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Replacing IUI with IVF for initial treatment of unexplained infertility: why this NICE recommendation is cause for concern.

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Abstract:

The latest guidelines from the National Institute for Health and Care Excellence (NICE) for assisted conception (NICE CG156, 2013) recommend that people experiencing unexplained infertility should no longer be offered stimulated intra-uterine insemination (IUI) as a first-line treatment, but rather be directed towards IVF treatment, or alternatively be left to expectant management (EM). NICE has acknowledged that the cited evidence leading to this decision was not sufficiently robust. As such, we are concerned that accordance with these new NICE guidelines may result in people with no identifiable cause of their infertility being prematurely referred for IVF treatment. IVF constitutes a more invasive and expensive treatment process, which also represents an additional and unnecessary cost pressure to the National Health Service. There is a longstanding need for a robust clinical trial to resolve the uncertainty as to whether one treatment is more appropriate than another. Until such data is available, we suggest that provision of stimulated IUI, in centres achieving a satisfactory live birth rate, represents a significant cost-saving to those commissioning fertility services, with lower risks to people treated.

Introduction

This manuscript aims to highlight some basic concerns regarding an aspect of recent guidance by the National Institute for Health and Care Excellence (NICE) for assisted conception. NICE is a well-respected public body which aims to improve outcomes for people using the National Health Service (NHS) and other public health and social care services. As such, NICE guidance may be adopted by the NHS, local authorities, commissioners, employers, voluntary groups and anyone else involved in delivering care or promoting wellbeing. NICE reviews available evidence and gives advice accordingly, including consideration of health economics. In the absence of robust evidence that a specific treatment is effective, NICE has historically concluded that there is no evidence to support implementation of that treatment.

Our concern is with regard to the NICE decision to cease the recommendation of stimulated IUI (intra-uterine insemination) as a first-line treatment for people with no identifiable cause of their infertility. Stimulated IUI therapy has been used extensively and successfully for many years. However, there is wide variation in various aspects of the IUI process, including the type of people who are offered treatment, the type of ovarian stimulation prescribed, and threshold levels for sperm quality. As a result, IUI success rates, measured as live births per cycle started, can vary significantly.

It is not the intention of this manuscript to make the case for stimulated IUI as a first-line treatment for couples with unexplained infertility, but rather, to demonstrate that in these guidelines NICE did not make a sufficiently robust case to warrant the rejection of stimulated IUI. It is of interest that since the publication of the guideline recommendations, only a small proportion of UK clinics have made significant changes to their practice by reducing the number of IUI cycles or restricting the clinical indications for IUI (Kim, Child, & Farquhar, 2015). With this in mind, we consider that the NICE consultation's conclusion in terms of the direction of future guidance should have been to maintain the status quo until such time as more robust data is made available.

The evidence against stimulated IUI

The rejection of stimulated of IUI relied heavily on just four key studies by Bhattacharya et al. (2008), Goverede et al. (2000), Steures et al. (2006) and Tummon, Asher, Martin, & Tulandi, (1997). NICE has consistently classified this underpinning evidence as "low quality", i.e. confidence in the effect estimate is limited (Balshem et al., 2011). The evidence is also somewhat contradictory since only two studies clearly reject IUI and one of these lacks validity since it describes couples undergoing unstimulated IUI.

The earliest of these studies (Tummon et al., 1997) compared 311 cycles from 103 couples, who were diagnosed with unexplained infertility and also associated minimal or mild endometriosis. A live birth rate (LBR) of 11.0% (14/127) was recorded for stimulated IUI compared to 2.2% (4/184) for expectant management (EM), giving an odds ratio of 5.6 (95% confidence interval 1.8 to 17.4) in favour of superovulation and IUI.

The next study (Goverede et al., 2000) directly compared stimulated IUI versus IVF for the treatment of unexplained infertility. A pregnancy rate (PR) per cycle of 8.7% was recorded for the IUI group (n=85), which was lower than for the IVF group at 12.2% (n=87). However, the cumulative PR for IVF was not significantly better than that for IUI, and couples in the IVF group were significantly more likely than those in the IUI group to give-up rather than embark upon repeat treatments. They concluded that for the couples treated, IUI offered the same likelihood of successful pregnancy as IVF, and was a more cost-effective approach. According to this study, costs per pregnancy resulting in at least one live birth were approximately three times higher after IVF compared to after IUI. Today, some 15 years after this study, little has changed in this cost ratio.

The randomised trial by Steures et al. (2006) compared IUI with EM, and should be viewed with caution. We feel that this study cannot be relied upon to be a useful comparator as their cohort included people with tubal pathology (e.g. one-sided tubal occlusion and hence not having unexplained infertility) and some treated with clomiphene citrate. Furthermore, the PR per cycle started was 6.5% with an ongoing PR of 4.1%, one of the lowest-ever published success rates. A comparison with the most recently published IUI data from the Human Fertilisation and Embryology Authority (HFEA) further demonstrates how poor their IUI PR was (Table 1). However, we accept

the HFEA data is observational and collected for legal reasons, and therefore does not include sufficient clinical data to be informative about outcomes in individual circumstances including clinic-specific results. Furthermore, we accept the strengths of randomised trials are superior to observational data in minimising bias, and also that cumulative pregnancy rates can be more revealing than pregnancy rates per cycle. In defence of the Steures study, after three years follow-up, 73% couples had an ongoing pregnancy rate in the IUI group, compared to 72% couples in the EM group, with the EM group requiring less medical interventions and cost (Custers et al., 2012).

The fourth study also compared IUI with EM (Bhattacharya et al., 2008). However, this study investigated IUI in people without any exogenous drug stimulation, and cannot be effectively used to compare against couples having stimulated IUI, as this is not comparing 'like with like'. This study also included couples with a mild male factor and mild endometriosis.

In conclusion, it seems that only one paper has been used to reject the use of superovulation and IUI for the treatment of unexplained infertility for NICE CG156. Furthermore, the cited study not only carried relatively low success rates per cycle, but was also carried out in people who did not meet the criteria for unexplained infertility.

Health economics profile

GD156 states that while the health economic analysis showed that IUI could be cost-effective, there were no apparent health benefits and indeed there were potentially increased risks with IUI (with or without stimulation) when compared with an alternative strategy of EM. Therefore the GDG concluded that considerable resources could be saved and used elsewhere if IUI was not offered.

However, the health economics study relied heavily on an economic evaluation (Wordsworth et al., 2011), based on the data from one RCT comparing EM with IUI as first-line treatments for unexplained infertility and reviewed above (Bhattacharya et al., 2008). This study concluded that IUI, whilst being a more expensive treatment than EM, did not offer better live birth rates and therefore was unlikely to represent a cost-effective use of NHS resources. The economic analysis made some significant assumptions: firstly, that the parent study (Bhattacharya et al., 2008) was truly a study of unexplained infertility; and secondly, that it was a valid comparison in terms of cost-benefit between this and a stimulated IUI service which carried a higher success rate. The economic profile was modelled on a service which provided a live birth rate (LBR) of 22% after a mean of 3.4 cycles of unstimulated treatment (LBR 6.5% per cycle). Interestingly, the authors also stated that with a modest increase in LBR from 22% to 27%, unstimulated IUI becomes cost-effective. As there was sufficient uncertainty associated with the inclusion criteria and with the IUI timing (reliant on compliance in the use of ovulation prediction kits), it would be reasonable to assume that even in unstimulated IUI, this LBR could easily increase. More importantly, the economic analysis used to reject IUI as a cost-effective treatment was based on unstimulated treatment only. Yet this study was highly influential on the GD156.

As far as we are aware, there is no published economic analysis comparing EM with stimulated IUI, other than a theoretical mathematical modelling based on estimates from a hypothetical cohort of subfertile couples (Pashayan, Lyratzopoulos, & Mathur, 2006). This modelling did not use population-based data on the effectiveness of stimulated IUI

but rather data from a single local centre. If a cost-benefit analysis were to be undertaken, then optimally it would be prospective and multi-centre to provide confirmed data with full consensus to ensure:

a. The IUI process is in line with accepted best practice

b. The stimulation and monitoring regime is aimed at maximising success whilst guarding against multiple pregnancies

c. Inclusion is restricted to people with unexplained infertility

d. The cost of laboratory and clinical processes is fully accounted for.

From the citations provided within the NICE consultation, there is no assurance of any of the points raised above. Rather, the data included people with both female and male factors, the costings were based in a single centre and unstimulated IUI was the treatment.

Multiple Pregnancies

The risk of multiple pregnancies is often cited as a reason to be cautious with stimulated IUI (Bhattacharya et al., 2008) and in this case has been used as reason to reject it. However, on this matter it seems the NICE consultation document was contradictory. The evidence statement reads as follows:

"Multiple births - No evidence reported"

"Multiple pregnancies - Low quality evidence from one study showed there were no significant differences in the number of multiple pregnancies with the use of IUI without ovarian stimulation when compared with expectant management."

This second point also emphasised in a Cochrane review on the use of IUI for people with unexplained infertility which quotes the need for further robust evidence (Veltman-Verhulst, Cohlen, Hughes, & Heineman, 2012). One could therefore argue that there is insufficient evidence to reject IUI over EM.

The use of IVF for unexplained infertility

NICE provides no direct evidence to make the leap from stimulated IUI to IVF as a first-line treatment after a period of EM, accepting that CG156 does not recommend IVF in people with fewer than two years of unexplained infertility. Some of the co-authors of studies cited earlier conducted a Cochrane review (Pandian, Gibreel, & Bhattacharya, 2012) comparing the use of IVF with IUI for unexplained infertility but were unable to draw firm conclusions either way. Furthermore, Custers et al. (2011) concluded that for people with unexplained or even mild male infertility, one cycle of stimulated IVF with elective single embryo transfer might be as effective as three cycles of stimulated IUI as primary treatment.

Additional support in favour of stimulated IUI has recently been presented by Bensdorp et al. (2015). This Dutch group performed a multicentre (17 clinics), open label, three arm, parallel group, randomised controlled non-inferiority trial, to compare IVF with a single embryo transfer, IVF in a modified natural cycle and stimulated IUI in couples with unexplained or mild male subfertility. Both IVF groups were considered non-inferior to the IUI group, with comparable times to pregnancy and rates of multiple pregnancy (<7%) in all arms. A subsequent publication from the same team concluded that both IVF strategies were significantly more expensive when compared with stimulated IUI, without being significantly more effective (Tjon-Kon-Fat et al., 2015)

Finally, IVF not only constitutes a more invasive treatment process involving higher dosage of controlled ovarian hyperstimulation, anaesthesia and oocyte aspiration medical procedures with their associated risks for the treated individual (risk factors that were also considered by Bensdorp et al. 2015), but there are also controversial suggestions that there are may be an increased risk in imprinting disorders for subsequent generations suggested to be caused by the embryo culture *in vitro* (Lazaraviciute, Kauser, Bhattacharya, Haggarty, & Bhattacharya, 2014). This may lead some to also consider that lower-technology treatment should be a first-line choice, as no such risks have been reported or hypothesised for children conceived through IUI. However, it is acknowledged that the extent to which birth defects after infertility treatment may be explained by underlying parental factors is uncertain (Davies et al., 2012).

A key role for diagnostic laboratory standards

One important factor that is missing from all of the above studies is detailed information on the male partner, specifically in terms of the accepted levels for IUI and the accuracy of his semen analysis. In the recent NICE quality standard QS73 (NICE, 2014), semen analysis is recognised as the primary assessment tool for male fertility potential. In QS73, NICE states that:

"The accuracy of the result is dependent on following accredited methods of analysis that are regularly audited and subject to quality control. Variations in laboratory techniques significantly influence the reliability of the results of semen analysis. This may lead to a longer process for investigating male infertility, and possibly to inappropriate treatment"

The United Kingdom Accreditation Service (UKAS) now provides a challenging accreditation process for andrology laboratories to a recognised international medical laboratory standard, ISO 15189:2012. We believe that to ensure precision and accuracy in diagnostic andrology, all UK semen analyses should be performed in laboratories which have attained the ISO 15189:2012 standard and this should be a pre-requisite for aligning people to a specific treatment modality.

With direct relevance to this issue, the recent British Fertility Society Policy and Practice document (Tomlinson, Lewis, & Morroll, 2013) highlighted the impact that sperm quality has on treatment outcome: when optimum numbers of highly motile sperm are used for artificial insemination, satisfactory PRs are achieved.

Conclusion

In conclusion, there is general agreement between the authors of this document and NICE CG156 that there is a clear need for more robust data on stimulated IUI from both economic and good clinical practice perspectives. . Publications are emerging that criticise the guidelines (e.g. Bahadur, Ilahibuccus, Al-Habib, & Okolo, 2015; Peeraer et al., 2015). Furthermore, the low proportion of clinics that are adhering to the recommendation to reject IUI as a first-line treatment provides further evidence that this advice has not be well received (Kim et al., 2015).As a final consideration, recent economic analyses suggests that if only cost per live birth is considered then IUI continues to be better value that IVF (Moolenaar et al., 2015; Tjon-Kon-Fat et al., 2015), even without taking into account any of the aforementioned associated risks. Until more robust clinical and economic data becomes available, we suggest that provision of stimulated IUI, in centres where a satisfactory live birth rate is achieved, represents a significant cost-saving to those commissioning fertility services, with lower risks than IVF and an improvement on providing no treatment.

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Table 1. Pregnancies per treatment cycle of IUI treatment undertaken with partner sperm, started in the calendar year 2013 (http://guide.hfea.gov.uk/guide/).

Age	National Average Pregnancy Rate
Under 35	11.8%
35-37	13.2%
38-39	10.1%
40-42	5.0%
43-44	3.9%