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human reproduction **OPINION**

First line fertility treatment strategies regarding IUI and IVF require clinical evidence

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ABSTRACT: The advent of intracytoplasmic sperm injection (ICSI) has contributed to a significant growth in the delivery of assisted conception technique, such that IVF/ICSI procedures are now recommended over other interventions. Even the UK National Institute for Health Care Excellence (NICE) guidelines controversially recommends against intrauterine insemination (IUI) procedures in favour of IVF. We reflect on some of the clinical, economic, financial and ethical realities that have been used to selectively promote IVF over IUI, which is less intrusive and more patient friendly, obviates the need for embryo storage and has a global application. The evidence strongly favours IUI over IVF in selected couples and national funding strategies should include IUI treatment options. IUI, practised optimally as a first line treatment in up to six cycles, would also ease the pressures on public funds to allow the provision of up to three IVF cycles for couple who need it. Fertility clinics should also strive towards ISO15189 accreditation standards for basic semen diagnosis for male infertility used to triage ICSI treatment, to reduce the over-diagnosis of severe male factor infertility. Importantly, there is a need to develop global guidelines on inclusion policies for IVF/ICSI procedures. These suggestions are an ethically sound basis for constructing the provision of publicly funded fertility treatments.

Key words: IVF / intrauterine insemination / first line treatment / male infertility / NICE guideline / economics / ethics

Background

The use of information regarding first line treatment within a clinical environment is heterogeneous and biases exist in triaging fertility treatment. We have drawn together the numerous strands of financial, economic and clinical considerations presented regarding first line fertility treatment.

A significant factor in defining first line fertility treatment in the UK has been The National Institute for Health and Care Excellence (NICE) evidence-based guidelines which recommends that IUI has a limited role in infertility treatment (NICE guideline, 2013). Some 284 concerns have been expressed to NICE about these fertility guidelines (Homburg and Bahadur, 2015). Surveys of clinics have shown uncertainty and even a rejection of the NICE guidelines on IUI (Kim *et al.*, 2015; Nandi *et al.*, 2015). This situation has arisen because, over the period when the NICE guidelines were being constructed, the use of data from a few studies (Bhattacharya *et al.*, 2008; Reindollar *et al.*, 2010; Gurunath *et al.*, 2011; Wordsworth *et al.*, 2011) disproportionately influenced the NICE guidelines and, consequently, fertility healthcare policies in the UK.

Funding bodies universally dictate the availability of treatment and throughout the UK, the National Health Service (NHS) Clinical Commissioning Groups (CCG, 2015) perform this role, typically establish costs for IUI and IVF at approximately £600 and £3200 per cycle, respectively. CCGs do not have to implement the NICE guidelines (2013) in full and, less than 25% of the CCGs fund three cycles of IVF despite the NICE recommendations to do so. Furthermore significant disparities on fertility funding policies and prices between neighbouring CCGs have emerged (Freedom of Information (FOI) Act, 2000). There are disparities in how treatment policies are developed, in the way funding priorities are approved and how a largely non-transparent process actually operates. CCGs display a high level of bureaucracy influenced by local pressure groups. In contrast with the government NHS hospitals, private IVF clinics have no accountability under their FOI contracts. Patients from neighbouring CCGs face strikingly different treatment prospects, at worst being denied treatment altogether. Serious concerns

from general practitioners (GPs) in the UK show that a third of those surveyed were against IVF funding (Matthews-King, 2016). While the UK experience will be recognized in other countries, we suggest the above inconsistencies can be overcome favourably for patients by having a uniform sensible policy which is also cost-effective for fertility healthcare purchasers to fund. This policy would recommend public funding of six cycles of IUI followed by three cycles of IVF, except in cases of blocked Fallopian tubes or severe male factor infertility where IVF/ICSI is the only option.

Studies on IUI

Studies on IUI have a substantial risk of bias, as noted in recent Cochrane reviews (Pandian *et al.*, 2012; Veltman-Verhulst *et al.*, 2012, 2016), mainly due to the comparative trials not being properly controlled, minimal information on allocation concealment and randomization, small sample sizes, no reporting of live-birth rates and follow-up periods being variable and inadequate. Only a few studies have reported adverse effects of IUI, such as multiple pregnancies and ovarian hyperstimulation syndrome (OHSS) (Pandian *et al.*, 2012; Veltman-Verhulst *et al.*, 2012). The most recent reports support the effectiveness of IUI (Bensdorp *et al.*, 2015; Tjon-Kon-Fat *et al.*, 2015). These studies have assessed whether IUI with conventional ovarian stimulation or traditional IVF with conventional ovarian stimulation and single embryo transfer (SET) then subsequent cryo-cycles, either stimulated or in a modified natural cycle (MNC), are to be preferred, as regards cost-effectiveness, for a first line treatment in couples with unexplained subfertility and an unfavourable prognosis for natural conception. Without any significant difference in efficacy, the IVF strategies were significantly more expensive when compared with stimulated IUI. When compared with IVF in an MNC, IUI-COH was the dominant strategy. The cost-effectiveness of IUI and IVF in relation to sperm count results has also been analysed. Van Voorhis *et al.* (2001) suggested that an average total motile sperm count of 10 million may be a useful threshold value for decisions regarding the treatment of a couple with IUI or IVF. The cost-effectiveness of IUI over IVF is confirmed when treatment occurs with a total motile sperm count (TMSC) of more than 3 million (Moolenaar *et al.*, 2015), thereby highlighting the need for more motile sperm for effectiveness of IUI. Applying a 'consecutive ejaculation' may overcome the sperm threshold (Bahadur *et al.*, 2016). The added costs necessary to achieve one additional healthy child in the IVF-SET group compared with stimulated IUI were €43 375 (Tjon-Kon-Fat *et al.*, 2015). Using economic modelling, in younger women with no obvious cause of infertility, IVF is not cost effective within 3 years of trying to conceive (Mol *et al.*, 2000). The duration of infertility often goes unmentioned in experimental and observational IVF research and this can distort the cost analyses. Thus, IUI has been misrepresented in the current NICE guidelines with huge cost implications for national funding bodies.

Since a significant question arising in this debate relates to the relative effectiveness of IUI compared with IVF, it is evident there is no easy way to answer this question effectively, partly due to the distorted manner in which first line treatments are practised. Many IVF clinics at the top end of the IVF performance league tables do not have an IUI programme, and if they do offer IUI, this approach is used to manage their difficult cases without IVF procedures. This necessarily begs the question relating to the extent of IVF overuse. In 2011, UK clinics had an average IUI pregnancy rate of 13.7% per cycle over 4174 IUI cycles in women younger than 37 years (HFEA, 2015). In the following year, this pregnancy rate was unchanged in 4657 cycles in younger women and a pregnancy rate of 12.4% per cycle was achieved in all women treated (5943 cycles). For UK IVF/ICSI in 2011, a total of 13 703 pregnancies were reported, resulting in pregnancy rates of 28.5% per woman treated (48 141 women), 22.2% per IVF cycle (61 726 cycles) and 15.3% per embryo transferred (89 648 embryos transferred) (NICE Costing Report, 2013; HFEA, 2015). Notable from these figures, there is a 15-fold greater use of IVF compared with IUI procedures. None of this shift away from IUI in favour of IVF has occurred based on good quality evidence.

Multiple births have been a single reason pitched against IUI, but there is no evidence whatsoever regarding this in the Cochrane reviews (Pandian *et al.*, 2012; Veltman-Verhulst *et al.*, 2012). This prejudice is based on historical practices involving the irresponsible induction of high numbers of follicles during IUI procedures (Dickey *et al.*, 2005). Careful monitoring of follicles has reduced the absolute rate of multiple pregnancies to 0.3% after monofollicular growth and 2.8% after multifollicular growth (van Rumste *et al.*, 2008). The risk of multiple pregnancies is estimated to increase by 6, 14 and 10% according to whether 2, 3 or 4 follicles are stimulated respectively (van Rumste *et al.*, 2008), while the development of bifollicular IUI cycles potentially increases the chance of achieving an IUI pregnancy by 3.4-fold compared with unifollicular cycles (Tomlinson *et al.*, 1996). The contribution of multiple pregnancies made by IUI in The Netherlands was much smaller than the contribution made by IVF (Steures *et al.*, 2007). Along with crucial monitoring to minimize higher order births, IUI can become an even stronger basis for first line treatment.

General problems with measuring cost-effectiveness for reproductive treatments

The NICE costings report (NICE Costing Report, 2013) remains extremely weak with numerous assumptions on risks, costings for multiple births and drug induction regimes, which are assumed to be similar for IUI and IVF and rely on outcome data from IUI clinics with poorer outcomes (Bahadur *et al.*, 2015a; Peeraer *et al.*, 2015). Use of fertility techniques and treatments has occurred without robust cost-effective analyses and the economic models which have been used are not robust. The UK NICE costings (NICE, 2013) adopted a quality adjusted life years (QALYs) model to allow comparisons between infertile women and other clinical conditions to generate its own guidelines. However, this approach is controversial because infertility care values cannot be easily captured in QALYs (Devlin and Parkin, 2003; Chambers *et al.*, 2010, 2013). The QALY-based approach is more suited to capturing health states in patients as opposed to the benefit of a newly created life and the lives of the individual parents, and therefore presents particular difficulties for fertility treatment. Infertility treatment represents a unique situation in contrast to all other health areas as there are at least three potential stakeholders: the subfertile woman, the subfertile man and the unborn child, and this number can increase in case of multiple births (ESHRE Capri Workshop Group, 2015). The lifetime costs of abnormalities through premature births also present considerable social and domestic challenges. They have the potential to dominate the economic analyses outcomes and therefore long-term follow-up

economic analyses of IVF costs are required. The current model also tends to be riddled with assumptions on multiple births being uniform across all fertility interventions. Such assumptions have tended to magnify unproven problems and thereby disadvantage IUI treatment while subsidizing IVF, placing it in a better perspective for cost-effectiveness studies, as seen in the NICE guidelines. There was no evidence to identify multiple births as a problem for IUI in the Cochrane review (Veltman-Verhulst *et al.*, 2012). Thus, NICE has erroneously incorporated QALYs in a superficial manner and healthcare providers are falsely reassured. Cost-effectiveness also depends on individual clinic success outcomes, which is not factored in. The cost of treatment failure also needs to be factored into the cost-benefit analyses, given that the true costs at numerous levels have never been factored in for each treatment type. The cost of unvalidated procedures during IVF, such as elective freezing of embryos, intracytoplasmic morphologically selected sperm injection (IMSI), physiological ICSI (PICSI), time lapse embryology and embryo biopsy have not been accounted for. Equally, there are immediate and long-term healthcare concerns for the mother and offspring after IVF, which need to be considered.

Private clinical practice and their impact on publicly funded clinics

Growth in treatment practices has been led by the private IVF sector, which in turn has created unfair pressures on NHS(UK) IVF clinics to match headline results and public expectations. The restriction of choices between IVF and IUI as a first line treatment has been publicly criticized and described as financially motivated (Rogers, 2015), and this public perception encapsulates the ethical, economic and financial realities associated with first line fertility treatment practices. Support for IUI is well established and couples with male or idiopathic subfertility should be counselled that IUI and IVF have a similar likelihood of a successful pregnancy with comparable low multiple pregnancy rates (Bensdorp *et al.*, 2009, 2015). For unexplained and moderate male factor infertility, stimulated IUI is cost-effective (Philips *et al.*, 2000). The economic analyses all favour IUI procedures (Chambers *et al.*, 2010; van Rumste *et al.*, 2014; Romundstad *et al.*, 2015; Tjon-Kon-Fat *et al.*, 2015).

The average IUI success rates of around 13% per cycle typically translate to around 20–25% of the cohort for most clinics (Khalil *et al.*, 2001; Bahadur *et al.*, 2015a,b; Peeraer *et al.*, 2015). Against this backdrop, one study with an unselected cohort of subfertile couples showed that 45.6% of 1001 continuing pregnancies were conceived spontaneously while awaiting IVF treatment, and overall 63 of the 1001 pregnancies were multiple pregnancies, 36 from IVF and 11 from IUI (Brandes *et al.*, 2010). The conclusion was that IVF in particular, should not be started as long as the spontaneous pregnancy prognosis is good. However expectant management against IVF analyses are rarely performed and in one report 45.6% of pregnancies occurred spontaneously whilst awaiting IVF treatment (Brandes *et al.*, 2010). One study showed that in 36% of couples with unexplained infertility, overtreatment had occurred despite the eligibility of the couples for expectant management of at least 6 months (Kersten *et al.*, 2015). This raises important questions about how artificially elevated IVF results actually are and how much clinical bias exists to triage patients towards more expensive IVF treatments. The underlying quality indicators showed that in 34% of couples, no prognosis was offered and in 42% expectant management was not recommended (Kersten *et al.*, 2015). A broad estimate of more than 50% of couples undergoing unnecessary IVF treatment is mooted by a leading IVF commentator (Romundstad *et al.*, 2015; Smith, 2015; Winston, 2015). In the USA, the number of IVF cycles per annum has increased from 90 000 in 2000 to 150 000 in 2010 (Kawwass *et al.*, 2013). In the UK, the figures for diagnosis of unexplained subfertility has tripled from 6204 to 19 552 cycles (Kamphuis *et al.*, 2014), while severe male infertility cases have increased 290% from 6771 to 19 643 from 2000 to 2011 (Kamphuis *et al.*, 2014). Severe male infertility can justify the use of IVF/ICSI procedures. None of these increases can be explained scientifically nor by evidence-based medicine, but can only be associated with commercial benefits for the clinics, about which there appears to be no regulatory guidance from professional or regulatory bodies such as the European Society of Human Reproduction and Embryology (ESHRE), British Fertility Society (BFS), American Society for Reproductive Medicine (ASRM), Association of Biomedical Andrologists (ABA), UK Royal College of Obstetricians and Gynaecologists (RCOG), and UK Human Fertilisation and Embryology Authority (HFEA).

Overuse of IVF raises other important questions in the way healthcare analyses of children born from IVF/ICSI are performed, especially since studies use normal controls as the comparator. In addition to IVF itself, factors predisposing to infertility are also linked with adverse perinatal outcomes (Silber and Repping, 2002; Rozen *et al.*, 2012; Li *et al.*, 2015). Recent reports also highlight possible concerns from cancers to mothers who have undergone IVF and the need to be vigilant of risks. The potential increased risk of central nervous system (CNS) tumours in patients undergoing ART has been interpreted with caution (Reigstad *et al.*, 2015), while long-term ovarian and uterine cancers need careful follow-up (Stewart and Hart, 2015; Kessous *et al.*, 2016). The long-term health of children conceived after IVF also require careful studies (Fauser *et al.*, 2014; Wale and Gardner, 2016).

Comparisons of outcomes from IUI and IVF procedures need to be treated extremely cautiously. For IUI to succeed, there needs to be a serious drive towards optimizing the outcomes, but there has been little motivation for fertility clinics to improve upon these. In fact, since its introduction in 1962 (Cohen, 1962), progress in IUI has remained static. The majority of couples undergoing three cycles of IUI are reported to prefer continuation of IUI over IVF, and the risks of multiple pregnancies did not affect their preference for IUI with ovarian stimulation (van Weert *et al.*, 2007). Couples generally look at IUI as a less stressful, less invasive and very safe procedure and therefore IUI will be better for patients. Furthermore, IUI does not involve the cost required with embryo culture facilities and cryopreservation facilities. On the issue of costings, it was suggested that private patients may be discouraged from paying for more expensive IVF treatment, despite IVF being more financially desirable for the clinic (Kim *et al.*, 2015). If such rational thinking can be applied to private patients can it not be applied to nationally funded NHS sector patients?

Excess embryos created through IVF procedures are frozen, possibly never used, and these monetary and emotional costs are not factored in when presenting the merits of IVF procedures. UK HFEA data from 1991 to 2012 showed (HFEA, 2012) that, of the 3 546 818 human embryos created, 93% (i.e. >3.3 million embryos) were never used to generate a pregnancy (Doughty, 2012). Of the embryos created, 839 325 were frozen for future use. In all, 1 388 443 embryos were transferred but just less than one in six resulted in a pregnancy. The remaining embryos, 1 691 090, were initially discarded and a further 23 480 were

discarded after being taken out of storage. The cryopreservation industry for human gametes and embryos has grown disproportionately and concerns exist regarding cost-effectiveness, resulting from the high disposal/non-use of embryos (Barcroft et al., 2013). Newer techniques using elective freeze all embryos while IVF is performed over two cycles will undoubtedly increase costs for incorporating the embryo freezing procedures and while comparisons of outcomes between fresh and frozen cycles are routinely made, they hide the actual costings of the procedures.

Publications with financial and economic agendas have so far served the interests of IVF clinics, but now these should balance the patients' interests through ethical considerations. Most patients around the world rely on experts and professionals to truthfully guide them through a decision-making process, with recommendations for the most effective, least intrusive and cost efficient treatments. Government bodies, which fund treatments, expect unbiased financial analyses for effectiveness in first line treatments. In a recent debate, we note with interest the use of the terminology of 'expert based evidence', which is the same as 'non-evidence' based medicine (Dahan et al., 2015).

Private clinics and male infertility

With regards to male infertility, there has been a 290% increase in the diagnosis of severe male factor infertility from 2000 to 2011 in the UK (Kamphuis et al., 2014). This highlights the issue related to standardized care. Despite the existence of accreditation and standards in basic semen analyses within fertility clinics, less than 5% of UK fertility clinics are accredited for the 5th WHO standards (WHO, 2010) through the ISO15189 accreditation scheme, although all clinics claim to abide by the rules in all their patient information. The lack of compliance to basic semen analyses in the 5th WHO guidelines through international ISO15189 (2012) accreditation has allowed for unaccountable practices of classifying sperm samples for ICSI and a disproportionate use of ICSI procedures. While lacking basic semen analyses accreditation, IVF clinics have been quick to fund and commodify unvalidated sperm detecting systems such as IMSI, PICSI and motile sperm organelle morphology examination (MSOME) (Fortunato et al., 2016).

Summary

Overall, the fertility industry needs a critical self-analysis to strike an ethical balance which can allow autonomous, informed, decision-making for patients to choose between IVF and IUI treatments, thereby creating realistic opportunities for three cycles of free IVF treatments for the couples who really need it. As professionals, we have a collective duty of care towards the public and towards patients in ensuring unfettered information is disseminated in the public domain. While some fertility clinics may not like to use IUI or may not practise IUI procedures optimally, there are 74 million couples worldwide affected by involuntary childlessness having no access to IVF procedures, but in need of proper guidance (Boivin et al., 2007).

The policy construction around first line fertility treatments have been clouded with IVF treatment procedures recommended preferentially over IUI without evidence. The belief in risks of multiple births for IUI remains unfounded. A battery of unvalidated high technology techniques are additionally sold to patients with a view to improving their IVF outcomes, including the elective freezing of embryos, the safety of which is under clinical scrutiny (Wale and Gardner, 2016).

Conclusion

The evidence of financial, economic and clinical considerations presented within this commentary strongly favours IUI as a first line treatment option for subfertility. Importantly, there is a need to develop global guidelines and inclusion policies for IVF and ICSI procedures. These suggestions would seem an ethically sound basis for constructing the provision of publicly funded fertility services and efficient IUI practice would release government funded fertility clinics to concentrate more on patients who require IVF. National funding strategies should include IUI for most first line treatment options, and the UK NICE guidelines need a radical review of IUI procedures.

Authors' roles

G.B., R.H., A.M., P.R., T.A., A.A.-H. and S.O. provided substantial contributions to the conception and design, the acquisition and analysis of information within the peer reviewed domain to enhance the intellectual content and in approving the publication of this manuscript. G.B. and R.H. were additionally involved in substantial final revisions. P.R. and G.B. provided financial and economic expertise for this manuscript.

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Conflict of interest

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