

Lack of evidence for interventions offered in UK fertility centres.

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Word count 2900

References 18 (plus 1 to BMJ Open submission)

Tables 1

Box 1

Analysis

Infertility is a significant problem, affecting about one in seven couples, many of whom seek medical help in order to have a child.¹ Assisted reproduction treatments, as all medical interventions, should be informed by reliable evidence. Many new fertility interventions and products have been developed over the last decade; however, there are concerns that the use of some new treatments additional to standard in vitro fertilisation (IVF) might not be evidence-based, and some clinics may be offering additional services, which carry extra costs, that are not based on the most up to date relevant research.²

IVF is expensive: a single cycle can cost £5,000, thus placing considerable financial burden on patients. Those who do not meet criteria for NHS funding can use private clinics; therefore the majority of IVF (59%) is through private practice.³ A range of additional investigations and treatments are offered at UK fertility treatment centres beyond standard IVF that may incur extra costs, [ref bmjopen-2016-013940.R1] which can range from as little as £50 for a single screening blood test to as much as £8,000 for egg freezing packages (see Box 1).

The independent regulator that oversees fertility treatment and research in the UK is the Human Fertilisation and Embryology Authority (HFEA).⁴ Over 200 clinics offering NHS or private services are registered with the HFEA. The HFEA recommend that women/couples discuss the evidence with their clinician, and consider their own “research” before making a final decision. We regard this as difficult, if not impossible, for non-specialists to do, and that even many clinicians might not be fully aware of the current evidence.

Box 1 Example of costs for interventions additional to standard IVF.

Individual screening blood tests – start at £50

Embryogluce – up to £160

Intralipid infusions – up to £250

Endometrial scratch – up to £325

Assisted hatching – up to £450

Blastocyst culture – up to £800

Time lapse imaging – up to £850 for the Eeva time-lapse incubator, up to £800 for the Embryoscope

Intracytoplasmic morphological sperm injection (IMSI) – up to £1,855

Percutaneous epididymal sperm aspiration/testicular sperm extraction:

Given concerns over the evidence base for fertility treatments, the implications for patients undergoing these treatments, and the resources needed to fund them, we set out to look at the evidence by answering the HFEA “research questions you may want to ask,” taken from their guidance for couples thinking about having fertility treatments. These questions are: 1) Is this treatment recommended by the National Institute for Health and Care Excellence (NICE)? If not, why? 2) Has this treatment been subjected to ‘randomised controlled clinical trials’ which show that it is effective and is there a ‘Cochrane review’ available? 3) Are there any adverse effects or risks (known or potential) of the treatment?²

What did we do?

We obtained from HFEA a list of all UK centres providing fertility treatments and examined their websites. From these sites we compiled a list of interventions offered in addition to standard IVF that are claimed to improve fertility outcomes. [ref bmjopen-2016-013940.R1] We excluded interventions aimed at patients with a pre-existing disease such as diabetes; diagnosed conditions such as polycystic ovarian syndrome; or neurological conditions such as spinal cord injury; we

excluded interventions related to donation of sperm or eggs; and we excluded complementary therapies such as homeopathy and nutrition. This gave a list of 38 fertility interventions additional to standard IVF, offered by UK fertility clinics: We classified 27 of these as 'Add-on' interventions; six as alternative treatments to IVF and five treatments for preservation of fertility. (Table 1)

For these 38 additional fertility interventions, we searched for evidence as HFEA suggests, and focused on the key outcome of whether they improve live birth rates. (Web Table 1) We checked each intervention with the current NICE guideline CG156 (Question 1). Nine researchers (NB, DC, OG, KM, DN, IO, AP, ES, JOS) independently searched MEDLINE (via PubMed) and the Cochrane library for systematic reviews and randomised controlled trials (RCTs) in April 2016. (Question 2). When we could not find any review of RCT evidence, we looked for the next highest level of available evidence (e.g. observational study) and categorised the evidence found using the Oxford CEBM levels of evidence.⁵ We also searched the Cochrane reviews and NICE guidance CG156 for information on harms up to Sep 2016. (Question 3)

What did we find?

1) Is this treatment recommended by the National Institute for Health and Care Excellence (NICE)? If not, why?

Of the 38 interventions investigated, NICE provides clear recommendations for 13 (34%). Of these, 11 are recommended in specific populations and 2 interventions are not (hysteroscopy, assisted hatching). There was no clear guidance for 19 interventions, and 6 interventions were recommended for research. (see Figure 1 and Web Table 1)

NICE guidance is generally clear about the populations to which the 13 recommendations apply. For example, sperm cryopreservation should be offered to men and adolescent boys who are preparing for medical treatment for cancer that is likely to make them infertile. Similarly, oocyte or embryo cryopreservation should be offered to those women preparing for medical treatment for cancer that is likely to make them infertile, and the routine measurement of thyroid function should not be offered to the general population but should be confined to women with symptoms of thyroid disease. NICE guidance also clearly states recommendations on interventions that should not be offered: assisted hatching and hysteroscopy are not recommended because they have not been shown to improve pregnancy rates.

However, for half of the interventions that are additional to standard IVF treatments, and currently offered at UK fertility clinics, there is no mention in CG156 as to whether they can be recommended or not.

2) Has this treatment been subjected to 'randomised controlled clinical trials' which show that it is effective and is there a 'Cochrane review' available?

For 27 of the 38 fertility interventions (71%) we found a relevant systematic review: 18 of these were Cochrane reviews and 9 were non-Cochrane. (Figure 1) We also found one Cochrane overview, published in 2015, including 59 systematic reviews examining the effectiveness of assisted reproductive technologies.⁶ These reviews reported that five of these interventions (5/38, 13.2%) improved live birth outcomes; for 13 interventions, the evidence was insufficient to make a summary estimate and for seven there was evidence that the intervention did not improve live birth rates. For one intervention - preimplantation genetic screening (PGS) - older methods of PGS worsened outcomes, whereas there was some evidence of benefit for PGS using more recently developed techniques.

Web Table 1 shows the five interventions for which we found evidence of improvements in live birth rates: blastocyst culture, endometrial scratching, adherence compounds, oral antioxidants and intrauterine insemination (IUI) in a natural cycle. However, for all of these interventions, the supporting studies had methodological problems that raise uncertainty about whether these improvements in live birth rates are actually true results.

A Cochrane systematic review ⁷ of blastocyst culture including 13 RCTs (n=1,630 participants) concluded that live birth rates were higher in the blastocyst group compared with culture to day 2 or 3 group: OR 1.48 (95% CI 1.20 to 1.82). Due to high dropout rates and poor randomisation method descriptions for many trials the evidence was judged low quality. Removal of the low quality studies meant differences in live birth rates were no longer statistically significant, OR 1.38 (95% CI 0.96 to 1.99). Variable embryo transfer policies between groups, and differences in the number of embryos available for freezing, further limited the robustness of the conclusions.

For endometrial injury (incorporating endometrial scratching) a Cochrane review ⁸ reported a significant increase in live birth rates compared with no injury, RR 1.42 (95% CI 1.08 to 1.85; 9 RCTs, n =1,496 participants), for injury between day 7 of cycle prior to embryo transfer and day 7 of the cycle of embryo transfer (there was evidence that endometrial injury on the day of embryo transfer was harmful). Due to low participant numbers, and limitations in the methods (in 5

studies both groups possibly received some degree of unintentional endometrial injury, and 3 studies were not published in full) the quality of the evidence was moderate. Removal of the low quality studies, however, made no difference to the effect estimate. The review authors highlighted the lack of information on harms: at present it is not known whether the intervention affects the risk of miscarriage, multiple pregnancies, or vaginal bleeding, or other outcomes that may be important to women undergoing the procedure. However, it was reported that as expected, the procedure does cause some pain. We identified one ongoing UK multicentre randomised trial (ISRCTN23800982): starting in July 2016 the trial aims to recruit 1,044 women aged under 37 undergoing IVF for the first time; the protocol includes collection of data on harms including miscarriage and ectopic pregnancy rates.⁹

A Cochrane systematic review of adherence compounds including hyaluronic acid (marketed as Embryogluue) reported an effect on live birth rates, OR 1.41 (95% CI, 1.17 to 1.69; 6 RCTs, n = 1,950 participants).¹⁰ However, the comparison was between high and no hyaluronic acid or low hyaluronic acid; in the three studies (n=324 participants) that only assessed high versus no hyaluronic acid there was no significant effect, OR 1.35 (95% 0.86 to 2.12). Moreover, in some of the studies, multiple pregnancy rates were increased due to the practice of transferring more embryos per woman in the intervention groups.

A Cochrane review of antioxidants including 4 small trials with few events (only 44 live births in total) reported a significant effect on live birth rates (OR 4.21, 95% CI 2.08 to 8.51, n= 277 men).¹¹ However, one study had inadequate methods (the numbers of participants initially randomised to each group were not available) and a high unexplained dropout rate (26%) occurred; in another, the principal investigator had a commercial agreement with the manufacturer. This practice has been shown to systematically lead to the publication of more favourable results than with sponsorship from other sources.¹²

Finally, a Cochrane review of 14 trials (n=1,867 women) of intrauterine insemination (IUI) reported an increase in live birth rate in the one trial (n = 396) that compared IUI in a natural cycle versus timed intercourse or expectant management in a stimulated cycle, OR 1.95 (95% CI 1.10 to 3.44).¹³ The introduction of another intervention component (natural vs. stimulated) meant this effect was confounded; for three other comparisons of IUI in the same review there was no significant effect on live birth rates observed (see Web Table 1).

A 2006 Cochrane review of preimplantation genetic screening (PGS) included 9 trials, and concluded PGS significantly lowered live birth rate.¹⁴ PGS is a technique for screening embryos for

chromosomal numerical abnormalities and initially it used cleavage stage biopsy and fluorescence in situ hybridization (FISH). This older version of PGS is now often referred to as version 1. PGS version 2 uses newer techniques such as array comparative genomic hybridisation (CGH). We therefore searched for more recent evidence to assess what is known on PGS version 2 (PGS-V2). Firstly, a 2009 non-Cochrane review of seven trials showed PGS V1 led to lower rates of live births, RR=0.76 (95% CI 0.64 to 0.91); an absolute decrease in the number of live births of 147 per 1000 women.¹⁵ A 2015 non-Cochrane systematic review¹⁶ of 4 RCTs of PGS V2 targeted generally at younger women reported that in one trial delivery rates per cycle were higher in the intervention group compared to the control group; however, in the pooled analysis including identified cohort studies, there was no significant effect. NHS England's 2013 Clinical Commissioning Policy reports that in the "absence of evidence of its clinical and cost effectiveness, there is no intention to support the introduction of PGS into NHS clinical practice."¹⁷

For eleven interventions we were unable to find systematic review evidence. For Intralipid infusion and sperm freezing we found one RCT each, and these did not report improvements in live birth rates. For ovarian tissue freezing; endometrial receptivity array; early embryo viability assessment; AneVivo; PGD; autoimmunity to the HCG receptor we found only one observational study per intervention. For three interventions (segmented IVF, dummy embryo transfer and quad therapy) we were unable to find any evidence beyond expert opinion or mechanism of action.

3) Are there any adverse effects or risks (known or potential) of the treatment?

NICE guidance CG156 was not helpful: for only two interventions (intracytoplasmic sperm injection (ICSI) and ovulation induction & cycle monitoring) was there any comment on harms. For IVF with or without ICSI, NICE guidance states that women should be informed that the absolute risks of long-term adverse outcomes are low, but that a small increased risk of ovarian tumours cannot be excluded (Web Table 2. Harms reporting). For ovulation induction and cycle monitoring the guidance states the lowest effective dose and duration of use of ovulation induction or ovarian stimulation agents should be used - an indirect comment on harms.

The Cochrane reviews gave limited information on harms. In many of the reviews the included trials either provided no information, inadequate information or inconsistently reported information on adverse events and only a few reported any meaningful information. For example, the review on assisted hatching reported that miscarriage rates were similar in both groups and multiple pregnancy rates were significantly increased in the assisted hatching group. However,

there was insufficient data on ectopic pregnancy, congenital or chromosomal abnormalities, blastocyst formation or embryo damage.¹⁸ Harms that are important to patients, such as miscarriage rates, should be central to all trials and reviews of fertility interventions; yet they were often so poorly reported in the original trials that meaningful conclusions cannot be drawn. For example, in a review of aspirin, miscarriage rates were reported in only five of 13 trials; multiple pregnancy rates in four and ectopic pregnancy rates in only three trials. [Web Table 2. Harms reporting]

What could be done differently

People seeking fertility treatment need good quality evidence to make informed choices. The current approach by HFEA leaves patients and clinicians to seek evidence either for themselves, or from staff in private clinics selling fertility services to them. We do not believe this approach is realistic, nor does it reflect the resources available to patients. Patients may be desperate, and therefore vulnerable. They are unlikely to have specialist skills in seeking and critically appraising clinical evidence.

Our related publication reports how fertility interventions are offered without supporting evidence to back up claims of effect [ref bmjopen-2016-013940.R1]. We previously recommended that fertility centres should keep up to date with the evidence and reflect this in the information on their websites. [ref bmjopen-2016-013940.R1]

NICE provides some recommendations in specific populations, but it does not cover the range of interventions currently on offer. NICE together with HFEA should provide guidance on what is offered, and provide recommendations for or against each of the available interventions. There is an incoherent framework as to which treatments should be offered in which populations, the potential for indication creep is therefore significant: expanding treatment use from people who have clearly benefitted, to those for whom the evidence is much more shaky or non-existent. NICE should also consider adopting the GRADE system for making recommendations, which allows for strong (offer to everyone) or weak (offer to some individuals) recommendations, with or without certain conditions.¹⁹ Furthermore, the key patient-relevant outcome for assisted reproductive health should be live birth; however, guidance often refers to pregnancy rates to form recommendations, which is inadequate for a number of reasons, not least because about 5% of pregnancies are lost between the 1st trimester and birth.²⁰ Adoption of the IMPRINT modifications to the CONSORT checklist, which aim to improve the reporting of infertility treatments, should be mandatory for clinical trials if they are to prove meaningful.²¹ Guidance also needs continually updating if it is to be relevant and meaningful, particularly because of the growing number of available tests, techniques and treatments. Furthermore, clinics awareness and

uptake of guidance needs improving: a recent survey of 46 UK clinics licensed to provide IUI, found that whilst the majority of clinics were aware of NICE guidance only ten clinics reduced the number of IUI cycles or restricted its use according to NICE recommendations.²²

Cochrane systematic review evidence covers less than half of the available treatments. To find information we had to look at non-Cochrane reviews or lower quality evidence, some of which is not freely available to the public. The reporting of harms was very poor and therefore for many treatments it is impossible to be informed about adverse effects. Furthermore, there are no maintained relevant information resources appropriate for use by non-clinicians. Initiatives such as PubMed Health and Cochrane's Plain Language Summaries are welcome but they can only be fully useful if they cover the range of treatments being offered, are based on reviews that are updated regularly, and go beyond published papers to overcome the reporting bias that affects much of the published research in the fertility field.

What can we conclude?

The evidence for these additional interventions is both poor, and potential patients may find it challenging to access the evidence. Of the 38 interventions we reviewed, there are 11 for which NICE guidance recommends use in targeted populations. Our appraisal of the evidence shows only one intervention, endometrial scratching, for which the review evidence robustly supports an increase in live birth rate, yet even this evidence is only moderate quality, and the observed benefit is only in women with more than two previous embryo transfers. A UK multicentre trial is investigating the use of endometrial injury in women undergoing IVF for the first time, which should provide relevant information for a broader patient population.⁹

It is possible that we did not find some higher quality evidence, but our current analysis reflects what we could find, and whilst the Cochrane reviews are accessible, some of the evidence we found is not freely available. Asking patients to do their own research, as the HFEA does, is inappropriate and for many interventions not possible. For complex issues such as PGS we consider the HFEA's advice, that "you should talk to your GP to go through the options available", unreasonable, as there is likely to be insufficient knowledge available to correctly reflect the potential benefits and harms of such interventions.²

There is an urgent need for randomized controlled trials for many interventions that are currently being offered. We recommend that treatments with uncertain effects (benefits and harms) are only licensed for use in the context of meaningful research. Clinics vary significantly in what they offer and there is a lack of clarity on what actually constitutes an 'Add-on' intervention. Clear

classification systems could aid understanding and reduce variation in what is offered to couples. There is also a lack of evidence on the use of multiple interventions: the benefit and harms of multiple, simultaneous interventions is not known, although this is likely to incur even greater cost. Fertility care requires treatments based on the best available evidence. Existing evidence is scarce and where available, largely of low to moderate quality, and is not necessarily being made available to facilitate decision making. We consider that the HFEA and NICE should provide a systematic and periodically updated overview of the evidence to better inform those seeking advice on the benefits and harms of fertility treatments.

Funding

This project received no specific funding.

Competing interests

All authors have completed the ICMJE uniform disclosure form at http://www.icmje.org/coi_disclosure.pdf and declare: CH has received grant funding from the WHO, the National Institute for Health Research (NIHR) and the NIHR School of Primary Care and on occasion he receives expenses for teaching EBM and CEBM jointly runs the EvidenceLive Conference with the BMJ. BG has received research funding from the Laura and John Arnold Foundation, the Wellcome Trust, the NIHR, the Health Foundation, and the WHO; he also receives personal income from speaking and writing for lay audiences on the misuse of science. KM has received funding from the NIHR and the RCGP for independent research projects. AT, NB, DN, DC, ES, OG, IO and AP have nothing to declare. All authors declare that they have no financial relationships with any organisations that might have an interest in the submitted work in the previous three years [or describe if any], no other relationships or activities that could appear to have influenced the submitted work [or describe if any].

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Contribution statement:

CH devised the study and all authors reviewed the methods. KM and AR managed the data extraction. AT, NB, DN, DC, ES, OG, IO and AP contributed to the searches for evidence and the data extraction. CH, ES, BG and KM discussed and analysed the issues arising and all authors commented on and approved the final draft,

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