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Review

Systematic review of the clinical efficacy of vaginal progesterone for luteal phase support in assisted reproductive technology cycles

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KEY MESSAGE
The vaginal progesterone preparations Crinone, Cyclogest, Lutigest and Utrogestan Vaginal were found to be equally safe and effective vaginal progesterone products for luteal phase support in assisted reproductive technology cycles.

A B S T R A C T

Vaginal progesterone via capsule, gel or tablet is the most common route for luteal phase support (LPS) in Europe. Although there is a wealth of data comparing products used at other stages of assisted reproductive technology cycles, there is a lack of systematically identified evidence comparing the wide range of vaginal progesterone products. This systematic review queried the MEDLINE, Embase and Cochrane Library databases on 30 June 2016 to identify head-to-head randomized controlled trials (RCTs) comparing the efficacy or safety of vaginal progesterone preparations (Crinone, Cyclogest, Lutigest or Utrogestan Vaginal) for LPS in assisted reproductive technology cycles. Of 1914 results, 18 RCTs were included. No significant difference in clinical pregnancy rate was identified in comparisons of Utrogestan Vaginal with Crinone. Utrogestan Vaginal and Lutigest were non-inferior to Crinone in ongoing pregnancy rate comparisons. Differences in patient-reported perineal irritation with Crinone and Lutigest were not significantly different to Cyclogest. In studies comparing varying timing or dosage of Utrogestan Vaginal or Crinone, no significant differences were observed. These results suggest Crinone, Cyclogest, Lutigest and Utrogestan Vaginal represent equally safe and effective choices of vaginal progesterone for LPS in assisted reproductive technology cycles. Future quantitative analyses could provide further support for these findings.

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Introduction

The World Health Organization (WHO) defines infertility as 'a disease of the reproductive system defined by the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse' (World Health Organization, 2016). In 2010, the WHO estimated that 48.5 million couples worldwide were unable to have a child after five years, while 2013 estimates suggested that one in seven couples in the UK were affected by some form of fertility problem (HFEA, 2016; Mascarenhas et al., 2012). This substantial burden of infertility is leading to increasing use of assisted reproductive technologies, with 2.1% of babies born through these methods in the UK in 2013 (HFEA, 2016).

Different treatments are available depending on the cause of infertility. These consist of intrauterine insemination (IUI) or intracytoplasmic sperm injection (ICSI) in the case of low sperm count or motility and IVF if previous assisted reproductive technologies have not been successful (Inhorn and Patrizio, 2015; Mesen and Young, 2015; Palermo et al., 1992).

During natural menstrual cycles, the endometrium prepares for implantation of an embryo, starting in the follicular phase and continuing through the luteal phase. A surge in luteinizing hormone (LH) triggers ovulation; LH also causes granulosa cells to produce progesterone, which prepares the endometrium for implantation and occurs approximately six days post-fertilization (van der Linden et al., 2015). Post-implantation, the placenta secretes syncytiotrophoblastic cells that produce progesterone to maintain the pregnancy until the placenta takes over steroid hormone production at approximately seven weeks (van der Linden et al., 2015).

Assisted reproductive technology cycles are known to have an insufficient luteal phase, probably due to the supra-physiologic oestrogen levels in IVF and ICSI in the follicular phase, as a result of ovarian stimulation used to prepare for oocyte retrieval. Therefore, sufficient luteal phase support (LPS) is essential during these cycles to improve implantation and pregnancy rates (van der Linden et al., 2015; Yanushpolsky, 2015). LPS may be achieved by direct use of progesterone, or by substituting deficient LH with gonadotrophin-releasing hormone (GnRH) agonists or human chorionic gonadotrophin (HCG) (van der Linden et al., 2015; Yanushpolsky, 2015). Both HCG and progesterone have been investigated and approved as agents for LPS (van der Linden et al., 2015).

Progesterone is a naturally-occurring hormone during pregnancy and poses no known additional risk when administered to women during the first trimester following assisted reproductive technologies; furthermore, long-term experience of vaginally administered progesterone provides a well-known safety profile (Mesen and Young, 2015). The available evidence suggests similar efficacy between progesterone and HCG; however, HCG is associated with a significantly greater risk of ovarian hyperstimulation syndrome (OHSS) (Mesen and Young, 2015; van der Linden et al., 2015).

Progesterone for LPS is administered via a range of different routes including vaginal, intramuscular injection (IM), oral and rectal. There is evidence in the scientific literature on the comparative efficacy of these various administration routes, including a systematic review by the Cochrane Collaboration which demonstrated no significant difference between IM and vaginal progesterone in terms of live birth rate and ongoing pregnancy rate. The review identified no significant differences in terms of miscarriage and multiple pregnancy rate and showed no differences between vaginal or rectal administration versus oral administration, nor between IM and oral or between vaginal and rectal routes in terms of live birth, ongoing pregnancy and miscarriage rates (Daya and Gunby, 2008; Fatemi et al., 2007; van der Linden et al., 2015; Zarutskie and Phillips, 2009).

While the comparative efficacy of the various routes of progesterone administration has been demonstrated, further factors should be taken into consideration for the comparison of these formulations. IM can be complicated by injection site reactions and is often not the patient's first choice (Polyzos et al., 2010; Propst et al., 2001). Oral administration leads to variable levels of absorption and high first-pass hepatic metabolism, which can result in the production of teratogenic liver metabolites (Carmichael et al., 2005). Rectal administration has improved uterine progesterone levels over the oral route. However, vaginal administration shows high uterine levels of progesterone with low systemic exposure (Kleinstein, 2005).

Evidence from clinical practice suggests that vaginal progesterone is the preferred method for LPS in assisted reproductive technologies with approximately 77% of 284,600 IVF cycles reporting the use of vaginal progesterone in a 2012 survey of 408 IVF units across 82 countries (Beltsos et al., 2014; Ho et al., 2008; IVF Worldwide, 2012; Silverberg et al., 2012). A combination of vaginal progesterone with IM or oral progesterone was the next most common administration route, used in 17.3% of cycles, while 4.6% and 0.5% of cycles used IM progesterone alone or oral progesterone alone, respectively (Daya and Gunby, 2004, 2008).

Despite this common usage and the variation in posology of the vaginal progesterone products (i.e. gel once daily [Crinone], pessaries twice daily [Cyclogest], capsules [Utrogestan Vaginal] or tablets three times daily [Lutigest]; **Table 1**), there have been few attempts to systematically identify and evaluate the comparative efficacy and safety of this wide range of different vaginal progesterone preparations. To our knowledge, just one meta-analysis, conducted in 2009, has investigated this topic. The aim was to compare the efficacy and safety of vaginal gel progesterone preparations (Crinone) with any other form of vaginal progesterone specifically for IVF/ICSI cycles (Polyzos et al., 2010). This study identified no significant difference between vaginal gel and the other vaginal progesterone preparations in terms of clinical pregnancy rates. In order to bridge this apparent evidence gap, a systematic literature review was conducted to identify randomized controlled trial (RCT) evidence comparing the efficacy and safety of any vaginal progesterone product with any other for any type of assisted reproductive technology cycle.

Materials and methods

Search strategy

A pre-defined search strategy was used to query the following electronic databases: MEDLINE and MEDLINE In-Process (searched via OvidSP), Embase (searched via OvidSP), The Cochrane Database of Systematic Reviews (CDSR; searched via Cochrane Library), The Database of Abstracts of Reviews of Effects (DARE; via Cochrane Library) and The Cochrane Central Register of Controlled Trials (CENTRAL; via Cochrane Library). These searches were conducted on 30 June 2016; detailed search strategies used in each of the electronic databases are presented in **Supplementary Table S1** and **Supplementary Table S2**.

As well as searching electronic databases, the proceedings of the last 2 years of the Royal College of Obstetricians and Gynaecologists

World Congress in Obstetrics and Gynaecology (RCOG), the European Society of Human Reproduction and Embryology Annual Meeting (ESHRE), the American Society for Reproductive Medicine Annual Meeting (ASRM) and the Association of Clinical Embryologists (ACE) Biennial Conference were manually hand-searched to identify further publications. Only the last 2 years of conference proceedings for each congress were searched as it was expected that data presented at earlier congresses would be represented within the peer-reviewed literature and therefore captured by the electronic database searches. Searches of conference proceedings were conducted in July 2016; detailed search strategies for each congress are presented in **Supplementary Table S3**.

Finally, the reference lists of any systematic literature reviews and meta-analyses identified as relevant during the record screening process were hand-searched in order to identify any additional relevant studies for inclusion in the review.

Study selection

Full details of the eligibility criteria can be found in **Table 2**. Briefly, eligible publications were those presenting novel data from RCTs which compared the efficacy and/or safety of any vaginal progesterone preparations with approval for LPS in assisted reproductive technology cycles. The following vaginal progesterone preparations used as monotherapy for LPS in assisted reproductive technology cycles were eligible: Utrogestan Vaginal (including Progestan and publications where the brand of micronized progesterone preparation was not specified but known to be Utrogestan Vaginal; in addition, Prometrium and Progeffik were considered to be equivalent preparations), Cyclogest, Crinone and Lutigest (including Endometrin and Lutinus). These were the only vaginal progesterone products with approval for LPS in assisted reproductive technology cycles in any major market at the time the searches were conducted. The indications and posology of these four products are presented in **Table 1**. Studies comparing the same product but using different timings or dosages were also eligible for inclusion.

Studies investigating vaginal progesterone preparations in combination with any other form of LPS (e.g. oestradiol) were excluded, along with abstracts and journal publications not in the English language or not investigating human patients undergoing LPS as part of assisted reproductive technology cycles.

Following de-duplication of records from the different databases, each article's abstract was reviewed against the eligibility criteria by two independent reviewers. Where the applicability of the eligibility criteria was unclear, the article was included at this stage in order to ensure that all potentially relevant studies were captured. The independent reviewers then compared their results and any disagreements were resolved by discussion until a consensus was met. When necessary, a third independent reviewer made the final decision.

Full-text articles of all records that met the eligibility criteria in the first round of screening were then obtained and evaluated in more detail against the same pre-defined eligibility criteria in a second round of screening. In cases where the article did not give enough information to be sure that it met the inclusion criteria, the article was excluded to ensure that only relevant articles were ultimately included in the systematic review. This second assessment was also undertaken by two independent reviewers, with any disagreements discussed with a third reviewer, if required.

Data extraction and quality assessment

Included studies were extracted into pre-specified data extraction tables by a single individual in the first instance. When the initial extraction was complete, a second individual then independently verified the extracted information and checked that no relevant information had been missed. Any discrepancies or missing information identified by the second individual were discussed by both individuals until a consensus was reached on the information that should be extracted. When necessary, a third individual was enlisted to arbitrate the final decision.

The quality of each included RCT was assessed by one reviewer and verified by a second reviewer using the criteria provided by the University of York's Centre for Reviews and Dissemination (CRD) (2009).

Results

A total of 1914 articles were identified through the electronic database searches. Of these, 18 publications on 18 unique RCTs were ultimately included in the systematic literature review (**Figure 1**, **Table 3**) (Baruffi et al., 2003; Bergh et al., 2012; Biberoglu et al., 2016; Doody et al., 2009; Fanchin et al., 2001; Ganesh et al., 2011; Geber

Table 1 – Indications and posology of the four vaginal progesterone preparations.

Vaginal progesterone	Relevant indication	Posology
Crinone 8% w/w progesterone vaginal gel	For use during IVF, where infertility is mainly due to tubal, idiopathic or endometriosis-linked sterility associated with normal ovulatory cycles.	Daily application of Crinone 8% gel should be continued for 30 days if there is laboratory evidence of pregnancy.
Cyclogest 400 mg pessaries	Luteal phase support as part of an assisted reproductive technology treatment for women.	400 mg administered vaginally twice a day starting at oocyte retrieval. Administration should be continued for 38 days if pregnancy has been confirmed.
Lutigest 100 mg vaginal tablets	Luteal support as part of an assisted reproductive technology treatment programme for infertile women.	100 mg administered vaginally three times daily starting at oocyte retrieval. Administration should be continued for 30 days if pregnancy has been confirmed.
Utrogestan vaginal 200 mg capsules	Supplementation of the luteal phase during assisted reproductive technology cycles.	The recommended dosage is 600 mg/day, in three divided doses, from the day of embryo transfer until at least the 7th week of pregnancy and not later than the 12th week of pregnancy.

Medicines and Healthcare Products Regulatory Agency (http://www.mhra.gov.uk/spc-pil/).

Table 2 – Study eligibility criteria.

Eligibility criteria	Inclusion criteria	Exclusion criteria
Population	Females receiving LPS during assisted reproductive technology cycles.	Individuals not receiving any LPS during assisted reproductive technology cycles. Alternatively, studies where outcomes were not presented separately for the specific patient population of interest.
Interventions	Any of the following progesterone therapies for LPS as monotherapy: • Utrogestan Vaginal (including Progestan and publications where the brand of micronized progesterone preparation was not specified but known to be Utrogestan Vaginal; in addition, Prometrium and Progeffik were considered to be equivalent preparations)[a] • Cyclogest • Crinone • Lutigest (including Endometrin and Lutinus)[b]	Studies where only one arm of the trial had a relevant intervention or comparator, or studies where outcomes for relevant interventions were not presented separately to those for interventions not of interest.
Comparators	Any of the following progesterone therapies for LPS as monotherapy: • Utrogestan • Cyclogest • Crinone • Lutigest/Endometrin/Lutinus[b]	Studies where only one arm of the trial had a relevant intervention or comparator, or studies where outcomes for relevant interventions were not presented separately to those for interventions not of interest.
Outcomes	Any of the following: • Number of cycles • Clinical pregnancy rate • Ongoing pregnancy rate • Live birth rate • Multiple pregnancy rate • Multiple delivery rate • Patient-reported outcomes • Tolerability • Safety outcomes including OHSS and bleeding and/or breakthrough bleeding	Studies not presenting relevant outcomes.
Study designs/ types	Phase II, III or IV RCTs (including retrospective analyses of these).	Any other study designs including: • Phase I clinical trials • Non-RCT study designs
Publication type	• Primary research publications • Letters reporting data from a relevant study design Systematic reviews and meta-analyses were included at the title/abstract screening stage and used for identification of any additional primary studies that were not identified through the electronic database searchers, but were excluded during the full-text review.	• Comments • Editorials • Non-systematic/narrative reviews
Other considerations	Abstracts and articles published in the English language. Studies involving human subjects.	Abstracts and articles published in languages other than English. Studies involving non-human subjects.

LPS = luteal phase support; MA = meta-analysis; OHSS = ovarian hyperstimulation syndrome; RCT = randomized controlled trial; SLR = systematic literature review.

[a] The brand Utrogestan Vaginal is used in the UK but in other countries the brand Progestan may be used; Progeffik is a branded generic approved based on Utrogestan as the original brand; the FDA approval for Prometrium capsules was based on data provided by Besins Healthcare to Solvay US and, although the capsules differ slightly from Utrogestan Vaginal, they may be considered clinically equivalent although they are not formally bioequivalent as per FDA requirements.

[b] The brand Lutigest is used in the UK but in other countries the brands Endometrin or Lutinus are used.

et al., 2007; Kleinstein, 2005; Kohls et al., 2012; Kyrou et al., 2011; Ludwig et al., 2002; Mochtar et al., 2006; Ng et al., 2003, 2007; Nyboe Andersen et al., 2002; Simunic et al., 2007; Tay and Lenton, 2005; Williams et al., 2001).

The most commonly used stimulation protocol, reported in seven RCTs, was a GnRH agonist in combination with FSH (Baruffi et al., 2003; Bergh et al., 2012; Fanchin et al., 2001; Ganesh et al., 2011; Kyrou et al., 2011; Nyboe Andersen et al., 2002; Simunic et al., 2007), followed by FSH alone in two RCTs (Geber et al., 2007; Nyboe Andersen et al., 2002). Seven of the remaining eight trials used GnRH agonists, FSH and HMG in varying combinations or as monotherapy (Biberoglu et al., 2016; Doody et al., 2009; Kleinstein, 2005; Kohls et al., 2012; Ludwig et al., 2002; Ng et al., 2003, 2007). Two trials did not record the stimulation protocol (Mochtar et al., 2006; Tay and Lenton,

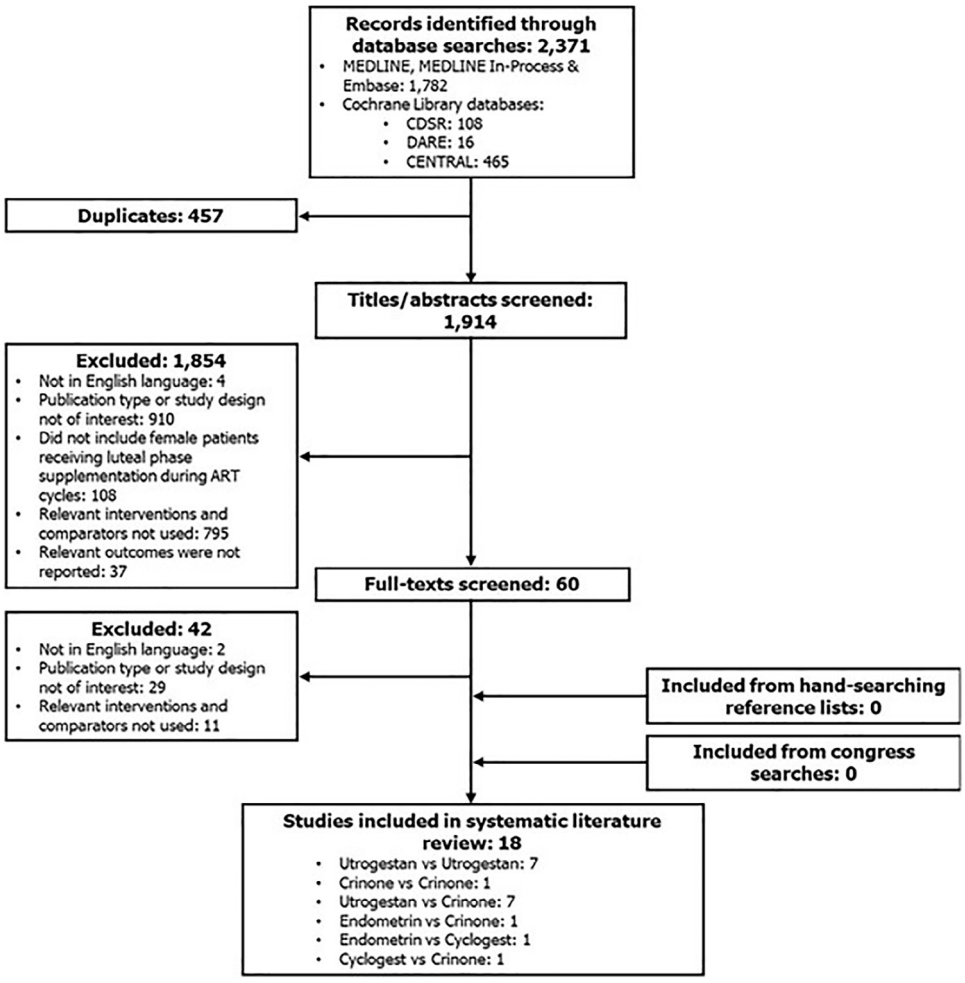

Figure 1 – PRISMA flow diagram. ART = assisted reproductive technology; CDSR = Cochrane Database of Systematic Reviews; CENTRAL = Cochrane Central Register of Controlled Trials; DARE = Database of Abstracts of Reviews of Effects.

2005). The vaginal progesterone products used were: Utrogestan Vaginal capsules (Progestan/Prometrium/vaginal micronized progesterone), Crinone 8% vaginal gel, Endometrin (Lutigest/Lutinus) vaginal tablets and Cyclogest vaginal pessaries.

A total of 10 RCTs compared different vaginal progesterone preparations. Seven compared Utrogestan Vaginal with Crinone (Bergh et al., 2012; Ganesh et al., 2011; Geber et al., 2007; Kleinstein, 2005; Ludwig et al., 2002; Simunic et al., 2007; Tay and Lenton, 2005), one compared Lutigest with Crinone (Doody et al., 2009), one compared Lutigest with Cyclogest (Ng et al., 2007) and another compared Cyclogest with Crinone (Ng et al., 2003). This evidence network is displayed in **Figure 2**. A further eight trials tested differing doses or schedules of administration of vaginal progesterone rather than comparing against a different product (Baruffi et al., 2003; Biberoglu et al., 2016; Fanchin et al., 2001; Kohls et al., 2012; Kyrou et al., 2011; Mochtar et al., 2006; Nyboe Andersen et al., 2002; Williams et al., 2001); seven trials compared Utrogestan Vaginal and one compared Crinone. The 18 trials comprised 3596 patients randomized to Utrogestan Vaginal, with 1537 of these patients enrolled in studies investigating differing timing or dosage of Utrogestan Vaginal only. A total of 2598 patients were randomized to Crinone, 874 to Lutigest and 96 to Cyclogest.

Quality assessments of the included studies are presented in **Table 4**. Appropriate randomization was carried out in 12 of the 18 RCTs (Baruffi et al., 2003; Biberoglu et al., 2016; Doody et al., 2009; Ganesh et al., 2011; Kleinstein, 2005; Kohls et al., 2012; Kyrou et al., 2011; Ludwig et al., 2002; Mochtar et al., 2006; Ng et al., 2003, 2007; Nyboe Andersen et al., 2002); however, five RCTs contained insufficient information on the randomization process (Fanchin et al., 2001; Geber et al., 2007; Simunic et al., 2007; Tay and Lenton, 2005; Williams et al., 2001) and one RCT reported an error in patient data input, resulting in an imbalance in the distribution of patients by age (Bergh et al., 2012). All other RCTs showed little variation between treatment arms in terms of patient characteristics and retention. Concealment of treatment allocation was widely unreported, with just five of the 18 RCTs reporting sufficient information to establish appropriate concealment (Geber et al., 2007; Kleinstein, 2005; Kohls et al., 2012; Kyrou et al., 2011; Mochtar et al., 2006). Furthermore, as an inherent feature of the comparison between different progesterone formulations (e.g. vaginal tablets versus a gel), no studies were double-blinded. Three RCTs implemented blinding of the outcome assessors (Bergh et al., 2012; Doody et al., 2009; Ganesh et al., 2011) and one reported open-label administration of LPS (Kleinstein, 2005).

Of the 18 RCTs, 10 were conducted in Europe (Bergh et al., 2012; Biberoglu et al., 2016; Fanchin et al., 2001; Kleinstein, 2005; Kohls et al., 2012; Ludwig et al., 2002; Mochtar et al., 2006; Nyboe Andersen et al., 2002; Simunic et al., 2007; Tay and Lenton, 2005), two in the

Table 3 – Characteristics of included RCTs.

Study	Location	Intervention	Comparator	Cycle details	Outcomes reported[a]	Analysis type
Baruffi et al., 2003	Brazil	Utrogestan Vaginal 400 mg from the evening of the day of OR (*n* = 51)	Utrogestan Vaginal 400 mg from the evening of the day of ET (*n* = 52)	Stimulated with GnRH-a and recombinant FSH One fresh cycle of ICSI per patient	*Clinical pregnancy rate* Implantation rate	NR
Bergh et al., 2012	18 fertility centres in Denmark and Sweden	Crinone 8% 90 mg administered od, commencing on the day of ET (day 2 after OR), for a total of 19 days or until a negative pregnancy test. Pregnancy was detected using a urinary or serum HCG test on day 14 after ET (*n* = 1026)	Vaginal micronized progesterone tablet (Utrogestan Vaginal) (in Danish patients: Progestan[b] 200 mg; in Swedish patients: Progesteron MIC[b] 400 mg) administered tid, commencing on the day of ET (day 2 after OR), for a total of 19 days or until a negative pregnancy test. Pregnancy was detected using a urinary or serum HCG test on day 14 after ET (*n* = 1016)	Stimulated with GnRH-a and FSH Fresh cycles (further details NR)	*Ongoing pregnancy rate* Miscarriage rate Live birth rate Multiple birth rate Patient-reported bleeding before and after pregnancy test Patients' overall impression Adverse event rate	Equivalence
Biberoglu et al., 2016	Infertility Outpatient Clinic, Gazi University Medical School, Ankara, Turkey	100 mg Progestan, administered vaginally tid, beginning two days after IUI and continued until menstruation or end of the 10th week of pregnancy, depending on the outcome of the cycle (*n* = 100)	200 mg Progestan, administered vaginally tid, beginning two days after IUI and continued until menstruation or end of the 10th week of pregnancy, depending on the outcome of the cycle (*n* = 100)	Stimulated with either recombinant FSH or HMG One cycle of IUI per patient	*Ongoing pregnancy rate* Total pregnancy rate Multiple pregnancy rate	NR
Doody et al., 2009	25 sites across USA	Endometrin 100 mg bd from the day after OR (*n* = 404) Endometrin 100 mg tid from the day after OR (*n* = 404) Endometrin was taken for at least 2 weeks and those who conceived continued until approximately 10 weeks after OR (i.e. 12 weeks' gestation)	Crinone 8% gel from the day after OR for at least two weeks and those who conceived continued until approximately 10 weeks after OR (i.e. 12 weeks' gestation) patients (*n* = 403)	Stimulated with HMG and FSH One fresh cycle of IVF per patient	*Ongoing pregnancy rate* Biochemical pregnancy rate Clinical pregnancy rate Live birth rate Adverse event rate	Non-inferiority
Fanchin et al. 2001	Departments of Obstetrics and Gynecology and Reproductive Endocrinology, Hôpital Antoine Béclère, Clamart, France	Crinone 8% gel od from the day of OR until at least the timepoint at which pregnancy was ruled out by negative serum HCG measurement (*n* = 43)	Crinone 8% gel od from the evening of ET until at least the timepoint at which pregnancy was ruled out by negative serum HCG measurement (*n* = 41)	Stimulated with GnRH-a and recombinant FSH One fresh cycle of IVF per patient	*Clinical pregnancy rate* Ongoing pregnancy rate	NR
Ganesh et al., 2011	Institute of Reproductive Medicine, Kolkata, India	Crinone 8% gel, 90 mg od from the day of ET up to 12 weeks' gestation (*n* = 482)	Utrogestan Vaginal 200 mg capsule tid from the day of ET up to 12 weeks' gestation (*n* = 459)	Stimulated with GnRH-a and FSH Fresh IVF cycles (number per patient NR)	*Clinical pregnancy rate* Miscarriage rate	NR
Geber et al., 2007	ORIGEN, Centre of Reproductive Medicine, Belo Horizonte, Brazil	Utrogestan Vaginal 200 mg capsules tid from the day of OR for at least 13 days until a pregnancy test was conducted then until 12 weeks' gestation in confirmed pregnancies (*n* = 122)	Crinone 8% gel, 90 mg od from the day of OR for at least 13 days until a pregnancy test was conducted then for at least 13 days and until 12 weeks' gestation in confirmed pregnancies (*n* = 122)	Stimulated with recombinant FSH Fresh cycles (further details NR)	*Clinical pregnancy rate* Miscarriage rate Multiple pregnancy rate	NR

(*continued on next page*)

Table 3 – (*continued*)

Study	Location	Intervention	Comparator	Cycle details	Outcomes reported[a]	Analysis type
Kleinstein 2005	17 German IVF centres	Utrogestan Vaginal 200 mg capsules tid from the evening of the day of ET up to 12 weeks' gestation in confirmed pregnancies (*n* = 218)	Crinone 8% gel bd from the evening of the day of ET up to 12 weeks' gestation in confirmed pregnancies (*n* = 212)	Stimulated with either HMG or FSH Fresh IVF/ICSI cycles (number per patient NR)	*Ongoing pregnancy rate* Implantation rate Miscarriage rate Adverse events	Non-inferiority
Kohls et al., 2012	Spain	200 mg natural micronized vaginal P (Utrogestan Vaginal) bd, beginning the evening after OR until day of first US (week 5), before they were randomized to LPS cessation at week 5 of gestation (*n* = 110)	200 mg natural micronized vaginal P (Utrogestan Vaginal) bd, beginning the evening after OR until day of first US (week 5), before they were randomized to LPS cessation at week 8 of gestation (*n* = 110)	Stimulated with GnRH-a Fresh IVF/ICSI cycles (number per patient NR)	*Ongoing pregnancy rate* Mean number of live births Singleton pregnancy rate Multiple pregnancy rate Bleeding episodes Miscarriage rate	NR
Kyrou et al., 2011	NR	200 mg Utrogestan Vaginal tid, beginning one day after OR (on day of ET), for 14 days, before they were randomized to cessation of 200 mg Utrogestan Vaginal tid 16 days post-ET (*n* = 100)	200 mg Utrogestan Vaginal tid, beginning 1 day after OR (on day of ET), for 14 days, before they were randomized to cessation of 200 mg Utrogestan Vaginal tid at seven weeks of gestation (*n* = 100)	Stimulated with GnRH-a and recombinant FSH One fresh cycle of IVF/ICSI per patient	*Ongoing pregnancy rate* Biochemical pregnancy rate Ectopic pregnancy rate Miscarriage rate Bleeding episodes Multiple ongoing pregnancy rate	Non-inferiority
Ludwig et al., 2002	Germany	Vaginal administration of Crinone 8% vaginal gel once daily beginning on the evening before ET until either menstrual bleeding occurred or there was a positive pregnancy test (*n* = 73)	Vaginal administration of Utrogestan Vaginal 200 mg capsules three times daily beginning on the evening before ET until either menstrual bleeding occurred or there was a positive pregnancy test (*n* = 53)	Stimulated with GnRH-a and either HMG or FSH Fresh IVF/ICSI cycles (number per patient NR)	*Clinical pregnancy rate* Clinical abortions Patient-reported comfort, difficulty with application and time consumption	NR
Mochtar et al., 2006	Centre of Reproductive Medicine at the Academic Medical Centre, Amsterdam, the Netherlands	HCG group: began LPS in the form of 200 mg Utrogestan Vaginal bd, beginning at the evening of HCG administration for final oocyte maturation (*n* = 130) ET group: began LPS in the form of 200 mg Utrogestan Vaginal bd, beginning at the evening after ET (*n* = 127) Both groups continued LPS until the onset of menstruation or until 18 days following OR	OR group: began LPS in the form of 200 mg Utrogestan Vaginal bd, beginning at the evening of OR, until the onset of menstruation or until 18 days following OR (*n* = 128)	Stimulation protocol NR First IVF cycle (fresh ET)	*Ongoing pregnancy rate* Biochemical pregnancy rate Clinical pregnancy rate Live birth rate	Superiority
Ng et al., 2003	Assisted Reproduction Unit at the Department of Obstetrics and Gynaecology, Queen Mary Hospital, Hong Kong	Cyclogest 400 mg vaginal pessaries bd, beginning on the day of ET for 14 days (*n* = 30)	Crinone 8% vaginal gel od, beginning on the day of ET for 14 days (*n* = 30)	Stimulated with GnRH-a and HMG Fresh IVF/ICSI cycles (number per patient NR)	*Patient-reported perineal irritation* Clinical pregnancy rate Patient-reported inconvenience of administration, leaking and interference with coitus Adverse events	NR

(*continued on next page*)

Table 3 – (*continued*)

Study	Location	Intervention	Comparator	Cycle details	Outcomes reported[a]	Analysis type
Ng et al., 2007	Assisted Reproduction Unit at the Department of Obstetrics and Gynaecology, The University of Hong Kong	Cyclogest 400 mg vaginal pessaries bd, beginning on the day of ET for 14 days (*n* = 66)	Endometrin 100 mg vaginal tablets bd beginning on the day of ET for 14 days (*n* = 66)	Stimulated with GnRH-a and HMG First, second or third IVF/ICSI cycle (fresh)	*Patient-reported perineal irritation* Clinical pregnancy rate Multiple pregnancy rate Miscarriage rate Difficulty with administration Adverse events	NR
Nyboe Andersen et al., 2002	Fertility Clinics at Rigshospitalet and Braedstrup Hospital in Denmark	200 mg Progestan (Utrogestan Vaginal) tid from the day of ET until HCG measurement 14 days (range 13–15) later. This was the day of randomization to cessation of LPS at the day of the positive HCG test (*n* = 150)	200 mg Progestan (Utrogestan Vaginal) tid from the day of ET until HCG measurement 14 days (range 13–15) later. This was the day of randomization to continuation of LPS for another 3 weeks following the positive HCG test (*n* = 153)	Stimulated with recombinant FSH One fresh cycle of IVF/ICSI per patient	*Delivery rate* Biochemical pregnancy rate Ectopic pregnancy rate Miscarriage rate Ongoing pregnancy rate Multiple pregnancy rate	NR
Simunic et al., 2007	*In vitro* Fertilization Polyclinic, Zagreb, Croatia	Crinone 8% vaginal gel, 90 mg administered od from the day of oocyte retrieval and continued until the day of testing for pregnancy, 2 weeks after ET. In the case of a pregnancy, continued until week 12 (*n* = 130)	Two 100 mg Utrogestan Vaginal capsules administered tid from the day of oocyte retrieval and continued until the day of testing for pregnancy, 2 weeks after ET. In the case of a pregnancy, continued until week 12 (*n* = 136)	Stimulated with GnRH-a and recombinant FSH Fresh cycles (further details NR)	*Clinical pregnancy rate* Patient-reported ease of administration, convenience of use and preference Adverse event rate	NR
Tay and Lenton, 2005	Sheffield Fertility Centre, UK	Crinone 8% vaginal gel, 90 mg administered od from day of ET between 18:00 and 21:00h, starting on the 4th day and continued daily until the 14th day after OR (*n* = 36)	Utrogestan Vaginal 200, 400 and 600 mg administered vaginally with divided doses two to three times daily, starting on the 4th day and continued daily until the 14th day after OR (*n* = 55) The number of patients receiving each dose of Utrogestan Vaginal was NR	Stimulation protocol NR One fresh cycle of IVF per patient	*Expected birth rate* Implantation rate Pregnancy rate	NR
Williams et al., 2001	Jones Institute for Reproductive Medicine, Norfolk, Virginia, USA	Prometrium (Utrogestan Vaginal) 200 mg tid intra-vaginally beginning on the morning of the 3rd day after OR. All patients underwent a serum β-HCG test 2 weeks after OR. LPS was continued until 10 weeks' gestation if positive pregnancy, otherwise it was discontinued (*n* = 59)	Prometrium (Utrogestan Vaginal) 200 mg tid intra-vaginally beginning on the morning of the 6th day after OR. All patients underwent a serum β-HCG test 2 weeks after OR. LPS was continued until 10 weeks' gestation if positive pregnancy, otherwise it was discontinued (*n* = 67)	Stimulated either with GnRH-a and FSH or with FSH alone One fresh cycle of IVF per patient	*Clinical pregnancy rate* Implantation rate	NR

bd = twice daily; ET = embryo transfer; FSH = follicle-stimulating hormone; GnRH-a = gonadotrophin-releasing hormone agonist; HCG = human chorionic gonadotrophin; HMG = human menopausal gonadotrophin; LPS = luteal phase support; NR = not reported; OR = oocyte retrieval; od = once daily; tid = three times daily; US = ultrasound.

[a] Italic font indicates the primary outcome measure.

[b] Progestan is a brand name version of Utrogestan Vaginal however Progesteron MIC cannot be considered as a generic of Utrogestan Vaginal. The proportion of patients receiving Progesteron MIC was considered sufficiently small to enable inclusion of this study as a majority Utrogestan Vaginal population.

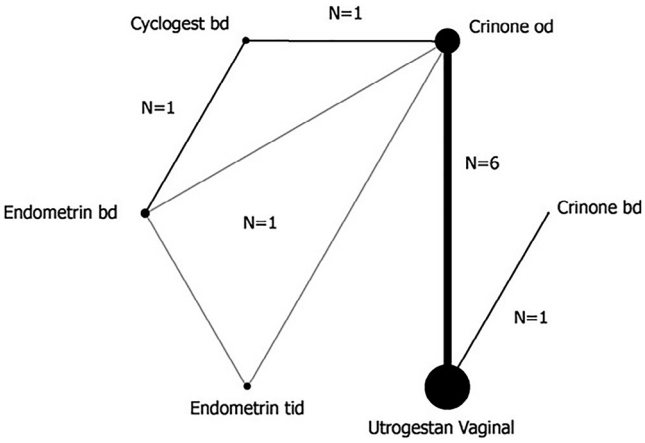

Figure 2 – Network of evidence identified in the systematic literature review. Black lines represent trials with two comparators in the network, grey lines trials with three comparators in the network; line thickness denotes the number of trials making each comparison. A variety of outcomes were reported in the included trials and the network for any given outcome is likely to be smaller than that shown. Included trials: Bergh et al. (2012), Doody et al. (2009), Ganesh et al. (2011), Geber et al. (2007), Kleinstein (2005), Ludwig et al. (2002), Ng et al. (2003, 2007), Simunic et al. (2007), Tay and Lenton (2005). od = omni die (once daily); bd = bis die (twice daily); tid = ter in die (thrice daily).

USA, (Doody et al., 2009; Williams et al., 2001), two in Brazil (Baruffi et al., 2003; Geber et al., 2007), two in Hong Kong (Ng et al., 2003, 2007), one in India (Ganesh et al., 2011) and one study did not report its location (Kyrou et al., 2011).

The primary and secondary outcomes investigated within the 18 studies spanned relative efficacy, safety and tolerability of each progesterone regimen. Specifically, the efficacy outcomes measured included pregnancy rates (including clinical, ongoing and multiple pregnancy rates), delivery and expected live birth rates. Safety was evaluated through the reporting of a variety of adverse events, including OHSS. Tolerability was measured as patient-reported outcomes captured through questionnaires. The primary outcomes of the 18 included RCTs are presented in **Table 5**.

Primary outcomes

Ongoing pregnancy rate was one of the most frequently reported primary outcomes, in seven studies, although each study had different definitions of how and when ongoing pregnancy was measured (Bergh et al., 2012; Biberoglu et al., 2016; Doody et al., 2009; Kleinstein, 2005; Kohls et al., 2012; Kyrou et al., 2011; Mochtar et al., 2006). Clinical pregnancy rate was also identified as a common primary outcome, across seven studies (Baruffi et al., 2003; Fanchin et al., 2001; Ganesh et al., 2011; Geber et al., 2007; Ludwig et al., 2002; Simunic et al., 2007; Williams et al., 2001). Each of these studies had varying definitions of the time point at which clinical pregnancy rate was measured. Expected live birth rate was the primary outcome for one study (Tay and Lenton, 2005), delivery rate was the primary outcome for another study (Nyboe Andersen et al., 2002) and two studies investigated patient-reported outcomes as their primary outcome (Ng et al., 2003, 2007).

Three of the 18 studies used non-inferiority analysis (Doody et al., 2009; Kleinstein, 2005; Kyrou et al., 2011). Two studies used a pre-specified non-inferiority margin of 10%, and both were able to establish non-inferiority of the intervention against the comparator: Endometrin versus Crinone (Doody et al., 2009) and Cyclogest versus Crinone (Kleinstein, 2005). The third study used a non-inferiority margin of 7% and was also able to establish non-inferiority of cessation of Utrogestan Vaginal at 16 days post-embryo transfer to cessation at seven weeks of gestation (Kyrou et al., 2011). One study specified that it was designed as a superiority study, although it was unable to establish statistically significant findings between the initiation of Utrogestan Vaginal from HCG administration or from the day of oocyte retrieval (Mochtar et al., 2006).

Only one of the 18 RCTs identified itself as an equivalence study. However, the results revealed that equivalence of the two regimens (once-daily Crinone and thrice-daily Progestan 200 mg [i.e. Utrogestan Vaginal]) could not be demonstrated because the lower bound of the confidence interval (CI) for the Crinone versus Progestan comparison was lower than the pre-specified margin, indicating that once-daily Crinone may not have been as effective as Progestan (i.e. Utrogestan Vaginal) (Bergh et al., 2012). Nonetheless the study found no significant difference in efficacy or safety between the comparators, in line with other studies.

The remaining seven RCTs, which compared two different active interventions did not specify the analysis type; however, none found significant differences between the interventions (Ganesh et al., 2011; Geber et al., 2007; Ludwig et al., 2002; Ng et al., 2003, 2007; Simunic et al., 2007; Tay and Lenton, 2005). The four RCTs which compared clinical pregnancy rates with Utrogestan Vaginal versus Crinone found no statistically significant difference between the two formulations (Ganesh et al., 2011; Geber et al., 2007; Ludwig et al., 2002; Simunic et al., 2007). A further RCT comparing ongoing pregnancy rates between Utrogestan Vaginal and Crinone also found no significant difference between the two comparators (Bergh et al., 2012). One RCT compared expected live birth rates between Utrogestan Vaginal and Crinone and found no significant difference (Tay and Lenton, 2005). Two studies which investigated patient-reported perineal irritation in Cyclogest versus Endometrin and Cyclogest versus Crinone found no significant differences between the interventions (Ng et al., 2003, 2007).

Only one RCT specifically investigated the effect of dosage of progesterone for LPS using 300 mg versus 600 mg Utrogestan Vaginal but found no significant difference in ongoing pregnancy rate (Biberoglu et al., 2016). Due to the lack of studies investigating the impact of dose on outcomes, it was not possible to draw any further conclusions on the impact of progesterone dosage.

Where patient-reported outcomes such as comfort and tolerability were measured, some studies did show variability in terms of patient preference between the regimens. Five studies investigated patient preference and convenience (Bergh et al., 2012; Ludwig et al., 2002; Ng et al., 2003, 2007; Simunic et al., 2007). Four of the five studies included Crinone in one of the treatment arms, and all subsequently identified Crinone as the significantly preferred intervention, over Cyclogest (in one study) and Utrogestan Vaginal (in three studies) (all $P < 0.05$) (Bergh et al., 2012; Ludwig et al., 2002; Ng et al., 2003; Simunic et al., 2007). The reasons stated for preference of Crinone included: ease of administration, convenience for daily use, lower incidence of leaking, discharge and interference with coitus. The fifth study presenting patient-reported outcomes compared Cyclogest with Endometrin and found a significantly greater number of patients

Table 4 – Quality assessment of included studies.

Trial	Was randomization carried out appropriately?	Was the concealment of treatment allocation adequate?	Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Were the care providers, participants and outcome assessors blind to treatment allocation?	Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	Is there any evidence to suggest that the authors measured more outcomes than they reported?	Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?
Baruffi et al., 2003	Yes	Not clear	Yes	Not clear	No	No	Yes
Bergh et al., 2012	No	Not clear	No	No, although outcome assessors were blinded	No	No	Yes, for the secondary outcomes
Biberoglu et al., 2016	Yes	Not clear	Yes	Not clear	Not clear	No	No
Doody et al., 2009	Yes	Not clear	Yes	No, although outcome assessors were blinded	Not clear	No	Yes
Fanchin et al., 2001	Not clear	Not clear	Yes	Not clear	No	Yes	Yes
Ganesh et al., 2011	Yes	Not clear	Yes	No, although outcome assessors were blinded	No	Yes	Not clear
Geber et al., 2007	Not clear	Yes	Yes	Not clear	No	No	Not clear
Kleinstein, 2005	Yes	Yes	Yes	No	No	No	Yes
Kohls et al., 2012	Yes	Yes	Yes	Not clear	No	No	Yes
Kyrou et al., 2011	Yes	Yes	Yes	Not clear	No	No	Yes
Ludwig et al., 2002	Yes	Not clear	Yes	Not clear	No	No	Not clear
Mochtar et al., 2006	Yes	Yes	Yes	Not clear	No	No	Yes
Ng et al., 2007	Yes	Not clear	Yes	Not clear	No	No	Not clear
Ng et al., 2003	Yes	Not clear	Yes	Not clear	No	No	Not clear
Nyboe Andersen et al., 2002	Yes	Not clear	Yes	Not clear	No	No	Not clear
Simunic et al., 2007	Not clear	Not clear	Yes	Not clear	No	No	No
Tay and Lenton, 2005	Not clear	Not clear	Yes	Not clear	No	No	Not clear
Williams et al., 2001	Not clear	Not clear	Yes	Not clear	No	No	Not clear

reported difficulty with administration of Cyclogest over Endometrin ($P = 0.002$) (Ng et al., 2007).

Timing and duration of LPS

The impact of timing and/or duration of LPS was investigated in six RCTs that compared different regimens of Utrogestan Vaginal (Baruffi et al., 2003; Fanchin et al., 2001; Kohls et al., 2012; Kyrou et al., 2011; Mochtar et al., 2006; Nyboe Andersen et al., 2002; Williams et al., 2001) and one that compared different regimens of Crinone (Fanchin et al., 2001). Of these studies, five reported both the point of initiation and cessation of Utrogestan Vaginal and the comparison of these RCTs is presented in **Figure 3** (Kohls et al., 2012; Kyrou et al., 2011; Mochtar et al., 2006; Nyboe Andersen et al., 2002; Williams et al., 2001). Two RCTs reported the point of initiation only and so have not been included in the figure (Baruffi et al., 2003; Fanchin et al., 2001). Across all studies, no significant differences were identified between any of the regimens investigated, with the exception of two RCTs that did not report statistical analysis; however, numerical differences between the arms in these studies were negligible (Fanchin et al., 2001; Kohls et al., 2012).

Three RCTs investigated differing points of initiation of Utrogestan Vaginal. In one RCT, initiation of Utrogestan Vaginal at three or six days post-oocyte retrieval with cessation at 10 weeks of pregnancy was compared and reported no significant difference between regimens in terms of clinical pregnancy rate (Williams et al., 2001). One RCT initiated Utrogestan Vaginal on the day of HCG administration, the day of embryo transfer or the day of oocyte retrieval with cessation 18 days after oocyte retrieval (approximately 4.5 weeks' gestation). Initiation from oocyte retrieval acted as the reference group and neither the HCG or embryo transfer groups were significantly different to the oocyte retrieval group in terms of ongoing pregnancy rate (Mochtar et al., 2006). The RCT that reported the point of initiation only, started Utrogestan Vaginal on the evening of oocyte retrieval compared with the evening of embryo transfer and found no significant difference in terms of clinical pregnancy rate between the two arms (Baruffi et al., 2003). Three RCTs compared differing points of cessation of Utrogestan Vaginal. One RCT compared cessation of Utrogestan Vaginal at five weeks' versus eight weeks' gestation after initiation on the day of oocyte retrieval. While statistical analysis of the difference between the arms was not provided, ongoing pregnancy was reported in 75 of 110 patients randomized to week 5

Table 5 – Primary outcome measures.

Primary outcome measure	Study	Definition	Intervention	Comparator	Statistical analysis
Clinical pregnancy rate	Baruffi et al., 2003	Confirmation of gestational sac and fetal heart activity 6 weeks after ET	Utrogestan Vaginal from evening of OR n/N = NR 27.4%	Utrogestan Vaginal from evening of ET n/N = NR 28.8%	*P* = NS
	Ganesh et al., 2011	US scan confirming fetal heart activity 7 weeks after ET	Crinone n/N = 138/482 28.63%	Utrogestan Vaginal n/N = 104/459 22.65%	*P* = NS
	Fanchin et al., 2001	Confirmation of gestational sac with cardiac activity	Crinone from OR n/N = NR 42%	Crinone from evening of ET n/N = NR 29%	NR
	Geber et al., 2007	US scan confirming fetal heart activity 2–4 weeks after OR	Utrogestan Vaginal n/N = 44/122 36.1%	Crinone n/N = 54/122 44.3%	*P* = NS
	Ludwig et al., 2002	US scan confirming fetal heartbeats	Crinone n/N = 21/73 28.8%	Utrogestan Vaginal n/N = 10/53 18.9%	*P* = NS
	Simunic et al., 2007	US scan confirming fetal heart activity 4–6 weeks after ET	Crinone n/N = 43/130 33.1%	Utrogestan Vaginal n/N = 42/136 30.9%	*P* = NS
	Williams et al., 2001	US scan confirming presence of a gestational sac with appropriately rising β-HCG levels	Utrogestan Vaginal day 3 after OR group: n/N = 36/59 61.0%	Utrogestan Vaginal day 6 after OR group: n/N = 30/67 44.8%	*P* = NS
Ongoing pregnancy rate	Bergh et al., 2012	Defined as a sonographically verified intrauterine pregnancy, with a fetus with a heartbeat, 5 weeks after ET (gestational week 7)	Crinone: n/N = NR 30.2% (95% CI: 27.3–33.0%)	Utrogestan Vaginal n/N = NR 32.7% (95% CI: 29.7–35.6%)	*P* = NS
	Biberoglu et al., 2016	Determined at the end of the first trimester	Progestan (Utrogestan Vaginal) 300 mg (Group A): n/N = 19/100 19.0%	Progestan (Utrogestan Vaginal) 600 mg (Group B): n/N = 12/100 12.0%	*P* = NS
	Doody et al., 2009	Identification of fetal heart movement at approximately 6 weeks after ET	Endometrin bd: n/N = 156/404 39% (lower bound 95% CI −10.3%) Endometrin tid: n/N = 171/404 42% (lower bound 95% CI −6.7%)	Crinone n/N = 170/403 42%	On the basis of the lower bound of 95% CI, Endometrin bd and tid were non-inferior to Crinone
	Kleinstein, 2005	US scan confirming fetal heart activity measured at the end of the 12th week of gestation	Utrogestan Vaginal n/N = 55/218 25.2% 95% CI: (19.6–31.5%)	Crinone n/N = 47/212 22.2% 95% CI: (16.8–28.4%)	On the basis of the lower bound of the 90% CI, Utrogestan Vaginal was non-inferior to Crinone
	Kohls et al., 2012	Defined as the presence of at least one developing embryo of >12 weeks' gestation	Utrogestan Vaginal cessation at 5 weeks' gestation: n/N = 75/110 68.2%	Utrogestan Vaginal cessation at 8 weeks' gestation: n/N = 73/110 66.4%	*P* = NR
	Kyrou et al., 2011	Defined as pregnancy developing beyond 12 weeks of gestation	Utrogestan Vaginal early cessation (Group A): n/N = 82/100 82.0%	Utrogestan Vaginal cessation after 7 weeks' gestation (Group B): n/N = 73/100 73.0%	% difference (95% CI): 9.0 (−2.6 to 20.3%) *P* = NS
	Mochtar et al., 2006	Defined as a positive fetal heartbeat by transvaginal US 10 weeks after OR	Utrogestan Vaginal from HCG group: n/N = 27/130 20.8% Utrogestan Vaginal from ET group: n/N = 30/127 23.6%	Utrogestan Vaginal from OR group: *n* (%) = 29/128 22.7%	(Reference group is UV from OR group for relative risk [RR] calculations and accompanying 95% CI) Utrogestan Vaginal from HCG versus Utrogestan Vaginal from OR, RR (95% CI): 0.92 (0.58–1.45), *P* = NS Utrogestan Vaginal from ET versus Utrogestan Vaginal from OR, RR (95% CI): 1.04 (0.66–1.62), *P* = NS

(*continued on next page*)

Table 5 – (*continued*)

Primary outcome measure	Study	Definition	Intervention	Comparator	Statistical analysis
Delivery rate	Nyboe Andersen et al., 2002	Defined as the rate of babies delivered	Utrogestan Vaginal early cessation (Group A): n/N = 118/150 78.7%	Utrogestan Vaginal cessation 3 weeks following positive HCG test (Group B): n/N = 126/150 82.4%	*P* = NS
Expected live birth rate	Tay and Lenton, 2005	Expected live birth rate was not defined[a]	Crinone n/N = 13/36 36%	Utrogestan n/N = 19/55 35%	*P* = NS
Patient-reported outcomes	Ng et al., 2007	Perineal irritation	Cyclogest On day 6 after ET: n/N = 8/66 12.1% On day 16 after ET: n/N = 10/66 15.2%	Endometrin On day 6 after ET: n/N = 6/66 9.1% On day 16 after ET: n/N = 5/66 7.6%	*P* = NS
	Ng et al., 2003	Perineal irritation due to vaginal discharge	Cyclogest: Day 6 after ET: ~ 20%[b] Day 16 after ET: ~ 20%[b]	Crinone: Day 6 after ET: ~ 20%[b] Day 16 after ET: ~ 20%[b]	*P* = NS

bd = twice daily; CI = confidence interval; ET = embryo transfer; NS = not significant; OR = oocyte retrieval; tid = three times daily; US = ultrasound.
[a] Due to the lack of definition of expected live birth rate, the authors of this manuscript were contacted for clarification. No response was received.
[b] Actual data values were not reported.

cessation and 73 of 110 patients randomized to week 8 cessation, suggesting that the numerical difference between the arms was negligible (Kohls et al., 2012). Early versus late cessation of Utrogestan Vaginal was investigated in two further RCTs. One RCT initiated Utrogestan Vaginal one day after oocyte retrieval and compared cessation at five weeks' gestation with seven weeks' cessation but found no significant difference in ongoing pregnancy rate (Kyrou et al., 2011). The other RCT initiated Utrogestan Vaginal on the day of embryo transfer and compared cessation on the day of positive pregnancy test (approximately 4.5 weeks' gestation) with cessation three weeks later and found no significant difference in delivery rate between these regimens (Nyboe Andersen et al., 2002).

The one RCT that investigated the effect of day of initiation of Crinone compared clinical and ongoing pregnancy rates between initiation of LPS on the day of oocyte retrieval versus on the evening of embryo transfer. Clinical pregnancy rate was 42% in the oocyte

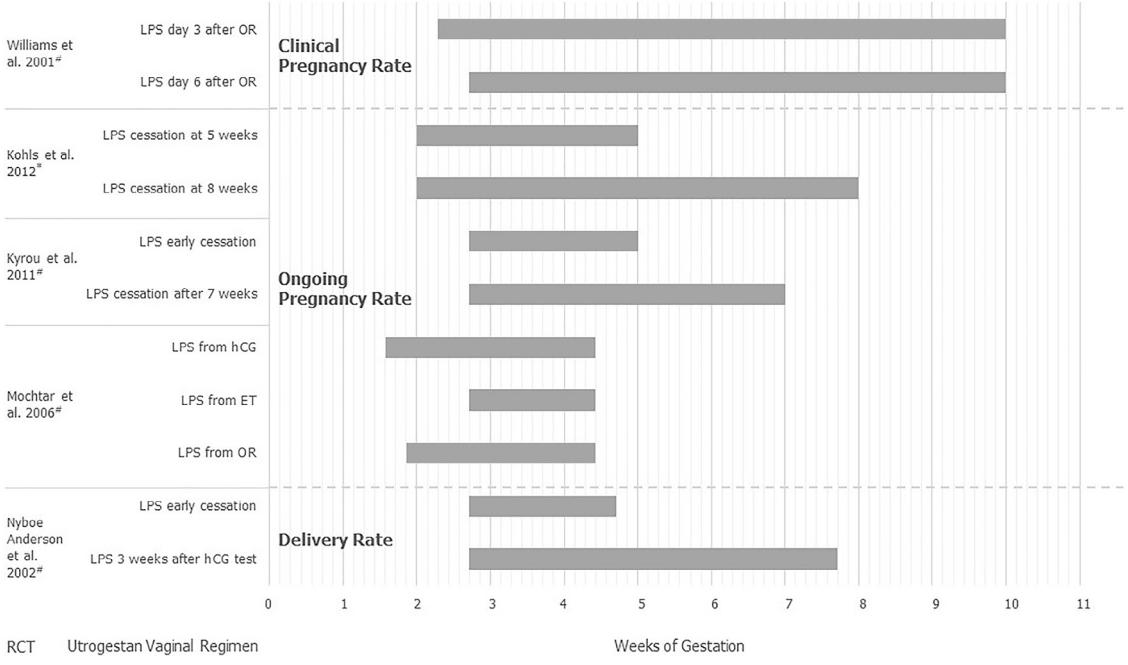

Figure 3 – Impact of Utrogestan Vaginal LPS duration on efficacy. #*P* = not significant, *statistical comparison not conducted. ET = embryo transfer; HCG = human chorionic gonadotrophin; LPS = luteal phase support; OR = oocyte retrieval.

retrieval group and 29% in the embryo transfer group. The ongoing pregnancy rate (≥12 weeks' amenorrhoea) was 35% in the oocyte retrieval group and 22% in the embryo transfer group; however, no formal statistical comparison of these rates was conducted (Fanchin et al., 2001).

Miscarriage rate

Miscarriage rate was reported in eight RCTs but none reported significant differences between treatment arms. Of the five RCTs that compared Utrogestan Vaginal with Crinone, none reported significant differences (Bergh et al., 2012; Ganesh et al., 2011; Geber et al., 2007; Kleinstein, 2005; Ludwig et al., 2002). No significant difference in miscarriage rate was identified between Cyclogest and Endometrin (Ng et al., 2007). Three RCTs investigating different timing of administration of Utrogestan Vaginal also did not identify any significant difference between regimens in terms of miscarriage rate (Kohls et al., 2012; Kyrou et al., 2011; Nyboe Andersen et al., 2002).

Multiple pregnancy rate

Multiple pregnancy rate was reported in seven RCTs. Of these, two RCTs compared Utrogestan Vaginal with Crinone and all found no significant difference in multiple pregnancy rate (Bergh et al., 2012; Geber et al., 2007). One RCT that compared Cyclogest with Endometrin also did not find a significant difference (Ng et al., 2007). No significant difference in multiple pregnancy rate between 300 mg and 600 mg Utrogestan Vaginal daily was identified (Biberoglu et al., 2016) and those studies that compared different timing/duration of Utrogestan Vaginal also found no significant difference between regimens in terms of multiple pregnancies (Kohls et al., 2012; Kyrou et al., 2011; Nyboe Andersen et al., 2002).

Bleeding episodes

Three RCTs reported bleeding episodes. A significantly greater proportion of patients who received Crinone (52.1%) experienced bleeding before the pregnancy test compared with those who received Utrogestan Vaginal (38.0%) ($P < 0.0001$); however, in those patients with ongoing pregnancies, there was no significant difference in bleeding before the pregnancy test (Bergh et al., 2012). The other two RCTs investigated timing of Utrogestan Vaginal and reported conflicting results. When Utrogestan Vaginal was initiated at the day of oocyte retrieval and stopped at either five or eight weeks' gestation, the mean number of bleeding episodes before 12 weeks' gestation was significantly greater in the patients who stopped LPS at week 5 ($P < 0.001$); however, there was no significant difference in bleeding during twin pregnancies between the regimens (Kohls et al., 2012). When Utrogestan Vaginal was initiated one day after oocyte retrieval and stopped at either five or seven weeks' gestation, no significant difference in bleeding was reported (Kyrou et al., 2011).

Safety

Adverse event profiles were compared between preparations in five studies: Crinone versus Utrogestan Vaginal (Kleinstein, 2005; Simunic et al., 2007), Endometrin versus Crinone (Doody et al., 2009), Cyclogest versus Endometrin (Ng et al., 2007) and Cyclogest versus Crinone (Ng et al., 2003). The most commonly reported adverse events were abdominal pain, nausea and/or vomiting, perineal irritation, vaginal itching and OHSS across all four preparations.

In one RCT comparing Crinone with Utrogestan Vaginal, no significant differences were identified in terms of nausea and/or vomiting, abdominal pain, vaginal leakage, headaches, breast fullness or burning; however, perineal irritation and vaginal itching occurred more commonly in Utrogestan Vaginal patients than Crinone patients ($P < 0.05$ for both events) (Simunic et al., 2007). The other RCT comparing adverse events between Utrogestan Vaginal and Crinone reported no significant difference in the rate of adverse events between the two arms nor between the rate of local intolerance between the arms; however, the patient-reported tolerability rating for Utrogestan Vaginal was found to be significantly higher than for Crinone ($P < 0.001$) (Kleinstein, 2005).

The adverse event profiles of Endometrin and Crinone were described as similar; however, statistical analysis was not conducted to formally compare the rates in this RCT (Doody et al., 2009). There were no significant differences between the adverse event profiles of Cyclogest versus Endometrin or Cyclogest versus Crinone (Ng et al., 2003, 2007).

Discussion

Head-to-head RCT evidence has demonstrated no significant differences in efficacy or safety between Utrogestan Vaginal and Crinone, between each of the other comparators and Crinone, and between Cyclogest and Endometrin, reflecting the fact that these products represent a choice of formulations for vaginal administration of the same naturally occurring hormone, rather than being different xenobiotic substances.

Furthermore, no significant differences were identified between Utrogestan Vaginal regimens initiating at oocyte retrieval versus at embryo transfer, nor between Crinone regimens initiating at these same time points. No significant differences were identified between Utrogestan Vaginal regimens starting three days versus six days after oocyte retrieval, or between Utrogestan Vaginal regimens starting at HCG administration versus oocyte retrieval. No significant differences were identified between regimens withdrawing Utrogestan Vaginal on the day of a positive pregnancy test versus three weeks after a positive pregnancy test or between regimens withdrawing Utrogestan Vaginal 16 days after embryo transfer versus at seven weeks of gestation. These results are supported by the vaginal progesterone findings of a meta-analysis conducted in 2013, which investigated the impact of timing of LPS with any form of progesterone (Connell et al., 2015). There was also no significant difference in ongoing pregnancy rate with 300 mg versus 600 mg Utrogestan Vaginal, highlighting the limited impact of timing and dosage of vaginal progesterone on clinical efficacy.

While formal statistical equivalence of each of the progesterone regimens in terms of formulation and administration schedule has not yet been established, partly due to the absence of further RCTs designed as equivalence studies, similar outcomes were reported among all interventions and comparators included in this review. Authors across these studies have suggested that each regimen may be interchangeable in their use for LPS during assisted reproductive technology cycles, which is in line with their status as different formulations of the same active ingredient, progesterone.

A number of limitations within the evidence base were identified in this review. These include factors potentially limiting the conclusions

that can be drawn from individual studies, and also across studies. However, there are mitigating factors for a number of these limitations, and the evidence base also exhibited strengths.

Factors identified as potentially affecting the risk of bias in individual studies include the fact that the methods used to generate random allocation sequences were not reported in all studies. Additionally, none of the studies were double-blinded; however, this is not expected to have resulted in significant performance or detection bias because the outcome measures for pregnancy are objectively defined rather than clinically judged, and participants were aware that they were receiving an active treatment that was expected to be equivalent to the other treatment allocation.

Among the included studies, methods were not consistently reported and not all studies presented a sample size calculation. Therefore, it was unclear whether all trials were adequately powered to detect statistically significant differences between the treatment arms. However, given that a number of the included studies did clearly lay out power calculations and non-inferiority measures, and that the results across all trials were consistent, it is clear that the main comparisons within trials have been adequately undertaken and that less detailed reports provide confirmatory evidence.

In terms of our ability to compare results across studies, firstly the primary and secondary outcome measures were not completely defined in all studies, and not all studies adequately indicated how and when outcomes were assessed. Nonetheless, as previously noted, pregnancy outcomes are categorical variables and based on the presence of objective signs rather than clinical judgement; as such, a failure to define the outcome measurement in the study report is less concerning than would otherwise be the case and is unlikely to have introduced significant bias into the results, particularly in the comparison of two active treatments. Ongoing pregnancy rate results were reported as a primary outcome in approximately half of the studies (Bergh et al., 2012; Biberoglu et al., 2016; Doody et al., 2009; Kleinstein, 2005; Kohls et al., 2012; Kyrou et al., 2011; Mochtar et al., 2006). However, definitions for how and when ongoing pregnancy was to be determined differed across the studies.

The inclusion and exclusion criteria also varied between trials. It was notable that baseline demographics were not reported in great detail across all studies and that where mean and median age was reported, it ranged across the studies between 27.8 and 35; it is known that age greater than 35 is an influential factor on the success rate of assisted reproductive technologies. The trials also varied in that patients may have been undergoing their first assisted reproductive technology cycle or may have had a history of previous cycles. Furthermore, concomitant study medications alongside but not related to LPS varied between the trials and were dependent upon which protocol was being followed for ovarian stimulation, including the use of a variety of supplemental hormones.

Despite these numerous differences between the included clinical trials, it is important to note that all identified studies reported very similar results. These consistent findings of no significant differences in efficacy and safety across trials taken together with the variety of the populations across trials may provide reassurance that the results have been demonstrated in a wide range of populations, which may more pragmatically represent real-world clinical practice than highly selected patient populations.

As well as consistent findings across varying patient populations, the alignment of timing and/or duration of LPS with clinical practice was also identified as a topic of interest during this review. Many LPS regimens were stopped at between four and five weeks' gestation, around the time of a positive pregnancy test, and showed no significant differences in obstetric and perinatal outcomes as compared with more extended regimens (up to 10 weeks' gestation). This does not reflect clinical practice, which appears to show that 44% of patients who conceive continue LPS until 8–10 weeks' gestation and a further 28% continue until 12 weeks' gestation (Kohls et al., 2012; Kyrou et al., 2011; Nyboe Andersen et al., 2002). This suggests a requirement for clinical practice to more closely align with the evidence base, rather than continue with the generally accepted practice of prolonging LPS into early pregnancy (Aboulghar et al., 2008).

For the purposes of this review, the effect of progesterone dosage on the obstetric and perinatal outcomes reported was not considered due to the scarcity of existing evidence. However, it must be noted that some RCTs used unlicensed doses in one or both treatment arms (Baruffi et al., 2003; Biberoglu et al., 2016; Doody et al., 2009; Kleinstein, 2005; Kohls et al., 2012; Mochtar et al., 2006; Ng et al., 2007; Tay and Lenton, 2005). The effect of progesterone dose on obstetric and perinatal outcomes is therefore unclear and further investigation is warranted (Fatemi et al., 2007).

Additionally, while little evidence was identified to differentiate the progesterone formulations in terms of efficacy, Crinone was found to be preferable to both Cyclogest and Utrogestan Vaginal, and Lutigest was also found to be preferable to Cyclogest in terms of patient-reported outcomes. The investigation of patient-reported outcomes as primary outcomes was not common however, and just five of the 18 RCTs reported these types of outcomes in some capacity (Bergh et al., 2012; Ludwig et al., 2002; Ng et al., 2003, 2007; Simunic et al., 2007). Of these five RCTs, three enrolled fewer than 140 patients across both treatment arms (Ludwig et al., 2002; Ng et al., 2003, 2007). This highlights a requirement for further larger-scale RCTs to include a patient-reported outcome element. This increased evidence base may enable more accurate differentiation of the vaginal progesterone formulations for LPS in assisted reproductive technology cycles on the basis of patient preference, rather than the traditionally used outcomes of efficacy and safety.

While this comprehensive literature review has identified all available English language data at the time of the searches, further data may have been available in other languages, which will not have been included in this review; however, it is expected that most major RCTs will have been published in international journals in the English language.

Furthermore, since the date that the searches for this systematic literature review were conducted, little further evidence has been published, with the exception of a recently published RCT investigating 100 mg Utrogestan Vaginal versus 200 mg Utrogestan Vaginal for LPS in IVF and ICSI cycles, which found no significant differences in obstetric and perinatal outcomes between these two doses (Zhu et al., 2017).

While previous quantitative analyses of interventions for LPS have investigated a broad scope encompassing intramuscular, oral, rectal and vaginal routes of progesterone for LPS (Green et al., 2017; van der Linden et al., 2015) just one previous analysis based on a literature review conducted in 2009 had investigated vaginal progesterone preparations for LPS in IVF/ICSI cycles specifically, comparing Crinone with Utrogestan Vaginal, Cyclogest or Endometrin (Polyzos et al., 2010). The current review compared any vaginal progesterone formulation with any other, including studies that investigated dosage and timing of administration of LPS, for any type of assisted reproductive technology cycle including IVF and ICSI, as well as IUI, thus providing a broader picture of the role that vaginal progesterone plays as LPS in assisted reproductive technology cycles.

This current systematic literature review therefore updates and expands the existing systematically identified evidence base (Polyzos et al., 2010; van der Linden et al., 2015) providing further evidence for a lack of significant differences between vaginal progesterone preparations for any assisted reproductive technology cycle and also between the various timing and dosage schedules available for LPS. It also supports an assumption made in the 2015 review by the Cochrane Collaboration, which assumed that different vaginal progesterone preparations were interchangeable, with no difference between 'low' and 'high' dose vaginally administered progesterone (van der Linden et al., 2015).

While differences in the identified trials were examined, none were found to be likely to bias the conclusions on relative effectiveness of the comparators. Therefore, this study supports existing evidence which suggests that different formulations or schedules of administration of vaginal progesterone can be considered indistinguishable in terms of efficacy and safety for use in LPS during assisted reproductive technology cycles.

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Appendix: Supplementary material

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REFERENCES

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. Hum. Reprod. 23, 857–862.

Baruffi, R., Mauri, A.L., Petersen, C.G., Felipe, V., Franco, J.G., Jr., 2003. Effects of vaginal progesterone administration starting on the day of oocyte retrieval on pregnancy rates. J. Assist. Reprod. Genet. 20, 517–520.

Beltsos, A.N., Sanchez, M.D., Doody, K.J., Bush, M.R., Domar, A.D., Collins, M.G., 2014. Patients' administration preferences: progesterone vaginal insert (Endometrin®) compared with intramuscular progesterone for luteal phase support. Reprod. Health 11, 78.

Bergh, C., Lindenberg, S., Nordic Crinone Study Group, 2012. A prospective randomized multicentre study comparing vaginal progesterone gel and vaginal micronized progesterone tablets for luteal support after *in vitro* fertilization/intracytoplasmic sperm injection. Hum. Reprod. 27, 3467–3473.

Biberoglu, E.H., Tanrikulu, F., Erdem, M., Erdem, A., Biberoglu, K.O., 2016. Luteal phase support in intrauterine insemination cycles: a prospective randomized study of 300 mg versus 600 mg intravaginal progesterone tablet. Gynecol. Endocrinol. 32, 55–57.

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. Arch. Pediatr. Adolesc. Med. 159, 957–962.

Centre for Reviews and Dissemination (CRD), 2009. Systematic reviews: CRD's guidance for undertaking reviews in health care. https://www.york.ac.uk/crd/guidance/. (Accessed 13th July 2017).

Connell, M.T., Szatkowski, J.M., Terry, N., Decherney, A.H., Propst, A.M., Hill, M.J., 2015. Timing luteal support in assisted reproductive technology: a systematic review. Fertil. Steril. 103, 939–946, e3.

Daya, S., Gunby, J., 2004. Luteal phase support in assisted reproduction cycles. Cochrane Database Syst. Rev. CD004830.

Daya, S., Gunby, J.L., 2008. Withdrawn: luteal phase support in assisted reproduction cycles. Cochrane Database Syst. Rev. CD004830.

Doody, K.J., Schnell, V.L., Foulk, R.A., Miller, C.E., Kolb, B.A., Blake, E.J., Yankov, V.I., 2009. Endometrin for luteal phase support in a randomized, controlled, open-label, prospective in-vitro fertilization trial using a combination of Menopur and Bravelle for controlled ovarian hyperstimulation. Fertil. Steril. 91, 1012–1017.

Fanchin, R., Righini, C., De Ziegler, D., Olivennes, F., Ledee, N., Frydman, R., 2001. Effects of vaginal progesterone administration on uterine contractility at the time of embryo transfer. Fertil. Steril. 75, 1136–1140.

Fatemi, H.M., Popovic-Todorovic, B., Papanikolaou, E., Donoso, P., Devroey, P., 2007. An update of luteal phase support in stimulated IVF cycles. Hum. Reprod. Update 13, 581–590.

Ganesh, A., Chakravorty, N., Mukherjee, R., Goswami, S., Chaudhury, K., Chakravarty, B., 2011. Comparison of oral dydrogesterone with progesterone gel and micronized progesterone for luteal support in 1,373 women undergoing *in vitro* fertilization: a randomized clinical study. Fertil. Steril. 95, 1961–1965.

Geber, S., Moreira, A.C., De Paula, S.O., Sampaio, M., 2007. Comparison between two forms of vaginally administered progesterone for luteal phase support in assisted reproduction cycles. Reprod. Biomed. Online 14, 155–158.

Green, K.A., Zolton, J.R., Schermerhorn, S.M., Lewis, T.D., Healy, M.W., Terry, N., Decherney, A.H., Hill, M.J., 2017. Progesterone luteal support after ovulation induction and intrauterine insemination: an updated systematic review and meta-analysis. Fertil. Steril. 107, 924–933, e5.

HFEA, 2016. Fertility treatment in 2014: Trends and figures.

Ho, C.H., Chen, S.U., Peng, F.S., Chang, C.Y., Yang, Y.S., 2008. Luteal support for IVF/ICSI cycles with crinone 8% (90 mg) twice daily results in higher pregnancy rates than with intramuscular progesterone. J. Chin. Med. Assoc. 71, 386–391.

Inhorn, M.C., Patrizio, P., 2015. Infertility around the globe: new thinking on gender, reproductive technologies and global movements in the 21st century. Hum. Reprod. Update 21, 411–426.

IVF Worldwide, 2012. An updated survey: The use of progesterone for luteal phase support. http://www.ivf-worldwide.com/survey/an-updated-survey-on-the-use-of-progesterone-for-luteal-phase-support-in-stimulated-ivf-cycles/results-an-updated-survey-on-the-use-of-progesterone-for-luteal-phase-support-in-stimulated-ivf-cycles.html. (Accessed 13 July 2017).

Kleinstein, J., 2005. Efficacy and tolerability of vaginal progesterone capsules (Utrogest 200) compared with progesterone gel (Crinone 8%) for luteal phase support during assisted reproduction. Fertil. Steril. 83, 1641–1649.

Kohls, G., Ruiz, F., Martinez, M., Hauzman, E., De La Fuente, G., Pellicer, A., Garcia-Velasco, J.A., 2012. Early progesterone cessation after *in vitro* fertilization/intracytoplasmic sperm injection: a randomized, controlled trial. Fertil. Steril. 98, 858–862.

Kyrou, D., Fatemi, H.M., Zepiridis, L., Riva, A., Papanikolaou, E.G., Tarlatzis, B.C., 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. Hum. Reprod. 26, 1020–1024.

Ludwig, M., Schwartz, P., Babahan, B., Katalinic, A., Weiss, J.M., Felberbaum, R., Al-Hasani, S., Diedrich, K., 2002. Luteal phase support using either Crinone 8% or Utrogest: results of a prospective, randomized study. Eur. J. Obstet. Gynecol. Reprod. Biol. 103, 48–52.

Mascarenhas, M.N., Flaxman, S.R., Boerma, T., Vanderpoel, S., Stevens, G.A., 2012. National, regional, and global trends in infertility prevalence since 1990: a systematic analysis of 277 health surveys. PLoS Med. 9, e1001356.

Mesen, T.B., Young, S.L., 2015. Progesterone and the luteal phase: a requisite to reproduction. Obstet. Gynecol. Clin. North Am. 42, 135–151.

Mochtar, M.H., van Wely, M., van der Veen, F., 2006. Timing luteal phase support in GnRH agonist down-regulated IVF/embryo transfer cycles. Hum. Reprod. 21, 905–908.

Ng, E.H., Miao, B., Cheung, W., Ho, P.C., 2003. A randomized comparison of side effects and patient inconvenience of two vaginal progesterone formulations used for luteal support in *in vitro* fertilization cycles. Eur. J. Obstet. Gynecol. Reprod. Biol. 111, 50–54.

Ng, E.H., Chan, C.C., Tang, O.S., Ho, P.C., 2007. A randomized comparison of side effects and patient convenience between Cyclogest suppositories and Endometrin tablets used for luteal phase support in IVF treatment. Eur. J. Obstet. Gynecol. Reprod. Biol. 131, 182–188.

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

Palermo, G., Joris, H., Devroey, P., van Steirteghem, A.C., 1992. Pregnancies after intracytoplasmic injection of single spermatozoon into an oocyte. Lancet 340, 17–18.

Polyzos, N.P., Messini, C.I., Papanikolaou, E.G., Mauri, D., Tzioras, S., Badawy, A., Messinis, I.E., 2010. Vaginal progesterone gel for luteal phase support in IVF/ICSI cycles: a meta-analysis. Fertil. Steril. 94, 2083–2087.

Propst, A.M., Hill, J.A., Ginsburg, E.S., Hurwitz, S., Politch, J., Yanushpolsky, E.H., 2001. A randomized study comparing crinone 8% and intramuscular progesterone supplementation in *in vitro* fertilization-embryo transfer cycles. Fertil. Steril. 76, 1144–1149.

Silverberg, K.M., Vaughn, T.C., Hansard, L.J., Burger, N.Z., Minter, T., 2012. Vaginal (crinone 8%) gel versus Intramuscular progesterone in oil for luteal phase support in *in vitro* fertilization: a large prospective trial. Fertil. Steril. 97, 344–348.

Simunic, V., Tomic, V., Tomic, J., Nizic, D., 2007. Comparative study of the efficacy and tolerability of two vaginal progesterone formulations, crinone 8% gel and utrogestan capsules, used for luteal support. Fertil. Steril. 87, 83–87.

Tay, P.Y., Lenton, E.A., 2005. The impact of luteal supplement on pregnancy outcome following stimulated IVF cycles. Med. J. Malaysia 60, 151–157.

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. CD009154.

Williams, S.C., Oehninger, S., Gibbons, W.E., van Cleave, W.C., Muasher, S.J., 2001. Delaying the initiation of progesterone supplementation results in decreased pregnancy rates after *in vitro* fertilization: a randomized, prospective study. Fertil. Steril. 76, 1140–1143.

World Health Organization, 2016. Infertility definitions and terminology. http://www.who.int/reproductivehealth/topics/infertility/definitions/en/. (Accessed 15 July 2016).

Yanushpolsky, E.H., 2015. Luteal phase support in *in vitro* fertilization. Semin. Reprod. Med. 33, 118–127.

Zarutskie, P.W., Phillips, J.A., 2009. A meta-analysis of the route of administration of luteal phase support in assisted reproductive technology: vaginal versus intramuscular progesterone. Fertil. Steril. 92, 163–169.

Zhu, X., Ye, H., Fu, Y., 2017. Use of utrogestan during controlled ovarian hyperstimulation in normally ovulating women undergoing *in vitro* fertilization or intracytoplasmic sperm injection treatments in combination with a "freeze all" strategy: a randomized controlled dose-finding study of 100 mg versus 200 mg. Fertil. Steril. 107, 379–386, e4FIGURES.