

IUI and IVF for unexplained subfertility: where did we go wrong?

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ABSTRACT: IUI is a first-line treatment for couples with unexplained or mild male subfertility and has become one of the most widely used fertility-enhancing treatments. The results of a recent trial comparing IVF to IUI, demonstrating similar live birth rates, have been used to build a case supporting the effectiveness of IUI. Yet, this conclusion might be somewhat premature, as the superiority of neither IUI nor IVF over no treatment has ever been proven. The evidence on the effectiveness and safety of IUI and IVF has been evaluated in two Cochrane reviews which both suggested that there is insufficient evidence to conclude that IUI or IVF is effective compared to sexual intercourse in couples with unexplained subfertility. Recommendations for clinical practice have been given in the most recent National Institute for Health and Care Excellence fertility guideline that advises not to offer IUI any longer and suggests 2 years of sexual intercourse followed by IVF. This recommendation has generated an ongoing debate, with only 4% of all gynecologists in the UK discontinuing the use of IUI. We feel that it is high time to provide proper scientific evidence for the effectiveness of IUI, or lack thereof, and invite the medical community to start RCTs comparing IUI to sexual intercourse.

Key words: intrauterine insemination / in vitro fertilisation / first-line treatment / unexplained subfertility / effectiveness

Introduction

Unexplained subfertility affects up to a quarter of all couples who are unable to conceive after 12 months of unprotected intercourse (Brandes *et al.*, 2010). IUI is often the first intervention that is offered and has become one of the most widely used fertility-enhancing treatments for these couples (Ferraretti *et al.*, 2013). The concept behind IUI is simple: it brings spermatozoa closer to the oocyte for fertilization at the appropriate time. IUI can be complemented by the addition of controlled ovarian stimulation (COS), increasing the number of mature oocytes available for fertilization. Yet, this results in high multiple pregnancy rates, estimated at 10% of ongoing pregnancies (Steures *et al.*, 2006; van Rumste *et al.*, 2008).

Recently, we evaluated in the INeS trial whether alternative interventions—IVF with single embryo transfer or IVF in a modified natural cycle—could reduce the number of multiple pregnancies while maintaining similar live birth rates compared to IUI-COS (Bendsdorp *et al.*, 2015). After 1 year, the number of couples who delivered a healthy child was similar in all three strategies with low multiple pregnancy rates. Both versions of IVF cost significantly more compared to IUI (Tjon-Kon-Fat *et al.*, 2015).

The results of this trial have been used as evidence of the effectiveness of IUI (Bahadur *et al.*, 2016). Yet, this conclusion might be somewhat premature. First, it assumes that the superiority of IUI over no treatment has already been proven and second, it assumes that IVF has added value over sexual intercourse in couples with unexplained subfertility.

In this article, we appraise the existing literature on the effectiveness and safety of IUI and IVF as a first-line treatment for couples with unexplained subfertility with the help of the most recent Cochrane reviews and thereafter discuss the recommendations of the fertility guideline of the National Institute for Health and Care Excellence (NICE) and its aftermath, followed by how we feel the field should progress.

The effectiveness and safety of IUI: evidence from the Cochrane Collaboration

The recently updated Cochrane review on IUI for unexplained subfertility evaluated whether IUI with or without COS leads to higher live birth rates compared to unprotected sexual intercourse, with or

without cycle monitoring (Veltman-Verhulst et al., 2016). In this review, the authors found three relevant RCTs (Deaton et al., 1990; Steures et al., 2006; Bhattacharya et al., 2008). The studies included a total of 690 couples with an average female age of 33 years who had been trying to conceive for an average of 2 to 4 years. One of these studies compared IUI to sexual intercourse timed with cycle monitoring (Deaton et al., 1990), while the other two studies compared IUI with sexual intercourse without any medical co-interventions (Steures et al., 2006; Bhattacharya et al., 2008).

The odds ratio (OR) of clinical pregnancy for IUI without COS compared to sexual intercourse was 1.53 (95% CI: 0.88–2.64), while the pooled OR of clinical pregnancy for IUI with COS compared to sexual intercourse was 1.00 (95% CI: 0.59–1.67). The OR for multiple pregnancy was 0.50 (95% CI: 0.04–5.53) for IUI without COS compared to sexual intercourse and 2.00 (95% CI: 0.18–22.34) for IUI with COS compared to sexual intercourse. Additional costs of offering IUI were not considered in this review.

Based on these results, the authors inferred that the evidence of a difference in pregnancy outcomes was inconclusive. They stressed the need to investigate whether the risk of a multiple pregnancy following treatment with IUI can be reduced to acceptable levels while still keeping fair live birth rates by comparing IUI without COS to IUI with COS with low-dose gonadotrophins.

The effectiveness and safety of IVF: evidence from the Cochrane Collaboration

One of the objectives of the Cochrane review on IVF for unexplained subfertility was to evaluate the effectiveness and safety of IVF compared with sexual intercourse (Pandian et al., 2015). The authors retrieved two relevant RCTs (Soliman et al., 1993; Hughes et al., 2004). Only 35 of the 245 couples included in the first study were diagnosed with unexplained subfertility and could be analyzed in this review, and only 51 of the 139 couples included in the second study. The first study compared one cycle of IVF with 6 months of sexual intercourse, during which other treatments apart from IVF were permitted; the second study compared one cycle of IVF with 90 days of sexual intercourse. The studies included in total 86 couples with an average female age of 33 years who had been trying to conceive for approximately 5 years.

The results of the two trials showed opposite directions of a treatment effect and thus there was high heterogeneity. The first study gave an OR of 0.30 (95% CI: 0.02–3.67) for clinical pregnancy, while the second study gave an OR of 8.00 (95% CI: 1.89–33.85). The pooled OR of clinical pregnancy for IVF compared to sexual intercourse was 3.24 (95% CI: 1.07–9.80). These studies did not report on costs, multiple pregnancy, ovarian hyperstimulation syndrome or miscarriage.

Based on these results, the authors concluded that there was insufficient evidence to draw firm conclusions. They stressed the need for similar study designs, methods and presentation of results in subfertility trials, to better allow pooling of the results, as well as studies that would focus on the appropriate time to switch from sexual intercourse to more invasive treatment options.

Recommendations for clinical practice: the NICE guideline and its aftermath

The NICE guideline does not recommend routinely offering IUI to couples with unexplained subfertility, mild endometriosis or mild male subfertility (National Institute for Health and Care Excellence, 2013). They advise sexual intercourse for a total of 2 years before continuing with IVF and thus advocate abolishing an intervention that has been widely used for over 30 years. This has not been well received in the UK and has led to much apprehension among gynecologists, with <4% of fertility clinics in the UK discontinuing IUI (Kim et al., 2015; Nandi et al., 2015). An online survey in the UK revealed that there are two main arguments being used against implementing the NICE recommendations: firstly, the evidence on which the recommendation was made was generally regarded of low to very low quality, leading to many gynecologists being reluctant to discontinue the use of IUI; secondly, IVF was not regarded as an established first-line option for unexplained subfertility compared to IUI (Nandi et al., 2015), resulting in many gynecologists continuing to offer IUI, instead of IVF, as first-line treatment (Kim et al., 2015).

How to progress

IUI has been offered for over three decades, yet there are only three trials that have evaluated the effectiveness of IUI. It is clear from the results of these three trials that up to now the superiority of IUI over sexual intercourse has not been proven. In addition, the only economic evaluation ever performed showed costs for IUI of £98 per cycle, compared to £0 for sexual intercourse (Wordsworth et al., 2011). IUI is therefore not only a possibly ineffective treatment but also carries an additional economic burden. Therefore, we can sympathize with the NICE recommendation to no longer offer IUI to these couples, as this is in line with not offering a possibly ineffective treatment with adverse effects. Yet, it is puzzling that NICE would recommend IVF after 2 years of sexual intercourse, as also here there is no firm evidence of its effectiveness.

IUI is a widely established fertility treatment, and possibly there is an uneasiness of many clinicians to stop this intervention owing to a deeply rooted belief of its effectiveness, as well as an inclination to intervene when confronted with a desperate plea for help from these couples.

IUI is not the only intervention in Reproductive Medicine for which there is no evidence of an effect but also one of many that are nevertheless practiced on a smaller or larger scale (Bhattacharya et al., 2001; Mastenbroek and Repping, 2014; Armstrong et al., 2015; Gleicher, 2016; Smit et al., 2016). Interventions in Reproductive Medicine seem to find their way into daily clinical practice merely on theoretical appeal, without solid scientific evidence. This then burdens the system as usually others need to design and perform clinical trials in which these interventions are usually refuted, followed by a gradual, albeit reluctant, abandoning of its use in clinical practice. In our view, this is an immoral form of medicine, as it should be the proponents of an intervention who have the obligation to provide proof of its effectiveness and safety. In 2016, innate beliefs in the effects of IUI by doctors and patients are no longer valid reasons to keep offering treatment of unproven effectiveness. It is our obligation to ascertain the effectiveness of IUI for couples with unexplained subfertility before

we continue exposing couples to a possibly ineffective intervention, which does carry risks and costs money.

We thus need to provide proper scientific evidence for the effectiveness of IUI compared to sexual intercourse as soon as possible. There will be resistance from those that believe unequivocally in the effectiveness of IUI. Yet the only way to demonstrate that IUI is more effective than sexual intercourse is to perform more and larger studies. Currently there are two ongoing RCTs. The intrauterine insemination study (TUI), comparing IUI with COS to expectant management, is being performed in New Zealand (ACTRN12612001025820), and the exIUI study, also comparing IUI to expectant management, will start recruiting couples this year in the Netherlands (NTR5599). Let us hope that the researchers will be able to finish these important studies, which will guide us in our next steps. Our greatest anxiety in this respect would be a scenario in which fertility specialists are reluctant to partake in this study stemming from their belief in the effectiveness of this intervention and also their belief that couples might be reluctant to opt for no treatment since IUI is a well-established intervention. This would close the vicious circle.

Authors' roles

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Conflict of interest

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