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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 (RCT) 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 RCT 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 5 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 LH triggers ovulation; LH also causes granulosa cells to produce progesterone, which prepares the endometrium for implantation and occurs approximately 6 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 7 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.

Methods

Search strategy

A predefined 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

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