Review of traffic light ratings for treatment add-ons – October 2019

Strategic delivery:	☒ Safe, ethical, effective treatment	☐ Consistent outcomes and support	☐ Improving standards through intelligence
Details:			
Meeting	SCAAC		
Agenda item	5 and 6		
Paper number	HFEA (14/10/2019) 005		
Meeting date	14 October 2019		
Author	Rasheda Begum, Scientific Policy Officer Dina Halai, Scientific Policy Manager		
Output:			
For information or recommendation?	For recommendation		
Recommendation	The committee is asked to: • consider the quality of evidence for each treatment add-on based on the findings from an independent assessor at annex A; and • agree and recommend traffic light categories for each treatment add-on		
Resource implications	None		
Implementation date	Recommendations will be considered by the HFEA for implementation in due course		
Communication(s)	Communication of revised traffic light ratings if any change in a Clinic Focus and HFEA website update		
Organisational risk	☒ Low	☐ Medium	☐ High
Annexes	Annex A: Treatment add-ons traffic light ratings review		

1. Introduction

1.1. Treatment add-ons are optional extras, offered on top of the main fertility treatment such as in vitro fertilisation (IVF) or intracytoplasmic sperm injection (ICSI), that claim to improve patients' chances of having a baby. They're sometimes emerging techniques that may have shown some promising results in initial studies, or they may have been around for a number of years but haven't necessarily been proven to improve pregnancy or birth rates. In January 2019, the HFEA published a consensus statement co-signed by ten leading professional and patient fertility groups, outlining agreed principles on how treatment add-ons should be offered ethically in clinical practice in the UK.

1.2. Since Spring 2017, the HFEA have published patient information on 11 add-ons, each assigned with a traffic light rating agreed by the SCAAC reflecting the evidence available on the efficacy and safety of the add-on. The HFEA agreed that these were the treatment add-ons that patients most need information about, but this is not the complete list of additional treatments that patients may be offered on top of the main fertility treatment. The list of add-ons that the HFEA currently provides patient information on with a traffic light rating are:

- Artificial egg activation
- Assisted hatching
- Elective freeze-all
- Embryo glue
- Endometrial scratching
- Intrauterine culture
- Preimplantation genetic screening
- Reproductive immunology
- Time-lapse imaging
- Intracytoplasmic morphologic sperm injection (IMSI)
- Physiological intracytoplasmic sperm injection (PICSI)

1.3. Information is also provided for DNA fragmentation which may be offered to patients in several clinics. There is no traffic light rating for DNA fragmentation as after consulting with an andrology expert, at the October 2018 SCAAC meeting it was decided that, as DNA fragmentation is a diagnostic test and does not directly influence live birth rate, assigning a traffic light rating for this add-on was not considered to be feasible.

1.4. At the September 2019 meeting of the Authority, the Authority asked for the commonly opted for holistic therapies (eg massage, acupuncture and nutritional therapy) to be included in HFEA's information on add-ons, which the executive have undertaken to begin to develop accordingly. A review of the evidence on efficacy and safety of the commonly opted for holistic therapies will be brought to a future SCAAC meeting for consideration to recommend a traffic light rating.

2. Traffic light system

2.1. A traffic light system is used alongside our patient information to give a quick, visual indication of whether the add-on is supported by good quality evidence for use in clinical practice or not. The traffic light ratings of the eleven treatment add-ons assessed so far are:

Traffic light rating	Definition	Add-ons currently under this rating
 Red	No evidence to show that it is effective and safe	Assisted hatching PGS (day 3) IMSI PICSI Intrauterine culture Reproductive immunology tests and treatment
 Amber	There is a conflicting body of evidence for this add-on, further research is required	Artificial egg activation calcium ionophore Elective freeze all cycles Embryo glue Endometrial scratching PGS (Day 5) Time-lapse imaging
 Green	There is more than one good quality RCT which shows that the procedure is effective and safe	None

2.2. To account for new evidence that arises from randomised clinical trials (RCTs) conducted investigating treatment add-ons, the list of treatment add-ons and their assigned traffic light ratings are reviewed regularly to determine whether the traffic light rating should change. Traffic light ratings could both be promoted to a higher rating (e.g. red to amber or amber to green) or demoted (e.g. amber to red).

3. Independent assessment of the quality of evidence

3.1. In order to categorise the treatment add-ons under consideration, it is necessary not only to identify the published evidence around each add on, but also to assess the quality of that evidence. For this reason, we sought advice from an expert in systematic reviews and evidence assessment to carry out an independent assessment of the quality of evidence (using the GRADE methodology[1]) for each treatment add-on. The independent reviewer reassessed the traffic light ratings in light of the additional studies published since the last review (conducted in 2018).

[1] GRADE is an approach for grading the quality of evidence and the strength of recommendations. It was developed by the Grading of Recommendations, Assessment, Development and Evaluation Working Group.

3.2. Critical review of studies included assessment of risk of bias from allocation method, blinding, selective reporting, unexplained attrition, unplanned interim analysis and other miscellaneous errors in the design, conduct or reporting of results.

3.3. The findings of this assessment for each add-on and the independent reviewer's recommended ratings can be found at Annex A, alongside the current traffic light rating agreed previously in consultation with the committee, last in June 2018. The assessments made by the independent reviewer are from a methodological perspective without expertise in the clinical or scientific context.

4. Recommendations

4.1. The committee is now asked to:

- consider the quality of new evidence for each treatment add-on based on the findings from an independent assessor at annex A; and
- agree and recommend traffic light categories for each treatment add-on

Annex A: Treatment add-ons traffic light ratings review

1. Artificial egg activation

Current traffic light category		Traffic light category recommended by independent reviewer - October 2019	
Amber	There is a conflicting body of evidence for this add-on, further research is required	Amber	There is a conflicting body of evidence for this add-on, further research is required

1.1. Independent reviewer comments:

1.2. *The previous review in 2017 included two studies: one within-patient design on sibling oocytes (experimental more than clinical) and one RCT that suggested early promise in couples with diminished ovarian reserve but normal sperm parameters and no previous fertilisation failure.*

1.3. *This review considers the additional evidence from Aydinuraz 2016 and Fawzy 2018. Aydinuraz 2016 presented a further within-patient, sibling oocyte design in couples with teratozoospermia and a low fertilisation rate in the previous cycle. Unfortunately, their presentation and all analyses ignored the matching of the design, precluding statistical interpretation of their data. However, it is clear that only 13 of the 21 couples produced at least one top quality embryo from artificially activated oocyte, whereas 20 achieved this from conventionally cultured oocytes.*

1.4. *Fawzy 2018 presented the largest RCT to date with 443 participants randomised evenly between three groups: two active arms using either strontium chloride or calcymicin and a control. Participants had either a diagnosis of male factor infertility or at least two previous cycles with <30% fertilisation rate. Their results show statistically significant clinical advantage for artificial activation in both active arms: OR (95% CI) = 3.0 (1.6 to 4.5) and 2.2 (1.2 to 4.0) for strontium chloride and calcymicin respectively. Several methodological issues raise caution. In particular, early randomisation (day 21 of previous cycle) may have resulted in opportunity for selection bias. It is noteworthy that participants in the active arms had both more oocytes retrieved and more mature oocytes than those in the control arm. The trial also finished early following an interim analysis of the data but with no clear specification of any statistical stopping rule applied.*

1.5. ***Recommendation: Amber***

2. Assisted hatching

Current traffic light category		Traffic light category recommended by independent reviewer - October 2019	
Red	No evidence to show that it is effective and safe.	Red	No evidence to show that it is effective and safe.

2.1. Independent reviewer comments:

2.2. *Fresh embryos*

2.3. *The previous review in 2017 included eight RCTs (over 1700 participants) and a retrospective cohort study. The RCTs included laser thinning and creation of a hole either by laser or chemically. Estimated odds ratios for clinical outcomes were consistently around 1.0.*

2.4. *This update adds a further 326 participants from the RCT of Nada 2018. This study reported on laser thinning for couples presenting with endometriosis and no male factor. It was at high risk of bias from allocation processes and it was unclear why more embryo transfer procedures took place in the assisted hatching (active) arm despite there being more and higher quality embryos in the control arm. They reported a live birth rate result marginally better than that of the eight preceding trials: OR (95% CI) = 1.8 (1.0 to 3.1). Applicability to the UK setting may be doubtful given that no single embryo transfer took place: 56% double (44% triple) in the active and 13% double (87% triple) in the control arm.*

2.5. ***Recommendation: Red***

2.6. *Frozen embryos*

2.7. *The previous review in 2017 included four RCTs all published by 2010, plus one matched experimental design and a retrospective cohort. Three of the RCTs investigated laser thinning and one compared different approaches to mechanical piercing of the zona pellucida (ZP). For the three trials comparing assisted hatching with control, results were conflicting with the possible suggestion proposed by Martins 2011 review that vitrification was a factor: Valojerdi 2010 used vitrification and found statistically significant detriment, whereas Balaban 2006 and Ge 2009 had reported promising results.*

2.8. *The current review added a further randomised trial. Safari 2017 compared two assisted hatching groups – one with cosmetic micromanipulation, the other without – versus control. The population studied was couples with vitrified-warmed day 2 to 3 embryos of good grade, and assisted hatching was achieved by laser piercing of the ZP. The results were consistent with those of Valojerdi 2010. Pooling the assisted hatching groups for live birth gave OR (95% CI) = 0.51 (0.19 to 1.3).*

2.9. ***Recommendation: Red***

3. Embryo glue

3.1. Background

Current traffic light category		Traffic light category recommended by independent reviewer - October 2019	
Amber	There is a conflicting body of evidence for this add-on, further research is required	Amber	There is a conflicting body of evidence for this add-on, further research is required

3.2. Independent reviewer comments:

3.3. *The previous review in 2017 covered nine studies, including eight RCTs with a total of over 2600 participants. The overall quality of studies was low with most at high risk of bias. The largest and methodologically strongest study, Urman 2008, included over 1200 participants and found significantly increased live birth rate with use of embryo glue.*

3.4. *This review considers the additional evidence from Zborilova 2018. Available only as an abstract (Czech journal article not available for review) it is not clear that this represents a randomised trial rather than a report of routine clinical data. The latter seems more likely given the ratio of sample size between groups of around 7:3. It is not possible to assess risk of bias in other regards. There is no comparison of clinical outcomes between intervention groups other than "the chances of conception increased by approximately 9%". In short, there is nothing here to alter the conclusion based on the original nine studies reviewed.*

3.5. ***Recommendation: Amber***

4. Endometrial scratching

Current traffic light category		Traffic light category recommended by independent reviewer - October 2019	
Amber	There is a conflicting body of evidence for this add-on, further research is required	Amber	There is a conflicting body of evidence for this add-on, further research is required

4.1. Independent reviewer comments:

4.2. *The previous review in 2017 included 10 RCTs, reporting on 1651 participants, with substantial variation in populations, clinical protocols and duration of follow-up for outcomes. Despite this variation in multiple small trials there was consistent and moderate evidence supporting the use of endometrial scratching.*

4.3. *This review considers a further nine studies reporting 2700 participants with similarly substantial variation in populations and clinical protocols. All but two of these studies found estimated clinical effects in favour of endometrial scratching but they were typically small studies (40 to 150 participants per group) and those that reported an adequate allocation method reported statistically non-significant differences.*

4.4. *The two most recent studies both reported concealed randomisation processes.*

4.5. *Frantz 2019 appears to have been a well-designed study of reasonably good prognosis women undergoing fresh IVF or ICSI cycles. Unfortunately, the value of the data is limited. The trial stopped just over halfway through its scheduled recruitment following an unplanned futility analysis that was initiated by the independent data monitoring committee. That is, because success rates were observed to be lower in the scratch group, the chance of concluding a statistically significant benefit at the scheduled end was deemed too low to justify continuation. The consequence is that we are left with a biased treatment effect estimate with a wide confidence interval that does not rule out benefit.*

4.6. *Lensen 2019 also reports a well-designed, pragmatic (no sham procedure or blinding) study that recruited nearly 700 participants per group. They appear to rule out a major benefit of endometrial scratch for women undergoing IVF: live birth OR (95% CI) = 1.0 (0.78 to 1.3). However, uniquely this study allowed the endometrial scratch to be undertaken any time between day 3 of the preceding cycle and day 3 of the index cycle.*

4.7. *Further exploration of the totality of reviewed studies across both the original review and this update shows that the evidence for the 7 studies (2410 participants) of IVF and ICSI populations reporting clinical outcomes give odds ratios ranging from 0.61 to 3.8: inconsistent results but with the larger and more reliable studies giving estimated treatment effects close to 'no difference'. The 8 studies using IUI (1424 participants) give odds ratios ranging from 1.3 to 4.4: consistent results but from typically smaller studies of more questionable quality. The three studies (449 participants) using natural or stimulated cycles give odds ratios ranging from 3.1 to 4.5: consistent with those for IUI.*

4.8. *It may therefore be worth considering stratification in this case, depending on the biological plausibility of mechanistic differences in the two populations leading to benefit in one but not the other. If this is considered plausible, I would recommend 'red' when using embryo transfer, 'amber' or even 'green' otherwise.*

4.9. ***Recommendation: Amber***

5. Freeze-all

Current traffic light category		Traffic light category recommended by independent reviewer - October 2019	
Amber	There is a conflicting body of evidence for this add-on, further research is required	Amber	There is a conflicting body of evidence for this add-on, further research is required

5.1. Independent reviewer comments:

5.2. *The previous review in 2017 included three randomised trials, although one had been retracted following "results of an investigation" due to "serious methodological flaws". The other two were from the same team as each other covering 'normal' and 'high' responders to stimulation. Both suggested slightly increased rates of ongoing pregnancy with the freeze-all policy but interpretation was limited by insecure allocation and other sources of bias.*

5.3. *This review adds a further trial in a different population: couples undergoing ICSI following unexplained, recurrent implantation failure in at least three previous ICSI cycles with fresh embryo transfer. Results for ongoing pregnancy were promising even after adjustment of the report for an intention to treat approach: OR = 2.2 (1.1 to 4.2). Unfortunately, the trial from Magdi 2018 used alternation rather than randomisation, leaving high risk of selection bias. The high number of embryos transferred in each cycle (>2 in each trial arm) may also limit applicability to the UK setting.*

5.4. ***Recommendation: Amber***

6. IMSI

6.1. No new evidence from RCTs was identified for this add-on.

Current traffic light category		Traffic light category recommended by independent reviewer - October 2019
Red	No evidence to show that it is effective and safe.	No new evidence from RCTs was identified for this add-on.

7. PGS (Day 3)

Current traffic light category		Traffic light category recommended by independent reviewer - October 2019	
Red	No evidence to show that it is effective and safe.	Red	No evidence to show that it is effective and safe.

7.1. Independent reviewer comments:

7.2. *This update includes one further trial, Rubio 2017, studied older women (37 to 41 years) on their first or second ICSI cycle. It randomised 278 participants far too early and lost over 25% prior to intervention due to failure to proceed to later stages. Importantly it reported comparisons after both the first transfer and cumulatively to 6 months using vitrified embryos. Comparison of the first transfer suggests improved live birth rates due to markedly reduced miscarriage in the PGS arm. However, comparison of the cumulative experience showed very similar success rates, balanced by many more cryo-transfers occurring in the control arm: OR (95% CI) = 1.1 (0.62 to 1.8).*

7.3. *There remains some promise in particular groups from the earlier studies and for earlier success from Rubio 2017, but reduced availability following PGS may counter any short-term benefit (as in Rubio 2017)*

7.4. ***Recommendation: Red***

8. PGS (Day 5)

Current traffic light category		Traffic light category recommended by independent reviewer - October 2019	
Amber	There is a conflicting body of evidence for this add-on, further research is required	Red	No evidence to show that it is effective and safe.

8.1. Independent reviewer comments:

8.2. *The previous review in 2017 included three small RCTs (50 to 90 participants per group) making subtly difference comparisons: one eSET on Day 6 in both groups; one comparing eSET in the PGS with DET in controls, both on Day 6; and one comparing DET on Day 6 after PGS with DET on Day 5 in controls. The first and third of these reported statistically significant benefits of PGS whereas the second reported non-significant detriment.*

8.3. *This update includes two further trials. The first, Ozgur 2019, randomised 220 couples undergoing eSET in freeze-all ICSI cycles. Couples were required to have at least two high-grade, Day 5 blastocysts and younger women (<35 years). Other than lack of clarity regarding the allocation process the study appeared well-designed. Live birth was non-significantly lower in the active arm: OR (95% CI) = 0.75 (0.44 to 1.3).*

8.4. *The second, Munné 2019, was also the largest: 661 couples with similar eligibility criteria to those of Ozgur 2019 but with broader female age range of 25 to 40 years. Live birth results were also similar with OR (95% CI) = 0.93 (0.69 to 1.3). The abstract highlighted a subgroup (selectively pooled randomisation strata) of a strongly biased subgroup (those reaching the transfer stage) that should be interpreted with extreme caution, if at all.*

8.5. *There are now five studies with contrasting conclusions but based on quite different populations and control comparisons. It appears possible that reduced availability of embryos for transfer following PGS may counter any benefit of selection and that the balance of these competing risks may vary between clinical populations.*

8.6. ***Recommendation: Red***

9. PICSI

Current traffic light category		Traffic light category recommended by independent reviewer - October 2019	
Red	No evidence to show that it is effective and safe.	Red	No evidence to show that it is effective and safe.

9.1. Independent reviewer comments:

9.2. *Six studies, including three RCT totalling around 800 participants, were previously reviewed in 2018. These did not show any evidence of benefit. At the time of the review David Miller provided an unpublished abstract of the HabSelect study. This is now published as Miller 2019.*

9.3. *Miller 2019 was a pragmatically designed, well conducted and well-reported trial of more than 2700 participants across 16 sites. ICSI had been recommended on the basis of semen assessment in over 95% of participants. The primary analysis ruled out major differences in the outcome of live birth between PICSI and ICSI: OR (95% CI) = 1.1 (0.95 to 1.3). Further secondary analyses considered stratification by factors identified in the earlier trials including, for example, hyaluronan sperm binding score, none of which showed evidence of differential effects.*

9.4. *Of note, Miller 2019 observed similar percentages of participants in each group attaining clinical pregnancy and similar advantages in the PICSI group of around 2 to 3 percentage points in both miscarriage and live birth.*

9.5. *In conclusion, Miller 2019 rules out any meaningful detriment or major benefit of PICSI. It does however leave open the possibility of a small (two to three percentage points) benefit of PICSI, not through increased fertilisation or implantation but through reduction of miscarriage. If this mechanism is considered to have biological plausibility the committee should consider an amber rating. However, the magnitude of study required to confirm such a small effect makes the collection of further robust evidence seem unlikely. A randomised trial with 90% power to detect a difference in live birth rates between, say 25% and 27%, would require in excess of 20,000 participants.*

9.6. ***Recommendation: Red***

10. Reproductive immunology

10.1. There are only a few numbers of studies that have investigated these therapies and they do not suggest that reproductive immunology has any benefit for achieving better pregnancy outcomes.

Current traffic light category		Traffic light category recommended by independent reviewer - October 2019
Red	No evidence to show that it is effective and safe.	Not reviewed as part of October 2019 review. We hope to bring the review of this add-on to the February SCAAC meeting.

11. Time-lapse imaging

11.1. There have been several small-to-medium sized studies investigating this add-on and the they have demonstrated conflicting findings.

Current traffic light category		Traffic light category recommended by independent reviewer - October 2019
Amber	There is a conflicting body of evidence for this add-on, further research is required	Not reviewed as part of October 2019 review. We hope to bring the review of this add-on to the February SCAAC meeting.

References - Reviewed studies (bold indicates references added for this 2019 review)

Adjunct	Study	DOI/reference
Artificial Egg Activation	Meerschaut 2012	10.1093/humrep/des097
	Aytac 2015	10.1016/j.fertnstert.2015.07.1163
	Aydinuraz 2016	**10.1080/14647273.2016.1240374**
	Fawzy 2018	**10.1093/humrep/dey258**
Endometrial Scratching	Raziel 2007	10.1016/j.fertnstert.2006.05.062
	Karimzadeh 2009	10.1111/j.1479-828X.2009.01076
	Narvekar 2010	10.4103/0974-1208.63116
	Abdelhamid 2012	10.1007/s00404-013-2785-0
	Gibreel 2013	10.1111/j.1447-0756.2012.02016.x
	Parsanezhad 2013	IRCT:2012082510657NI
	Zarei 2014	IRCT:2012070810210NI
	Wadhwa 2015	J Hum Reprod Sci 2015;8(3):151-8.
	El Khayat 2015	10.1016/j/ejogrb.2015.08.025
	Mahey 2015	10.1016/j.fertnstert.2015.07.1163
	Maged 2016	10.1177/1933719115602776
	Goel 2017	**10.1007/s10815-017-0949-8**
	Mak 2017	**10.1016/j.rbmo.2017.04.004**
	Aleyamma 2017	**10.1016/j.ejogrb.2017.05.005**
	Helmy 2017	**10.1002/ijgo.12178**
	Senocak 2017	**10.1016/j.jogoh.2017.09.003**
	Ashrafi 2017	**10.1111/jog.13401**
	Maged 2018	**10.1002/ijgo.12355**
	Frantz 2019	**10.1093/humrep/dey334**
	Lensen 2019	**10.1056/NEJMoa1808737**
Embryo Glue	Morbeck 2007	NCT005882250
	Mahani 2007	EMHJ 2007;13(4):876-80.
	Friedler 2007	10.1093/humrep/dem220
	Korosec 2007	RBM0 2007;15(6):701-7.
	Hazlett 2008	10.1016/j.fertnstert.2007.05.063
	Urman 2008	10.1016/j.fertnstert.2007.07.1294
	Dittmann-Muller 2009	Hum Reprod 2009;24 Suppl 1:167.
	Fancsovits 2015	10.1007/s00404-014-3541-9
	Singh 2015	10.4103/0974-1208.170398
	Zbořilová 2018	**https://europepmc.org/abstract/med/30764616**
PGS (Day 3)	Mastenbroek 2007	NEJM 2007;357:9-17.
	Hardarson 2008	10.1093/humrep/den217
	Staessen 2008	10.1093/humrep/den367
	Blockeel 2008	RBMO 2008;17(6):848-54.
	Meyer 2009	10.1016/j.fertnstert.2008.02.162

	Schoolcraft 2009	10.1016/j.fertnstert.2008.05.029
	Sher 2009	10.1016/j.fertnstert.2008.11.029
	Debrock 2010	10.1016/jfertnstert.2008.10.072
	Rubio 2017	**10.1016/j.fertnstert.2017.03.011**
PGS (Day 5)	Yang 2012	Molec Cytogen 2012;5:24
	Forman 2013	10.1016/j.fertnstert.2013.02.056
	Scott 2013	10.1016/j.fertnstert.2013.04.035
	Ozgur 2019	**10.1007/s10815-018-01399-1**
	Munné 2019	**10.1016/j.fertnstert.2019.07.1346**
Freeze All	Aflatoonian 2010	10.1007/s10815-010-9412-9
	Shapiro 2011a	10.1016/j.fertnstert.2011.05.050
	Shapiro 2011b	10.1016/j.fertnstert.2011.02.059
	Magdi 2017	**10.1016/j.fertnstert.2017.04.020**
Assisted Hatching: Fresh	Sagoskin 2007	10.1016/j.fertnstert.2006.07.1498
	Ge 2008fresh	RBMO 2008;16(4):589-96.
	Balakier 2009	10.1016/j.fertnstert.2008.07.1729
	Hagemann 2010	10.1016/j.fertnstert.2009.01.116
	Kutlu 2010young	10.1007/s10815-010-9431-6
	Kutlu 2010old	10.1007/s10815-010-9431-6
	Razi 2013	Iran J reprod Med 2013;11(12):1021-6.
	Shi 2016	10.1177/1933719116641764
	Chang 2016	F&S 2016;106(3) Suppl:e314
	Nada 2018	**10.1007/s00404-017-4604-5**
Assisted Hatching: Frozen	Balaban 2006	10.1093/humrep/del097
	Ge 2008froz	RBMO 2008;16(4):589-96.
	Valojerdi 2010	10.1016/j.rbmo.2009.11.002
	Fang 2010	10.1016/j.fertnstert.2009.08.014
	Wang 2016	10.3892/br.2016.716
	Knudtson 2016	F&S 2016;106(3) Suppl:e141
	Safari 2017	**10.1016/j.repbio.2017.05.003**
PICSI	Worrilow 2013	10.1093/humrep/des417
	Majumdar 2013	10.1007/s10815-013-0108-9
	Mokanszki 2014	10.3109/19396368.2014.948102
	Troya 2015	10.5935/1518-0557.20150015
	Lohinova 2017	PMID: 29099693
	Erberelli 2017	10.5935/1518-0557.20170002
	Miller 2019	**10.1016/S0140-6736(18)32989-1**