COLLECTION OF CRITICALLY APPRAISED TOPICS ON CONTRACEPTION

Progestin only pills

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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 (progestin nly pills) and various medical conditions, as well as non-contraceptive benefits. 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.

Women using a progestin-only pill for contraception experience acne infrequently

Conclusion

Among progestin only pill users, complaints and reasons for discontinuation of their contraceptive include acne infrequently. Unlike use of the combined oral contraceptive, the effect of a progestin only pill on decreasing acne is not clear.

Clinical Question

Is there an increase in acne episodes among women taking progestin only pills?

Search Terms

Progestin-only pills, progestin-only oral contraceptives, acne

Citations

McCann MF, Potter LS. Progestin-only oral contraception: A comprehensive review. Contraception 1994:50(Supplement 1), S9-S195.

Collaborative Study Group on the Desogestrel-containing Progestogen-only Pill. A double-blind study comparing the contraceptive efficacy, acceptability and safety of two progestogen-only pills containing desogestrel 75 micrograms/day or levonorgestrel 30 micrograms/day. Eur J Contracept Reprod Health Care 1988 Dec;3(4):169-78.

Object of research

Progestin-only pills

Subject of research

Acne

Study Features

McCann and Potter

This is a review of 8 selected studies that included information about discontinuation of a progestin only pill due to a non-menstrual side effect. Of these, six were prospective and contained discontinuation rates for side effects. Two others reported discontinuation for non-menstrual side effects as a group and were excluded from this assessment. These four studies are as follows:

- England (1977): This is a prospective study with one year follow-up of three progestins; norethisterone 0.35 mg (n=200), chlormadinone acetate 0.5 mg (n=182), and mesgestrol acetate 0.5 mg (n=174). Most were less than six months postpartum though reports about breastfeeding were not included.
- United States (1974): This was an open label study of 2,202 women using norgestrel 0.075 mg studied from 1 to 67 cycles.
- UK, Jamaica, New Zealand (1982): This is multicenter study of norethisterone 0.35 mg of 913 women. The median age of these women was 27 and ranged from 16 to 54 years of age.

- England (1972): These data were obtained as part of the continuing follow-up of contraceptive users in the Oxford Family Planning Association. Only data from the norethisterone users (1746 women years of use). The study included other contraceptive users of both hormonal and non-hormonal methods.

Collaborative Group

This is a randomized, double-blind study of progestin-only pills in which 989 women were assigned to the desorgestrel 75 mcg group and 331 to the levonorgestrel 30 mcg group. Women were observed for 13 28-day cycles.

The Evidence

McCann and Potter

In the four studies, results were:

- England: There were no reports of discontinuation as a result of an acne episode in any of the progestin only pill user groups.
- United States: Less than $^1/_2$ of a percent of the users of norgestrel discontinued because of an acne episode.
- UK, Jamaica, New Zealand: No discontinuations were reported for acne though there was one discontinuation for an unspecified skin complaint.
- England/Oxford follow-up study: There were no reports of discontinuation as a result of an acne episode in any of the progestin only pill user groups.

Collaborative Group

4.1 percent of the women in the desogestrel group reported acne as an adverse event as compared to 4.2% in the levonorgestrel group.

Appraised by: The International Center for Evidence Based Medicine, East Tennessee State University

Update by: 14 January 2013

There is no association between use of a progestin only pill contraceptive and weight gain

Conclusion

Significant changes in weight were not a factor in discontinuation of the use of the progestin only pill. Not all studies documented weight gain, but for those who did, fluctuations in weight appeared mixed with some gaining, some losing and other staying about the same.

Clinical Question

Is there a use of a progestin only pill for contraception associated with weight gain?

Search Terms

Progestin only pill, POP, weight gain

Citations

McCann MF, Potter LS. Progestin-only oral contraception: A comprehensive review. Contraception 1994:50(Supplement 1), S9-S195.

Collaborative Study Group on the Desogestrel-containing progesterone-only pill. A double-blind study comparing the contraceptive efficacy, acceptability and safety of two progesterone-only pills containing desogestrel 75 mcg/day and levonorgestrel 30 mcg/day. European Journal of Contraception and Reproductive Health Care 1998;3:169-178

Object of research

Progestin only pills

Subject of research

Weight gain

Study Features

McCann and Potter

This is a literature review of earlier use of POPs (pre-1994) and change in weight among users. The review includes the following studies of non-breastfeeding women:

- An open label study in the United Kingdom of norethisterone 0.35 mg with 913 women using their POP for a total of 11,921 cycles.[1] Over half had switched from another oral contraceptive and 9% were postpartum and breastfeeding.
- An open label study of women in the United States (n=2,173) using norgestrel 0.075 mg for 1 to 47 cycles.[2]
- A record based study of 358 women in the United Kingdom using one or more of the three following progestin-only pills; norethindrone 0.35 mg, ethynodiol 0.5 mg and levonorgestrel 0.03 mg. These women used a POP for as long as 150 months for a cumulative total of 18,125 women-months.[3]

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[1] Lawson JP. Experience with norethisterone 0.35 mg daily as an oral contraceptive. Br J Fam Plann 1982;8:84-9.

[2] Korba VD, Paulson SR. five years of fertility control with microdose norgestrel: An updated clinical review. J Reprod Med 1974;13:71-5.

[3] Brooms M, Fotherby K. Clinical experience with the progesterone-only pill. Contraception 1990;42:489-495.

Collaborative Group

This is a double-blind comparison of two progestin-only pills, one containing desogestrel 75 mcg/day (n=979) and the other levonorgestrel 30 mcg/day (n=329). Weight measurements were routinely recorded at each visit during the study.

The Evidence

McCann and Potter

Not all of the studies provided information on weight fluctuations though the Lawson study reported that approximately 36% stayed within 2 pounds of their baseline weight, 33% lost more than 2 pounds and 31% gained more than 2 pounds. Other studies in this review reported a small number of patients (< 2%) complaining of weight gain

Collaborative Group

With respect to weight changes, no differences between treatment groups or significant changes from baseline body weight were noted during the study. Less than 3% of all women in the study reported weight gain as an adverse event.

Appraised by: The International Center for Evidence Based Medicine, East Tennessee State University

Update by: 24 December 2012

There is no association between use of a progestin only pill contraceptive and delays in return to fertility

Conclusion

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

Clinical Question

Is there a decrease in conception rate after cessation of a progestin only pill for contraception?

Search Terms

Progestin only pill, POP, return to fertility, conception rate.

Citations

McCann MF, Potter LS. Progestin-only oral contraception: A comprehensive review. Contraception 1994:50(Supplement 1), S9-S195.

Object of research

Progestin only pills

Subject of research

Cumulative conception rate within 1 year after termination of progestin-only pills, time to pregnancy.

Study Features

This is a literature review of earlier use of POPs (pre-1994) and return to fertility. The review includes

- 6 women in a study in the United Kingdom stopped use of their POP (norgestrel) in order to become pregnant, two within one cycle of use and the others after a period ranging from two to six months.
- 43 women in a study in the United Kingdom stopped use of their POP (norethisterone 0.35 mg)
- 83 women using a progestin-only pill in a study in the United Kingdom stopped use of their POP.

The Evidence

From these results of these studies, there does not appear to be any significant delays in return to fertility among women stopping their POP to become pregnant.

- In the study of 6 women, all these women became pregnant within six months, two of them within the first month

- In the study of 43 women using norethisterone 0.35 mg/day, the majority became pregnant within three months and 10 took longer than six months. The remainder of these women became pregnant between three and six months.
- In the study of 83 POP users, return to fertility was similar to those who stopped using a diaphragm to become pregnant.

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: The International Center for Evidence Based Medicine, East Tennessee State University

Update by: 20 December 2012

POPs are effective contraceptives in both breastfeeding and non-breastfeeding women when used correctly and consistently

Conclusion

Among studies among progestin-only pills, no significant differences among the different progestins were found with respect to contraceptive effectiveness. However, it should be noted that none of the studies comparing one progestin with another were sufficient in sample size to differentiate between differ progestins. Despite these limitations, it appears that when used correctly, progestin-only pills are effective in preventing pregnancy.

Clinical Question

Is the progestin-only pill effective contraception for women?

Search Terms

Progestogen-only pill, effectiveness

Citations

Grimes DA, Lopes LM, O`Brien PA, Raymond EG. Progestin-only pills for contraception: Cochrane Database of Systematic Reviews 2010, Issue 1. Art. No.: CD007541.DOI: 10.1002/14651858.Cd007541.pub2.

Object of research

Progestin-only pills

Subject of research

Breastfeeding and non-breastfeeding women

Study Features

This is a review of six randomized controlled trials of progestin-only pills assessing their efficacy. These studies included 2738 participants both breastfeeding and non-breastfeeding, and their sample sizes ranged from 86 to 1306 women. Trial locations included European countries, United Kingdom, United Stats, India, China, South Africa, Nigeria, and Kenya. Comparisons were made between progestin-only pills, between progestin-only pills and combined oral contraceptives, and the timing (six weeks or six months postpartum). It should be noted that none of the studies were of sufficient size to differentiate between any of the contraceptive methods.

The Evidence

The results for the pill comparisons were:

- no differences were found between the progestin-only pills containing desogestrel and levonorgestrel (Rate ratio=0.27; 95% CI 0.06-1.19). The Pearl index excluding

gross non-compliance was 0.14 for the desogestrel group and 1.17 for the levonorgestrel group.[1]

- no differences were found between the progestin-only pills containing mifepristone or those containing levonorgestrel (Odds ratio=0.71; 95% CI 0.07 to 6.95).
- in a WHO four-pill comparison, one year pregnancy rates were numerically highest with the progestin-only pill norethisterone 350 µg and lowest with the combination pill containing levonorgestrel 150 µg and ethinyl estradiol 30µg. At 360 days, the cumulative discontinuation rate for accidental pregnancy was lower with combined levonorgestrel and ethinyl estradiol (2.7%) than with the other pills: levonorgestrel alone (9.5%), combined norethisterone and mestranol (8.3%), and norethisterone alone (13.2%). No statistically significant differences were noted among the four regimens though the study was not planned with sufficient sample size to detect expected differences.
- in the small study of the progestin-only pill containing ethynodiol versus a combined oral contraceptive, no pregnancies were reported.

In one study in which the comparison was of a progestin-only pill taken at 6 weeks postpartum versus the same pill taken 6 months, postpartum, no differences in pregnancy rates were noted.

Appraised by: The International Center for Evidence Based Medicine, East Tennessee State University

Update by: 20 December 2012

[1] Collaborative study Collaborative Study Group on the Desogestrel-containing progesterone- only pill. A double-blind study comparing the contraceptive efficacy, acceptability and safety of two progesterone-only pills containing desogestrel 75 mcg/day and lveonorgestrel 30 mcg/day. European Journal of Contraception and Reproductive Health Care 1998;3:169-178

Progestin-only pills do not appear to decrease milk volume for women who are breast feeding and are safe for the breastfed infants

Conclusion

Progestin-only pills are safe as a method of contraception for breast feeding women and no significant changes were observed in either volume of milk or milk composition for their infants.

Clinical question

For the infants of breastfeeding women, are POPs safe?

Search terms

Progestin-only pills, POP, breast feeding

Citation

McCann MF, Potter LS. Progestin-only oral contraception: A comprehensive review. Contraception 1994:50(Supplement 1), S9-S195.

Truitt ST, Fraser A, Gallo MF, Lopez LM, Grimes DA, Schulz KF. Combined hormonal versus nonhormonal versus progestin-only contraception in lactation. Cochrane Database of Systematic Reviews 2003, Issue 2. Art. No.: CD003988. DOI:10.1002/14651858.CD003988.

Object of Research

Progestin-only pills.

Subject of Research

Milk volume, total fat, nitrogen, lactose, calcium, phosphorous, magnesium, sodium, potassium, osmolality, nursing frequency, supplementation, infant weight, morbidity.

Study Features

McCann and Potter

This is a literature review of earlier use of POPs (pre-1994) and the effect of a progestin-only pill on breast milk. The review includes the following studies of breastfeeding women in which there was documentation that the progestin only pill was started more than one week postpartum. Various methods of measurement were used.

- Egypt (1971): 10 women using a progestin only pill containing lynestrenol, 10 using a non-hormone releasing IUD and 30 using a combined oral contraceptive.
- India (1977): 30 women using a progestin only pill containing norgestrel, 28 using female sterilization.
- Egypt (1969): undetermined number of POP users (lynestrenol), but 120 total in the study.
- WHO (1994): Studies conducted in Chile, Egypt, Hungary, Kenya and Thailand. 475 women using a POP containing either levonorgestrel (n=246) or lynestrenol (n=229).

There were 1,115 users of other progestin-only methods and 876 users of non-hormonal methods.

Truitt et al.

This is a systematic review of studies including a progestin only pill which was used by breastfeeding women. Two studies included a progestin-only pill as well as a comparator and are as follows:

- Mexico (1976): Twelve women received a POP containing norethindrone 0.35 mg for 14 days and 8 women received a placebo for the same time period. Women were aged 18-36 years of age. Comparisons included milk production, biochemical composition of milk and infant weight.
- WHO (1984): Multicenter randomized double-blind trial conducted in Hungary and Thailand. 86 women received a combination oral contraceptive and 85 received norgestrel 0.075 mg. All interventions were initiated 6 weeks postpartum and women were followed for 24weeks.

The Evidence

McCann and Potter

Results were as follows:

- Egypt (1971): For those women using the progestin only pill, there were no changes in lactose content.
- India (1977): There was no change in milk quantity for women using a POP or the nonhormonal groups, but a significant reduction for women using a combined oral contraceptive.
- Egypt (1969): Overall POP users ranked better than the other treatment groups.
- WHO (1994): There were no significant differences among the different contraceptive groups with respect to infant weight, duration of exclusive breastfeeding, the number of breastfeeds per day, and tests of infant psycho-motor development.

Truitt et al.

Results were as follows.

- Mexico (1976): Between the POP and placebo groups, there were no significant differences in milk volume, infant growth or milk composition during the fourteen days of the study.
- WHO (1984): Statistically significant declines in milk volume were reported for the combination oral contraceptive group compared to the progestin-only pill users. Declines began at the initiation of the study at 6 weeks postpartum and continued throughout the study. For all centers in the study, milk volume declined 42% for the COC users versus 12% for the POP group. High lost to follow-up in this study makes interpretation of these data difficult.

Appraised by: The International Center for Evidence Based Medicine, East Tennessee State University

Update by: 12 January 2013

Use of a progestin only pill often results in menstrual cycle changes primarily in irregular bleeding or spotting

Conclusion

Progestin-only pills are associated with more bleeding disturbances than combined oral contraceptives and discontinuation for this reason can be as high as 10 percent in the first year of use. Among the different progestins, desogestrel was associated with more bleeding problems than the pill containing levonorgestrel.

Clinical Question

Do women who are not breastfeeding, but using progestin only pills, experience changes in vaginal bleeding?

Search Terms

Progestogen-only pill, vaginal bleeding

Citations

Grimes DA, Lopes LM, O`Brien PA, Raymond EG. Progestin-only pills for contraception: Cochrane Database of Systematic Reviews 2010, Issue 1. Art.No.: CD007541.DOI: 10.1002/14651858.Cd007541.pub2.

Object of research

Progestogen-only pills

Subject of research

Vaginal bleeding

Study Features

This systematic review examined six randomized controlled trials of progestin-only pills for differences in efficacy, acceptability, continuation rates, and bleeding disturbances. The POPs included in these studies contained one of the following progestins; levonorgestrel 35 mcg and 30 mcg, desogestrel 75 mcg, mifepristone 5 mg, ethynodiol diacetate 0.25 mg, norethisterone 350 mcg, norethisterone acetate 300 mcg and megestrol acetate 700 mcg. The trials enrolled 2738 participants, and sample sizes in the six studies ranged from 86 to 1306 women. Trial locations included European countries, United Kingdom, United Stats, India, China, South Africa, Nigeria, and Kenya.

The Evidence

In the trial comparing the desogestrel versus levonorgestrel progestin-only pill (Collaborative), desogestrel was associated with more bleeding problems than levonorgestrel. Discontinuation because of irregular bleeding was more common (rate ratio=1.32; 95% CI 0.99-1.78) though the difference was not statistically significant.

The trial comparing low-dose mifepristone versus a levonorgestrel progestin-only pill (Lakha) found a higher prevalence of amenorrhea occurred in the former group; about half of women assigned to mifepristone had no bleeding while taking the drug.

Bleeding irregularities were more common with the progestin-only pill (not currently available at this dose) than with the combined oral contraceptive in the Paulsen trial. Irregular cycles occurred more often in all women assigned to the progestin-only pill, in contrast to those assigned to the COC (odds ratio 135.96; 95% CI 7.63 to 2421.02). Bleeding between menstrual periods was also significantly more common with the progestin-only pill (odds ratio= 6.20; 95% CI 2.11-18.22)

In the WHO four-pill comparison study (Sheth), the four pills included norethisterone 350 µg, levonorgestrel 30 µg, norethisterone 1mg plus mestranol 50 µg, and levonorgestrel 150 µg plus ethinyl estradiol 30 µg). At 360 days, the cumulative discontinuation rate for bleeding disturbances was lower with combined levonorgestrel and ethinyl estradiol (2.7%) than with the other pills: combined norethisterone and mestranol (23.2%), norethisterone alone (24.2%), and levonorgestrel alone (26.0%).

In the Vessey trial, discontinuation related to menstrual disturbances was significantly less common with norethisterone acetate (rate ratio=0.30; 95% CI 0.15-0.62), than with norgestrel.

Appraised by: The International Center for Evidence Based Medicine, East Tennessee State University

Update by: 17 December 2012

Use of a progestin-only pill among non-breastfeeding women may be associated with amenorrhea

Conclusion

Among progestin only pill users, complaints and reasons for discontinuation of their contraceptive include amenorrhea.

Clinical Question

Is there an increase in amenorrhea among women taking progestin only pills?

Search Terms

Progestin-only pills, progestin-only oral contraceptives, amenorrhea

Citations

Belsey EM. Vaginal bleeding patterns among women using one natural and eight hormonal methods of contraception. Contraception. 1988;38:181-206.

Broome M, Fotherby K. Clinical experience with the progesterone-only pill. Contraception 1990;42(5): 498-495.

Collaborative Study Group on the Desogestrel-containing Progestogen-only Pill. A double-blind study comparing the contraceptive efficacy, acceptability and safety of two progestogen-only pills containing desogestrel 75 micrograms/day or levonorgestrel 30 micrograms/day. Eur J Contracept Reprod Health Care 1988 Dec;3(4):169-78.
[Note that information from this study was supplemented by information from the Cerazette Product Monograph]

Object of research

Progestin-only pills

Subject of research

Amenorrhea

Study Features

Belsey

This is a review of six clinical trials in which menstrual diary records were used to assess vaginal bleeding patterns. The review includes the experience of 5,257 women using one of the following contraceptive methods.

- the non-hormonal ovulation method,
- one of three different combined oral contraceptives containing either norethisterone acetate 1.0 mg + ethinyl estradiol 0.05 mg or levonorgestrel 0.25 mg + ethinyl estradiol 0.05 mg or levonorgestrel 0.15 mg + ethinyl estradiol 0.03 mg,
- one of two progestin only pills; norethisterone acetate 0.35 mg or levonorgestrel 0.03 mg,

- a vaginal ring releasing 20 mcg of levonorgestrel daily or
- depo provera given once every three months. The studies were carried out in 34 WHO centers worldwide.

Broome et al.

This was a study of 358 progesterone-only pills users at a clinic in England. Data were abstracted from clinic records. The POPs used contained either ethynodiol diacetate 500 mcg, noresthisterone 350 mcg or levonorgestrel 30 mcg. The women in this study used their selected POP for up to 150 months with 34 (9.5%) using theirs for less than 6 months.

Collaborative Group

This is a randomized, double-blind study of progestin-only pills in which 989 women were assigned to the desogestrel 75 mcg group and 331 to the levonorgestrel 30 mcg group. Women were observed for 13 28-day cycles. Bleeding patterns for non-breastfeeding and those for breastfeeding women were analyzed separately as lactation may affect the bleeding pattern.

The Evidence

Belsey

During the first year, no women using a progestin-only pill or the ovulation method recorded a period of amenorrhea. Less than 1% of all women who were using a combined oral contraception reported an episode of amenorrhea while over 40% of the depo provera users reported amenorrhea in the fourth quarter of the year.

Broome et al.

Of those women using their POP for more than six months, 29 (9.0%) reported a mixture of regular cycles and amenorrhea 20 (6.2%) reported a mixture of irregular cycles and amenorrhea and 3 (0.9%) reported a mixture of regular or irregular cycles and amenorrhea.

Collaborative Group

The incidence of amenorrhea was 3.4 times higher with the desogestrel group as compared to those using the levonorgestrel pill. Within this group, women who switched from another contraceptive to a progestin-only pill experienced a higher incidence of amenorrhea than those who were starting this regimen without an immediate prior contraceptive.

Appraised by: The International Center for Evidence Based Medicine, East Tennessee State University

Update by: 14 February 2013

Use of progestin-only pills does not appear to increase the rate of ectopic pregnancy when compared to rate in the general population

Conclusion

Among women using a progestin-only pill, there does not appear to be an increase in the ectopic pregnancy rate. While precise rates are difficult to estimate given the small number of POP users worldwide and the subsequent decrease in pregnancies, like all contraceptives, the absolute number of ectopic pregnancies does not increase as a result of the overall reduction of pregnancies. Note however though the absolute numbers of ectopic pregnancies are not increased, should a pregnancy occur while using a POP, there is a greater likelihood that it is ectopic than with other contraceptive methods.

Clinical Question

Is there an increase in the risk of ectopic pregnancies among women taking progestin only pills?

Search Terms

Progestin-only pills, progestin-only oral contraceptives, ectopic pregnancy

Citations

McCann MF, Potter LS. Progestin-only oral contraception: A comprehensive review. Contraception 1994:50(Supplement 1), S9-S195.

Collaborative Study Group on the Desogestrel-containing Progestogen-only Pill. A double-blind study comparing the contraceptive efficacy, acceptability and safety of two progestogen-only pills containing desogestrel 75 micrograms/day or levonorgestrel 30 micrograms/day. Eur J Contracept Reprod Health Care 1988 Dec;3(4):169-78.

Lesley-Anne Furlong, M.D. Ectopic Pregnancy Risk When Contraception Fails: A Review. The Journal of Reproductive Medicine: 11/November 2002 – Volume 47 – pp 881-885.

Object of research

Progestin-only pills

Subject of research

Ectopic pregnancy

Study Features

McCann and Potter

This is a review of 8 selected studies of ectopic pregnancies among users of progestin-only oral contraceptives. Six of the studies were retrospective and two prosepective. The progestin-only pill formulations included in this review are norgestrel and norethindrone.

Collaborative Group

This is a randomized, double-blind study of progestin-only pills in which 989 women were assigned to the desorgestrel 75 mcg group and 331 to the levonorgestrel 30 mcg group. Women were observed for 13 28-day cycles.

Lesley-Anne Furlong, M.D.

This narrative review focuses on 7 contraceptive drug products with an increased risk of ectopic pregnancy when the method fails. Data were extracted from reviews of clinical trials submitted to the FDA to support marketing application and from the medical literature.

The Evidence

McCann and Potter

In the five retrospective studies, results were:

- UK(n=1042 POP users): 1 ectopic pregnancy per 1000 women-years of use
- UK(n=135 POP users): 20 ectopic pregnancies per 1000 women-years of use
- Zimbabwe (2931 POP users): 3 ectopic pregnancies per 1000 women-years of use
- UK, Jamaica, New Zealand (n=913 POP users): 3 ectopic pregnancies per 1000 women-years of use
- Norway(n=206 POP users): 1.3 ectopic pregnancies per 1000 women-years of use

In the three prospective studies, results were:

- UK(n=613 users): 8 ectopic pregnancies per 1000 women-years of use
- UK (n=unspecified): 0 ectopic pregnancies per 1000 women-years of use
- India, Yugoslavia (n=302 POP users): 0.9 ectopic pregnancies per 1000 women-years of use

There were no non-hormonal control groups in these studies.

Collaborative Group

There was one ectopic pregnancy in the levonorgestrel group and none in the group using desogestrol.

Furlong, M.D.

The proportion of ectopic pregnancies among all pregnancies is 1:20 for users of progestin-only pills as compared to an estimate of 1:50 in women in the United States not using a contraceptive method.

Comment: It should be noted that the expected number of pregnancies among women using no contraceptive method would be expected to be greater than for those using a progestin-only pill. Thus, the absolute number of POP users having an ectopic pregnancy would not be expected to exceed that of those using no contraceptives. As McCann and Potter state, “the incidence of ectopic pregnancy (for women using a POP) is similar to that for women not using any contraceptive method. A history of ectopic pregnancy need not be considered a contraindication to POP use.” They emphasize that for women who become pregnant using a POP need to be alert to symptoms of ectopic pregnancy.

Appraised by: The International Center for Evidence Based Medicine, East Tennessee State University

Update by: 10 December 2012

While women using a progestin-only pill for contraception experience some nausea though current study designs do not allow an assessment of causality

Conclusion

Among progestin only pill users, complaints and reasons for discontinuation of their contraceptive include nausea. The extent to which nausea is caused by their pill use cannot be determined from the available data.

Clinical Question

Is there an increase in the risk of nausea among women taking progestin only pills?

Search Terms

Progestin-only pills, progestin-only oral contraceptives, nausea, gastrointestinal distress

Citations

McCann MF, Potter LS. Progestin-only oral contraception: A comprehensive review. Contraception 1994:50(Supplement 1), S9-S195.

Collaborative Study Group on the Desogestrel-containing Progestogen-only Pill. A double-blind study comparing the contraceptive efficacy, acceptability and safety of two progestogen-only pills containing desogestrel 75 micrograms/day or levonorgestrel 30 micrograms/day. Eur J Contracept Reprod Health Care 1988 Dec;3(4):169-78.

Object of research

Progestin-only pills

Subject of research

Nausea

Study Features

McCann and Potter

This is a review of 8 selected studies that included information about discontinuation of a progestin only pill due to a non-menstrual side effect. Of these, six were prospective and contained discontinuation rates for either nausea or gastrointestinal distress. Two others reported discontinuation for non-menstrual side effects as a group and were also excluded from this assessment. These four studies are as follows:

- England (1977): This is a prospective study with one year follow-up of three progestins; norethisterone 0.35 mg (n=200), chlormadinone acetate 0.5 mg (n=182), and mesgestrol acetate 0.5 mg (n=174). Most of the women initiating their POP were less than six months postpartum though reports about breastfeeding were not included.

- United States (1974): This was an open label study of 2,202 women using norgestrel 0.075 mg studied from 1 to 67 cycles.
- UK, Jamaica, New Zealand (1982): This is multicenter study of norethisterone 0.35 mg of 913 women. The median age of these women was 27 and ranged from 16 to 54 years of age.
- England (1972): These data were obtained as part of the continuing follow-up of contraceptive users in the Oxford Family Planning Association. Only data from the norethisterone users (1746 women years of use). The study included other contraceptive users of both hormonal and non-hormonal methods.

Collaborative Group

This is a randomized, double-blind study of progestin-only pills in which 989 women were assigned to the desorgestrel 75 mcg group and 331 to the levonorgestrel 30 mcg group. Women were observed for 13 28-day cycles.

The Evidence

McCann and Potter

In the five studies, results were:

- England: Less than 1 percent of the northesterone and megestrol acetate users discontinued for nausea. 1 percent of the chlormadinone acetate users discontinued for nausea.
- United States: Less than 1 percent of the users of norgestrel discontinued because of gastrointestinal distress.
- UK, Jamaica, New Zealand: No discontinuations were reported for nausea or gastrointestinal distress.
- England/Oxford follow-up study: Approximately 3 percent of all users norethisterone users discontinued because of gastrointestinal distress as compared to 1 percent of those using all other contraceptives included in the follow-up. Note these included both hormonal and non-hormonal contraceptives.

Collaborative Group

3.3 percent of the women in the desogestrel group reported nausea as an adverse event as compared to 1.5% in the levonorgestrel group.

Appraised by: The International Center for Evidence Based Medicine, East Tennessee State University

Update by: 14 January 2013

Women using a progestin-only pill for contraception do not appear to experience elevated levels of breast tenderness

Conclusion

Among progestin only pill users, complaints and reasons for discontinuation of their contraceptive include breast tenderness. However, the effect of a progestin only pill on increasing breast tenderness is not clear base on most available data.

Clinical Question

Is there an increase in breast tenderness among women taking progestin only pills?

Search Terms

Progestin-only pills, progestin-only oral contraceptives, breast tenderness, breast pain

Citations

McCann MF, Potter LS. Progestin-only oral contraception: A comprehensive review. Contraception 1994:50(Supplement 1), S9-S195.

Collaborative Study Group on the Desogestrel-containing Progestogen-only Pill. A double-blind study comparing the contraceptive efficacy, acceptability and safety of two progestogen-only pills containing desogestrel 75 micrograms/day or levonorgestrel 30 micrograms/day. Eur J Contracept Reprod Health Care 1988 Dec;3(4):169-78.

Object of research

Progestin-only pills

Subject of research

Breast tenderness, breast pain

Study Features

McCann and Potter

This is a review of 8 selected studies that included information about discontinuation of a progestin only pill due to a non-menstrual side effect. Of these, six were prospective and contained discontinuation rates for side effects. Two others reported discontinuation for non-menstrual side effects as a group and were excluded from this assessment. These four studies are as follows:

- England (1977): This is a prospective study with one year follow-up of three progestins; norethisterone 0.35 mg (n=200), chlormadinone acetate 0.5 mg (n=182), and mesgestrol acetate 0.5 mg (n=174). Most were less than six months postpartum though reports about breastfeeding were not included.
- United States (1974): This was an open label study of 2,202 women using norgestrel 0.075 mg studied from 1 to 67 cycles.

- UK, Jamaica, New Zealand (1982): This is multicenter study of norethisterone 0.35 mg of 913 women. The median age of these women was 27 and ranged from 16 to 54 years of age.
- England (1972): These data were obtained as part of the continuing follow-up of contraceptive users in the Oxford Family Planning Association. Only data from the norethisterone users (1746 women years of use). The study included other contraceptive users of both hormonal and non-hormonal methods.

Collaborative Group

This is a randomized, double-blind study of progestin-only pills in which 989 women were assigned to the desorgestrel 75 mcg group and 331 to the levonorgestrel 30 mcg group. Women were observed for 13 28-day cycles.

The Evidence

McCann and Potter

In the four studies, results were:

- England: There were no reports of discontinuation as a result of breast tenderness in any of the progestin only pill user groups.
- United States: Less than $^1/_2$ of a percent of the users of norgestrel discontinued because of a breast discomfort.
- UK, Jamaica, New Zealand: No discontinuations were reported for breast discomfort.
- England/Oxford follow-up study: In the norethisterone group, 5.1% of the women in the study discontinued because of breast discomfort. In this study, breast discomfort appeared to be somewhat more common among POP discontinuers.

Collaborative Group

4.0 percent of the women in the desogestrel group reported breast discomfort as an adverse event as compared to 3.1% in the levonorgestrel group.

Appraised by: The International Center for Evidence Based Medicine, East Tennessee State University

Update by: 15 January 2013

Because of a lack of data, no risk for progestin only pill (POP) users with respect to endometrial cancer can be assessed. However, among users of combined oral contraceptives, there appears to be a protective effect against endometrial cancer

Conclusion

Because use of the small numbers of POP users in available studies of the association between hormonal contraceptives and endometrial cancer, inferences must be drawn from studies involving combined oral contraceptives. Data from these studies suggest that combined oral contraceptives may confer a long-term protection against endometrial cancer.

Clinical Question

Are women who are taking or have taken progestin only pills at an increased risk for endometrial cancer?

Search Terms

Progestin only pills, endometrial cancer

Citations

McCann MF, Potter LS. Progestin-only oral contraception: A comprehensive review. Contraception 1994:50(Supplement 1), S9-S195.

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:

Progestin-only pills

Subject of Research:

Endometrial cancer

Study Features

McCann and Potter

This is a literature review of earlier use of POPs (pre-1994) and cancer risk among users of progestin-only pills. The article includes only two studies of the relationship of POP use and endometrial cancer. In all cases, the numbers of POP users are small and findings must be interpreted cautiously. The studies are:

- the Cancer and Steroid Hormones (CASH) study conducted by the US Centers for Disease Control and included only one case and six controls who had used POPs exclusively, and

- the WHO Collaborative Study of Neoplasia and Steroid Contraception in which not cases of exclusive use of POPs were found and only two controls.

Study features of the COC studies are as follows:

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.

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

McCann and Potter

Because of the small number of exclusive POP users identified in the case control, no inferences with respect to endometrial cancer can be made.

In the combined oral contraceptives studies, the evidence was the following:

Vessey and Painter

The rate ratio calculated in this study had never users as the reference group. The findings were:

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

Tao et al.

In this study, the findings are that

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

Comment: Use of COCs helps protect against endometrial cancer. This protection continues well after stopping use of the COC. (Reference: Family Planning: A Global Handbook for Providers)

Appraised by: The International Center for Evidence Based Medicine, East Tennessee State University;

Update by: 30 December 2012

Because of a lack of data, no risk for progestin only pill (POP) users with respect to ovarian cancer can be assessed

Conclusion

Because use of the small numbers of POP users in available studies of the association between hormonal contraceptives and ovarian cancer, inferences must be drawn from studies involving combined oral contraceptives. Data from these studies suggest that combined oral contraceptives may confer a long-term protection against ovarian cancer.

Clinical Question

Are women who are taking or have taken progestin only pills at an increased risk for ovarian cancer?

Search Terms

Progestin only pills, ovarian cancer

Citations

McCann MF, Potter LS. Progestin-only oral contraception: A comprehensive review. Contraception 1994:50(Supplement 1), S9-S195.

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: Progestin-only pills

Subject of Research: Ovarian cancer

Study Features

McCann and Potter

This is a literature review of earlier use of POPs (pre-1994) and cancer risk among users of progestin-only pills. The article includes only three studies of the relationship of POP use and ovarian cancer. In all cases, the numbers of POP users are small and findings must be interpreted cautiously. The studies are:

- the Cancer and Steroid Hormones (CASH) study conducted by the US Centers for Disease Control and included only one case and eight controls who had used POPs exclusively,
- the WHO Collaborative Study of Neoplasia and Steroid Contraception in which no cases of exclusive use of POPs were found and the number of cases among the controls was not reported,
- a third case control study included four cases and 57 controls who had ever used POPs and one case and 22 controls who had used POPs for at least three years.

Study features of the COC studies are as follows:

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

McCann and Potter

Because of the small number of exclusive POP users identified in the case control, no inferences with respect to ovarian cancer can be made.

In the combined oral contraceptives studies, the evidence was the following:

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 [95% CI: 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 [99% CI: 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: Use of COCs helps protect against ovarian cancer. This protection continues well after stopping use of the COC. (Reference: Family Planning: A Global Handbook for Providers)

Appraised by: The International Center for Evidence Based Medicine, East Tennessee State University

Update by: 30 December 2012

There is insufficient data to assess any relationship between POP use and an increased breast cancer risk. However, among the available small studies, there does not appear to be any increased risk of breast cancer for progestin only pill users

Conclusion

A significant main problem in assessing POP risk and breast cancer is that the number of women worldwide who have used the progestin only pill exclusively is very small and insufficient to assess risks for relatively rare events such as breast cancer. However, there does not appear to be any association between progestin only pill use and breast cancer. Note that this is based on small numbers, but the study results are consistent in suggesting that there is no association between the use of POPs and breast cancer. Further there is a suggestion that the longer the duration of use, the greater the protective effect.

Clinical Question

Are women who are taking or have taken progestin-only pills at an increased risk for breast cancer?

Search Terms

Progestin-only pills, breast cancer

Citations

McCann MF, Potter LS. Progestin-only oral contraception: A comprehensive review. Contraception 1994:50 (Supplement 1), S9-S195.

Object of Research

Progestin-only pills

Subject of Research

Breast cancer

Study Features

This is a literature review of earlier use of POPs (pre-1994) and cancer risk among users of progestin-only pills. In all cases, the numbers of POP users are small and findings must be interpreted cautiously. The article includes:

- a comprehensive review of POP users and breast cancer risk citing five different studies with two of them analyzing risk and duration of user,
- the UK National Case-Control Study of breast cancer among women age 35 or younger contains the largest number of POP users.
- Included were 123 cases and 116 controls who had used POPs. Whether or not the woman had ever breastfed was one of several variables controlled for in the analysis,

- a Danish case control study that evaluated duration of use. This included two groups of POP users; 28 cases and 29 controls,
- a British case control study among women up to age 50. It included 33 POP cases and 29 controls,
- a small French study of 9 POP cases and 10 controls were evaluated for breast cancer risk.

The Evidence

Comprehensive review

In the five studies in which progestin-only pill users were analyzed separately from combined oral contraceptive users, no evidence of an elevated risk was found in any of the studies. The two studies in this review that evaluated duration of POP use as a risk factor for breast cancer suggested a protective effect the longer the use. One of these reviewed studies was conducted by the CASH (Cancer and Steroid Hormone) breast cancer study group and they computed an adjusted odds ratio of 1.3 based on an unspecified number of POP users up to age 50.

UK National Case-Control Study

The adjusted odds ratio for this study was 1.0 suggesting neither an elevated nor decreased risk for breast cancer among POP users. However, there was a suggested protective effect with duration of use as the odds ratio was 1.35 for use up to 12 months, 0.73 for 13-24 months, 0.59 for more than 24 months of use.

Danish Case Control Study

In this study an odds ratio of 0.99 [95% CI: 0.6 - 6.17] was found for ever users of POPs. POP use of less than five years was associated with an odds ratio of 1.31 [95% CI: 0.7 – 2.6] was found compared with 0.65 [95% CI: 0.3 – 1.5] for five or more years of use.

British Case Control Study

In this study, among women POP users up to age 50, a crude odds ratio of 1.11 [95% CI: 0.7 – 1.8] was found.

French Study

An odds ratio of 1.1 [95% CI: 0.4 – 2.7] for breast cancer risk was found.

Appraised by: The International Center for Evidence Based Medicine, East Tennessee State University

Update by: 29 December 2012

The use of a progestin only pill for contraception is associated with an increase in the risk of a functional ovarian cyst

Conclusion

Based on the results of this study, use of the progestin only pill is associated with a high rate of symptomatic cyst formation.

Clinical Question

Is there an increase in the risk of functional ovarian cysts among women taking progestin only pills?

Search Terms

Progestin only pills, functional ovarian cysts

Citation

Tayob Y, Adams J, Jacobs HS, Guillebaud J. Ultrasound demonstration of increased frequency of functional ovarian cysts in women using progestogen-only oral contraception. Br J Obstetrics and Gynaecology 1985;92:1003-1009.

Object of research

Progestin only pills

Subject of research

Functional ovarian cysts

Study Features

This is a study of 21 progestin-only pill users with 21 controls. Six used a progestin-only pill containing 30 mcg of levonorgestrel, 8 used one containing 350 mcg of morethisterone, and the remaining 7 used a pill containing 500 mcg of ethynodiol diaceate. All progestin-only pill users were symptom free at the time of study initiation. Controls consisted of healthy volunteers aged between 24 and 37 years who reported regular menstrual cycles and were not exposed to any artificial hormones or any other medications. The majority used the diaphragm for contraception and none had a past history of ovarian cyst formation. Controls were similar to the progestin only pill users in terms of age, body weight and previous fertility.

The Evidence

Among the progestin only pills users, 8 (38%) had a functional cyst identified by an ultrasound scan at the end of the first bleeding episode as compared to 4 (19%) of the control group. For the progestin only pill group, three of the cysts regressed during the next cycle. Eleven of the 14 pill users who failed to ovulate also had a function cyst. In the control group

ovulation was demonstrated in 16 of the 21 women. In a sub study of 7 of the pill users, all cysts disappeared by the end of the second pill-free cycle.

Appraised by

The International Center for Evidence Based Medicine, East Tennessee State University

Update by:

11 November 2012

The association between POP use and the incidence of headache is not clear

Conclusion

There is some evidence available that POPs use is associated with the occurrence of headache, though the precise extent to which these common symptoms are actually caused by the pills cannot be determined from available data.

Clinical Question

Is the use of progestin-only pills associated with an increased risk of a headache?

SearchTerms

Progestin-only pills, progestin-only oral contraceptives, headache

Citations

Collaborative Study Group on the Desogestrel-containing Progestogen-only Pill. A double-blind study comparing the contraceptive efficacy, acceptability and safety of two progestogen-only pills containing desogestrel 75 micrograms/day or levonorgestrel 30 micrograms/day. Eur J Contracept Reprod Health Care 1988 Dec;3(4):169-78.

McCann MF, Potter LS. Progestin-only oral contraception: A comprehensive review. Contraception 1994:50(Supplement 1), S9-S195.

Object of research: Progestin-only pills

Subject of research: Headache

Study Features

Collaborative Group

This is a randomized, double-blind study of progestin-only pills in which 989 women were assigned to the desorgestrel 75 mcg group and 331 to the levonorgestrel 30 mcg group. Women were observed for 13 28-day cycles.

McCann and Potter

This is a literature review of earlier use of POPs (pre-1994) and reports of headache. Studies reporting discontinuation for and/or reports of headache include the following:

- a prospective study of 556 English women using a progestin-only pill containing norethendrone 0.35 mg, chlormadione acetate 0.5 mg, or megestrol acetate 0.05 mg,[1]
- a prospective, open label study of 2,202 women from eight clinical investigations in the United States and Puerto Rico who used a progestin-only pill containing 0.075 mg norgestrel continuously for 1 to 67 consecutive cycles,[2]
- a multi-center study of 913 women in the United Kingdom, Jamaica, and New Zealand using a progestin-only pill containing norethisterone 0.35 mg,[3]
- data from the continuing follow-up study of the Oxford, England Family Planning Association, reporting the use of women using either norethisterone 0.35 mg, norgestrel 0.075 mg, ethynodiol diacetate 0.5 mg, or levonorgestrel 0.03 mg and[4]

- a randomized double-blind clinical trial of 2 progestin-only pills (norethisterone 0.35 mg or levonorgestrel 0.03 mg) of 258 women in India and Yugoslavia.

The Evidence

Collaborative Group

No major differences were seen for any of the adverse experience, i.e. the occurrence of headache (desogestrel 75 mcg/day, 7.5%; levonorgestrel 30 mcg/day, 6,1%) were comparable in the two groups.

McCann and Potter

Selected results relating to the incidence of headaches with the use of a progestin-only pill from these studies are as follows:

- In the prospective study of 556 English women using a progestin-only pill, discontinuations in the study ranged from 1% for the noresthisterone group to 2.2% for the chlormadinone group.[1]
- In the prospective, open label study of 2,202 women from eight clinical investigations of norgestrel in the United States and Puerto Rico 1.2% discontinued due to headache.[2]
- In the multi-center study of 913 women in the United Kingdom, Jamaica, and New Zealand 3% discontinued due to either headache or migraine.[3]
- From the data of the continuing follow-up study of the Oxford, England Family Planning Association, 7.4% of the norethisterone users discontinued due to headache as compared to 6.1% for all other progestogen-only pill users.[4]
- The data from the WHO randomized double-blind clinical trial of 2 progestin-only pills (norethisterone 0.35 mg or levonorgestrel 0.03 mg) of 258 women in India and Yugoslavia the percentage of norethisterone discontinuations in the first year was given as 5.9% for all central nervous system reasons including headache and dizziness. The corresponding percentage for the levonorgestrel users was 2.7%.[5]

Comment: These discontinuation rates suggest that headache may be as a result of progestin-only pill use, but no causality can be established. For women of any age who develop a headache while using a POP the risks of continuing POP use may outweigh the benefits (there is no evidence of a causal association between POP use and headache).

Appraised by: The International Center for Evidence Based Medicine, East Tennessee State University

Update by: 27 December 2012

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[1] Hawkins DF, Benster B. A comparative study of three low-dose progestogens, chlormadinone acetate, megestrol acetate and norethisterone, as or contraceptives. Br J Obstet Gynaecol 1977;84:708-13.

[2] Korba VD, Paulson SR. Five years of fertility control with microdose norgestrel: An updated clinical review. J Reprod Med 1974;13:71-5.

[3] Lawson JP. Experience with norethisterone 0.35 mg daily as an oral contraceptive. Br J Fam Plann 1982;8:84-9.

[4] Vessey MP, Lawless M, Yeates D, McPherson K. Progestogen-only oral contraception. findings in a large prospective study with special reference to effectiveness. Br J Fam Plann 1985;10:117-21.

[5] WHO Task Force on Oral Contraceptives. A randomized, double blind study of two combined and two progestogen-only oral contraceptives. Contraception 1982;25:243-52.

The use of a progestin only pill for contraception is not associated with an increase in cardiovascular risk

Conclusion

There is no convincing evidence that the use of progestin only pills for contraception increase the risk of a cardiovascular event (hypertension, a myocardial infarction, thromboembolic cerebrovascular accident or a venous thromboembolism). However, data that support this conclusion are limited by the small number of exposed cases and should be interpreted cautiously.

Clinical Question

Is there an increase in cardiovascular risk among women using progestin only pills for contraception?

Search Terms

Progestin only pills, increased blood pressure, cardiovascular event

Citation

Heinemann LA, Assman A, DoMinh T, Garbe E, et al. Oral progestogen-only contraceptives and cardiovascular risk: results from the Transnational Study on Oral Contraceptives and the Health of Women. Eur J Contracept Reprod Health Care 1999; 4(2):67-73.

Hussain S. Progestogen-only pills and high blood pressure: is there an association? A literature review. Contraception 2004 (69):89-97.

Collaborative Study Group on the Desogestrel-containing progesterone-only pill. A double-blind study comparing the contraceptive efficacy, acceptability and safety of two progesterone-only pills containing desogestrel 75 mcg/day and lveonorgestrel 30 mcg/day. European Journal of Contraception and Reproductive Health Care 1998;3:169-178

Object of research

Progestin only pills

Subject of research

Cardiovascular risk, increased blood pressure

Study Features

Heinemann et al.

This is a case control study of 1058 women aged 16-44 in 16 centers across five countries. Cases included in this study were women with a myocardial infarction, a cerebrovascular accident or a venous thromboembolism. Two groups with a total of 3808 controls unaffected by these diseases were also enrolled. One control group was hospitalized women with other diagnoses while the other control group was comprised of community controls. All controls were matched to the same 5-year age group as the cases.

Hussain

This review included four studies, two from the United States and two from the United Kingdom. Three of these were prospective control trials and one was a cross-sectional household survey. Women included in the studies were normotensive who had used progesterone-only pills for at least six cycles. Comparators were women who were non users of a contraceptive method or using one that was nonhormonal. A woman's blood pressure was considered elevated if she had a diastolic measurement of at least 90 mmHg.

Collaborative Group

This is a double-blind comparison of two progestin-only pills, one containing desogestrel 75 mcg/day (n=979) and the other levonorgestrel 30 mcg/day (n=329). Blood pressure was routinely recorded at each visit during the study.

The Evidence

Heinemann et al.

There were no significant differences between the controls and those with a cardiovascular event. The odds ratio with the corresponding 95% confidence interval (CI) is follows:

- all cardiovascular events odds ratio=0.84 (95% CI: 0.45 – 1.58)

Hussain

The evidence from these four research studies consistently did not support a significant association of hypertension with use of POPs by normotensive women up to 2 years of follow-up. No meta analysis was included in this study as the three controlled studies and one cross-sectional were not similar with respect to design.

Collaborative Group

There were no significant changes in mean systolic or diastolic blood pressure compared to the baseline measurement. For the desogestrel group, only two cases of hypertension were reported during the study.

Appraised by: The International Center for Evidence Based Medicine, East Tennessee State University

Update by: 18 January 2013

The use of a progestin only pill for contraception is not associated with an increase in the risk of a myocardial infarction

Conclusion

There is no convincing evidence that the use of progestin only pills for contraception increases the risk of a cardiovascular event including myocardial infarction. However, data that support this conclusion are limited by the small number of exposed cases and should be interpreted cautiously.

Clinical Question

Is there an increase in the risk of a myocardial infarction among women using progestin only pills for contraception?

Search Terms

Progestin only pills, myocardial infarction

Citation

Heinemann LA, Assman A, DoMinh T, Garbe E, et al. Oral progestogen-only contraceptives and cardiovascular risk: results from the Transnational Study on Oral Contraceptives and the Health of Women. Eur J Contracept Reprod Health Care 1999; 4(2):67-73.

Object of research: Progestin only pills

Subject of research: Myocardial infarction

Study Features

This is a case control study of 1058 women aged 16-44 in 16 centers across five countries. Cases were women with a myocardial infarction, thromboembolic a cerebrovascular accident or venous thromboembolism were included in the study. Two groups with a total of 3808 controls unaffected by these diseases were also enrolled. One control group contained hospitalized women with other diagnoses while the other control group were comprised of community controls. All controls were matched to the same 5-year age group as the cases.

The Evidence

There were no significant differences between the controls and those with a cardiovascular event. Odds ratios with the corresponding 95% confidence intervals (CI) are as follows:

- all cardiovascular events odds ratio=0.84 (95% CI: 0.45 – 1.58)
- myocardial infarction odds ratio=0.94 (95% CI: 0.31 – 2.91)

Appraised by: The International Center for Evidence Based Medicine, East Tennessee State University

Update by: 4 November 2012

The use of a progestin only pill for contraception is not associated with an increase in the risk of a stroke

Conclusion

There is no convincing evidence that the use of progestin only pills for contraception increase the risk of a cardiovascular event including stroke. However, data that support this conclusion are limited by the small number of exposed cases and should be interpreted cautiously.

Clinical Question

Is there an increase in the risk of a stroke among women using progestin only pills for contraception?

Search Terms

Progestin only pills, stroke

Citation

Heinemann LA, Assman A, DoMinh T, Garbe E, et al. Oral progestogen-only contraceptives and cardiovascular risk: results from the Transnational Study on Oral Contraceptives and the Health of Women. Eur J Contracept Reprod Health Care 1999; 4(2):67-73.

Object of research: Progestin only pills

Subject of research: Stroke

Study Features

This is a case control study of 1058 women aged 16-44 in 16 centers across five countries. Cases included in the study were women with a myocardial infarction, thromboembolic a cerebrovascular accident or a venous thromboembolism. Two groups with a total of 3808 controls unaffected by these diseases were also enrolled. One control group was hospitalized women with other diagnoses while the other control group was comprised of community controls. All controls were matched to the same 5-year age group as the cases.

The Evidence

There were no significant differences between the controls and those with a cardiovascular event. Odds ratios with the corresponding 95% confidence intervals (CI) are as follows:

- all cardiovascular events odds ratio=0.84 (95% CI: 0.45 – 1.58)
- stroke odds ratio=1.60 (95% CI: 0.24 – 10.72)

Appraised by: The International Center for Evidence Based Medicine, East Tennessee State University

Update by: 23 November 2012

The use of a progestin only pill for contraception is not associated with an increase in the risk venous thromboembolism

Conclusion

The risk of venous thromboembolic disease (VTE) associated with the use of progestin only pills appears to be low or non-existent. However, data that support this conclusion are limited and should be interpreted with caution.

Clinical Question

Is there an increase in the risk of venous thromboembolism among women using progestin only pills for contraception?

Search Terms

Progestin only pills, venous thromboembolism, VTE

Citation

Gomes PV, Deitcher SR. Risk of venous thromboembolic disease associated with hormonal contraceptives and hormone replacement therapy. Arch Intern 2004; 164:1965-1976.

Object of research

Progestin only pills

Subject of research

Venous thromboembolism

Study Features

Data on POP-related risk and VTE are derived from 8 case control studies. Two of these studies included women using the POP for therapeutic reasons (e.g. menstrual bleeding). These may have contained higher progestin doses or different progestins altogether. Women were matched for selected demographic factors including no previous history of cardiovascular diseases.

The Evidence

In the 6 case control studies which included only use of progestin only pills for contraception, there were no significant increases in risk of thromboembolism for users of progestin only pills for contraception.

Appraised by: The International Center for Evidence Based Medicine, East Tennessee State University

Update by: 14 December 2012

There does not appear to be a strong association between use of a progestin-only pill (POP) and an increased risk of depression

Conclusion

No association between POP use and depressive symptoms in young women, who use POPs for contraceptive reasons. Physicians prescribing POPs for contraception need not be overly concerned about their use and an increased risk of depression.

Clinical Question

Is the use of a progestin-only pill associated with an increased risk of depression?

Search Terms

Progestin-only pills, depression.

Citation

Lawson J. Experience with norethisterone 0.35 mg daily as an oral contraceptive. Br J Fam Planning 1982;8:84-89.

Sheth A, Jain U, Sharma S, Adatia A, Patankar S. A randomized, double-blind study of two combined and two progestogen-only oral contraceptives. Contraception 1982;24(3):243-252.

Vessey MP, Lawless M, Yeates D, McPherson K. Progestogen-only oral contraception. findings in a large prospective study with special reference to effectiveness. Br J Fam Planning 1985;10:117-121.

Object of Research

Progestin-only pills

Subject of Research

Depression, mood changes/swings

Study Features

Lawson

This was an open-label, multicentre study of norethisterone 0.35 mg (POP) taken daily by 913 women. The centres were in the UK, New Zealand and Jamaica though most of the women were British. Approximately 9% of these women were breastfeeding. The ages of the women users ranged from 16 to 54 years and half were 27 years of age or younger. Seventy-eight percent of the women had previously been pregnant and over half switched to this POP directly from another oral contraceptive.

Sheth et al.

A total of 559 women attending family planning clinics between July 1975 and February 1978 in the WHO Collaborating Centres for Clinical Research in Human Reproduction in Bombay, India and Ljubljana, Yugoslavia participated in a randomized, double-blind study of two combined oral contraceptives and two progestogen-only pills (POPs). The four con-

traceptives contained norethisterone 350 mcg, levonorgestrel 30 mcg, mestranol 50 mcg plus norethisterone 1 mg, or ethynyl estradiol 30 mcg plus levonorgestrel 150 mcg.

Vessey et al.

This is a prospective study of 17.032 women who attended the Oxford Family Planning Association from 1975 to 1983. Women were aged 25 to 39 years of age using an oral contraceptive, a diaphragm or an intrauterine device (IUD). Types of progestogen-only pills (POPs) were principally those containing norethisterone 0.35 mg, norgestrel 75 mcg, ethynodiol diacetate 0.5 mg or levonorgestrel 30 mcg.

The Evidence

Lawson

During the first cycle of use, depression was reported as a side effect by 12% of the women. At the end of the first year of use, 4.8% reported experience depression in the last month. Fourteen (1.5%) withdrew from the study due to reported depression.

Sheth et al.

At the end of the first year, discontinuation for all medical events was lowest for the ethinyl estradiol/levonorgestrel containing pill (28.2%) and highest for the mestranol/norethisterone containing pill. The two progestogen-only pills had discontinuation rates for medical reasons of 46.4% and 45.7%, for those containing levonorgestrel and norethisterone. None of these were classified as depression though there were five unspecified cases classified as “discontinued for other medical reasons” though the authors state “there were too few of such cases to discern any pattern among the groups.

Vessey et al.

For the group using a POP containing norethisterone 0.35 mg, 3.8% discontinued for a psychological disturbance. This is assumed to include depression as well as mood swings. For all other POPs, the corresponding discontinuation rate was 3.6%. For the two combined oral contraceptives included in the publication, 7.5% and 9.0%, respectively discontinued for psychological reasons. No information was given on reasons for termination of use of the diaphragm.

Appraised by: The International Center for Evidence Based Medicine, East Tennessee State University;

Update by: 15 February, 2013

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: The International Center for Evidence Based Medicine, East Tennessee State University

Update by: 14 December 2011

Notes