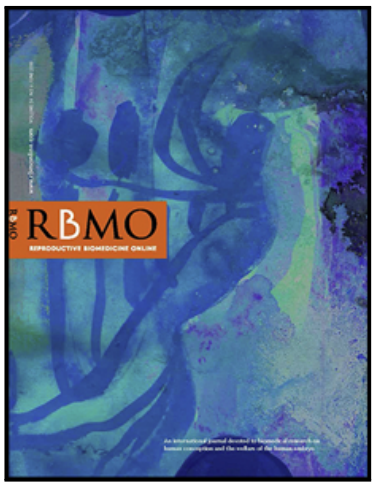
Journal Pre-proof



Endometrial scratch in women undergoing first time IVF treatment: A systematic review and meta-analysis of randomised controlled trials

Mostafa Metwally , Robin Chatters , David White , Jamie Hall , Stephen Walters

PII: S1472-6483(21)00596-4
DOI: https://doi.org/10.1016/j.rbmo.2021.11.021
Reference: RBMO 2860

To appear in: *Reproductive BioMedicine Online*

Received date: 9 September 2021
Revised date: 26 November 2021
Accepted date: 29 November 2021

Please cite this article as: Mostafa Metwally , Robin Chatters , David White , Jamie Hall , Stephen Walters , Endometrial scratch in women undergoing first time IVF treatment: A systematic review and meta-analysis of randomised controlled trials, *Reproductive BioMedicine Online* (2021), doi: https://doi.org/10.1016/j.rbmo.2021.11.021

Endometrial scratch in women undergoing first time IVF treatment: A systematic review and meta-analysis of randomised controlled trials.

Mostafa Metwally[1] (*corresponding author*), m.metwally@sheffield.ac.uk. ORCID: 0000-0003-4022-1740

Robin Chatters[2], r.chatters@sheffield.ac.uk

David White[2], d.a.white@sheffield.ac.uk

Jamie Hall[2], jamie.hall@sheffield.ac.uk

Stephen Walters[2], s.j.walters@sheffield.ac.uk

[1] Obstetrics, Gynaecology & Neonatology, Sheffield Teaching Hospitals NHS Foundation Trust and The University of Sheffield, Sheffield, UK, S10 2JF

[2] Sheffield Clinical Trials Research Unit, School of Health and Related Research, Sheffield, UK, S1 4DA

Abstract

The endometrial scratch (ES) procedure is an IVF óadd-onô that is sometimes provided prior to the first IVF cycle. A 2019 systematic review concluded that there was insufficient evidence regarding whether the ES has a significant effect on pregnancy outcomes (including live birth rate, LBR) when undertaken prior to the first IVF cycle. Further evidence has been published following this review, including the Endometrial Scratch Trial (ISRCTN23800982). The objective of this review was to synthesise and critically appraise the evidence for the clinical effectiveness and safety of the ES procedure in women undergoing their first IVF cycle. Databases searched include MEDLINE, EMBASE, CINAHL and ClinicalTrials.gov. Eligible RCTs included women undergoing IVF for the first time that reported the effectiveness and/or safety of the ES procedure. Twelve studies were included. Meta-analysis showed no evidence of a significant effect of the ES on LBRs (10 trials, odds ratio [OR] of 1.17, 95% confidence interval [CI], 0.76 to 1.79), and other pregnancy outcomes. This review confirms that there is a lack of evidence that ES improves pregnancy outcomes, including LBR, for women undergoing their first IVF cycle. Clinicians are recommended not to perform this procedure in individuals undergoing their first cycle of IVF.

Keywords: IVF, endometrial scratch, systematic review, first cycle, effectiveness, induced endometrial trauma.

Introduction

Endometrial scratch (ES) is a procedure that has been rapidly adopted into routine clinical practice at a rate that far exceeds the rate of production of good quality evidence (Lensen et al., 2016). While the procedure was initially adopted for women suffering from recurrent implantation failure during IVF treatment based on evidence from the initial study by Barash et al (2003), it then rapidly spread to other populations of women and other types of treatments (Barash et al., 2003).

Amongst these groups, are women undergoing their first IVF cycle, where ES had started to be offered to this group despite the lack of evidence (Lensen et al., 2016). Indeed there have since been

many studies, but these were mostly subject to significant confounding factors or not designed or powered to address this particular group (Vitagliano et al., 2019).

A systematic review on this topic, focussing on randomised controlled trials (RCTs) and the effectiveness of the ES procedure in women undergoing their first IVF cycle, was published by Vitagliano et al in 2019 (Vitagliano et al., 2019). The review included seven RCTs and concluded that there was no evidence that the ES followed by IVF compared to IVF alone increased the success of treatment, with a relative risk/risk ratio (RR) of live birth (or ongoing pregnancy if life birth rate [LBR] was not reported) of 0.99 (95% CI: 0.57 to 1.73, p=0.97) (Vitagliano et al., 2019). Secondary outcomes (miscarriage, multiple pregnancy and ectopic pregnancy) were also not significantly altered by undertaking the ES. Notably, the small sample sizes of the included studies resulted in huge uncertainty around the effects of ES in women undergoing their first IVF cycle so positive effect could not be rule out. In addition, the trials included were at either a high or unclear risk of bias making it difficult to make reliable conclusions. Consequently, the authors concluded that a robust and definitive RCT is required to assess the effect of ES on the chances of success of the first IVF cycle (Vitagliano et al., 2019).

Recently we have published evidence from a large definitive multicentre RCT in the United Kingdom (the Endometrial Scratch Trial) which focussed only women undergoing first IVF cycle, with or without intracytoplasmic sperm injection (ICSI) (Metwally et al., 2021). In this trial we did not find evidence for any significant benefit from the ES. Given the large number of other studies in the literature, some with similar and some with conflicting findings and given that often a meta-analysis of all published literature rather than a single RCT is important in propagating a certain research finding and implementing change in practice, we performed this meta-analysis to synthesise the effect of ES in increasing success rates of pregnancy outcomes in women undergoing first time IVF treatment with or without ICSI.

Methods

The review was conducted, and this manuscript written, in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines (Page et al., 2021).

Protocol registration
The systematic review was registered with PROSPERO (CRD42018111139, https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=111139) on 18th October 2018.

Study selection
Only RCTs examining the clinical effect or safety of ES in women undergoing their first IVF cycle with or without ICSI, compared to treatment as usual (IVF/ICSI without the use of ES), were eligible for inclusion. Studies that included participants who were undertaking intrauterine insemination (IUI) or ovulation induction (or other treatments not classed as IVF) and/or their second or subsequent IVF cycle were excluded from this review, unless separate outcome data could be extracted for a subset of women who have undertaken their first IVF cycle. We included all forms of ES regardless of the timing of the procedure during the cycle, however, procedures defined as a mock transfer, where the aim of the procedure was not to scratch the endometrium but to test embryo transfer techniques, were excluded.

We excluded reports published as abstracts only, and/or, reports published in languages other than English, where insufficient methodological details are reported in the abstract (if written in English) to allow extraction of study characteristics.

Outcomes measures
The following clinical and safety outcome measures were considered, which were included regardless of the definition or timing of assessments:

1- Primary: Live birth rate
2- Secondary:
    a. Implantation rate
    b. Clinical pregnancy rate
    c. Ongoing pregnancy rate
    d. Miscarriage rate
    e. Ectopic pregnancy rate
    f. Pain related to the procedure
    g. Adverse and serious adverse event rates (AEs and SAEs)

Search methods for identification of studies

Data sources and search period

The following electronic databases were searched without language restrictions on 10th January 2020 except for clinicaltrials.gov which was searched on 21st September 2020.

- MEDLINE via Ovid from 1948 to present (Appendix A)
- EMBASE (Ovid) from 1980 to present
- Cochrane database of systematic reviews from 2005 to present
- Clinicaltrials.gov (http://www.clinicaltrials.gov/)
- Cumulative Index to Nursing and Allied Health Literature (CINAHL) from 1981 to present
- CENTRAL via The Cochrane Register of Studies Online from 1898 to present

Language restrictions were applied after the search was undertaken.

Clinicaltrials.gov was searched using combinations of keywords - "endometrial biopsy" AND "infertility", "endometrial biopsy" AND "subfertility", "endometrial hysteroscopy" AND "infertility", "endometrial hysteroscopy" AND "subfertility".

We also hand searched the reference list of all retrieved articles, relevant journals and conference proceedings. In addition, we contacted the authors seeking data clarification and to obtain additional information on missing data.

Selection of studies and data extraction

Titles, abstracts and full-text articles were screened independently by two reviewers (JH and LR). Any disagreements regarding eligibility were resolved through discussion with RC.

Data were extracted from the studies by one researcher (JH) and all data checked by RC. Data extracted included the outcomes, study characteristics (e.g., country where research was conducted, number of trial arms, description of trial arms, control condition(s), timing of ES procedure in menstrual cycle, device used for ES) and participant characteristics (e.g., average age of trial

population, average duration of infertility, and egg source). Where further information was needed, the authors were contacted.

Quality assessment strategy

The methodological quality of the included RCTs was assessed using the Cochrane Collaboration risk of bias assessment criteria at an outcome level (Higgins et al., 2019). The risk of bias was assessed for each reported outcome. The assessment was undertaken independently by two reviewers (either PK, RC, AP or JH). Discrepancies were resolved by a third reviewer who had not been involved in the previous assessments of that study (RC or JH). Studies were graded with an overall risk of bias of óhighô, ólowô or óunclearô.

Data analysis

Statistical analysis was conducted according the guidelines outlined by the Cochrane Collaboration (Higgins et al., 2021). For each included RCT, summaries on the number of events and the denominator were recorded for binary outcomes and meta-analysis performed using RevMan software version 5.3 (Review Manager (RevMan). Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). Study specific treatment effects as measured by odds ratios (ORs) and RRs were combined together to produce pooled ORs or RRs with 95% CIs, where appropriate using Mantel-Haenszel method which performs relatively well in several settings (Piaget Rossel and Taffé, 2019). A random effects model was used when between study heterogeneity was viewed as substantial. Otherwise, a fixed effects model was used when there was no evidence of significant heterogeneity. We assessed heterogeneity between studies using the τ^2 and I^2 statistics (Higgins et al., 2003; Higgins and Thompson, 2002). For example, the I^2 statistic quantifies that the percentage of total variation in treatment effects estimates attributable to between study heterogeneity and a value of >50% indicates evidence of significant heterogeneity of treatment effects between studies (Deeks JJ, Higgins JPT, 2021). A subgroup analysis was conducted for two trials that reported óearlyô miscarriages (prior to 12 weeks) (Izquierdo Rodriguez et al., 2020; Maged, 2018). Only one trial separately reported ólateô miscarriages (occurring between 12 and 24 weeks) (Izquierdo Rodriguez et al., 2020), with all other trials reporting miscarriages up to 24 weeks (which also

included early miscarriages) ï therefore, due to the heterogeneity of this outcome, the late miscarriage subgroup was not included in this analysis.

In the evidence of significant heterogeneity, a random effects model was used in addition to an exploration of the causes of heterogeneity followed by a sensitivity analysis where appropriate. Meta-analysis are presented in forest plots. Some outcomes (pain scores, adverse events) were narratively assessed due to a small number of studies reporting these outcomes, and/or heterogeneity in the definition of outcomes.

Results

Screening and study eligibility

Searches identified a total of 1462 records. When needed, authors were contacted regarding missing data and to help assess eligibility. Of the 14 authors that were contacted, eight were not contactable. One author confirmed that the trial was not eligible for inclusion as recruitment to the trial never commenced (Checa, 2013). The authors of four trials that included participants undergoing their first IVF cycle but did not present their outcomes separately provided data and were included in the review (Izquierdo Rodriguez et al., 2020; Lensen et al., 2019; Mackens et al., 2020; Nastri et al., 2013). Polanski et al., which included women undergoing an unselected number of previous IVF cycles, could not be contacted to obtain data for first cycle participants only. However, unpublished data presented, received directly from the authors in a recent systematic review were used (Vitagliano et al., 2019). A risk of bias assessment could not be conducted for this study due to a lack of methodological details described in the abstract. After screening, 11 RCTs were eligible for inclusion in the review. We also included the results of our recently conducted Endometrial Scratch Trial, published after the searches were undertaken, thus bringing the total to 12 RCTs (Metwally et al., 2021) published between 2010 and 2021. Details of literature search and study selection can be seen in figure 1.

Characteristics of included trials

Table 1 summarises the characteristics of the 12 included RCTs comprising 3234 participants undergoing their first IVF/ICSI cycle.

Nature of trials and geographical coverage

Only three of the 12 studies were multicentre RCTs (Lensen et al., 2019; Mahran et al., 2016; Metwally et al., 2020), with other studies involving a single centre. All 12 studies were individually randomised and were conducted across ten countries: Iran, Hong Kong, Egypt (two studies), China, USA, Belgium, Spain, Turkey, Brazil, and the UK. One RCT was undertaken multi-nationally across five countries (Lensen et al., 2019). The total number of participants included in each trial undergoing their first IVF cycle ranged from 18 to 1048.

Eleven studies were two-arm RCTs (Eskew et al., 2019; Izquierdo Rodriguez et al., 2020; Karimzade et al., 2010; Lensen et al., 2019; Mackens et al., 2020; Maged et al., 2018; Mahran et al., 2016; Metwally et al., 2020; Nastri et al., 2013; Polanski et al., 2014; Yeung et al., 2014) and one was a four-arm RCT (Liu et al., 2017). Nine of the two-arm RCTs compared the ES procedure to usual care and two trials included a comparator involving a sham procedure (Eskew et al., 2019; Nastri et al., 2013). The four-arm trial compared ES at two different time points with a sham procedure undertaken at the same two different time points in the menstrual cycle ï proliferative and luteal (Liu et al., 2017).

Recruitment to three of the trials was prematurely ended due to an unplanned futility analysis showing no differences in clinical pregnancy rates between intervention and control groups in one trial (Eskew et al., 2019), a planned interim analysis identifying higher miscarriage rates in the ES arm in another trial (Mackens et al., 2020), and identifying a significant benefit of the ES during a planned interim analysis (Nastri et al., 2013).

Characterisation of ES procedure and timing

The method of undertaking ES was largely similar across studies. Most used a pipelle sampler to invoke injury, except for one trial that used an embryo transfer catheter (Izquierdo Rodriguez et al., 2020), one that used a Novak Curette (Karimzade et al., 2010), and another that used either a pipelle or Wallace endometrial sampler (Polanski et al., 2014). However, there was substantial variation in the timing of when ES was performed across trials. Two trials undertook ES during the IVF cycle, either on the day of egg collection (Karimzade et al., 2010), or during ovarian stimulation (Mackens et al., 2020). Ten trials undertook ES in the menstrual cycle prior to IVF, with seven within the luteal

phase (Eskew et al., 2019; Izquierdo Rodriguez et al., 2020; Maged et al., 2018; Mahran et al., 2016; Metwally et al., 2021; Polanski et al., 2014; Yeung et al., 2014), and one during the early or mid-luteal phase (Nastri et al., 2013). Lensen *et al.* undertook ES at any point between day three of the menstrual cycle prior to ES (Lensen et al., 2019), and day three of the cycle in which IVF was being undertaken. However, this trial reported that the median time (interquartile range, IQR) between ES and embryo transfer was 35 days (22 to 39), and therefore, it is likely that most women received ES in the menstrual cycle prior to IVF. Liu *et al.* undertook ES either the proliferative or luteal phases of the menstrual cycle (Liu et al., 2017), therefore in this review the two time points of delivery of ES, or the sham procedure, were combined, so that, for each outcome, there was one rate for the ES arm (both proliferative and luteal), and another for the sham arm (both proliferative and luteal). Two trials provided hysteroscopy to all trial participants, prior to IVF (Mahran et al., 2016; Yeung et al., 2014).

Participant eligibility

Trials used different participant eligibility criteria. Ten trials had age restrictions with an upper limit of between 35 and 49 years (Eskew et al., 2019; Karimzade et al., 2010; Lensen et al., 2019; Liu et al., 2017; Mackens et al., 2020; Maged et al., 2018; Mahran et al., 2016; Metwally et al., 2021; Nastri et al., 2013; Polanski et al., 2014). Three trials restricted the body mass index (BMI) to an upper limit ranging from 30 to 35 kg/m^2 (Karimzade et al., 2010; Maged et al., 2018; Metwally et al., 2021). Five trials selected women that were deemed to have a good ovarian reserve, by allowing only those with a certain level of follicle stimulating hormone (FSH) to participate, with a maximum level of 10 IU/mL and 12 IU/mL in two (Maged et al., 2018; Metwally et al., 2021), and three studies (Karimzade et al., 2010; Liu et al., 2017; Mahran et al., 2016), respectively. At eligibility screening, two studies set requirements for the number of oocytes collected or embryos replaced: Ó2 replaced in one study (Mahran et al., 2016), and four to 14 oocytes collected in another (Karimzade et al., 2010). Only one trial stipulated that the embryos replaced had to be of a certain quality, with Mahran *et al.* (Mahran et al., 2016) stating that the two or more embryos replaced had to be ógoodô quality. However, the exact method of grading embryo or defining a good quality embryo was not reported. Two trials excluded women receiving donor eggs (Mackens et al., 2020; Yeung et al., 2014), whilst one study only included those receiving donor eggs (Izquierdo Rodriguez et al., 2020).

Trial outcomes

Ten trials reported LBRs (Eskew et al., 2019; Izquierdo Rodriguez et al., 2020; Lensen et al., 2019; Liu et al., 2017; Mackens et al., 2020; Mahran et al., 2016; Metwally et al., 2021; Nastri et al., 2013; Polanski et al., 2014; Yeung et al., 2014). Clinical pregnancy rates were reported in all trials. However, this was defined inconsistently, with marked variation in the time point at which this outcome was assessed: at four weeks post embryo transfer in two trials (Maged et al., 2018; Mahran et al., 2016); five weeks in one trial (Karimzade et al., 2010); six weeks in four trials (Izquierdo Rodriguez et al., 2020; Lensen et al., 2019; Liu et al., 2017; Yeung et al., 2014); seven (Mackens et al., 2020) and eight weeks (Metwally et al., 2021); and not reported in three trials (Eskew et al., 2019; Nastri et al., 2013; Polanski et al., 2014). Ongoing pregnancy rates were reported in four trials, which was assessed at 12 (Izquierdo Rodriguez et al., 2020; Karimzade et al., 2010; Lensen et al., 2019) and 20 (Yeung et al., 2014) weeks post embryo transfer.

Implantation rates were reported in seven studies (Izquierdo Rodriguez et al., 2020; Karimzade et al., 2010; Liu et al., 2017; Maged et al., 2018; Mahran et al., 2016; Metwally et al., 2021; Yeung et al., 2014). Six studies defined this similarly as the number of gestational sacs, divided by the number of embryos transferred, whilst in Metwally *et al.*,(Metwally et al., 2021) this was defined as the number gestational sacs divided by the number of participants randomised to each arm (under intention to treat principles). In order to include our trial in this meta-analysis we therefore recalculated this outcome using the number as embryos transferred as the denominator. Miscarriage rates per clinical pregnancy were reported in 11 trials (Eskew et al., 2019; Izquierdo Rodriguez et al., 2020; Lensen et al., 2019; Liu et al., 2017; Mackens et al., 2020; Maged et al., 2018; Mahran et al., 2016; Metwally et al., 2021; Nastri et al., 2013; Polanski et al., 2014; Yeung et al., 2014), with the time point of data collection differing between 12 to 24 weeks of gestation, but unclear in two trials (Lensen et al., 2019; Mackens et al., 2020). A subjective assessment of pain of the ES procedure on a numerical rating scale was reported in three trials (Lensen et al., 2019; Metwally et al., 2021; Nastri et al., 2013), with four studies providing qualitative reports of pain (Liu et al., 2017; Mackens et al., 2020; Mahran et al., 2016; Yeung et al., 2014). Eight trials reported adverse events and/or complications in the participating women (Karimzade et al., 2010; Lensen et al., 2019; Liu et al., 2017; Mackens et al.,

2014) (NCT01977976)	China, March 2011 to October 2013	usual care	poulation		or without ICSI		7 days post LH surge / day 21 of cycle preceding IVF	CPR, IR, MR, MPR, QP, AE
Mahran 2016 (Mahran et al., 2016) (ISRCTN61316186)	Multi-centre (2 centres), Egypt, June 2012 to September 2014	Endometrial scratch vs usual care	20 to 40 years, FSH Ò12 mIU/mL and Ó2 good quality embryos replaced	418	IVF with or without ICSI	Pipelle	Prior to IVF Day 21 to 24 of cycle preceding IVF	LBR, OPR, CPR, IR, MR, MPR, QP, AE
Maged 2018	Single-	Endometrial	Age <	300	ICSI	Pipelle	Prior to	CPR,

(Maged et al., 2018) (NCT02660125)	centre, Egypt, January 2016 to March 2017	scratch vs usual care	40 years and FSH < 10 mIU/ mL				IVF	IR, MR, MPR, AE
Liu 2017 (Liu et al., 2017) (ChiCTR-IOR-17011506)	Single-centre, China February 2012 to November 2014	Endometrial scratch (proliferative phase)/ endometrial scratch (luteal phase) vs sham procedure (proliferative phase)/ sham procedure (luteal phase)	Age Ò40 years , FSH <12 mIU/ mL	142	IVF with or without ICSI	Pipelle	Prior to IVF Proliferative phase (day 10 to 12) or luteal phase (day 7 to 9) of preceding cycle	LBR, CPR, BPR, IR, MR, EPR, MPR, QP, AE
Eskew 2019 (Eskew et al., 2019) (Clinical trials registration	Single-centre, USA, Septemb	Endometrial scratch vs usual care	Age 18 to 43 years	66	IVF	Pipelle	Prior to IVF 7 to 13 days	LBR, CPR, MR

unknown)	er 2013 to July 2017						post LH surge in cycle precedi ng IVF	
Lensen 2019 (Lensen et al., 2019) (ACTRN12614000626662)	Multi-centre (13 centres), New Zealand, Belgium, Sweden and UK	Endometrial scratch vs usual care	Age > 18 years	626	IVF with or witho ut ICSI	Pipelle	Prior to IVF Day 3 of the precedi ng cycle to day 3 of the IVF cycle	LBR, OPR, CPR, MR, EPR, MPR, SBR, NP, AE
Mackens 2020 (Mackens et al., 2020) (NCT02061228)	Single-centre, Belgium, April 2014 to October	Endometrial scratch vs usual care	Age Ó18 and <40 years, BMI	148	IVF with or witho ut ICSI	Pipelle	During IVF Days 6 to 7 of ovarian stimula	LBR, CPR, MR, EPR, QP, AE

	2017		Ò 35 or Ó18 kg/m^2 and Excluded donor eggs				tion	
Izquierdo Rodriguez 2020 (Izquierdo Rodriguez et al., 2020) (NCT03108157)	Single-centre, Spain, Jan 2017 to October 2018	Endometrial scratch vs usual care	Only donor eggs	140	ICSI	Endometrial biopsy catheter	Prior to IVF Luteal phase ï 5 to 10 days before the start of the period	LBR, CPR, OPR, IR, MR, MPR
Nastri 2013 (Nastri et al., 2013) (NCT01132144)	Single-centre, Brazil, June 2010 to March 2012	Endometrial scratch vs sham procedure	Age <38 years	18	IVF with or without ICSI	Pipelle	Prior to IVF 7 to 14 days prior to planned start of	LBR, CPR, MR, NP

							controlled ovarian stimulation	
Metwally 2021 (Metwally et al., 2021) (ISRCTN23800982)	Multi-centre (16 sites), UK, July 2016 to October 2018	2 arms, endometrial scratch vs usual care	Age 18 to 37 years, BMIÓ 35 kg/m^{2}, FSH< 10 mIU/mL	1048	IVF with or without ICSI	Pipelle	Prior to IVF Mid-luteal phase defined as 5 to 7 days before the expected next period, or 7 to 9 days after a positive ovulation test	LBR, CPR, IR, SBR, NP, AE, PTR
Polanski 2014 (Polanski et al.,	Single-centre,	2 arms: Endometrial	Age <49	111	IVF with	Pipelle or	Prior to IVF	LBR, MPR,

2014) (NCT01882842)	UK, February 2013 to June 2015	scratch, usual care	years		or without ICSI	Wallace endometrial sampler	7 to 9 days post LH surge in the cycle preceding IVF	CPR, MR, EPR

AE – adverse events; CPR – clinical pregnancy rate; EPR – ectopic pregnancy rate; ICSI, Intracytoplasmic sperm injection; IR – implantation rate; IU: international units; IVF, in vitro fertilisation; kg/m^2 – kilograms per metre squared; LBR – live birth rate; LH, luteinizing hormone; mIU/ml – milli international units per milli litre; MBR –multiple birth rate; MPR – multiple pregnancy rate; NP - numerical pain score; OPR – ongoing pregnancy rate; PTR – preterm delivery rate; SBR – stillbirth rate; QP, qualitative pain score