

Treatment add ons- update

Strategic delivery: Safe, ethical, effective treatment Consistent outcomes and support Improving standards through intelligence

Details:

Meeting Scientific and Clinical Advances Advisory Committee (SCAAC)

Agenda item 5

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Output:

For information or decision? For decision

Recommendation Members are asked to:

- Consider whether they are aware of any further studies or developments for any of the add ons presented
- Discuss whether any traffic light ratings need to be revised

Resource implications None

Implementation date None

Communication(s) Possible communication of revised traffic light ratings

Organisational risk Low Medium High

1. Introduction

- 1.1.** Fertility treatment add ons are additional therapies and techniques which are claimed to increase the chance of pregnancy and birth from IVF or other fertility treatments. These add ons can be costly and may involve additional risks to the patient, and there is often limited evidence that they increase pregnancy or birth rates. Some add ons have been offered for a number of years while others are more recent developments.
- 1.2.** Centre to the HFEA's 2017-2020 strategy is publishing clear information for patients about the efficacy of treatments and treatment add ons. We want to increase lay people's insights into the science behind treatments and the evidence base for different treatment types, so that they can make informed decisions about their treatment options. To this end, new patient information and a traffic light rating system for treatment add ons were published on the HFEA website in Summer 2017.
- 1.3.** The patient information and traffic light rating system were developed in consultation with SCAAC during 2016, and finalised in 2017. Members developed patient information and traffic light ratings for the following nine add ons that they think patients most need information about:
- Artificial egg activation
 - Assisted hatching
 - Elective freeze-all
 - Embryo glue
 - Endometrial scratching
 - Intrauterine culture
 - Preimplantation genetic screening
 - Reproductive immunology
 - Time-lapse imaging
- 1.4.** For each treatment add on, the evidence published in the last 10 years was sent to an independent reviewer. Where there was a large body of evidence, only randomised controlled trials were sent in order to limit the time take for review. The reviewer then carried out an assessment of the quality of evidence for each add on using the GRADE methodology. The criteria for an add on to be rated red, amber, or green are as follows:
- A green symbol is used where there is more than one good quality study which shows the procedure is safe and effective
 - An amber symbol is used where there is a growing body of evidence which is showing promising results but where further research is still required
 - A red symbol is use if there is no evidence to show the add on is safe and effective.
- 1.5.** At its meeting in February 2017, SCAAC agreed to review the traffic light ratings for each treatment add on annually. This paper provides a brief update on any new evidence for the add ons that are currently headlined on the HFEA website. This does not include intrauterine culture or oocyte activation by calcium ionophore as these add ons have already been considered in detail in a previous meeting.

2. Assisted hatching

- 2.1.** The egg and early embryo are surrounded by a thick layer of proteins called the zona pellucida. Before an embryo can implant in the womb it has to break out or 'hatch' from its zona pellucida. Assisted hatching is a procedure that uses acid, lasers or other tools to thin or make a hole in the zona pellucida with the aim of helping the embryo to hatch.
- 2.2.** Assisted hatching currently has a red traffic light rating. The patient information on assisted hatching refers to the National Institute for Health and Care Excellence (NICE) who have advised that assisted hatching has not been shown to improve pregnancy rates.

New evidence

- 2.3.** A meta-analysis by Zeng et al., 2018 analysed 12 Randomised controlled trials (RCTs) that evaluated the effect of laser-assisted hatching on pregnancy outcomes, accounting for more than 2574 patients. The study showed that assisted hatching had higher rates of clinical pregnancy, embryo implantation and multiple pregnancy but did not show increase in live birth rates. A decrease in miscarriage rates was also observed.
- 2.4.** Another meta-analysis by Li et al., 2016 analysed 36 RCTs (6459 patients), which looked at studies that used laser, chemical and mechanical methods of assisted hatching. It was observed that assisted-hatching led to increased clinical pregnancy rate and increased multiple pregnancy.
- 2.5.** A study by Kanyo et al., 2016 included in the meta-analysis above assessed how laser-assisted hatching influenced clinical pregnancy rates in women of different ages. It was observed that there was increased pregnancy rates in patients older than 37.
- 2.6.** A large cohort study by Knudston et al., 2017 assessed the effect of assisted hatching on women who had first cycle frozen embryo transfers from 2004 to 2013. In women that had assisted hatching there was a slight decrease in live birth rates (34.2%, n=70,738) compared to those who did not have assisted hatching in their treatment (35.4%, n= 80,795). Decreased live birth rates were observed in patients older than 38.

3. Elective freeze-all

- 3.1.** Elective freeze all cycles involve creating embryos using IVF or ICSI and then freezing all of them so no embryos are transferred in the 'fresh' cycle. The embryos are thawed a few months later and transferred to the woman's womb as part of a frozen embryo transfer (FET) cycle.
- 3.2.** This add on currently has an amber rating and the information on the HFEA website informs patients of the ongoing E-Freeze clinical trial which they may be invited to participate in

New evidence

- 3.3.** In a systematic review by Wong et al., 2017, four RCTs accounting for 1892 patients that compared a freeze-all strategy with conventional IVF/ICSI were analysed. There was no clear difference observed for live birth rates. Low quality studies showed reduced risk of OHSS in freeze-all groups. Fewer miscarriages were also observed for freeze-all, however there was higher risk of pregnancy complications. The review identified 12 ongoing trials in trial registers that could inform future reviews, one being E-Freeze which is expected to end in 2020.

- 3.4.** Another systematic review included five RCTs and evaluated the effect of freeze-all based on the number of eggs retrieved (Dieamant et al., 2017). The reviewed identified better pregnancy outcomes when higher number of eggs were retrieved (>12 and <21), however did not find better outcomes where <15 eggs were retrieved.
- 3.5.** A retrospective cohort study by Braga et al., 2016 found that in an egg sharing programme, there were higher pregnancy and implantation rates for donor cycles where embryos were frozen and transferred during a subsequent cycle compared to cycles where fresh transfer was made.
- 3.6.** A small prospective cohort study by Magdi et al., 2017 assessed the outcomes of a freeze-all policy. Patients who had recurrent implantation failure were allocated either to a freeze-all policy group (n=81) or a fresh embryo transfer group (n=90). The freeze-all policy group had significantly higher clinical pregnancy rate (OR 1.86) and ongoing pregnancy rate (OR 2.2).
- 3.7.** A retrospective cohort study by Xue et al., 2018 assessed the effect of freeze-all cycles on poor ovarian responders. They found that live birth rates were comparable between patients in a freeze-all strategy and fresh embryo transfer cycles.
- 3.8.** An RCT by Coates et al., 2017 compared pregnancy outcomes in patients who had a freeze-all cycles to those who had fresh cycles. There were significantly higher ongoing pregnancy rates and live birth rates in the freeze-all group.

4. Embryo glue

- 4.1.** Embryo glue contains a natural substance called hyaluronan, which may improve the chance of the embryo implanting in the womb. It is added to the solution in the dish in which the embryos are kept before being transferred to the woman.
- 4.2.** This add on has an amber rating, with evidence showing that use of embryo glue can be beneficial though further evidence is required

New evidence

- 4.3.** In a retrospective cohort study (Fu et al., 2018) looking at 1721 cycles, use of embryo glue (347 cycles) compared to standard medium (1374 cycles) showed lower pregnancy rate and implantation rate in patients undergoing their first frozen embryo transfer attempt in the embryo glue treatment group. For third attempts pregnancy and implantation rates were higher when embryo glue was used. The authors concluded that embryo glue is more effective in patients who had repeated implantation failures.

5. Endometrial scratching

- 5.1.** Endometrial scratching is carried out before IVF and is intended to correct problems with the womb lining. During the procedure the lining of the womb (the endometrium) is 'scratched' using a small sterile plastic tube. This is thought to make the womb lining more receptive to an embryo.
- 5.2.** This add on has an amber rating, with evidence showing increased pregnancy rates though further evidence is needed to prove this.

New evidence

- 5.3.** In a systematic review (Vitagliano et al., 2018) which evaluated eight RCTs comprising of 1871 intrauterine insemination (IUI) cycles, higher clinical pregnancy rate (OR 2.27) and ongoing pregnancy rate (OR 2.04) were observed in patients who received endometrial scratch compared to patients who received no endometrial scratch. Furthermore, subgroup analysis showed the stage at which endometrial scratch had effect. The clinical and ongoing pregnancy rates were higher when endometrial scratch was performed during the course of IUI treatment. No benefit was found when endometrial scratch was performed at the menstrual cycle stage preceding the IUI phase.
- 5.4.** An RCT which tested the effect of saline infused endometrial scratch (Salehpour et al., 2016) found that in patients who received endometrial scratch had significantly lower rates of implantation (n=20, 4.7%) compared to controls (n=39, 41.6%).
- 5.5.** An RCT by Goel et al., 2017 examined IUI cycles in 144 patients, who received endometrial scratch (n=72) and compared pregnancy outcomes to patients who were controls (n=72). Higher rates of clinical pregnancy and ongoing pregnancy were observed in the endometrial scratch group.
- 5.6.** An RCT by Mak et al., 2017 assessed the effect of endometrial scratch on patients who underwent frozen embryo transfers. In 196 patients (93 who received endometrial scratch and 93 controls), no difference was found in implantation and pregnancy rate, as well as the clinical and ongoing pregnancy or live birth rates between the two groups.
- 5.7.** In a prospective RCT by Senocak et al., 2017, the effect of endometrial scratch was examined in 80 patients, where 40 patients received the intervention and 40 patients acted as controls. Pregnancy rates and clinical pregnancy rates were increased in the intervention group however this was not significant.
- 5.8.** A recent RCT in Egypt (Maged et al., 2018) looked at 300 patients who received endometrial scratch in first ICSI cycles (n=150) and compared rates of implantation and clinical pregnancy to controls (n=150). Both the rates of implantation and clinical pregnancy were significantly higher in the patients who received endometrial scratch.

6. Pre-implantation genetic screening

- 6.1.** Pre-implantation genetic screening or PGS (also known as aneuploidy screening, PGT-A or PGD-A) involves checking embryos for abnormalities in the number of chromosomes. Embryos with an abnormal number of chromosomes may stop developing very early on, end in a miscarriage or a still birth, or the child may be born with a disorder such as Down's Syndrome.
- 6.2.** PGS has two traffic light ratings depending on when the screening is carried out. A red rating has been given for PGS carried out on day three of embryonic development and an amber rating for when PGS is carried out on day five.

New evidence

- 6.3.** In an RCT by Rubio et al., 2017, the clinical value of PGD-A in patients aged between 38 and 41 years was assessed. 100 patients received PGD-A at day 3 and delivery and birth rates were compared with 105 controls. There were significantly fewer embryo transfer carried out in the PGD-A group (68.0% vs. 90.5%). After the first blastocyst transfer attempt, both the delivery and birth rates were increased in the PGD-A group.

- 6.4.** A prospective, long term follow-up study assessed whether children born after IVF with PGS developed normally at nine years old compared to controls (Kuiper et al., 2018). There were no significant differences in adverse outcomes observed between the two groups.

7. Reproductive immunology

- 7.1.** Reproductive immunology is a field of study that looks at how a woman's immune system reacts when she becomes pregnant. It is thought that infertility or miscarriage could be a result of the mother's immune system rejecting an embryo.
- 7.2.** This add on has a red rating, indicating that there is no convincing evidence to support immunology treatments that might aim to suppress the immune system.

New evidence

- 7.3.** A small study compared the peripheral blood autoimmune profile of 158 women with recurrent miscarriage after IVF with 76 control patients who had a successful first IVF attempt (Motak-Pochrzest et al., 2018). The study found that patients with recurrent implantation failure had higher levels of autoantibodies in their blood.
- 7.4.** In a study by Li et al., 2017, the use of hCG-activated autologous human peripheral blood mononuclear cells was analysed on patients who had previous failed implantations. Clinical pregnancy, live birth and implantation rates were significantly increased in patients who had four or more failed embryo transfers, but this was not observed in patients who had one to three failed embryo transfers.
- 7.5.** A prospective trial looked at the effect of anti-oxidants on 70 patients who had a history of recurrent miscarriage or implantation failure (Marron et al., 2018) who had raised cytokine levels. After a 10-week regime of Omega 3, vitamin D3, and B complex, levels of cytokine were normalised in 43 patients, improved in 12 patients and unchanged in 15 patients. This study suggests a dietary regime could be an effective and safer treatment for elevated cytokines. There is a possible link between cytokines and implantation success as raised cytokine levels have been identified in women with recurrent pregnancy losses.
- 7.6.** A retrospective cohort study looked at 13,372 transfers at a multi-site IVF clinic and the effect of various adjuncts (Shirlow et al., 2017). Steroid treatment from stimulation up until the pregnancy test or first trimester had reduced clinical pregnancy loss and improved birth rates. The results for other adjuncts in the study including intralipids did not reach statistical significance.
- 7.7.** A small non-randomised trial studied the effect of intravenous immunoglobulin G on Th17 and Treg cells in patients with recurrent miscarriage. IVIG down-regulated Th17 cells population and function and up-regulated Treg cells population and function. In the trial 38 out of 44 women who received IVIG had successful pregnancy outcome (86.3%) whereas 21 out of 50 untreated women had a successful pregnancy outcome (42%).

8. Time-lapse imaging

- 8.1.** Time-lapse imaging allows the embryologist to take thousands of images of embryos as they grow without disturbing them. Not only does this mean the embryos do not have to be removed from the incubator, it also allows the embryologist to get a continuous view of each embryo as it develops, rather than just viewing them once a day.

- 8.2.** This add on has an amber rating, with early results showing promise but more evidence is required.

New evidence

- 8.3.** A pilot study found that embryo selection by time-lapse analysis in conjunction with standard morphology did not have an effect on ongoing pregnancy rate, and also found that lower quality embryos had been transferred in the time-lapse analysis group compared to the control group.
- 8.4.** A meta-analysis by Pribenszky et al., 2017 looked at five RCTs that compared time-lapse imaging with standard morphology. Time-lapse imaging was associated with significantly higher ongoing clinical pregnancy rate, and significantly increase live birth rate. The studies were rated as moderate to low quality.
- 8.5.** A pilot RCT (Kaser et al, 2017) examined clinical pregnancy rate at 7 weeks and ongoing pregnancy rate at 12 weeks across three study arms: one arm where time-lapse was carried out with embryo transfer at day three, a second time-lapse arm where embryo transfer occurred at day five and the third arm where conventional morphology was used with embryo transfer occurring at day five. In the 163 patients that took part in the trial, there were no significant differences in the clinical pregnancy rate or ongoing pregnancy rate between the study arms.

9. Conclusion

- 9.1.** As add ons become more frequently offered to patients, it is important to keep ahead of all the evidence available for these add ons. It may be necessary to revisit the traffic light ratings, particularly for assisted hatching, elective freeze-all and endometrial scratching which have seen several new RCTs and systematic reviews come to light.
- 9.2.** Members are asked to:
- consider whether they are aware of any further studies or developments for any of the add ons
 - discuss whether traffic light ratings need to be revised

10. References

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