Endometrial scratch to increase live birth rates in women undergoing first-time in vitro fertilisation: RCT and systematic review

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Scientific summary

Endometrial scratch in first-time in vitro fertilisation

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Scientific summary

Background

In vitro fertilisation (IVF), with or without intracytoplasmic sperm injection (ICSI), is a widely used reproductive technique in women unable to conceive naturally. An array of expensive 'add-on' treatments are often offered, many of which lack robust evidence to support their use. One such add-on is the endometrial scratch (ES) procedure, in which the endometrium is abraded prior to embryo transfer. ES is hypothesised to increase the chances of live birth by improving embryo implantation. However, in women undergoing their first IVF cycle, several controlled trials have identified contradictory evidence, with the most recent systematic review concluding that there is a lack of high-quality evidence. Many of these previous studies included both women undergoing their first IVF cycle and women undergoing subsequent cycles, and were therefore not powered to detect clinically worthwhile effects in those undergoing their first IVF cycle. A high-quality randomised controlled trial (RCT) is required to definitively determine if the ES procedure is effective and safe.

Objectives

The Endometrial Scratch Trial

This aimed to assess the clinical effectiveness, safety and cost-effectiveness of the ES procedure performed in the mid-luteal phase prior to the first IVF cycle, with or without ICSI.

Systematic review and meta-analysis

This aimed to synthesise evidence of the clinical effectiveness and safety of the ES, by combining the results of this trial with the results of similar RCTs in this population.

Qualitative substudy

The objective of the substudy was to understand the experiences of trial participants and fertility unit staff participating in the trial, including recruitment, receiving/delivering the ES, data collection methods and withdrawal from the ES procedure.

Methods

The Endometrial Scratch Trial

Design and setting

The trial was a pragmatic, two-arm, superiority, open-label, parallel-group, multicentre, individually randomised controlled trial undertaken at 16 fertility units in the UK, two of which were run privately.

Participants

Participants were women who:

- were aged 18–37 years (inclusive)
- were undergoing their first IVF cycle (with or without ICSI)
- were expected to be using fresh embryos and a single embryo transfer
- had a regular menstrual cycle, normal uterine cavity, good ovarian reserve and no relevant vaginal/uterine infections
- if randomised to receive ES, were willing to use a barrier method of contraception prior to the procedure.

Participants were excluded if they had received previous trauma to the endometrium, had a body mass index of ≥ 35 kg/m^2, were participating in another interventional fertility study or had grade 4 endometriosis.

Interventions

The ES procedure was performed by a doctor or nurse in the mid-luteal phase of the menstrual cycle preceding IVF. ES was performed by inserting a speculum into the vagina. A pipelle or similar device was then inserted into the cavity of the uterus and negative pressure was applied by withdrawal of the plunger. The sampler was rotated and withdrawn three or four times so that tissue appeared in the transparent tube.

Treatment-as-usual (TAU) participants received IVF treatment (with or without ICSI) in accordance with the usual care practice of their fertility unit. ES participants received the ES procedure followed by TAU.

Randomisation and blinding

Participants were randomised (1 : 1) via a web-based system to receive either TAU or ES using block randomisation stratified by fertility unit and planned treatment protocol. Only trial statisticians and a health economist were blinded.

Outcomes

The primary outcome was live birth after completion of 24 weeks' gestation within 10.5 months post egg collection. Secondary outcomes included implantation, pregnancy, miscarriage, ectopic pregnancy, multiple birth, preterm delivery, stillbirth, pain and tolerability of ES, safety, health resource use and treatment costs.

Sample size

The trial's recruitment target was 1044 participants (522 per group) to preserve a 90% power and 5% two-sided type 1 error, and to detect a 10% absolute difference (AD) in live birth rate (LBR), which was viewed to be of clinical importance to change practice. This assumed a 30% control LBR and 5% inflation to account for uncertainty around this LBR and dropouts.

Statistical analysis

Primary analysis was based on an intention-to-treat analysis population that included all randomised participants regardless of circumstances after randomisation. For the primary outcome, AD in LBRs between groups was the treatment effect of interest. Participants with missing data on live birth were assumed to have not achieved a live birth. Normal approximation to the binomial distribution was used to calculate the 95% confidence interval (CI) around the differences in LBRs and the associated *p*-value was calculated using Pearson's chi-squared test. Corresponding unadjusted odds ratio (uOR) and unadjusted relative risk (uRR) with 95% CIs were estimated using simple logistic regression and binomial generalised linear model with a log-link function, respectively. Sensitivity analysis was performed by adjusting for fixed stratification factors and potential prognostic factors.

Health economic evaluation

The cost-effectiveness analysis presented results as cost per extra live birth from the NHS and social care perspective in accordance with the National Institute for Health and Care Excellence guidelines. Women were asked to complete a questionnaire to collect their resource use data at baseline, 3 months post egg collection and 6 weeks post partum. A patient cost questionnaire sent at 3 months post egg collection requested information about the time taken to travel to appointments and loss of productivity. Unit costs were derived from appropriate national sources, which included NHS reference costs, Personal Social Service Research Unit costs and data from the Office for National Statistics. Results were presented in the net-benefit framework and allowed for uncertainty using bootstrapping and probabilistic sensitivity analysis.

Systematic review

Literature search
The electronic databases were searched in January 2020 and these included MEDLINE, EMBASE, Cumulative Index to Nursing and Allied Health Literature (CINAHL) and The Cochrane Library, including the Cochrane Database of Systematic Reviews (CDSR), the Cochrane Central Register of Controlled Trials (CENTRAL), Health Technology Assessment (HTA) and Database of Abstracts of Reviews of Effects (DARE) (archive only). ClinicalTrials.gov was searched in September 2020. The reference lists of included manuscripts and relevant systematic reviews were checked to identify any further potentially eligible studies.

Eligibility criteria
Eligible RCTs included women undergoing IVF for the first time that reported the effectiveness and/or safety of the ES procedure. No restrictions were imposed regarding the timing or method of the ES, the trial comparator, outcomes or date published. If there were insufficient details to allow extraction of study characteristics, we excluded reports published as abstracts only and reports published in languages other than English, including those where an abstract in English was provided.

Data extraction
One reviewer extracted data, which was checked by another reviewer. Two reviewers independently assessed within-study risks of bias using the Cochrane risk-of-bias tool (version 2.0).

Meta-analysis
This was undertaken in RevMan (v5.4; The Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen, Denmark) using random-effects models. Statistical heterogeneity was assessed using the I^2 statistic. Sensitivity analysis using a fixed-effects model was undertaken when there was little heterogeneity between trials.

Qualitative substudy

Participants sampling
Interviewees were purposively sampled from six of the trial sites, which were selected while ensuring variation in site type (NHS/private), size of centre and consent rate during the trial. Participants were selected ensuring variability in age, duration of infertility and live birth status. Participants who chose not to undergo ES were also interviewed.

Staff were sampled from the selected centres. Staff from other centres were also sampled because of the lack of staff availability at the selected centres.

Interviews and analysis
Potential interviewees were contacted by e-mail and consent was sought by telephone. Interviews were undertaken by telephone using a semistructured interview guide and were audio-recorded. Recordings were transcribed verbatim and analysed using an inductive framework approach. Staff and participant interviews were analysed separately. Two individuals coded four of the transcripts for the participant interviews and two for the staff interviews independently, and agreed on the final codes. The remaining transcripts were coded by one individual. All analysis was undertaken using NVivo (v12; QSR International, Warrington, UK).

Results

The Endometrial Scratch Trial
A total of 3454 potential participants were identified, of whom 1048 eligible women were randomised to either TAU ($n = 525$) or ES ($n = 523$), and followed up between July 2016 and October 2019. In the ES group,

86.6% (453/523) of women received the ES procedure as per protocol and 85.9% (449/523) subsequently received IVF, with only 9.2% (48/523) receiving IVF without ES. In the TAU group, 94.1% (494/525) of women received IVF, of whom only 1.0% (5/494) received the ES procedure outside the trial.

The median [interquartile range (IQR)] time from ES to embryo transfer was 34.0 (26.0–42.0) days ranging from 16.0 to 346.0 (outlier) days. A total of 99.8% (448/449) of women viewed the ES procedure as tolerable. The median (IQR) pain rating score within 30 minutes of the ES procedure and at 1 day and at 7 days after the ES procedure was 4.0 (2.0–6.0), 1.0 (0.0–3.0) and 0.0 (0.0–0.0), respectively.

The LBR was 37.1% (195/525) in the TAU group and 38.6% (202/523) in the ES group [unadjusted AD of 1.5% (95% CI −4.4% to 7.4%; $p = 0.621$), uRR of 1.04 (95% CI 0.89 to 1.21) and uOR of 1.06 (95% CI 0.83 to 1.37)]. Sensitivity analyses produced similar results even after adjusting for baseline covariates. The results were also generally consistent across prespecified subgroups. There were no statistical differences in the rates of secondary outcomes. Safety events were comparable across groups, although the proportions of babies of low or very low birthweight and small for gestational age were slightly lower in the ES group than in the TAU group. No neonatal deaths were reported. Only three severe congenital abnormalities were recorded, all in the TAU group.

The health economic analysis found that ES was more costly than TAU, with ES costing, on average, £316 more than TAU. However, the incremental cost-effectiveness ratio per successful live birth of £11.90 (95% CI −£134 to £127) was relatively low.

Systematic review and meta-analysis

Twelve trials were included. One trial contributed substantial heterogeneity to the meta-analysis of LBRs and pregnancy rates, and was therefore excluded, reducing heterogeneity to moderate or low levels. Meta-analysis showed no evidence of a significant effect of ES on LBRs [nine trials; odds ratio (OR) 1.03, 95% CI 0.87 to 1.22] and pregnancy rates (11 trials; OR 1.06, 95% CI 0.84 to 1.35) using a random-effects model, with consistent results when a fixed-effects model was used. Similar results were found for miscarriage rate using a random-effects model (10 trials; OR 0.96, 95% CI 0.57 to 1.63) and for multiple pregnancy rate (five trials; OR 1.09, 95% CI 0.68 to 1.74), with consistent results when a fixed-effects model was used. No significant effects on ectopic pregnancy rates were found (five trials; OR 0.66, 95% CI 0.17 to 2.51), but with high uncertainty. A meta-analysis was not undertaken for stillbirth or preterm delivery rates owing to the small number of studies reporting these outcomes.

Only six trials reported pain post procedure; few participants reported severe pain. Three studies reported a numerical measure of pain (from 0 to 10), with all three reporting moderate pain post procedure [with mean (standard deviation) scores of 4.1 (2.4), 4.2 (2.5) and 6.42 (2.35)]. Eight trials reported adverse events; however, seven trials recorded such events only in participants who received ES, limiting the conclusions that can be reached.

Qualitative substudy

Twenty-seven trial participants and seven staff members were interviewed. Both were generally happy with the recruitment process, and participants were prepared to receive the ES procedure. Three participants felt that recruitment was too informal. Some participants and staff stated that more information was required regarding the evidence base for or against ES. Eighteen of the interviewed participants discussed having positive preconceptions regarding the effect of the ES on the outcome of their IVF cycle, with staff, in some instances, appearing to have contributed to these. Some participants were unaware of the potential harms of participating in a RCT.

Participants' positive preconceptions meant that the recruitment process was challenging, as some participants felt demoralised when they were randomised to the TAU arm. Staff developed mechanisms to assist participants who felt this way. Five participants described the procedure as being more painful than they expected.

The participants who declined the ES procedure did so for personal reasons that could not have been prevented; however, the withdrawal of two participants could have been prevented by improved organisation at the fertility unit.

Conclusions

In this definitive trial, performing the ES procedure in the mid-luteal phase in women undergoing their first IVF cycle was found to be safe and well tolerated. However, the ES procedure did not result in a significant increase in the proportion of women achieving pregnancy and a live birth compared with TAU. Furthermore, it did not improve other secondary pregnancy outcomes, as their rates were comparable in the ES and TAU groups. The cost-effectiveness analysis found that ES may be cost-effective compared with TAU. However, this should be interpreted within the context of the clinical effectiveness analysis that showed that ES did not significantly improve LBR. Given the lack of consensus regarding cost-effectiveness thresholds for these outcomes, and high uncertainty in the cost-effectiveness estimates, we recommend that ES is not undertaken in this population.

A meta-analysis combining our trial results with the results of other trials undertaken in this population showed no significant clinical benefit of undertaking ES prior to the first IVF cycle to improve pregnancy outcomes.

A major strength of the study was the focus on one population in order to minimise heterogeneity. The trial recruited the target number of participants, with negligible contamination in the TAU arm. The response to treatment was good in both arms, with a high proportion of participants receiving a day 5 embryo transfer. The trial was open label and did not include a sham procedure in the TAU arm; however, this is unlikely to have biased the key trial results, as the key outcome measures are unlikely to have been influenced by a placebo effect. Nearly 10% of women randomised to receive ES did not receive it, which may have diluted the treatment effect; however, post hoc analysis excluding these participants produced consistent results and conclusions.

Despite identifying three safety outcomes (i.e. small for gestational age, low birthweight and very low birthweight) that suggested a potential positive effect on outcomes, we believe that future work in this area is unwarranted owing to the small number of events involved in these analyses and the likelihood that these findings are due to chance. An individual patient data meta-analysis is planned by Lensen and colleagues, the results of which should be received before carrying out any further research into the effectiveness of the ES procedure.

Trial registration

The trial is registered as ISRCTN23800982.

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This report

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