

Towards single embryo transfer? Modelling clinical outcomes of potential treatment choices using multiple data sources: predictive models and patient perspectives

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Executive summary

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Executive summary

Background

In vitro fertilisation (IVF) treatments involve an egg retrieval process, fertilisation and culture of the eggs in the laboratory, and the transfer of resultant embryos back to the mother over one or more embryo replacement cycles. The first such transfer is usually of fresh embryos, while the remaining embryos may be cryopreserved for future frozen cycles. Most commonly in UK practice two embryos are transferred (double embryo transfer, DET). IVF techniques have led to a dramatic increase in the number of multiple births. Around 25% of all IVF births are twins, carrying an increased risk of maternal and infant morbidity. During the lifespan of this project the UK Human Fertilisation and Embryology Authority (HFEA) has adopted a multiple birth minimisation strategy, requiring clinics to systematically reduce the proportion of multiple births. One direct strategy to achieve this would be by increased use of single embryo transfer (SET).

Objectives

- To collate high-quality cohort data from a series of individual treatment centres to be considered alongside data collated by the HFEA for regulatory purposes.
- To develop predictive models from each of the data sources for successful live birth and twinning probabilities from fresh and frozen embryo transfers.
- To understand, through qualitative work, patients' perspectives as they travel through the treatment process, including appropriate outcome measures, attitudes towards twins, opinions on SET and potential policies for reducing the number of twin births.
- To predict outcomes for treatment scenarios, based on proposals in the literature and developed with patients and clinicians.
- To use the modelling results to investigate with patients the acceptability of twin reduction policies within the current regulatory, funding and clinical environment.
- To consider the need for future randomised controlled trials and surveys of patient attitudes.

Methods

We adopted a multidisciplinary approach combining state-of-the-art statistical modelling with in-depth qualitative exploration of patient perspectives. The components were integrated formally through statistical modelling of scenarios proposed by patients and presentation of the modelling results to patient groups. Less formally, components were integrated through cross-disciplinary discussions within the research team. The specific components included:

- semi-structured interviews with 27 couples at various stages of IVF treatment at both UK NHS and private clinics
- collation of a UK dataset of over 90,000 patients from the HFEA registry covering the 2000–5 period
- collation of a more detailed dataset from 2000–5 of nearly 9000 patients from five diverse centres
- analysis for live birth and twin outcomes: we developed logistic regression models, including models for the implantation probability of each embryo and the receptivity of the uterus; additional models estimated effects of cryopreservation and inpatient correlations
- use of the models to predict the outcomes of policies for selecting patients for SET or DET in the fresh cycle following egg retrieval and fertilisation; we used these predictions in simulations of treatments spanning several embryo transfer procedures
- convening two focus groups, one in the NHS and one web based on a patient organisation's website; results of the statistical analyses were presented and potential treatment policies explored.

Results

The interviews indicate that, despite having had the risks explained, for many patients a twin birth is the ideal outcome. There was scepticism concerning the motivation to reduce twin numbers. Many equated this to saving money and a lack of due priority for fertility treatments. Potential restrictions on DET were seen to conflict with the

NHS Patient Choice agenda. Scepticism exists over the use of cryopreservation and frozen transfers.

The statistical analysis revealed no characteristics that specifically predicted multiple birth outcomes beyond those that predicted treatment success. A number of prognostic factors were confirmed and it was possible to identify some acting specifically through the embryo viability or uterine receptivity. In the fresh transfer following egg retrieval SET would lead to a reduction of approximately one-third in the live birth probability compared with DET, a result consistent with the limited data from clinical trials. Furthermore this reduction showed only weak dependence on patient characteristics.

Unless there is antagonism between embryos, it is a simply demonstrable mathematical truth that any individual woman will have a lower chance of a successful outcome in a given transfer cycle from SET compared with DET. However, from the population or clinic perspective, selection of patients based on prognostic indicators might mitigate about half of the loss in live births associated with SET in the initial fresh transfer while achieving a twin rate of 10% or less. A number of strategies based on the woman's age and the number and quality of available embryos performed broadly similarly.

Any meaningful comparison of IVF treatments must take a complete treatment perspective, comparing success rates after use of all available frozen embryos from an egg retrieval. Our data-based simulations suggested that, if all good-quality embryos are replaced over multiple frozen embryo transfers, repeated SET has the potential to produce more live birth events than repeated DET. This would critically depend on optimising cryopreservation procedures. Universal SET could both reduce the number of twin births and lead to more couples having a child, but at an average cost of one more embryo transfer procedure per egg retrieval.

The interview and focus group data suggest that, despite the potential to maintain overall success rates, patients would prefer DET: the potential for twins is seen as positive, while additional transfer procedures are emotionally, physically and, for some, financially draining.

Conclusions

Implications for practice

1. We found significant resistance to SET and reducing twin rates, although a sizeable

minority of NHS patients do accept SET. Many patients were well-informed and would challenge inaccurate or misleading information. There is a need to develop clear and accurate information if multiple birth minimisation policies are not to be perceived negatively.

2. The measure of treatment success will be crucial to the acceptance of SET. If the reporting focus continues to be the initial fresh transfer, SET can only appear disadvantageous. If the focus shifts to complete cycles, SET may match or outperform DET. However patient scepticism of cryopreservation needs to be addressed and the burden of additional transfers needs to be considered.
3. Cryopreservation then becomes crucial to maintaining success rates. This study identified scope for optimisation.
4. Selection of patients for SET may help clinics reduce the loss in fresh cycle success rates. Selection policies would be perceived as unfair by some patients limited to SET.
5. Embryo selection procedures need to be approached carefully in the context of complete treatment programmes. Processes involving invasive selection may improve fresh cycle rates at the expense of the overall cumulative live birth rate. However, there may be a role for such methods in reducing the number of cycles necessary to achieve a live birth.
6. The present UK policy of requiring clinics to reduce twin rates requires a degree of sophistication in the monitoring process. The number treated in any given centre does not allow for robust auditing or evaluation of policy changes.
7. Clinics will need reliable data to monitor and audit policy and performance. This is likely to require the development of better information systems.

Recommendations for research

1. There is an urgent need for better-quality data that permit the evaluation of complete cycles (fresh plus frozen) and link multiple treatments of the same women. Existing clinical and regulatory database systems do not in practice provide data that can robustly and directly answer the key questions. With such data our conclusions could be confirmed and analyses extended to consider interclinic differences and additional covariates.
2. Research is needed to adapt existing data monitoring tools for use in monitoring twin

- rate targets and provide evaluation tools to clinics and regulators.
3. Some patient antipathy to SET may be amenable to carefully tailored and accurate information that takes account of patients' beliefs and experiences. Surveys are needed to quantify the extent of these beliefs and develop approaches to meeting patients' information needs.
 4. Our methods could readily be extended to consider various embryo selection policies, based on either biomarkers or extended culture. As data become available, further simulation studies would be informative in determining their optimal use.
 5. Ultimately, methods for optimising success rates while reducing twin rates need to be tested in properly designed randomised trials with full treatment end points. Although previous efforts to compare DET with SET in the NHS have failed to recruit, a move towards increased SET provides a unique opportunity to answer these questions.

Key messages

- For any one transfer, SET has about a one-third loss of success rate relative to DET.

- The loss can be only partially mitigated by patient and treatment cycle selection, and criteria may be criticised as unfair: all patients receiving SET will have a lower chance of success than they would with DET.
- If we consider complete cycles (fresh plus frozen transfers), it is possible for repeat SET to produce more live births than repeat DET.
- Such a strategy would require support from funders and acceptance by patients of both cryopreservation and the burden of additional transfer cycles.

Publication

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