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Short Versus Extended Progesterone Supplementation for Luteal Phase Support in fresh IVF cycles: a systematic review and meta-analysis

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Highlights:

- Duration of luteal support for fresh IVF cycles is highly variable between centres
- Early cessation of progesterone does not significantly impact clinical outcomes
- Randomisation of >4000 women with positive hCG would confirm non inferiority

Abstract

This review and meta-analysis aims to assess the effect of prolonged progesterone support on pregnancy outcomes in women undergoing a fresh embryo transfer after IVF/ICSI. Two independent authors searched EMBASE, MEDLINE and grey literature from inception to January 2019 for RCTs of prolonged progesterone support vs early cessation. Risk of bias was assessed. Outcome measures were live birth, miscarriage and ongoing pregnancy rate. The study was registered with PROSPERO (CRD42018088605). Seven trials involving 1,627 participants were included: 3 reported live birth rate (672/830), 7 the miscarriage rate (178/1,627) and 7 the ongoing pregnancy rate (1,351/1,627). Clinical outcomes were similar between early progesterone cessation vs progesterone continuation: live birth rate (RR: 0.94, 95% CI: 0.88-1.00), miscarriage rate (RR: 0.91, 95% CI: 0.69-1.20), ongoing pregnancy rate (RR: 0.98, 95% CI: 0.91-1.05). Ongoing pregnancy rates were similar when we restricted analyses to those with cessation of progesterone on the day of a positive hCG (RR: 0.93, 95% CI 0.83-1.06). This meta-analysis suggests that prolonged progesterone support may be unnecessary after fresh embryo transfer. Further larger RCTs would be useful to corroborate and lead to standardised duration of progesterone luteal phase support across IVF/ICSI centres.

Keywords

IVF

Live birth rate

Luteal phase

Miscarriage rate

Ongoing pregnancy rate

Progesterone

Key Message

Meta-analysis of a relatively limited number of randomised participants suggests progesterone supplementation in hCG-triggered fresh IVF cycles may be stopped as early as first positive hCG test with limited impact on ongoing pregnancy, miscarriage and live birth rate. Further studies with substantially increased numbers are required to provide robust estimates.

Introduction:

Luteal phase support is widely recognised as a critical component of fresh in vitro fertilisation (IVF) cycles, due to ovarian stimulation effectively inducing a luteal phase defect. Whereas in natural ovulatory cycles the progesterone level rises with luteinisation and remains stable during the luteal phase, controlled ovarian stimulation (COS) is associated with an gradual decline in serum progesterone after the maturation trigger injection and oocyte recovery (OR) (Hutchinson-Williams et al, 1989, Smitz et al. 1988). This fall in progesterone is multifactorial, but is predominantly believed to be due to inhibition of luteinising hormone (LH) release by the supraphysiological steroid hormone levels associated with multifollicular maturation (Fauser et al. 2003). Other factors involved may be the disruption of corpus lutea associated with follicular aspiration, slow recovery of the pituitary after prolonged exposure to GnRH-agonist and GnRH-antagonist administration and the negative effect of exogenous HCG on the release of LH by the pituitary (Garcia et al. 1981). These effects are ameliorated by the administration of luteal phase support in the form of human chorionic gonadotrophin (hCG) and/or progesterone (van der Linden et al. 2015). Given that hCG is associated with a significant rise in the incidence of ovarian hyperstimulation syndrome, progesterone is the preferred option (van der Linden et al. 2015).

While there is consensus over the importance of exogenous progesterone supplementation in fresh IVF, global practice regarding the duration of luteal support differs widely (Russell et al. 2015). Early studies by Csapo et al., highlight that the luteoplacental shift, whereby the placental trophoblastic cells take over production of progesterone from the corpus luteum, occurs at 7-8 weeks gestation (Csapo et al. 1972). Consequently, many IVF clinicians stop progesterone at this gestation or later. Others advocate stopping progesterone shortly after the positive pregnancy test, on the basis that trophoblastic-derived hCG should support the corpus

lutea to produce progesterone (Kohls et al. 2012). Indeed, some studies have highlighted no detrimental effect of early cessation of progesterone in fresh IVF cycles (Kyrou et al. 2011, Nyboe Andersen et al. 2002, Schmidt et al. 2001). With early cessation further supported by the suggestion of potential teratogenic effects of prolonged fetal progestin exposure in pregnancy (Carmichael et al. 2005, Silver 2004) and the undesirable side-effects of prolonged administration of progestins.

To date several studies have compared short versus extended progesterone supplementation in fresh IVF, however, there is still clinical equipoise and widely differing clinical practices on progesterone duration. To be able to evaluate the necessity for prolonged progesterone administration, we performed a systematic review and meta-analysis of the available randomised control trials (RCTs) comparing short versus prolonged progesterone administration in IVF/ICSI cycles, focusing on the outcomes of live birth, miscarriage and on-going pregnancy rate.

Materials and Methods:

This is a systematic review and meta-analysis of randomized controlled trials (RCTs) evaluating the effectiveness of short or extended progesterone luteal support in IVF. The study protocol was registered in PROSPERO before starting the literature search (CRD42018088605). The review was written following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Search strategy

Two independent authors (M.W. and M.N.) searched electronic databases (MEDLINE, Scopus, EMBASE, Science- Direct, the Cochrane Database of Systematic Reviews, grey literature and ClinicalTrials.gov) from their inception until 1 January 2019. The search terms were designed to include studies involved in IVF, ICSI, luteal phase support and progesterone. The terms were reviewed by a medical sciences librarian. After initial title and abstract screening, studies were imported to online software (Covidence.org) and reviewed independently (M.W and M.N.) to reach the final cohort of studies included in the review.

The key search terms were as follows: [Mesh/Entree] progesterone AND in vitro fertilization OR assisted reproductive techniques, embryo transfer, intracytoplasmic sperm injection (ICSI).

Inclusion criteria

Only RCTs reported in the English language investigating the duration of progesterone supplementation for luteal phase support in fresh IVF/ICSI cycles. Trials assessing frozen embryo transfers were excluded.

Study outcomes

The preferred primary outcome was the live birth rate (baby born alive at ≥ 24 weeks gestation) whenever available. Alternatively, the ongoing pregnancy rate (pregnancy beyond 12 weeks) (OPR) was used. The main secondary outcome was the miscarriage rate (failure to achieve live birth after a positive pregnancy test).

Study Selection and Data Extraction

Titles and abstracts were screened independently by two authors (M.W., M.N.). The same authors independently assessed studies for inclusion and extracted data about study features (design, country, and time of study), populations (number and characteristics of participants), type of intervention, ovarian stimulation cycles (drugs, duration of luteal support), and IVF outcomes. A manual search of references within the included studies was also performed to avoid any missing relevant data. Any disagreement concerning the extracted data was resolved by consensus, and, whenever necessary, a third author was consulted (S.M.N). RCTs selected for meta-analysis were read in full by M.W., M.N., and S.M.N.

Assessment or Risk of Bias

The risk of bias in the included studies was assessed independently by two reviewers according to the guidelines recommended in the Cochrane Handbook for Systematic Review of Intervention. For each study, we assessed the risk of bias related to sequence generation, allocation, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other sources of bias. A judgment of 'Yes' meant a low risk of bias, a judgment of 'No' meant a high risk of bias, and 'Unclear' indicated an unclear risk of bias. Disagreements were discussed and resolved by consensus.

Statistical Analysis

Data analysis was performed by two authors (M.W., M.N.) using Review Manager Version 5.3 (the Cochrane Collaboration, Software Update). All analyses were carried out with an intention-to-treat approach (number of events per women randomized) using the random effects model (DerSimonian and Laird, assuming that the data being analyzed were drawn from a hierarchy of different populations). Dichotomous variables were analyzed using the risk ratio (RR) with a 95% confidence interval (CI). $P < .05$ was considered statistically significant. Heterogeneity was measured using Higgins I^2 .

We performed a sensitivity analysis by assessing on which day patients were randomised, either on the day of positive hCG or for those who continued until clinical pregnancy and were then randomised. For on-going pregnancy rate, a random effects model was used since results were heterogenous between studies. We also performed a sensitivity analysis serially excluding each study and different study subgroups according to the methodological quality judgement from the pooled analysis for the primary outcomes.

Results:

Literature search results

The initial search revealed a total of 682 journal articles (Figure 1). After screening for duplicates (187), 495 articles remained. Four hundred and eighty six of these were excluded during title and abstract review because of not meeting the inclusion criteria. On review of the nine full text articles, two papers were excluded (Abate et al. 1999, Schmidt et al. 2001). One of these was a trial comparing luteal support with no luteal support and was excluded on the basis of incorrect comparator (Abate et al. 1999). The other described a retrospective analysis and so did not meet inclusion criteria (Schmidt et al. 2001). After literature search and screening 7 articles remained for inclusion in the analysis (Aboulghar et al. 2008, Gazvani et al. 2012, Goudge et al. 2010, Kohls et al. 2012, Kyrou et al. 2011, Nyboe Andersen et al. 2002, Prietl et al. 1992).

Included studies

The total patient pool included 1627 participants undergoing a single IVF/ICSI cycle; 818 women were assigned to the short luteal support group and 809 to the control group. Study characteristics are summarized in Table 1.

Methodological quality of included studies

All seven of the included trials had low risk random sequence generation meaning that participants were adequately randomised reducing selection bias. Three of the trials were identified as having high risk allocation concealment (Kohls et al. 2012, Nyboe Andersen et al. 2002, Prietl et al. 1992) indicating concern of possible selection bias due to inadequate concealment of allocations. Only one of the trials adequately blinded participants, personnel

and outcome assessors (Gazvani et al. 2012). This was also the only placebo-controlled trial (Gazvani et al. 2012). A summary of the methodological quality of included studies is provided in Table 2.

Live birth rate

Three studies presented data on live birth rate (Gazvani et al. 2012, Goudge et al. 2010, Nyboe Andersen et al. 2002). Overall 672 live births were reported in 830 participants. There were 328 live births in the early P cessation group (where progesterone was stopped at 11th or 14th day post embryo transfer after achieving a positive hCG). There were 344 live births in the P continuation group (where P was continued to week 6, 7 or 10 after embryo transfer or oocyte retrieval). The overall continuation to a live birth for the early P cessation group was 78.5% (328/418) and for the P continuation group 83.5% (344/412), with confidence intervals crossing unity, implying there was no difference (RR: 0.94, 95% CI: 0.88-1.00; $p=0.07$). No statistical heterogeneity was observed between the studies ($\text{Chi}^2 = 0.13$, $df = 2$ ($p=0.94$); $I^2 = 0\%$)(Figure 2A).

Ongoing pregnancy rate

All trials reported the ongoing pregnancy rate with 1,351 ongoing pregnancies in 1,627 participants, of which 670 out of 818 were in the early P cessation group and 681 out of 809 were in the P continuation group. A meta-analysis of all seven trials yielded an RR of 0.98 (95% CI: 0.91-1.05; $p=0.49$), showing that there was no statistically significant difference between the early P cessation and P continuation groups in terms of ongoing pregnancy rate. Heterogeneity was detected in the overall results, likely due to the difference in protocols used. ($\text{Chi}^2 = 18.69$, $df = 6$ ($p=0.005$), $I^2 = 68\%$).

A subgroup analysis was performed due to study differences in timing of early cessation of progesterone supplementation. In five of the studies P was withdrawn on the day of a positive hCG test (Gazvani et al. 2012, Goudge et al. 2010, Kyrou et al. 2011, Andersen et al. 2002, Prietl et al. 1992) and in two studies P was withdrawn on the day that clinical pregnancy was confirmed at 5-7 weeks gestation (Aboulghar et al. 2008, Kohls et al. 2012). This stratified analysis revealed no significant differences between the studies in which P was stopped on day of positive hCG (RR: 0.93, 95% CI: 0.83-1.06; p=0.27) or on the day that clinical pregnancy was verified (RR 1.01, 95% CI: 0.97, 1.06, p=0.55) (Figure 2B).

Miscarriage rate

Miscarriage data were available from seven studies with 178 events out of 1627 participants (Aboulghar et al. 2008, Gazvani et al. 2012, Goudge et al. 2010, Kohls et al. 2012, Kyrou et al. 2011, Nyboe Andersen et al. 2002, Prietl et al. 1992). In the early P cessation group, there was 86/818 and 92/809 in the P continuation group. No statistical heterogeneity was observed between the two groups. There were no significant differences in the number of miscarriages between patients who received early P cessation and those who were in the P continuation group. (RR 0.91, 95% CI: 0.69, 1.20, P= 0.52) No statistical heterogeneity was observed between the studies ($\text{Chi}^2 = 4.46$, $\text{df} = 6$ ($p = 0.61$); $I^2 = 0\%$) (Figure 2C).

Discussion

The use of luteal phase support in fresh IVF is ubiquitous. While some clinics stop luteal support at the time the pregnancy test is positive, several recent surveys have highlighted that the majority of clinics continue progesterone well into the first trimester (Russell et al. 2015, Vaisbuch et al. 2012). This current systematic review and meta-analysis suggests that prolonged progesterone supplementation may not be required, and early cessation may not be detrimental to clinical outcomes. In particular, there was no difference in ongoing pregnancy, live birth and miscarriage rates between groups in which progesterone supplementation was stopped early as compared with prolonged progesterone supplementation. Furthermore, in those women where progesterone supplementation was stopped early, we did not observe a substantive detrimental effect if progesterone was stopped on the day of the initial pregnancy test, as compared with after a clinical pregnancy was confirmed.

Our results are consistent with the previous meta-analysis by Liu and colleagues (Liu et al. 2012). However, the current review includes the additional RCT by Gazvani and colleagues, which is the only one of the included studies to be double blinded and placebo controlled and randomised 461 participants with a positive pregnancy test. All other included studies did not take steps to blind participants, personnel or assessors. However, it is unlikely that the

objective outcomes of live birth, ongoing pregnancy and miscarriage rate would be significantly affected by this.

The definition of early cessation differed between studies. In the majority of studies (five out of seven) the early cessation group luteal support was stopped in week four, at time of pregnancy test (Gazvani et al. 2012, Goudge et al. 2010, Kyrou et al. 2011, Nyboe Andersen et al. 2002, Prietl et al. 1992). However, in two studies early cessation was defined as at the time of first USS, which was week five in one study (Kohls et al. 2012) and week six-seven in the other (Aboulghar et al. 2008). Consequently, subgroup analysis based on the definition of early P cessation was undertaken for the outcome of ongoing pregnancy rate (Figure 2B).

Within both subgroups the ongoing pregnancy rate, albeit apparently lower, did not differ significantly between stopping at the time pregnancy was confirmed versus administering progesterone for a prolonged duration. In all three studies that reported live birth rate, patients that were randomised to early P cessation had P supplementation end on the day of positive hCG test, with no difference demonstrated between stopping P at this time versus prolonged administration (Gazvani et al. 2012, Goudge et al. 2010, Nyboe Andersen et al. 2002). These results if substantiated suggest that prolonged luteal support may not be necessary beyond the positive pregnancy test. This supports the hypothesis that the rise in endogenous hCG associated with implantation provides adequate luteal support early in an IVF pregnancy in advance of the luteoplacental shift, which is believed to occur at seven to eight weeks' gestation. Notably only one study, Prietl et al 1992, provided oestrogen during the luteal phase and only the study by Goudge et al monitored serum progesterone and recommenced progesterone in one patient when it fell below 15ng/ml. Whilst bleeding after embryo transfer but before randomisation was an exclusion criteria for all trials, there is recent evidence for the benefit of progesterone supplementation in those women with a

history of recurrent miscarriage even after spontaneous conception, (Coomarasamy et al. 2019). Overall these data suggest that unmonitored progesterone supplementation in isolation may be adequate for uncomplicated pregnancies. However, for cycles where there are concerns regarding potential defective corpus luteal function, or threatened miscarriage, progesterone continuation will be critical (Coomarasamy et al. 2019). Future studies defining appropriate thresholds in the absence of clinical symptoms to identify the need for recommencement of progesterone would need to be product specific given their different terminal half-lives.

Most of the included studies utilised gonadotrophin releasing hormone agonists for suppression of the hypothalamic-pituitary-ovarian (HPO) axis down-regulation during ovarian stimulation. However, in two of the included studies the short protocol, incorporating a GnRH-antagonist, was used (Kohls et al. 2012, Kyrou et al. 2011) and in one study a variety of protocols was employed (Goudge et al. 2010). Due to the limited number of studies, it was not possible to carry out subgroup analyses based on this variation. However, given that the luteal phase defect in fresh IVF cycles is primarily believed to be due to the negative effect of supraphysiological hormone levels associated with controlled ovarian stimulation on the HPO axis (Coomarasamy et al. 2019), rather than any potential differences in the severity of luteolysis between GnRH antagonist and agonist cycles, it is likely that the findings of this meta-analysis are applicable to both agonist and antagonist protocols. Confirmation of the applicability of these findings to GnRH antagonist cycles given the limited number of patients studied (n=420) would be beneficial.

Our study showed no difference in rate of miscarriage between early P cessation and continued exposure. The role of progesterone for treatment of miscarriage has been widely

explored. In women with a history of recurrent miscarriage exogenous supplementation has not been shown to be beneficial if the pregnancy is uncomplicated (Coomarasamy et al. 2015). In contrast in women with a threatened miscarriage, the recent PRISM trial would suggest that initiation of progesterone is beneficial particularly in those with three or more previous miscarriages (Coomarasamy et al. 2019). Given the lower point estimate for ongoing pregnancy rates with stopping progesterone at the time of the initial pregnancy test, clinicians may be reluctant to stop progesterone until there is clear evidence of a positive fetal heart beat, and a lower risk of bleeding and threatened miscarriage.

Our study has a number of strengths including an extensive search, identification of previously unpublished trials, and use of appropriate methodology. We do, however, acknowledge some limitations. All the included studies involved the administration of hCG as the oocyte maturation trigger prior to oocyte retrieval, and we would not wish our findings to be extrapolated to cycles where a GnRH agonist trigger has been used. The luteal phase defect after GnRH agonist triggering is substantially more profound than that observed with hCG (Lanzone et al. 1994, Nevo et al. 2003) and the optimal luteal phase rescue still debated. The timing of initiation of luteal phase support differed between studies with most commencing luteal support on the day of or the day after OR (Gazvani et al. 2012, Kohls et al. 2012, Kyrou et al. 2011, Goudge et al. 2010, Aboulghar et al 2008) and one study starting luteal progesterone on the day of embryo transfer (Nyobe Andersen et al. 2002). Notably, one study (Goudge et al. 2010) commenced luteal support at different timing for each study group with initiation on the day of OR for the early P cessation group and on the day of ET for the P continuation group. Given the limited pool of studies it was not feasible to perform subgroup analysis to determine whether this variation would impact upon outcomes, but recent trials have suggested equivalence when progesterone is commenced on the day of hCG trigger or

on the day after oocyte retrieval (Gao et al. 2018). We were unable to assess the reported associations of exogenous progesterone and congenital urogenital malformations in male babies (Carmichael et al. 2005, Silver 2004) as congenital anomaly data were not provided. The timing of embryo transfer differed between the studies, but in general cleavage stage transfer dominated, reflecting when these trials were undertaken. Lastly, the power of all the studies and even this meta-analysis are limited. To be able to confirm non-inferiority with a margin of -8%, of early progesterone cessation using the observed frequencies from the trials reporting live birth, more than 4000 women with a positive hCG would need to be randomised.

Conclusions

This meta-analysis on the basis of otherwise a relatively limited number of randomised participants suggests that in fresh IVF cycles with an hCG trigger and proceeding to a fresh embryo transfer, progesterone supplementation may be stopped as early as the first positive hCG test with limited impact on ongoing clinical pregnancy, miscarriage and live birth rate. However, the total number of participants enrolled from all studies is limited, with a substantial increase in trial size required to provide robust estimates and ensure that early cessation is not associated with a small increase in adverse clinical outcomes.

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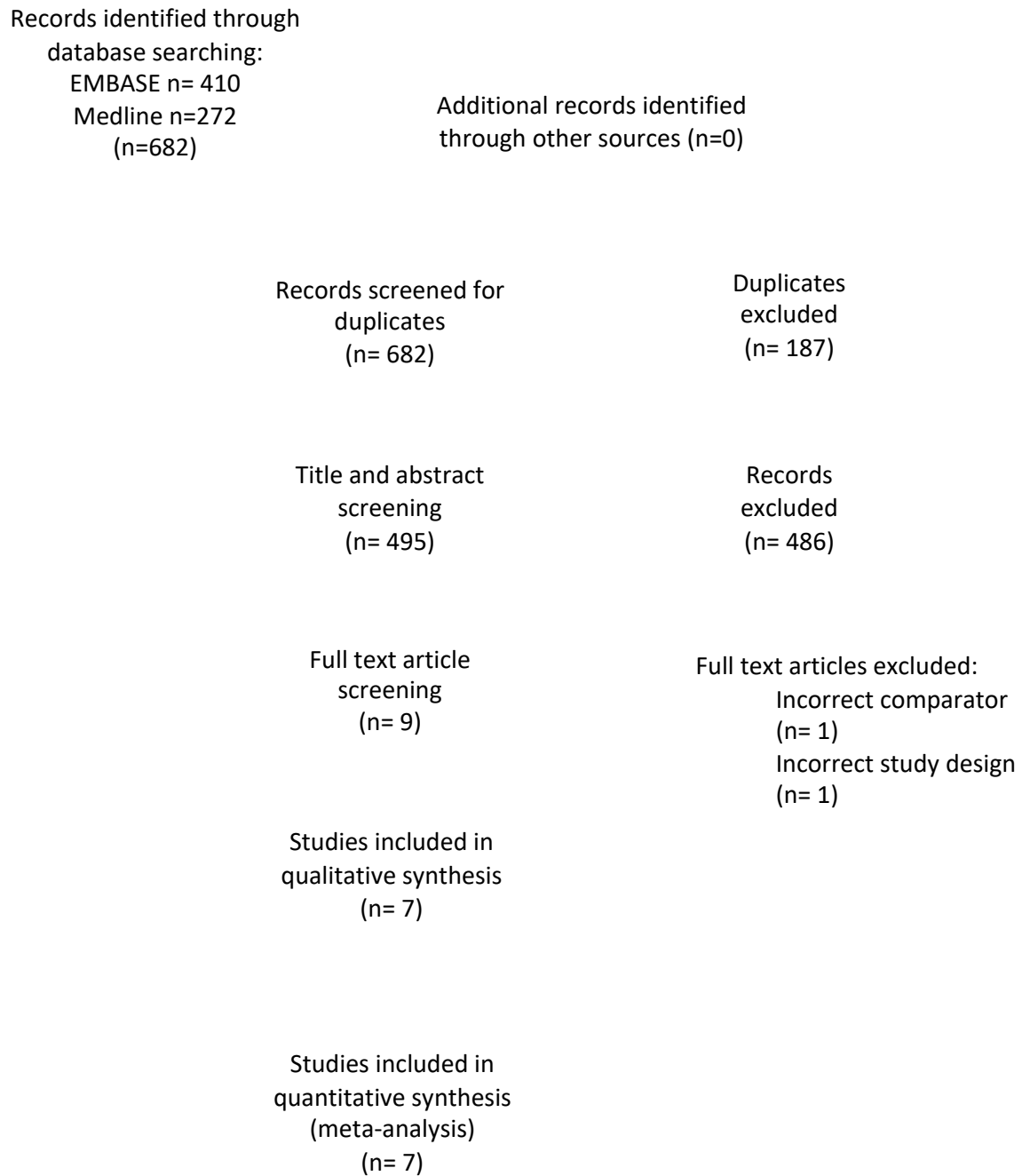
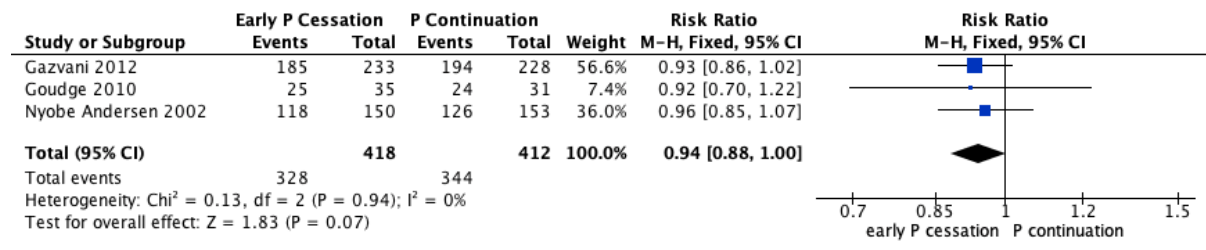


Figure 1: Flow chart of studies included in systematic review and meta-analysis.

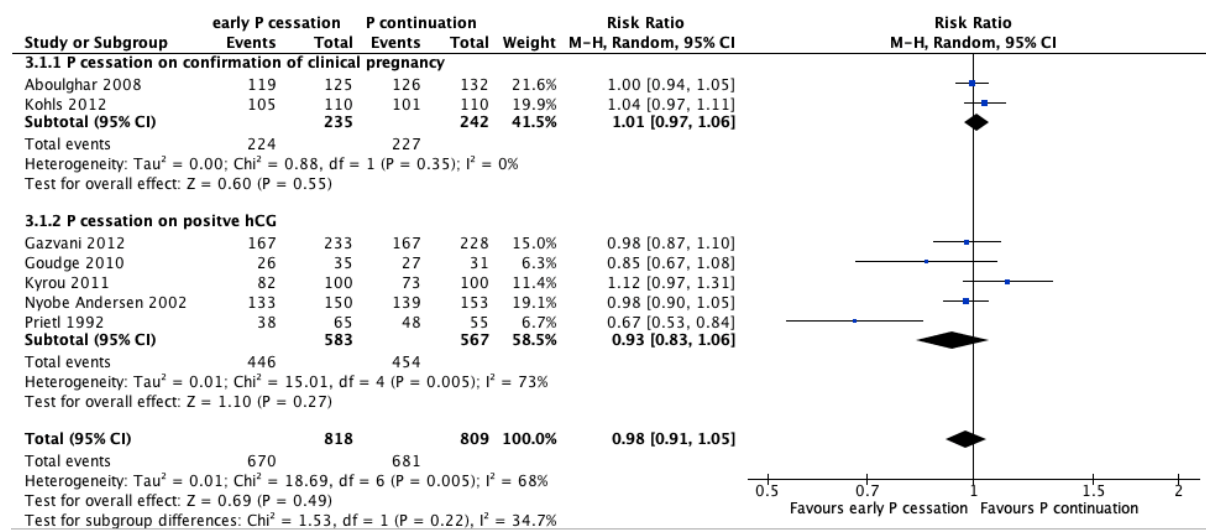
Figure 2: Meta-analysis for live birth rates, ongoing pregnancy rates and miscarriage of women who underwent early P cessation versus P continuation.

Panel A live birth, Panel B ongoing pregnancy, Panel C miscarriage.

A



B



C

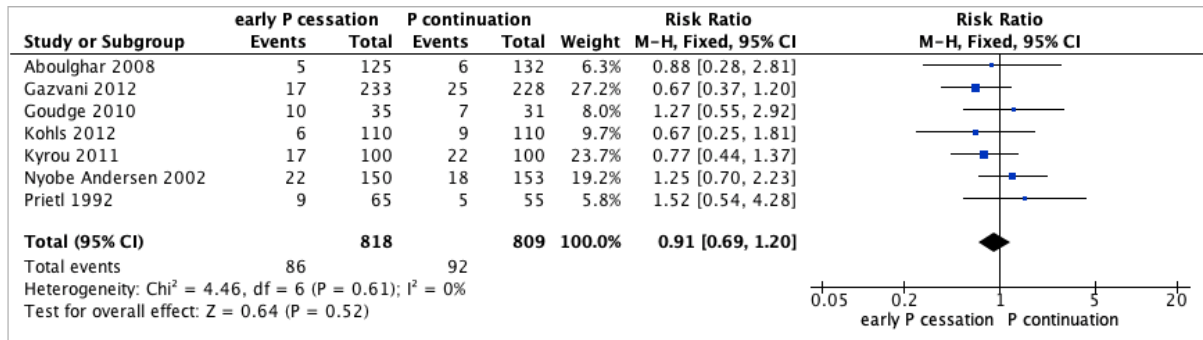


Table 1: Summary of included studies

Study Author, year	Timing of randomisation	ART	COH protocols	Trigger medication	Total	Initiation of P	Dose and route of administration	No.	Early P cessation (gestational age)	No.	P continuation (gestational age)	Notes
Gazvani, 2012	Positive hCG test	IVF/ICSI	GnRH-a	HCG	461	OR	vaginal or PR P 400mg bd	233	Week 4 (16 days post-OR at urinary pregnancy test)	228	Week 10	
Kohls, 2012	Clinical pregnancy	IVF/ICSI	GnRH-anta	HCG	220	Day after OR	vaginal P 200mg bd	110	Week 5 (after USS)	110	week 8	
Kyrou, 2011	Positive hCG test	IVF/ICSI	GnRH-anta	HCG	200	Day after OR	vaginal P 200mg tid	100	Week 4 (16 days post-ET at urine pregnancy test)	100	week 7	
Goudge, 2010	COH	IVF/ICSI	GnRH-a/anta	HCG	101	Day of OR (early P cessation) Or Day of ET (P continuation)	IM P 50mg qid	53 ^a	Week 4 (at urinary pregnancy test)	48 ^a	week 6	One patient in study group had serum P of <15ng/ml on day of UPT had IM progesterone restarted. Patient remained in analysis.
Aboulghar, 2008	Clinical pregnancy	ICSI	GnRH-a	HCG	257	Day of OR	IM 50mg (frequency unspecified) or vaginal P600mg (frequency unspecified)	125	Week 6-7 (after USS)	132	week 9-10	
Nyobe Andersen 2002	Positive hCG test	IVF/ICSI	GnRH-a	HCG	303	ET	vaginal P 200mg tid	150	Week 4 (14th day post-ET at urinary/serum HCG)	153	week 7	
Prieti, 1992	Positive hCG test	IVF	GnRH-a	HCG	120	unstated	PC 500mg/EV 10mg tiw	65	Week 4 (day 15 after OR)	55	week 12	

a) Goudge et al total number enrolled in early P cessation was 53 and 48 in prolonged P supplementation but only confirmed biochemical pregnancies - 35 in early P cessation and 31 in prolonged P supplementation were included in analysis

ART – assisted reproductive technology
BD – twice daily
COH – controlled ovarian
hyperstimulation
ET – embryo transfer
EV – estradiol valerate
GnRH-a - GnRH agonist
GnRH-anta – GnRH antagonist
OR – oocyte retrieval
P – progesterone
PC -17a-hydroxyprogesterone caproate
QID – four times daily
TID – three times daily
TIW – three times weekly

Table 2: Methodological quality of included studies

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Aboulghar 2008	+	+	-	-	+	+	+
Nyobe Andersen 2002	+	-	-	-	+	+	+
Gazvani 2012	+	+	+	+	?	?	+
Goudge 2010	+	+	-	-	-	+	+
Kohls 2012	+	-	-	-	+	+	+
Kyrou 2011	+	+	-	-	+	+	+
Priehl 1992	+	-	-	-	+	+	+

References

Abate, A., Brigandi, A., Abate, F., Manti, F., Unfer, V., & Perino, M., 1999. Luteal phase support with 17 α -hydroxyprogesterone versus unsupported cycles in in vitro fertilization: a comparative randomized study. *Gynecologic and obstetric investigation*. 48, 78-80.

Aboulghar, M. A., Amin, Y. M., Al-Inany, H. G., Aboulghar, M. M., Mourad, L. M., Serour, G. I., Mansour, R.T., 2008. Prospective randomized study comparing luteal phase support for ICSI patients up to the first ultrasound compared with an additional three weeks. *Human reproduction*. 23, 857-862.

Carmichael, S. L., Shaw, G. M., Laurent, C., Croughan, M. S., Olney, R. S., & Lammer, E. J., 2005. Maternal progestin intake and risk of hypospadias. *Archives of pediatrics & adolescent medicine*. 159, 957-962.

Coomarasamy, A., Devall, A.J., Cheed, V., Harb, H., Middleton, L.J., Gallos, I.D., Williams, H., Eapen, A.K., Roberts, T., Ogwulu, C.C. and Goranitis, I., 2019. A Randomized Trial of Progesterone in Women with Bleeding in Early Pregnancy. *New England Journal of Medicine*. 380, 1815-1824.

Coomarasamy, A., Williams, H., Truchanowicz, E., Seed, P.T., Small, R., Quenby, S., Gupta, P., Dawood, F., Koot, Y.E., Atik, R.B. and Bloemenkamp, K.W., 2016. PROMISE: first-trimester progesterone therapy in women with a history of unexplained recurrent miscarriages-a randomised, double-blind, placebo-controlled, international multicentre trial and economic evaluation. *Health technology assessment*. 20, 1.

Csapo, A. I., Pulkkinen, M. O., Ruttner, B., Sauvage, J., & Wiest, W., 1972. The significance of the human corpus luteum in pregnancy maintenance: I. Preliminary studies. *American journal of obstetrics and gynecology*, 112, 1061-1067.

Fausser, B. C., & Devroey, P., 2003. Reproductive biology and IVF: ovarian stimulation and luteal phase consequences. *Trends in Endocrinology & Metabolism*. 14, 236-242.

Gao, J., Gu, F., Miao, B.-Y., Chen, M.-H., Zhou, C.-Q., & Xu, Y.-W., 2018. Effect of the initiation of progesterone supplementation in in vitro fertilization–embryo transfer outcomes: a prospective randomized controlled trial. *Fertility and sterility*. 109, 97-103.

Garcia, J., Jones, G. S., Acosta, A. A., & Wright Jr, G. L., 1981. Corpus luteum function after follicle aspiration for oocyte retrieval. *Fertility and sterility*. 36, 565-572.

Gazvani, R., Russell, R., Sajjad, Y., & Alfirevic, Z., 2012. Duration of luteal support (DOLS) with progesterone pessaries to improve the success rates in assisted conception: study protocol for a randomized controlled trial. *Trials*. 13, 118.

Goudge, C. S., Nagel, T. C., & Damario, M. A., 2010. Duration of progesterone-in-oil support after in vitro fertilization and embryo transfer: a randomized, controlled trial. *Fertility and sterility*. 94, 946-951.

Hutchinson-Williams, K.A., Lunenfeld, B., Diamond, M.P., Lavy, G., Boyers, S.P. and DeCherney, A.H., 1989. Human chorionic gonadotropin, estradiol, and progesterone profiles in conception and nonconception cycles in an in vitro fertilization program. *Fertility and Sterility*. 52, 441-445.

Kohls, G., Ruiz, F., Martínez, M., Hauzman, E., de la Fuente, G., Pellicer, A. and Garcia-Velasco, J.A., 2012. Early progesterone cessation after in vitro fertilization/intracytoplasmic sperm injection: a randomized, controlled trial. *Fertility and sterility*. 98, 858-862.

Kyrou, D., Fatemi, H.M., Zepiridis, L., Riva, A., Papanikolaou, E.G., Tarlatzis, B.C. and Devroey, P., 2011. Does cessation of progesterone supplementation during early pregnancy in patients treated

with recFSH/GnRH antagonist affect ongoing pregnancy rates? A randomized controlled trial. *Human reproduction*. 26, 1020-1024.

Lanzone, A., Fulghesu, A.M., Villa, P., Guida, C., Guido, M., Nicoletti, M.C., Caruso, A. and Mancuso, S., 1994. Gonadotropin-releasing hormone agonist versus human chorionic gonadotropin as a trigger of ovulation in polycystic ovarian disease gonadotropin hyperstimulated cycles. *Fertility and sterility*. 62, 35-41.

Liu, X.-R., Mu, H.-Q., Shi, Q., Xiao, X.-Q., & Qi, H.-B., 2012. The optimal duration of progesterone supplementation in pregnant women after IVF/ICSI: a meta-analysis. *Reproductive Biology and Endocrinology*. 10, 107.

Nevo, O., alia Eldar-Geva, T., Kol, S., & Itskovitz-Eldor, J., 2003. Lower levels of inhibin A and pro- α C during the luteal phase after triggering oocyte maturation with a gonadotropin-releasing hormone agonist versus human chorionic gonadotropin. *Fertility and sterility*. 79, 1123-1128.

Nyobe Andersen, A., Popovic-Todorovic, B., Schmidt, K.T., Loft, A., Lindhard, A., Højgaard, A., Ziebe, S., Hald, F., Hauge, B. and Toft, B., 2002. Progesterone supplementation during early gestations after IVF or ICSI has no effect on the delivery rates: a randomized controlled trial. *Human Reproduction*. 17, 357-361.

Priehl, G., Diedrich, K., van der Ven, H. H., Luckhaus, J., & Krebs, D., 1992. The effect of 17 α -hydroxyprogesterone caproate/oestradiol valerate on the development and outcome of early pregnancies following in vitro fertilization and embryo transfer: A prospective and randomized controlled trial. *Human Reproduction*. 7, 1-5.

Russell, R., Kingsland, C., Alfirevic, Z., & Gazvani, R, 2015. Duration of luteal support after IVF is important, so why is there no consistency in practice? The results of a dynamic survey of practice in the United Kingdom. *Human Fertility*. 18, 43-47.

Schmidt, K. L. T., Ziebe, S., Popovic, B., Lindhard, A., Loft, A., & Andersen, A. N., 2001. Progesterone supplementation during early gestation after in vitro fertilization has no effect on the delivery rate. *Fertility and sterility*. 75, 337-341.

Silver, R.I., 2004. Endocrine abnormalities in boys with hypospadias., in: Baskin, L (Ed.), *Hypospadias and Genital Development*. Springer., pp. 45-72.

Smitz, J., Devroey, P., Camus, M., Deschacht, J., Khan, I., Staessen, C., Van Waesberghe, L., Wisanto, A. and Van Steirteghem, A.C., 1988. The luteal phase and early pregnancy after combined GnRH-agonist/HMG treatment for superovulation in IVF or GIFT. *Human Reproduction*. 3, 585-590.

Vaisbuch, E., Leong, M., & Shoham, Z., 2012. Progesterone support in IVF: is evidence-based medicine translated to clinical practice? A worldwide web-based survey. *Reproductive biomedicine online*. 25, 139-145.

Van der Linden, M., Buckingham, K., Farquhar, C., Kremer, J. A., & Metwally, M., 2015. Luteal phase support for assisted reproduction cycles. *Cochrane Database Syst Rev*(7), CD009154

