decreased bone mineral density?

Search Terms

DMPA, fractures, bone health

Citation

Lopez LM, Grimes DA, Schulz KF, Curtis KM. Steroidal contraceptive effects on bone fractures in women. Cochrane Database Reviews 2006, Issue 4. Art. No.: CD006033. DOI: 10.1002/14651858.CD006033.pub2.

Scholes, Delia; LaCroix, Andrea Z.; Ichikawa, Laura E.; Barlow, William E.; Ott, Susan M. njectable hormonal contraception and bone density: results from a prospective study Epidemiology. 13(5):581-587, September 2002.

Object of Research

Depot-medroxyprogesterone acetate (DMPA)

Subject of Research

Bone mineral density and fracture.

Study Features

Lopez et al.

Three studies of DMPA were found to include bone density measurements, but none involved a study of fractures. Two of these studies involved an estrogen or placebo supplement among a group of DMPA users. One of these studies involved 112 adolescents followed for one year while the other was a study of 38 women followed for two years. The third study compared DMPA with an implant (Norplant) and involved 22 women randomized to one of the two methods. The study duration was six months.

Scholes et al.

Between 1994 and 1999, a population-based prospective cohort study among women enrollees of a USA health maintenance organization was conducted. 457 non-pregnant women, ages 18-39 years (183 DMPA users and 274 non-users) were included in the study. Bone density was measured by dual-energy x-ray absorptiometry every 6 months for 3 years.

The Evidence

Lopez et al.

- In two studies of DMPA users involving an estrogen supplement or a placebo, those with DMPA plus the supplement had increases in bone mass density at 12 and 24 months. Women in the DMPA plus placebo supplement had decreases for the same time period.
- In the comparative study of DMPA and an implant, bone mass density in the forearm increased 2.9% in the implant group and decreased an insignificant 0.4% in the DMPA group.

Scholes et al.

Relative to non users, bone density decreased notably among DMPA-exposed women as follows:

- 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) which represents an annualized mean rate of change of -0.87% among DMPA users compared to +0.40% among non-users
- for total hip (-0.0060 gm/cm2 compared with -0.0002 gm/cm2) which represents an annualized mean rate of change of -1.12% among DMPA users compared with -0.05% among non-users.

For discontinuers of DMPA (N = 110), at each 6-month interval,

- gains in bone density at the spine were greater than that in the non-user group,
- gains in bone density at the spine were greater in magnitude than the losses in the continuing user group
- gains in bone density at the hip were greater than that in the non-user group
- gains in bone density at the hip were not greater in magnitude than the losses in the continuing user group.

Appraised by:

1. The International Center for Evidence Based Medicine, East Tennessee State University;
2. The Evidence Based Medicine Center, Department of Obstetrics, Gynecology and Reproductology, Ukraine National Medical Academy of Postgraduate Education;
3. Together for Health project.

Update by: 27 July 2012

Association between use of intrauterine devices and return to fertility is delayed when compared to women using a barrier method, but overall fertility rate is unaffected

Conclusion

Two studies of women wanting to become pregnant after using an IUD found no increased risk of infertility. However, when compared to those who had used a barrier method, there appeared to be some delay in return. For nulliparous women, there appeared to be a suggestion of increased risk of infertility after 78 months of use. Few nulliparous women use an IUD for long term use and this should not be a rationale for not providing them with their contraceptive choice. However, for those nulliparous women who wish to use the IUD long term, this should be considered in their counseling.

Clinical Question

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

Search Terms

Intrauterine device, infertility, fertility rate

Citations

Hov GG, Skjeldestad FE, Hilstad T. Use of IUD and subsequent fertility – follow-up after participation in a randomized clinical trial. Contraception 2007;75:88-92.

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

Andersson K, Batar I, Rybo G. Return to fertility after removal of a levonorgestrel releasing intrauterine device and Nova-T. Contraception 1992;46:575-584.

Object of research

Intra-uterine devices

Subject of research

Fertility rate; infertility

Study Features

Hov et al.

This was a prospective cohort study of 205 Norwegian women who withdrew from a randomized study and stopped using a copper IUD. 109 women had their IUD removed in order to become pregnant. A second group of 96 women from the same randomized control trial became pregnant or planned to become pregnant after having their device removed because of a complication.

Doll et al.

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

Anderson et al.

Women participating in a European randomized multicenter study and who withdrew to become pregnant were followed to assess return to fertility among women using a levonorgestrel releasing intrauterine device. Their return to fertility was compared to the Nova-T. In all 209 women were followed, 71 after use of the Nova-T and 138 after use of the levonorgestrel releasing device. Women were followed for at least 24 months or until the end of their pregnancy.

The Evidence

Hov et al.

After 12 months 90% of the women who stopped using an IUD to get pregnant became pregnant. Time to conception was not influenced by parity order, duration of use, or age at the time of removal. In the second group that planned a pregnancy after a complicated removal, 94% had become pregnant within 24 months. These figures are similar to the fertility rates shown by fertile aged women who use no contraceptives.

Doll et al.

- After 12 months, 39% of the women who had been using an IUD became pregnant compared to 32% of those who used COCs, and 54% of those who used natural or barrier methods.
- After 24 months 76.5% of the women who had been using an IUD became pregnant compared to 80.1% of those who used COCs, and 85.6% of those who used natural or barrier methods.

Comment: None of these differences were statistically significant. Overall, among women who had the device removed within 42 months of insertion, there does not appear to be any difference between IUD users and those using barrier methods in terms of return to fertility. Among nulliparous women, there was some suggestion of impairment of fertility among those using the method more than 78 months. For nulliparous women who plan on using an IUD over five years before becoming pregnancy, contraceptive counseling for this group should be considered.

Andersson et al.

For the Nova-T group, the cumulative rate of 71.2/100 as compared to 79.1/100 for the levonorgestrel IUD group. The corresponding rates at 24 months were 79.7 and 86.6, respectively. Approximately 85 percent of all women in the follow-up study had a normal delivery.

Appraised by:

1. The International Center for Evidence Based Medicine, East Tennessee State University;
2. The Evidence Based Medicine Center, Department of Obstetrics, Gynecology and Reproductology, Ukraine National Medical Academy of Postgraduate Education;
3. Together for Health project.

Update by: 19 January 2012

Among current users of intrauterine devices there is no increased risk of an ectopic pregnancy

Conclusion

Based on the results of a review of studies involving ectopic pregnancy, among current users of an IUD, there is no increased risk of an ectopic pregnancy, but there appears to be a slightly increased risk among past users.

Clinical Question

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

Search Terms

Intrauterine device, ectopic pregnancy

Citations

Xiong X, Buekens P, Wollast E. IUD use and the risk of ectopic pregnancy: A meta-analysis of case-control studies. Contraception 1995;52:23-43.

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

Object of research

Intrauterine devices

Subject of research

Ectopic pregnancy rate

Study Features

Xiong et al. study

This study includes 16 case-control studies involving 21,986 women (5,568 cases and 16,418 controls). Current IUD use were compared to pregnant controls as well as non-pregnant controls. The participants included women from Finland, USA, Australia, Sweden, Italy, China, France, Greece and Indonesia who were current users or past users of IUDs. Their ages ranged from 16 to 48 years.

Mol et al. study

The study was a meta-analysis of 12 case control studies and 1 cohort study. Cases in the case control studies were women with an ectopic pregnancy. Controls were non-pregnant or pregnant women actively using an IUD, or a former user.

The Evidence

Xiong et al.

- Current IUD users
  - Compared to pregnant controls, there was an increased risk of ectopic pregnancy (adjusted OR 6.29, 95% CI 4.23-9.34).

- Compared non-pregnant controls, there was no increased risk of ectopic pregnancy (adjusted OR 1.06, 95% CI .89-1.28).

- Past IUD use was associated with a small increase in risk of ectopic pregnancy (adjusted OR 1.4, 95% CI 1.23-1.59).

Mol et al.

- Current IUD users
  - Compared to pregnant controls, there was an increased risk of ectopic pregnancy in all four studies.
  - Compared to non-pregnant controls, there was no increased risk of ectopic pregnancy in
- Past IUD users
  - Compared to non-pregnant controls, there was an increased risk of ectopic pregnancy in each of the three studies with these controls.
  - Compared to a pregnant control, there was a suggestion of a significant increase in risk among past users, though this was not statistically significant.

Comment: Note that current IUD use does not increase the risk of an ectopic pregnancy, but if a woman becomes pregnant with the IUD in situ, the pregnancy is more likely to be ectopic than a pregnancy without an IUD. Simply stated, there is no evidence that women using an IUD have more ectopic pregnancies than those not using an IUD.

Appraised by:

1. The International Center for Evidence Based Medicine, East Tennessee State University;
2. The Evidence Based Medicine Center, Department of Obstetrics, Gynecology and Reproductology, Ukraine National Medical Academy of Postgraduate Education;
3. Together for Health project.

Update by: 4 January 2012

The use of intrauterine devices is associated with a small increase in the risk of PID with most cases occurring within 20 days after insertion

Conclusion

Findings suggest that PID among IUD users is most strongly related to the insertion process and to background risk of sexually transmissible disease. PID is an infrequent event beyond the first 20 days after insertion.

Clinical Question

Is there an increase in the risk of PID among women using an IUD?

Search Terms

Intrauterine device, pelvic inflammatory disease

Citations

Farley TMM, Rosenberg MJ. Intrauterine devices and pelvic inflammatory disease: An international perspective. Lancet 1992;339:785-788.

Gareen IF, Greenland S, Morgenstern H. Intrauterine devices and pelvic inflammatory disease: meta-analysis of published studies, 1974-1990. Epidemiology 2000;11:589-597.

Lee NC, Rubin GL, Ory HW, Burkman RT. Type of intrauterine device and the risk of pelvic inflammatory disease. Obstet Gynecol 1983;Jul;(62(1)1-6.

Grimes DA. Intrauterine device and upper genital tract infection.
Lancet 2000; 356: 1013–19.

Object of research

Intra-uterine devices

Subject of research

pelvic inflammatory disease

Study Features

Farley et al.

This was an analysis of 12 randomized control trials plus 1 cohort study under the auspices of the WHO Special Program for Research, Development, and Research Training in Human Reproduction. 22,908 women had one of ten types of IUD inserted; 84% of the IUDs were copper; 16% were hormonal. Results include data from 7 European countries, 8 Asian countries, 6 North, Central, and South American countries, 15 centers in China, and 1 in Africa.

Gareen et al.

This analysis included 36 studies of IUDs and PID from Denmark, Britain, Norway, Sweden, Finland, the Netherlands, Israel, Thailand, Nigeria, India, the Philippines, Chile, Korea, the United States, and Canada. The types of studies ranged from cross-sectional to case con-

trol to cohort to randomized control trial (only 1 study). The reference controls were of those using no contraception or a non-IUD contraceptive. The authors included studies published between 1974-1990.

Lee et al.

This analysis was based on data from the Women's Health Study (supported by grants from the National Institute of Health in the United States. The analysis included data from interviews of 622 women hospitalized with an initial episode of pelvic inflammatory disease (PID) and 2,369 hospitalized control subjects reporting no pelvic inflammatory disease.

Grimes

This is a review of intrauterine devices and their association with upper-genital tract infection. The review include large multicenter studies as well as WHO reviewed studies. Additionally, it includes data involving the levonorgestrel-releasing intrauterine system (IUS).

The Evidence

Farley et al.

The overall rate of PID among 22 908 IUD insertions and during 51399 woman-years of follow-up was 1.6 cases per 1000 woman-years of use. After adjustment for confounding factors, PID risk was more than six times higher during the 20 days after insertion than during later times (unadjusted rates, 9.7 vs. 1.4 per 1000 woman-years, respectively).

- The risk was low and constant for up to eight years of follow-up. Rates varied according to geographical area (highest in Africa and lowest in China) and were inversely associated with age. The highest PID rates were for women aged 15-24 at the time of insertion; older women had less than half the risk.
- No significant differences were found among device types.
- A sub-analysis for year of insertion showed that rates of PID were lower for more recent insertions. For example, the rate for PID since 1984 was only 0.48 per 1000 women years, or 4 cases for 5533 insertions.

Gareen et al.

The results showed a slightly increased risk of PID with IUD use. It should be noted that there were substantial differences across the studies for both symptomatic and asymptomatic PID. The rate ratio estimates ranged from 0.51 to 12 for symptomatic PID and 1 to 132 for asymptomatic PID. (Note: The rate ratio of 132 from a US study is likely an outlier.)

Note: Unlike, the Farley study, the timing of the PID diagnosis in this study was not included in this study.

Lee et al.

Findings were that:

- the relative risk of a diagnosed case of PID among current IUD users compared to those using no method was 1.6 (95% C.I. 1.2-2.0) which is statistically significant.
- most of the increased risk of PID occurring among women currently using an IUD (excluding Dalkon Shield users) occurred in the first four months after insertion.

Grimes

The author notes that choice of an inappropriate comparison group, over diagnosis of salpingitis in IUD users, and inability to control for the confounding effects of sexual behavior have exaggerated the apparent risk.

- Epidemiological studies have confirmed that the risk of upper-genital-tract infection associated with IUDs is temporally linked to insertion. The first large cohort study in the USA in the 1960s showed an inverse relation between risk and time since insertion. By five months and thereafter, the risk of PID was not significantly increased.
- Evidence from large cohort studies, case-control studies, and randomized controlled trials suggests that the risk of upper-genital-tract infection after the first month is small.

The author also reviewed two studies of the levonorgestrel-releasing intrauterine system (IUS).

- A multicentre randomized controlled trial from Europe compared the levonorgestrel IUD and the Nova T, a copper device. The cumulative 36-month gross discontinuation rates for PID were 0,5 and 2,0 per 100 women ($p<0,02$) and the 60-month rates were 0,8 and 2,2 per 100 women, respectively ($p<0,01$)
- A second randomized controlled trial compared the levonorgestrel IUD with the Copper T 380A. In this multicentre study, the incidence of PID was low and nearly identical in both groups after 7 years of use.
- In WHO trials, no case of PID occurred among 1552 women who received the levonorgestrel IUD.

Comment: Conflicting studies make it difficult to suggest that the IUS is associated with less risk of PID than a copper device. But each of the reviewed studies shows that the risk of PID with any IUD is low and transient.

Appraised by:

1. The International Center for Evidence Based Medicine, East Tennessee State University;
2. The Evidence Based Medicine Center, Department of Obstetrics, Gynecology and Reproductology, Ukraine National Medical Academy of Postgraduate Education;
3. Together for Health project.

Update by: 18 May 2012

Among users of intrauterine devices, there appears to be a protective effect against endometrial cancer

Conclusion

In this review of studies involving the use of an IUD, there appears to be a protective effect against endometrial cancer. Data were not sufficient to differentiate between medicated and non-medicated IUDs.

Clinical Question

Are women who are using an intrauterine device at an increased risk for endometrial cancer?

Search Terms

Intrauterine devices, endometrial cancer

Citations

Hubacher D, Grimes DA. Noncontraceptive health benefits of intrauterine devices: a systematic review. Obstet Gynecol Surv 2002;57:120-128.

Object of research

Intrauterine devices

Subject of research

Endometrial cancer

Study Features

In this review of intrauterine devices and the risk of endometrial cancer, seven case control studies were identified. Both medicated and non-medicated devices were included though sample sizes for the medicated device were too small to draw any definitive conclusions.

The Evidence

Results from the case control studies on endometrial cancer are shown below. Note that all but one of the studies show a suggested or statistically significant protective effect except the Shu study which is a Chinese publication involving the steel ring. In this study there is no statistically significant association between IUD use and endometrial cancer

Publication		
Study	**Year**	**Odds Ratio* [95% CI]**
Salazar-Martinez et al.	1999	0.4 [0.2–1.0]
Sturgeon et al.	1997	0.6 [0.3–1.0]
Hill et al.	1997	0.6 [0.4–0.9]

Rosenblatt and Thomas	1996	0.7 [0.4–1.3]
Parazzini et al.	1994	0.4 [0.1–1.0]
Castellsague et al.	1993	0.5 [0.3–0.8]
Shu et al.	1991	1.1 [0.5–2.5]

* *Odds ratios adjusted for potential confounders.*

CI=Confidence interval.

No consistent pattern emerged to suggest that length or timing of use was associated with either an increase or decrease in the risk of endometrial cancer.

Appraised by:

1. The International Center for Evidence Based Medicine, East Tennessee State University;
2. The Evidence Based Medicine Center, Department of Obstetrics, Gynecology and Reproductology, Ukraine National Medical Academy of Postgraduate Education;
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Update by: 9 June 2011

Among users of intrauterine devices, there appears to be no increased risk of cervical cancer

Conclusion

There does not appear to be either an increase or decrease in risk of cervical cancer for women using an IUD.

Clinical Question

Are women who are using an intrauterine device at an increased risk for cervical cancer?

Search Terms

Intrauterine devices, cervical cancer

Citations

Hubacher D, Grimes DA. Noncontraceptive health benefits of intrauterine devices: a systematic review. Obstet Gynecol Surv 2002;57:120-128.

Object of research

Intrauterine devices

Subject of research

Cervical cancer

Study Features

In this review of intrauterine devices and the risk of cervical cancer, three case control studies were identified. Both medicated and non-medicated devices were included though sample sizes for the medicated device were too small to draw any definitive conclusions.

The Evidence

Results from the case control studies on cervical cancer are as follows. None of the findings were statistically significant.

Publication		
Study	**Year**	**Odds Ratio* [95% CI]**
Li et al.	2000	0.9 [0.7–1.1]
Parazzini et al.	1992	0.6 [0.3–1.1]
Lassise et al.	1991	0.8 [0.5–1.2]

* *Odds ratios adjusted for potential confounders.*

CI=Confidence interval.

No consistent pattern emerged to suggest that length or timing of use was associated with either an increase or decrease in the risk of cervical cancer.

Appraised by:

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Update by: 9 June 2011

The use of prophylactic antibiotics at the time of insertion of intrauterine devices is not associated with a decrease in the risk of infection as the risk of infection is very low

Conclusion

Based on the results of a systematic review of studies involving the routine use of antibiotics at the time of insertion of an IUD, it appears there is no benefit with regard to a reduced incidence of infection.

Clinical Question

Is there a decrease in the risk of infection with the routine use of antibiotics at the time of IUD insertion?

Search Terms

Intrauterine device, pelvic infection, endometritis

Citation

Grimes DA, Schulz KF. Antibiotic prophylaxis for intrauterine contraceptive device insertion (Cochrane Review). In: The Cochrane Library, Issue 3, 2004.

Object of research

Intra-uterine devices

Subject of research

Pelvic and intrauterine infection rates; also unscheduled visits to a clinic

Study Features

The study was a meta-analysis of four randomized control trials, one each from Kenya, Nigeria, Turkey and the USA. These data also include two pilot studies from the Kenya and USA studies. In the USA study, women were randomly assigned to receive azithromycin 500 mg by mouth one hour before insertion or an identical-appearing placebo. In each of the other studies, women were randomly assigned to receive doxycycline 200 mg by mouth one hour before IUD insertion or an identical-appearing placebo. The total number of women included in these four trials was 2906 receiving antibiotic treatment prior to IUD insertion and 2891 who received the placebo. The primary diagnosis outcome measure was pelvic inflammatory disease within three months after insertion.

The Evidence

No differences in the two groups were found with respect to any of the three outcome measures.

- There was no significant decrease in the rate of pelvic inflammatory disease (PID) in the 4 studies. The rate ratio was 0.89, (95% C.I. 0.53-1.50).

- There was no difference in the rate of IUD removal within 90 days after insertion. The risk ratio was 1.05, (95% C.I. 0.69-1.60)
- There was a small, but significant decrease in unscheduled visits to a clinic among those treated with an antibiotic (but for any reason). The rate ratio was 0.86, (95% C.I. 0.75-0.98).

Appraised by:

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Update by: 17 December 2011

The insertion of an intrauterine device immediately after an abortion is safe and effective

Conclusion

Women who have an IUD inserted immediately after an abortion have slightly higher expulsion rates in the first year after the abortion compared with women who have a delayed IUD insertion. However, significant numbers of women who opt for a delayed insertion do not return to have their IUD inserted and may be at risk for an unwanted pregnancy.

Clinical Question

Is the insertion of an IUD immediately following an abortion safe and effective?

Search Terms

Post abortion, intrauterine device, efficacy/effectiveness

Citations

Grimes DA, Lopez LM, Schulz KF, Stanwood NL. Immediate postabortal insertion of intrauterine devices. *Cochrane Database of Systematic Reviews* 2004, Issue 4. Art. No.: CD001777. DOI: 10.1002/14651858.CD001777.pub2.

Object of research

Safety of immediate post-abortion IUD insertion

Subject of research

Discontinuation rates for accidental pregnancy, expulsion, uterine perforation, upper genital tract infection

Study Features

Nine studies were included in this review. Two WHO trials compared three different IUDs, the Lippes Loop, the TCu 220C, and the Copper 7. In the first of these studies, the device was inserted immediately after a spontaneous abortion. In the other study, the device was inserted after an induced abortion. Three immediate post abortion IUD insertion studies compared the Nova-T, the levonorgestrel intrauterine system (IUS), the TCu 200, and the Multiload 250. One other trial compared the Multiload 375 versus the Multiload 250. There was one comparative study of immediate versus delayed insertion of the Copper 7 device while the other three studies involved experimental devices (Lippes Loop D with copper sleeves and the Spring Coil with topical hydrogel) and are not included in this data summary.

The Evidence

In the two WHO trials involving 3400 women,

- the pregnancy and expulsion rates of the TCu 200 were less than the Copper 7 or Lippes Loop D,

- only four (0.12%) perforations were reported,
- among those women with an induced abortion, discontinuation for upper genital tract infection ranged from 2 to 8 percent,
- among women with a spontaneous abortion, discontinuation for upper genital tract infection ranged from 0 to 4 percent.

In the only study comparing immediate versus delayed insertion of the Copper 7,

- immediate insertion was associated with a suggested higher, though statistically non-significant, risk of expulsion,
- 42 percent of those assigned to delayed insertion did not return.

Appraised by:

1. The International Center for Evidence Based Medicine, East Tennessee State University;
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3. Together for Health project.

Update by: 9 March 2012