

**ESHRE 2020 Virtual (5-8 July 2020)

Questions for the speakers

**Session 55: Cochrane session - Better evidence, better policies

**Where do we go after the RCTs - Sally Cheshire (United Kingdom)

**Q: Multicenter RCTs in ART only confirm non-inferiority, diluting possible differences due to lack of equal center-specific technical expertise. Comment?**

A: When reviewing the effectiveness of treatments, well-designed RCTs are thought to provide the most reliable source of evidence and therefore are considered to be the ‘gold standard’. Findings from RCTs can then inform training requirements for clinical and laboratory staff, and protocols for technical application, to encourage best practice and uniformity of treatment provision within and between clinics.

We encourage UK clinics and research centres to share their protocols and to make available or formally publish all their research findings including in non-RCT research, including where data has been collected within a centre to inform the centre’s own protocols.

**Q: PGTA is on red, however majority of the countries do it extensively—what are your thoughts?**

A: The HFEA’s traffic light system indicates whether the evidence, in the form of high-quality randomised control trials (RCTs), shows that a treatment add-on can safely improve the live birth rate for someone undergoing fertility treatment. We give a red symbol for an add-on where there is no evidence to show that it can improve live birth rates.

There is no evidence from RCTs that PGT-A carried out at the blastocyst stage on day five or six increases the chances of having a baby, for most patients undergoing IVF.

In addition, there have been no RCTs conducted where the main objective of the study was to assess the effect of PGT-A on the rate of miscarriage. There is some secondary outcome evidence from RCTs that suggests that PGT-A may be beneficial for certain categories of women, particularly older women, in relation to a potential reduction in miscarriage. It is important to keep in mind that this reduction in the rate of miscarriage does not increase the chances of a live birth. It is likely that, with PGT-A, embryos that express a chromosomal abnormality that could lead to a miscarriage are not selected for embryo transfer.

**Q: Lack of funding and support for robust RCTs infertility is clear. How to engage private clinics to join public research centers in RCTs?**

A: For many reasons including funding and the difficulty in obtaining sufficiently large sample sizes, we acknowledge that it is unlikely that treatments will have a well-designed RCT for the foreseeable future, which as a regulator we would like to see happen more often. It will be important for us to work with the professional and patient bodies to explore their challenges around financing research in the fertility sector.

All practitioners have a duty of care to patients. This should separate pressure practitioners may be coming under from individual patients to offer them specific add-ons and any commercial interests the practitioners may have in relation to IVF add-ons, from their best practice advice. Clearly this best practice advice must be informed by knowledge gathered from good quality research. The fertility
sector should continue to work together in compiling the evidence for treatments with a view to publication and consensus around how treatments should be offered to patients.

Q: Does HFEA have a way of measuring the use of add-ons in the UK? If yes, what has it shown, if no how is the impact of the consensus statement be measured?

A: In 2018, we commissioned a national survey of fertility patients in the UK to understand the experiences of patients and their partners in fertility clinics, to understand what matters most, and to understand what changes could have the greatest impact on their experiences. Summary of key findings then were:

- For those that had treatment in the last two years, three quarters (74%) had at least one type of treatment add-on, similar to 71% of those in the past five years.
- The most commonly used treatment add-ons for those that used a fertility clinic in the past two years were clinical techniques, such as an endometrial scratch (27%), embryo glue (23%) or embroyscope (22%).
- For those that used a fertility clinic in the past five years, the most popular add-ons were endometrial scratch (25%), acupuncture (24%) and embryo glue (21%).

The HFEA currently only collect data from UK clinics on the use of two add-ons: assisted hatching and PGT-A; we plan to review the data collected in terms of trends in use of these add-ons over time and the quality of data already collected. We will then carefully consider whether it would be sensible to start to collect data on all traffic light rated treatment add-ons listed on our website (including the impact this would have on UK clinics to be required to collect and return these data), and to consider what data points we would want to collect, in light of the purposes this data could be needed for.

We will shortly be introducing a treatment add-ons audit tool which we will expect all clinics to complete, we hope to determine from the information gathered this way, whether each clinic’s patient information and practices used to deliver treatment add-ons conform to the specifications of the 2019 consensus statement. Where the specifications of the consensus statement are not met, we expect an action plan to be developed and documented to ensure the specifications are met within a reasonable time period.

Q: HFEA has not given any add-ons a green light, what factors do you feel have contributed to increasing pregnancy rates and reduced multiples.

A:

Green rated add-ons: According to the HFEA’s definition of the traffic light ratings, treatment add-ons that are rated green may be routinely used in fertility treatments, therefore will not be included in the HFEA’s traffic light rated list. A routinely used treatment add-on is where there is more than one good quality RCT which shows that the procedure is effective at improving live birth rates and is shown to be safe for patients to use.

Factors contributing to increased live birth rate: According to the UK statistics for IVF and DI treatment, storage, and donation published on 30 June 2020, the average age of an IVF patient was 35.3 years in 2018. In 2018, birth rates per embryo transferred were 25% for patients aged 35-37, 19% for patients aged 38-39, and 11% for patients aged 40-42. Clinical advancements and improvements, in areas including egg donation, embryo cryopreservation, addressing male infertility, in addition to refinement of techniques and use of technology, have led to increased chances of a live birth for all patients below 43 years old. In 2018, patients aged 40-42 had a higher chance of a live birth (11% per embryo transferred) than patients aged under 35 in 1991 (9% per embryo transferred). Patients aged
43 and above have consistently had birth rates below 5% per embryo transferred when using their own eggs. However, birth rates remained higher (above 25%) for all ages when donor eggs were used as egg donors are five years younger on average (30.2) than IVF patients (35.6).

Factors contributing to the reduce multiple birth rate: Multiple births are the biggest single health risk from IVF to mothers and babies. In 2017, the 10% multiple birth rate target was achieved for the first time nationally in the UK, but not across all age groups. In 2018, further progress was made, as the 10% target was reached across all age groups and nationally only 8% of IVF births resulted in a multiple birth. Besides our campaign to raise awareness, we have an outcome-based regulatory policy to reduce multiple births. We set a maximum multiple birth rate target and allow clinics to develop their own strategy for reducing their multiple birth rate to meet that target. Clinics can choose the approach that suits their practices and patients, whilst giving them something to aim for. Our inspectors monitor each clinic’s progress and give them early warning if they are likely to miss the target. The inspector and the clinic worked together to bring the rate down.

Q: Have you evaluated the traffic light system with patients to check for impact?

A: We believe that the key to providing high quality care is ensuring that patients’ and partners’ voices are heard, and feedback is acted upon. It’s only through listening to those who have been through fertility treatment that real, impactful improvements can be made. We know informally from feedback from patients and clinics that they have found it useful to have some evidence-based information provided on our website, for patients to take into account when making decisions around add-ons. To further understand patients’ understanding of the information we offer around treatment add-ons and the traffic light ratings on the HFEA’s website, the HFEA will be conducting user acceptance testing of specific web pages over the coming months via a questionnaire aimed at patients who have recently undergone or are planning to undergo fertility treatment. Information about this and a link to this questionnaire will be publicised on the HFEA website and social media channels with an open invitation for patients to take part. We will also be sending this questionnaire link to professional bodies and patient groups to share on their social media platforms and websites, for them to invite participation, where appropriate.

We will continue to work with patients, professional bodies and patient groups to improve the information around treatment add-ons and the traffic light ratings that we publish.

Q: Sure there are misuses, however ICSI had been started as experimental. Time is very important for patients, is there a dilemma?

A: The HFEA acknowledge that going through fertility treatment can be a very difficult and emotional journey for patients and their partners. We advise patients, that are going through fertility treatment in the UK, that the most important thing they can do when making decisions about fertility treatment is to ensure they are well informed. Patients must be clearly informed of the experimental nature of any treatment which is offered, where there is no robust evidence of its safety and/or effectiveness. Patients should not be charged extra to take part in research, including clinical trials. These principles give clinics the space to innovate, whilst also ensuring structures are in place to allow new treatments to be introduced through preclinical and clinical testing to confirm safety and efficacy. Treatments offered responsibly can be a sign of healthy innovation in the fertility sector.

Practitioners have a duty of care to patients and clinics should only offer treatments under the following conditions:
a) Where more than one high quality study demonstrates a treatment to be safe and effective, clinics should continue to monitor their success rates and long-term follow-up data and report adverse incidents. Clinics should stop offering the treatment to patients if concerns are raised regarding safety or effectiveness.

b) Where there is no evidence to support safety and efficacy, treatments should only be offered to patients in a research setting with sound methodology and approval from a research ethics committee.