IVF add-ons for the endometrium

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Abstract

TBA

Introduction

There are a plethora of adjunct or add-on interventions offered to patients undergoing IVF, promising to offer patients incremental increased likelihood at the chance of a baby. Despite very few add-ons having any robust evidence of effectiveness or safety, their use is widespread: 74% of women undergoing IVF in the UK used one or more add-on in 2018 (HFEA report).

These add-ons range from interventions suggested to increase the follicular response to ovarian stimulation, improve the culture conditions and quality of the developing embryos, and priming the endometrium for impending implantation. The role of the endometrium has come under increased focus as rates of implantation appear to have plateaued and observations that high quality euploid embryos fail to implant. In this review we summarise the evidence for common add-ons which are suggested to improve the health or receptivity of the endometrium during an IVF cycle.

Methods

The add-ons were selected from those included in recent add-ons publications (Spencer 2016, Datta 2015), and assessed by the UK HFEA traffic light system (REF). Using these sources we developed a long list of add-ons, and then selected those suggested to improve the endometrial receptivity specifically. Similar add-ons were merged into add-on categories (for example, GCSF and NK cell testing and treatment are considered under the add-on 'immune therapies').

We then searched for recent Cochrane systematic reviews of randomised trials assessing these add-ons, published in 2016 or more recently. Cochrane reviews have been demonstrated as higher quality and less biased than other systematic reviews, in general (Goldkuhle, Gøtzsche 2006). If no Cochrane review was available, we expanded the search in for recent systematic reviews published in any journal (Pubmed, last search June 2019). When no systematic review was available for a specific add-on, we then searched for individual RCTs. We did not consider evidence from non-randomised trials (e.g. cohort, observational or case-control studies) as this evidence is prone to bias and does not provide robust evidence of the safety or effectiveness.

Results

We identified five IVF add-ons suggested to improve endometrial receptivity: immune therapies, endometrial scratching, endometrial receptivity array, hcg instillation, and uterine artery vasodilation. For four add-ons, recent systematic reviews were available; for one add-on, only an interim analysis of an RCT was available.

Immune therapies

TBA – Norman, INCLUDING Granulocyte stimulating factor

This add-on is currently rated 'red' by the HFEA.

Endometrial scratching

Endometrial scratching is a technique suggested to disrupt or injure the endometrium through the action of a simple pipelle biopsy. The resulting inflammation and activation of immune pathways is suggested to improve the receptivity of the endometrium to an implanting embryo, although a number of other theories have also been put forward. Commonly, endometrial scratching is perofmred in the luteal phase of the cycle prior to the IVF cycle, with a simple biopsy catheter such as a pipelle. The biological plausibility of endometrial scratching has been questioned, not least because it is difficult to conceive how any beneficial effect is retained when the entire functional layer of the endometrium is shed and replaced between the intervention and embryo implantation (Simon – scratching beneath). This procedure has been subject to intense interest world-wide, and was the most common IVF add on offered to fertility patients in the UK in 2016 (Spencer 2016); in 2018 endometrial scratching was used by 27% of IVF cycles (HFEA report). Over 80% of clinicians in a survey reported to recommend this procedure to their patients, at a cost of between $65 - $500 USD (equivalent) (Lensen 2016).

Early trials evaluating this intervention appeared promising, and a 2012 Cochrane review of five trials suggested the procedure was beneficial when performed in the cycle prior to the IVF cycle – and harmful when preformed on the day of oocyte retrieval (Nastri 2012). This review was updated in 2015 after the publication of a further nine studies and reported similar but less pronounced benefit; with subgroup analysis suggesting the procedure may only help women with recurrent implantation failure (Nastri 2015). More recently, similar conclusions have been reported by a number of systematic reviews (REFs).

Today, there have been over 30 trials published on this topic – and more are coming. Despite the wealth of trial data, it is difficult to make sense of it: reported effects from endometrial scratching range from implausible benefit to significant harm (Cochrane update 2019: in press?). An Egyptian trial in women undergoing their first IVF cycle reported a live birth rate of 67% vs 28% in the control group; producing an OR 4.88 (95% CI 3.22-7.40) in favour of endometrial scratching. Such a large effect size, and a live birth rate of 67%, is difficult to believe. As such, pooled analysis for the main comparison in the current update of this Cochrane review has not been possible. The heterogeneity of trial results may arise in part due to differences in methodology – such as the timing or intensity of the procedure, or the population recruited; however a more likely explanation may be poor quality of the included trials.

The results of a large trial of more than 1300 women was recently published which reports no benefit from endometrial scratching in women undergoing IVF, and subgroup analysis did not identify any subgroup of women who might benefit (Lensen 2019). Results from a large Dutch study recruiting 942 women are now available. This trial also reports no effect of endometrial scratching in women with one previous failed IVF cycle (ESHRE). While some researchers consequently call for

abandoning scratching (Mol 2019), others cling to the hope of a subgroup effect or suggest the procedure should be continued as the biopsy can be used for the ERA – apparently failing to see the irony of using another unproven IVF add-on to defend their position (F&S rebuttal+Quenby correspondence).

This add-on is currently rated 'amber' by the HFEA.

The Endometrial Receptivity Array (ERA)

The endometrial receptivity array is a novel diagnostic test based on microarray technology, created by Igenomix. The test requires an appropriately timed endometrial biopsy to measure the endometrial expression of 238 genes. A sophisticated prediction model is then applied to categorise a women's endometrium as one of: receptive, prereceptive, or proliferative. This categorisation then enables women to undergo a personalised embryo transfer, where the timing has been tailored to their personal window of implantation.

In the hands of Igenomix, the test has repeatedly demonstrated that women with recurrent implantation failure are more likely to suffer from non-receptive endometrium: ~25% of women with recurrent implantation failure have a displaced window, and that the test applied to same women biopsied on multiple cycles will consistently produce the same result. However, to date, only preliminary results from a single RCT are available (ASRM 2016). This trial was originally registered as a 5-arm trial with an intended sample size of 2442 (NCT01954758); the interim results for 3 arms were presented after the recruitment of only 356 women. The authors reported an improvement in positive pregnancy test from personalised embryo transfer, however this benefit did not persist for the outcomes of clinical and ongoing pregnancy. The full-text publication is pending, and is anticipated to include a p-value adjustment for the one or more interim analyses evidently undertaken, an explanation for the loss of two trial arms and the dramatic reduction in sample size.

Despite any robust evidence of benefit from RCTs, the ERA is widely used by IVF centres (Spencer 2016), at the cost of approximately $800 USD a pop. Perhaps Igenomix should be applauded for going to the trouble of conducting an RCT, and risking a negative result, given the clear propensity for subfertility clinicians and patients to pay for a test without a robust evidence base. However, evaluation of the ERA by researchers outside of Igenomix would provide independent evidence evaluating this add-on, as has been suggested by others (Cho). At the cost of $800 USD per test, an adequately powered randomised trial recruiting >1000 women would require in order of $400,000 USD to cover the cost of the test alone; which makes it extremely difficult for independent researchers to conduct such a trial. We invite Igenomix to welcome such collaboration.

This add-on is not currently rated by the HFEA.

Uterine artery vasodilation

Thin endometrium, often defined as less than 7 or 8mm, is associated with reduced probability of pregnancy during an IVF cycle (REF- Check 2011, Gonen 1990). Therefore, interventions which may

increase the thickness of the endometrium may improve the probability of implantation and pregnancy. Vasodilators such as sildenafil are suggested to cause vascular uterine relaxation, increasing blood flow to the uterus and resulting in thicker endometrium and consequently improved endometrial receptivity. If beneficial, such treatment would be cost-effective as the cost of sildenafil is approximately $50 USD.

A recent Cochrane review included 15 trials evaluating vasodilators in women undergoing IVF (2018). The results report increased endometrial thickness from vasodilators, and suggest vasodilators may increase the chance of pregnancy in women having IVF, however the effect on live birth is unclear due to the small number of trials reporting this outcome. Additionally, vasodilators were associated with increased adverse events such as headache and tachycardia. Indeed, sildenafil is known to cause increased risk of numerous drug reactions, including flushing, headache, abnormal vision, and insomnia (REF).

This add-on is not currently rated by the HFEA.

Intrauterine human chorionic gonadotropin (hCG)

Human chorionic gonadotropin (hCG) is a hormone produced by the placenta following implantation. hCG is believed to regulate implantation by supporting apposition, adhesion and invasion of the trophoblast invasion, enabling successful implantation of embryo. Injection or instillation of hCG into the uterine cavity prior to embryo transfer is therefore suggested to increase the probability of successful implantation by ensuring sufficient levels of hCG are present.

A 2018 Cochrane review identified 17 randomised studies (Craciunas 2018). The authors found high statistical heterogeneity between trials and were therefore unable to pool the trials overall. However, in subgroup analyses the authors observed that among women undergoing cleavage stage embryo transfer, hCG was observed to increase the probability of clinical pregnancy and live birth. As this finding was observed only in a subgroup analysis, the authors conclude that current evidence does not support the use of hCG injection in routine practice. More recent reviews (Osman 2016, Hou 2018) have only identified one further trial from Iran which reports significantly higher ongoing pregnancy rates among women receiving hCG instillation (Navali 2016).

This add-on is not currently rated by the HFEA.

Quality of the evidence

Four of the five included add-ons were evaluated by recent Cochrane reviews, which include a GRADE assessment of the quality of evidence. In all cases, the quality of evidence was between very-low to moderate quality; and in no case was the evidence suggested to be high-quality. This aligns with none of the add-ons being rated green by the HFEA traffic-light labelling.

The Cochrane authors downgraded the evidence for risk of bias, inconsistency and imprecision. Many of the included studies suffered from serious risk of bias, such as lack of blinding, no clear description of randomisation and allocation concealment, and premature termination of the study following (often unplanned) interim analysis, and lack of prospective trial registration . These

methodological issues are illustrated by a recent evaluation of which found that many endometrial scratching trials do not appear to be truly randomised according to the distribution of baseline data, suffer from critical statistical issues, and report results which could not be reproduced (Wentao TBA). Additionally, the majority of trials for all five add-ons recruited too few women to have enough statistical power to detect clinically relevant effect sizes; for the outcome of live birth two thirds of the trials recruited 200 women or fewer. A trial of 200 women would be powered to detect only an impressive improvement of 20 percentage points (e.g. from 25% to 45%, at 80% power and 5% significance level) – an increase in live birth rate that IVF itself barely achieves.

Discussion

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Limitations

- The add ons we included were based on those which appear to be most commonly used and this is not exhaustive and may have missed some
- This is not a classical systematic review and no specific search was undertaken

Conclusion

Current evidence suggests none of these add-ons can be used in routine practice should therefore only be offered in experimental settings – such as a randomised controlled trial.

Reference dump

https://www.manchesterfertility.com/prices/price-list/ - ERA price tag

emailed wan too

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