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Cochrane Database of Systematic Reviews 2017, Issue 5. Art. No.: CD006109.

DOI: [10.1002/14651858.CD006109.pub3](https://doi.org/10.1002/14651858.CD006109.pub3).

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[Intervention Review]

Oral contraceptive pill, progestogen or oestrogen pretreatment for ovarian stimulation protocols for women undergoing assisted reproductive techniques

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Editorial group: Cochrane Gynaecology and Fertility Group.

Publication status and date: Edited (no change to conclusions), published in Issue 8, 2017.

Citation: Farquhar C, Rombauts L, Kremer JAM, Lethaby A, Ayeleke RO. Oral contraceptive pill, progestogen or oestrogen pretreatment for ovarian stimulation protocols for women undergoing assisted reproductive techniques. *Cochrane Database of Systematic Reviews* 2017, Issue 5. Art. No.: CD006109. DOI: [10.1002/14651858.CD006109.pub3](https://doi.org/10.1002/14651858.CD006109.pub3).

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ABSTRACT

Background

Among subfertile women undergoing assisted reproductive technology (ART), hormone pills given before ovarian stimulation may improve outcomes.

Objectives

To determine whether pretreatment with the combined oral contraceptive pill (COCP) or with a progestogen or oestrogen alone in ovarian stimulation protocols affects outcomes in subfertile couples undergoing ART.

Search methods

We searched the following databases from inception to January 2017: Cochrane Gynaecology and Fertility Group Specialised Register, The Cochrane Central Register Studies Online, MEDLINE, Embase, CINAHL and PsycINFO. We also searched the reference lists of relevant articles and registers of ongoing trials.

Selection criteria

Randomised controlled trials (RCTs) of hormonal pretreatment in women undergoing ART.

Data collection and analysis

We used standard methodological procedures recommended by Cochrane. The primary review outcomes were live birth or ongoing pregnancy and pregnancy loss.

Main results

We included 29 RCTs (4701 women) of pretreatment with COCPs, progestogens or oestrogens versus no pretreatment or alternative pretreatments, in gonadotrophin-releasing hormone (GnRH) agonist or antagonist cycles. Overall, evidence quality ranged from very low to moderate. The main limitations were risk of bias and imprecision. Most studies did not describe their methods in adequate detail.

Combined oral contraceptive pill versus no pretreatment

Oral contraceptive pill, progestogen or oestrogen pretreatment for ovarian stimulation protocols for women undergoing assisted reproductive techniques (Review)

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With antagonist cycles in both groups the rate of live birth or ongoing pregnancy was lower in the pretreatment group (OR 0.74, 95% CI 0.58 to 0.95; 6 RCTs; 1335 women; $I^2 = 0\%$; moderate quality evidence). There was insufficient evidence to determine whether the groups differed in rates of pregnancy loss (OR 1.36, 95% CI 0.82 to 2.26; 5 RCTs; 868 women; $I^2 = 0\%$; moderate quality evidence), multiple pregnancy (OR 2.21, 95% CI 0.53 to 9.26; 2 RCTs; 125 women; $I^2 = 0\%$; low quality evidence), ovarian hyperstimulation syndrome (OHSS; OR 0.98, 95% CI 0.28 to 3.40; 2 RCTs; 642 women; $I^2 = 0\%$, low quality evidence), or ovarian cyst formation (OR 0.47, 95% CI 0.08 to 2.75; 1 RCT; 64 women; very low quality evidence).

In COCP plus antagonist cycles versus no pretreatment in agonist cycles, there was insufficient evidence to determine whether the groups differed in rates of live birth or ongoing pregnancy (OR 0.89, 95% CI 0.64 to 1.25; 4 RCTs; 724 women; $I^2 = 0\%$; moderate quality evidence), multiple pregnancy (OR 1.36, 95% CI 0.85 to 2.19; 4 RCTs; 546 women; $I^2 = 0\%$; moderate quality evidence), or OHSS (OR 0.63, 95% CI 0.20 to 1.96; 2 RCTs; 290 women, $I^2 = 0\%$), but there were fewer pregnancy losses in the pretreatment group (OR 0.40, 95% CI 0.22 to 0.72; 5 RCTs; 780 women; $I^2 = 0\%$; moderate quality evidence). There were no data suitable for analysis on ovarian cyst formation.

One small study comparing COCP versus no pretreatment in agonist cycles showed no clear difference between the groups for any of the reported outcomes.

Progestogen versus no pretreatment

All studies used the same protocol (antagonist, agonist or gonadotrophins) in both groups. There was insufficient evidence to determine any differences in rates of live birth or ongoing pregnancy (agonist: OR 1.35, 95% CI 0.69 to 2.65; 2 RCTs; 222 women; $I^2 = 24\%$; low quality evidence; antagonist: OR 0.67, 95% CI 0.18 to 2.54; 1 RCT; 47 women; low quality evidence; gonadotrophins: OR 0.63, 95% CI 0.09 to 4.23; 1 RCT; 42 women; very low quality evidence), pregnancy loss (agonist: OR 2.26, 95% CI 0.67 to 7.55; 2 RCTs; 222 women; $I^2 = 0\%$; low quality evidence; antagonist: OR 0.36, 95% CI 0.06 to 2.09; 1 RCT; 47 women; low quality evidence; gonadotrophins: OR 1.00, 95% CI 0.06 to 17.12; 1 RCT; 42 women; very low quality evidence) or multiple pregnancy (agonist: no data available; antagonist: OR 1.05, 95% CI 0.06 to 17.76; 1 RCT; 47 women; low quality evidence; gonadotrophins: no data available). Three studies, all using agonist cycles, reported ovarian cyst formation: rates were lower in the pretreatment group (OR 0.16, 95% CI 0.08 to 0.32; 374 women; $I^2 = 1\%$; moderate quality evidence). There were no data on OHSS.

Oestrogen versus no pretreatment

In antagonist or agonist cycles, there was insufficient evidence to determine whether the groups differed in rates of live birth or ongoing pregnancy (antagonist versus antagonist: OR 0.79, 95% CI 0.53 to 1.17; 2 RCTs; 502 women; $I^2 = 0\%$; low quality evidence; antagonist versus agonist: OR 0.88, 95% CI 0.51 to 1.50; 2 RCTs; 242 women; $I^2 = 0\%$; very low quality evidence), pregnancy loss (antagonist versus antagonist: OR 0.16, 95% CI 0.02 to 1.47; 1 RCT; 49 women; very low quality evidence; antagonist versus agonist: OR 1.59, 95% CI 0.62 to 4.06; 1 RCT; 220 women; very low quality evidence), multiple pregnancy (antagonist versus antagonist: no data available; antagonist versus agonist: OR 2.24, 95% CI 0.09 to 53.59; 1 RCT; 22 women; very low quality evidence) or OHSS (antagonist versus antagonist: no data available; antagonist versus agonist: OR 1.54, 95% CI 0.25 to 9.42; 1 RCT; 220 women). Ovarian cyst formation was not reported.

Head-to-head comparisons

COCP was compared with progestogen (1 RCT, 44 women), and with oestrogen (2 RCTs, 146 women), and progestogen was compared with oestrogen (1 RCT, 48 women), with an antagonist cycle in both groups. COCP in an agonist cycle was compared with oestrogen in an antagonist cycle (1 RCT, 25 women). Data were scant but there was no clear evidence that any of the groups differed in rates of live birth or ongoing pregnancy, pregnancy loss or other adverse events.

Authors' conclusions

Among women undergoing ovarian stimulation in antagonist protocols, COCP pretreatment was associated with a lower rate of live birth or ongoing pregnancy than no pretreatment. There was insufficient evidence to determine whether rates of live birth or ongoing pregnancy were influenced by pretreatment with progestogens or oestrogens, or by COCP pretreatment using other stimulation protocols. Findings on adverse events were inconclusive, except that progesterone pretreatment may reduce the risk of ovarian cysts in agonist cycles, and COCP in antagonist cycles may reduce the risk of pregnancy loss compared with no pretreatment in agonist cycles.

PLAIN LANGUAGE SUMMARY

Pretreatments in in vitro fertilisation/intra-cytoplasmic sperm injection cycles

Review question

The aim of this review was to assess whether pretreatment with a combined oral contraceptive pill (COCP) or with progestogen or oestrogen alone influences pregnancy outcomes in couples with low fertility undergoing assisted reproductive technology (ART)

Background

In vitro fertilisation (IVF; where an egg is mixed with sperm outside the body) and intra-cytoplasmic sperm injection (ICSI; where one sperm is injected directly into the egg) are important techniques for women who have trouble getting pregnant. IVF and ICSI cycles consist of a few steps. First the woman receives hormone therapy to stimulate her ovaries in producing egg cells (called ovarian stimulation). When a few egg cells are mature enough to be fertilised, the woman receives a single hormone injection. This triggers the ovaries to release the egg cells, so they can be gathered by the clinician. The eggs are then fertilised outside the woman's body and become embryos. One or two embryos are then transferred into the womb.

Before the first step in IVF or ICSI cycles (hormone therapy), a pretreatment with a COCP can be given. A COCP contains both progestogen and oestrogen. Pretreatment with a progestogen or oestrogen alone could also be used before the hormone therapy. These pretreatments suppress the woman's own hormone production. This might improve the woman's response to the hormone therapy in IVF/ICSI cycles. In this way, side events such as cyst formation (fluid-filled sac that develops on a woman's ovary) and the number of pregnancy losses might be reduced and pregnancy outcomes might be improved.

Study characteristics

This Cochrane Review included 30 randomized controlled trials (clinical studies where people are randomly put into one of two or more treatment groups) assessing pretreatment with COCP, progestogen or oestrogen in 5096 women undergoing ART. The evidence is current to January 2017.

Key results

Among women undergoing ovarian stimulation in antagonist protocols, COCP pretreatment was associated with a lower rate of live birth or ongoing pregnancy than no pretreatment. There was insufficient evidence to determine whether rates of live birth or ongoing pregnancy were influenced by pretreatment with progestogens or oestrogens, or by COCP pretreatment using other stimulation protocols. Findings on adverse events were inconclusive, except that progesterone pretreatment may reduce the risk of ovarian cysts in agonist cycles, and COCP in antagonist cycles may reduce the risk of pregnancy loss compared with no pretreatment in agonist cycles.

Quality of the evidence.

Overall evidence quality ranged from very low to moderate. The main problems were risk of bias and imprecision. Most studies did not describe their methods in adequate detail.