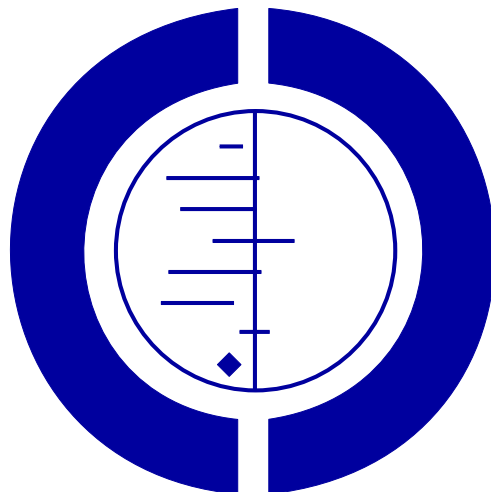


Oral contraceptives for functional ovarian cysts (Review)

Grimes DA, Jones LB, Lopez LM, Schulz KF



**THE COCHRANE
COLLABORATION®**

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2007, Issue 2

<http://www.thecochranelibrary.com>



TABLE OF CONTENTS

ABSTRACT	1
PLAIN LANGUAGE SUMMARY	1
BACKGROUND	2
OBJECTIVES	2
CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW	2
SEARCH METHODS FOR IDENTIFICATION OF STUDIES	3
METHODS OF THE REVIEW	3
DESCRIPTION OF STUDIES	3
METHODOLOGICAL QUALITY	4
RESULTS	4
DISCUSSION	5
AUTHORS' CONCLUSIONS	5
POTENTIAL CONFLICT OF INTEREST	5
ACKNOWLEDGEMENTS	5
SOURCES OF SUPPORT	5
REFERENCES	6
TABLES	7
Characteristics of included studies	7
Characteristics of excluded studies	8
ANALYSES	9
Comparison 01. Levonorgestrel 125 mcg plus ethinyl estradiol 50 mcg taken cyclically versus expectant management	9
Comparison 02. Norethindrone 1 mg plus mestranol 50 mcg daily versus expectant management	9
Comparison 03. Levonorgestrel 150 mcg plus ethinyl estradiol 30 mcg taken cyclically versus expectant management	9
Comparison 04. Desogestrel 150 mcg plus ethinyl estradiol 30 mcg taken cyclically versus expectant management	9
Comparison 05. Levonorgestrel 250 mcg plus ethinyl estradiol 50 mcg taken cyclically versus expectant management	10
Comparison 06. Levonorgestrel 50/75/125 mcg plus ethinyl estradiol 30/40/30 mcg taken cyclically versus expectant management	10
INDEX TERMS	10
COVER SHEET	10
GRAPHS AND OTHER TABLES	11
Analysis 01.01. Comparison 01 Levonorgestrel 125 mcg plus ethinyl estradiol 50 mcg taken cyclically versus expectant management, Outcome 01 Resolution of cyst within one menstrual cycle	11
Analysis 02.01. Comparison 02 Norethindrone 1 mg plus mestranol 50 mcg daily versus expectant management, Outcome 01 Resolution of cyst within nine weeks	12
Analysis 03.01. Comparison 03 Levonorgestrel 150 mcg plus ethinyl estradiol 30 mcg taken cyclically versus expectant management, Outcome 01 Resolution of cyst by third month	12
Analysis 03.02. Comparison 03 Levonorgestrel 150 mcg plus ethinyl estradiol 30 mcg taken cyclically versus expectant management, Outcome 02 Cyst volume after third month	13
Analysis 04.01. Comparison 04 Desogestrel 150 mcg plus ethinyl estradiol 30 mcg taken cyclically versus expectant management, Outcome 01 Resolution of cyst by 10 weeks	13
Analysis 05.01. Comparison 05 Levonorgestrel 250 mcg plus ethinyl estradiol 50 mcg taken cyclically versus expectant management, Outcome 01 Resolution of cyst by 10 weeks	14
Analysis 06.01. Comparison 06 Levonorgestrel 50/75/125 mcg plus ethinyl estradiol 30/40/30 mcg taken cyclically versus expectant management, Outcome 01 Resolution of cyst by 10 weeks	14

Oral contraceptives for functional ovarian cysts (Review)

Grimes DA, Jones LB, Lopez LM, Schulz KF

This record should be cited as:

Grimes DA, Jones LB, Lopez LM, Schulz KF. Oral contraceptives for functional ovarian cysts. *Cochrane Database of Systematic Reviews* 2006, Issue 4. Art. No.: CD006134. DOI: 10.1002/14651858.CD006134.pub2.

This version first published online: 18 October 2006 in Issue 4, 2006.

Date of most recent substantive amendment: 30 June 2006

ABSTRACT

Background

Functional ovarian cysts are a common gynecological problem among women of reproductive age worldwide. When large, persistent, or painful, these cysts may require operations, sometimes resulting in removal of the ovary. Since early oral contraceptives were associated with a reduced incidence of functional ovarian cysts, many clinicians inferred that birth control pills could be used to treat cysts as well. This became a common clinical practice in the early 1970s.

Objectives

This review examined all randomized controlled trials that studied oral contraceptives as therapy for functional ovarian cysts.

Search strategy

We searched the computer databases of CENTRAL, PubMed, POPLINE, and EMBASE for randomized controlled trials. We also examined the reference lists of articles and wrote to authors of all studies identified to seek articles we had missed.

Selection criteria

We included randomized controlled trials in any language that included oral contraceptives used for treatment and not prevention of functional ovarian cysts. Criteria for diagnosis of cysts were those used by authors of studies.

Data collection and analysis

Two authors independently abstracted data from the articles and entered them into RevMan 4.2. We used Peto odds ratios with 95% confidence intervals for dichotomous outcomes.

Main results

We identified four randomized controlled trials from three countries; the studies included a total of 227 women. Treatment with combined oral contraceptives did not hasten resolution of functional ovarian cysts in any trial. This held true for cysts that occurred spontaneously as well as those that 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.

Authors' conclusions

Although widely used for treating functional ovarian cysts, combined oral contraceptives appear to be of no benefit. Watchful waiting over several cycles is appropriate. Should cysts persist, surgical management is often indicated.

PLAIN LANGUAGE SUMMARY

Oral contraceptives to treat cysts of the ovary

Women of reproductive age usually release an egg about once a month. The ovary gets an egg from the inside of the ovary to its surface by creating a blister or fluid-filled space around the developing egg. When the blister (or cyst) reaches the surface of the ovary, it bursts and releases the egg into the abdominal cavity. After this occurs, the blister can develop into another type of cyst, which makes a

hormone (progesterone) that helps the pregnancy to grow. Most of these cysts come and go without problems. Sometimes, however, the cysts get large or painful; others may remain for months. Several decades ago, clinicians learned that women who were taking oral contraceptives (birth control pills) had fewer cysts, since the pills usually kept an egg from being released. Based on this fact, many clinicians started treating these cysts with oral contraceptives to make them go away faster.

This review searched for all the randomized controlled trials in the world that studied use of birth control pills to treat these benign (also called functional) cysts. We found four trials from three countries; they included 227 women. Two trials included women receiving drugs to help them get pregnant. The other two included women who developed cysts without fertility treatment. In none of these trials did oral contraceptives help the cysts go away faster. Thus, birth control pills should not be used for this purpose. Waiting several months for the cysts to go away on their own is a better approach.

BACKGROUND

Functional ovarian cysts (follicular and corpus luteum) are a common gynecological problem among women of reproductive age worldwide. Hospital-based studies in the U.K. and U.S. have provided a range of reported incidences. In England and Wales from 1983-85, the annual hospital discharge rate for women with a main diagnosis of ovarian cyst was 67 per 100,000 women (Westhoff 1992). From 1984-6 in the U.S., the comparable figure was 131 per 100,000 women. In recent U.S. reports, more than a quarter million women per year have been discharged from hospitals with a diagnosis of ovarian cysts (ICD-9 codes 620.0, 620.1, and 620.2; follicular, corpus luteum, and other and unspecified, respectively) (Kozak 2005). In cross-sectional studies using ultrasound evaluation of women, 4 to 7% had ovarian cysts >30 mm in diameter (Teichmann 1995; Christensen 2002). While many of these physiological cysts will resolve spontaneously, some require surgical intervention, with its attendant discomfort, risk, and expense (Chiaffarino 1998).

Early epidemiological studies reported an inverse relationship between use of oral contraceptives and surgically confirmed functional cysts (Anonymous 1974; Walnut Creek 1981; Booth 1992; Vessey 1987). Based on the apparent strong protective effect against functional cysts, some clinicians inferred that oral contraceptives might be useful for treatment as well as prevention. Since pituitary gonadotropins promote follicular growth and since combined oral contraceptives suppress gonadotropins, pills might decrease cyst size.

An uncontrolled case-series report popularized this approach. Spanos (Spanos 1973) described 286 reproductive-age women with adnexal masses ranging from 4 to 10 cm in diameter; he treated each with a combined oral contraceptive. Most cysts regressed, and those that did not were found at operation to be neoplasms. Despite the lack of a comparison group in this report, many clinicians (Anderson 1990; Muram 1990; Starks 1984) concluded that combined oral contraceptives hastened resolution of functional ovarian cysts, for example, claiming that "others have demonstrated that functional ovarian cysts regress more quickly when OCs are provided to women" (Anonymous 1982).

Despite the absence of an association between low-dose oral contraceptive use and the occurrence of functional ovarian cysts in more recent studies (Holt 1992; Lanes 1992; Parazzini 1996), this treatment continues to be recommended: "...higher dose formulations should be considered for treatment purposes, although the overall risk/benefit ratio must be evaluated with caution" (Chiaffarino 1998). Others, however, caution that, "The results of two small trials do not support the prescription of oral contraceptives to treat preexisting ovarian cysts" (ESHRE 2001).

Due to the frequency of ovarian cysts and the uncertainty concerning treatment with oral contraceptives, this review evaluated the randomized controlled trials addressing this question.

OBJECTIVES

To evaluate the usefulness of treating functional ovarian cysts with combined oral contraceptives.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

We included all randomized controlled trials in any language that include oral contraceptives as treatment of ovarian cysts. We excluded trials that focused on prevention of cysts. The definitions of functional ovarian cysts were those used in trial reports; the minimum cyst diameter varied between studies. Cysts associated with ovulation induction were also included.

Types of participants

All women of reproductive age enrolled in the randomized controlled trials were included; eligibility criteria were those used by the trial investigators.

Types of intervention

Any type of oral contraceptive (estrogen plus progestin or progestin alone) used in any regimen (cyclic or continuous) and for any

duration was included. Comparisons could include no treatment, placebo treatment, or treatment with alternative drugs such as other oral contraceptives or danazol.

Types of outcome measures

Resolution of cysts at follow up, as judged by ultrasound or physical examination, was the principal outcome; time to resolution was reported in some trials.

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: Cochrane Fertility Regulation Group methods used in reviews.

We searched CENTRAL using the following strategy: cyst and contraception

We searched PubMed using the following strategy: (contraceptives, oral OR estrogens/therapeutic use OR progesterones/therapeutic use) AND functional ovarian cysts

We searched POPLINE using the following strategy: ovarian cysts & treat* & (oral contraceptives/ progestin*/ progesterone*/estrogen*) !(polycystic/dermoid)

We searched EMBASE using the following strategy: (oral contraceptive agent AND ovary cyst) NOT polycystic

METHODS OF THE REVIEW

We assessed all titles and abstracts found for inclusion. We evaluated the methodological quality of the trials for potential biases by qualitatively assessing the study design, randomization method, allocation concealment, blinding, premature discontinuation rates, and loss to follow-up rates. Two reviewers independently abstracted data from the studies identified to improve accuracy. One reviewer entered data into RevMan 4.2, and a second confirmed correct data entry. Peto odds ratios with 95% confidence intervals were used for dichotomous outcomes, such as resolution of cysts. We analyzed weighted mean differences for continuous variables, such as cyst diameter or days to resolution. Subgroup analyses were not done. Sensitivity analyses were not done to examine the impact of inclusion of trials with weaker methods; instead, weak trials or those with ambiguous methods were excluded.

We wrote to authors of all published trial reports to solicit other published or unpublished trials that we may have missed; none responded. We also contacted trial-report authors as needed to supplement published information, again without success. In addition, we examined the reference lists of all reports found to seek other trials.

In addition to publication of the review in the Cochrane Library, we plan to submit a derivative manuscript for publication in the peer-reviewed literature.

DESCRIPTION OF STUDIES

We found four randomized controlled trials including a total of 227 participants. Two trials were from Turkey (Taskin 1996; Turan 1994) and one each from Israel (Ben-Ami 1993) and the United States (Steinkampf 1990). Two trials included participants receiving ovulation induction treatment (Ben-Ami 1993; Steinkampf 1990), while the other two had patients with cysts unrelated to fertility treatment (Taskin 1996; Turan 1994). Two reports that claimed to be randomized trials were not; one allocated participants by birth date (Graf 1995) and the other by alternate weeks (MacKenna 2000). Two other reports (Nezhat 1994; Nezhat 1996) were excluded because of possible overlap of participants and methodological concerns.

Ben-Ami (Ben-Ami 1993) randomized 54 women with ovarian cysts after ovulation to induction to either a combined oral contraceptive or expectant management. The ovulation-induction techniques included clomiphene citrate and human chorionic gonadotropins or human menopausal gonadotropins and human chorionic gonadotropin. All women were confirmed by ultrasound examination to have ovarian cysts at least 2.0 cm in diameter. Women were randomized to a pill containing levonorgestrel 125 μg plus ethinyl estradiol 50 μg or to expectant management. Participants had a repeat ultrasound examination after one cycle. If the cyst had not resolved, oral contraceptive treatment continued or was begun for the expectant-management group. However, this review includes only data from the first cycle of parallel comparison of the two approaches.

Steinkampf (Steinkampf 1990) randomized 48 women with ovarian cysts after ovulation induction to either a combined oral contraceptive or to expectant management. The ovulation-induction regimen included clomiphene, human menopausal gonadotropin, or both. Eligibility criteria included an adnexal cyst of 1.5 cm diameter or greater on vaginal ultrasound examination. The mean diameters of the largest cysts in the two groups were similar (3.0 and 2.9 cm, respectively). Women allocated to oral contraceptives received a monophasic pill containing norethindrone 1 mg and mestranol 50 μg daily for up to six weeks. Repeat ultrasound examinations took place at three, six, and nine weeks after beginning therapy. Those with a persistent cyst at nine weeks were referred for an operation.

Taskin (Taskin 1996) randomized 45 women with ovarian cysts with a diameter of four to six cm to either a combined oral contraceptive or to expectant management. Exclusion criteria included previous surgery, endometriosis, pregnancy, masses not purely cystic, cysts larger than six cm in diameter, and contraindications to

oral contraceptives. Women allocated to pills received a preparation containing levonorgestrel 150 µg plus ethinyl estradiol 30 µg in cyclical fashion for three cycles. Treatment began with the first cycle after ultrasound evaluation. All participants were followed with repeat ultrasound examinations “every four weeks and at the end of the second and third month just after menses.” Outcomes included cyst resolution and cyst volume, measured by ultrasound.

Turan (Turan 1994) randomly assigned 80 women with simple cysts to one of four treatment arms, three different combined oral contraceptives or expectant management. One oral contraceptive was monophasic and contained desogestrel 150 µg plus ethinyl estradiol 30 µg. Another monophasic pill contained levonorgestrel 250 µg plus ethinyl estradiol 50 µg. The third pill studied was multiphasic and contained levonorgestrel 50/75/125 µg plus ethinyl estradiol 30/40/30 µg. The fourth treatment group was expectant management. Women had to have unilateral, mobile, unilocular, thin-walled cysts without internal echoes; the size had to be from three to six cm in diameter. Exclusion criteria included ovarian dysfunction, use of drugs that might alter hormone metabolism, and known contraindications to oral contraceptives. Women were randomized into four groups “by stratification according to cyst diameter and patient age.” Twenty were assigned to each treatment arm. Repeat ultrasound examinations were done at five and 10 weeks after starting treatment. Because of the similarity of results in the three oral-contraceptive groups, in this review each oral contraceptive has been compared to the expectant management arm rather than with other oral contraceptives.

METHODOLOGICAL QUALITY

Ben-Ami (Ben-Ami 1993) provided limited information about the methods used. The method of randomization was not described, and allocation concealment was not mentioned. The sample size used was not explained. All patients had uniform ultrasound examinations, and no participants were lost to follow up. Blinding was not used.

Steinkampf (Steinkampf 1990) described Institutional Review Board approval and signed informed consent. The method of randomization was not specified in the report, nor was allocation concealment. Blinding was not possible. One participant was non-compliant with the protocol and was dropped from analysis; her treatment group was not stated. In addition, six women with persistent cysts at nine weeks and who had operations were removed from the analysis, which was restricted to women with cysts that resolved within nine weeks (22 and 19 participants, respectively). Thus, 7 of 48 participants (15%) were excluded from analysis.

Taskin (Taskin 1996) reported using a table of random numbers for sequence generation. This was a four-arm trial: fifty women without cysts were allocated to the pill or expectant management

to study cyst prevention. These participants were not considered further. Forty-five women with cysts were also allocated to the same two treatments. Allocation concealment was not described, and the sample size was not explained. The authors addressed power only in the discussion section of the report. No losses to follow up were reported.

Turan (Turan 1994) reported a randomization stratified by cyst size and age, but further details were not provided. No mention was made of allocation concealment or treatment blinding. The report was unclear regarding losses to follow-up. Eighty women were enrolled. One participant assigned to expectant management was reported lost to follow up, and three other women whose cysts had resolved by five weeks did not return as requested at 10 weeks. Nevertheless, follow up information was provided for only 72 women at five weeks and 69 women at 10 weeks. One explanation may be that the authors dropped from analysis the eight women (10%) with persistent ovarian cysts who were referred for surgical evaluation.

RESULTS

The resolution of functional cysts was not hastened by use of oral contraceptives; this held true for spontaneously occurring cysts and those related to ovulation induction. Ben-Ami (Ben-Ami 1993) found administration of oral contraceptives of no value in the setting of ovulation induction. Twenty-three of 27 women (85%) given oral contraceptives had resolution of the cyst within one menstrual cycle, in contrast to 24 of 27 (89%) allocated to expectant management (OR 0.72; 95% CI 0.14, 3.57). No cysts persistent at the first observation period subsequently resolved with a second cycle of treatment. Of the seven women with persistent cysts, all had laparoscopy done. Two had dermoid cysts, two had para-ovarian cysts, two had hydrosalpinges, and one had a follicular (functional) cyst.

In another population having ovulation induction, investigators (Steinkampf 1990) found no benefit of oral contraceptives. The analysis was restricted to participants with cysts that resolved. At three weeks, 20 of 22 (91%) participants given oral contraceptives had resolution, in contrast to 16 of 19 (84%) assigned to expectant management. At six weeks, 21 of 22 (95%) and 18 of 19 (95%) had cyst resolution, respectively. By the final observation at nine weeks, all participants in both groups had cyst resolution. Six participants had persistent cysts; three had endometriomas and three had hydrosalpinges found at operation.

The Taskin trial (Taskin 1996) found no benefit of oral contraceptives on cyst resolution in a population not undergoing ovulation induction. Among 25 women allocated to the oral contraceptive, 13 (52%) had resolution of the cyst by the third cycle of treatment. Among 20 assigned to expectant management, the corresponding figure was 10 (50%). No significant difference was

seen in the mean cyst volume at the end of treatment. The mean volume in the group assigned to the oral contraceptive was 12.8 mL (SD 9.2), while that in the expectant management group was 9.6 mL (SD 4.3). Eight women with cysts three to four cm in diameter that failed to regress underwent further treatment: three had percutaneous cyst aspiration under ultrasound guidance, and five had operations. Two of the five women having operations were found to have endometriomas, and the remainder had persistent corpus luteum cysts.

Turan (Turan 1994) found no benefit of oral contraceptives in hastening cyst resolution in another population not undergoing ovulation induction. Cysts had disappeared by five weeks in 16 of 18 participants (89%) assigned to the desogestrel monophasic pill, 18 of 19 (95%) assigned to the monophasic levonorgestrel pill, 16 of 18 (89%) allocated to the multiphasic levonorgestrel pill, and 13 of 17 (76%) assigned to expectant management. This difference was not statistically significant. By 10 weeks, cysts had resolved in all women given the desogestrel monophasic pill, the levonorgestrel monophasic pill, and the multiphasic levonorgestrel pill; 16 of 17 (94%) assigned to expectant management had cyst resolution. Again, these differences were not statistically significant. Eight participants with persistent cysts had surgical evaluation; three were found to have endometriomas, three had para-ovarian cysts, one had a hydrosalpinx, and one had a simple cyst that was not further characterized.

DISCUSSION

Treatment of functional ovarian cysts with oral contraceptives appears no better than watchful waiting. Most such cysts resolve spontaneously with or without treatment. The observation that cysts resolved after oral contraceptive administration (Spanos 1973) led to the clinical impression that oral contraceptives had benefit (Anonymous 1982), an example of *post hoc ergo propter hoc* reasoning (after the fact, therefore on account of the fact). In this common error in logic, a temporal association is inappropriately considered a causal association. Only with contemporaneous control groups could the putative effect of the contraceptives have been assessed. In none of these small trials (Ben-Ami 1993; Steinkampf 1990; Taskin 1996; Turan 1994) was any important difference found. This held true for cysts discovered during ovulation induction (Ben-Ami 1993; Steinkampf 1990) and for those unrelated to fertility drugs (Taskin 1996; Turan 1994).

Limitations of these studies include incomplete descriptions of randomization and allocation concealment. Because of the small sample sizes and, in one report (Turan 1994) multiple treatment arms, the power of these trials to detect important differences was limited. Because of differences in oral contraceptives used and

definition of outcome measures, we did not aggregate the reports in a meta-analysis. Nevertheless, taken as a whole, these trials do not suggest an important benefit of oral contraceptives in treating functional ovarian cysts.

Cystic masses that did not resolve within several months were unlikely to be functional cysts. Endometriomas, para-ovarian cysts, and other pathology accounted for most of these. In these circumstances, surgical evaluation of persistent or painful adnexal masses is appropriate (Stein 1990).

AUTHORS' CONCLUSIONS

Implications for practice

Adnexal masses thought to be functional ovarian cysts can be followed expectantly for several menstrual cycles. Treatment with combined oral contraceptives does not appear to hasten resolution. Persistent cysts and those that are large or painful usually merit surgical management.

Implications for research

Larger trials may be required to demonstrate any benefit of oral contraceptives in treating functional cysts, but based on existing evidence, this should not be a research priority.

POTENTIAL CONFLICT OF INTEREST

Dr Grimes has consulted with or served on a speakers bureau for Berlex Laboratories, Mead Johnson, Organon, Ortho-McNeil, Parke-Davis, Schering, Searle and Wyeth-Ayerst. These pharmaceutical companies have marketed oral contraceptive pills.

ACKNOWLEDGEMENTS

Carol Manion assisted with the literature searches.

SOURCES OF SUPPORT

External sources of support

- US Agency for International Development USA
- National Institute of Child Health and Human Development USA

Internal sources of support

- No sources of support supplied

REFERENCES

References to studies included in this review

Ben-Ami 1993 *{published data only}*

Ben-Ami M, Geslevich Y, Battino S, Matilsky M, Shalev E. Management of functional ovarian cysts after induction of ovulation. A randomized prospective study. *Acta Obstetrica Gynecologica Scandinavica* 1993;**72**:396–7.

Steinkampf 1990 *{published data only}*

Steinkampf MP, Hammond KR, Blackwell RE. Hormonal treatment of functional ovarian cysts: a randomized, prospective study. *Fertility and Sterility* 1990;**54**:775–7.

Taskin 1996 *{published data only}*

Taskin O, Young DC, Mangal R, Aruh I. Prevention and treatment of ovarian cysts with oral contraceptives: a prospective randomized study. *Journal of Gynecologic Surgery* 1996;**12**:21–4.

Turan 1994 *{published data only}*

Turan C, Zorlu CG, Ugur M, Ozcan T, Kaleli B, Gokmen O. Expectant management of functional ovarian cysts: an alternative to hormonal therapy. *International Journal of Gynecology and Obstetrics* 1994;**47**:257–60.

References to studies excluded from this review

Biljan 1998

Biljan MM, Mahutte NG, Dean N, Hemmings R, Bissonnette F, Tan SL. Pretreatment with an oral contraceptive is effective in reducing the incidence of functional ovarian cyst formation during pituitary suppression by gonadotropin-releasing hormone analogues. *Journal of Assisted Reproduction and Genetics* 1998;**15**:599–604.

Egarter 1995

Egarter C, Putz M, Strohmmer H, Speiser P, Wenzl R, Huber J. Ovarian function during low-dose oral contraceptive use. *Contraception* 1995;**51**:329–33.

Graf 1995

Graf M, Krussel JS, Conrad M, Bielfeld P, Rudolf K. Regression of functional cysts: high dosage ovulation inhibitor and gestagen therapy has no added effect [Zur Ruckbildung funktioneller Zysten: Hochdosierte Ovulationshemmer und Gestagentherapie ohne zusatzlichen Effekt]. *Geburtshilfe und Frauenheilkunde* 1995;**55**:387–92.

Grimes 1994

Grimes DA, Godwin AJ, Rubin A, Smith JA, Lacarra M. Ovulation and follicular development associated with three low-dose oral contraceptives: a randomized controlled trial. *Obstetrics and Gynecology* 1994;**83**:29–34.

MacKenna 2000

MacKenna A, Fabres C, Alam V, Morales V. Clinical management of functional ovarian cysts: a prospective and randomized study. *Human Reproduction* 2000;**15**:2567–9.

Muzii 2000

Muzii L, Marana R, Caruana P, Catalano GF, Margutti, Panici PB. Postoperative administration of monophasic combined oral contraceptives after laparoscopic treatment of ovarian endometriomas: a prospective, randomized trial. *American Journal of Obstetrics and Gynecology* 2000;**183**:588–92.

Nezhat 1994

Nezhat F, Nezhat CH, Borhan S, Nezhat CR. Is hormonal suppression efficacious in treating functional ovarian cysts?. *Journal of the American Association of Gynecologic Laparoscopists* 1994;**1**:S26.

Nezhat 1996

Nezhat CH, Nezhat F, Borhan S, Seidman DS, Nezhat CR. Is hormonal treatment efficacious in the management of ovarian cysts in women with histories of endometriosis?. *Human Reproduction* 1996;**11**:874–7.

Peres 1991

Peres JAT, Baracat EC, Novo NF, Juliano Y, de Lima GR. Behavior of cystic tumor of the ovary after wait-and-see management and hormonal treatment [Comportamento dos tumores cisticos do ovario apos conduta expectante e tratamento hormonal]. *Revista Paulista de Medicina* 1991;**109**:165–73.

Teichmann 1995

Teichmann AT, Brill K, Albring M, Schnitker J, Wojtynek P, Kustra E. The influence of the dose of ethinylestradiol in oral contraceptives on follicle growth. *Gynecological Endocrinology* 1995;**9**:299–305.

Young 1992

Young RL, Snabes MC, Frank ML, Reilly M. A randomized, double-blind, placebo-controlled comparison of the impact of low-dose and triphasic oral contraceptives on follicular development. *American Journal of Obstetrics and Gynecology* 1992;**167**:678–82.

Additional references

Anderson 1990

Anderson RE, Serafini PC, Paulson RJ, Sauer MV, Marrs RP. Detection and management of pathological, non-palpable, cystic adnexal masses. *Human Reproduction* 1990;**5**:279–81.

Anonymous 1974

Anonymous. Functional ovarian cysts and oral contraceptives. Negative association confirmed surgically. A cooperative study. *Journal of the American Medical Association* 1974;**228**:68–9.

Anonymous 1982

Anonymous. Should OCs be prescribed to prevent adnexal masses?. *Contraceptive Technology Update* 1982;**3**:116–8.

Anonymous 2001

Anonymous. Retraction. *Surgical Laparoscopy Endoscopy and Percutaneous Techniques* 2001;**11**:1.

Booth 1992

Booth M, Beral V, Maconochie N, Carpenter L, Scott C. A case-control study of benign ovarian tumors. *Journal of Epidemiology and Community Health* 1992;**46**:528–31.

Carlson 2001

Carlson W, Russell S. Journal retracts Stanford doctors' research articles. Co-author admits using inaccurate data on women's surgeries in report. *San Francisco Chronicle*, February 21 2001.

Chiaffarino 1998

Chiaffarino F, Parazzini F, La Vecchia C, Ricci E, Crosignani PG. Oral contraceptive use and benign gynecologic conditions. *Contraception* 1998;**57**:11–8.

Christensen 2002

Christensen J, Boldsen J, Westergaard J. Functional ovarian cysts in premenopausal and gynecologically healthy women. *Contraception* 2002;**66**:153–7.

ESHRE 2001

The ESHRE Capri Workshop Group. Ovarian and endometrial function during hormonal contraception. *Human Reproduction* 2001;**16**:1527–35.

Holt 1992

Holt VL, Daling JR, McKnight B, Moore D, Stergachis A, Weiss NS. Functional ovarian cysts in relation to the use of monophasic and triphasic oral contraceptives. *Obstetrics and Gynecology* 1992;**79**:529–33.

Kozak 2005

Kozak LJ, Owings MF, Hall MJ. National Hospital Discharge Survey: 2002 annual summary with detailed diagnosis and procedure data. *Vital and Health Statistics* 2005;**13 (158)**:1–207.

Lanes 1992

Lanes SF, Birnman B, Walker AM, Singer S. Oral contraceptive type and functional ovarian cysts. *American Journal of Obstetrics and Gynecology* 1992;**166**:956–61.

Muram 1990

Muram D, Gale CL, Thompson E. Functional ovarian cysts in patients cured of ovarian neoplasms. *Obstetrics and Gynecology* 1990;**75**:680–3.

Parazzini 1996

Parazzini F, Moroni S, Negri E, La Vecchia C, Dal Pino D, Ricci E. Risk factors for functional ovarian cysts. *Epidemiology* 1996;**7**:547–9.

Spanos 1973

Spanos WJ. Preoperative hormonal therapy of cystic adnexal masses. *American Journal of Obstetrics and Gynecology* 1973;**116**:551–6.

Starks 1984

Starks GC. Therapeutic uses of contraceptive steroids. *Journal of Family Practice* 1984;**19**:315–21.

Stein 1990

Stein AL, Koonings PP, Schlaerth JB, Grimes DA, d'Ablaing G 3d. Relative frequency of malignant parovarian tumors: should parovarian tumors be aspirated?. *Obstetrics and Gynecology* 1990;**75**:1029–31.

Teichmann 1995

Teichmann AT, Brill K, Albring M, Schnitker J, Wojtynek P, Kustra E. The influence of the dose of ethinylestradiol in oral contraceptives on follicle growth. *Gynecological Endocrinology* 1995;**9**:299–305.

Vessey 1987

Vessey M, Metcalfe A, Wells C, McPherson K, Westhoff C, Yeates D. Ovarian neoplasms, functional ovarian cysts, and oral contraceptives. *British Medical Journal* 1987;**294**:1518–20.

Walnut Creek 1981

Walnut Creek Contraceptive Drug Study. *A prospective study of the side effects of oral contraceptives, vol. 3*. Bethesda, MD: National Institutes of Health, 1981.

Westhoff 1992

Westhoff C, Clark CJ. Benign ovarian cysts in England and Wales and in the United States. *British Journal of Obstetrics and Gynaecology* 1992;**99**:329–32.

T A B L E S**Characteristics of included studies**

Study	Ben-Ami 1993
Methods	Randomized controlled trial without blinding
Participants	54 women in Israel found to have ovarian cysts with mean diameter larger than 2.0 cm after ovulation induction. Mean ages of 34 and 33 years in treatment and control groups, respectively. Mean cyst diameters 2.9 and 2.8 cm, respectively
Interventions	Oral contraceptive containing levonorgestrel 125 mcg and ethinyl estradiol 50 mcg versus expectant management for one cycle, after which ultrasound examination was repeated.
Outcomes	Resolution of cyst, defined as complete disappearance on ultrasound examination.
Notes	Method of randomization and allocation concealment not described. Sample size calculation not provided.
Allocation concealment	B – Unclear

Study **Steinkampf 1990**

Methods Randomized controlled trial

Participants	48 women in the U.S. who had an adnexal cyst 1.5 cm in diameter or larger document by vaginal ultrasound examination. All participants were having ovulation induction with clomiphene, human menopausal gonadotropin, or both. Mean ages of 33 and 32 years in treatment and control groups, respectively. Mean cyst diameters 3.0 and 2.9 cm, respectively
Interventions	Oral contraceptive containing norethindrone 1 mg and mestranol 50 mcg, taken daily for up to six weeks versus expectant management.
Outcomes	Resolution of cyst on vaginal ultrasound follow-up examinations at three, six, and nine weeks.
Notes	Method of randomization and allocation concealment not specified. Sample size calculation not provided. One participant excluded from analysis because of noncompliance (treatment group unknown). An additional six women with persistent cysts were deleted from the analysis.
Allocation concealment	B – Unclear

Study	Taskin 1996
--------------	--------------------

Methods	Randomized controlled trial
Participants	45 women aged 18-34 years in Turkey who had newly diagnosed “ovarian cysts” four to six cm in diameter. Exclusion criteria included prior surgery, endometriosis, pregnancy, masses not purely cystic, cysts more than six cm in diameter, and contraindications to oral contraceptives.
Interventions	Oral contraceptive containing levonorgestrel 150 mcg plus ethinyl estradiol 30 mcg given cyclically for three months versus expectant management.
Outcomes	Resolution of cyst on vaginal ultrasound examination “every four weeks and at the end of the second and third month just after menses.” Cyst volumes were also measured, using the prolate ellipsoid formula.
Notes	Table of random numbers used for sequence generation; allocation concealment not mentioned. Sample size not explained. A parallel trial was done in women without ovarian cysts.
Allocation concealment	B – Unclear

Study	Turan 1994
--------------	-------------------

Methods	Randomized controlled trial, with randomization stratified by cyst diameter and participant age
Participants	80 women of reproductive age in Turkey with unilateral, mobile, unilocular, thin-walled ovarian cysts without internal echoes and from three to six cm in diameter on ultrasound examination. Exclusion criteria were ovarian dysfunction, drug use that might interfere with hormone metabolism, and known contraindications to oral contraceptives.
Interventions	Oral contraceptive containing desogestrel 150 mcg plus ethinyl estradiol 30 mcg versus oral contraceptive containing levonorgestrel 250 mcg plus ethinyl estradiol 50 mcg versus multiphasic oral contraceptive containing levonorgestrel 50/75/125 mcg plus ethinyl estradiol 30/40/30 mcg versus expectant management.
Outcomes	Resolution of cyst on vaginal ultrasound examination after 5 and 10 weeks of therapy.
Notes	Method of randomization not specified, and allocation concealment not described. Sample size justification not provided. Blinding as to therapy not described.
Allocation concealment	B – Unclear

Characteristics of excluded studies

Study	Reason for exclusion
--------------	-----------------------------

Biljan 1998	Not a randomized controlled trial; observational study of prevention, not treatment.
Egarter 1995	Not a treatment trial of ovarian cysts.
Graf 1995	Participants allocated to three treatment groups based on birthdate.

Characteristics of excluded studies (Continued)

Grimes 1994	Not a treatment trial of ovarian cysts.
MacKenna 2000	Participants allocated to two treatments by alternate weeks of enrollment.
Muzii 2000	Prevention, rather than treatment, trial.
Nezhat 1994	Abstract described 95 participants with cysts, 29 of whom had a history of endometriosis. Potential overlap with participants reported in Nezhat 1996. Method of randomization and allocation concealment not specified, and corresponding author did not reply to query. Authors have had two published papers retracted by another journal (Anonymous 2001; Carlson 2001).
Nezhat 1996	Possible overlap of participants reported in Nezhat 1994. Corresponding author did not reply to query. Authors have had two published papers retracted by another journal (Anonymous 2001; Carlson 2001).
Peres 1991	No mention of randomization in article.
Teichmann 1995	Not a treatment trial of ovarian cysts.
Young 1992	Not a treatment trial of ovarian cysts.

ANALYSES**Comparison 01. Levonorgestrel 125 mcg plus ethinyl estradiol 50 mcg taken cyclically versus expectant management**

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Resolution of cyst within one menstrual cycle	1	54	Odds Ratio (Fixed) 95% CI	0.72 [0.14, 3.57]

Comparison 02. Norethindrone 1 mg plus mestranol 50 mcg daily versus expectant management

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Resolution of cyst within nine weeks	1	41	Odds Ratio (Fixed) 95% CI	Not estimable

Comparison 03. Levonorgestrel 150 mcg plus ethinyl estradiol 30 mcg taken cyclically versus expectant management

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Resolution of cyst by third month	1	45	Odds Ratio (Fixed) 95% CI	1.08 [0.33, 3.51]
02 Cyst volume after third month	1	45	Weighted Mean Difference (Fixed) 95% CI	3.20 [-0.87, 7.27]

Comparison 04. Desogestrel 150 mcg plus ethinyl estradiol 30 mcg taken cyclically versus expectant management

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Resolution of cyst by 10 weeks	1	34	Odds Ratio (Fixed) 95% CI	3.18 [0.12, 83.76]

Comparison 05. Levonorgestrel 250 mcg plus ethinyl estradiol 50 mcg taken cyclically versus expectant management

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Resolution of cyst by 10 weeks	1	34	Odds Ratio (Fixed) 95% CI	3.18 [0.12, 83.76]

Comparison 06. Levonorgestrel 50/75/125 mcg plus ethinyl estradiol 30/40/30 mcg taken cyclically versus expectant management

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Resolution of cyst by 10 weeks	1	35	Odds Ratio (Fixed) 95% CI	3.36 [0.13, 88.39]

INDEX TERMS

Medical Subject Headings (MeSH)

Contraceptives, Oral, Combined [*therapeutic use]; Ovarian Cysts [*drug therapy]; Randomized Controlled Trials; Remission, Spontaneous

MeSH check words

Female; Humans

COVER SHEET

Title	Oral contraceptives for functional ovarian cysts
Authors	Grimes DA, Jones LB, Lopez LM, Schulz KF
Contribution of author(s)	Dr Grimes developed the idea and registered the title. Ms Jones and Dr Lopez assisted with data abstraction and writing. Dr Schulz edited the review and provided statistical oversight.
Issue protocol first published	2006/3
Review first published	2006/4
Date of most recent amendment	23 August 2006
Date of most recent SUBSTANTIVE amendment	30 June 2006
What's New	Information not supplied by author
Date new studies sought but none found	Information not supplied by author
Date new studies found but not yet included/excluded	Information not supplied by author
Date new studies found and included/excluded	Information not supplied by author
Date authors' conclusions section amended	Information not supplied by author
Contact address	Prof David Grimes Vice President of Biomedical Affairs Clinical Research Department

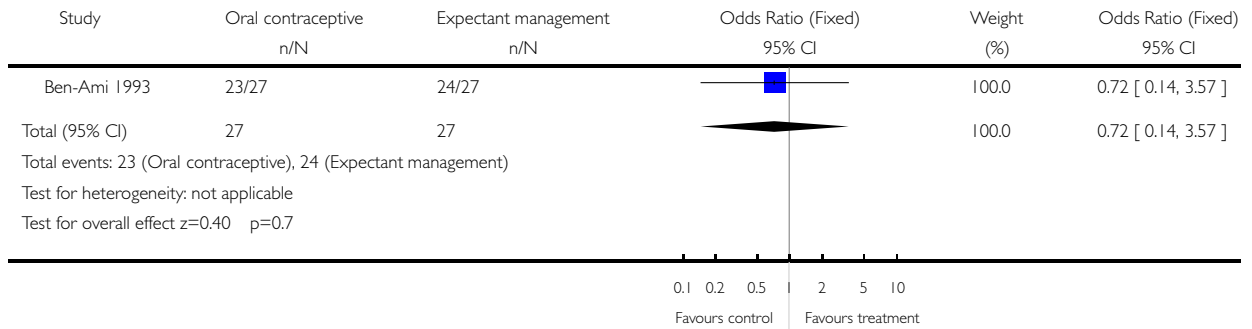
Family Health International
 PO Box 13950
 Research Triangle Park
 Durham
 North Carolina
 NC 27709
 USA
 E-mail: dgrimes@fhi.org
 Tel: +1 919 5447040
 Fax: +1 919 5447261

DOI 10.1002/14651858.CD006134.pub2
Cochrane Library number CD006134
Editorial group Cochrane Fertility Regulation Group
Editorial group code HM-FERTILREG

GRAPHS AND OTHER TABLES

Analysis 01.01. Comparison 01 Levonorgestrel 125 mcg plus ethinyl estradiol 50 mcg taken cyclically versus expectant management, Outcome 01 Resolution of cyst within one menstrual cycle

Review: Oral contraceptives for functional ovarian cysts
 Comparison: 01 Levonorgestrel 125 mcg plus ethinyl estradiol 50 mcg taken cyclically versus expectant management
 Outcome: 01 Resolution of cyst within one menstrual cycle

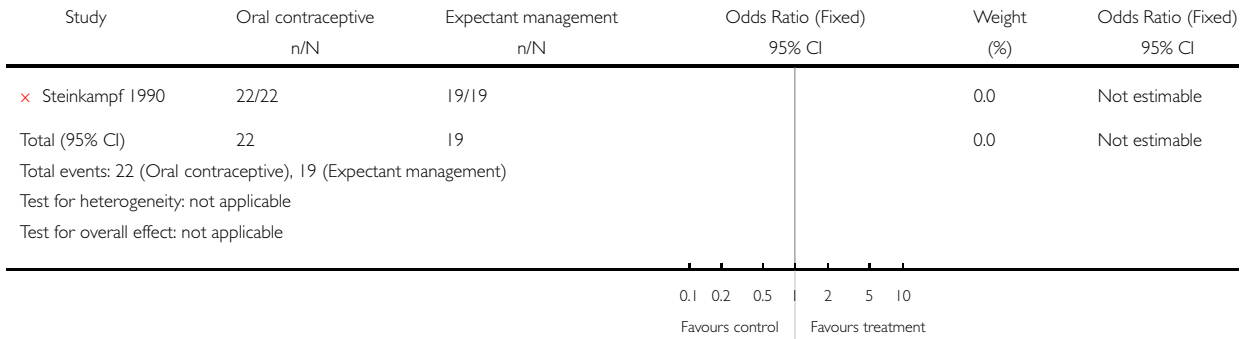


Analysis 02.01. Comparison 02 Norethindrone 1 mg plus mestranol 50 mcg daily versus expectant management, Outcome 01 Resolution of cyst within nine weeks

Review: Oral contraceptives for functional ovarian cysts

Comparison: 02 Norethindrone 1 mg plus mestranol 50 mcg daily versus expectant management

Outcome: 01 Resolution of cyst within nine weeks

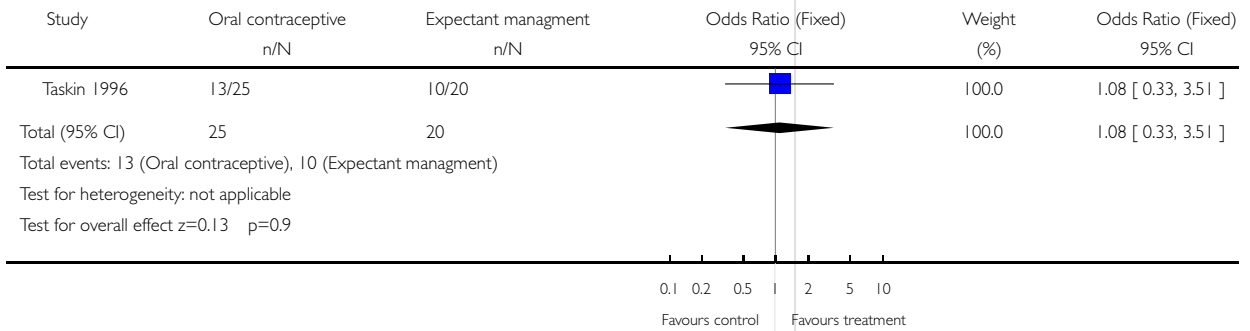


Analysis 03.01. Comparison 03 Levonorgestrel 150 mcg plus ethinyl estradiol 30 mcg taken cyclically versus expectant management, Outcome 01 Resolution of cyst by third month

Review: Oral contraceptives for functional ovarian cysts

Comparison: 03 Levonorgestrel 150 mcg plus ethinyl estradiol 30 mcg taken cyclically versus expectant management

Outcome: 01 Resolution of cyst by third month

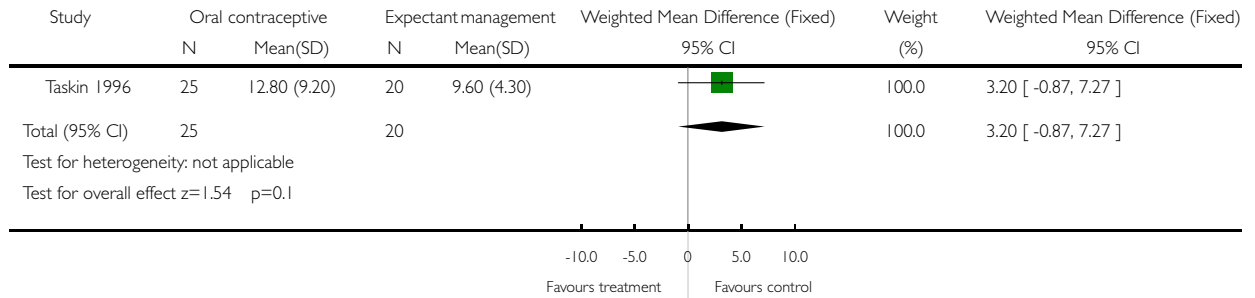


Analysis 03.02. Comparison 03 Levonorgestrel 150 mcg plus ethinyl estradiol 30 mcg taken cyclically versus expectant management, Outcome 02 Cyst volume after third month

Review: Oral contraceptives for functional ovarian cysts

Comparison: 03 Levonorgestrel 150 mcg plus ethinyl estradiol 30 mcg taken cyclically versus expectant management

Outcome: 02 Cyst volume after third month

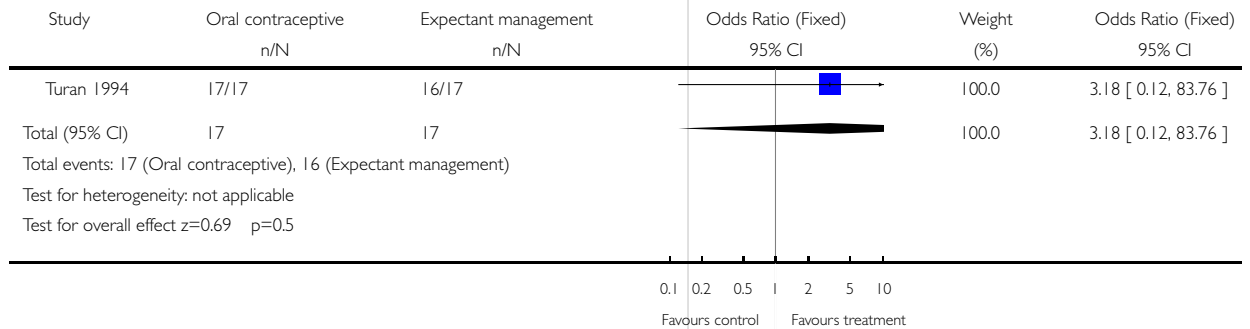


Analysis 04.01. Comparison 04 Desogestrel 150 mcg plus ethinyl estradiol 30 mcg taken cyclically versus expectant management, Outcome 01 Resolution of cyst by 10 weeks

Review: Oral contraceptives for functional ovarian cysts

Comparison: 04 Desogestrel 150 mcg plus ethinyl estradiol 30 mcg taken cyclically versus expectant management

Outcome: 01 Resolution of cyst by 10 weeks

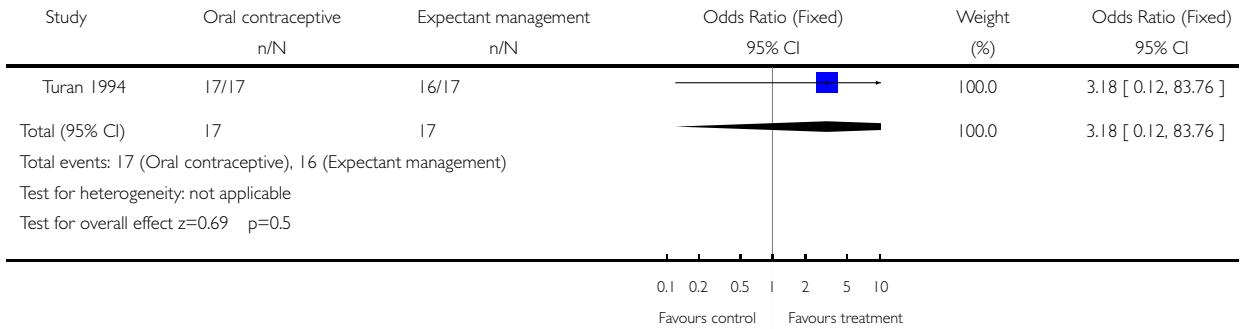


Analysis 05.01. Comparison 05 Levonorgestrel 250 mcg plus ethinyl estradiol 50 mcg taken cyclically versus expectant management, Outcome 01 Resolution of cyst by 10 weeks

Review: Oral contraceptives for functional ovarian cysts

Comparison: 05 Levonorgestrel 250 mcg plus ethinyl estradiol 50 mcg taken cyclically versus expectant management

Outcome: 01 Resolution of cyst by 10 weeks



Analysis 06.01. Comparison 06 Levonorgestrel 50/75/125 mcg plus ethinyl estradiol 30/40/30 mcg taken cyclically versus expectant management, Outcome 01 Resolution of cyst by 10 weeks

Review: Oral contraceptives for functional ovarian cysts

Comparison: 06 Levonorgestrel 50/75/125 mcg plus ethinyl estradiol 30/40/30 mcg taken cyclically versus expectant management

Outcome: 01 Resolution of cyst by 10 weeks

