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Danazol for unexplained subfertility (Review)

Hughes E, Brown J, Tiffin G

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Danazol for unexplained subfertility.
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[Intervention Review]

Danazol for unexplained subfertility

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ABSTRACT

Background

The synthetic androgen Danazol, was developed in the 1970's as a treatment for endometriosis. Its use was soon advocated in women with unexplained subfertility. Two randomised trials were subsequently conducted to assess the effectiveness of danazol in this population.

Objectives

The objective of this review was to assess the effect of danazol on live birth rate in women with unexplained subfertility.

Search methods

We searched the Cochrane Menstrual Disorders and Sub-fertility Group's specialised register of trials (searched November , 2006) the Cochrane Register of Controlled Trials (The Cochrane Library, Issue 4, 2006), MEDLINE (1966-November 2006), EMBASE (1980 - November 2006) and reference lists of articles.

Selection criteria

Randomised trials of danazol compared with placebo or no treatment in women with unexplained subfertility.

Data collection and analysis

Data were extracted by two reviewers EH and GT.

Main results

Two trials involving seventy-one women were included. There was no statistically significant difference in the live birth/ ongoing pregnancy rate between danazol and placebo at the end of treatment (OR 1.16, 95% CI 0.0 to 8.29; p=0.36) or at the end of follow-up (OR 2.41; 95% CI 0.59 to 9.82; p=0.22). There was no significant difference in clinical pregnancies following treatment (OR 0.14, 95% CI 0.01 to 2.26; p=0.17), however there were significantly more clinical pregnancies during the follow-up period in the danazol group compared with the placebo group (OR 3.15, 95%CI 0.98 to 10.10; p<0.05). Multiple side effects were reported.

Authors' conclusions

Available data demonstrate no evidence of the benefit of danazol for unexplained subfertility. Although there is insufficient evidence to be certain of this, the need for contraception during treatment and the adverse effects and costs of danazol, make its use for this problem unwarranted. The increased pregnancy rate in the long term follow-up data may be attributable to additional therapies and did not influence the live birth/ongoing pregnancy data.

PLAIN LANGUAGE SUMMARY

Danazol for treating subfertility

The drug danazol (Danocrine) was the most frequently prescribed medication for endometriosis but has also been tested as a treatment for unexplained subfertility. The review of trials found that there is no evidence that low doses of danazol improve live births/ ongoing pregnancy rates. Other negative factors include adverse effects.

BACKGROUND

Danazol, a synthetic derivative of ethisterone, was originally developed as a treatment for endometriosis. It is administered as an oral tablet. Kennedy 1990 summarises that the possible modes of action for Danazol include direct effects on ovarian steroidogenesis (Olsson 1986;Steingold 1986), endometrial growth (Rose 1988), and testosterone displacement from sex hormone-binding globulin; the suppression of which results in elevated free testosterone levels (Nilsson 1983). Danazol induced ovarian suppression results in amenorrhoea, endometrial atrophy and improvement in endometriotic lesions. It does however have anabolic and androgenic side effects including weight gain, oily skin, hirsutism, acne (Burry 1989) and hot flushes, depression, mood swings, changes in libido. The associated side effects prompted the term 'pseudomenopause' for the ovarian suppression resulting from danazol therapy (Dmowski 1976). Its use was advocated in women with unexplained infertility (Greenblatt 1974).

OBJECTIVES

The objective of this review was to test the hypothesis that danazol is more effective than placebo in the treatment of unexplained subfertility in terms of increasing the live birth/ongoing pregnancy rate.

METHODS

Criteria for considering studies for this review

Types of studies

Only randomised trials were considered for inclusion, quasi randomised trials were excluded.

Types of participants

Participants were women with unexplained subfertility. Unexplained subfertility was defined as a duration of >1 year; tubal patency confirmed by hysterosalpingogram or laparoscopy; ovulation confirmed by a serum progesterone level considered to be in the ovulatory range by the authors, endometrial biopsy showing evidence of secretory change, or regular menstrual cycle of 21 to 42 days duration; semen quality considered normal based on acceptable standard at the time of publication.

Types of interventions

Oral danazol in any dose, compared with placebo or no treatment administered for any duration.

Types of outcome measures

Primary outcome measure was live birth/ongoing pregnancies per woman randomised and clinical pregnancies per woman randomised.

Secondary outcome measures were spontaneous miscarriage, ectopic pregnancies and side effects.

Search methods for identification of studies

We searched for all publications which describe (or might describe) randomised controlled trials of danazol for unexplained sub-fertility. The original search was performed in 1995 and updated in 1999, 2005 and 2006.

Electronic searches

1) We searched the Cochrane Menstrual Disorders and Sub-fertility Group's specialised register of trials (searched November, 2006). See review group details for more details on the make-up of the Specialised Register.
2) The Cochrane Central Register of Controlled Trials (CENTRAL) on The Cochrane Library, Issue 4, 2006 was searched in all fields
3) The following electronic databases were searched using Ovid software using search string see Appendix 1

Searching other resources

4) The citation lists of relevant publications, review articles and included studies were also searched.

Data collection and analysis

S tudy selection
The study selection was undertaken by two reviewers (EH and GT). The titles and abstracts of articles found in the search were screened by EH and GT, who discarded studies that were clearly ineligible. Then EH, and GT independently assessed whether the studies met the inclusion criteria, with disagreements resolved by discussion. Further information was sought from the authors where papers contained insufficient information to make a decision about eligibility. An updated search was conducted in November 2006 by JB.
A ssessment of Methodological Quality
The quality of all studies that were deemed eligible for the review were assessed independently by the two reviewers (EH and GT), any discrepancies were resolved by discussion. The quality of allocation concealment was graded as adequate (A), unclear (B), or inadequate (C), following the detailed descriptions of these categories provided by the Menstrual Disorders and Subfertility Review Group.
D ata and extraction and analysis
Data extraction was performed independently by the two reviewers (EH and GT). Discrepancies were resolved by discussion. For each included trial, information was collected regarding the location of the study, methods of the study, the participants (age range, eligibility criteria), the nature of the interventions, and data relating to the outcomes specified above. Where possible, missing data was sought from the authors.

Statistical analysis was performed in accordance with the guidelines for statistical analysis developed by the Cochrane Collaboration. Heterogeneity (variations) between the results of different studies was examined by inspecting the scatter in the data points on the graphs and the overlap in their confidence intervals and, more formally, by checking the results of the chi-squared tests. The I^2 statistic for heterogeneity between groups was computed and used. Where possible, the outcomes were pooled statistically.
For dichotomous data, results for each study were expressed as an odds ratio with 95% confidence interval and combined for meta-analysis with RevMan software using the Peto method and a Fixed-effect model.

RESULTS

Description of studies

Two small studies were identified (Iffland 1989; van Dijk 1979). van Dijk 1979 included forty women with unexplained subfertility, treating them with Danazol 200 mg or placebo, daily for one hundred days. During this time, contraception does not appear to have been advised, despite the potential adverse effects of danazol during early pregnancy. Follow up was for six months and only pregnancies occurring during that period were included in the analysis.
Iffland 1989 included thirty-nine women with primary unexplained subfertility. Treatment with Danazol 200 mg daily or placebo lasted for three months. Eight women were excluded from analysis because of failure to complete treatment or medical illness. Three further women were withdrawn from the Danazol group during the follow up phase, which lasted twelve months. Iffland 1989 reported that nineteen women underwent additional therapies including superovulation, intrauterine artificial insemination, IVF and embryo transfer or gamete intrafallopian transfer post study treatment.

Risk of bias in included studies

See Table 1. Neither of these studies explicitly stated the method of allocation nor randomisation method used. The high incidence of oligomenorrhoea associate with active treatment makes blinding virtually impossible. One study (van Dijk 1979) reported complete follow-up among forty couples, but excluded one patient from the analysis (placebo group) because she conceived during the six month treatment phase, rather than in the six month post-treatment period. This decision undermines the validity of their conclusions. This patient has been included as part of the intention-to treat for the meta-analysis.

A second study [Iffland 1989] described the eight patients who left their trial post randomization, but did not report the pregnancy rate in this group. Interestingly, although side effects were reported with a similar frequency between groups in this study, more women left the Danazol than the placebo group, leaving eleven and seventeen women respectively. Neither trial used a crossover design and co-intervention did not appear to be present.

Effects of interventions

Two trials involving seventy-one women were included (Iffland 1989; van Dijk 1979). There was no statistically significant difference in the live birth/ ongoing pregnancy rate between Danazol and placebo at the end of treatment (OR 1.16, 95% CI 0.0 to 8.29; P=0.36) or at the end of follow-up (OR 2.41; 95% CI 0.59, 9.82; P=0.22). There was no significant difference in clinical pregnancies following treatment (OR 0.14, 95% CI 0.01, 2.26; P=0.17), however there were significantly more clinical pregnancies during the follow-up period in the Danazol group compared with the placebo group (OR 3.15, 95%CI 0.98, 10.10; P<0.05). Multiple side effects were reported by Iffland 1989 although no significant differences were observed between treatment and placebo groups. Menstrual irregularities were reported by both papers (Iffland 1989; van Dijk 1979) with significantly more women reporting menstrual irregularities and amenorrhoea in the Danazol group compared to placebo (OR13.60; 95%CI 4.96, 37.31; P<0.0001).

DISCUSSION

These studies are limited by their small sample size and lack of methodological quality. The results indicated no evidence of benefit of Danazol over placebo on live births/ongoing pregnancies. The significant effect on clinical pregnancies in the long term follow up may be attributable to the use of additional therapies which women had undergone in that time period. The significant effect of menstrual irregularities is a treatment effect although the statistical heterogeneity in the studies is high (I^2 = 77.9%).

When the evidence of lack of treatment effect and the known adverse effects of Danazol, including weight gain, acne and hirsutism are considered, it is the authors opinion that Danazol cannot be recommended in women with unexplained subfertility.

AUTHORS' CONCLUSIONS

Implications for practice

There is no evidence of benefit of Danazol in women with unexplained subfertility.

Implications for research

Larger trials do not appear to be warranted based on these findings.

ACKNOWLEDGEMENTS

The review authors wish to acknowledge the support of the MDSG for their help and support.

REFERENCES

References to studies included in this review

Iffland 1989 *{published data only}*
Iffland CA, Shaw RW, Beynon JL. Is danazol a useful treatment in unexplained primary infertility?. *European Journal Obstetric Gynecological Reproductive Biology* 1989; **32**:115–21.

van Dijk 1979 *{published data only}*
van Dijk JG, Frolich M, Brand EC, van Hall EV. The treatment of unexplained infertility with danazol. *Fertility and Sterility* 1979;**31**:481–5.

References to studies excluded from this review

Need 1992 *{published data only}*
Need JA, Forbes KL, Milazzo L, McKenzie E. Danazol in the treatment of menorrhagia: The effect of a 1 month induction dose (200 mg) and 2 month's maintenance therapy (200 mg, 100 mg, 50 mg or placebo). *Australian New Z ealand Journal Obstetrics and Gynaecology* 1992;**32**: 346–52.

Additional references

Burry 1989
Burry K, Patton P, Illingworth D. Metabolic changes during medical treatment of endometriosis: Nafarelin acetate versus danazol. *American Journal of Obstetrics and Gynecology* 1989;**160**(6):1454–61.

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infertility. *American Journal Obstetrics and Gynecology* 1974; **118**:783.

Kennedy 1990
Kennedy S, Williams I, Brodribb J, Barlow D, Shaw R. A comparison of nafarelin acetate and danazol in the treatment of endometriosis. *Fertility and Sterility* 1990;**53** (6):998–1003.

Nilsson 1983
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Olsson 1986
Olsson J, Hillensjo T, Nilsson L. Inhibitory effects of danazol on steroidogenesis in cultured human granulosa cells. *Fertility and Sterility* 1986;**46**:237.

Rose 1988
Rose G, Dowsett M, Mudge J, White J, Jeffcoate S. The inhibitory effects of danazol, danazol metabolites, gestrinone, and testosterone on the growth of human endometrial cells in vitro. *Fertility and Sterility* 1988;**49**: 224.

Steingold 1986
Steingold KA, Lu JKH, Judd HL, Meldrum DR. Danazol inhibits steroidogenesis by the human embryo in vivo. *Fertility and Sterility* 1986;**45**:649.

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Iffland 1989

Methods	Random allocation. Method not stated. No details of allocation concealment. Double blind design. Attrition was 8/39 see quality table for details
Participants	UK study. 39 women with primary unexplained subfertility. Women were aged 20-38, mean age Danazol group 30.8 +/- 3.3, placebo group 30.9 +/- 3.5 years. Inclusion criteria were for no known endocrine disorder, regular menstrual cycles, ovulating, normal laparoscopy at least 6 months prior to study entry, +ve post coital test. Normal semen analysis and no variocoele in male partner. No other details of exclusion
Interventions	Danazol 200 mg daily for 12 weeks, n=14 patients vs Placebo one tablet daily for 12 weeks, n=17 patients Long term follow up for up to 36 months.
Outcomes	Pregnancy Haematologic and liver function tests Side effects
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

van Dijk 1979

Methods	Random allocation. Method not stated. No details of concealment. There was an attempt to blind the women to treatment allocation but investigators were aware of which treatment arm women were in as study progressed. Attrition was 1/40 see quality table for details
Participants	Dutch study. Participants were 40 women with unexplained infertility (primary and secondary); BBT, luteal serum progesterone, HSG, normal semen, PCT. Median age of placebo group was 29.5 (range 26-37), and of Danazol group was 30 (range 27-38 years). Only women who had undergone laparoscopy at least 6 months earlier were included
Interventions	Danazol 200 mg orally daily for 6 months, n=21 vs Placebo one tablet daily for 6 months, n=19 Women were followed up for six months at 2 monthly intervals
Outcomes	Pregnancy FSH, LH, prolactin, estradiol, progesterone, side effects.

van Dijk 1979 (*Continued*)

Notes	Author's analysis excludes 1 pregnancy in the placebo group; this has been included as ITT in this meta-analysis. Follow-up duration was 6 months

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Need 1992	Study of danazol for menorrhagia. Pregnancy data not recorded

DATA AND ANALYSES

Comparison 1. Danazol versus placebo in unexplained subfertility

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Live birth/ongoing pregnancies per woman randomised following treatment	1	31	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.16 [0.00, 8.29]
2 Live births/ongoing pregnancies per woman randomised during treatment and follow up	2	71	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.41 [0.59, 9.82]
3 Pregnancy per woman randomised following treatment	2	71	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.14 [0.01, 2.26]
4 Pregnancies per woman randomised during treatment and follow up	2	71	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.15 [0.98, 10.10]
5 Miscarriage per woman randomised	1	31	Peto Odds Ratio (Peto, Fixed, 95% CI)	9.88 [0.58, 167.86]
6 Ectopic pregnancy per woman randomised	1	40	Peto Odds Ratio (Peto, Fixed, 95% CI)	7.06 [0.42, 117.50]
7 Adverse events/side effects	2		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
7.1 Skin changes	1	31	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.74 [0.17, 3.29]
7.2 Headache/migraine	1	31	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.15 [0.01, 2.58]
7.3 Abdominal bloating/discomfort	1	31	Peto Odds Ratio (Peto, Fixed, 95% CI)	5.07 [0.76, 33.62]
7.4 Tender breasts	1	31	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.15 [0.01, 2.58]
7.5 Oligomenorrhea/amenorrhoea	2	71	Peto Odds Ratio (Peto, Fixed, 95% CI)	13.60 [4.96, 37.31]
7.6 Weight gain	1	31	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.29 [0.26, 6.33]
7.7 Other reported side effects	1	31	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.38 [0.09, 1.56]

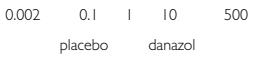
Analysis 1.1. Comparison 1 Danazol versus placebo in unexplained subfertility, Outcome 1 Live birth/ongoing pregnancies per woman randomised following treatment.

Review: Danazol for unexplained subfertility

Comparison: 1 Danazol versus placebo in unexplained subfertility

Outcome: 1 Live birth/ongoing pregnancies per woman randomised following treatment

Study or subgroup	Danazol n/N	Placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Iffland 1989	0/14	1/17		100.0 %	0.16 [0.00, 8.29]
Total (95% CI)	**14**	**17**		**100.0 %**	**0.16 [0.00, 8.29]**
Total events: 0 (Danazol), 1 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.91 (P = 0.36)					
Test for subgroup differences: Not applicable					



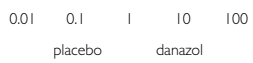
Analysis 1.2. Comparison 1 Danazol versus placebo in unexplained subfertility, Outcome 2 Live births/ongoing pregnancies per woman randomised during treatment and follow up.

Review: Danazol for unexplained subfertility

Comparison: 1 Danazol versus placebo in unexplained subfertility

Outcome: 2 Live births/ongoing pregnancies per woman randomised during treatment and follow up

Study or subgroup	Danazol n/N	Placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Iffland 1989	3/14	3/17		63.6 %	1.26 [0.22, 7.36]
van Dijk 1979	3/21	0/19		36.4 %	7.45 [0.73, 76.26]
Total (95% CI)	**35**	**36**		**100.0 %**	**2.41 [0.59, 9.82]**
Total events: 6 (Danazol), 3 (Placebo)					
Heterogeneity: Chi^2 = 1.42, df = 1 (P = 0.23); I^2 =30%					
Test for overall effect: Z = 1.23 (P = 0.22)					
Test for subgroup differences: Not applicable					



Analysis 1.3. Comparison 1 Danazol versus placebo in unexplained subfertility, Outcome 3 Pregnancy per woman randomised following treatment.

Review: Danazol for unexplained subfertility

Comparison: 1 Danazol versus placebo in unexplained subfertility

Outcome: 3 Pregnancy per woman randomised following treatment

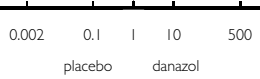
Study or subgroup	Danazol n/N	Placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Iffland 1989	0/14	1/17		49.8 %	0.16 [0.00, 8.29]
van Dijk 1979	0/21	1/19		50.2 %	0.12 [0.00, 6.17]
Total (95% CI)	**35**	**36**		**100.0 %**	**0.14 [0.01, 2.26]**

Total events: 0 (Danazol), 2 (Placebo)

Heterogeneity: Chi^2 = 0.01, df = 1 (P = 0.92); I^2 =0.0%

Test for overall effect: Z = 1.39 (P = 0.17)

Test for subgroup differences: Not applicable

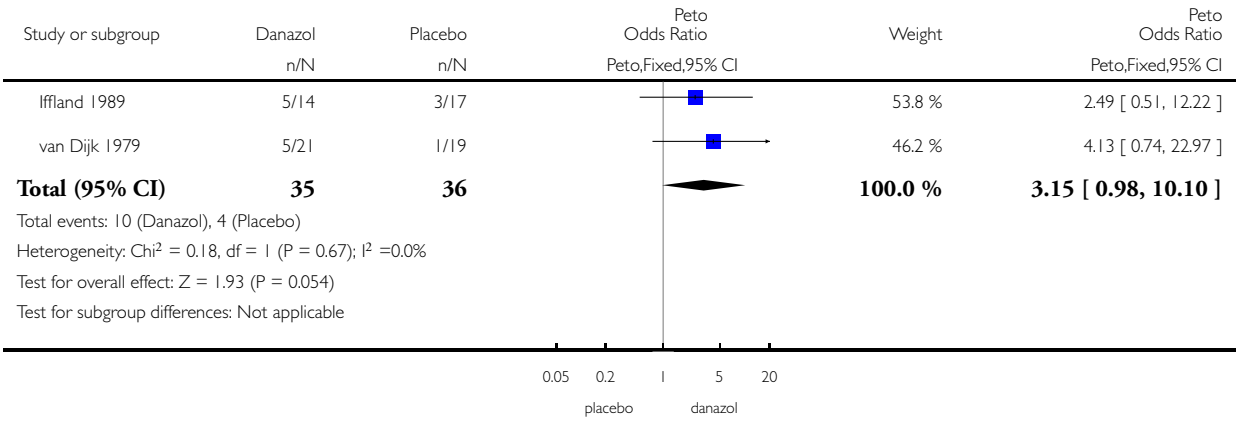


Analysis 1.4. Comparison 1 Danazol versus placebo in unexplained subfertility, Outcome 4 Pregnancies per woman randomised during treatment and follow up.

Review: Danazol for unexplained subfertility

Comparison: 1 Danazol versus placebo in unexplained subfertility

Outcome: 4 Pregnancies per woman randomised during treatment and follow up

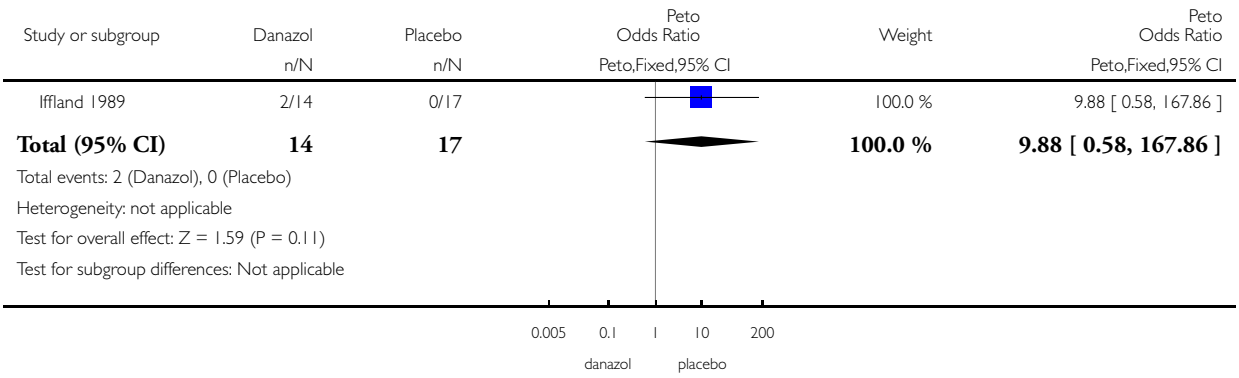


Analysis 1.5. Comparison 1 Danazol versus placebo in unexplained subfertility, Outcome 5 Miscarriage per woman randomised.

Review: Danazol for unexplained subfertility

Comparison: 1 Danazol versus placebo in unexplained subfertility

Outcome: 5 Miscarriage per woman randomised



Analysis 1.6. Comparison 1 Danazol versus placebo in unexplained subfertility, Outcome 6 Ectopic pregnancy per woman randomised.

Review: Danazol for unexplained subfertility

Comparison: 1 Danazol versus placebo in unexplained subfertility

Outcome: 6 Ectopic pregnancy per woman randomised

Study or subgroup	Danazol n/N	Placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
van Dijk 1979	2/21	0/19		100.0 %	7.06 [0.42, 117.50]
Total (95% CI)	**21**	**19**		**100.0 %**	**7.06 [0.42, 117.50]**

Total events: 2 (Danazol), 0 (Placebo)

Heterogeneity: not applicable

Test for overall effect: Z = 1.36 (P = 0.17)

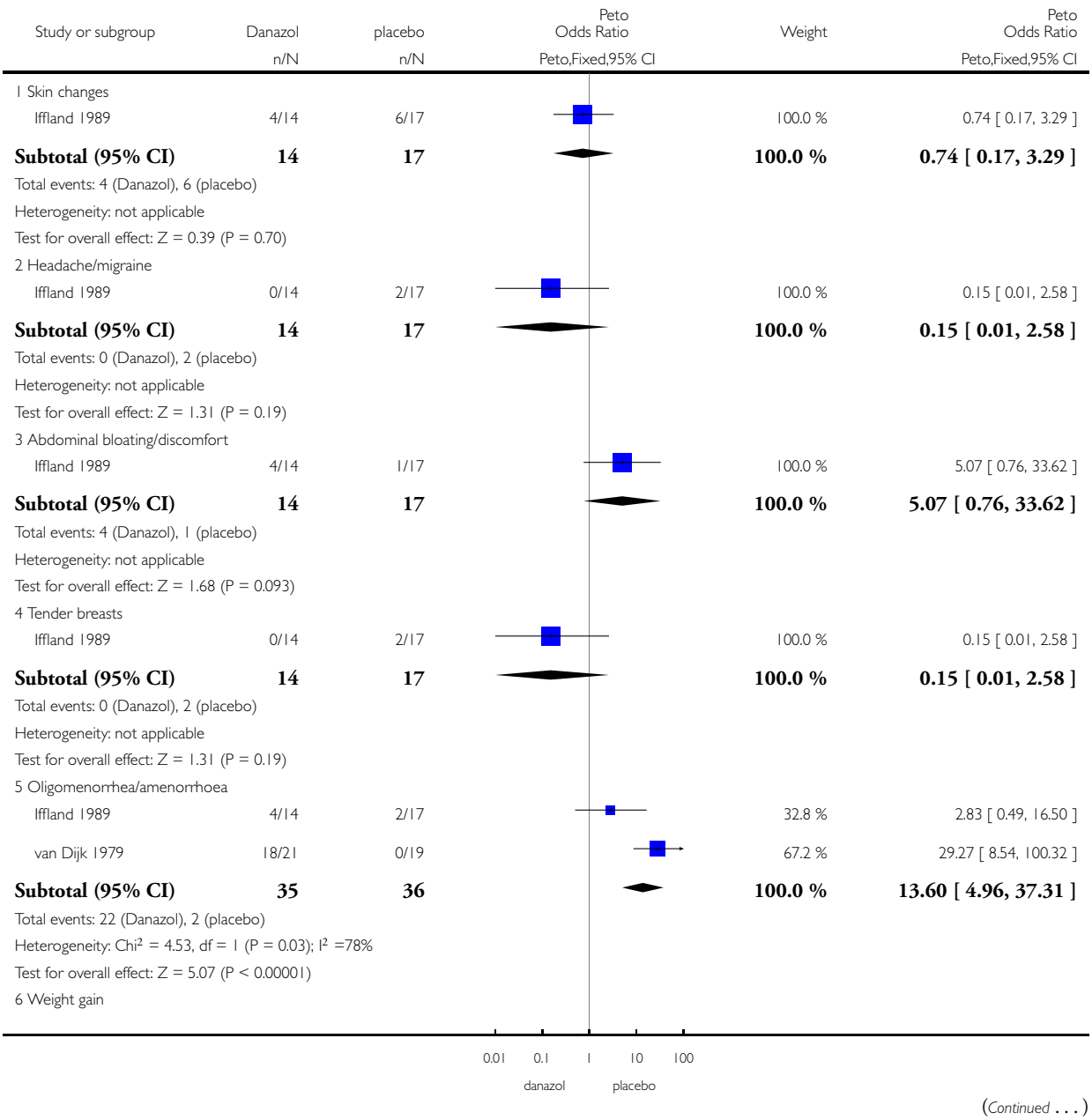
Test for subgroup differences: Not applicable

Analysis 1.7. Comparison 1 Danazol versus placebo in unexplained subfertility, Outcome 7 Adverse events/side effects.

Review: Danazol for unexplained subfertility

Comparison: 1 Danazol versus placebo in unexplained subfertility

Outcome: 7 Adverse events/side effects



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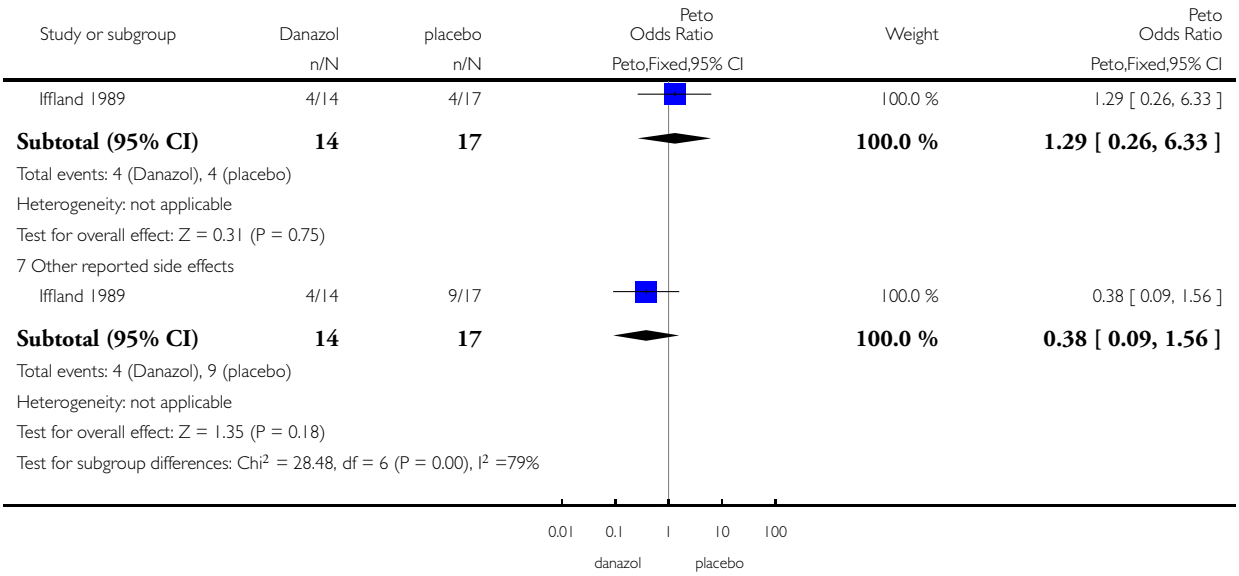

ADDITIONAL TABLES

Table 1. Risk of bias table

Study ID	Randomisation	Concealment	Power	Intent-to Treat	Attrition	Funding
Iffland 1989	No details of randomisation method	No details of allocation concealment	No details	No details	Eight women excluded. Six failed to start or complete the treatment , 1 was diagnosed as a diabetic and 1 with hypothyroidism	Winthrop laboratories, UK
Van Dijk 1979	No details of randomisation method	No details of allocation concealment	No details	No details, 1 pregnancy in the placebo group during treatment was excluded from the analysis but has been included as the ITT population in this meta-analysis	n=1, one woman was excluded due to pregnancy in the placebo group	No details

APPENDICES

Appendix 1. Search string

MEDLINE (1966-November 2006)
EMBASE (1980 - November 2006)
1 (unexplained adj3 infertil$).mp.
2 (unexplained adj3 subfertil$).mp.
3 (idiopathic adj3 infertil$).mp.
4 (idiopathic adj3 subfertil$).mp.
5 or/1-4
6 danazol.mp. or exp DANAZOL/
7 5 and 6
8 randomized controlled trial.pt.
9 controlled clinical trial.pt.
10 randomized controlled trials/
11 random allocation/
12 double-blind method/
13 single-blind method/
14 or/8-13
15 clinical trial.pt.
16 exp clinical trials/
17 (clin$ adj25 trial$).ti,ab,sh.
18 ((singl$ or doubl$ or tripl$ or trebl$) adj25 (blind$ or mask$)).ti,ab,sh.
19 placebos/
20 placebo$.ti,ab,sh.
21 random$.ti,ab,sh.
22 research design/
23 or/15-22
24 animal/ not (human/ and animal/)
25 14 or 23
26 25 not 24
27 7 and 26

WHAT'S NEW

Last assessed as up-to-date: 14 November 2006.

Date	Event	Description
10 November 2008	Review declared as stable	The MDSG feel that there are unlikely to be any further RCT's in this topic area and therefore this review was closed following its publication Issue 1,2007
7 November 2008	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 1, 1996

Review first published: Issue 1, 1996

Date	Event	Description
15 November 2006	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Julie Brown was involved in the most recent update of this review October 2006. She ran the latest electronic search and updated the style of the review to the the MDSG standards.

DECLARATIONS OF INTEREST

None known

SOURCES OF SUPPORT

Internal sources

- Ministry of Health, New Zealand.

External sources

- Royal Commission on New Reproductive Technologies, Not specified.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The search has been revised

NOTES

The MDSG feel that there are unlikely to be any further RCT's in this topic area and therefore this review will be closed following its publication Issue 1,2007

INDEX TERMS

Medical Subject Headings (MeSH)

Danazol [*therapeutic use]; Estrogen Antagonists [*therapeutic use]; Infertility, Female [*drug therapy]

MeSH check words

Female; Humans