Traffic Light System for Treatment Add-ons

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INTRODUCTION

The HFEA website provides patients with digestible information on treatment add-ons in the form of a 'traffic light' system. To date this has focused on evidence for clinical effectiveness (i.e. the relative ability of add-ons to achieve the desired endpoint of live birth).

This report provides a summary of the evidence regarding preimplantation genetic screening of Day 5 blastocysts. It updates the review of randomised trial evidence of this specific add-on with information concerning additional endpoints.

TRIALS

References to studies under consideration are given below. In brief:

1) Yang (2012) studied a population with good prognosis undergoing elective single embryo transfer and randomised before the start of IVF treatment.
2) All other studies considered couples with at least two good quality blastocysts and randomised at this stage.
3) Forman (2013) compared single embryo transfer following PGS with double embryo transfer in control participants. 30% of participants opted for frozen embryo transfer.
4) Scott (2013) was the same research team as Forman (2013) and used very similar methods but compared a policy of fresh double embryo transfer in each group.
5) Ozgur (2019) and Munné (2019) each compared under a policy of elective single embryo transfer in freeze-all cycles.

OUTCOMES

All five studies studied a single cycle of treatment. As a consequence none was able to compare either cumulative live birth rates or the time taken to achieve success.

Most also considered a population undergoing elective single embryo transfer, whether fresh or frozen. Only Scott (2013) was able by design to sensibly compare multiple pregnancy rates. Despite consideration of the issues under the *Discussion* section the authors did not report the relevant data. Forman reported 43 singleton and 27 multiple pregnancies from 86 control participants undergoing DET, but had no comparison given the eSET policy in their PGS group.

Miscarriage rates were reported or calculable for all five studies. For consistency I have counted all losses between clinical pregnancy and either ongoing pregnancy (20 weeks for Yang 2012, 24 weeks for Forman 2013) or delivery. My figures therefore include some later miscarriages and elective terminations and differ slightly from those reported as 'miscarriage' in the manuscripts.

RESULTS

As previously reported, the smaller early studies reported benefit in terms of live birth or ongoing pregnancy. The exception to this was Forman 2013, where it may be concluded that the co-intervention of double rather than single embryo transfer may have balanced any benefit of embryo selection, resulting in similar success rates between arms. The later and much larger studies both reported marginal and statistically non-significant differences that favoured controls.

All five studies reported miscarriage rates that favoured PGS although none individually was statistically significant. Estimated Odds Ratios ranged from 0.41 to 0.87 per woman randomised and from 0.26 to 0.97 per pregnancy. This gives a consistent picture of lower miscarriage rates occurring under a range of IVF protocols and populations when using PGS for embryo selection.

DISCUSSION

The studies consider a range of clinical populations undergoing different IVF protocols. Risks of bias were not out of the ordinary and yet there appears to be a difference in qualitative conclusions arising from the earlier and later studies.

Importantly, reported studies to date could not by design report the most clinically relevant outcomes – cumulative live birth and time to success. Consistent benefit in terms of reducing the occurrence of miscarriage does not lead to higher success rates from the first embryo transfer.

Caution is required as the assessments above are made from a methodological perspective without expertise in the clinical or scientific context. I am not able to comment on the wisdom of undertaking a meta-analysis of these studies and have avoided doing so.

REFERENCES

Adjunct	Study	DOI/reference
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