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Endometrial preparation for women undergoing embryo transfer with frozen embryos or embryos derived from donor oocytes (Review)

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Glujovsky D, Pesce R, Sueldo C, Quinteiro Retamar AM, Hart RJ, Ciapponi A.
Endometrial preparation for women undergoing embryo transfer with frozen embryos or embryos derived from donor oocytes.
Cochrane Database of Systematic Reviews 2020, Issue 10. Art. No.: CD006359.
DOI: 10.1002/14651858.CD006359.pub3.

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[Intervention Review]

Endometrial preparation for women undergoing embryo transfer with frozen embryos or embryos derived from donor oocytes

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Editorial group: Cochrane Gynaecology and Fertility Group.
Publication status and date: New search for studies and content updated (conclusions changed), published in Issue 10, 2020.

Citation: Glujovsky D, Pesce R, Sueldo C, Quinteiro Retamar AM, Hart RJ, Ciapponi A. Endometrial preparation for women undergoing embryo transfer with frozen embryos or embryos derived from donor oocytes. *Cochrane Database of Systematic Reviews* 2020, Issue 10. Art. No.: CD006359. DOI: 10.1002/14651858.CD006359.pub3.

ABSTRACT

Background

A frozen embryo transfer (FET) cycle is when one or more embryos (frozen during a previous treatment cycle) are thawed and transferred to the uterus. Some women undergo fresh embryo transfer (ET) cycles with embryos derived from donated oocytes. In both situations, the endometrium is primed with oestrogen and progestogen in different doses and routes of administration.

Objectives

To evaluate the most effective endometrial preparation for women undergoing transfer with frozen embryos or embryos from donor oocytes with regard to the subsequent live birth rate (LBR).

Search methods

The Cochrane Gynaecology and Fertility Group trials register, CENTRAL, MEDLINE, Embase, PsycINFO, LILACS, trials registers and abstracts of reproductive societies' meetings were searched in June 2020 together with reference checking and contact with study authors and experts in the field to identify additional studies.

Selection criteria

Randomised controlled trials (RCTs) evaluating endometrial preparation in women undergoing fresh donor cycles and frozen embryo transfers.

Data collection and analysis

We used standard methodological procedures recommended by Cochrane. We analysed all available interventions versus placebo, no treatment, or between each other. The primary review outcome was live birth rate. Secondary outcomes were clinical and multiple pregnancy, miscarriage, cycle cancellation, endometrial thickness and adverse effects.

Main results

Thirty-one RCTs (5426 women) were included. Evidence was moderate to very low-quality: the main limitations were serious risk of bias due to poor reporting of methods, and serious imprecision.

Stimulated versus programmed cycle

We are uncertain whether a letrozole-stimulated cycle compared to a programmed cycle, for endometrial preparation, improves LBR (odds ratio (OR) 1.26, 95% confidence interval (CI) 0.49 to 3.26; 100 participants; one study; very low-quality evidence).

Stimulating with follicle stimulating hormone (FSH), letrozole or clomiphene citrate may improve clinical pregnancy rate (CPR) (OR 1.63, 95% CI 1.12 to 2.38; 656 participants; five studies; I^2 = 11%; low-quality evidence). We are uncertain if they reduce miscarriage rate (MR) (OR 0.79, 95% CI 0.36 to 1.71; 355 participants; three studies; I^2 = 0%; very low-quality evidence). Endometrial thickness (ET) may be reduced with clomiphene citrate (mean difference(MD) -1.04, 95% CI -1.59 to -0.49; 92 participants; one study; low-quality evidence). Other outcomes were not reported.

Natural versus programmed cycle

We are uncertain of the effect from a natural versus programmed cycle for LBR (OR 0.97, 95% CI 0.74 to 1.28; 1285 participants; four studies; I^2 = 0%; very low-quality evidence) and CPR (OR 0.79, 95% CI 0.62 to 1.01; 1249 participants; five studies; I^2 = 60%; very low-quality evidence), while a natural cycle probably reduces the cycle cancellation rate (CCR) (OR 0.60, 95% CI 0.44 to 0.82; 734 participants; one study; moderate-quality evidence). We are uncertain of the effect on MR and ET. No study reported other outcomes.

Transdermal versus oral oestrogens

From low-quality evidence we are uncertain of the effect transdermal compared to oral oestrogens has on CPR (OR 0.86, 95% CI 0.59 to 1.25; 504 participants; three studies; I^2 = 58%) or MR (OR 0.55, 95% CI 0.27 to 1.09; 414 participants; two studies; I^2 = 0%). Other outcomes were not reported.

Day of starting administration of progestogen

When doing a fresh ET using donated oocytes in a synchronised cycle starting progestogen on the day of oocyte pick-up (OPU) or the day after OPU, in comparison with recipients that start progestogen the day prior to OPU, probably increases the CPR (OR 1.87, 95% CI 1.13 to 3.08; 282 participants; one study, moderate-quality evidence). We are uncertain of the effect on multiple pregnancy rate (MPR) or MR. It probably reduces the CCR (OR 0.28, 95% CI 0.11 to 0.74; 282 participants; one study; moderate-quality evidence). No study reported other outcomes.

Gonadotropin-releasing hormone (GnRH) agonist versus control

A cycle with GnRH agonist compared to without may improve LBR (OR 2.62, 95% CI 1.19 to 5.78; 234 participants; one study; low-quality evidence). From low-quality evidence we are uncertain of the effect on CPR (OR 1.08, 95% CI 0.82 to 1.43; 1289 participants; eight studies; I^2 = 20%), MR (OR 0.85, 95% CI 0.36 to 2.00; 828 participants; four studies; I^2 = 0%), CCR (OR 0.49, 95% CI 0.21 to 1.17; 530 participants; two studies; I^2 = 0%) and ET (MD -0.08, 95% CI -0.33 to 0.16; 697 participants; four studies; I^2 = 4%). No study reported other outcomes.

Among different GnRH agonists

From very low-quality evidence we are uncertain if cycles among different GnRH agonists improves CPR or MR. No study reported other outcomes.

GnRH agonists versus GnRH antagonists

GnRH antagonists compared to agonists probably improves CPR (OR 0.62, 95% CI 0.42 to 0.90; 473 participants; one study; moderate-quality evidence). We are uncertain of the effect on MR and MPR. No study reported other outcomes.

Aspirin versus control

From very low-quality evidence we are uncertain whether a cycle with aspirin versus without improves LBR, CPR, or ET.

Steroids versus control

From very low-quality evidence we are uncertain whether a cycle with steroids compared to without improves LBR, CPR or MR. No study reported other outcomes.

Authors' conclusions

There is insufficient evidence on the use of any particular intervention for endometrial preparation in women undergoing fresh donor cycles and frozen embryo transfers. In frozen embryo transfers, low-quality evidence showed that clinical pregnancy rates may be improved in a stimulated cycle compared to a programmed one, and we are uncertain of the effect when comparing a programmed cycle to a natural cycle. Cycle cancellation rates are probably reduced in a natural cycle. Although administering a GnRH agonist, compared to without, may improve live birth rates, clinical pregnancy rates will probably be improved in a GnRH antagonist cycle over an agonist cycle.

In fresh synchronised oocyte donor cycles, the clinical pregnancy rate is probably improved and cycle cancellation rates are probably reduced when starting progestogen the day of or day after donor oocyte retrieval.

Adequately powered studies are needed to evaluate each treatment more accurately.

PLAIN LANGUAGE SUMMARY

Endometrial preparation for egg donor recipients or for frozen embryo transfers

Review question

What is the most effective method for endometrial preparation in women undergoing embryo transfers with frozen embryos or embryos derived from donor oocytes?

Background

Couples undergo infertility treatments due to male factor, female factors or unexplained infertility. After an unsuccessful fresh embryo transfer cycle, a frozen-thawed embryo transfer can be performed when frozen embryos are available. Adequate hormonal preparation of the endometrium is of utmost importance for both egg donor and frozen embryo replacement cycles to provide the optimal chances of pregnancy. Many drugs and various modes of administration have been tried by several investigators in order to optimise implantation rates and consequently improve the success rates of the embryo transfer procedures: stimulated cycles (to generate endogenous oestradiol), programmed cycles (administering exogenous oestradiol) or natural cycles (allowing the ovaries to produce oestradiol without stimulation) are some of the options; avoiding spontaneous ovulation with gonadotropin-releasing hormone (GnRH) agonists and antagonists could have some impact; or using some other drugs such as aspirin or steroids that could potentially enhance the endometrial receptivity were also evaluated.

Study characteristics

We found 31 randomised controlled trials comparing different interventions such as the dose and route of administration of oestrogens and progestogen, the use of drugs that stop the patient from ovulating prematurely (GnRH agonists), and the use of other medications to improve the endometrium in a total of 5426 women. The evidence is current to June 2020.

Key results

We are uncertain whether a stimulated cycle (with letrozole) compared to a programmed cycle, for endometrial preparation, improves live birth. The evidence suggests that if the chance of live birth following a programmed cycle is assumed to be 24%, the chance following a stimulated cycle would be between 13% and 51%. We are also uncertain of the impact on miscarriage rate and endometrial thickness. A stimulated cycle may improve clinical pregnancy rate. Data were lacking on multiple pregnancy, cycle cancellation and other adverse effects.

We are uncertain whether a natural cycle improves the live birth rate, pregnancy rate, miscarriage rate and endometrial thickness in comparison with a programmed cycle. Data were lacking for all other outcomes.

We are uncertain if transdermal (delivered via the skin) oestrogens compared with oral (by mouth) oestrogens improve clinical pregnancy rate and miscarriage rate. Data were lacking for all other outcomes in this comparison.

Starting progestogen on the day of the donor oocyte retrieval or the day after probably increases the clinical pregnancy rate and probably reduces the cycle cancellation rate. We are uncertain if it reduces the miscarriage rate. Data were lacking for all other outcomes.

A cycle with GnRH agonist compared to without may improve live birth rate. We are uncertain of the effect of a GnRH cycle compared to no GnRH for the outcomes of clinical pregnancy rate, miscarriage rate, and endometrial thickness. No study reported on the other outcomes for this comparison.

We are uncertain if any GnRH agonist is better than other: a cycle with daily leuprolide or with deposit tryptorelin improves clinical pregnancy rate, or if daily acetate leuprolide or daily nafarelin reduces the miscarriage rate. Other outcomes were not reported.

GnRH antagonists compared to agonists probably improve clinical pregnancy rate. We are uncertain of the effect on miscarriage rate and multiple pregnancy rate. No study reported the other outcomes.

We are uncertain whether a cycle with aspirin compared to a cycle without improves live birth, clinical pregnancy rate or endometrial thickness. Data were lacking for all other outcomes.

We are also uncertain whether a cycle with steroids compared to a cycle without steroids improves live birth rate, clinical pregnancy rate or miscarriage rate. No study reported on the other outcomes.

Quality of the evidence

The evidence was of moderate to very low-quality. The main limitations in the evidence were poor reporting of study methods, and lack of precision in the findings for live birth.

SUMMARY OF FINDINGS

Summary of findings 1. Stimulated cycle compared to programmed for women undergoing embryo transfer with frozen embryos or embryos derived from donor oocytes

Stimulated cycle compared to programmed for women undergoing embryo transfer with frozen embryos or embryos derived from donor oocytes

Patient or population: women undergoing embryo transfer with frozen embryos or embryos derived from donor oocytes
Setting: IVF unit
Intervention: stimulated cycle
Comparison: programmed cycle

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with programmed	Risk with Stimulated cycle				
Live birth rate	240 per 1000	285 per 1000 (134 to 507)	OR 1.26 (0.49 to 3.26)	100 (1 RCT)	⊕⊝⊝⊝ VERY LOW [a b]	Letrozole stimulation versus programmed cycle
Clinical pregnancy rate	191 per 1000	278 per 1000 (210 to 360)	OR 1.63 (1.12 to 2.38)	656 (5 RCTs)	⊕⊕⊝⊝ LOW [a c]	
Miscarriage rate	87 per 1000	70 per 1000 (33 to 140)	OR 0.79 (0.36 to 1.71)	355 (3 RCTs)	⊕⊝⊝⊝ VERY LOW [a b]	
Multiple pregnancy rate						Not reported in any study
Cycle cancellation rate						Not reported in any study
Endometrial thickness (mm)	The mean endometrial thickness (mm) was 8.7 mm	MD -0.05 mm (-0.19 lower to 0.10 higher)	-	362 (2 RCTs)	⊕⊕⊝⊝ LOW [a c]	Letrozole stimulation versus programmed cycle
Other adverse effects						Not reported in any study

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: Confidence interval; **OR:** Odds ratio; **RCT:** randomised controlled trial.

GRADE Working Group grades of evidence

High quality: further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: we are very uncertain about the estimate.

[a] Downgraded one level due to risk of bias. It is unclear the sequence generation and method of allocation concealment that was used.
[b] Downgraded two levels due to very serious imprecision. The confidence interval is too wide. The intervention could improve or reduce the outcome.
c Downgraded one level due to imprecision. The confidence interval is too wide.

Summary of findings 2. Natural cycle compared to programmed cycle for women undergoing embryo transfer with frozen embryos or embryos derived from donor oocytes

Natural cycle compared to programmed cycle for women undergoing embryo transfer with frozen embryos or embryos derived from donor oocytes

Patient or population: women undergoing embryo transfer with frozen embryos or embryos derived from donor oocytes
Setting: IVF unit
Intervention: natural cycle
Comparison: programmed cycle

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with programmed cycle	Risk with Natural cycle				
Live birth rate	233 per 1000	228 per 1000 (184 to 280)	OR 0.97 (0.74 to 1.28)	1285 (4 RCTs)	⊕⊝⊝⊝ VERY LOW [a b c]	
Clinical pregnancy rate	347 per 1000	296 per 1000 (248 to 350)	OR 0.79 (0.62 to 1.01)	1249 (5 RCTs)	⊕⊝⊝⊝ VERY LOW [a b d]	
Miscarriage rate	50 per 1000	32 per 1000 (13 to 82)	OR 0.64 (0.25 to 1.63)	485 (3 RCTs)	⊕⊝⊝⊝ VERY LOW [a e]	
Multiple pregnancy rate						Not reported in any study
Cycle cancellation rate	365 per 1000	256 per 1000 (202 to 320)	OR 0.60 (0.44 to 0.82)	734 (1 RCT)	⊕⊕⊕⊝ MODERATE [b]	
Endometrial thickness (mm)	The mean difference endometrial thickness (mm) was 0.42	MD 0.22 higher (0.25 lower to 0.69 higher)	-	485 (3 RCTs)	⊕⊕⊝⊝ LOW [a d]	

Other adverse effects						Not reported in any study

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: Confidence interval; **OR:** Odds ratio; **RCT:** randomised controlled trial

GRADE Working Group grades of evidence

High quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: we are very uncertain about the estimate.

[a] We downgraded the evidence by one level, due to risk of bias: unclear or high risk of bias for allocation concealment.
[b] We downgraded the evidence by one level, due to risk of bias: high risk of attrition bias.
[c] We downgraded the evidence by one level, due to imprecision: the confidence interval is too wide. The intervention could improve or reduce the outcome.
[d] We downgraded the evidence by one level for inconsistency due to heterogeneity.
[e] We downgraded two levels for serious imprecision, few events.

Summary of findings 3. Transdermal oestrogens compared to oral oestrogens for women undergoing embryo transfer with frozen embryos or embryos derived from donor oocytes

Transdermal oestrogens compared to oral oestrogens for women undergoing embryo transfer with frozen embryos or embryos derived from donor oocytes

Patient or population: women undergoing embryo transfer with frozen embryos or embryos derived from donor oocytes
Setting: IVF unit
Intervention: transdermal oestrogens
Comparison: oral oestrogens

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with oral oestrogens	Risk with Transdermal oestrogens				
Live birth rate					-	Not reported in any study
Clinical pregnancy rate	506 per 1000	468 per 1000 (377 to 561)	OR 0.86 (0.59 to 1.25)	504 (3 RCTs)	⊕⊕⊖⊖ LOW [a b]	
Miscarriage rate	119 per 1000	69 per 1000	OR 0.55	414	⊕⊕⊖⊖	

	(35 to 128)	(0.27 to 1.09)	(2 RCTs)	LOW [a b]	
Multiple pregnancy rate				-	Not reported in any study
Cycle cancellation rate				-	Not reported in any study
Endometrial thickness (mm)				-	Not reported in any study
Other adverse effects				-	Not reported in any study

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: Confidence interval; **OR:** Odds ratio; **RCT:** randomised controlled trial.

GRADE Working Group grades of evidence

High quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: we are very uncertain about the estimate.

[a] We downgraded the evidence by one level, due to risk of bias: unclear or high risk of bias for allocation concealment.
[b] We downgraded the evidence by one level, due to very wide confidence interval. The intervention could improve or reduce the outcome.

Summary of findings 4. Starting administration of the progestogen earlier compared to starting administration of the progestogen later for women undergoing embryo transfer with frozen embryos or embryos derived from donor oocytes

Starting administration of the progestogen earlier compared to starting administration of the progestogen later for women undergoing embryo transfer with frozen embryos or embryos derived from donor oocytes

Patient or population: women undergoing embryo transfer with frozen embryos or embryos derived from donor oocytes
Setting: IVF unit
Intervention: starting administration of progestogen earlier
Comparison: starting administration of progestogen later

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with starting administration of the progestogen earlier	Risk with starting administration of the progestogen later				

Live birth rate						Not reported in any study
Clinical pregnancy rate	381 per 1000	536 per 1000 (433 to 634)	OR 1.87 (1.13 to 3.08)	282 (1 RCT)	⊕⊕⊕⊖ MODERATE [a]	Day before oocyte retrieval (T1) versus day of oocyte retrieval or day after(T2) in Oocyte donation
Miscarriage Rate	128 per 1000	62 per 1000 (23 to 155)	OR 0.45 (0.16 to 1.25)	191 (1 RCT)	⊕⊖⊖⊖ VERY LOW [a b]	Day before oocyte retrieval (T1) versus day of oocyte retrieval (T2) in Oocyte donation
Multiple pregnancy rate	189 per 1000	144 per 1000 (79 to 249)	0.72 (0.37 to 1.42)	282 (1 RCT)	⊕⊖⊖⊖ VERY LOW [a b]	Day before oocyte retrieval (T1) versus day of oocyte retrieval or day after(T2) in Oocyte donation
Cycle cancellation rate	38 per 1000	11 per 1000 (4 to 28)	OR 0.28 (0.11 to 0.74)	282 (1 RCT)	⊕⊕⊕⊖ MODERATE [a]	
Endometrial thickness						Not reported in any study
Other adverse effects						Not reported in any study

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: Confidence interval; **OR:** Odds ratio; **RCT:** randomised controlled trial.

GRADE Working Group grades of evidence

High quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: we are very uncertain about the estimate.

[a] We downgraded the evidence by one level, due to risk of bias: unclear risk of bias for allocation concealment and unclear risk of attrition bias.
[b] We downgraded the evidence by two levels, due to a very wide confidence interval. The intervention could improve or reduce the outcome.

Summary of findings 5. GnRH agonists compared to control for women undergoing embryo transfer with frozen embryos or embryos derived from donor oocytes

GnRH agonists compared to control for women undergoing embryo transfer with frozen embryos or embryos derived from donor oocytes

Patient or population: women undergoing embryo transfer with frozen embryos or embryos derived from donor oocytes

Setting: IVF unit
Intervention: GnRH agonists
Comparison: control

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with control	Risk with GnRH agonists				
Live birth rate	85 per 1000	197 per 1000 (100 to 351)	OR 2.62 (1.19 to 5.78)	234 (1 RCT)	⊕⊕⊖⊖ LOW [a b]	
Clinical pregnancy rate	184 per 1000	199 per 1000 (151 to 264)	OR 1.08 (0.82 to 1.43)	1289 (8 RCTs)	⊕⊕⊖⊖ LOW [c d]	In frozen-embryo transfers
Miscarriage rate	30 per 1000	26 per 1000 (11 to 58)	OR 0.85 (0.36 to 2.00)	828 (4 RCTs)	⊕⊕⊖⊖ LOW [d e]	
Multiple pregnancy rate						Not reported in any study
Cycle cancellation cycles	60 per 1000	30 per 1000 (13 to 69)	OR 0.49 (0.21 to 1.17)	530 (2 RCTs)	⊕⊕⊖⊖ LOW [d e]	
Endometrial thickness (mm)	The mean endometrial thickness (mm) was 9.4 mm	MD 0.08 mm lower (0.33 lower to 0.16 higher)	-	697 (4 RCTs)	⊕⊕⊖⊖ LOW [d e]	
Other adverse effects						Not reported in any study

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: Confidence interval; **GnRH:** gonadotropin-releasing hormone; **OR:** Odds ratio; **RCT:** randomised controlled trial.

GRADE Working Group grades of evidence

High quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: we are very uncertain about the estimate.

[a] We downgraded the evidence by one level, due to high risk of bias in allocation concealment.
[b] We downgraded one level due to imprecision, one small study (less than 300).

[c] We downgraded the evidence by one level, due to unclear or high risk of bias in allocation concealment and unclear risk of bias in reporting bias.
[d] We downgraded the evidence by one level, due to imprecision: a wide confidence interval. The intervention could improve or reduce the outcome.
[e] We downgraded the evidence by one level, due to high risk of bias in randomisation method and allocation concealment.

Summary of findings 6. Among different GnRH agonists compared to placebo for women undergoing embryo transfer with frozen embryos or embryos derived from donor oocytes

Among different GnRH agonists compared to placebo for women undergoing embryo transfer with frozen embryos or embryos derived from donor oocytes

Patient or population: women undergoing embryo transfer with frozen embryos or embryos derived from donor oocytes
Setting: IVF unit
Intervention: among different GnRH agonists
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with placebo	Risk with Among different GnRH agonists				
Live birth rate						Not reported in any study
Clinical pregnancy rate	406 per 1000	569 per 1000 (391 to 730)	OR 1.93 (0.62 to 5.98)	50 (1 RCT)	⊕⊖⊖⊖ VERY LOW [a b]	tryptorelin (deposit) versus Leuprolide (daily) in Oocyte donation in ovulating recipients
Miscarriage rate	143 per 1000	181 per 1000 (57 to 448)	OR 1.33 (0.36 to 4.87)	68 (1 RCT)	⊕⊖⊖⊖ VERY LOW [a b]	tryptorelin (deposit) versus Leuprolide (daily) in Oocyte donation in ovulating recipients
Multiple pregnancy rate						Not reported in any study
Cycle cancellation rate						Not reported in any study
Endometrial thickness (mm)						Not reported in any study
Other adverse effects						Not reported in any study

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **GnRH:** gonadotropin-releasing hormone; **OR:** Odds ratio; **RCT:** randomised controlled trial.

GRADE Working Group grades of evidence

High quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: we are very uncertain about the estimate.

[a] We downgraded the evidence by two levels, due to high risk of bias in randomisation method and in allocation concealment
[b] We downgraded the evidence by two levels due to very serious imprecision: the confidence interval is too wide. The intervention could improve or reduce the outcome.

Summary of findings 7. GnRH agonists compared to GnRH antagonists for women undergoing embryo transfer with frozen embryos or embryos derived from donor oocytes

GnRH agonists compared to GnRH antagonists for women undergoing embryo transfer with frozen embryos or embryos derived from donor oocytes

Patient or population: women undergoing embryo transfer with frozen embryos or embryos derived from donor oocytes
Setting: IVF unit
Intervention: GnRH agonists
Comparison: GnRH antagonists

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with GnRH antagonists	Risk with GnRH agonists				
Live birth rate						Not reported in any study
Clinical pregnancy rate	681 per 1000	570 per 1000 (473 to 658)	OR 0.62 (0.42 to 0.90)	473 (1 RCT)	⊕⊕⊕⊖ MODERATE [a]	
Miscarriage rate	86 per 1000	66 per 1000 (35 to 123)	OR 0.75 (0.38 to 1.49)	473 (1 RCT)	⊕⊕⊖⊖ LOW [a b]	
Multiple pregnancy rate	254 per 1000	190 per 1000 (133 to 267)	OR 0.69 (0.45 to 1.07)	473 (1 RCT)	⊕⊕⊖⊖ LOW [a b]	
Cycle cancellation rate						Not reported in any study

Endometrial thickness (mm)				Not reported in any study
Other adverse effects				Not reported in any study

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: Confidence interval; **GnRH:** gonadotropin-releasing hormone; **OR:** Odds ratio; **RCT:** randomised controlled trial.

GRADE Working Group grades of evidence

High quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: we are very uncertain about the estimate.

[a] We downgraded the evidence by one level, due to risk of bias: unclear risk of bias in randomisation method and in allocation concealment
[b] We downgraded the evidence by one level, due to imprecision: wide confidence interval.

Summary of findings 8. Aspirin compared to control for women undergoing embryo transfer with frozen embryos or embryos derived from donor oocytes

Aspirin compared to control for women undergoing embryo transfer with frozen embryos or embryos derived from donor oocytes

Patient or population: women undergoing embryo transfer with frozen embryos or embryos derived from donor oocytes
Setting: IVF unit
Intervention: aspirin
Comparison: control

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with control	Risk with Aspirin				
Live birth rate	100 per 1000	400 per 1000 (141 to 730)	OR 6.00 (1.48 to 24.30)	60 (1 RCT)	⊕⊖⊖⊖ VERY LOW [a b]	
Clinical pregnancy rate	167 per 1000	400 per 1000 (167 to 690)	OR 3.33 (1.00 to 11.14)	60 (1 RCT)	⊕⊖⊖⊖ VERY LOW [a b]	

Miscarriage rate						Not reported in any study
Multiple pregnancy rate						Not reported in any study
Cycle cancellation rate						Not reported in any study
Endometrial thickness (mm)	The mean endometrial Thickness (mm) was 9.1 mm	MD 0.4 mm lower (0.95 lower to 0.15 higher)	-	60 (1 RCT)	⊕⊖⊖⊖ VERY LOW [a b]	
Other adverse effects						Not reported in any study

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: Confidence interval; **OR:** Odds ratio; **RCT:** randomised controlled trial.

GRADE Working Group grades of evidence

High quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: we are very uncertain about the estimate.

[a] Downgraded one level for risk of bias: live birth and pregnancy rates were lower than usual in the group that did not use the intervention. It is unclear if other bias exist.
[b] Downgraded two levels due to imprecision. It is only one very small study (n = 60). The intervention could improve or have no effect on the outcome.

Summary of findings 9. Steroids compared to control for women undergoing embryo transfer with frozen embryos or embryos derived from donor oocytes

Steroids compared to control for women undergoing embryo transfer with frozen embryos or embryos derived from donor oocytes

Patient or population: women undergoing embryo transfer with frozen embryos or embryos derived from donor oocytes
Setting: IVF unit
Intervention: steroids
Comparison: control

Outcomes	Anticipated absolute effects* (95% CI)	Relative effect (95% CI)	№ of participants	Quality of the evidence	Comments

	Risk with control	Risk with Steroids		(studies)	(GRADE)	
Live birth rate	85 per 1000	58 per 1000 (13 to 224)	OR 0.66 (0.14 to 3.11)	99 (1 RCT)	⊕⊖⊖⊖ VERY LOW [a b]	
Clinical pregnancy rate	200 per 1000	184 per 1000 (91 to 337)	OR 0.90 (0.40 to 2.03)	160 (2 RCTs)	⊕⊖⊖⊖ VERY LOW [a b]	
Miscarriage rate	38 per 1000	55 per 1000 (12 to 215)	OR 1.49 (0.32 to 7.03)	160 (2 RCTs)	⊕⊖⊖⊖ VERY LOW [a b]	
Multiple pregnancy rate						One study measured the multiple pregnancy rate and reported none in either group (n = 99)
Cycle cancellation rate						Not reported in any study
Endometrial thickness (mm)						Not reported in any study
Other adverse effects						Not reported in any study

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: Confidence interval; **OR:** Odds ratio; **RCT:** randomised controlled trial.

GRADE Working Group grades of evidence

High quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: we are very uncertain about the estimate.

[a] Downgraded one level due to risk of bias in allocation concealment.
[b] Downgraded two levels due to very serious imprecision: the confidence interval is too wide, and few events. The intervention could improve or reduce the outcome.

BACKGROUND

Description of the condition

It is estimated that about 15% of couples will fail to achieve conception after 12 months of unprotected intercourse (Smarr 2017; te Velde 2000). Ultimately, more than half of these infertile couples will undergo an assisted reproductive technology (ART) procedure such as in vitro fertilisation (IVF) or intracytoplasmic sperm injection (ICSI). Less than 50% of the women under 40 years of age and only 10% to 15% of those over 40 years will get pregnant through a fresh ART cycle (SART 2016). Increasingly, couples are trying to achieve conception later in their reproductive life and, given that pregnancy rates decrease as women's ages increase, more and more of these women present with subfertility problems.

When a fresh cycle is unsuccessful and frozen embryos are available, a frozen-thawed embryo transfer may be performed. About 15% to 20% of all ART cycles performed using the woman's own oocytes use frozen embryos (De Geyter 2018; SART 2016).

Oocyte donation is a frequent treatment option that is increasingly used for infertile women given the high percentage of patients undergoing ART who are over 40 years of age in most ART programs. Twenty-two per cent of all ART cycles in Latin America (LA Register 2015), about 10% in the USA (SART 2016), and around 10% of the fresh ART cycles reported in Europe (De Geyter 2018) are performed using donated oocytes.

Description of the intervention

Although more subfertile women undergo ART procedures every year, implantation failure of a fresh transferred embryo remains one of the most important limiting factors that prevents conception. Most women undergoing ART obtain an acceptable number of oocytes and embryos, but only few of these embryos implant after being transferred into the endometrial cavity (Garcia-Velasco 2000). Thus, the endometrial preparation and profile is one of the main variables to be evaluated in women undergoing an embryo transfer procedure using donated oocytes, and also in frozen-thawed embryo transfers.

In order to carry out the embryo transfer, an endometrial preparation is needed. The endometrial needs to be thickened with oestrogens and, then, some progestogen is needed to open the implantation window. There are several types of oestrogens, several dosages and several administration routes, and the luteal phase support with progestogen could be started with different timings.

On the other hand, in order to avoid a spontaneous ovulation, sometimes, gonadotropin-releasing hormone (GnRH) agonists or antagonists are used. The reason to avoid a spontaneous ovulation is that, when ovulation occurs, progesterone starts rising, which could result in the implantation window opening too early and, therefore, miss the synchronisation with the embryo that is going to be implanted.

Finally, there are some add-ons that have been proposed to improve the endometrial preparation. One of them is aspirin, which used in low doses (75-325 mg/day) orally, works as an antiplatelet agent enhancing the prostacyclin synthesis. This action promotes vasodilation and, eventually, could improve the perfusion of some organs such as the endometrium (Kuo 1997). Another one is sildenafil citrate, which can be taken orally or vaginally at 25-50 mg/day. It could also promote an improvement in the uterine blood flow by potentiating the effect of nitric oxide on vascular smooth muscles (Malinova 2013). On the other hand, steroids has also been proposed as a potentially useful add on. Steroids, such as dexamethasone 0.5 mg orally or methylprednisolone 4 mg orally are proposed to be used for a short period of 4-5 days before the embryo transfer. They are immunomodulatory agents that could affect positively on the implantation rate by suppressing uterine natural killers cells cytotoxicity and cytokine secretion, and promoting the proliferation and invasion of trophoblast (Abdolmohammadi-Vahid 2016).

How the intervention might work

In the implantation process an interaction between the embryo and the endometrium exists. This process seems to be affected by two crucial factors (Devroey 1998; Fox 2016). These are: endometrial receptivity and, synchronisation between the embryo developmental stage and the endometrial profile during the window of implantation (Nawroth 2005). Endometrial receptivity depends on the hormone replacement protocol used for this purpose. In normal physiology, the proliferative phase is characterised by a progressive mitotic growth of the functional endometrium in response to the increasing circulating oestrogen levels. The secretory phase commences after ovulation, when progesterone is secreted by the corpus luteum, and is responsible for the histological and molecular changes in the endometrium that occur during the luteal phase. Therefore, in simple terms, progesterone completes the endometrial preparation after adequate estrogenic priming (Steiner 2006).

Finally, there are many other interventions that have been used in order to improve the implantation rate and, this way, increase the live birth rate. These interventions promote the improvement of uterine blood flow (aspirin and sildenafil) or impact on the immunological system (steroids) (Abdolmohammadi-Vahid 2016; Kuo 1997; Malinova 2013).

Why it is important to do this review

With artificial endometrial preparation (programmed cycle) for women undergoing embryo transfer with frozen embryos or the transfer of fresh embryos derived from donated oocytes the aim is to stimulate the growth of the endometrium in a similar fashion to the natural cycle, by the sequential administration of oestrogen and progestogen. Devroey has reported that hormonal replacement is different in women with functioning ovaries from those women with amenorrhoea; the former group may spontaneously ovulate leading to the decidualisation of endometrial cells (Devroey 1998). Due to this possibility, drugs that suppress ovarian function (such as GnRH agonists) are frequently used in conjunction with oestrogens. Different routes and doses of hormone administration have been used worldwide in order to provide adequate endometrial preparation. However, no clear evidence exists about which is the best endometrial preparation protocol for maximising the receptivity of the endometrium. This review set out to summarise and compare the evidence about the benefits and disadvantages of the different endometrial preparation methods. This is an update of the systematic review originally published in 2010 (Glujovsky 2010).

OBJECTIVES

To evaluate the most effective endometrial preparation for women undergoing embryo transfer with frozen embryos, or from using donor oocytes, with regard to the subsequent live birth rate.

METHODS

Criteria for considering studies for this review

Types of studies

We included only randomised controlled trials (RCTs). We excluded quasi-RCTs and cross-over studies unless pre-cross-over data were available.

Types of participants

Infertile women undergoing an assisted reproductive technology (ART) procedure utilising either fresh donor cycles or frozen embryo transfers were considered.

Types of interventions

The interventions were compared with placebo, no treatment, or between different interventions, both in frozen embryo replacement cycles and in donor oocyte embryo replacement cycles.

1. Programmed cycle versus stimulated cycle
2. Programmed cycle versus natural cycle
3. Transdermal oestrogens versus oral oestrogens
4. Day of starting administration of the progestogen
5. GnRH agonists versus control
6. Among different gonadotropin-releasing hormone (GnRH) agonists
7. GnRH agonists versus GnRH antagonists
8. Aspirin versus control
9. Steroids versus control

After data collection, the review authors considered that outcomes not listed in the protocol should also be included, to meet the objectives of the review. The following outcomes were added to the inclusion criteria: day of starting the progestogen (which is important as some egg donor programs delay the time to starting the progestogen in order to avoid a cycle cancellation in the case of a total failed fertilisation); programmed cycle versus cycle with ovarian stimulation (some authors claim that ovarian stimulation makes a more natural environment than artificial stimulation).

Types of outcome measures

Primary outcomes

1. Live birth rate (number of births of one or more living infants per number of women randomised) (Zegers-Hochschild 2006)

Secondary outcomes

1. Clinical pregnancy rate (number of pregnancies with at least one sac per number of women randomised)
2. Miscarriage rate (number of pregnancies ending in the spontaneous loss of the embryo or fetus before 20 weeks of gestation) per woman randomised
3. Multiple pregnancy rate (number of pregnancies with two or more fetuses per woman randomised
4. Cycle cancellation rate (number of women with at least one cancelled cycle per number of women randomised)
5. Endometrial thickness (in millimetres), by ultrasound scan
6. Other adverse effects such as local adverse effects, hot flushes (at least one adverse effect (excluding miscarriage) per number of women randomised)

Search methods for identification of studies

We searched for all published and unpublished RCTs, of women undergoing embryo transfer cycles with frozen embryos or donated oocytes, without language restriction and in consultation with the Gynaecology and Fertility Group (CGF) Information Specialist.

Electronic searches

We searched following databases:

1. The Cochrane Gynaecology and Fertility Group (CGFG) specialised register, PROCITE platform; searched 24 June 2020 (Appendix 1);
2. CENTRAL via The Cochrane Register of Studies Online (CRSO), Web Platform, searched 24 June 2020 (Appendix 2) (CENTRAL now contains records from CINAHL and the trial registries; clinicaltrials.gov and the World Health Organisation International Trials Registry Platform search portal);
3. MEDLINE, OVID platform, searched from 1946 to 24 June 2020 (Appendix 3);
4. Embase, OVID platform, searched from 1980 to 24 June 2020 (Appendix 4);
5. PsycINFO, OVID platform, searched from 1806 to 24 June 2020 (Appendix 5);
6. LILACS, Web platform, searched 24 June 2020 (Appendix 6).

Searching other resources

We searched the following other resources:

1. We searched the National Institute of Clinical Excellence fertility assessment and treatment guidelines (Nice 2017);
2. We checked references of identified RCTs and relevant systematic reviews;
3. We personally contacted manufacturers, experts, and specialists in the field;
4. We handsearched the conference abstracts of the European Society of Human Reproduction and Embryology, and the American Society for Reproductive Medicine.

Data collection and analysis

Selection of studies

Two review authors (DG, RP) independently undertook the study selection; both are experts in subfertility. Both review authors screened the titles and abstracts of articles found in the search. They discarded studies that were clearly ineligible but were overly inclusive rather than risking the loss of relevant studies. Both review authors independently assessed whether the studies met the inclusion criteria, with disagreements being resolved by discussion. If there was still no agreement, the disagreement was settled by a third review author (CS). Further information

was sought from the authors if papers contained insufficient information to make a decision about eligibility. 'Risk of bias' assessment was done using a pro forma. The selection process is documented in a PRISMA flow chart (Figure 1).

Figure 1.

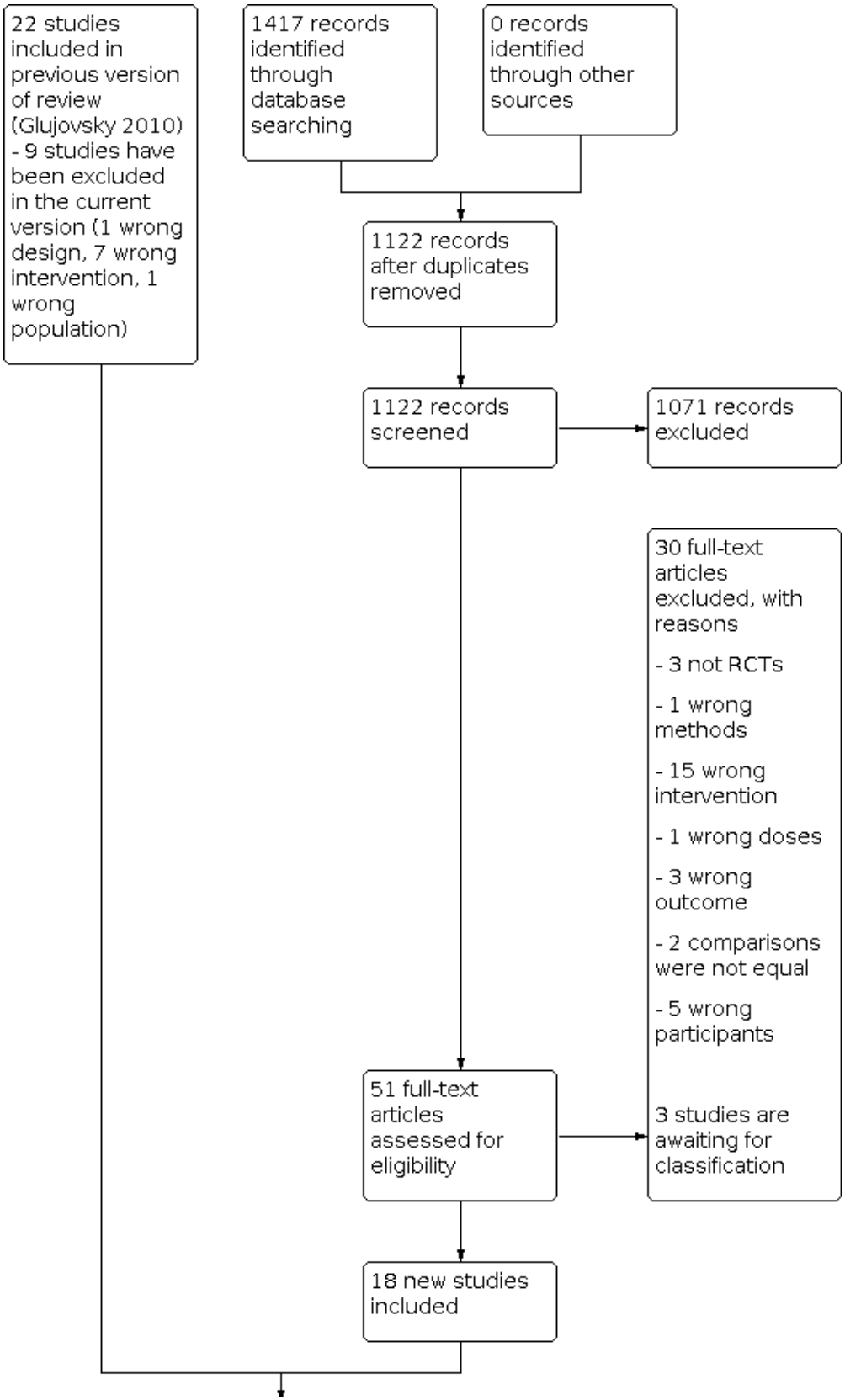
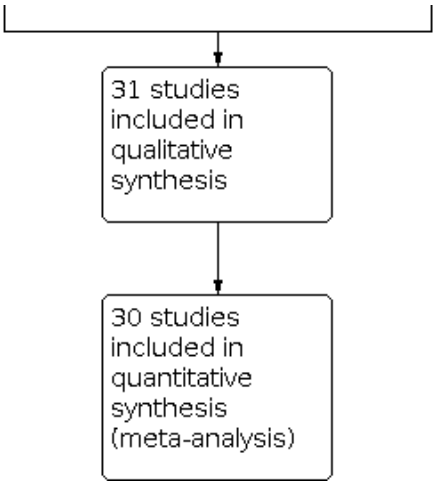


Figure 1. (Continued)



Data extraction and management

The same two review authors independently extracted information from the results sections of the included studies using the pro forma's designed by the Review Group. Discrepancies were resolved by discussion. If there was still no agreement, the discrepancy was resolved by a third review author. For each included trial, information was collected regarding the location of the study, methods of the study (as per the quality assessment checklist), the participants (age range, eligibility criteria), the nature of the interventions, and data relating to the outcomes specified above. See data extraction table for details, Appendix 7. If cross-over trials had been included, we would only have used data from the first stage.

Assessment of risk of bias in included studies

Review authors DG and RP independently assessed the risk of bias of all studies that were deemed eligible for the review using the Cochrane 'Risk of bias' assessment tool (Higgins 2011) to assess: selection (random sequence generation and allocation concealment); performance (blinding of participants and personnel); detection (blinding of outcome assessors); attrition (incomplete outcome data); reporting (selective reporting); and other bias. The categories are briefly described in additional Table 1. Judgements were assigned as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* Section 8.5 (Higgins 2011), and the conclusions presented in the 'Risk of bias' tables. Disagreements were resolved by discussion. If there was still no agreement, the discrepancy was settled by a third review author (AC). We incorporated the assessment of bias judgements into the interpretation of review findings by means of sensitivity analyses.

Measures of treatment effect

For dichotomous data (e.g. live birth rates), results for each study were expressed as odds ratio (OR) with 95% confidence intervals (CIs) and combined for meta-analysis with RevMan software.For continuous data (e.g. endometrial thickness), we calculated the mean difference (MD) and 95% CIs between treatment groups.

Unit of analysis issues

The primary analysis was per woman randomised. If studies reported only 'per cycle' data, we contacted study authors to request 'per woman randomised' data, and put them in awaiting classification if no reply was received from the authors. We counted multiple live births (e.g. twins, triplets) as one live birth event.

Dealing with missing data

We analysed data on an intention-to-treat basis as far as possible and attempted to collect missing data from the trial authors. When data on live birth could not be obtained, we undertook imputation and assumed that the outcome did not occur. For other outcomes, we analysed only available data. Any imputed data were subject to sensitivity analysis.

If studies reported sufficient detail to calculate the MD, but no information on the associated standard deviation (SD), we assumed the outcome had an SD equal to the highest SD from other studies within the same analysis.

Assessment of heterogeneity

Clinical and methodological characteristics of the included studies were examined by visual inspection of the forest-plot graphs, the overlap in CIs and, more formally, by checking the results of the I^2 statistic. An I^2 measurement greater than 50% was taken to indicate substantial heterogeneity (Higgins 2011). When possible, and if no heterogeneity was present, the outcomes were pooled.

Assessment of reporting biases

We aimed to minimise the potential impact of publication bias and other reporting biases by ensuring a comprehensive search for eligible studies. If 10 or more studies were included in an analysis, we planned to use a funnel plot to explore the possibility of small-study effects (a tendency for estimates of the intervention effect to be more beneficial in smaller studies; Higgins 2011).

Data synthesis

Data synthesis and analyses were done using the Review Manager 5.3 (Review Manager 2014). Dichotomous outcomes were reported as odds ratios (OR) and continuous outcomes as mean differences (MD), both with 95% CIs. The mean change was used in continuous outcomes, where possible, otherwise mean results at final follow-up were used. Studies reporting change differences and end of treatment differences were entered into the same analyses.

Interventions were compared on the basis of drug class. Where studies randomised recipients across arms involving comparisons of members of the same drug class, the data for arms comparing the same drug class were combined.

Heterogeneity in treatment effects across studies was assessed using inspection of forest plots, the Cochran Q test and I^2 quantity (where $P < 0.10$ and $> 60\%$, respectively, were considered evidence of substantial heterogeneity). Where the authors considered it was reasonable to pool studies, the fixed-effect model was used to combine study results where estimates of heterogeneity were minimal and the random-effects method of DerSimonian and Laird (DerSimonian 1986) where heterogeneity was moderate ($I^2 > 40\%$). Where substantial heterogeneity was evident, summary estimates were not calculated, but the estimates of effect were investigated further using subgroup and sensitivity analyses.

Subgroup analysis and investigation of heterogeneity

We performed a subgroup analysis for frozen-thawed embryo transfers and fresh transfers of embryos coming from donor oocytes. Although heterogeneity was expected due to some variables (amenorrhoea versus non-amenorrhoea, endometrial thickness, women's age, embryo quality, embryo transfer) a subgroup analysis was only performed for studies where amenorrhoea was clearly stated, as most studies were inadequately described for other variables.

A post-hoc subgroup analysis was performed when evaluating the stimulated cycles with clomiphene citrate for the outcome endometrial thickness. As clomiphene citrate works as a selective oestrogen receptor modulator, it is expected to result in some thinner endometrium in comparison to other stimulation protocols.

Sensitivity analysis

We performed a sensitivity analysis using fixed-effect and random-effects models to confirm or discard the consistency of results. For continuous data, results from each study were expressed as MD with 95% CsI and combined for meta-analysis. Meta-analytic methods for continuous data assume that the underlying distribution of the measurements is normal. If data were clearly skewed and results were reported in the publication as median and range, with non-parametric tests of significance, the results would also have been reported in the 'Other data' section of the review.

Higgins 2011

Summary of findings and assessment of the certainty of the evidence

We prepared a 'Summary of findings' tables using GRADEpro and Cochrane methods (Higgins 2011; GRADEpro GDT 2015). These tables evaluated the overall quality of the body of evidence for the main review outcomes (live birth, clinical pregnancy, miscarriage, multiple pregnancy, cycle cancellation, endometrial thickness, other adverse effects) for the main review comparison (Programmed cycles versus Stimulated cycles versus Natural cycles). Additional 'Summary of findings' tables were also prepared for the main review outcomes for other important comparisons (Transdermal oestrogens versus oral oestrogens; day of starting administration of the progestogen; GnRH agonists versus control versus GnRH antagonists; low-dose aspirin versus control and steroids versus control). We assessed the quality of the evidence using GRADE criteria: risk of bias, consistency of effect, imprecision, indirectness and publication bias). Judgements about the quality of the evidence (high, moderate, low or very low) were made by two review authors working independently, with disagreements resolved by discussion. Judgements were justified, documented, and incorporated into reporting of results for each outcome. We extracted study data, format our comparisons in data tables and prepared 'Summary of findings' tables before writing the results and conclusions of our review.Higgins 2011

RESULTS

Description of studies

Results of the search

The search for this update retrieved 1417 articles. Fifty-one studies were added at this update as potentially eligible and were retrieved in full text. Considering the 22 studies that were included in the original review, 73 studies met our inclusion criteria. We excluded 39 studies (nine from the previous version and 30 from the current search). Three studies are awaiting classification until more information is received about their methods. See study tables: Characteristics of included studies, Characteristics of excluded studies, Characteristics of studies awaiting classification, and PRISMA flow chart (Figure 1).

Included studies

Study design and setting

Thirty one parallel-design randomised controlled trials (RCTs) involving 5426 women were included. All were conducted in IVF units. One of the included studies was not included in the primary analysis because it was a study with a very low number of randomised women (less than 10) and were a subgroup of women with previous cancellation due to thin endometrium (Check 2002).

Participants

Five of the 31 studies were performed in women undergoing fresh donor oocyte embryo replacement cycles (Escriba 2006; Gutierrez 1999; Remohi 1994; Tocino 2007; Vidal 2009) and the remaining 26 studies involved frozen embryo replacement cycles (Agha-Hosseini 2018; Aleyasin 2017; Nekoo 2015; Bider 1996; Check 2002; Child 2013; Dal Prato 2002; Davar 2007; Davar 2016; Davar 2020; Ding 2007; El-Toukhy 2004; Greco 2016; Groenewoud 2016; Kahraman 2018; Lee 2008; Madani 2019; Matsuura 2014; Moffitt 1995; Movahedi 2018; Ramos 2007; Samsami 2018; Samsami 2019; Sheikhi 2018; Tehraninejad 2018; Wright 2006).
Most treatment regimens varied from one study to the other. The publication dates of included studies were from 1994 to 2020.

Interventions

A variety of different protocols for endometrial preparation were used. Programmed cycle (priming with oestrogens) versus stimulated cycle with follicle stimulating hormone (FSH) (Wright 2006), letrozole (Aleyasin 2017; Matsuura 2014; Samsami 2019) or clomiphene citrate (Sheikhi 2018), transdermal oestrogens versus oral oestrogens (Davar 2016; Kahraman 2018; Tehraninejad 2018). The types of gonadotropin-releasing hormone (GnRH) agonist used were daily leuprolide acetate (Gutierrez 1999; Remohi 1994), daily variopeptyl (Davar 2020), nasal buserelin (El-Toukhy 2004; Movahedi 2018), subcutaneous buserelin (Davar

2007; Samsami 2018), daily nafarelin (Gutierrez 1999), depot leuprolide acetate (Tocino 2007), and daily tryptorelin (Tocino 2007) and depot tryptorelin (Dal Prato 2002; Ramos 2007). Also, the use of GnRH antagonists versus GnRH agonists (Vidal 2009). Glucocorticoids used also varied from one study to the other: dexamethasone (Bider 1996) and 6-alfa-methylprednisolone (Moffitt 1995) Sildenafil (Check 2002) and aspirin (Madani 2019) were evaluated as well.

During the data collection, we found six studies where the comparisons (starting day of progestogen, programmed cycle versus stimulated or natural cycles) had not been included in our protocol; however, we decided to include them in the review because of the importance of the results (Agha-Hosseini 2018; Ding 2007; Escriba 2006; Greco 2016; Groenewoud 2016; Lee 2008).

Outcomes

The primary outcome was live birth rate but only eight studies (Agha-Hosseini 2018; Aleyasin 2017; Bider 1996; Child 2013; El-Toukhy 2004; Greco 2016; Groenewoud 2016; Madani 2019) evaluated this outcome. secondary outcomes were clinical pregnancy rate (which is a proxy of the primary outcome), multiple pregnancy rate, cycle cancellation rate, miscarriage rate, and endometrial thickness (before the embryo transfer). Finally, nine different comparison types were performed. Heterogeneity was evaluated for each intervention. In those cases where we found heterogeneity, pre-specified sensitivity and subgroup analyses were performed. We also evaluated ad hoc subgroups. We added 'Summary of findings' tables for all the outcomes.

Excluded studies

Of the 39 excluded studies, four were not RCTs (Check 1998; Nardo 2006; Neuspiller 1998; Stadtmauer 2009), one used an inadequate method of randomisation (Sathanandan 1991), 22 did not appear to use one of our specified treatments for endometrial preparation (Arun Muthuvel 2016; Bernabeu 2006; Bjuresten 2011; Boostanfar 2016; Caligara 2003; Cambiaghi 2013; Davar 2015; Eftekhar 2013; Gibbons 1998; Gogce 2015; Hershko 2016; Lan 2008; Li 2014; Lightman 1999; Llacer 2017; Moon 2004; Prapas 2009a; Prapas 2009b; Sanchez 2009; Shiotani 2006; Tesarik 2003; Zegers-Hochschild 2000), one used doses for vaginal progestogen that were bellow the standard doses (Feliciani 2004), three did not evaluate a primary or secondary outcome stated in our protocol (Krasnow 1996; Lewin 2001; Taskin 2002), two used comparisons that were not equal (both treatment groups had more than one intervention in their treatment regimen) (Check 2004; Simon 1998) and six included participants that did not met our criteria (Davar 2016a; Davari-Tanha 2016; Huang 2017; Weckstein 1997; Xu 2015; Zolghadri 2014).

Three studies are awaiting classification because the outcomes were reported 'per cycle' and not per woman randomised, in which more than one cycle was performed on each randomised woman (Masrour 2018; Page 2005; Tur-Kaspa 2010).

Risk of bias in included studies

Details on the quality of each individual study are described in the table 'Characteristics of included studies', where the individual quality criteria were rated for each study.

Although most authors gave a description of the randomisation method, only some of them described the allocation method. As a placebo was not used in most of the trials, there was no blinding of patients; blinding of healthcare workers was not described. Nevertheless, we do not think that lack of blindness can bias the results in this case. Live birth rate was reported in a minority of cases; the remainder of the authors used pregnancy rate, which was the most frequently reported final outcome. Even when comparability at baseline was not measured, it was generally evaluated. There were very few trials with a relevant loss to follow-up. There was heterogeneity in intention-to-treat analysis and it was not done by all the authors. Finally, outcome assessment was not generally described in terms of blinding of the evaluator. Both a 'Risk of bias' table (Figure 2) and a 'Risk of bias' graph (Figure 3) are presented.

Figure 2. 'Risk of bias' summary: review authors' judgments about each risk of bias item for each included study.

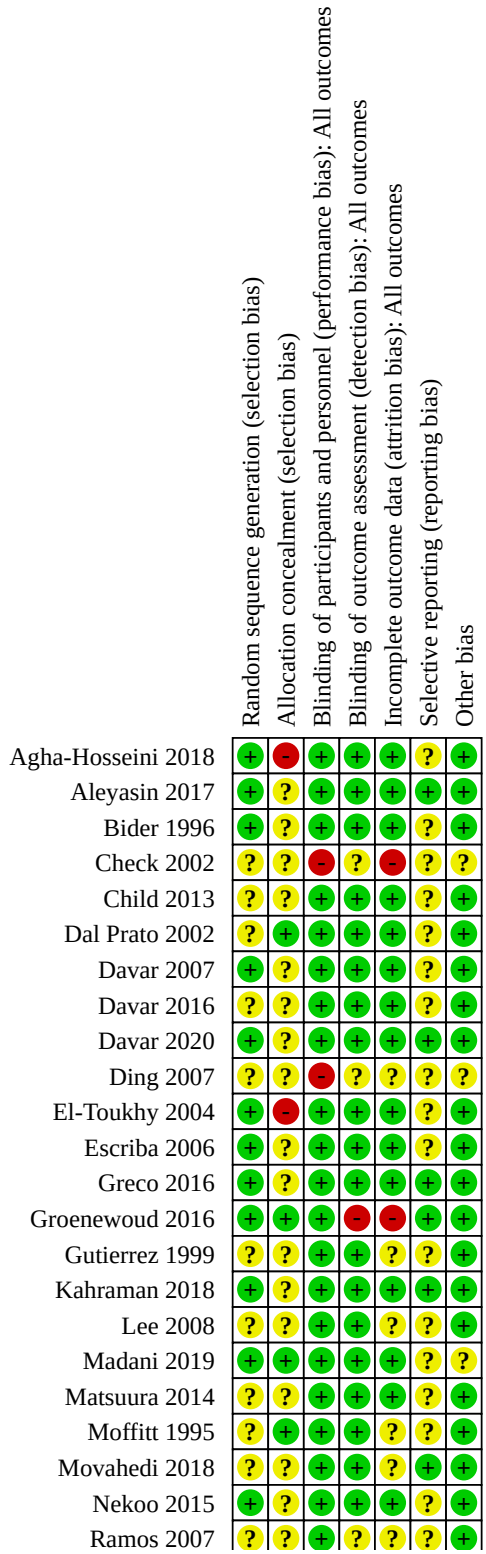


Figure 2. (Continued)

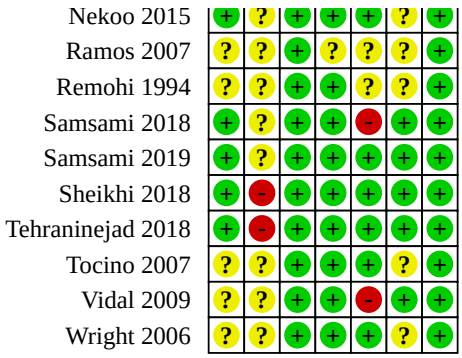
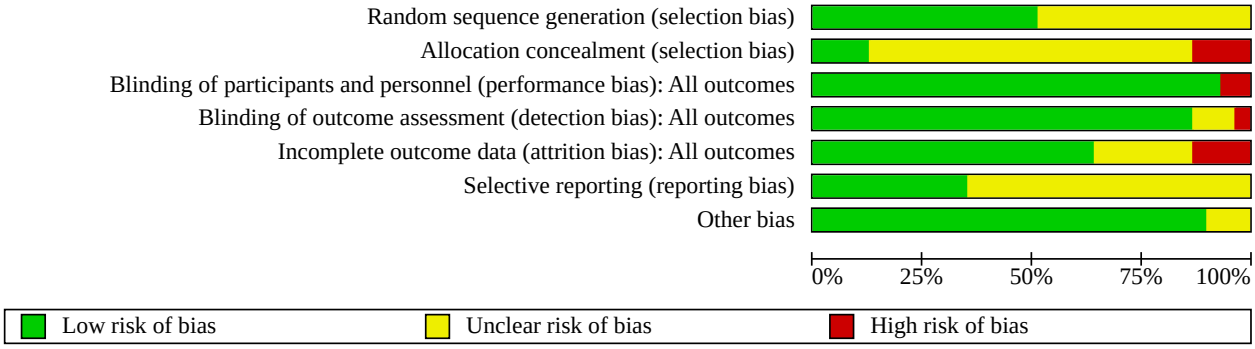


Figure 3. 'Risk of bias' graph: review authors' judgments about each risk of bias item presented as percentages across all included studies.



Allocation

In four studies the method of concealing allocation was adequate (Dal Prato 2002; Groenewoud 2016; Madani 2019; Moffitt 1995), while in four other studies there was high risk of bias (Agha-Hosseini 2018; El-Toukhy 2004; Sheikhi 2018;Tehraninejad 2018) The remaining studies are unclear as the allocation concealment method was not explained and authors did not respond when they were contacted.

Blinding

Quality limitations were mainly in blinding, given that only one study stated that participants were blinded to treatment (Moffitt 1995). Because the assessed outcomes were very objective, lack of blinding of the outcome assessors did not introduce as high a risk of bias if the outcomes had been subjective. We considered that lack of blinding could only impact on cancellation rates.

Incomplete outcome data

In three studies we found a high risk of bias due to a high proportion of the participants that were not followed up (Check 2002; Groenewoud 2016; Samsami 2018).

The sample size of the analysed studies and subgroups varied from a minimum of 16 to a maximum of 354 women.

We contacted the authors for more information, as required.

Selective reporting

Only eight studies (Agha-Hosseini 2018; Aleyasin 2017; Bider 1996; Child 2013; El-Toukhy 2004; Greco 2016; Groenewoud 2016; Madani 2019) reported the live birth rate, our primary outcome. This could represent a potential selective reporting bias.

Other potential sources of bias

All studies except four (Gutierrez 1999; Lee 2008; Ramos 2007; Tocino 2007) reported baseline equality between groups with respect to age at stimulation, diagnosis of infertility, number of transferred embryos and number of previous pregnancies.

Effects of interventions

See: **Summary of findings 1** Stimulated cycle compared to programmed for women undergoing embryo transfer with frozen embryos or embryos derived from donor oocytes; **Summary of findings 2** Natural cycle compared to programmed cycle for women undergoing embryo transfer with frozen embryos or embryos derived from donor oocytes; **Summary of findings 3** Transdermal oestrogens compared to oral oestrogens for women undergoing embryo transfer with frozen embryos or embryos derived from donor oocytes; **Summary of findings 4** Starting administration of the progestogen earlier compared to starting administration of the progestogen later for women undergoing embryo transfer with frozen embryos or embryos derived from

donor oocytes; **Summary of findings 5** GnRH agonists compared to control for women undergoing embryo transfer with frozen embryos or embryos derived from donor oocytes; **Summary of findings 6** Among different GnRH agonists compared to placebo for women undergoing embryo transfer with frozen embryos or embryos derived from donor oocytes; **Summary of findings 7** GnRH agonists compared to GnRH antagonists for women undergoing embryo transfer with frozen embryos or embryos derived from donor oocytes; **Summary of findings 8** Aspirin compared to control for women undergoing embryo transfer with frozen embryos or embryos derived from donor oocytes; **Summary of findings 9** Steroids compared to control for women undergoing embryo transfer with frozen embryos or embryos derived from donor oocytes

1) Programmed cycle (priming with oestrogens) versus stimulated cycle (with follicle stimulating hormone (FSH), letrozole or clomiphene citrate)

Only one study (Wright 2006) compared the outcomes for women having a cycle in which the ovaries were stimulated with recombinant follicle stimulating hormone (rFSH) and programmed cycles in which the endometrium was stimulated with oestrogen (17-beta oestradiol). A total of 100 women undergoing a frozen-thaw embryo transfer were stimulated with rFSH injections (150 international units (IU)) on days six, eight, and 10 of the menstrual cycle and then continued until the endometrium was thicker than 7 mm or follicles were bigger than 16 mm to 20 mm. The 99 women in the control group, with a programmed cycle, received 17-beta oestradiol (4 mg) daily until the thickness of the endometrium was greater than 7 mm.

Three other studies(Aleyasin 2017; Matsuura 2014; Samsami 2019) analysed 369 women and compared a stimulation with letrozole (2.5 mg to 5 mg) and a programmed cycle with oral oestrogens for a frozen embryo transfer.

One study (Sheikhi 2018) analysed 92 women and compared a stimulation with clomiphene citrate (50 mg per day for five days) and a programmed cycle with oral oestrogens for a frozen embryo transfer.

Primary outcome

1.1-Live birth rate (Analysis 1.1)

We are uncertain whether stimulation with letrozole (followed by rFSH from the seventh day) improves the live birth rate in comparison to a programmed cycle (odds ratio (OR) 1.26, 95% confidence interval (CI) 0.49 to 3.26; participants = 100; studies = 1, very low-quality evidence). This suggests that if the chance of live birth following a programmed cycle is assumed to be 24%, the chance following a stimulated cycle with letrozole would be between 13% and 51%.

There are no results on this outcome in studies that evaluated stimulation with FSH only.

Secondary outcomes

1.2- Clinical pregnancy rate (Analysis 1.2)

Stimulating with FSH, letrozole or clomiphene citrate may improve the clinical pregnancy rate (OR 1.63, 95% CI 1.12 to 2.38; participants = 656; studies = 5; I^2 = 11%, low-quality evidence). This suggests that if the chance of a clinical pregnancy following a programmed cycle is assumed to be 19%, the chance following a stimulated cycle would be between 21% and 36%.

1.3- Miscarriage rate (Analysis 1.3)

We are uncertain whether administrating FSH, letrozole or clomiphene citrate decreases the miscarriage rate (OR 0.79, 95% CI 0.36 to 1.71; participants = 355; studies = 3; I^2 = 0%, very low-quality evidence)**.** This suggests that if the chance of miscarriage following a programmed cycle is assumed to be 9%, the chance following a stimulated cycle would be between 3% and 14%.

Multiple pregnancy rate

Not reported.

Cycle cancellation rate

Not reported.

1.4- Endometrial thickness (Analysis 1.4)

We are uncertain whether administrating FSH or letrozole increases the endometrial thickness compared to a programmed cycle (mean difference (MD) -0.05, 95% CI -0.19 to 0.10; participants = 362; studies = 2; I^2 = 0%, low-quality evidence). This suggests that if endometrial thickness following a programmed cycle is assumed to be 8.7 mm, following a stimulated cycle it could be between 8.4 mm and 8.9 mm.

When administering clomiphene citrate, endometrial thickness may be thinner in comparison with a programmed cycle (MD -1.04, 95% CI -1.59 to -0.49; participants = 92; studies = 1; low-quality evidence). This suggests that if endometrial thickness following a programmed cycle is assumed to be 8.7 mm, following a stimulated cycle with clomiphene citrate it could be between 7.1 mm and 8.2 mm.

Other adverse effects

Not reported.

2) Programmed cycle (priming with oestrogens) versus natural cycle

Six studies (Agha-Hosseini 2018; Child 2013; Greco 2016; Groenewoud 2016; Lee 2008; Sheikhi 2018) compared 830 women with a natural cycle who received an human chorionic gonadotropin (hCG) injection (10000 IU) for triggering the ovulation versus 860 women who received oral micronised estradiol (programmed cycle) between 2 mg/day up to 8 mg/day if the endometrial thickness was inadequate.

Primary outcome

2.1-Live birth rate (Analysis 2.1)

We are uncertain whether a natural cycle improves the live birth rate in comparison with a programmed cycle (OR 0.97, 95% CI 0.74 to 1.28; participants = 1285; studies = 4; I^2 = 0%, very low-quality evidence). This suggests that if the chance of live birth following a programmed cycle is assumed to be 23%, the chance following a natural cycle would be between 18% and 28%.

Secondary outcomes

2.2-Clinical pregnancy rate (Analysis 2.2)
We are uncertain of the effect on the clinical pregnancy rate between a programmed cycle stimulating with oestradiol, and a natural cycle (OR 0.79, 95% CI 0.62 to 1.01; participants = 1249; studies = 5; I^2 = 60%, very low-quality evidence). This suggests that if the chance of a clinical pregnancy following a programmed cycle is assumed to be 35%, the chance following a natural cycle would be between 25% and 35%.

2.3-Miscarriage rate (Analysis 2.3)
We are uncertain whether a programmed cycle or natural cycle will decrease the miscarriage rate (OR 0.64, 95% CI 0.25 to 1.63; participants = 485; studies = 3; I^2 = 0%, very low-quality evidence). This suggests that if the chance of miscarriage following a programmed cycle is assumed to be 5%, the chance following a natural cycle would be between 1% and 8%.

Multiple pregnancy rate

Not reported.

2.4- Cycle cancellation rate

The cycle cancellation rate is probably lower with a modified natural than in a programmed cycle mainly due to insufficient endometrium thickness within the first 14 days (OR 0.60, 95% CI 0.44 to 0.82; participants = 734; studies = 1; moderate-quality evidence). This suggests that if the chance of a cycle cancellation following a programmed cycle is assumed to be 37%, the chance following a natural cycle would be between 20% and 32%.

2.5-Endometrial thickness (Analysis 2.5)

We are uncertain if endometrial thickness is increased when using a natural cycle or a programmed cycle (MD 0.22, 95% CI -0.25 to 0.69; participants = 485; studies = 3; I^2 = 85%, low-quality evidence). This suggests that if the endometrial thickness following a programmed cycle is assumed to be 9.1 mm, the thickness following a natural cycle is between 8.8 mm and 9.8 mm.

Other adverse effects

Not reported.

3) Transdermal oestrogens versus oral oestrogens

Three studies (Davar 2016; Kahraman 2018; Tehraninejad 2018) evaluated 457 women that used oestrogens either transdermal (3.9 mg to 6 mg/day) or oral (6 mg/day to 8 mg/day).

Primary outcome

Live birth rate

Not reported.

Secondary outcomes

3.1- Clinical pregnancy rate (Analysis 3.1)

We are uncertain if the transdermal or oral oestrogens increases the pregnancy rate (OR 0.86, 95% CI 0.59 to 1.25; participants = 504; studies = 3; I^2 = 58%; low-quality evidence). This suggests that if the chance of a clinical pregnancy following oral oestrogens is assumed to be 51%, the chance following transdermal oestrogens would be between 38% and 56%.

3.2- Miscarriage rate (Analysis 3.2)

We are uncertain whether transdermal or oral oestrogens decreases the miscarriage rate (OR 0.55, 95% CI 0.27 to 1.09; participants = 414; studies = 2; I^2 = 0%; low-quality evidence)**.** This suggests that if the chance of a miscarriage following oral oestrogens is assumed to be 12%, the chance following transdermal oestrogens would be between 4% and 13%.

Multiple pregnancy rate

Not reported.

Cycle cancellation rate

Not reported

Endometrial thickness

Not reported.

Other adverse effects

Not reported.

4) Day of starting progesterone

Two trials evaluated the outcomes for 331 women in order to identify the optimal day for starting micronised intravaginal progesterone (800mg/day) in a fresh synchronised oocyte donor program. One of the trials evaluated cycles that were transferred on day three after the oocyte retrieval (Escriba 2006). Three interventions were compared: i) starting progesterone the day before oocyte pick up (OPU); ii) starting progesterone the day of OPU; and iii) starting progesterone the day after OPU. All recipients used vaginal suppositories of progesterone and had the embryo transfer on day three. Besides, one trial (Ding 2007) evaluated the start of progesterone six days versus seven days before the frozen embryo transfer.

Primary outcome

Live birth rate

Not reported.

Secondary outcomes

4.1-Clinical pregnancy rate (Analysis 4.1)
Starting progesterone on the day of OPU may improve the clinical pregnancy rate in comparison with starting the day before the OPU (OR 1.92, 95% CI 1.08 to 3.42; participants = 191; studies = 1, low-quality evidence). Starting progesterone on the day after OPU may improve the clinical pregnancy rate in comparison with starting the day before the OPU (OR 1.81, 95% CI 1.01 to 3.24; participants = 188; studies = 1; low-quality evidence). When analysed together (Analysis 4.6: ad hoc), starting progesterone either on the OPU day or the day after OPU probably improves the clinical pregnancy rate in comparison to starting the day before (OR 1.87, 95% CI 1.13 to 3.08, participants = 282, studies = 1, moderate-quality evidence). Due to a wide confidence interval, we are uncertain of the effect of starting progesterone the day of OPU or the day after on the clinical pregnancy rate (OR 0.94, 95% CI 0.53 to 1.68; participants = 99;

studies = 1; low-quality evidence) (Escriba 2006). This suggests that if the chance of a clinical pregnancy when starting the progesterone the day before OPU is assumed to be 38%, the chance when starting the day of OPU or the day after OPU may be between 43% and 64%.

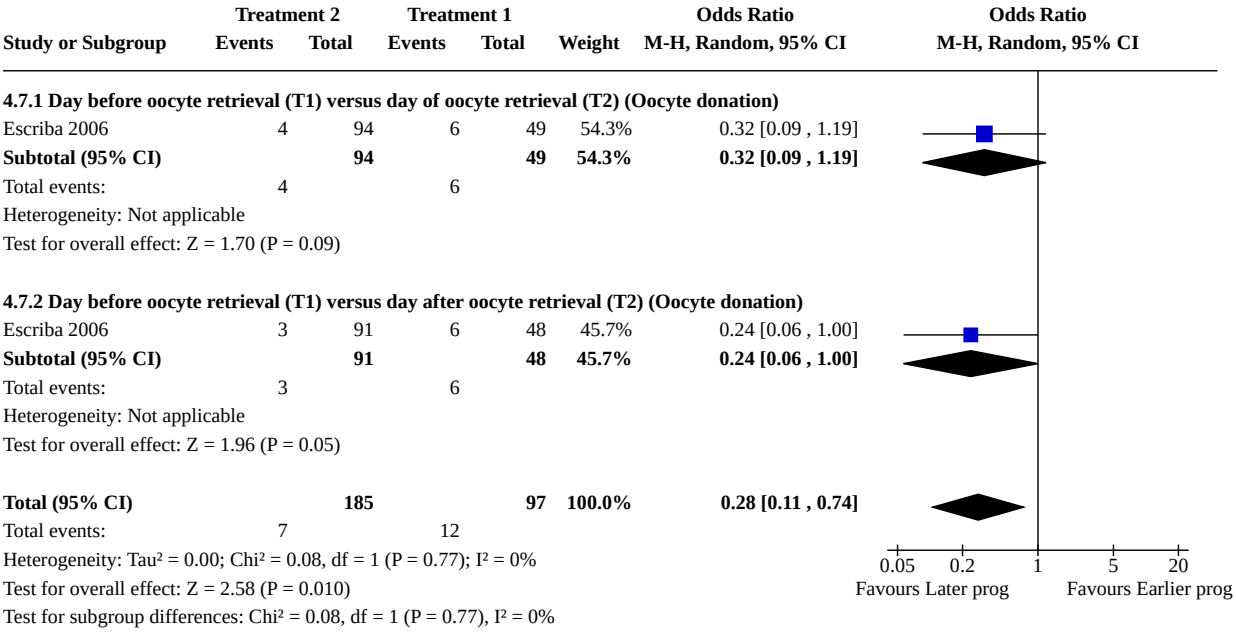
Due to wide confidence interval, we are uncertain of the effect of starting progesterone six days or seven days before a frozen embryo transfer on clinical pregnancy rate (OR 0.75, 95% CI 0.24 to 2.34; participants = 49; studies = 1, very low-quality evidence) (Ding 2007).

4.2-Miscarriage rate (Analysis 4.2)
We are uncertain of the effect of starting the progesterone before or on the day of OPU (OR 0.45, 95% CI 0.16 to 1.25; participants = 191; studies = 1; very low-quality evidence), on the day of OPU or the day after OPU (OR 2.52, 95% CI 0.85 to 7.46; participants = 185; studies = 1; very low-quality evidence), or on the day before or after OPU (OR 1.13, 95% CI 0.33 to 3.85; participants = 188; studies = 1; very low-quality evidence). This suggests that if the chance of a miscarriage when starting the progesterone the day before OPU is assumed to be 13%, the chance when starting the day of OPU would be between 2% and 16%.

4.3-Multiple pregnancy rate (Analysis 4.3)
We are uncertain of the effect of any of the three intervention groups on the multiple pregnancy rate (OR 0.72, 95% CI 0.37 to 1.42; participants = 282; studies = 1; very low-quality evidence). This suggests that if the chance of a multiple pregnancy when starting the progesterone the day before OPU is assumed to be 19%, the chance when starting the day of OPU or the day after OPU is between 8% and 25%.

4.4-Cycle cancellation rate (Analysis 4.4)
Starting progesterone on the day after OPU or the day of OPU probably reduces the cancellation rate when compared to starting the day before OPU (OR 0.28, 95% CI 0.11 to 0.74; participants = 282; studies = 2; I^2 = 0%; moderate-quality evidence) (see Analysis 4.7 and Figure 4). We are uncertain of the effect on cycle cancellation rate when comparing the start of the progesterone on the day of OPU or the day after OPU (OR 0.77, 95% CI 0.17 to 3.53; participants = 185; studies = 1, low-quality evidence). Starting the progesterone the day after the OPU may reduce the risk of cancellation in comparison to starting the progesterone the day of OPU or the day before OPU. However, the analysis ruled out a clinically relevant difference when starting the progesterone the day after the OPU in comparison to starting one or two days before, but the quality of the evidence is low (OR 0.10, 95% CI 0.01 to 1.82; participants = 282; studies = 1; I^2 = 0%; low-quality evidence) (Escriba 2006). This suggests that if the chance of a cycle cancellation when starting the progesterone the day before OPU is assumed to be 4%, the chance when starting the day of OPU or the day after OPU is probably between 0% and 3%.

Figure 4. Forest plot of comparison: 4 Day of starting administration of the Progesterone, outcome: 4.7 Cancelled cycles (by subgroups).



Endometrial thickness

Not reported.

Other adverse effects

Not reported.

5) GnRH agonist versus no treatment

In nine studies, a total of 1358 women were included for an analysis of gonadotropin-releasing hormone (GnRH) agonist versus control. Type of agonist and administration route were varied.

Primary outcome

5.1-Live birth rate (Analysis 5.1)

Live birth rate was described by only one trial (El-Toukhy 2004), in which nasal buserelin was compared with no treatment in 334 women undergoing a frozen-thaw embryo transfer. Nasal buserelin may improve live birth rate in comparison with no GnRH agonists (OR 2.62, 95% CI 1.19 to 5.78; participants= 234; studies = 1; low-quality evidence). This suggests that if the chance of a live birth following no GnRH agonists is assumed to be 9%, the chance following GnRH agonists would be between 10% and 35%.

Secondary outcomes

5.2-Clinical pregnancy rate (Analysis 5.2)
Clinical pregnancy rate was determined by eight trials (Nekoo 2015; Dal Prato 2002; Davar 2007; Davar 2020; El-Toukhy 2004; Movahedi 2018; Ramos 2007; Samsami 2018), which evaluated the efficacy of intramuscular diphereline, nasal and subcutaneous buserelin, subcutaneous variopeptyl, and intramuscular depot tryptorelin for women undergoing a frozen-thaw embryo transfer. A ninth study (Remohi 1994) tested daily leuprolide acetate in oocyte donor recipients. The comparator was no treatment in all nine studies.

Frozen-thawed embryo transfers

We are uncertain of the effect of GnRH agonists on clinical pregnancy rate (OR 1.08, 95% CI 0.82 to 1.43; participants = 1289; studies = 8; I^2 = 20%; low-quality evidence) in frozen-thawed embryo transfers. This suggests that if the chance of a clinical pregnancy following no GnRH agonists is assumed to be 18%, the chance following GnRH agonists would be between 15% and 26%.

Fresh oocyte donor transfers

We are uncertain of the effect of GnRH agonists on clinical pregnancy rate (OR 0.86, 95% CI 0.33 to 2.22; participants = 54; studies = 1; low-quality evidence) in fresh oocyte donor transfers.

5.3- Miscarriage rate (Analysis 5.3)
Three studies (Nekoo 2015; Dal Prato 2002; Samsami 2018) evaluated the miscarriage rate. We are uncertain of the effect of the GnRH on miscarriage rate (OR 0.85, 95% CI 0.36 to 2.00; participants = 828; studies = 4; I^2 = 0%, low-quality evidence). This suggests that if the chance of a miscarriage following no GnRH agonists is assumed to be 3%, the chance following GnRH agonists would be between 1% and 6%.

Multiple pregnancy rate

Not reported.

5.4- Cycle cancellation rate (Analysis 5.4)
Two of the five studies (Dal Prato 2002; El-Toukhy 2004) described the cycle cancellation rates in a total of 530 women being prepared to undergo a frozen-thaw embryo transfer. We are uncertain if the use of GnRH agonists reduces the cycle cancellation rate (OR 0.49, 95% CI 0.21 to 1.17; participants = 530; studies = 2; I^2 = 0%, low-quality evidence). This suggests that if the chance of a miscarriage following no GnRH agonists is assumed to be 6%, the chance following GnRH agonists would be between 1% and 7%.

5.5- *Endometrial thickness* (Analysis 5.5)
In 697 women involved in four studies (Dal Prato 2002; El-Toukhy 2004; Davar 2020; Movahedi 2018), the analysis ruled out a clinically relevant difference in the endometrial thickness, but the quality of the evidence is low (MD -0.08, 95% CI -0.33 to 0.16, four RCTs, N = 697, I^2=4%, low-quality evidence). This suggests that if the endometrial thickness following GnRH agonists is assumed to be 9.4 mm, the endometrial thickness following no treatment is probably between 9.1 mm and 9.6 mm.

Other adverse effects

Not reported.

6) One GnRH agonist versus other types of GnRH agonists
Two studies evaluated the use of different types of GnRH agonists in fresh donor oocyte recipient cycles. One study (Gutierrez 1999) reported results from a comparison between leuprolide acetate (1 mg/day subcutaneously) and nafarelin (100 µg twice a day) starting at mid-luteal phase. The other study compared daily leuprolide acetate (0.1 mL/day) versus depot tryptorelin (3.75 mg intramuscularly) both starting 5 days before ending the contraceptive pill (Tocino 2007). A total of 118 women were analysed.

Primary outcome

Live birth rate

Not reported.

Secondary outcomes

6.1- Clinical pregnancy rate (Analysis 6.1)
We are uncertain whether any specific GnRH agonist improves the clinical pregnancy rate. When comparing daily leuprolide acetate and deposit tryptorelin (OR 1.93, 95% CI 0.62 to 5.98; participants = 50; studies = 1; very low-quality evidence). This suggests that if the chance of a clinical pregnancy following daily leuprolide acetate is assumed to be 41%, the chance following deposit tryptorelin would be between 39% and 73%.

6.2-Miscarriage rate (Analysis 6.2)
We are uncertain whether any specific GnRH agonist reduces the miscarriage rate. When comparing daily leuprolide acetate and daily nafarelin (OR 1.33, 95% CI 0.36 to 4.87; participants = 68; studies = 1; very low-quality evidence). This suggests that if the chance of a miscarriage following daily leuprolide acetate is assumed to be 6%, the chance following daily nafarelin would be between 1% and 20%.

Multiple pregnancy rate

Not reported.

Cycle cancellation rate
Not reported.

Endometrial thickness

Not reported.

Other adverse effects

Not reported.

7) GnRH agonists versus GnRH antagonists

One study (Vidal 2009) analysed 473 women who underwent preparation of the endometrium for oocyte donation with either a 7 day dosage of GnRH antagonist (cetrorelix 0.25mg) versus

conventional single dose GnRH agonist (tryptorelin, 3.75 mg intramuscularly) on day 21 of the menstrual cycle.

Primary outcome

Live birth rate

Not reported.

Secondary outcomes

7.1- Clinical pregnancy rate

Administrating GnRH antagonists probably increases the clinical pregnancy rate (OR 0.62, 95% CI 0.42 to 0.90; participants = 473; studies = 1; moderate-quality evidence). This suggests that if the chance of a clinical pregnancy following GnRH antagonists is assumed to be 68%, the chance following GnRH agonists would be between 47% and 66%.

7.2- Miscarriage rate

We are uncertain whether administrating GnRH agonist or antagonists increases the miscarriage rate (OR 0.75, 95% CI 0.38 to 1.49; participants = 473; studies = 1; low-quality evidence). This suggests that if the chance of a miscarriage following GnRH antagonists is assumed to be 9%, the chance following GnRH agonists would be between 4% and 12%.

7.3- Multiple pregnancy rate

We are uncertain whether administrating GnRH agonist or antagonists reduces the multiple pregnancy rate (OR 0.69, 95% CI 0.45 to 1.07; participants = 473; studies = 1, low-quality evidence). This suggests that if the chance of a miscarriage following GnRH antagonists is assumed to be 25%, the chance following GnRH agonists would be between 13% and 27%.

Cycle cancellation rate

Not reported.

Endometrial thickness

Not reported

Other adverse effects

Not reported.

8) Low-dose aspirin versus no treatment

One study (Madani 2019) involving 60 women undergoing a frozen embryo transfer were randomised to receive either low dose aspirin (100 mg/day orally) or placebo which was administered at the same time as estradiol valerate..

Primary outcome

8.1-Live birth rate (Analysis 8.1)

We are uncertain whether administering low-dose aspirin increases the live birth rate (OR 6.00, 95% CI 1.48 to 24.30; participants = 60; studies = 1; very low-quality evidence). This suggests that if the chance of a live birth following no administration of aspirin is assumed to be 10%, the chance following aspirin would be between 14% and 73%.

Secondary outcomes

8.2-Clinical pregnancy rate (Analysis 8.2)

It is uncertain whether the low-dose aspirin increases the clinical pregnancy rate (OR 3.33, 95% CI 1.00 to 11.14; participants = 60; studies = 1, very low-quality evidence). This suggests that if the chance of a clinical pregnancy following no administration of aspirin is assumed to be 17%, the chance following aspirin would be between 17% and 69%.

Miscariage rate

Not reported.

Multiple pregnancy rate

Not reported

Cycle cancellation rate

Not reported.

8.3-Endometrial thickness (Analysis 8.3)

We are uncertain whether there is a clinically relevant difference between using aspirin or not (MD -0.40, 95% CI -0.95 to 0.15; participants = 60; studies = 1; very low-quality evidence). This suggests that if the endometrial thickness following no administration of aspirin is assumed to be 9.1 mm, the chance of the endometrial thickness following administration of aspirin would be between 8.9 mm and 10 mm.

Other adverse effects

Not reported.

9) Steroids versus no treatment

Two studies (Bider 1996; Moffitt 1995) involving a total of 160 women who underwent a frozen-thaw embryo transfer evaluated the impact of taking steroids for one or two days prior to embryo transfer on reproductive outcomes. One trial used dexamethasone 0.5 mg orally for five days and the other used methylprednisolone 4 mg orally for four days.

Primary outcome

9.1-Live birth rate (Analysis 9.1)

Live birth rate was described by one trial (Bider 1996). It is uncertain whether corticosteroids improves the live birth rate compared to control (OR 0.66, 95% CI 0.14 to 3.11; participants = 99; studies = 1; very low-quality evidence). This suggests that if the chance of a live birth following no administration of steroids is assumed to be 9%, the chance following steroids would be between 1% and 22%.

Secondary outcomes

9.*2-Clinical pregnancy rate* (Analysis 9.2)

Clinical pregnancy rate was described by two trials (Bider 1996; Moffitt 1995). It is uncertain whether corticosteroids improves the clinical pregnancy rate (OR 0.90, 95% CI 0.40 to 2.03; participants = 160; studies = 2; I^2 = 0%; very low-quality evidence). This suggests that if the chance of a clinical pregnancy following no administration of steroids is assumed to be 20%, the chance following steroids would be between 9% and 34%.

9.3-Miscarriage rate (Analysis 9.3)

It is uncertain whether corticosteroids improves the miscarriage rate (OR 1.49, 95% CI 0.32 to 7.03; participants = 160; studies = 2; I^2 = 0%; very low-quality evidence). This suggests that if the chance of a miscarriage following no administration of steroids is assumed to be 4%, the chance following steroids would be between 1% and 22%.

9.4-Multiple pregnancy rate (Analysis 9.4)
Not reported.

Cycle cancellation rate

Not reported.

Other adverse effects

Not reported.

There were not enough studies with low risk of bias for randomisation method and allocation concealment to make a sensitivity analysis by quality of evidence.

DISCUSSION

Summary of main results

This systematic review of endometrial preparation has demonstrated that few properly performed studies exist comparing the pre-specified interventions. However, some few conclusions can be retrieved.

In frozen embryo transfers, low-quality evidence showed that clinical pregnancy rates may be improved in a stimulated cycle compared to a programmed one, and we are uncertain of the effect when comparing a programmed cycle to a natural cycle. Cycle cancellation rates are probably reduced in a natural cycle. Although administering a gonadotropin-releasing hormone (GnRH) agonist, compared to without, may improve live birth rates, clinical pregnancy rates will probably be improved in a GnRH antagonist cycle over an agonist cycle.

In fresh synchronised oocyte donor cycles, clinical pregnancy rate is probably improved and cancellation rates are probably reduced when starting progestogen the day of or day after donor oocyte retrieval.

Although frozen embryo replacement and oocyte donation cycles have been used clinically for several years (Leeton 1986; Mohr 1985), there is no agreement about the optimal way to prepare the endometrium prior to and immediately following embryo transfer.

More double-blinded randomised controlled trials (RCTs) with adequate power are required in the future in order to determine if any of the interventions assessed in our review do enhance the chances of live births among those infertile women undergoing frozen embryo transfer or oocyte donation cycles.

Overall completeness and applicability of evidence

The exhaustive search strategy of published and unpublished studies and the limited body of evidence make it unlikely that any relevant study was omitted. Although patients, settings, and interventions could be representative of clinical practice, applicability could be limited by other sources as we found insufficient evidence.

The evidence provided by this review applies to women who are going to have a frozen embryo transfer or a fresh synchronised embryo transfer of embryos derived from donor oocytes. These are interventions in everyday practice, for the general population, and should not be applied to specific cases such as women with a thin endometrium. As most studies do not report live birth rates, we do not have enough evidence, though some of the information could be carefully extrapolated from secondary outcomes such as clinical pregnancy rate.

Quality of the evidence

The quality of the included studies limited our conclusions. The present review shows that endometrial preparation for frozen embryo transfers and fresh embryo transfers in oocyte donation cycles have been evaluated in many different ways. We investigated the need to use GnRH agonists for ovarian suppression, different types and modes of endometrial estrogenic stimulation, different types and timing of initiating progestogen, and other peripheral interventions such as the use of low-dose aspirin or steroids prior to embryo transfer procedures. More than one intervention may impact on clinical results and so we included RCTs where only one intervention was evaluated.

Overall, the quality of the evidence was low to very low because of methodological limitations, with some moderate-quality evidence. Few authors described the allocation method, there was no blinding of patients, and blinding of healthcare-workers was not described. Live birth rate was reported in a minority of cases. Finally, outcome assessment was not generally described in terms of blinding of the evaluator (*see* Figure 2; Figure 3).

Potential biases in the review process

Since we followed the updated version of the for *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), we are confident the review process was not biased. Although the search strategy was comprehensive, there could be some studies that could have been missed.

Agreements and disagreements with other studies or reviews

Five studies compared different types of GnRH agonists but none demonstrated statistically significant differences. Endometrial development should be analysed in future studies in order to determine if depot and daily formulations can impact in a different way on endometrial implantation. We did not find any other review of this particular topic.

AUTHORS' CONCLUSIONS

Implications for practice

There is insufficient evidence to support the use of any particular intervention in endometrial preparation that clearly improves treatment outcomes for women undergoing embryo transfers with frozen embryos or embryos derived from donor oocytes. The results of this review should be carefully considered because of the heterogeneity between some trials. However, we still could draw some potential conclusions given the moderate- to low-quality evidence. Clinical pregnancy rates may be improved in a stimulated cycle compared to a programmed cycle, and cycle cancellation rates are probably reduced in a natural cycle in comparison with

programmed cycles. The use of gonadotropin-releasing hormone (GnRH) analogues, compared to without, may improve live birth rates (some data showed that GnRH antagonists may be more effective than GnRH agonists). In fresh synchronised oocyte donor cycles, starting progestogen the day of, or day after donor oocyte retrieval probably improves the live birth rate and probably reduces the cycle cancellation rate. Finally, we did not find benefits with the other medications evaluated.

Implications for research

There is little comparative information on each of the treatments that might impact on endometrial preparation for women undergoing embryo transfers with frozen embryos or embryos derived from donor oocytes. Adequately powered randomised controlled trials (RCTs) are needed, with a longer follow-up to report live birth rates, and to evaluate each of the treatments more accurately. More studies are needed to analyse if stimulated, programmed or natural cycles are different or not. And more studies are needed to specifically evaluate if GnRH agonist use is associated with fewer cycle cancellations, to see if this medication impacts on the development of the endometrium, and to see if GnRH antagonists are better than agonists. More studies are needed to confirm the timing of the administration of progestogen and to analyse if adding low-dose aspirin to the endometrial preparation is beneficial or not. Furthermore, more studies are needed to evaluate if testing the endometrial receptivity could help identify the appropriate day to start progestogen. Finally, more studies would help to determine if there is a subgroup of women who may benefit from any specific medication.

ACKNOWLEDGEMENTS

Marian Showell who contributed to the update of the search strategy. Daniel Comande, librarian, who contributed to the search strategy and identification of the cited studies. Paul Bergh MD, Antonio Pellicer MD and Mark Sauer MD have been consulted as experts in the field in order to be thorough and include all the studies that should be part of this review. We wish to also thank Katie Stocking and Drs Elizabeth Glanvlle and Emily Liu for peer review comments on the draft full review.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Agha-Hosseini 2018

Study characteristics	
Methods	The enrolled women were divided randomly into two groups to undergo either a modified natural cycle (NC) FET (group A) or artificial cycle (AC) FET (group B) using computerised software in a 1:1 fashion.
Participants	All women who were aged between 18 and 40 years and had regular menses (25 to 34 days) and who had at least two cryopreserved embryos derived from intracytoplasmic sperm injection (ICSI) treatment cycles from January 2012 to December 2014 were enrolled. Women with endometriosis, immune diseases, recurrent abortion, donated sperm or oocyte, uterine abnormality, ovarian cyst or previous ovarian surgery, history of previous IVF failure, and any known contraindications or allergy for oral estradiol or progesterone therapy were excluded from participating in the study. In addition, patients were excluded if their clinical history included percutaneous epididymal sperm aspiration or testicular sperm extraction.
Interventions	85 patients were considered as group A (NC FET) and 85 were classified as group B (AC-FET) and were assigned to receive the related protocol. NC FET: An ultrasound examination was performed on days 10 to 12 of the cycle after a spontaneous menses to detect the leading follicle. When at least one dominant follicle reached ≥18 mm in diameter and the thickness of the endometrium was at least 8 mm, a bolus of 10.000 IU of human chorionic gonadotropin (hCG) (Pregnyl; N.V. Organon, Oss, the Netherlands) was injected intramuscularly for the induction of ovulation and the embryos were thawed and transferred 4 days later. Artificial cycle FET: from the 21st day of the previous cycle, 500 µg/day of buserelin acetate (Suprecur; Hoechst UK Ltd, Hounslow, UK) was subcutaneously injected. Oral estradiol valerate (Progynova, Bayer, Germany) was then administered from day 2 of the next cycle from 2 mg/day to 2 mg/day ×4. The E dosage was adjusted based on the endometrial thickness as assessed using transvaginal ultrasound.
Outcomes	A total of 63 clinical pregnancies occurred in the NC-FET and the AC-FET groups [33 (38.9%) versus 30 (35.3%) clinical pregnancies; P = 0.4, respectively].
Notes	Trial registration: not mentioned Funding: this work was financially supported by the Research Deputy of Tehran University of Medical Sciences (Grant Number: 94-01-01-2051) Conflict of interest: the authors declare that there are no conflicts of interest that could be perceived as prejudicing the impartially of the research reported.

Agha-Hosseini 2018 *(Continued)*

Study dates: cycles from January 2012 to December 2014

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The enrolled women were divided randomly into two groups to undergo either a modified natural cycle FET (group A) or artificial cycle FET (group B) using computerized software in a 1:1 fashion"
Allocation concealment (selection bias)	High risk	The treating physicians (n = 2) gave treatment based on the allocated chart
Blinding of participants and personnel (performance bias) All outcomes	Low risk	We did not consider that blinding was likely to influence finding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	We did not consider that blinding was likely to influence finding
Incomplete outcome data (attrition bias) All outcomes	Low risk	3 of 85 women discontinued the intervention in the group of AC-FET
Selective reporting (reporting bias)	Unclear risk	No protocol was found
Other bias	Low risk	The study appears to be free of other sources of bias

Aleyasin 2017

Study characteristics

Methods	This randomised clinical trial included 100 women (18 to 42 years) randomly assigned to two groups based on Bernoulli distribution.
Participants	Inclusion criteria were all women (18 to 42 years old) who were undergoing endometrial preparation for first frozen embryo transfer. Infertile couples with male infertility undergone testicular sperm extraction (TESE) or percutaneous epididymal sperm aspiration (PESA); severe endometriosis (stage 3 or 4); uterine myoma ≥ 4 cm, and fresh embryo transfer were excluded. 50 women were allocated to each arm.
Interventions	Group I received GnRH agonist (Buserelin, 500 µg subcutaneously) from the previous mid luteal cycle, then estradiol valerate (2 mg/ daily orally) was started on the second day and was increased until the observation of 8 mm endometrial thickness. Group II received letrozole (Iran hormone, Iran, 5 mg/daily) on the second day of the cycle for five days, then HMG 75 IU was injected on the seventh day. After the observation of 18 mm follicle in transvaginal ultrasound, human chorionic gonadotropin (hCG) (Ferring, Germany, 10,000 IU, and IM) was injected for ovulation induction.
Outcomes	The main outcome was the live birth rate. The rate of live birth, implantation, chemical, and clinical pregnancy, abortion, cancellation and endometrial thickness were compared between two groups.

Aleyasin 2017 *(Continued)*

Notes	Trial registration: IRCT201306256689N3 Funding: no Conflict of interest: Quote: "There is no conflict of interest in this article" Study dates: between February 2014 and February 2016 Authors were contacted for missing information - no response

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomly method based on Bernoulli distribution
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	We did not consider that blinding was likely to influence finding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	We did not consider that blinding was likely to influence findings
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss of follow-up.
Selective reporting (reporting bias)	Low risk	Protocol IRCT201306256689N3
Other bias	Low risk	The study appears to be free of other sources of bias

Bider 1996

Study characteristics

Methods	Single-centre trial. Trial design: parallel. Allocation: participants were randomised using a computer-generated randomisation list. Assignment method was not stated. Blinding: not stated. Follow-up: until live birth.
Participants	N = 99. Women mean age at time of oocyte retrieval was not reported. Their mean age at time of embryo transfer was 33.7 years for dexamethasone group and 32.9 years for control group. Cause of infertility: tubal factor in 100%.
Interventions	Dexamethasone (0.5 mg orally nightly for five days, beginning on the day of ovulation) versus no treatment.

Bider 1996 *(Continued)*

Outcomes	Pregnancy rate (dexamethasone versus no treatment): 13.5% versus 12.8%.
Notes	Dexamethasone group transferred a mean of 2.8 embryos and the control group transferred 2.1 embryos. Trial registration: no Funding: no Conflict of interest: no Study dates: during a 23-month period that ended in December 1994 Authors were contacted for missing information - no response

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The participants were treated according to a computer-based randomisation
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	We did not consider that blinding was likely to influence findings
Blinding of outcome assessment (detection bias) All outcomes	Low risk	We did not consider that blinding was likely to influence findings
Incomplete outcome data (attrition bias) All outcomes	Low risk	There are no losses of follow-up (<10%)
Selective reporting (reporting bias)	Unclear risk	No protocol available
Other bias	Low risk	The study appears to be free of other sources of bias

Check 2002

Study characteristics

Methods	The present study randomly assigned women attempting frozen embryo transfer (ET)
Participants	Women attempting frozen embryo transfer (ET) who failed to attain an 8 mm endometrial thickness following graduating dosages of oral E2. Sixteen patients with a mean number of 1.5 attempted but cancelled frozen ET cycles were selected. The mean endometrial thickness for those cycles following oral E2 treatment was 6.6 mm and was 6.3 mm on cycles immediately prior to the study.
Interventions	Treatment with oral E2 plus 25 mg 4 times per day of sildenafil from day 3 to 9 of cycle (vaginal wash day 10) or oral E2 plus 2 mg 2 times per day of vaginal E2 from day 2 to peak thickness.

Check 2002 *(Continued)*

Outcomes	Seven women randomised to vaginal E2 had a mean endometrial thickness of 7.2 mm.
Notes	Trial registration: not stated Funding: not stated Conflict of interest: not stated Study dates: not described Authors were contacted for missing information - no response

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The present study randomly assigned women attempting frozen embryo transfer (ET)
Allocation concealment (selection bias)	Unclear risk	The present study randomly assigned women attempting frozen embryo transfer (ET)
Blinding of participants and personnel (performance bias) All outcomes	High risk	No attempts to blind were done.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No mention of blinding outcome assessment
Incomplete outcome data (attrition bias) All outcomes	High risk	Frozen ET was attempted in only 6 of the 16 women (4 with sildenafil and 2 with vaginal E2)
Selective reporting (reporting bias)	Unclear risk	No protocol available
Other bias	Unclear risk	It is an abstract from a meeting a there is no enough information to discard other bias

Child 2013

Study characteristics

Methods	Prospective open randomised controlled trial. Pilot study.
Participants	Regular ovulatory cycles; age less than 40 years at original IVF. 159 women were randomised (80 Natural; 79 HRT)
Interventions	Women were randomised to Natural FET (Group 1) or HRT FER (Group 2) for a single cycle. Natural FET. Embryo transfer was scheduled 5-7 days after a positive urine LH surge. 1 or 2 embryos were replaced under abdominal ultrasound guidance. Following a positive urine pregnancy test scans were performed at 6 and 10 weeks gestation. No drugs were used. HRT FET. Nasal nafarelin was started on cycle D21 followed by estradiol valerate (2mg orally increasing to 6mg/day) when pituitary suppression was confirmed. After 2 weeks of estradiol and an endometrial thickness of at least 7mm progesterone

Child 2013 *(Continued)*

	pessaries were started and the embryo transfer undertaken. HRT was continued until 10 weeks gestation.
Outcomes	Live birth rate per cycle. Live birth rates were 26.3% (Natural) and 31.7% (HRT) per randomised patient (P = NS)
Notes	Trial registration: no Funding: Oxford Fertility Unit Conflict of interest: no Study dates: not described Authors were contacted for missing information - no response

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	It is not described how randomisation was performed
Allocation concealment (selection bias)	Unclear risk	It is not described how allocation was performed
Blinding of participants and personnel (performance bias) All outcomes	Low risk	We did not consider that blinding was likely to influence finding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	We did not consider that blinding was likely to influence findings
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat analysis and less than 10% of follow-up loss. 159 women were randomised (80 Natural; 79 HRT) and 145 had embryo transfer and completed the study (72 Natural; 73 HRT)
Selective reporting (reporting bias)	Unclear risk	No protocol available.
Other bias	Low risk	The study appears to be free of other sources of bias

Dal Prato 2002

Study characteristics

Methods	Single-centre trial. Trial design: parallel. Allocation: on an individual basis by using sealed envelopes and randomly assigned sequential numbers. Blinding: not stated. Follow-up: until pregnancy. Therefore live birth rate not included in outcomes.

Dal Prato 2002 *(Continued)*

Participants	N = 296. Women mean age at time of oocyte retrieval was 32.9 years for tryptorelin group and 32.5 years for the no-treatment group. Their mean age at time of embryo transfer was 34.6 years for tryptorelin group and 33.9 years for the no-treatment group. Cause of infertility: not stated.
Interventions	A single IM injection of tryptorelin 3.75 mg was administered in the mid-luteal phase of the cycle to the tryptorelin group. No injection was given to the other group of women.
Outcomes	Pregnancy rate (tryptorelin versus no treatment): 19.1% versus 22.6%.
Notes	Both groups transferred a mean of 2.1 embryos. Trial registration: no Funding: no Conflict of interest: no Study dates: From April 1999 to September 2000 Authors were contacted for missing information - no response

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Randomization was performed on an individual basis by using sealed envelopes containing the name of one of the two treatments". This sentence does not explain the method of randomisation, which is not stated.
Allocation concealment (selection bias)	Low risk	Assignment was made when an eligible patient agreed to participate. Each envelope and allocation was sequentially numbered to avoid allocating a patient out of sequence.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	We did not consider that blinding was likely to influence finding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	We did not consider that blinding was likely to influence findings
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss of follow-up
Selective reporting (reporting bias)	Unclear risk	No protocol was found
Other bias	Low risk	The study appears to be free of other sources of bias

Davar 2007

Study characteristics

Methods	Single-centre trial. Trial design: parallel.

Davar 2007 *(Continued)*

	Allocation: randomisation by computer-generated list. Allocation method: not stated. Blinding: no. Follow-up: until pregnancy. Therefore live birth rate not included in outcomes.
Participants	N = 60. Women mean age at time of oocyte retrieval was 28.1 years for buserelin group and 27.8 years for the no-treatment group.
Interventions	Group A commenced steroid supplementation without prior pituitary desensitization. Group B had pituitary suppression prior to steroid hormone administration with Buserelin acetate starting in mid-luteal phase (day 21) at a dose of 0.5 mg, subcutaneously, and continued until day 11 of the cycle. Both groups received increasing doses of valerate estradiol from 2 to 6 mg/day. orally.
Outcomes	Pregnancy rate (buserelin versus no treatment): 10% versus 6.6%
Notes	Cryopreservation was performed on pro nuclear stage. Transfer was performed when endometrial thickness was at least 8 mm. Trial registration: no Funding: no Conflict of interest: no Study dates: between January 2005 and October 2006 Authors were contacted for missing information - no response

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The study population was randomly divided into two groups according to a computer-generated list
Allocation concealment (selection bias)	Unclear risk	No information was found about the allocation concealment.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	We did not consider that blinding was likely to influence finding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	We did not consider that blinding was likely to influence findings
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss of follow-up
Selective reporting (reporting bias)	Unclear risk	No protocol was found
Other bias	Low risk	The study appears to be free of other sources of bias

Davar 2016

Study characteristics	
Methods	Patients were randomly allocated to oral estradiol or 17 beta-estradiol transdermal patch
Participants	A total number of 90 patients who underwent frozen-thawed embryo transfer cycles were enrolled in this study
Interventions	In the study group with transdermal route (n = 45), 100 µg of 17-B estradiol transdermal patch (Novartis, Turkey) was applied every other day from the second day of menstruation cycle, and each patch was removed after four days. In the control group with oral route (n = 45), at the time of cycle, 6 mg of oral estradiol valerate (Aburaihan, Iran) was started daily.
Outcomes	Clinical pregnancy rate per transfer (36.4% versus 28.6%, respectively, P = 0.29)
Notes	Trial registration: IRCT2012112610328N2 Funding: Vice chancellor of Yazd Research and Clinical Center for Infertility Conflict of interest: the authors declare they have no conflict of interest Study dates: between April 2012 and Jan 2013 Authors were contacted for missing information - no response

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Only states "Randomized"
Allocation concealment (selection bias)	Unclear risk	No information listed
Blinding of participants and personnel (performance bias) All outcomes	Low risk	We did not consider that blinding was likely to influence finding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	We did not consider that blinding was likely to influence finding
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss of follow-up
Selective reporting (reporting bias)	Unclear risk	No protocol was found
Other bias	Low risk	The study appears to be free of other sources of bias

Davar 2020

Study characteristics

Davar 2020 *(Continued)*

Methods	Computer-generated randomisation
Participants	67 infertile women with history of idiopathic RIF (at least two implantation failures). All women with endometrial polyp, uterine myoma, and uterine anomaly were excluded from the study
Interventions	The case group (n = 34) received 0.1 mg/day of the GnRH agonist (Variopeptyl, VarianDarou, Iran), SC, from day 21 of the cycle preceding the actual FET cycle. On the second day of the cycle, the dose of GnRH agonist was reduced to 0.05 mg and 6 mg/day oral estradiol valerate (2 mg, Aburaihan Co., Tehran, Iran) was also started. When the endometrial thickness reached to 7.5 mm, vaginal supplementation of Cyclogest® pessaries (Cox Pharmaceuticals, Barnstaple, UK) at 400 mg twice daily was started and the GnRH agonist was also stopped. The control group (n = 33), received 6 mg/day oral estradiol valerate (2 mg, Aburaihan Co., Tehran, Iran) from the second day of the cycle without the GnRH agonist. In the two groups, frozen-thawed embryos were transferred on the fourth day of progesterone treatment.
Outcomes	Clinical pregnancy was approved by the detection of a fetal heartbeat 2 wk after positive β-hCG.
Notes	in Yazd Reproductive Sciences Institute, Yazd, Iran between August and November 2017 IRCT: 201708292604N3

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomised using a computer-generated randomisation list
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	We did not consider that blinding was likely to influence finding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	
Incomplete outcome data (attrition bias) All outcomes	Low risk	Less than 10% of missing outcomes
Selective reporting (reporting bias)	Low risk	IRCT: 201708292604N3
Other bias	Low risk	No other risk of bias was reported

Ding 2007

Study characteristics

Methods	Frozen-thawed blastocyst transfer was randomly performed on either 6th or 7th day of progestogen administration.

Ding 2007 *(Continued)*

Participants	Frozen-thawed blastocyst transfers during 49 consecutive cycles were randomised into two groups according to the number of days of progestogen administration
Interventions	In Group 1 (23 cycles), frozen blastocysts were thawed and transferred on the 6th and in Group 2 (26 cycles) on the 7th day of progestogen administration
Outcomes	After transfer, the presence of intrauterine gestational sac was defined as clinical pregnancy (Clinical PR) and the presence of fetal cardiac activity as ongoing pregnancy (Ongoing PR).
Notes	Trial registration: not stated Funding: not stated Conflict of interest: not stated Study dates: not described Authors were contacted for missing information - no response

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Frozen-thawed blastocyst transfer was randomly performed on either 6th or 7th day of progesterone administration
Allocation concealment (selection bias)	Unclear risk	Frozen-thawed blastocyst transfer was randomly performed on either 6th or 7th day of progesterone administration
Blinding of participants and personnel (performance bias) All outcomes	High risk	No attempts to blind were done.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No mention of blinding outcome assessment
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not stated if there were missing data
Selective reporting (reporting bias)	Unclear risk	No protocol available
Other bias	Unclear risk	It is an abstract from a meeting and there is not enough information to discard other bias

El-Toukhy 2004

Study characteristics

Methods	Single-centre study. Trial design: parallel. Allocation: 117 women were allocated to each arm. Participants were randomised using a computer-generated randomisation list. Woman enrolment and assignment to their treatment groups was carried out at the time of participation by medical staff not involved in the study.

El-Toukhy 2004 *(Continued)*

	Blinding: not stated. Follow-up: until live birth.
Participants	N = 234. Women mean age at time of embryo transfer was 32.8 years for buserelin group and 33.2 years for the no treatment group. Cause of infertility: not stated.
Interventions	Group A (n = 117) had pituitary suppression prior to steroid hormone administration, while group B (n = 117) commenced steroid supplementation without prior pituitary desensitization. (Fig. 1) Pituitary suppression in group A patients was performed using buserelin nasal spray (Superfact, Hoechst UK Ltd., Hounslow, Middlesex, UK) starting in the mid-luteal phase (day 21) of the menstrual cycle. On day 1 of subsequent menstruation, oestrogen stimulation was initiated using oral estradiol valerate 6 mg daily in two divided doses (Climaval, Novartis Pharmaceuticals, Surrey, UK). Group B patients started oestrogen stimulation on day 1 of menstruation using the same dose of Climaval (6mg/day). In both groups, patients remained on this dose for 12±14 days, after which endometrial thickness was evaluated using an ultrasound scanner with a 6.5 MHz probe (Hitachi EUB 525, Tokyo, Japan). The dose of Climaval was increased to 8mg/day for a further 7±12 days if endometrial thickness was less than 8mm. When endometrial thickness had reached 8mm or more, micronized progesterone pessaries (Cyclogest, Shire Pharmaceuticals Ltd., Hants, UK) 400 mg twice daily were commenced and buserelin nasal spray stopped in group A patients.
Outcomes	Live birth rate (buserelin versus no treatment): 20% versus 8.5% (P = 0.01).
Notes	Buserelin group transferred a mean of 2.3 embryos and the control group transferred 2.2 embryos. Trial registration: no Funding: no Conflict of interest: no Study dates: between January 1998 and July 2001 Authors were contacted for missing information - no response

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomised using a computer-generated randomisation list
Allocation concealment (selection bias)	High risk	Quote: "woman enrolment and assignment to their treatment groups was carried out at the time of participation by medical staff not involved in the study"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	We did not consider that blinding was likely to influence finding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	We did not consider that blinding was likely to influence findings
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss of follow-up
Selective reporting (reporting bias)	Unclear risk	No protocol was found

El-Toukhy 2004 *(Continued)*

Other bias	Low risk	The study appears to be free of other sources of bias

Escriba 2006

Study characteristics

Methods	Single-centre study. Trial design: parallel. Allocation: a computer-based randomisation divided recipients into three groups. Blinding: not stated. Follow-up: until pregnancy. Therefore live birth rate not included in outcomes.
Participants	N = 282. Oocyte recipients mean age was 39.4 years in both groups. Donor mean age was not reported. Cause of infertility: age 47.6%; poor responders 25.6%; implantation failure 8.5%; severe endometriosis 8.5%; other causes: 9.8%.
Interventions	The protocol for steroid replacement included pituitary desensitization with a single intramuscular ampule administration of 3.75 mg of tryptorelin (Decapeptyl depot 3.75, Ipsen Pharma, Madrid, Spain) in the mid-luteal phase of the menstrual cycle. Hormonal replacement therapy was initiated when ultrasound confirmed ovarian quiescence during the following menstruation. Two milligrams of E2 valerate (Progynova, Schering Spain, Madrid, Spain) were administered daily for the first 8 days, 4 mg for the next 3 days, and 6 mg from thereon. After 13 days of E2 valerate administration, endometrial thickness and pattern were tested. If a three-layer pattern was observed in a 7 mm endometrium, the aforementioned dose of E therapy was continued at least until the pregnancy test was performed. If the endometrium was not seen to be sufficiently developed, doses of E2 valerate were increased to 8 mg/day. Daily administration of 800 mg/day of micronized intravaginal P (Progeffik, Laboratories Effik S.A., Madrid, Spain) was initiated according to the randomisation. The first group (group A) began P supplementation the day before oocyte retrieval. In the second group (group B) P was administered from the day of oocyte retrieval. The third group (group C) began P one day after retrieval, once fertilization had been confirmed.
Outcomes	Pregnancy rate ("before" versus "day of" versus "After"): 38.1% versus 54.2% versus 52.7%. Cancellation rate: 12.4% (8 out of 12 were because of fertilisation failure) versus 4.2% (1 of 4 were because of fertilisation failure) versus 3.3% (0 out of 3 were because of fertilisation failure).
Notes	All embryo transfers were done on day 3. Endometrium was prepared with oral estradiol and intravaginal micronised progesterone. Trial registration: no Funding: no Conflict of interest: no Study dates: between September 2003 and September 2004 Authors were contacted for missing information - no response

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A computer-based randomisation divided recipients into three groups

Escriba 2006 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Not clear how allocation concealment was done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	We did not consider that blinding was likely to influence finding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	We did not consider that blinding was likely to influence findings
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss of follow-up
Selective reporting (reporting bias)	Unclear risk	No protocol was found
Other bias	Low risk	The study appears to be free of other sources of bias

Greco 2016

Study characteristics	
Methods	236 patients undergoing infertility treatment were randomised in 1:1 ratio; 118 received a frozen-thawed single euploid blastocyst transfer in a modified natural cycle and 118 in an artificial cycle with GnRH-agonist pituitary suppression
Participants	Inclusion criteria: maternal age <42 years, regular menstrual cycle, normal intrauterine cavity on pre-treatment assessment, the presence of at least one vitrified euploid blastocyst obtained after intracytoplasmic sperm injection (ICSI) followed by preimplantation genetic diagnosis by aCGH, and a consent to undergo a frozen-thawed single transfer in a modified-NC or after hormonal endometrium preparation. Exclusion criteria were as follows: ovulation disorders, BMI >29 kg/m2, endometriosis grade ≥III according to the American Fertility Society criteria, and the use of testicular sperm for ICSI.
Interventions	In the artificial protocol, GnRH-agonist (buserelin acetate; Suprefact®; Hoechst, Marion Roussel, Milan, Italy) was started at the dose of 0.2 mg twice daily on day 21 of the previous menstrual cycle. When serum estradiol concentrations were <40 pg/mL and progesterone <1.5 ng/mL and no ovarian cystic structures were observed by transvaginal ultrasound, increasing doses of oral estradiol valerate (Progynova, Bayer, New Zealand limited, Auckland) were given. In general, patients started estradiol at a dose of 2 mg twice a day. This dose was increased every 3–5 days up to a maximum dose of 2 mg three times a day. Serial serum estradiol measurements and transvaginal ultrasound evaluation of the endometrium were monitored. After adequate endometrial proliferation (>7 mm), serum estradiol (>200 pg) and progesterone concentration (<1.5 ng/mL) were documented, GnRH-agonist treatment was stopped, and treatment with intramuscular progesterone (Prontogest, IBSA, Lodi, Italy), 50 mg/day, was initiated. In cases of pregnancy, estradiol and progesterone were continued until the 12th gestational week. In modified-natural cycle, all patients assessed on cycle day 3 the FSH, LH, estradiol, and progesterone levels in order to check if they corresponded to the early follicular phase. Subsequently, serum estradiol and LH levels and transvaginal ultrasound evaluation of the endometrium were performed serially according to the physician's decision starting from day 8 of the cycle. Criteria for hCG administration included the following: mean diameter of dominant follicle of at least 17 mm, the endometrial thickness >7 mm, serum estradiol >200 pg, serum progesterone <1.5 ng/mL, and absence of a spontaneous LH surge. Final oocyte maturation was induced using 10.000 IU of hCG (Gonasi, 10.000 IU, IBSA, Lodi, Italy). The spontaneous LH surge was defined as LH concentration rise by

Greco 2016 *(Continued)*

	180 % above the latest available value. In these cases, hCG was not administrated and the cycles were cancelled. Intramuscular administration of progesterone at dose of 50 mg/day (Prontogest, IBSA, Lodi, Italy) was started in all patients 2 days after hCG.
Outcomes	The primary end-points were the clinical pregnancy and implantation rates
Notes	Trial registration: NCT02378584 Funding: no Conflict of interest: no Study dates: started on February 2015 and completed on September 2015 Authors were contacted for missing information - no response

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Two hundred thirty-six patients were included in the study and randomized in two groups according to computer-generated, not cancelled, simple randomization list with allocation assignment 1.1"
Allocation concealment (selection bias)	Unclear risk	Allocation method is not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	We consider that blinding was not likely to influence findings
Blinding of outcome assessment (detection bias) All outcomes	Low risk	We consider that blinding was not likely to influence findings
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss of follow-up.
Selective reporting (reporting bias)	Low risk	NCT02378584
Other bias	Low risk	The study appears to be free of other sources of bias

Groenewoud 2016

Study characteristics

Methods	This is a multicentre, non-inferiority, randomised controlled trial. Patients were randomised based on a 1:1 allocation to either one cycle of modified natural cycle (mNC-FET) or artificial cycle (AC-FET).
Participants	18 to 40 years old, had to have a regular menstruation cycle between 26 and 35 days and frozen-thawed embryos to be transferred had to derive from one of the first three IVF or IVF-ICSI treatment cycles. Patients with a uterine anomaly, a contraindication for one of the prescribed medications in this study or patients undergoing a donor gamete procedure were excluded from participation. 1032 patients were included.

Groenewoud 2016 *(Continued)*

Interventions	Patients undergoing modified NC-FET (mNC-FET) attended for ultrasound evaluation of the dominant follicle from Day 10 to 12 of their menstrual cycle. Ultrasound monitoring continued until the dominant follicle reached 16 – 20 mm in diameter. When the follicle had reached a size indicating maturity, hCG (5000 IU Pregnylw or 250 mg Ovitrellew, Merck, Kenilworth, USA) was given subcutaneously to trigger ovulation. No minimal endometrial thickness to precede treatment was appointed in the protocol and no additional endocrine monitoring was performed. Patients did not receive luteal support. In AC- FET cycles, oral oestrogen (Progynova 2 mg, three times daily; Bayer, Leverkusen, Germany) was commenced on the first or second day of the cycle with the aim of supporting endometrial proliferation and suppressing follicle growth. After 12 to 14 days, vaginal ultrasound examination was performed to confirm that no dominant follicle had emerged and to measure endometrial thickness. When the endometrial thickness reached ≥8 mm, vaginal micronised progesterone 200 mg three times daily was given. If the endometrial thickness was considered inadequate, the oestrogen dosage was raised to 8 mg daily and ultrasound examination was repeated after 1 week. If the endometrium remained,8 mm, the FET treatment cycle was cancelled.
Outcomes	Live birth rate (LBR) after mNC-FET was 11.5% (57/495) versus 8.8% in AC-FET (41/464). Main difference for cancellation in programmed cycle was insufficient endometrium thickness, while main reason for cancellation in natural cycle was spontaneous ovulation.
Notes	Trial registration: Netherlands trial register, number NTR 1586 Funding for this study was provided by an unrestricted educational grant was awarded by Merck Sharp Dohme (MSD). MSD had no input or influence on the realisation of the study protocol or execution of the study. Nor did MSD play any role in the analysis and interpretation of the data as well as the preparation and approval of this manuscript. N.S.M. is supported by the National Institute for Health Research, Biomedical Research Centres (NIHR BRC) Southampton in Nutrition. Conflict of interest: all reported competing interests are outside the submitted work. Study dates: from February 2009 to April 2014

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Stratified randomisation with variable block sizes (ranging 2 – 12) was used in order to achieve a balanced 1:1 allocation. Stratification was based on the origin of the frozen embryos (IVF versus ICSI) and fertility clinic. To ensure allocation concealment, a web-based randomisation module using a computerized list was used. The nature of the treatment interventions precluded blinding of patients and treating physicians"
Allocation concealment (selection bias)	Low risk	quote: "Stratified randomisation with variable block sizes (ranging 2 – 12) was used in order to achieve a balanced 1:1 allocation. Stratification was based on the origin of the frozen embryos (IVF versus ICSI) and fertility clinic. To ensure allocation concealment, a web-based randomisation module using a computerized list was used. The nature of the treatment interventions precluded blinding of patients and treating physicians."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	We did not consider that blinding was likely to influence findings
Blinding of outcome assessment (detection bias) All outcomes	High risk	For cancellation rate, absence of blinding was important as in natural cycles no minimal endometrial thickness to precede treatment was appointed but in the artifical cycles they needed 8 mm to go ahead.

Groenewoud 2016 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	High risk	29% did not receive the intervention
Selective reporting (reporting bias)	Low risk	Netherlands trial registry (number NTR 1586)
Other bias	Low risk	The study appears to be free of other sources of bias

Gutierrez 1999

Study characteristics	
Methods	Single-centre trial.. Trial design: parallel. Allocation: method of randomisation and assignment was not stated. Blinding: not stated. Follow-up: until pregnancy. Therefore live birth rate not included in outcomes.
Participants	N = 68. Neither donor nor recipient mean age was reported. All the recipients were ovulating women. Cause of infertility: not stated.
Interventions	1 mg/day SC of leuprolide acetate was given to one group of women and 100 µg twice a day daily of nafareline acetate was given to the other group of recipients, starting at mid-luteal phase.
Outcomes	Pregnancy rate (leuprolide versus nafareline): 48.5% versus 54.3%.
Notes	Data were obtained from the abstract. Trial registration: no Funding: no Conflict of interest: no Study dates: not stated Authors were contacted for missing information - no response

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomisation procedure not stated
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	We did not consider that blinding was likely to influence findings
Blinding of outcome assessment (detection bias)	Low risk	We did not consider that blinding was likely to influence findings

Gutierrez 1999 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not stated
Selective reporting (reporting bias)	Unclear risk	No protocol available
Other bias	Low risk	The study appears to be free of other sources of bias

Kahraman 2018

Study characteristics	
Methods	The RCT was designed as a non-inferiority study
Participants	Women with irregular menses or anovulatory cycles undergoing frozen thawed single blastocyst transfer cycles without GnRHa suppression, having at least one day 5 (n = 290) or day 6 (n = 12) vitrified blastocyst in the Assisted Reproductive Technologies and Reproductive Genetics Centre at Istanbul Memorial Hospital. Exclusion criteria were the following: female age above 38 years, two or more previous unsuccessful cycles, a history of two or more early pregnancy losses, severe endometriosis, severe uterine malformation, azoospermia, and a history of familial thrombophilia or an abnormality in the thrombophilia tests. In addition, women with polycystic ovarian syndrome with more than 30 cumulus oocyte complexes retrieved at the pick-up were considered to be ineligible and therefore were excluded.
Interventions	154 patients were allocated to receive 3.9 mg estradiol transdermal patch (Climara®, Bayer Turk, Turkey), whereas 160 women were allocated to endometrial preparation with a fixed dose of 2 mg three times per day oral of estradiol tablets (total 6 mg) (Estrofem®, Novo Nordisk, Denmark). If endometrial thickness was 7 mm or more, progesterone vaginal gel (Crinone® 8%; Merck Serono, Switzerland) twice a day, was started on the same day. Otherwise, oestrogen administration was continued to day 21. In cases where development had continued satisfactorily, embryo transfer was carried out 5 days after the commencement of progesterone administration.
Outcomes	The viable clinical pregnancy rate was also higher in the oral ERT group (69.9% versus 61%), although it did not reach statistical significance (P = 0.103). The clinical miscarriage rate was higher in the oral ERT group (19.3% versus 14.6% in the patch group) (P = 0.387).
Notes	Trial registration: NCT03155048 Funding: no Conflict of interest: the authors declare that they have no conflict of interest. Study dates: between May 2017 and October 2017 Authors were contacted but no proper explanation was found.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	www.randomization.com was used for randomisation

Kahraman 2018 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	No information about allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	We did not consider that blinding was likely to influence findings
Blinding of outcome assessment (detection bias) All outcomes	Low risk	We did not consider that blinding was likely to influence findings
Incomplete outcome data (attrition bias) All outcomes	Low risk	Less than 10% of loss of follow-up
Selective reporting (reporting bias)	Low risk	ClinicalTrials.gov identifier: NCT03155048
Other bias	Low risk	The study appears to be free of other sources of bias

Lee 2008

Study characteristics	
Methods	Single-centre trial. Trial design: parallel. Allocation method: not stated. Blinding: No. Follow-up: until pregnancy. Therefore live birth rate not included in outcomes.
Participants	Eighty four (N = 84) frozen thaw embryo transfers cycles were randomised into two groups: Group A (natural cycle) consist of 39 cycles and Group B (artificial cycles) consist of 45 cycles.
Interventions	Comparison of pregnancy rate and implantation rate of frozen thawed embryo transfer cycles, between natural and artificial (hormone treated) cycles.
Outcomes	Pregnancy rate (natural cycle vs artificial cycle): 74.4% versus 40.4%.
Notes	Natural cycle group received an hCG injection when the leader follicle got to 18 mm to 20 mm. Then, they received vaginal progesterone supplementation, 90 mg every other day, started on the day after embryo transfer. Artificial cycle group received oral micronised estradiol, 2 mg three times daily, introduced on cycle day 2; progesterone 100 mg in oil was administered via IM injection 4 days before the embryo transfer. Cryopreservation was performed by vilification. Trial registration: no Funding: no Conflict of interest: no Study dates: not stated Authors were contacted for missing information - no response

Lee 2008 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	It is not described how randomisation was performed
Allocation concealment (selection bias)	Unclear risk	It is not described how allocation was performed
Blinding of participants and personnel (performance bias) All outcomes	Low risk	We did not consider that blinding was likely to influence finding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	We did not consider that blinding was likely to influence findings
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not described
Selective reporting (reporting bias)	Unclear risk	No protocol available
Other bias	Low risk	The study appears to be free of other sources of bias

Madani 2019

Study characteristics

Methods	This study was a pilot randomised, double-blind placebo-controlled trial, performed in Royan Institute for Reproductive Biomedicine from May 2012 to February 2015. Randomisation was performed by a third party using computer-generated random numbers (SPSS version 18.0) prepared by the statistician. Concealed allocation was done by the Epidemiology Research Center.
Participants	Eligibility criteria of inclusion were as follow: age of under 40 years, long or antagonist protocol, frozen-thawed embryos available for another transfer, no history of uterine surgery, no uterine disorders, no endometriosis, no history of recurrent abortion (≥ 2 abortions) and no contraindications to aspirin. Overall, 60 available eligible women who were candidates for FET entered the study.
Interventions	Women were randomly assigned (1:1) to two groups with either one dose of 100 mg oral aspirin (study group; n = 30) or placebo (control group; n = 30) on a daily basis. For the endometrial preparation, first, all patients received OCP-LD from the 5th day of their previous menstrual cycle and 500 µg/day Buserelin (Aventis) as a GnRH agonist was administered subcutaneously from the 17th day of the cycle until pituitary desensitization (as confirmed by basal ultrasonography and serum E2 and LH levels) was obtained. Then, 2 mg of oral estradiol valerate (Aburaihan Co.) per day was initiated on the 2nd day of the cycle and the dose increased until the optimal endometrial thickness was obtained. Participants assigned to the study group received 100 mg aspirin (Pars Darou Co.) and those assigned to control group received placebo simultaneously, at the time of initiation of estradiol valerate administration. For endometrial thickness measurement, transvaginal ultrasound (Sonoline G20, Siemens Medical Solutions) was performed every 4 days from the 7th day of the cycle. After observation of at least 7-mm endometrial thickness, 100 mg progesterone in oil (Aburaihan Co.)

Madani 2019 *(Continued)*

	was administered intramuscularly or a twice-daily dose of 400mg progesterone (800 mg) was given vaginally.
Outcomes	The study group had significantly higher rates of clinical pregnancy, implantation and live birth compared to the control group (P = 0.042; P = 0.031 and P = 0.007, respectively)
Notes	Trial registration: no Funding: no Conflict of interest: the present study has no conflict of interest Study dates: from May 2012 to February 2015

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was performed by a third party using computer-generated random numbers (SPSS version 18.0) prepared by the statistician"
Allocation concealment (selection bias)	Low risk	Concealed allocation was done by the Epidemiology Research Center
Blinding of participants and personnel (performance bias) All outcomes	Low risk	We did not consider that blinding was likely to influence finding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	We did not consider that blinding was likely to influence finding
Incomplete outcome data (attrition bias) All outcomes	Low risk	No exclusions from analysis
Selective reporting (reporting bias)	Unclear risk	No protocol available
Other bias	Unclear risk	Live birth and pregnancy rates were very low in the group that did not use aspirin, which raise some concerns to generalise. Authors were contacted but no proper explanation was found.

Matsuura 2014

Study characteristics

Methods	Prospective RCT in a private ART centre
Participants	102 infertile women under 42 years of age were treated with hormone replacement cycle undergoing the frozen-thawed single blastocyst transfer
Interventions	Group A (n=55) : The estradiol supplementation was initiated on day 2 from the menstruation cycle, thereafter the dydrogesterone was added. The frozen-thawed single blastocyst was transferred to uterine cavity on day 20.

Matsuura 2014 *(Continued)*

	Group B (n=47) : Taking the estradiol initiated with letrozole (2.5mg), 3 consecutive days together.
Outcomes	Clinical and ongoing pregnancy rates. Ongoing pregnancy rate was significantly higher in the Group B with Group A (38.3% versus 20.0%, P < 0.05)
Notes	2 mg of oral estradiol valerate (Aburaihan Co.) per day was initiated on the 2nd day of the cycle and the dose increased until the optimal endometrial thickness was obtained Trial registration: no Funding: no Conflict of interest: no Study dates: not stated Authors were contacted for missing information - no response

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	We did not consider that blinding was likely to influence findings
Blinding of outcome assessment (detection bias) All outcomes	Low risk	We did not consider that blinding was likely to influence findings
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were no losses of follow-up (<10%)
Selective reporting (reporting bias)	Unclear risk	No protocol available
Other bias	Low risk	The study appears to be free of other sources of bias

Moffitt 1995

Study characteristics

Methods	Multicentre. Trial design: parallel. Allocation: randomised by pharmacist who equally packaged the tablets/placebo and randomly assigned sequential numbers. Blinding: double-blind, placebo control. Follow-up: until live birth, however the paper was written before all women delivered. Therefore live birth rate not included in outcomes.

Moffitt 1995 *(Continued)*

Participants	61 cryopreservation patients. women mean age at time of oocyte retrieval was not reported. Their mean age at time of embryo transfer was 34.3 years for 6-alpha-methylprednisolone group and 33.6 years for control group. Cause of infertility: variety of causes.
Interventions	In cryopreservation cycles, thawed embryos were transferred in either a natural cycle or a programmed cycle. For the natural cycle, monitoring began 2 to 3 days before the anticipated date of ovulation as judged by knowledge of previous cycle lengths. Thawing was performed on the day of ovulation as defined by the day after the peak of the serum LH surge or the day of disappearance of the dominant follicle by US. Natural cycles were supplemented with 25 mg 1M P in oil starting the day of transfer. Patients undergoing a programmed cycle applied a 0.1 mg transdermal E2 patch (Estraderm; CIBA Pharmaceuticals, Summit, NJ) on the day of menses and replaced it every 2 days. The Estraderm dose was increased to 0.2 on day 9, to 0.3 on day 11, and to 0.4 on day 13. From day 15 on, a constant dose of 0.2 mg was used for the entire luteal phase. Progesterone in oil was administered daily (50 mg 1M) starting on day 15. Group A received Methylprednisolone (4 mg orally nightly for four days, beginning the day before embryo thaw) and group B received placebo.
Outcomes	Pregnancy rate (methylprednisolone versus placebo): 25% versus 30.3%.
Notes	Trial registration: no Funding: no Conflict of interest: no Study dates: from January to September 1993

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised by pharmacist who equally packaged the tablets/ placebo and randomly assigned sequential numbers
Allocation concealment (selection bias)	Low risk	Randomised by pharmacist who equally packaged the tablets/ placebo and randomly assigned sequential numbers
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, placebo control
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind, placebo control
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not described
Selective reporting (reporting bias)	Unclear risk	No protocol available
Other bias	Low risk	The study appears to be free of other sources of bias

Movahedi 2018

Study characteristics	
Methods	Participants were randomly allocated into two treatment groups
Participants	100 women with a functioning ovary and with a normal cavity of uterus were enrolled in the study. All participants were 25 to 38 years old and were eligible for infertility treatments. The analysis was confined to FET cycles which were not donor-related. All participants who had previously undergone intracytoplasmic sperm injection (ICSI) cycle with embryo cryopreservation and the transfer of their frozen-thawed embryos prospectively participated in this interventional study. We excluded patients above 39 years old, and those whose FSH was above 11, had endometriosis and hypothalamic amenorrhoea.
Interventions	In study group (A) 60 patients used oral contraceptive- LD (manufactured by Aburaihan Co., Tehran-Iran) the month before the embryo transfer, GnRH agonist suppression (buserelin: Superfact-manufactured by Aventis Pharma Deutschland) 0.5mg/day was administered from the day 21 of the cycle. The control group (B) was composed of 40 patients who did not use GnRH agonist. In both groups endometrial preparation was achieved by the use of estradiol valerate pill 2 mg (manufactured by Aburaihan Co. Tehran-Iran), which were started from the second day of the menstruation and were used every day, with initial dose of 2 mg/day and after 3 days increased to 4 mg/day and after 3 days again increased to 6 mg/day. Trans-vaginal ultrasound (TVU) was performed on the 13th day of estradiol treatment. Stimulation characteristics and protocol for the collection ICSI cycle were standard. If endometrial thickness (ET) was measured (EM) ≥ 7 mm, progesterone was added to the estradiol regimen and if the ET was < 7 mm, 2 mg estradiol valerate was added for four days before repeating TVU and starting progesterone (Cyclogest 400 mg pessaries manufactured by Actavis, Barnstaple, UK) was used vaginally, at a dose of 800 mg/day.
Outcomes	Clinical pregnancy (positive fetal heart on TVU)
Notes	IRCT201109224572N2 July 2008 to April 2009

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	We did not consider that blinding was likely to influence finding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	We did not consider that blinding was likely to influence finding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	It is not stated if there were missing outcome reports
Selective reporting (reporting bias)	Low risk	IRCT201109224572N2
Other bias	Low risk	No other risks of bias were found

Nekoo 2015

Study characteristics	
Methods	Computerised random allocation program: patients were randomly divided into two groups with different endometrial preparation regimen for frozen embryo transfer from January 2010 to February 2011
Participants	infertile patients (male factor) aged 20 to 37 years who had regular menstrual cycles and previously undergone IVF or ICSI with the same induction protocol with embryo cryopreservation
Interventions	In both groups, oral Estradiol Valerate was taken at 4 mgdailyfromday2today5,at6mgperdayfrom day 6 to the day of the pregnancy test. In day 13 of cycle, an ultrasound examination was performed. After ultrasound confirmation of endometrial thickness (≥8 mm) and if a periovulatory follicle was not present at the day 13 ultrasound, progesterone in cyclogest supp (400 mg /Bd) was added. The dose of estradiol would be increased to 8 mg per day if the endometrial thickness was less than 8mm. In group A (93 patients), diphereline (3.75 mg IM), as a depot GnRH agonist was administered in the mid-luteal phase (day 21). In the other group B (n = 83) commenced steroid supplementation without prior pituitary desensitisation.
Outcomes	Clinical pregnancy rate was 22.6% in the GnRH agonist group and 30.1% in the non-GnRH agonist group
Notes	Trial registration: no Funding: no Conflict of interest: Quote: "There is no conflict of interests among the authors" Study dates: from January 2010 to February 2011 Authors were contacted for missing information - no response

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "according to computerized random allocation program were randomly divided into two groups with different endometrial preparation regimen"
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	We did not consider that blinding was likely to influence finding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	We did not consider that blinding was likely to influence finding
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss of follow-up
Selective reporting (reporting bias)	Unclear risk	No protocol was found
Other bias	Low risk	The study appears to be free of other sources of bias

Ramos 2007

Study characteristics	
Methods	Single-centre trial. Trial design: parallel. Allocation: not stated. Blinding: no. Follow-up: until evolutive pregnancy. Live birth rate not included in outcomes.
Participants	N = 119. Women in treatment for frozen-thawed embryo transfer were randomised for this study and all of them used oral contraceptives pills the month before the embryo transfer. Average patients´ age was 35 years old, and the number of embryo transfer was 1.3. Endometrial thickness previous progesterone was 8 mm .
Interventions	119 patients in treatment for frozen-thawed transfer were randomised for this study and all of them used oral contraceptive pills the month before the embryo transfer, starting on day one of the cycle. 66 patients were randomised to the group A, which used GnRH agonist suppression (tryptorelin 3.75 mg depot, 1 ampoule IM) the day of contraceptive pill number 16. The group B was composed of 53 patients randomised who did not use GnRH agonist. In both groups endometrial preparation was achieved by the use of estradiol transdermical patches, which were started from the second day of the menstruation and used every other day, with an initial dose of 100 mg/d and after two days increased to 200 mg/d. Progesterone was used vaginally, at a dose of 800 mg/d, starting after at least 11 days of transdermical estradiol, on the day 0 of embryo development previous ultrasound examination and serum estradiol and progesterone levels
Outcomes	Pregnancy rate (Group A tryptorelin, estradiol and+ progesterone versus group B estradiol plus progesterone alone):25.6% versus 24.3%. Ongoing pregnancy rate: 14.1%versus 17.1%, Miscarriage rate: 11.5% versus 7.1%
Notes	GnRH agonist suppression (tryptorelin 3.75 mg depot, 1 ampoule IM) was given on the day of contraceptive pill number 16 (in the previous cycle). In both groups endometrial preparation was performed with estradiol transdermic patches, which were started from the second day of menstruation and used every other day, with an initial dose of 100 mg/day and after two days increased to 200 mg/day. Progesterone was used vaginally, at a dose of 800 mg/day, started at least 11 days after transdermic estradiol was started. Trial registration: no Funding: no Conflict of interest: no Study dates: not stated Authors were contacted for missing information - no response

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	It is not described how randomisation was performed
Allocation concealment (selection bias)	Unclear risk	It is not described how allocation was performed

Ramos 2007 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	We did not consider that blinding was likely to influence finding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	We did not consider that blinding was likely to influence findings
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information to evaluate this
Selective reporting (reporting bias)	Unclear risk	Protocol not available
Other bias	Low risk	The study appears to be free of other sources of bias

Remohi 1994

Study characteristics	
Methods	Single-centre trial. Trial design: parallel. Allocation: not stated. Blinding: not stated. Follow-up: until pregnancy. Therefore live birth rate not included in outcomes.
Participants	N = 69. Oocyte recipients mean age was 37.1 years for daily leuprolide acetate group and 37.9 years for the no-treatment group. Donor mean age were 31.4 years and 31.1 years, respectively. Cause of infertility: poor responders 85%; premature ovarian failure 15%.
Interventions	One group of recipients was desensitised with daily subcutaneous administration of 1 mg leuprolide acetate and the other group was not desensitised.
Outcomes	Pregnancy rate (leuprolide daily versus no treatment): 54.5% versus 58.3%.
Notes	Trial registration: no Funding: no Conflict of interest: no Study dates: not stated Authors were contacted for missing information - no response

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	It was not stated how performed
Allocation concealment (selection bias)	Unclear risk	It was not stated how performed

Remohi 1994 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	We did not consider that blinding was likely to influence findings
Blinding of outcome assessment (detection bias) All outcomes	Low risk	We did not consider that blinding was likely to influence findings
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No data available
Selective reporting (reporting bias)	Unclear risk	No abstract available
Other bias	Low risk	The study appears to be free of other sources of bias

Samsami 2018

Study characteristics	
Methods	A total of 237 women were randomly allocated in two groups (119 and 118 cases in groups A and B, respectively).
Participants	All individuals with established medical diagnosis of infertility who referred to Shahid Faghighi hospital, affiliated to Shiraz University of Medical Sciences, Shiraz, Iran for IVF from November 2014 to November 2015 were invited to participate in the study. Inclusion criteria for this study were as follows: -history of infertility - age 20-39 years - couples undergoing ART with their own gamete - couples having frozen embryo available for transfer Participants with the following criteria were excluded from the study: - high-grade endometriosis - existence of myoma or adhesion in uterus - BMI more than 29 or less than 18 kg/m2 - oocyte donation cycles
Interventions	In group A, 0.5 mg of Buserelin acetate (a GnRH agonist) (Suprefact, Hoechst AG, Germany) was injected SC daily starting on the 21st day of menstrual cycle (mid-luteal phase). On the first day of menstruation, GnRH agonist dose was reduced to 0.3 mg/day SC. Participants in group B did not receive GnRH agonist for pituitary down-regulation. In both groups, Estradiol Valerate (Abureyhan, Iran) was administered orally, starting on the second day of the target cycle with a dosage of 6 mg/day for endometrial preparation.
Outcomes	Ongoing pregnancy until 12th week of gestation was achieved in 18 cases in group A and 16 patients in group B

Samsami 2018 *(Continued)*

Notes	Thawed embryos were transferred on the 3rd day following progesterone administration Trial registration: IRCT2017052834184N1 Funding: Shiraz University of Medical Sciences (grant No 5665) Conflict of interest: authors declared no conflict of interests Study dates: from November 2014 to November 2015 Authors were contacted for missing information - no response

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computerised randomisation codes
Allocation concealment (selection bias)	Unclear risk	No data about allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	We did not consider that blinding was likely to influence findings
Blinding of outcome assessment (detection bias) All outcomes	Low risk	We did not consider that blinding was likely to influence findings
Incomplete outcome data (attrition bias) All outcomes	High risk	37 out of the 237 randomised women were not analysed
Selective reporting (reporting bias)	Low risk	Registration ID in RCT: IRCT2017052834184N1
Other bias	Low risk	The study appears to be free of other sources of bias

Samsami 2019

Study characteristics

Methods	Randomisation table
Participants	Women aged 18 to 42 years having frozen embryos, normal uterine cavity, normal endometrium without any endometrial polyp or sub-mucosal myoma (according to normal hysterosalpingography, saline infusion sonography or 2 hysteroscopy), and BMI < 35 kg/m^2. The exclusion criteria were other maternal medical disease and hydrosalpinx.
Interventions	167 women, 82 in the letrozole group and 87 in the HR group. Stimulated: participants were prescribed 5 mg letrozole/day from the third day to the seventh day of the menstrual cycle. Follicular development was monitored by vaginal ultrasonography starting on the 10th day of the menstrual cycle; if the follicular diameter was ≥ 17 mm and the endometrial thickness reached 7 mm to 9 mm, they were given 10,000 units of HCG, and 36 to 48 hours after that, they were progesterone ampoule 100 mg was given IM/day.

Samsami 2019 *(Continued)*

	Programmed: the participants were prescribed oral estradiol valerate (2 mg three times a day) starting on the second to the third day of menstrual cycle, and on the 10th day, the endometrial thickness was monitored by vaginal ultrasonography. If the endometrial thickness was 7 mm to 9 mm and three-line pattern, oestrogen was continued and progesterone therapy was initiated 100 mg IM/day
Outcomes	Ultrasonography was performed 28 to 30 days after the embryo transfer, having a fetal heart beat was defined as a clinical pregnancy
Notes	For a period of 12 months, commencing on January 2018

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation table
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	We did not consider that blinding was likely to influence finding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	We did not consider that blinding was likely to influence finding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Lost of follow-up < 10%
Selective reporting (reporting bias)	Low risk	IRCT: 20190327043121N1
Other bias	Low risk	No other bias reported

Sheikhi 2018

Study characteristics

Methods	The randomisation was done at the start of the cycle us-ing sequential numbering based on a computer-generated list that had been prepared at the Statistics Center of the Babol University of Medical Science and sent to us. Then, the participants were randomly assigned to either modified natural cycle with HCG (n = 31), mildly hormonally stimulated cycle (n = 30) or artificial regimen (n = 62), in a ratio 1:1:2. The participant and the infertility expert were not blinded for treatment allocation.
Participants	A total of 131 patients submitted to vitrified thawed blastocyst transfer in our IVF laboratory were invited from March 2015 to January 2016. Women undergoing vitrification thawed blastocyst transfer (VTBT) were eligible for the study when they were normo-ovulatory women, between 20 to 40 years of age, with "19<BMI <30." The exclusion criteria included women with PCOS, basal FSH>10 IU/mL and basal E2 <70 pg/mL, those with untreated thyroid disorders, severe endometriosis, recurrent implantation failure, uterine pathology, recurrent abortion, repeated implantation failure, smokers, athletes and patients who had used

Sheikhi 2018 *(Continued)*

	any medication in the two previous months that could interfere with the normal function of the hypothalamic-pituitary-gonadal axis.
Interventions	We used the natural cycle with HCG for the patients in this group; no medication was administered during the endometrial preparation. The follicles were monitored by TVS until the dominant follicles reached a diameter of 18 mm to 20 mm and endometrium thickness > 8 mm. Then, 10,000 IU of human chorionic gonadotropin (CG, Daroupakhsh, Iran) was administered for ovulation. The mild hormonally-stimulated group with clomiphene citrate (Clomid, Iran Hormone Company) was administered 50 mg daily from day 3 of the menstrual cycle for 5 days. If during TVS a follicle 18 mm to 20 mm was visible, ovulation was deemed to have occurred. "Then, 10,000 IU of urinary" The mild hormonally-stimulated group with clomiphene citrate (Clomid, Iran Hormone Company) was administered 50 mg daily from day 3 of the menstrual cycle for 5 days. If during TVS a follicle 18 mm to 20 mm was visible, ovulation was deemed to have occurred. Then, 10, 000 IU of urinary HCG was administered and the blastocyst were transferred 36 to 38 hours after HCG. The Artificial cycles began on the third day of the menstrual cycle or progesterone withdrawal. The dose of oral estradiol valerate (E2) (Aburaihan Pharmaceutical Co., Tehran, Iran) was 2mg bid (4mg/day). A higher initial dose of estradiol (6mg) was administered if the patient showed inadequate endometrial thickness in a previous cycle. TVS was carried out on day 10. If the endometrial thickness reached 8 mm and further, 50mg progesterone was given IM for 3 days (Aburaihan Pharmaceutical Co., Tehran, Iran) and estradiol was continued as well, then the blastocysts were transferred on the fourth day of progesterone administration. If the endometrial thickness was 8mm or less on day 10, the dose of estradiol valerate was increased to 4mg twice/day and the blastocyst were transferred 4-5 days following initiation of progesterone administration if the signs of ovulation were observed upon TVS. If the endometrial thickness did not reach 8 mm up to day 20, or the ovulation was not confirmed, the cycle was cancelled
Outcomes	A clinical pregnancy was defined as the visualisation of a gestational sac with fetal heart activity on TVS in week five of gestation.
Notes	IRCT: 201408021760N36

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Sequential numbering based on a computer-generated list that had been prepared at the Statistics Center of the Babol University of Medical Science
Allocation concealment (selection bias)	High risk	Quote: "The participant and the infertility expert were not blinded for treatment allocation."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	We did not consider that blinding was likely to influence finding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	We did not consider that blinding was likely to influence finding
Incomplete outcome data (attrition bias) All outcomes	Low risk	MIssing outcomes less than 10%
Selective reporting (reporting bias)	Low risk	IRCT: 201408021760N36

Sheikhi 2018 *(Continued)*

Other bias	Low risk	No other risk of bias were found

Tehraninejad 2018

Study characteristics	
Methods	Prospective, randomised, single-blind clinical trial. The study was carried out in Reproductive Health Research Center, Tehran University of Medical Sciences between September 2015 and November 2016.
Participants	One hundred volunteers for FET cycle (due to premature ovarian failure, ovarian hyper stimulation syndrome (OHSS) or other reasons)
Interventions	All participants received GnRH agonist (Decapeptyl, Ferring, Switzerland) 0.1 mg subcutaneously from the 21st day of the cycle and it was continued for at least 14 days. In the first day of menstrual cycle suppression of ovary have been confirmed by ultrasonography. In group I estradiol valerate tablet (8 mg/day) (Progynova, Schering, Berlin, Germany) and in group II topical estradiol gel (6 mg/day) (Oestrogel, 17B estradiol 0.06% gel, Besins, France) was started from the first day of menstruation. One week after the start of estradiol, ultrasonography was performed to estimate endometrial thickness and repeated if necessary. On day 13 of menstrual cycle, the second ultrasound was performed and the thickness of the endometrium was estimated. If endometrial thickness was more than 8 mm, based on the embryonic age, progesterone (Cyclogest, 400 mg, Cox Pharmaceuticals, Barnstaple, UK,) was given for four to six days before embryo transfer.
Outcomes	24% of participants in group II and 16% of women in group I had a clinical pregnancy
Notes	Trial registration: IRCT2016092429951N1 Funding: no Conflict of interest: the authors report no conflicts of interest Study dates: between September 2015 and November 2016

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation list
Allocation concealment (selection bias)	High risk	Participants have been allocated by a nurse
Blinding of participants and personnel (performance bias) All outcomes	Low risk	We did not consider that blinding was likely to influence findings
Blinding of outcome assessment (detection bias) All outcomes	Low risk	We did not consider that blinding was likely to influence findings
Incomplete outcome data (attrition bias) All outcomes	Low risk	There was no loss of follow-up

Tehraninejad 2018 *(Continued)*

Selective reporting (reporting bias)	Low risk	Registration ID in IRCT: IRCT2016092429951N1
Other bias	Low risk	The study appears to be free of other sources of bias

Tocino 2007

Study characteristics	
Methods	Singl- centre trial. Trial design: parallel. Allocation method: not stated. Blinding: no Follow-up: until pregnancy. Therefore live birth rate not included in outcomes.
Participants	Forty-eight (N = 48) recipients for oocyte donation, were randomised into two groups: Group A (N = 23) used daily GnRH agonist suppression (Leuprolide Acetate 0.1 mL/day) and Group B (N = 23) used a GnRH agonist depot (tryptoreline 3.75 mg/IM)
Interventions	Forty-eight (N = 48) recipients for oocyte donation, received oral contraceptive pills the month before the embryo transfer, and were randomised into two groups: Group A (N = 23) used daily GnRH agonist suppression (Leuprolide Acetate 0.1 mL/day) starting 5 days before ending the contraceptive pill. Group B (N = 23) used a GnRH agonist depot (tryptoreline, 3.75 mg/IM) 5 days before ending the contraceptive pill. In both groups the endometrial preparation was achieved by using estradiol transdermic patches, started from the second day of the menstruation and increasing the doses
Outcomes	Pregnancy rate (daily leuprolide acetate versus depot tryptoreline): 65% versus 50%, Implantation rate: 48.8% versus 36.1%, Abortion rate (6.7% versus 40%)
Notes	In both groups, the average patient age was 38 years old and the mean number of embryos transferred was 1.8. the endometrial thickness and estradiol levels previous to donation were similar in both groups. Trial registration: no Funding: no Conflict of interest: no Study dates: between September 2006 and March 2007 Authors were contacted for missing information - no response

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No description of how allocation and randomisation was performed
Allocation concealment (selection bias)	Unclear risk	No description of how allocation and randomisation was performed

Tocino 2007 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	We did not consider that blinding was likely to influence finding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	We did not consider that blinding was likely to influence findings
Incomplete outcome data (attrition bias) All outcomes	Low risk	Less than 10% of follow-up
Selective reporting (reporting bias)	Unclear risk	No protocol available
Other bias	Low risk	The study appears to be free of other sources of bias

Vidal 2009

Study characteristics	
Methods	A prospective, blinded, RCT was carried out in our centre (EudraCT: 2007-000212-89) from January, 2007 to September, 2009
Participants	The population randomised was 560 patients. The inclusion criteria were as follows: recipients with preserved ovarian function under 45 years old, BMI < 28 kg/m2, 1st or 2nd egg donation cycle, 1 to 2 good embryos transferred. Exclusion criteria were uterine diseases (polyps, myomas, Müllerian defects, adenomyosis), severe male factor (motile sperm < 5mill.), abnormal FISH spermatozoa, thrombophilia and recurrent pregnancy losses.
Interventions	To compare a new approach for endometrial priming with the 7 day dosage of GnRH antagonist (cetrorelix 0.25 mg) in an oocyte donation programme with the conventional single dose GnRH agonist (tryptorelin, 3.75 IM) on day 21st of the menstrual cycle
Outcomes	Ongoing pregnancy rate (OPR) was the primary endpoint. Implantation rate (IR), ectopic, and miscarriage rates were the secondary outcome measures. Clinical pregnancy rate in antagonists group: 68.1% and in agonist group: 56.8 %
Notes	Trial registration: no Funding: no Conflict of interest: no Study dates: from January, 2007 to September, 2009 Authors were contacted for missing information - no response

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not stated

Vidal 2009 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	We did not consider that blinding was likely to influence finding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	We did not consider that blinding was likely to influence findings
Incomplete outcome data (attrition bias) All outcomes	High risk	Population randomised: 560. From the total number of patients randomly allocated to each group, 473 underwent embryo transfer, and received 7 days GnRH antagonists (group A, 232 patients) or a single IM injection of 3.75 mg tryptorelin (group B, 241 patients) or A total of 87 dropped out of the study due to insufficient endometrial preparation or to transfer cancellation.
Selective reporting (reporting bias)	Low risk	EudraCT: 2007-000212-89
Other bias	Low risk	The study appears to be free of other sources of bias

Wright 2006

Study characteristics	
Methods	Single-centre trial. Trial design: parallel. Allocation: not stated. Blinding: not stated. Follow-up: until pregnancy. Therefore live birth rate not included in outcomes.
Participants	N=199. Women's mean age at time of oocyte retrieval was not reported. Their mean age at time of embryo transfer was 34 years for both groups. Cause of infertility: not stated.
Interventions	Stimulated women received recombinant FSH injections 150 IU on days 6, 8 and 10 of the menstrual cycle, and continued until endometrium was thicker than 7 mm or follicles were bigger than 16 mm to 20 mm. Women who had artificial cycles received 17-beta-estradiol 4 mg per day until endometrium over 7 mm.
Outcomes	Pregnancy rate (FSH versus estradiol): 12.1% versus 11%.
Notes	Both groups received progesterone 300 mg in vaginal suppositories. Trial registration: not stated Funding: not stated Conflict of interest: not stated Study dates: not stated Authors were contacted for missing information - no response
Risk of bias	

Wright 2006 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method used was not stated
Allocation concealment (selection bias)	Unclear risk	Method used was not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	We did not consider that blinding was likely to influence finding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	We did not consider that blinding was likely to influence findings
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were no losses to follow-up (<1 0%)
Selective reporting (reporting bias)	Unclear risk	No protocol available
Other bias	Low risk	The study appears to be free of other sources of bias

ART: assisted reproductive technology; **β-HCG:** beta human chorionic gonadotropin; **BMI:** body mass index; **FET:** frozen-thawed embryo transfer; **FSH:** follicle stimulating hormone; **GnRH:** gonadotropin-releasing hormone; **HMG:** human chorionic gonadotropin; **HRT:** hormone replacement therapy; **IVF:** in vitro fertilisation; **ICSI:** intracytoplasmic sperm injection; **IM:** intramuscular; **IU:** international unit; **IVF:** in vitro fertilisation; **RCT:** randomised controlled trial; **RIF:** recurrent implantation failure; **SC:** subcutaneous; **TVU:** trans-vaginal ultrasound.

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

Study	Reason for exclusion
Arun Muthuvel 2016	Wrong intervention: the study is about luteal phase support
Bernabeu 2006	Wrong intervention: indomethacin was not used for endometrial preparation; it was used just before embryo transfer.
Bjuresten 2011	Wrong intervention:the study is about luteal phase support
Boostanfar 2016	Wrong intervention: participants did not use one of our specified treatments for endometrial preparation: Women were randomised to a single injection of 150 µg of corifollitropin alfa or daily 300 IU of recombinant follicle-stimulating hormone for the first 7 days of controlled ovarian stimulation (COS) in a gonadotropin-releasing hormone (GnRH) antagonist protocol.
Caligara 2003	Wrong intervention: the study is about luteal phase support
Cambiaghi 2013	Wrong intervention: the study is not about endometrial preparation.
Check 1998	Wrong study design:the study was not a randomised controlled trial.
Check 2004	Wrong intervention: the study compares different kinds of stimulation (sildenafil versus oestradiol)

Study	Reason for exclusion
Davar 2015	Wrong intervention: the study evaluated the effects of single dose GnRH agonist as luteal support
Davar 2016a	Wrong population: participants did not meet our criteria: women with a history of thin endometrium
Davari-Tanha 2016	Wrong population: participants did not meet our criteria: women with a history of recurrent implantation failure
Eftekhar 2013	Wrong intervention: the study is about luteal phase support
Feliciani 2004	Wrong intervention: doses used for vaginal progesterone were below the standard doses
Gibbons 1998	Wrong intervention: the study is about luteal phase support
Gogce 2015	Wrong intervention: participants did not use one of our specified treatments for endometrial preparation: GnRH agonists in the luteal phase of Artificial Cycle Frozen-Thawed Embryo Transfers
Hershko 2016	Wrong intervention: the study is about luteal phase support
Huang 2017	Wrong population: participants did not meet our criteria: women with history of recurrent implantation failure
Krasnow 1996	The study does not evaluate our primary or secondary outcomes: the outcomes were endometrial histology and beta-3-integrin expression
Lan 2008	Wrong intervention: the study is about luteal phase support
Lewin 2001	The study does not evaluate our primary or secondary outcomes: histological outcome
Li 2014	Wrong intervention: in the intervention group (letrozole) more than one intervention is applied (i.e. ovulation triggering with human chorionic gonadotropin or with tryptorelin
Lightman 1999	Wrong intervention: the study concerns luteal phase support
Llacer 2017	Wrong intervention: the study concerns luteal phase support
Moon 2004	Wrong intervention: piroxicam was not used for endometrial preparation, it was used just before embryo transfer.
Nardo 2006	Wrong study design: It is not a randomised controlled trial.
Neuspiller 1998	Wrong study design: the study is a quasi-randomised study
Prapas 2009a	Wrong intervention: this study evaluates the use of hCG, which was not stated in our protocol
Prapas 2009b	Wrong intervention: no comparison included in our protocol was evaluated
Sanchez 2009	Wrong intervention: this study evaluated when to start the oestradiol replacement, which is not an intervention that was stated in our protocol.
Sathanandan 1991	Wrong study design: randomisation was not adequate.
Shiotani 2006	Wrong intervention: this study evaluates the use of hCG, which was not stated in our protocol.

Study	Reason for exclusion
Simon 1998	There was a co-intervention that was not similar in the two arms, which does not make it possible to analyse if the observed result was caused by the intervention or by the co-intervention.
Stadtmauer 2009	Wrong study design:this is not a randomised controlled trial because randomisation was not done for embryo transfer. It was done for endometrial biopsy and just some of them (less than 10) decided to have a transfer.
Taskin 2002	The study does not evaluate our primary or secondary outcomes: excluded because the outcome was not clinical (but histological).
Tesarik 2003	Wrong intervention: this study evaluates the use of hCG, which was not stated in our protocol
Weckstein 1997	Wrong population: women with a history of thin endometrium
Xu 2015	Wrong population: women with a history of thin endometrium
Zegers-Hochschild 2000	Wrong intervention: the study is about luteal phase support
Zolghadri 2014	Wrong population: women with a history of thin endometrium

HCG: human chorionic gonadotropin;**IU:** international unit.

Characteristics of studies awaiting classification *[ordered by study ID]*

Masrour 2018

Methods	After initial screening and fulfilment of inclusion and exclusion criteria, research participants were randomised, using a table of random numbers, to one of two groups: natural FET (n = 100) and HRT FET (n = 100). All participants intending to commence the intervention and meeting the study criteria were invited to the fertility unit between days 1 and 3 of their monthly cycle for baseline scan and study enrolment. At the first visit those who wished to take part, completed written consent form and were randomly assigned into mentioned groups.
Participants	Women aged 19 to 39 years, planning an FET cycle at the Infertility Clinic of Shahid Akbar Abadi hospital were invited to take part in this trial. They were eligible to participate if they were assisted reproductive techniques such as IVF and ICSI with frozen embryo transfer cycles due to male factor, had a regular menstrual cycle, serum levels of follicle stimulating hormone (FSH) less than 10 IU/dL and a normal serum prolactin level. Women were excluded from participating in the trial if they were allergic to estradiol or progesterone, had uterine anomaly, polycystic ovary syndrome (PCOS), endometriosis stage III/IV, preimplantation genetic diagnosis cycles, tubal factor and history of receiving donated oocytes.
Interventions	The women in the hormonal group were administered 4 mg to 6 mg of oestrogen in the form of oral estradiol valerate (Progynova®; Schering, Madrid, Spain) on the third day of their cycles as the intervention after a transvaginal ultrasound. A second transvaginal ultrasound was performed after 10 to 12 days of oestrogen treatment. If endometrial thickness was at least 8 mm, embryo transfer (Only blastocyst embryos) were planned. Natural micronised progesterone (Utrogestan®; Seid, Madrid, Spain) was vaginally administered at a dose of 400 mg/12 hours for 3 or 5 complete days before embryo transfer, depending on the cleavage stage of embryos (embryo age +1 day). Progesterone supplementation continued if pregnancy occurred until 12 weeks of pregnancy.
Outcomes	Chemical pregnancy (based on hormone levels of β-HCG) was considered as the primary outcome and clinical pregnancy (existing fetal heartbeat) was considered as the secondary outcome.
Notes	IRCT code: IRCT2017081335670N1

Page 2005

Methods	Patients randomised to the stimulated protocol began rec-FSH every other day beginning on day 4 of their menstrual cycle. Ultrasound and hormone assays were performed beginning on day 9 to 10. Rec-hCG was administered when the endometrial thickness was ≥ 7 mm and a follicle reached 16 mm to 20 mm. Vaginal P was begun the following day. Patients randomised to the artificial cycle began taking oral 17-beta estradiol (E_2) 2 mg twice per day beginning on day 1 of their menstrual cycle. Ultrasound and hormone assays were begun on day 9 to 10; if the endometrial thickness was < 7 mm on day 9 to 10, patients were switched to vaginal E_2 2 mg once per day. Patients began vaginal micronised P once the endometrial thickness was > 7 mm.
Participants	165 women with functional ovaries undergoing 199 FET cycles were randomised
Interventions	Patients randomised to the stimulated protocol began rec-FSH every other day beginning on day 4 of their menstrual cycle. Ultrasound and hormone assays were performed beginning on day 9 to 10. Rec-hCG was administered when the endometrial thickness was ≥ 7 mm and a follicle reached 16 mm to 20 mm. Vaginal P was begun the following day. Patients randomised to the artificial cycle began taking oral 17-beta estradiol (E_2) 2 mg twice per day beginning on day 1 of their menstrual cycle. Ultrasound and hormone assays were begun on day 9 to 10; if the endometrial thickness was < 7 mm on day 9 to 10, patients were switched to vaginal E_2 2 mg once per day. Patients began vaginal micronised P once the endometrial thickness was > 7 mm.
Outcomes	Endometrial thickness
Notes	

Tur-Kaspa 2010

Methods	Patients undergoing FET or ED cycles were equally randomised for down regulation with daily antagonist injection (Cetrotide, EMD Serono, Inc.) from day 9 to 11 of oestrogen treatment or with mid-luteal daily agonist injection (Lupron, Tap Pharmaceuticals).
Participants	Recipients for frozen embryo transfer (FET) and egg donation (ED) cycles
Interventions	Daily antagonist injection (Cetrotide, EMD Serono, Inc.) from day 9 to 11 of oestrogen treatment or with mid-luteal daily agonist injection (Lupron, Tap Pharmaceuticals)
Outcomes	The primary end-points for this interim analysis were embryo implantation and clinical pregnancy rates. Secondary end-points were patient satisfaction and ongoing pregnancy/delivery rate.
Notes	www.ClinicalTrials.gov (NCT00460642)

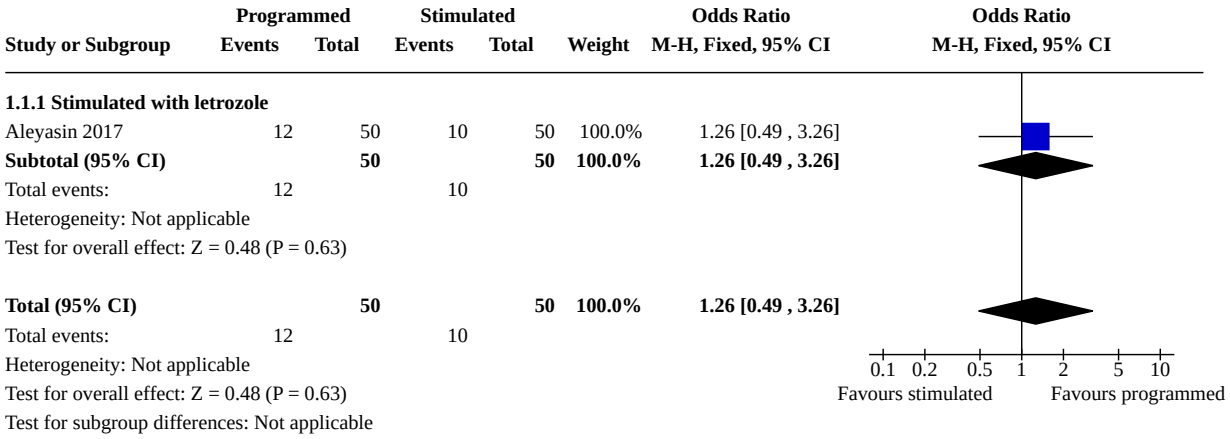
Outcomes that were reported only 'per cycle' and not per randomised woman, in which more than one cycle was performed on each randomised woman. No reply from the authors yet.
β-HCG: beta human chorionic gonadotropin; BMI: body mass index; **FET:** frozen-thawed embryo transfer; FSH: follicle stimulating hormone; **HRT:** hormone replacement therapy; **IVF:** in vitro fertilisation; **ICSI:** intracytoplasmic sperm injection; **IM:** intramuscular; **IU:** international unit; **IVF:** in vitro fertilisation.

DATA AND ANALYSES

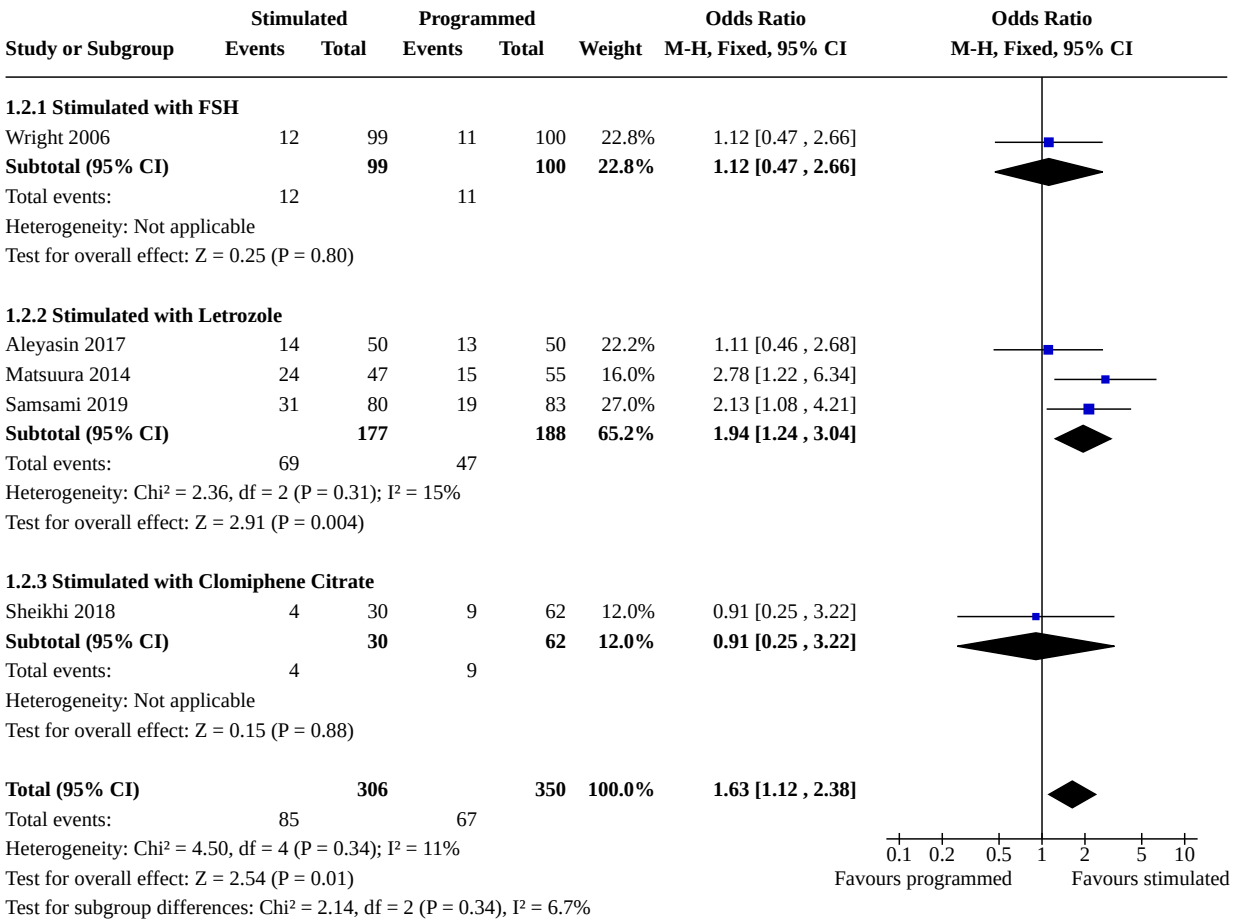
Comparison 1. Programmed cycle versus stimulated cycle

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Live birth rate	1	100	Odds Ratio (M-H, Fixed, 95% CI)	1.26 [0.49, 3.26]
1.1.1 Stimulated with letrozole	1	100	Odds Ratio (M-H, Fixed, 95% CI)	1.26 [0.49, 3.26]
1.2 Clinical pregnancy rate	5	656	Odds Ratio (M-H, Fixed, 95% CI)	1.63 [1.12, 2.38]
1.2.1 Stimulated with FSH	1	199	Odds Ratio (M-H, Fixed, 95% CI)	1.12 [0.47, 2.66]
1.2.2 Stimulated with Letrozole	3	365	Odds Ratio (M-H, Fixed, 95% CI)	1.94 [1.24, 3.04]
1.2.3 Stimulated with Clomiphene Citrate	1	92	Odds Ratio (M-H, Fixed, 95% CI)	0.91 [0.25, 3.22]
1.3 Miscarriage rate	3	355	Odds Ratio (M-H, Fixed, 95% CI)	0.79 [0.36, 1.71]
1.3.1 Stimulated with Letrozole	2	263	Odds Ratio (M-H, Fixed, 95% CI)	0.93 [0.41, 2.13]
1.3.2 Stimulated with Clomiphene Citrate	1	92	Odds Ratio (M-H, Fixed, 95% CI)	0.21 [0.01, 4.09]
1.4 Endometrial thickness (mm)	3	454	Mean Difference (IV, Fixed, 95% CI)	-0.11 [-0.25, 0.03]
1.4.1 Stimulated with FSH	1	199	Mean Difference (IV, Fixed, 95% CI)	0.00 [-0.29, 0.29]
1.4.2 Stimulated with Letrozole	1	163	Mean Difference (IV, Fixed, 95% CI)	-0.06 [-0.22, 0.10]
1.4.3 Stimulated with Clomiphene Citrate	1	92	Mean Difference (IV, Fixed, 95% CI)	-1.04 [-1.59, -0.49]

Analysis 1.1. Comparison 1: Programmed cycle versus stimulated cycle, Outcome 1: Live birth rate

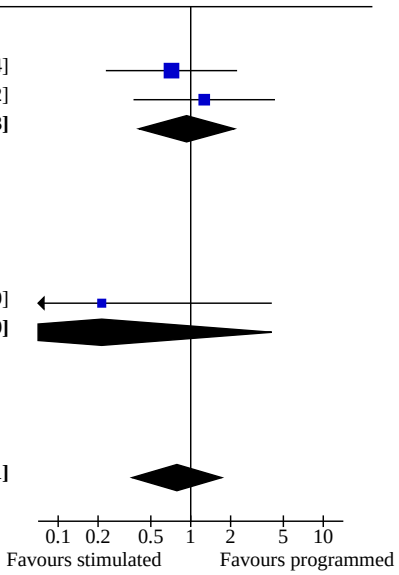


Analysis 1.2. Comparison 1: Programmed cycle versus stimulated cycle, Outcome 2: Clinical pregnancy rate



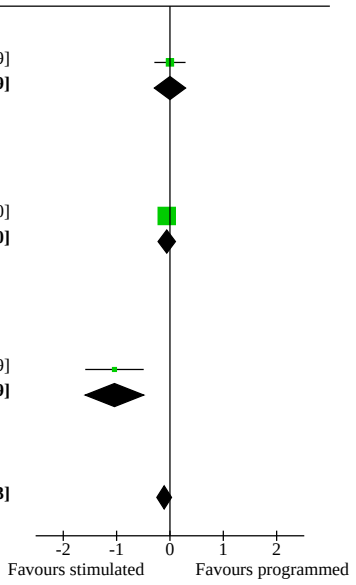
Analysis 1.3. Comparison 1: Programmed cycle versus stimulated cycle, Outcome 3: Miscarriage rate

Study or Subgroup	Stimulated Events	Stimulated Total	Programmed Events	Programmed Total	Weight	Odds Ratio M-H, Fixed, 95% CI
1.3.1 Stimulated with Letrozole						
Aleyasin 2017	6	50	8	50	48.6%	0.72 [0.23 , 2.24]
Samsami 2019	6	80	5	83	31.3%	1.26 [0.37 , 4.32]
Subtotal (95% CI)		**130**		**133**	**79.9%**	**0.93 [0.41 , 2.13]**
Total events:	12		13			
Heterogeneity: Chi² = 0.44, df = 1 (P = 0.51); I² = 0%						
Test for overall effect: Z = 0.17 (P = 0.87)						
1.3.2 Stimulated with Clomiphene Citrate						
Sheikhi 2018	0	30	4	62	20.1%	0.21 [0.01 , 4.09]
Subtotal (95% CI)		**30**		**62**	**20.1%**	**0.21 [0.01 , 4.09]**
Total events:	0		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.03 (P = 0.31)						
Total (95% CI)		**160**		**195**	**100.0%**	**0.79 [0.36 , 1.71]**
Total events:	12		17			
Heterogeneity: Chi² = 1.35, df = 2 (P = 0.51); I² = 0%						
Test for overall effect: Z = 0.61 (P = 0.54)						
Test for subgroup differences: Chi² = 0.89, df = 1 (P = 0.35), I² = 0%						



Analysis 1.4. Comparison 1: Programmed cycle versus stimulated cycle, Outcome 4: Endometrial thickness (mm)

Study or Subgroup	Stimulated Mean	Stimulated SD	Stimulated Total	Programmed Mean	Programmed SD	Programmed Total	Weight	Mean Difference IV, Fixed, 95% CI
1.4.1 Stimulated with FSH								
Wright 2006	8.7	1	100	8.7	1.1	99	22.1%	0.00 [-0.29 , 0.29]
Subtotal (95% CI)			**100**			**99**	**22.1%**	**0.00 [-0.29 , 0.29]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.00 (P = 1.00)								
1.4.2 Stimulated with Letrozole								
Samsami 2019	8.2	0.58	80	8.26	0.47	83	71.6%	-0.06 [-0.22 , 0.10]
Subtotal (95% CI)			**80**			**83**	**71.6%**	**-0.06 [-0.22 , 0.10]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.72 (P = 0.47)								
1.4.3 Stimulated with Clomiphene Citrate								
Sheikhi 2018	7.3	1.4	30	8.34	0.89	62	6.3%	-1.04 [-1.59 , -0.49]
Subtotal (95% CI)			**30**			**62**	**6.3%**	**-1.04 [-1.59 , -0.49]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.72 (P = 0.0002)								
Total (95% CI)			**210**			**244**	**100.0%**	**-0.11 [-0.25 , 0.03]**
Heterogeneity: Chi² = 11.98, df = 2 (P = 0.003); I² = 83%								
Test for overall effect: Z = 1.55 (P = 0.12)								
Test for subgroup differences: Chi² = 11.98, df = 2 (P = 0.003), I² = 83.3%								



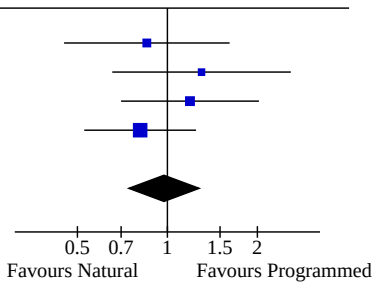
Comparison 2. Programmed cycle versus natural cycle

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Live birth rate	4	1285	Odds Ratio (M-H, Fixed, 95% CI)	0.97 [0.74, 1.28]
2.2 Clinical pregnancy rate	5	1249	Odds Ratio (M-H, Fixed, 95% CI)	0.79 [0.62, 1.01]
2.3 Miscarriage rate	3	485	Odds Ratio (M-H, Fixed, 95% CI)	0.64 [0.25, 1.63]
2.4 Cycle cancellation rate	1	734	Odds Ratio (M-H, Fixed, 95% CI)	0.60 [0.44, 0.82]
2.5 Endometrial thickness (mm)	3	485	Mean Difference (IV, Random, 95% CI)	0.22 [-0.25, 0.69]

Analysis 2.1. Comparison 2: Programmed cycle versus natural cycle, Outcome 1: Live birth rate

Study or Subgroup	Programmed Events	Programmed Total	Natural Events	Natural Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Agha-Hosseini 2018	27	85	30	85	19.3%	0.85 [0.45 , 1.61]
Child 2013	25	79	21	80	13.4%	1.30 [0.65 , 2.59]
Greco 2016	50	109	47	113	23.5%	1.19 [0.70 , 2.02]
Groenewoud 2016	41	340	57	394	43.7%	0.81 [0.53 , 1.25]
Total (95% CI)		**613**		**672**	**100.0%**	**0.97 [0.74 , 1.28]**
Total events:	143		155			

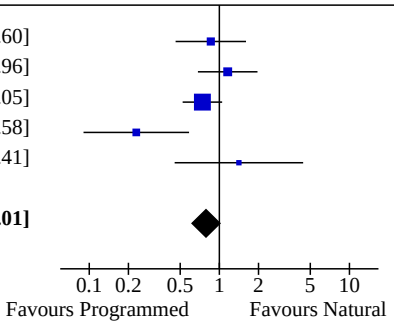
Heterogeneity: Chi² = 2.09, df = 3 (P = 0.55); I² = 0%
Test for overall effect: Z = 0.19 (P = 0.85)
Test for subgroup differences: Not applicable



Analysis 2.2. Comparison 2: Programmed cycle versus natural cycle, Outcome 2: Clinical pregnancy rate

Study or Subgroup	Natural Events	Natural Total	Programmed Events	Programmed Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Agha-Hosseini 2018	30	85	33	85	14.9%	0.86 [0.46 , 1.60]
Greco 2016	59	109	57	113	17.9%	1.16 [0.68 , 1.96]
Groenewoud 2016	75	340	94	340	51.0%	0.74 [0.52 , 1.05]
Lee 2008	18	45	29	39	13.0%	0.23 [0.09 , 0.58]
Sheikhi 2018	6	31	9	62	3.4%	1.41 [0.45 , 4.41]
Total (95% CI)		**610**		**639**	**100.0%**	**0.79 [0.62 , 1.01]**
Total events:	188		222			

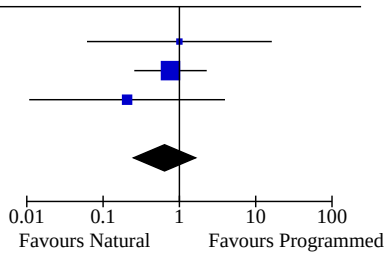
Heterogeneity: Chi² = 9.95, df = 4 (P = 0.04); I² = 60%
Test for overall effect: Z = 1.89 (P = 0.06)
Test for subgroup differences: Not applicable



Analysis 2.3. Comparison 2: Programmed cycle versus natural cycle, Outcome 3: Miscarriage rate

Study or Subgroup	Natural Events	Natural Total	Programmed Events	Programmed Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Agha-Hosseini 2018	1	85	1	85	8.7%	1.00 [0.06 , 16.25]
Greco 2016	6	109	8	113	65.1%	0.76 [0.26 , 2.28]
Sheikhi 2018	0	31	4	62	26.2%	0.21 [0.01 , 3.96]
Total (95% CI)		**225**		**260**	**100.0%**	**0.64 [0.25 , 1.63]**
Total events:	7		13			

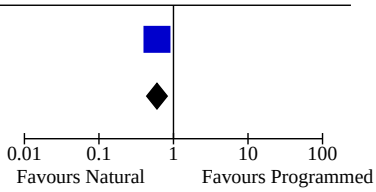
Heterogeneity: Chi² = 0.77, df = 2 (P = 0.68); I² = 0%
Test for overall effect: Z = 0.94 (P = 0.35)
Test for subgroup differences: Not applicable



Analysis 2.4. Comparison 2: Programmed cycle versus natural cycle, Outcome 4: Cycle cancellation rate

Study or Subgroup	Natural cycle Events	Natural cycle Total	Programmed cycle Events	Programmed cycle Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Groenewoud 2016	101	394	124	340	100.0%	0.60 [0.44 , 0.82]
Total (95% CI)		**394**		**340**	**100.0%**	**0.60 [0.44 , 0.82]**
Total events:	101		124			

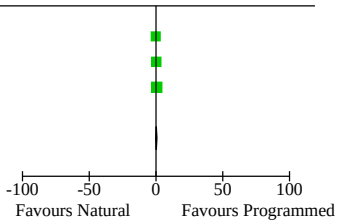
Heterogeneity: Not applicable
Test for overall effect: Z = 3.16 (P = 0.002)
Test for subgroup differences: Not applicable



Analysis 2.5. Comparison 2: Programmed cycle versus natural cycle, Outcome 5: Endometrial thickness (mm)

Study or Subgroup	Natural Mean	Natural SD	Natural Total	Programmed Mean	Programmed SD	Programmed Total	Weight	Mean Difference IV, Random, 95% CI
Sheikhi 2018	8.13	0.95	31	8.34	0.89	62	30.8%	-0.21 [-0.61 , 0.19]
Greco 2016	9.6	1.3	113	9.4	1.4	109	32.4%	0.20 [-0.16 , 0.56]
Agha-Hosseini 2018	8.6	0.6	85	8.01	0.79	85	36.8%	0.59 [0.38 , 0.80]
Total (95% CI)			**229**			**256**	**100.0%**	**0.22 [-0.25 , 0.69]**

Heterogeneity: Tau² = 0.14; Chi² = 13.09, df = 2 (P = 0.001); I² = 85%
Test for overall effect: Z = 0.91 (P = 0.36)
Test for subgroup differences: Not applicable



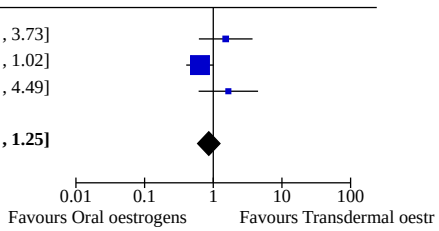
Comparison 3. Transdermal oestrogens versus oral oestrogens

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Clinical pregnancy rate	3	504	Odds Ratio (M-H, Fixed, 95% CI)	0.86 [0.59, 1.25]
3.2 Miscarriage rate	2	414	Odds Ratio (M-H, Fixed, 95% CI)	0.55 [0.27, 1.09]

Analysis 3.1. Comparison 3: Transdermal oestrogens versus oral oestrogens, Outcome 1: Clinical pregnancy rate

Study or Subgroup	Transdermal oestrogens Events	Total	Oral oestrogens Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Davar 2016	16	45	12	45	13.1%	1.52 [0.62 , 3.73]
Kahraman 2018	89	154	109	160	76.6%	0.64 [0.40 , 1.02]
Tehraninejad 2018	12	50	8	50	10.3%	1.66 [0.61 , 4.49]
Total (95% CI)		**249**		**255**	**100.0%**	**0.86 [0.59 , 1.25]**
Total events:	117		129			

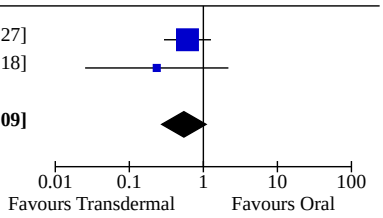
Heterogeneity: Chi² = 4.76, df = 2 (P = 0.09); I² = 58%
Test for overall effect: Z = 0.79 (P = 0.43)
Test for subgroup differences: Not applicable



Analysis 3.2. Comparison 3: Transdermal oestrogens versus oral oestrogens, Outcome 2: Miscarriage rate

Study or Subgroup	Transdermal oestrogens Events	Total	Oral oestrogens Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Kahraman 2018	13	154	21	160	82.8%	0.61 [0.29 , 1.27]
Tehraninejad 2018	1	50	4	50	17.2%	0.23 [0.03 , 2.18]
Total (95% CI)		**204**		**210**	**100.0%**	**0.55 [0.27 , 1.09]**
Total events:	14		25			

Heterogeneity: Chi² = 0.64, df = 1 (P = 0.42); I² = 0%
Test for overall effect: Z = 1.73 (P = 0.08)
Test for subgroup differences: Not applicable



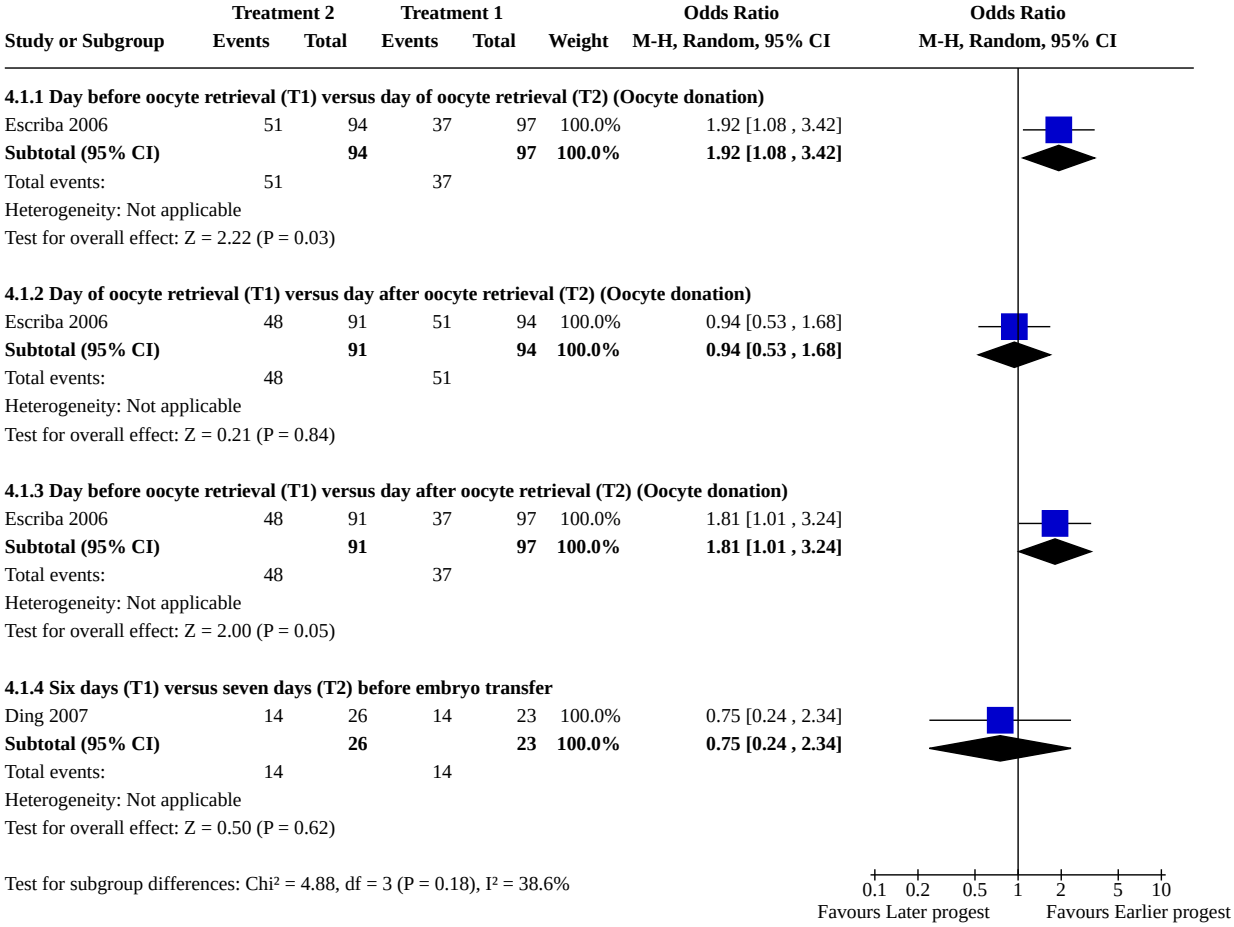
Comparison 4. Day of starting administration of the progesterone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Clinical Pregnancy Rate	2		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
4.1.1 Day before oocyte retrieval (T1) versus day of oocyte retrieval (T2) (Oocyte donation)	1	191	Odds Ratio (M-H, Random, 95% CI)	1.92 [1.08, 3.42]
4.1.2 Day of oocyte retrieval (T1) versus day after oocyte retrieval (T2) (Oocyte donation)	1	185	Odds Ratio (M-H, Random, 95% CI)	0.94 [0.53, 1.68]
4.1.3 Day before oocyte retrieval (T1) versus day after oocyte retrieval (T2) (Oocyte donation)	1	188	Odds Ratio (M-H, Random, 95% CI)	1.81 [1.01, 3.24]
4.1.4 Six days (T1) versus seven days (T2) before embryo transfer	1	49	Odds Ratio (M-H, Random, 95% CI)	0.75 [0.24, 2.34]
4.2 Miscarriage Rate	1		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
4.2.1 Day before oocyte retrieval (T1) versus day of oocyte retrieval (T2) (Oocyte donation)	1	191	Odds Ratio (M-H, Random, 95% CI)	0.45 [0.16, 1.25]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.2.2 Day of oocyte retrieval (T1) versus day after oocyte retrieval (T2) (Oocyte donation)	1	185	Odds Ratio (M-H, Random, 95% CI)	2.52 [0.85, 7.46]
4.2.3 Day before oocyte retrieval (T1) versus day after oocyte retrieval (T2) (Oocyte donation)	1	188	Odds Ratio (M-H, Random, 95% CI)	1.13 [0.33, 3.85]
4.3 Multiple Pregnancy Rate	1		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
4.3.1 Day before oocyte retrieval (T1) versus day of oocyte retrieval (T2) (Oocyte donation)	1	191	Odds Ratio (M-H, Random, 95% CI)	0.62 [0.29, 1.32]
4.3.2 Day of oocyte retrieval (T1) versus day after oocyte retrieval (T2) (Oocyte donation)	1	185	Odds Ratio (M-H, Random, 95% CI)	1.37 [0.65, 2.88]
4.3.3 Day before oocyte retrieval (T1) versus day after oocyte retrieval (T2) (Oocyte donation)	1	188	Odds Ratio (M-H, Random, 95% CI)	0.85 [0.39, 1.89]
4.3.4 Day before oocyte retrieval (T1) versus day of or day after oocyte retrieval (T2) (Oocyte donation)	1	282	Odds Ratio (M-H, Random, 95% CI)	0.72 [0.37, 1.42]
4.4 Cycle cancellation rate	1		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
4.4.1 Day before oocyte retrieval (T1) versus day of oocyte retrieval (T2) (Oocyte donation)	1	191	Odds Ratio (M-H, Random, 95% CI)	0.31 [0.10, 1.01]
4.4.2 Day of oocyte retrieval (T1) versus day after oocyte retrieval (T2) (Oocyte donation)	1	185	Odds Ratio (M-H, Random, 95% CI)	0.77 [0.17, 3.53]
4.4.3 Day before oocyte retrieval (T1) versus day after oocyte retrieval (T2) (Oocyte donation)	1	188	Odds Ratio (M-H, Random, 95% CI)	0.24 [0.07, 0.89]
4.5 Cycle cancellation rate because of failed fertilization (by subgroups)	1		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
4.5.1 Day before or day of oocyte retrieval (T1) versus day after of oocyte retrieval (T2) (Oocyte donation)	1	282	Odds Ratio (M-H, Random, 95% CI)	0.10 [0.01, 1.82]
4.6 Clinical Pregnancy Rate (by subgroups)	1		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
4.6.1 Day before oocyte retrieval (T1) versus day of oocyte retrieval (T2) (Oocyte donation)	1	191	Odds Ratio (M-H, Random, 95% CI)	1.92 [1.08, 3.42]
4.6.2 Day before oocyte retrieval (T1) versus day after oocyte retrieval (T2) (Oocyte donation)	1	188	Odds Ratio (M-H, Random, 95% CI)	1.81 [1.01, 3.24]

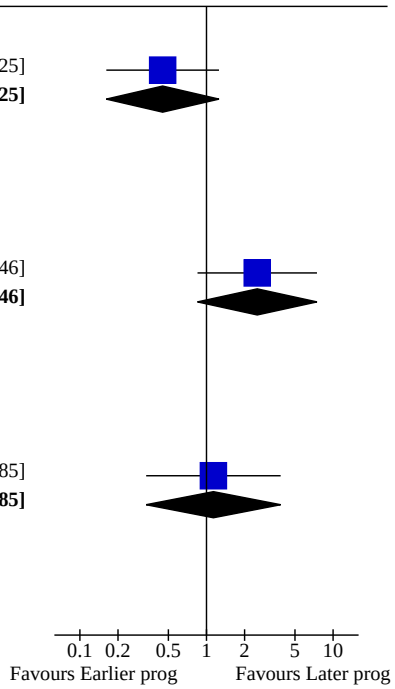
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.6.3 Day before oocyte retrieval (T1) versus day of or after oocyte retrieval (T2) (Oocyte donation)	1	282	Odds Ratio (M-H, Random, 95% CI)	1.87 [1.13, 3.08]
4.7 Cycle cancellation rate (by subgroups)	1	282	Odds Ratio (M-H, Random, 95% CI)	0.28 [0.11, 0.74]
4.7.1 Day before oocyte retrieval (T1) versus day of oocyte retrieval (T2) (Oocyte donation)	1	143	Odds Ratio (M-H, Random, 95% CI)	0.32 [0.09, 1.19]
4.7.2 Day before oocyte retrieval (T1) versus day after oocyte retrieval (T2) (Oocyte donation)	1	139	Odds Ratio (M-H, Random, 95% CI)	0.24 [0.06, 1.00]

Analysis 4.1. Comparison 4: Day of starting administration of the progesterone, Outcome 1: Clinical Pregnancy Rate



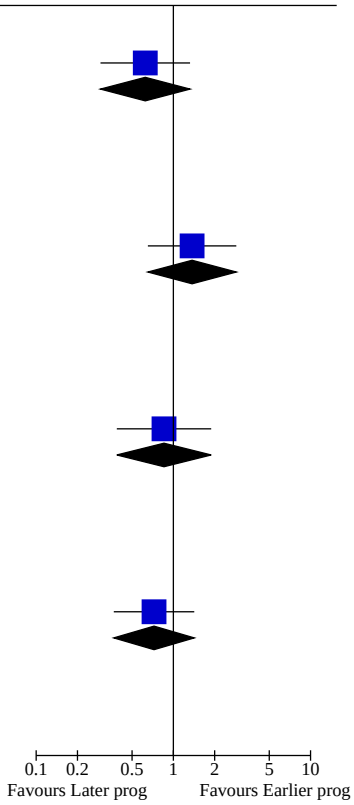
Analysis 4.2. Comparison 4: Day of starting administration of the progesterone, Outcome 2: Miscarriage Rate

Study or Subgroup	Treatment 1 Events	Total	Treatment 2 Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
4.2.1 Day before oocyte retrieval (T1) versus day of oocyte retrieval (T2) (Oocyte donation)						
Escriba 2006	6	97	12	94	100.0%	0.45 [0.16 , 1.25]
Subtotal (95% CI)		**97**		**94**	**100.0%**	**0.45 [0.16 , 1.25]**
Total events:	6		12			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.53 (P = 0.13)						
4.2.2 Day of oocyte retrieval (T1) versus day after oocyte retrieval (T2) (Oocyte donation)						
Escriba 2006	12	94	5	91	100.0%	2.52 [0.85 , 7.46]
Subtotal (95% CI)		**94**		**91**	**100.0%**	**2.52 [0.85 , 7.46]**
Total events:	12		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.67 (P = 0.10)						
4.2.3 Day before oocyte retrieval (T1) versus day after oocyte retrieval (T2) (Oocyte donation)						
Escriba 2006	6	97	5	91	100.0%	1.13 [0.33 , 3.85]
Subtotal (95% CI)		**97**		**91**	**100.0%**	**1.13 [0.33 , 3.85]**
Total events:	6		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.20 (P = 0.84)						
Test for subgroup differences: Chi² = 5.12, df = 2 (P = 0.08), I² = 61.0%						



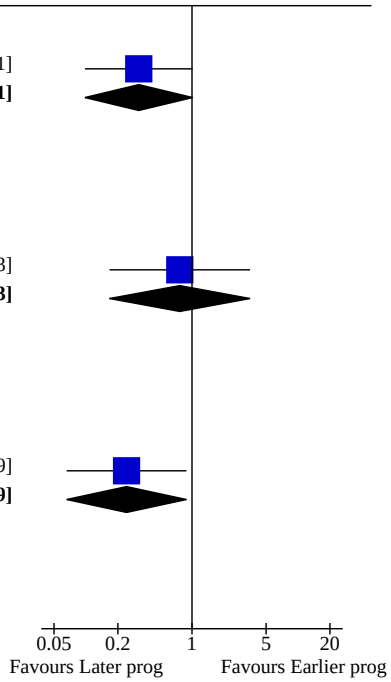
Analysis 4.3. Comparison 4: Day of starting administration of the progesterone, Outcome 3: Multiple Pregnancy Rate

Study or Subgroup	Treatment 1 Events	Treatment 1 Total	Treatment 2 Events	Treatment 2 Total	Weight	Odds Ratio M-H, Random, 95% CI
4.3.1 Day before oocyte retrieval (T1) versus day of oocyte retrieval (T2) (Oocyte donation)						
Escriba 2006	14	97	20	94	100.0%	0.62 [0.29 , 1.32]
Subtotal (95% CI)		**97**		**94**	**100.0%**	**0.62 [0.29 , 1.32]**
Total events:	14		20			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.23 (P = 0.22)						
4.3.2 Day of oocyte retrieval (T1) versus day after oocyte retrieval (T2) (Oocyte donation)						
Escriba 2006	20	94	15	91	100.0%	1.37 [0.65 , 2.88]
Subtotal (95% CI)		**94**		**91**	**100.0%**	**1.37 [0.65 , 2.88]**
Total events:	20		15			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.83 (P = 0.41)						
4.3.3 Day before oocyte retrieval (T1) versus day after oocyte retrieval (T2) (Oocyte donation)						
Escriba 2006	14	97	15	91	100.0%	0.85 [0.39 , 1.89]
Subtotal (95% CI)		**97**		**91**	**100.0%**	**0.85 [0.39 , 1.89]**
Total events:	14		15			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.39 (P = 0.70)						
4.3.4 Day before oocyte retrieval (T1) versus day of or day after oocyte retrieval (T2) (Oocyte donation)						
Escriba 2006	14	97	35	185	100.0%	0.72 [0.37 , 1.42]
Subtotal (95% CI)		**97**		**185**	**100.0%**	**0.72 [0.37 , 1.42]**
Total events:	14		35			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.94 (P = 0.35)						



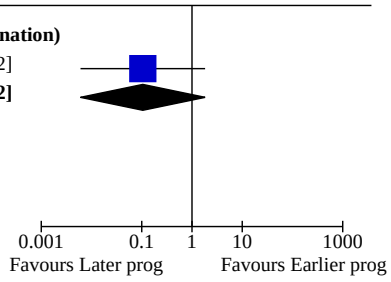
Analysis 4.4. Comparison 4: Day of starting administration of the progesterone, Outcome 4: Cycle cancellation rate

Study or Subgroup	Treatment 2 Events	Total	Treatment 1 Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
4.4.1 Day before oocyte retrieval (T1) versus day of oocyte retrieval (T2) (Oocyte donation)						
Escriba 2006	4	94	12	97	100.0%	0.31 [0.10 , 1.01]
Subtotal (95% CI)		**94**		**97**	**100.0%**	**0.31 [0.10 , 1.01]**
Total events:	4		12			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.94 (P = 0.05)						
4.4.2 Day of oocyte retrieval (T1) versus day after oocyte retrieval (T2) (Oocyte donation)						
Escriba 2006	3	91	4	94	100.0%	0.77 [0.17 , 3.53]
Subtotal (95% CI)		**91**		**94**	**100.0%**	**0.77 [0.17 , 3.53]**
Total events:	3		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.34 (P = 0.73)						
4.4.3 Day before oocyte retrieval (T1) versus day after oocyte retrieval (T2) (Oocyte donation)						
Escriba 2006	3	91	12	97	100.0%	0.24 [0.07 , 0.89]
Subtotal (95% CI)		**91**		**97**	**100.0%**	**0.24 [0.07 , 0.89]**
Total events:	3		12			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.14 (P = 0.03)						
Test for subgroup differences: Chi^2 = 1.36, df = 2 (P = 0.51), I^2 = 0%						



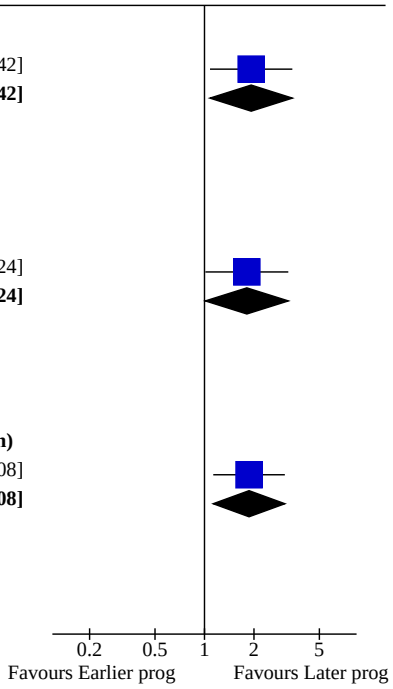
Analysis 4.5. Comparison 4: Day of starting administration of the progesterone, Outcome 5: Cycle cancellation rate because of failed fertilization (by subgroups)

Study or Subgroup	Treatment 2 Events	Total	Treatment 1 Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
4.5.1 Day before or day of oocyte retrieval (T1) versus day after of oocyte retrieval (T2) (Oocyte donation)						
Escriba 2006	0	91	9	191	100.0%	0.10 [0.01 , 1.82]
Subtotal (95% CI)		**91**		**191**	**100.0%**	**0.10 [0.01 , 1.82]**
Total events:	0		9			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.55 (P = 0.12)						
Test for subgroup differences: Not applicable						



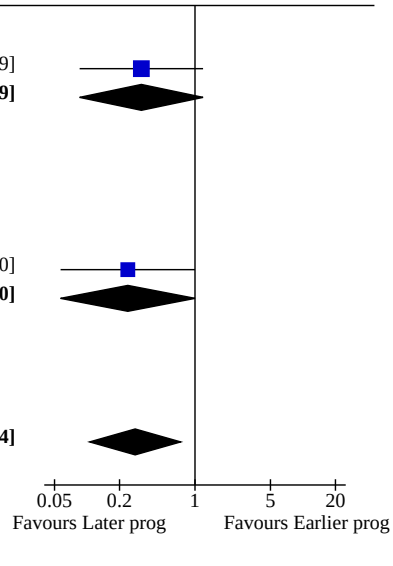
Analysis 4.6. Comparison 4: Day of starting administration of the progesterone, Outcome 6: Clinical Pregnancy Rate (by subgroups)

Study or Subgroup	Treatment 2 Events	Treatment 2 Total	Treatment 1 Events	Treatment 1 Total	Weight	Odds Ratio M-H, Random, 95% CI
4.6.1 Day before oocyte retrieval (T1) versus day of oocyte retrieval (T2) (Oocyte donation)						
Escriba 2006	51	94	37	97	100.0%	1.92 [1.08 , 3.42]
Subtotal (95% CI)		**94**		**97**	**100.0%**	**1.92 [1.08 , 3.42]**
Total events:	51		37			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.22 (P = 0.03)						
4.6.2 Day before oocyte retrieval (T1) versus day after oocyte retrieval (T2) (Oocyte donation)						
Escriba 2006	48	91	37	97	100.0%	1.81 [1.01 , 3.24]
Subtotal (95% CI)		**91**		**97**	**100.0%**	**1.81 [1.01 , 3.24]**
Total events:	48		37			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.00 (P = 0.05)						
4.6.3 Day before oocyte retrieval (T1) versus day of or after oocyte retrieval (T2) (Oocyte donation)						
Escriba 2006	99	185	37	97	100.0%	1.87 [1.13 , 3.08]
Subtotal (95% CI)		**185**		**97**	**100.0%**	**1.87 [1.13 , 3.08]**
Total events:	99		37			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.44 (P = 0.01)						
Test for subgroup differences: Chi² = 0.02, df = 2 (P = 0.99), I² = 0%						



Analysis 4.7. Comparison 4: Day of starting administration of the progesterone, Outcome 7: Cycle cancellation rate (by subgroups)

Study or Subgroup	Treatment 2 Events	Treatment 2 Total	Treatment 1 Events	Treatment 1 Total	Weight	Odds Ratio M-H, Random, 95% CI
4.7.1 Day before oocyte retrieval (T1) versus day of oocyte retrieval (T2) (Oocyte donation)						
Escriba 2006	4	94	6	49	54.3%	0.32 [0.09 , 1.19]
Subtotal (95% CI)		**94**		**49**	**54.3%**	**0.32 [0.09 , 1.19]**
Total events:	4		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.70 (P = 0.09)						
4.7.2 Day before oocyte retrieval (T1) versus day after oocyte retrieval (T2) (Oocyte donation)						
Escriba 2006	3	91	6	48	45.7%	0.24 [0.06 , 1.00]
Subtotal (95% CI)		**91**		**48**	**45.7%**	**0.24 [0.06 , 1.00]**
Total events:	3		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.96 (P = 0.05)						
Total (95% CI)		**185**		**97**	**100.0%**	**0.28 [0.11 , 0.74]**
Total events:	7		12			
Heterogeneity: Tau² = 0.00; Chi² = 0.08, df = 1 (P = 0.77); I² = 0%						
Test for overall effect: Z = 2.58 (P = 0.010)						
Test for subgroup differences: Chi² = 0.08, df = 1 (P = 0.77), I² = 0%						

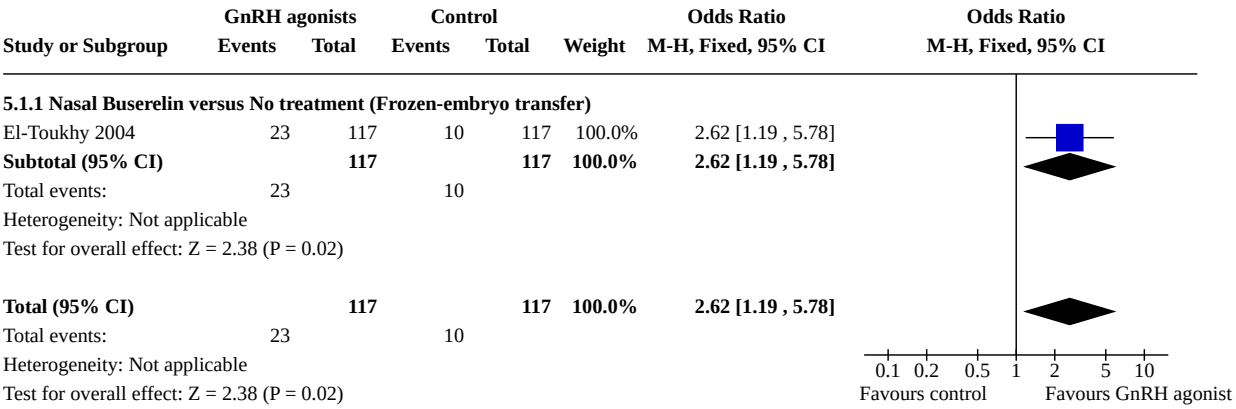


Comparison 5. GnRH agonists versus control

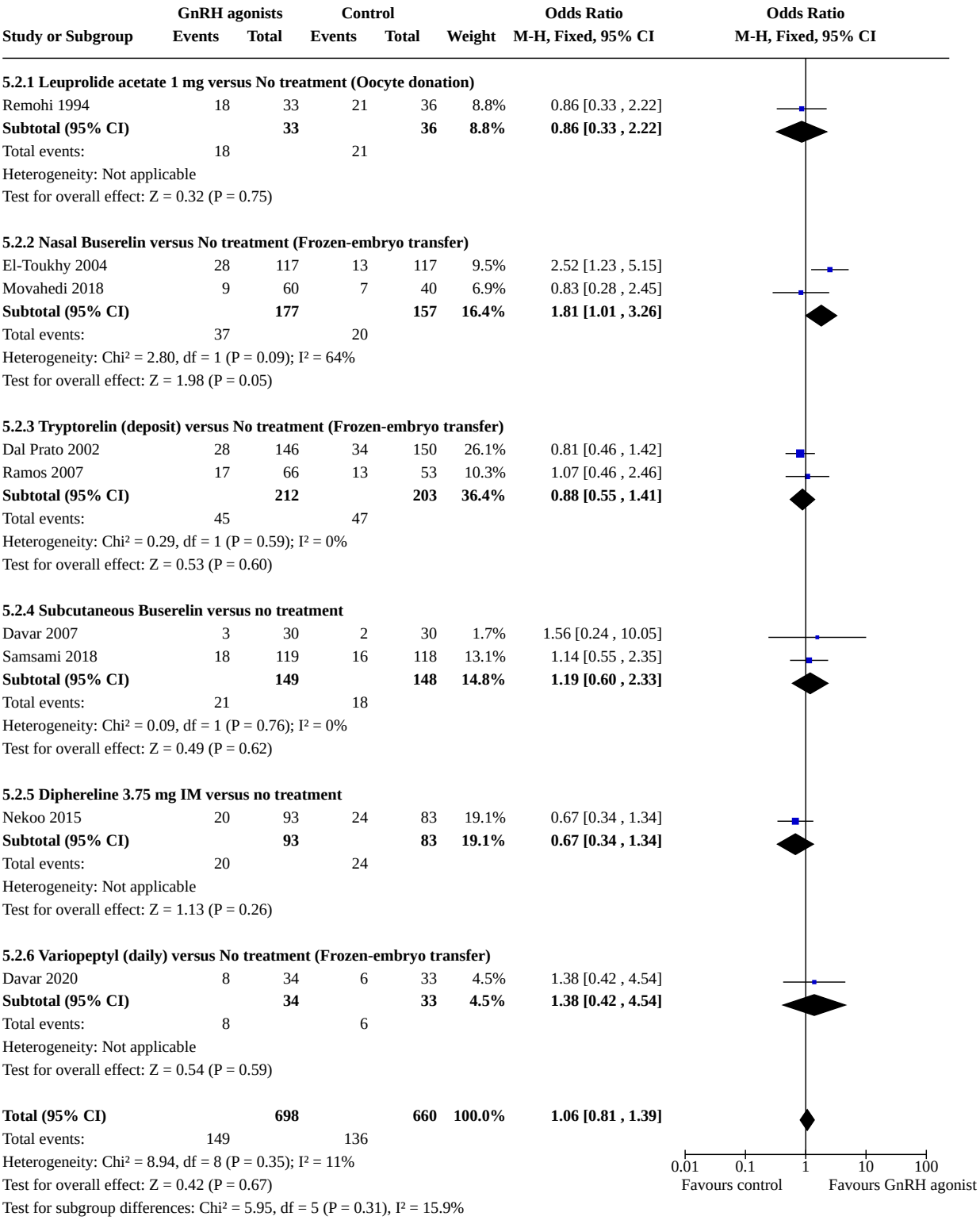
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 Live Birth Rate	1	234	Odds Ratio (M-H, Fixed, 95% CI)	2.62 [1.19, 5.78]
5.1.1 Nasal Buserelin versus No treatment (Frozen-embryo transfer)	1	234	Odds Ratio (M-H, Fixed, 95% CI)	2.62 [1.19, 5.78]
5.2 Clinical Pregnancy Rate	9	1358	Odds Ratio (M-H, Fixed, 95% CI)	1.06 [0.81, 1.39]
5.2.1 Leuprolide acetate 1 mg versus No treatment (Oocyte donation)	1	69	Odds Ratio (M-H, Fixed, 95% CI)	0.86 [0.33, 2.22]
5.2.2 Nasal Buserelin versus No treatment (Frozen-embryo transfer)	2	334	Odds Ratio (M-H, Fixed, 95% CI)	1.81 [1.01, 3.26]
5.2.3 Tryptorelin (deposit) versus No treatment (Frozen-embryo transfer)	2	415	Odds Ratio (M-H, Fixed, 95% CI)	0.88 [0.55, 1.41]
5.2.4 Subcutaneous Buserelin versus no treatment	2	297	Odds Ratio (M-H, Fixed, 95% CI)	1.19 [0.60, 2.33]
5.2.5 Diphereline 3.75 mg IM versus no treatment	1	176	Odds Ratio (M-H, Fixed, 95% CI)	0.67 [0.34, 1.34]
5.2.6 Variopeptyl (daily) versus No treatment (Frozen-embryo transfer)	1	67	Odds Ratio (M-H, Fixed, 95% CI)	1.38 [0.42, 4.54]
5.3 Miscarriage Rate	4	828	Odds Ratio (M-H, Random, 95% CI)	0.85 [0.36, 2.00]
5.3.1 Tryptorelin (deposit) versus No treatment (Frozen-embryo transfer)	2	415	Odds Ratio (M-H, Random, 95% CI)	0.92 [0.29, 2.96]
5.3.2 Diphereline 3.75 mg IM versus no treatment	1	176	Odds Ratio (M-H, Random, 95% CI)	0.43 [0.08, 2.43]
5.3.3 Subcutaneous Buserelin versus no treatment	1	237	Odds Ratio (M-H, Random, 95% CI)	1.50 [0.25, 9.14]
5.4 Cycle cancellation rate	2	530	Odds Ratio (M-H, Random, 95% CI)	0.49 [0.21, 1.17]
5.4.1 Nasal Buserelin (Frozen-embryo transfer)	1	234	Odds Ratio (M-H, Random, 95% CI)	0.56 [0.16, 1.95]
5.4.2 Tryptorelin (deposit) versus No treatment (Frozen-embryo transfer)	1	296	Odds Ratio (M-H, Random, 95% CI)	0.44 [0.13, 1.47]
5.5 Endometrial Thickness (mm)	4	697	Mean Difference (IV, Random, 95% CI)	-0.08 [-0.33, 0.16]
5.5.1 Nasal Buserelin (Frozen-embryo transfer)	2	334	Mean Difference (IV, Random, 95% CI)	-0.14 [-0.99, 0.72]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.5.2 Tryptorelin (deposit) versus No treatment (Frozen-embryo transfer)	1	296	Mean Difference (IV, Random, 95% CI)	-0.10 [-0.43, 0.23]
5.5.3 Variopeptyl (daily) versus No treatment (Frozen-embryo transfer)	1	67	Mean Difference (IV, Random, 95% CI)	-0.24 [-0.82, 0.34]
5.6 Clinical Pregnancy Rate with most used GnRH agonists	2	365	Odds Ratio (M-H, Random, 95% CI)	0.82 [0.51, 1.33]
5.6.1 Leuprolide acetate 1 mg versus No treatment (Oocyte donation)	1	69	Odds Ratio (M-H, Random, 95% CI)	0.86 [0.33, 2.22]
5.6.2 Tryptorelin (deposit) versus No treatment (Frozen-embryo transfer)	1	296	Odds Ratio (M-H, Random, 95% CI)	0.81 [0.46, 1.42]

Analysis 5.1. Comparison 5: GnRH agonists versus control, Outcome 1: Live Birth Rate

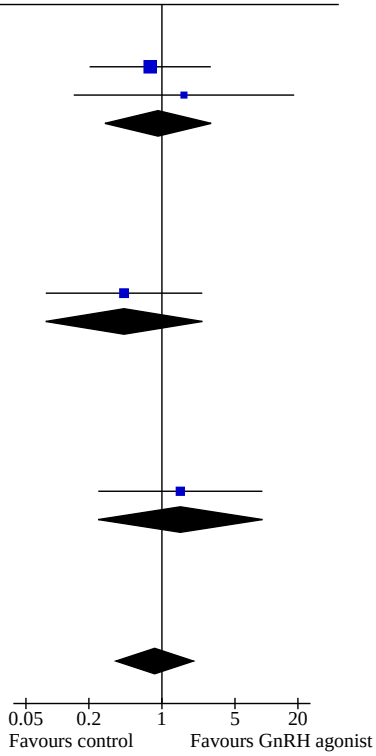


Analysis 5.2. Comparison 5: GnRH agonists versus control, Outcome 2: Clinical Pregnancy Rate



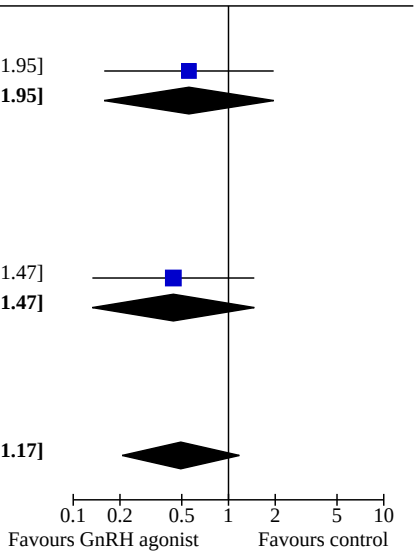
Analysis 5.3. Comparison 5: GnRH agonists versus control, Outcome 3: Miscarriage Rate

Study or Subgroup	Control Events	Control Total	GnRH agonists Events	GnRH agonists Total	Weight	Odds Ratio M-H, Random, 95% CI
5.3.1 Tryptorelin (deposit) versus No treatment (Frozen-embryo transfer)						
Dal Prato 2002	4	150	5	146	40.9%	0.77 [0.20 , 2.94]
Ramos 2007	2	66	1	53	12.4%	1.63 [0.14 , 18.42]
Subtotal (95% CI)		**216**		**199**	**53.2%**	**0.92 [0.29 , 2.96]**
Total events:	6		6			
Heterogeneity: Tau² = 0.00; Chi² = 0.28, df = 1 (P = 0.60); I² = 0%						
Test for overall effect: Z = 0.14 (P = 0.89)						
5.3.2 Diphereline 3.75 mg IM versus no treatment						
Nekoo 2015	2	93	4	83	24.5%	0.43 [0.08 , 2.43]
Subtotal (95% CI)		**93**		**83**	**24.5%**	**0.43 [0.08 , 2.43]**
Total events:	2		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.95 (P = 0.34)						
5.3.3 Subcutaneous Buserelin versus no treatment						
Samsami 2018	3	119	2	118	22.3%	1.50 [0.25 , 9.14]
Subtotal (95% CI)		**119**		**118**	**22.3%**	**1.50 [0.25 , 9.14]**
Total events:	3		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.44 (P = 0.66)						
Total (95% CI)		**428**		**400**	**100.0%**	**0.85 [0.36 , 2.00]**
Total events:	11		12			
Heterogeneity: Tau² = 0.00; Chi² = 1.26, df = 3 (P = 0.74); I² = 0%						
Test for overall effect: Z = 0.37 (P = 0.71)						
Test for subgroup differences: Chi² = 0.98, df = 2 (P = 0.61), I² = 0%						

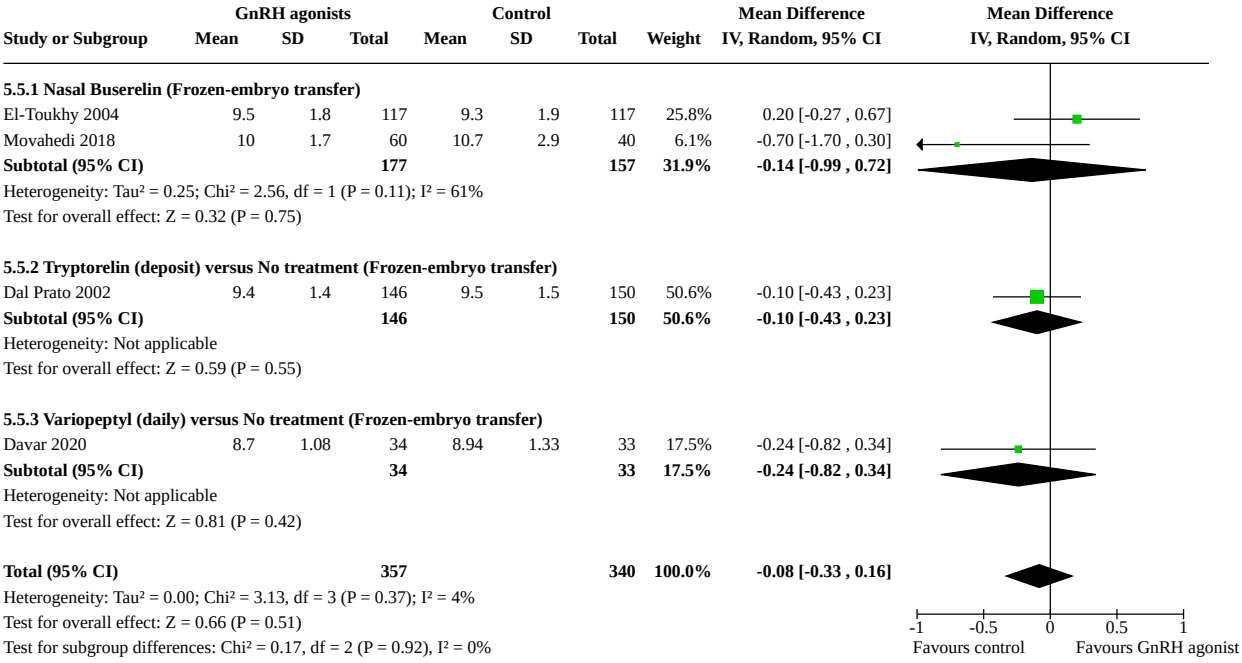


Analysis 5.4. Comparison 5: GnRH agonists versus control, Outcome 4: Cycle cancellation rate

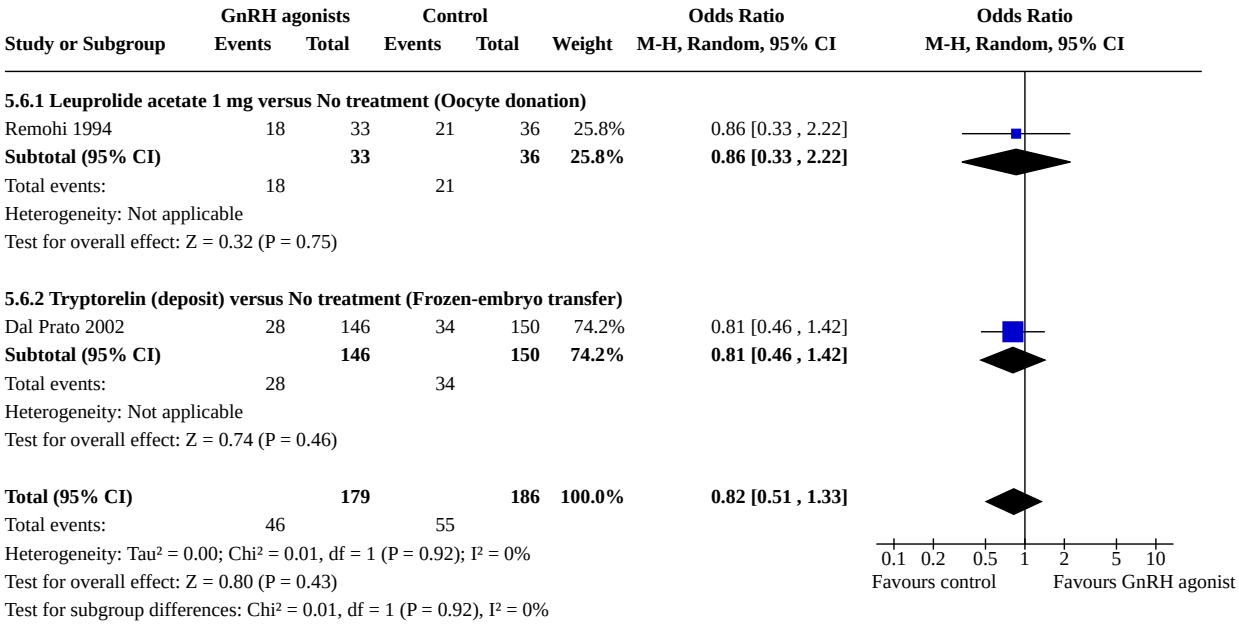
Study or Subgroup	GnRH agonists Events	GnRH agonists Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
5.4.1 Nasal Buserelin (Frozen-embryo transfer)						
El-Toukhy 2004	4	117	7	117	47.7%	0.56 [0.16 , 1.95]
Subtotal (95% CI)		**117**		**117**	**47.7%**	**0.56 [0.16 , 1.95]**
Total events:	4		7			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.92 (P = 0.36)						
5.4.2 Tryptorelin (deposit) versus No treatment (Frozen-embryo transfer)						
Dal Prato 2002	4	146	9	150	52.3%	0.44 [0.13 , 1.47]
Subtotal (95% CI)		**146**		**150**	**52.3%**	**0.44 [0.13 , 1.47]**
Total events:	4		9			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.34 (P = 0.18)						
Total (95% CI)		**263**		**267**	**100.0%**	**0.49 [0.21 , 1.17]**
Total events:	8		16			
Heterogeneity: Tau² = 0.00; Chi² = 0.07, df = 1 (P = 0.79); I² = 0%						
Test for overall effect: Z = 1.60 (P = 0.11)						
Test for subgroup differences: Chi² = 0.07, df = 1 (P = 0.79), I² = 0%						



Analysis 5.5. Comparison 5: GnRH agonists versus control, Outcome 5: Endometrial Thickness (mm)



Analysis 5.6. Comparison 5: GnRH agonists versus control, Outcome 6: Clinical Pregnancy Rate with most used GnRH agonists

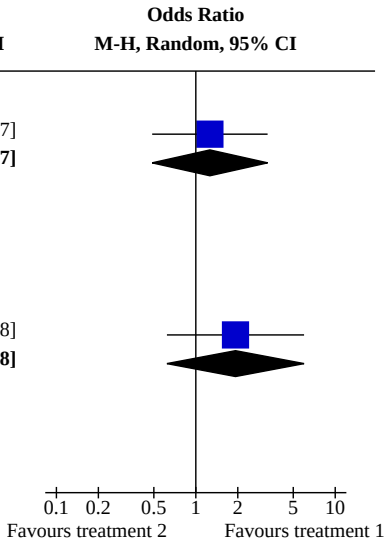


Comparison 6. Among different GnRH agonists

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 Clinical Pregnancy Rate	2		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
6.1.1 Nafareline (daily) vs Leuprolide (daily) (Oocyte donation - ovulating recipients)	1	68	Odds Ratio (M-H, Random, 95% CI)	1.26 [0.49, 3.27]
6.1.2 Leuprolide (daily) vs Tryptorelin (deposit) (Oocyte donation - ovulating recipients)	1	50	Odds Ratio (M-H, Random, 95% CI)	1.93 [0.62, 5.98]
6.2 Miscarriage Rate	1		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
6.2.1 Leuprolide vs Nafareline (Oocyte donation - non-amenorrhea recipients)	1	68	Odds Ratio (M-H, Random, 95% CI)	1.33 [0.36, 4.87]

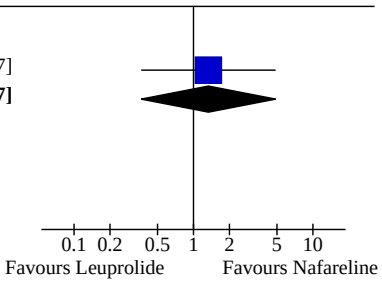
Analysis 6.1. Comparison 6: Among different GnRH agonists, Outcome 1: Clinical Pregnancy Rate

Study or Subgroup	Treatment 1 Events	Total	Treatment 2 Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
6.1.1 Nafareline (daily) vs Leuprolide (daily) (Oocyte donation - ovulating recipients)						
Gutierrez 1999	19	35	16	33	100.0%	1.26 [0.49 , 3.27]
Subtotal (95% CI)		**35**		**33**	**100.0%**	**1.26 [0.49 , 3.27]**
Total events:	19		16			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.48 (P = 0.63)						
6.1.2 Leuprolide (daily) vs Tryptorelin (deposit) (Oocyte donation - ovulating recipients)						
Tocino 2007	16	25	12	25	100.0%	1.93 [0.62 , 5.98]
Subtotal (95% CI)		**25**		**25**	**100.0%**	**1.93 [0.62 , 5.98]**
Total events:	16		12			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.13 (P = 0.26)						
Test for subgroup differences: Chi² = 0.31, df = 1 (P = 0.58), I² = 0%						



Analysis 6.2. Comparison 6: Among different GnRH agonists, Outcome 2: Miscarriage Rate

Study or Subgroup	Leuprolide Events	Leuprolide Total	Nafareline Events	Nafareline Total	Weight	Odds Ratio M-H, Random, 95% CI
6.2.1 Leuprolide vs Nafareline (Oocyte donation - non-amenorrhea recipients)						
Gutierrez 1999	6	33	5	35	100.0%	1.33 [0.36 , 4.87]
Subtotal (95% CI)		**33**		**35**	**100.0%**	**1.33 [0.36 , 4.87]**
Total events:	6		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.44 (P = 0.66)						

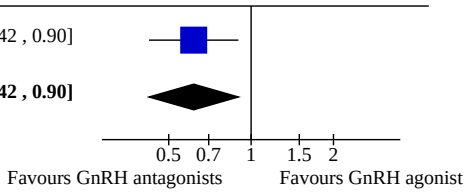


Comparison 7. GnRH agonists versus GnRH antagonists

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.1 Clinical pregnancy rate	1	473	Odds Ratio (M-H, Fixed, 95% CI)	0.62 [0.42, 0.90]
7.2 Miscarriage rate	1	473	Odds Ratio (M-H, Fixed, 95% CI)	0.75 [0.38, 1.49]
7.3 Multiple Pregnancy Rate	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only

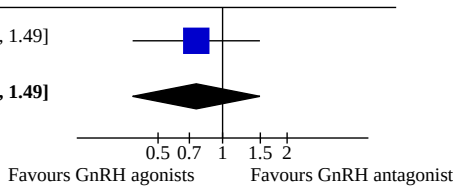
Analysis 7.1. Comparison 7: GnRH agonists versus GnRH antagonists, Outcome 1: Clinical pregnancy rate

Study or Subgroup	GnRH agonists Events	GnRH agonists Total	GnRH antagonists Events	GnRH antagonists Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Vidal 2009	137	241	158	232	100.0%	0.62 [0.42 , 0.90]
Total (95% CI)		**241**		**232**	**100.0%**	**0.62 [0.42 , 0.90]**
Total events:	137		158			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.52 (P = 0.01)						
Test for subgroup differences: Not applicable						



Analysis 7.2. Comparison 7: GnRH agonists versus GnRH antagonists, Outcome 2: Miscarriage rate

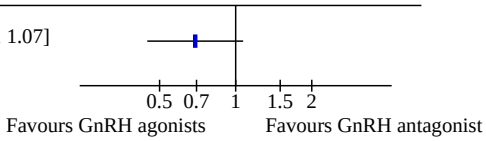
Study or Subgroup	GnRH agonists Events	GnRH agonists Total	GnRH antagonists Events	GnRH antagonists Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Vidal 2009	16	241	20	232	100.0%	0.75 [0.38 , 1.49]
Total (95% CI)		**241**		**232**	**100.0%**	**0.75 [0.38 , 1.49]**
Total events:	16		20			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.81 (P = 0.42)						
Test for subgroup differences: Not applicable						



Analysis 7.3. Comparison 7: GnRH agonists versus GnRH antagonists, Outcome 3: Multiple Pregnancy Rate

Study or Subgroup	GnRH agonists Events	Total	GnRH antagonists Events	Total	Odds Ratio M-H, Fixed, 95% CI
Vidal 2009	46	241	59	232	0.69 [0.45 , 1.07]

Test for subgroup differences: Not applicable

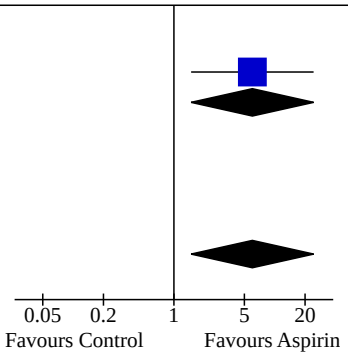


Comparison 8. Aspirin versus control

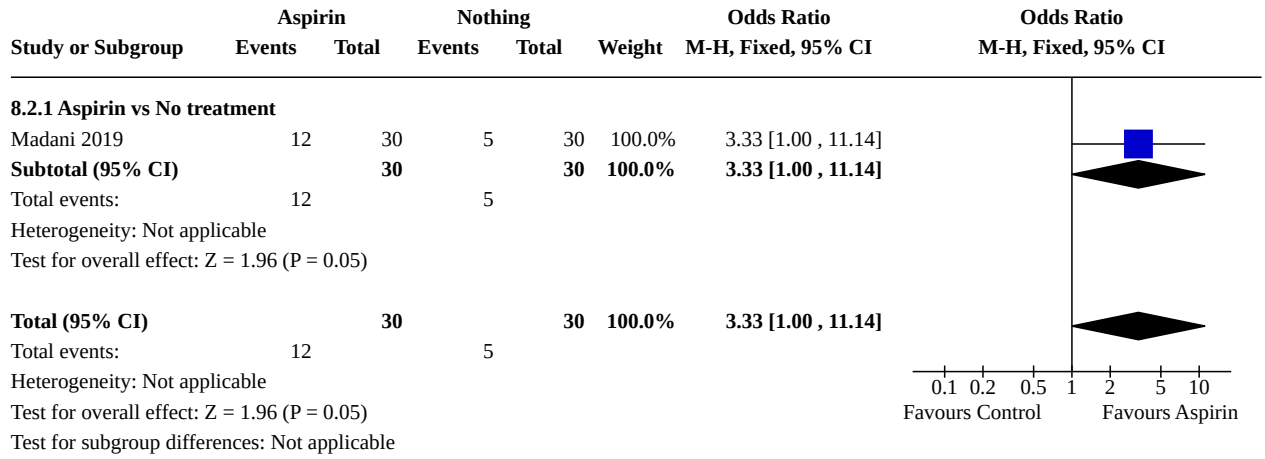
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.1 Live Birth Rate	1	60	Odds Ratio (M-H, Fixed, 95% CI)	6.00 [1.48, 24.30]
8.1.1 Aspirin vs No treatment	1	60	Odds Ratio (M-H, Fixed, 95% CI)	6.00 [1.48, 24.30]
8.2 Clinical Pregnancy Rate	1	60	Odds Ratio (M-H, Fixed, 95% CI)	3.33 [1.00, 11.14]
8.2.1 Aspirin vs No treatment	1	60	Odds Ratio (M-H, Fixed, 95% CI)	3.33 [1.00, 11.14]
8.3 Endometrial Thickness (mm)	1	60	Mean Difference (IV, Fixed, 95% CI)	-0.40 [-0.95, 0.15]
8.3.1 Aspirin vs No treatment	1	60	Mean Difference (IV, Fixed, 95% CI)	-0.40 [-0.95, 0.15]

Analysis 8.1. Comparison 8: Aspirin versus control, Outcome 1: Live Birth Rate

Study or Subgroup	Aspirin Events	Total	Nothing Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
8.1.1 Aspirin vs No treatment						
Madani 2019	12	30	3	30	100.0%	6.00 [1.48 , 24.30]
Subtotal (95% CI)		**30**		**30**	**100.0%**	**6.00 [1.48 , 24.30]**
Total events:	12		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.51 (P = 0.01)						
Total (95% CI)		**30**		**30**	**100.0%**	**6.00 [1.48 , 24.30]**
Total events:	12		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.51 (P = 0.01)						
Test for subgroup differences: Not applicable						

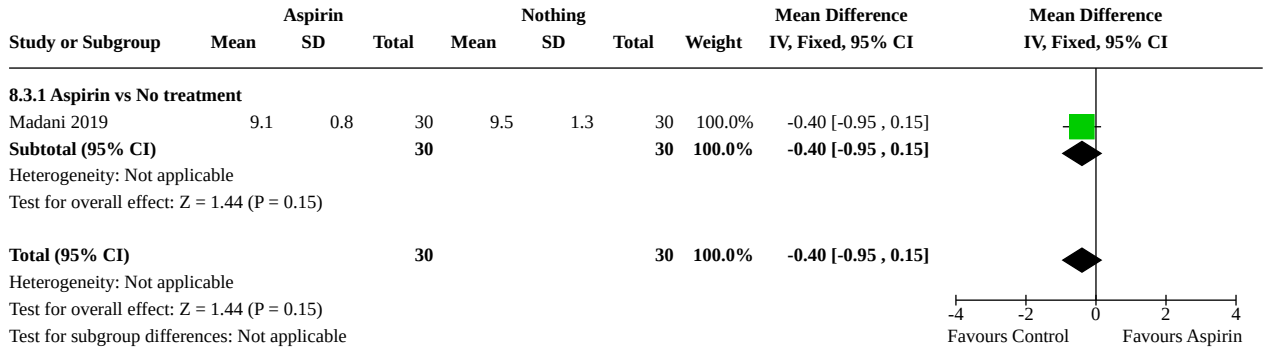


Analysis 8.2. Comparison 8: Aspirin versus control, Outcome 2: Clinical Pregnancy Rate



Study or Subgroup	Aspirin Events	Aspirin Total	Nothing Events	Nothing Total	Weight	Odds Ratio M-H, Fixed, 95% CI
8.2.1 Aspirin vs No treatment						
Madani 2019	12	30	5	30	100.0%	3.33 [1.00 , 11.14]
Subtotal (95% CI)		**30**		**30**	**100.0%**	**3.33 [1.00 , 11.14]**
Total events:	12		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.96 (P = 0.05)						
Total (95% CI)		**30**		**30**	**100.0%**	**3.33 [1.00 , 11.14]**
Total events:	12		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.96 (P = 0.05)						
Test for subgroup differences: Not applicable						

Analysis 8.3. Comparison 8: Aspirin versus control, Outcome 3: Endometrial Thickness (mm)



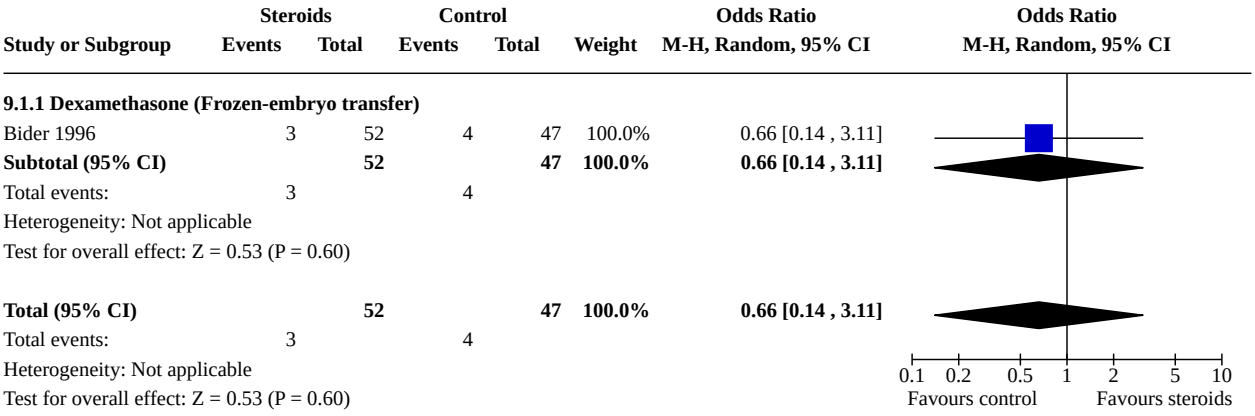
Study or Subgroup	Aspirin Mean	Aspirin SD	Aspirin Total	Nothing Mean	Nothing SD	Nothing Total	Weight	Mean Difference IV, Fixed, 95% CI
8.3.1 Aspirin vs No treatment								
Madani 2019	9.1	0.8	30	9.5	1.3	30	100.0%	-0.40 [-0.95 , 0.15]
Subtotal (95% CI)			**30**			**30**	**100.0%**	**-0.40 [-0.95 , 0.15]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.44 (P = 0.15)								
Total (95% CI)			**30**			**30**	**100.0%**	**-0.40 [-0.95 , 0.15]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.44 (P = 0.15)								
Test for subgroup differences: Not applicable								

Comparison 9. Steroids versus control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9.1 Live Birth Rate	1	99	Odds Ratio (M-H, Random, 95% CI)	0.66 [0.14, 3.11]
9.1.1 Dexamethasone (Frozen-embryo transfer)	1	99	Odds Ratio (M-H, Random, 95% CI)	0.66 [0.14, 3.11]
9.2 Clinical Pregnancy Rate	2	160	Odds Ratio (M-H, Random, 95% CI)	0.90 [0.40, 2.03]
9.2.1 Dexamethasone (Frozen-embryo transfer)	1	99	Odds Ratio (M-H, Random, 95% CI)	1.06 [0.33, 3.42]
9.2.2 6-alpha-methylprednisolone (Frozen-embryo transfer)	1	61	Odds Ratio (M-H, Random, 95% CI)	0.77 [0.25, 2.38]
9.3 Miscarriage Rate	2	160	Odds Ratio (M-H, Random, 95% CI)	1.49 [0.32, 7.03]

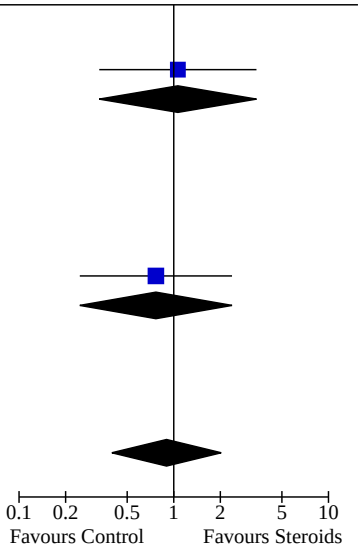
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9.3.1 Dexamethasone (Frozen-embryo transfer)	1	99	Odds Ratio (M-H, Random, 95% CI)	0.90 [0.05, 14.84]
9.3.2 6-alpha-methylprednisolone (Frozen-embryo transfer)	1	61	Odds Ratio (M-H, Random, 95% CI)	1.86 [0.29, 12.01]
9.4 Multiple Pregnancy Rate	1	99	Odds Ratio (M-H, Random, 95% CI)	Not estimable
9.4.1 Dexamethasone (Frozen-embryo transfer)	1	99	Odds Ratio (M-H, Random, 95% CI)	Not estimable

Analysis 9.1. Comparison 9: Steroids versus control, Outcome 1: Live Birth Rate



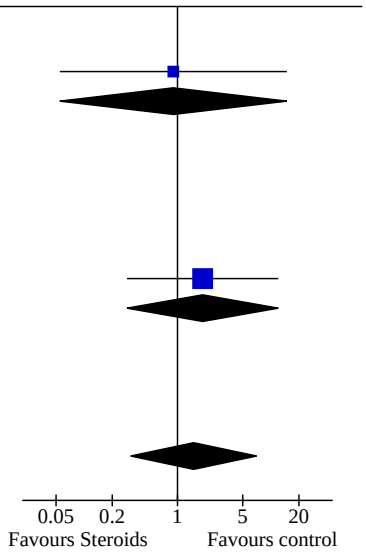
Analysis 9.2. Comparison 9: Steroids versus control, Outcome 2: Clinical Pregnancy Rate

Study or Subgroup	Steroids Events	Steroids Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
9.2.1 Dexamethasone (Frozen-embryo transfer)						
Bider 1996	7	52	6	47	48.4%	1.06 [0.33 , 3.42]
Subtotal (95% CI)		**52**		**47**	**48.4%**	**1.06 [0.33 , 3.42]**
Total events:	7		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.10 (P = 0.92)						
9.2.2 6-alpha-methylprednisolone (Frozen-embryo transfer)						
Moffitt 1995	7	28	10	33	51.6%	0.77 [0.25 , 2.38]
Subtotal (95% CI)		**28**		**33**	**51.6%**	**0.77 [0.25 , 2.38]**
Total events:	7		10			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.46 (P = 0.65)						
Total (95% CI)		**80**		**80**	**100.0%**	**0.90 [0.40 , 2.03]**
Total events:	14		16			
Heterogeneity: Tau² = 0.00; Chi² = 0.15, df = 1 (P = 0.69); I² = 0%						
Test for overall effect: Z = 0.26 (P = 0.80)						
Test for subgroup differences: Chi² = 0.15, df = 1 (P = 0.69), I² = 0%						



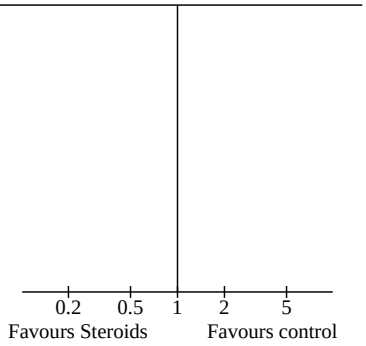
Analysis 9.3. Comparison 9: Steroids versus control, Outcome 3: Miscarriage Rate

Study or Subgroup	Steroids Events	Steroids Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
9.3.1 Dexamethasone (Frozen-embryo transfer)						
Bider 1996	1	52	1	47	30.7%	0.90 [0.05 , 14.84]
Subtotal (95% CI)		**52**		**47**	**30.7%**	**0.90 [0.05 , 14.84]**
Total events:	1		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.07 (P = 0.94)						
9.3.2 6-alpha-methylprednisolone (Frozen-embryo transfer)						
Moffitt 1995	3	28	2	33	69.3%	1.86 [0.29 , 12.01]
Subtotal (95% CI)		**28**		**33**	**69.3%**	**1.86 [0.29 , 12.01]**
Total events:	3		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.65 (P = 0.51)						
Total (95% CI)		**80**		**80**	**100.0%**	**1.49 [0.32 , 7.03]**
Total events:	4		3			
Heterogeneity: Tau² = 0.00; Chi² = 0.18, df = 1 (P = 0.67); I² = 0%						
Test for overall effect: Z = 0.50 (P = 0.62)						
Test for subgroup differences: Chi² = 0.18, df = 1 (P = 0.67), I² = 0%						



Analysis 9.4. Comparison 9: Steroids versus control, Outcome 4: Multiple Pregnancy Rate

Study or Subgroup	Steroids Events	Steroids Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
9.4.1 Dexamethasone (Frozen-embryo transfer)						
Bider 1996	0	52	0	47		Not estimable
Subtotal (95% CI)		**52**		**47**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**52**		**47**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Test for subgroup differences: Not applicable						



ADDITIONAL TABLES

Table 1. Quality assessment criteria

Assesment	Yes	Unclear	No
Allocation concealment	Adequate e.g. central randomisation / allocation, sealed envelopes, etc.	Not reported / unclear	Inadequate
Treatment blinding	Statement that containers were identical, drugs were identical in appearance and taste	Not reported / unclear	Interventions were not identical
Outcome assessment	Blinded, standardised assessment	Assesment procedures not stated	Assessment not blinded or not standardised
Follow-up completeness for first outcome (live birth rate)	Live birth rate reported	Pregnancy rate reported	Other outcome
Baseline equality	Groups balanced in terms of age and angina frequency	Balance not reported	Groups not balanced
Losses to follow-up (not including early cessation of therapy followed up)	Losses of 10% or less	Not reported / unclear	Losses of more than 10%
Bias in the analysis: intention-to-treat (ITT)	ITT analysis done by the authors	Unclear	Not ITT analysis done by the authors
Risk of bias	All of the previous criteria met (all are assessment quality A)	One or more of the previous criteria partly met (at least one assessment quality B and no assessment quality C)	One or more of the previous criteria not met (at least one assessment quality C)

APPENDICES

Appendix 1. Cochrane Gynaecology and Fertility Group specialised register search strategy

PROCITE platform

Searched 24 June 2020

Keywords CONTAINS "Oocyte donation" or "oocyte donors" or "oocyte recipient-age" or "frozen embryo transfer" or "frozen embryos" or "frozen-thawed cycle" or "frozen-thawed embryo transfer" or "frozen-thawed embryos" or "FET" or "cryopreserved embryos" or "cryopreserved-thawed embryos" or "embryo vitrification" or Title CONTAINS "Oocyte donation" or "oocyte donors" or "oocyte recipient-age" or "frozen embryo transfer" or "frozen embryos" or "frozen-thawed cycle" or "frozen-thawed embryo transfer" or "frozen-thawed embryos" or "FET" or "cryopreserved embryos" or "cryopreserved-thawed embryos" or "embryo vitrification"

AND

Keywords CONTAINS "endometrial development" or "endometrial preparation" or "endometrial priming" or "endometrial receptivity" or "endometrial proliferation" or "endometrial response" or "endometrial thickness" or "utrogestan" or "Endometrin" or "estrogen" or "Sildenafil" or "Glucocorticoids" or "GnRH a" or "GnRH agonist" or "GnRH analog" or "GnRH analogue" or "GnRH analogues" or "GnRHa" or "GnRHa-gonadotropin" or "Gonadorelin" or "Leuprolide" or "leuprolide acetate" or "Nafarelin" or "Progesterone" or "Luteinising hormone releasing hormone" or "luteinizing hormone" or "luteinizing hormone supplementation" or "Lutenising hormone releasing hormone" or "HCG" or "human chorionic gonadotropin" or "Piroxicam" or "oestrodiol" or "estradiol" or "rFSH" or "recombinant FSH" or "Steroids" or "steroid pretreatment" or "low-dose aspirin" or "aspirin" or "stimulated cycle" or "natural cycle" or "natural cycles" or "pituitary desensitisation" or "pituitary desensitization" or "indomethacin"

(376 records)

Appendix 2. CENTRAL via The Cochrane Register of Studies Online (CRSO)

Web platform

Searched 24 June 2020

#1 (pituitary adj2 suppress*):TI,AB,KY 234

#2 (artificial cycle*):TI,AB,KY 67

#3 (stimulated cycle*):TI,AB,KY 184

#4 (natural* cycle*):TI,AB,KY 299

#5 aspirin:TI,AB,KY 13312

#6 (acetylsalicylic acid):TI,AB,KY 5093

#7 sildenafil:TI,AB,KY 1924

#8 antibiotic*:TI,AB,KY 28369

#9 steroid*:TI,AB,KY 28651

#10 gonadorelin:TI,AB,KY 709

#11 GnRHa:TI,AB,KY 464

#12 (GnRH agonist*):TI,AB,KY 1594

#13 MESH DESCRIPTOR Gonadotropin-Releasing Hormone EXPLODE ALL TREES 2578

#14 MESH DESCRIPTOR Leuprolide EXPLODE ALL TREES 678

#15 MESH DESCRIPTOR Nafarelin EXPLODE ALL TREES 77

#16 (gonadotropin-releasing hormone*):TI,AB,KY 2264

#17 (GnRH analogue*):TI,AB,KY 322

#18 (GnRH a):TI,AB,KY 386

#19 lhrh:TI,AB,KY 666

#20 rec-FSH:TI,AB,KY 40

#21 (recombinant follicle stimulating hormone):TI,AB,KY 287

#22 rFSH:TI,AB,KY 458

#23 leuprolide:TI,AB,KY 988

#24 nafarelin:TI,AB,KY 140

#25 progesterone*:TI,AB,KY 6853

#26 glucocorticoid*:TI,AB,KY 8106

#27 (luteinizing hormone):TI,AB,KY 3484

#28 indomethacin:TI,AB,KY 2872

#29 (estradiol or oestradiol):TI,AB,KY 10656

#30 piroxicam:TI,AB,KY 1202

#31 estrogen:TI,AB,KY 11038

#32 corticosteroid*:TI,AB,KY 19549

#33 hcg:TI,AB,KY 2956

#34 (human chorionic gonadotropin*):TI,AB,KY 1012

#35 (endometrin or utrogestin):TI,AB,KY 30

#36 (endometri* adj2 prepar*):TI,AB,KY 218

#37 (uter* adj2 receptiv*):TI,AB,KY 40

#38 (endometri* adj2 receptiv*):TI,AB,KY 291

#39 (endometri* adj2 thick*):TI,AB,KY 1554

#40 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 120828

#41 FET:TI,AB,KY 404

#42 (frozen embryo*):TI,AB,KY 408

#43 (egg dona*):TI,AB,KY 51

#44 (frozen thaw*):TI,AB,KY 486

#45 (oocyte* adj2 don*):TI,AB,KY 353

#46 (thaw* adj2 cycle*):TI,AB,KY 227

#47 (cryopreserv* adj2 embryo*):TI,AB,KY 356

#48 (cryopreserv* adj2 blastocyst*):TI,AB,KY 21

#49 nidation:TI,AB,KY 351

#50 (embryo* adj2 implant*):TI,AB,KY 1001

#51 MESH DESCRIPTOR Cryopreservation EXPLODE ALL TREES 545

#52 MESH DESCRIPTOR Vitrification EXPLODE ALL TREES 40

#53 vitrification:TI,AB,KY 362

#54 cryopreservation:TI,AB,KY 983

#55 #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 3457

#56 #40 AND #55 1420

Appendix 3. MEDLINE search strategy

OVID platform

Searched from 1946 to 24 June 2020

1 (pituitary adj2 suppress$).tw. (1114)
2 artificial cycle$.tw. (168)
3 stimulated cycle$.tw. (775)
4 natural cycle$.tw. (1328)
5 aspirin.tw. (48032)
6 acetylsalicylic acid.tw. (8901)
7 sildenafil.tw. (6571)
8 antibiotic$.tw. (332582)
9 steroid$.tw. (231804)
10 gonadorelin.tw. (216)
11 GnRHa.tw. (1568)
12 GnRH agonist$.tw. (4450)
13 exp gonadotropin-releasing hormone/ or exp leuprolide/ or exp nafarelin/ (32156)
14 gonadotropin-releasing hormone$.tw. (14080)
15 GnRH analogue$.tw. (1480)
16 GnRH a.tw. (1084)
17 sildenafil.tw. (6571)
18 lhrh.tw. (6329)
19 rec-FSH.tw. (53)
20 recombinant follicle stimulating hormone.tw. (479)
21 rFSH.tw. (614)
22 leuprolide.tw. (1884)
23 nafarelin.tw. (259)
24 progesterone$.tw. (82786)
25 glucocorticoid$.tw. (67560)
26 luteinizing hormone.tw. (29065)
27 indomethacin.tw. (35656)
28 (estradiol or oestradiol).tw. (93099)
29 piroxicam.tw. (2992)
30 estrogen.tw. (118624)
31 corticosteroid$.tw. (101899)
32 hcg.tw. (24712)
33 human chorionic gonadotropin$.tw. (13998)
34 (endometrin or utrogestin).tw. (14)
35 (endometri$ adj2 prepar$).tw. (570)
36 (uter$ adj2 receptiv$).tw. (796)
37 (endometri$ adj2 receptiv$).tw. (1676)
38 (endometri$ adj2 thick$).tw. (3091)
39 or/1-38 (1017621)
40 FET.tw. (3288)
41 frozen embryo$.tw. (1607)
42 egg dona$.tw. (405)
43 frozen thaw$.tw. (5139)
44 (oocyte$ adj2 don$).tw. (2421)
45 (thaw$ adj2 cycle$).tw. (3408)
46 (oocyte$ adj2 recipient$).tw. (533)
47 (cryopreserv$ adj2 embryo$).tw. (2176)
48 nidation.tw. (512)
49 (embryo$ adj2 implant$).tw. (6323)

50 or/40-49 (23181)
51 50 and 39 (4339)
52 randomized controlled trial.pt. (508061)
53 controlled clinical trial.pt. (93724)
54 randomized.ab. (483710)
55 placebo.tw. (214488)
56 clinical trials as topic.sh. (191681)
57 randomly.ab. (335695)
58 trial.ti. (220488)
59 (crossover or cross-over or cross over).tw. (85078)
60 or/52-59 (1326942)
61 (animals not (humans and animals)).sh. (4676244)
62 60 not 61 (1220054)
63 51 and 62 (485)

Appendix 4. Embase search strategy

OVID platform

Searched from 1980 to 24 June 2020

1 (pituitary adj2 suppress$).tw. (1219)
2 artificial cycle$.tw. (235)
3 stimulated cycle$.tw. (1149)
4 natural cycle$.tw. (2089)
5 aspirin.tw. (110276)
6 acetylsalicylic acid.tw. (11089)
7 sildenafil.tw. (10312)
8 antibiotic$.tw. (413013)
9 steroid$.tw. (300613)
10 gonadorelin.tw. (335)
11 GnRHa.tw. (2333)
12 GnRH agonist$.tw. (6693)
13 exp exp gonadorelin/ or exp leuprolide/ or exp nafarelin/ (11780)
14 gonadotropin-releasing hormone$.tw. (15789)
15 GnRH analogue$.tw. (2302)
16 GnRH a.tw. (1387)
17 sildenafil.tw. (10312)
18 lhrh.tw. (7286)
19 rec-FSH.tw. (107)
20 recombinant follicle stimulating hormone.tw. (654)
21 rFSH.tw. (1182)
22 leuprolide.tw. (2830)
23 nafarelin.tw. (336)
24 progesterone$.tw. (90966)
25 glucocorticoid$.tw. (84702)
26 luteinizing hormone.tw. (27513)
27 indomethacin.tw. (38550)
28 (estradiol or oestradiol).tw. (101236)
29 piroxicam.tw. (4210)
30 estrogen.tw. (142938)
31 corticosteroid$.tw. (142746)
32 hcg.tw. (31147)
33 human chorionic gonadotropin$.tw. (14799)
34 (endometrin or utrogestin).tw. (106)
35 (endometri$ adj2 prepar$).tw. (990)
36 (uter$ adj2 receptiv$).tw. (1120)
37 (endometri$ adj2 receptiv$).tw. (2898)
38 (endometri$ adj2 thick$).tw. (5367)
39 or/1-38 (1303046)
40 FET.tw. (4647)
41 frozen embryo$.tw. (3143)
42 egg dona$.tw. (866)

43 frozen thaw$.tw. (6523)
44 (oocyte$ adj2 don$).tw. (4468)
45 (thaw$ adj2 cycle$).tw. (4623)
46 (oocyte$ adj2 recipient$).tw. (779)
47 (cryopreserv$ adj2 embryo$).tw. (3460)
48 nidation.tw. (284)
49 (embryo$ adj2 implant$).tw. (8913)
50 or/40-49 (32238)
51 50 and 39 (7349)
52 Clinical Trial/ (965973)
53 Randomized Controlled Trial/ (603591)
54 exp randomization/ (87107)
55 Single Blind Procedure/ (39191)
56 Double Blind Procedure/ (170262)
57 Crossover Procedure/ (63315)
58 Placebo/ (337422)
59 Randomi?ed controlled trial$.tw. (229960)
60 Rct.tw. (37375)
61 random allocation.tw. (2011)
62 randomly allocated.tw. (35202)
63 allocated randomly.tw. (2544)
64 (allocated adj2 random).tw. (815)
65 Single blind$.tw. (24707)
66 Double blind$.tw. (202693)
67 ((treble or triple) adj blind$).tw. (1148)
68 placebo$.tw. (302824)
69 prospective study/ (606319)
70 or/52-69 (2191222)
71 case study/ (69825)
72 case report.tw. (403092)
73 abstract report/ or letter/ (1099122)
74 or/71-73 (1561443)
75 70 not 74 (2137697)
76 75 and 51 (1231)

Appendix 5. PsycINFO search strategy

OVID platform

Searched from 1806 to 24 June 2020

1 (pituitary adj2 suppress$).tw. (37)
2 artificial cycle$.tw. (4)
3 stimulated cycle$.tw. (4)
4 natural cycle$.tw. (59)
5 aspirin.tw. (1183)
6 acetylsalicylic acid.tw. (212)
7 sildenafil.tw. (599)
8 antibiotic$.tw. (2841)
9 steroid$.tw. (9950)
10 gonadorelin.tw. (3)
11 GnRHa.tw. (51)
12 GnRH agonist$.tw. (75)
13 gonadotropin-releasing hormone$.tw. (775)
14 GnRH analogue$.tw. (26)
15 GnRH a.tw. (11)
16 sildenafil.tw. (599)
17 lhrh.tw. (215)
18 rec-FSH.tw. (0)
19 recombinant follicle stimulating hormone.tw. (3)
20 rFSH.tw. (1)
21 leuprolide.tw. (84)
22 nafarelin.tw. (1)

23 progesterone$.tw. (4291)
24 glucocorticoid$.tw. (6211)
25 luteinizing hormone.tw. (1387)
26 indomethacin.tw. (681)
27 (estradiol or oestradiol).tw. (6555)
28 piroxicam.tw. (45)
29 estrogen.tw. (7044)
30 corticosteroid$.tw. (3112)
31 hcg.tw. (106)
32 human chorionic gonadotropin$.tw. (96)
33 (endometri$ adj2 prepar$).tw. (1)
34 (uter$ adj2 receptiv$).tw. (3)
35 (endometri$ adj2 thick$).tw. (14)
36 exp Gonadotropic Hormones/ (4220)
37 or/1-36 (36686)
38 FET.tw. (69)
39 frozen embryo$.tw. (27)
40 egg dona$.tw. (123)
41 frozen thaw$.tw. (4)
42 (oocyte$ adj2 don$).tw. (60)
43 (thaw$ adj2 cycle$).tw. (19)
44 (oocyte$ adj2 recipient$).tw. (2)
45 (cryopreserv$ adj2 embryo$).tw. (23)
46 (embryo$ adj2 implant$).tw. (52)
47 or/38-46 (361)
48 37 and 47 (13)

Appendix 6. LILACS search strategy

Web platform

Searched 24 June 2020

((MH Donación de Oocito OR MH Implantación del Embrión OR MH Criopreservación) OR (Pt Cryopreserv$ OR Pt frozen thaw$)) AND ((MH Aspirina OR MH Esteroides OR MH Agentes Antibacterianos OR MH Gonadorelina) OR ((Pt Sildenafil OR Pt Antibiotic$ OR Pt Gonado$ OR Pt GnRH$ OR PT lhrh$)) OR (MH Implantación del Embrión/efectos de drogas)) AND ((Pt ENSAYO CONTROLADO ALEATORIO OR Pt ENSAYO CLINICO CONTROLADO OR Mh ENSAYOS CONTROLADOS ALEATORIOS OR Mh DISTRIBUCIÓN ALEATORIA OR Mh METODO DOBLE CIEGO OR Mh METODO SIMPLECIEGO OR Pt ESTUDIO MULTICÉNTRICO) or ((tw ensaio or tw ensayo or tw trial) and (tw azar or tw acaso or tw placebo or tw control$ or tw aleat$ or tw random$ or (tw duplo and tw cego) or (tw doble and tw ciego) or (tw double and tw blind)) and tw clinic $)) AND NOT ((Ct ANIMALES OR Mh ANIMALES OR Ct CONEJOS OR Ct RATÓN OR MH Ratas OR MH Primates OR MH Perros OR MH Conejos OR MH Porcinos) AND NOT (Ct HUMANO AND Ct ANIMALES)) [Palavras]

Appendix 7. Data extraction form

Reviewer 1
Reviewer 1
Reviewer 2
Covidence
Last Name Year of report
Title
Intervention
Live Birth Rate (n/N)

(Continued)

Clinical Pregnancy Rate (n/N)
Miscarriage Rate (n/N)
Multiple PR (n/N)
Cycle cancellation rate (n/N)
Endometrial thickness (mm)
Other adverse effects (n/N)
Comparator
Live Birth Rate (n/N)
Clinical Pregnancy Rate (n/N)
Miscarriage Rate (n/N)
Multiple PR (n/N)
Cycle cancellation rate (n/N)
Endometrial thickness (mm)
Other adverse effects (n/N)
Methods
Participants
Interventions
Outcomes
Notes
Adequate sequence generation?
Allocation concealment?
Blinding?
Incomplete outcome data addressed
Free of selective reporting?
Free of other bias?
Risk of bias

WHAT'S NEW

Date	Event	Description
24 June 2020	New search has been performed	New search has been performed with an update to the review and literature. Gabriel Fiszbajn is no longer an author as he could not participate in the update. His contribution is described in the Acknowledgements. Andrea Quinteiro Retamar was included as an author and participated in the update. Contact details were also updated.
21 August 2019	New citation required and conclusions have changed	Some conclusions have changed, and new comparisons were added; 18 new studies were included and 39 studies were excluded. Nine studies from the previous review version were excluded as they no longer meet the inclusion criteria for this review update.
21 August 2019	Amended	The review has a new outline: studies that evaluated luteal phase support were excluded as it will not be evaluated in this review any more; and some comparisons were excluded i.e. those in which the intervention is progesterone versus nothing or different types of progesterone (but we included day to start administration of progesterone in egg donor cycles).

HISTORY

Protocol first published: Issue 1, 2007
Review first published: Issue 1, 2010

Date	Event	Description
27 January 2010	Amended	Minor editing made to text
8 April 2008	Amended	Converted to new review format.
18 February 2008	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Demian Glujovsky: conceived the protocol of the review, and coordinated the whole review process.

Romina Pesce: conceived the protocol of the review and participated in the selection, assessment and data extraction.

Agustin Ciapponi: supervised the methods. He resolved discrepancies of selection or assessment and conducted the analysis.

Carlos Sueldo: provided general advice on the protocol. He assisted in writing the review and resolved discrepancies of selection or assessment.

Andrea Quinteiro: participated in the update by carrying out the screening, assessment of eligibility and data extraction.

Roger Hart: provided general advice on and assistance with the review and contributed to writing the review.

Gabriel Fiszbajn: conceived the review and participated in the selection, assessment and data extraction of the first published review in 2010.

DECLARATIONS OF INTEREST

Demian Glujovsky: None

Romina Pesce: None

Carlos Sueldo: None

Andrea Quinteiro Retamar: None

Roger Hart: RH is the Medical Director of Fertility Specialists of Western Australia and has equity interests in Western IVF and has received research grant funding from Ferring Pharmaceuticals and Merck.

Agustin Ciapponi: None

SOURCES OF SUPPORT

Internal sources

- None form of support is provided to the authors of this review, Argentina

External sources

- None form of support is provided to the authors of this review, Argentina

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Administration of progesterone in relation to oocyte retrieval was not pre-specified but was added as a comparison when the review was being prepared, after protocol publication. The authors considered that this was a clinically significant comparison.

Authors also added, in this review update, the route of administration for oestrogens and comparisons between GnRH agonists and antagonists as they considered relevant.

Studies comparing progesterone versus nothing or placebo, and studies comparing different routes of administering progesterone, were excluded from this review.

Studies with clomiphene citrate were analysed as a post-hoc subgroup for the outcome endometrial thickness.

INDEX TERMS

Medical Subject Headings (MeSH)

Abortion, Spontaneous [epidemiology]; Bias; Clomiphene [administration & dosage]; *Cryopreservation; Drug Administration Schedule; Embryo Implantation [physiology]; Embryo Transfer [*methods]; *Embryo, Mammalian; Endometrium [*drug effects] [physiology]; Follicle Stimulating Hormone [administration & dosage]; Gonadotropin-Releasing Hormone [*agonists]; Letrozole [administration & dosage]; Live Birth [epidemiology]; *Oocyte Donation; Pregnancy Rate; Progesterone [administration & dosage]; Progestins [administration & dosage]; Randomized Controlled Trials as Topic

MeSH check words

Female; Humans; Pregnancy