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Multiple Pregnancies Following Assisted Conception

This is the second edition of this paper, first published in January 2011 under the same title.

1. Background

Multiple pregnancy, caused by the practice of transferring more than one embryo into the uterus, is the commonest iatrogenic adverse outcome of in vitro fertilisation (IVF). Although preventable to a degree by adopting a policy of elective single embryo transfer (eSET), current rates of multiple pregnancies following IVF remain high. According to data published by the UK Human Fertilisation and Embryology Authority (HFEA), nearly one in five (19.8%) IVF deliveries in the UK in 2011 involved a multiple births. In contrast, the multiple birth rate in Sweden (a country with comparable live birth rates, but a high proportion of eSET) during the same period was 4.9%.

High IVF multiple birth rates have also been reported across Europe and the USA. The European IVF-Monitoring Consortium reported a 19.2% multiple birth rate after fresh IVF treatment in 2011. In the USA, data published by the Centers for Disease Control and Prevention (CDC) showed that approximately 46% infants born in 2011 following assisted conception were either twins or higher order multiples.

The inexorable rise in the multiple pregnancy rate resulting from the use of assisted reproductive technology (ART), has led to many publications highlighting the significant maternal, fetal and neonatal risks associated with these pregnancies. Maternal complications include increased risk of pregnancy-induced hypertension, gestational diabetes, peripartum haemorrhage, operative delivery and postpartum depression. Multiple pregnancy is also associated with a six-fold increase in the risk of preterm birth, which is a leading cause of infant mortality and long-term mental and physical disabilities, including cerebral palsy, learning difficulties and chronic lung disease. According to the CDC, in the USA 39.7% of ART-conceived infants in 2013 were born either preterm (less than 37 weeks of gestation) or very preterm (less than 32 weeks of gestation). The cost of care for children born prematurely as a result of multiple births is also considerable. According to one study, the estimated neonatal cost to the NHS for a twin is 16 times higher than that for a singleton baby.

This paper describes current knowledge and progress made to date, since the publication of the previous edition, to reduce multiple pregnancies following assisted reproduction in the UK.

2. Why is the multiple pregnancy rate high and how can it be reduced?

Despite the substantial risks associated with multiple pregnancy, double embryo transfer (DET) during IVF treatment continues to be widely practiced. Variation in IVF regulation worldwide has resulted in significant differences in embryo transfer practices between countries. Until recently in the UK, the HFEA published the live birth rate per fresh IVF cycle started rather than the cumulative outcome of the fresh IVF cycle and its related frozen cycle(s). Competition among IVF clinics, many of which are in the private sector, meant that the perceived reputation...
of the clinic became closely related to its success rate per fresh IVF cycle. This competitive environment led to the development of so-called ‘league tables’ for IVF clinics.

Patients and health professionals alike often hold an understanding that the success rate of IVF treatment is higher following the transfer of two embryos rather than one embryo, thus overriding safety concerns regarding twin pregnancies.\(^\text{17,18}\) This perception is in contrast to published literature,\(^\text{19,20}\) which has clearly demonstrated that the cumulative live birth rate after eSET, followed by the transfer of a thawed embryo in a subsequent frozen embryo transfer cycle is comparable to that after DET, but with a significantly lower risk of multiple pregnancy.

To encourage eSET, several methods have been studied\(^\text{21-23}\) to help identify the embryo with the highest implantation potential, such as blastocyst culture, preimplantation genetic screening and time-lapse imaging, in order to eliminate the gap in pregnancy rates between eSET and DET, while minimising the risk of multiple pregnancy.

Strategies for patient education about the advantages of eSET can be more effective when combined with favourable IVF funding policies that support access to several fresh and frozen IVF cycles. International experience indicates that the uptake of eSET is closely related to access to IVF state funding. In Europe, countries with higher rates of eSET, such as Belgium, Norway and Denmark, have generous IVF state funding arrangements.\(^\text{15}\) Likewise, a study by Velez et al.\(^\text{24}\) showed that the implementation of public funding of IVF in the state of Quebec in Canada resulted in a significant rise in the eSET rate from 1.6% to 31.6% \((P < 0.001)\) within 1 year. As a result, the multiple pregnancy rate fell from 29.4% to 6.4% \((P < 0.001)\) within the same period.

### 3. Progress towards reducing multiple pregnancy rates in the UK

In the UK, the HFEA has recognised the need for a change in IVF practices to curb the soaring numbers of multiple pregnancies following IVF treatment. The Expert Group on Multiple Births after IVF was formed, chaired by Professor P Braude, who were commissioned to produce a report, which was published in October 2006, entitled ‘One child at a time’.\(^\text{25}\) Along with the publication of the British Fertility Society and the Association of Clinical Embryologists practice guidelines,\(^\text{26}\) these have formed the basis for the HFEA strategy for setting a maximum multiple birth rate for IVF clinics to meet.

After careful consideration, and working closely with IVF clinics, professional bodies, patient groups and National Health Service (NHS) commissioners, the HFEA set a maximum multiple birth rate target for clinics, which started at a modest 24% in 2009 and reduced gradually over 4 years to no more than 10% of all live births. In order to achieve the maximum target for multiple births, IVF clinics were requested to develop their own ‘multiple birth minimisation strategy’. A series of HFEA workshops were initiated aimed at reducing multiple births and promoting eSET facilitated sharing of experiences, review of minimisation strategies and dissemination of best practice among IVF clinics. In effect, this model combined a regulatory framework with clinician autonomy in deciding who could benefit from eSET, and identifying those for whom the clinical situation deemed that transferring more than one embryo would be appropriate.

As a whole, IVF clinics embraced the new strategy and made significant progress in terms of reducing DET and increasing eSET rates by 2014. Compared with 2008, the eSET rate has increased from less than 5% to almost 29% (Table 1). Importantly, in the year ending 2014 the
eSET rate reached 38% in women below 35 years of age, the group who are considered at the highest risk of multiple pregnancy.\textsuperscript{27,28} This substantial rise in the eSET rate has been associated with improvement in laboratory techniques as a means of better embryo selection. In addition, many, albeit not all, NHS commissioners moved to include funding for the frozen cycles to further encourage the practice of eSET, thus bringing the definition of a ‘full IVF cycle’ in line with the current National Institute for Health and Care Excellence (NICE) guidance on infertility treatment.\textsuperscript{29}

Table 1 Trends in eSET, pregnancy and multiple pregnancy rates from IVF, UK HFEA data 2008–14\textsuperscript{28}

<table>
<thead>
<tr>
<th></th>
<th>2008</th>
<th>2011</th>
<th>2014</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportion of all embryo transfers by number of embryos transferred (eSET/DET)</td>
<td>4.9%/78.4%</td>
<td>16.8%/60.2%</td>
<td>28.7%/48.2%</td>
</tr>
<tr>
<td>Overall multiple pregnancy rate for IVF treatment cycles</td>
<td>26.6%</td>
<td>20.6%</td>
<td>15.9%</td>
</tr>
<tr>
<td>Overall pregnancy rate per embryo transfer for IVF treatment cycles</td>
<td>30%</td>
<td>33.8%</td>
<td>36.3%</td>
</tr>
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</table>

As a result of these collective efforts, the UK has seen a consistent decline in the multiple pregnancy rate after IVF treatment from 26.6% in 2008 to 15.9% by mid-2014, a relative reduction of 40% (Table 1).\textsuperscript{28} With advances in clinical and laboratory procedures leading to improved embryo selection techniques, and greater experience in identifying women who are most suitable for eSET, the decline in the multiple pregnancy rate has been accompanied by a modest, but important, increase in the overall pregnancy rate per cycle from 30% in 2008 to 36.3% in 2014, allaying fears that the rise in eSET rate could compromise the success of IVF treatment (Table 1).\textsuperscript{28}

4. Opinion

Multiple pregnancy is the greatest avoidable risk of IVF. The health and financial burdens it places on families and the NHS cannot be overstated. There is incontrovertible evidence that over the last 5 years, progress has been made to control the escalating rate of multiple pregnancy after IVF treatment. The reduction in the multiple pregnancy rate has been achieved through a combination of statutory regulation, cooperation of clinicians and patient education to develop a successful strategy to reduce multiple pregnancies without a concomitant reduction in the pregnancy rate.

It is also clear from the experience of other countries, such as Sweden and Belgium, that further reduction in the multiple pregnancy rate to single figures is feasible. So, what should be done to reach this target?

Clearly, there needs to be wider application of eSET based on continued refinement of laboratory conditions and techniques to allow selection of a single developmentally competent embryo more easily. Organisations, including the HFEA, British Fertility Society, Royal College of Obstetricians and Gynaecologists, Association of Clinical Embryologists, Twins and Multiple Births Association and Multiple Births Foundation among others, should continue to work
closely in conjunction with patient groups, to promote and disseminate best practice and encourage the application of eSET to all good prognosis patients below the age of 40 years, which is the patient group at greatest risk of multiple pregnancy after DET.

Although the HFEA has removed the maximum multiple birth rate of 10% as a licence condition for IVF centres, the proposals to change the way IVF clinics results are published by the HFEA are anticipated to promote eSET, through placing greater emphasis on the cumulative pregnancy rate after each IVF cycle, including pregnancies resulting from fresh as well as frozen embryo transfers.\(^3\) It is encouraging that the HFEA now publishes the live birth rate per embryo transferred to promote the transfer of fewer embryos, and that further steps towards linking the outcome between fresh and the related frozen cycles should follow soon.

However, there is little doubt that the single most important factor that could enhance the acceptance of eSET among patients and practitioners is the provision of appropriate government funding for IVF treatment, which still falls short of what is required, such that six out of ten IVF cycles in the UK are currently funded by the patients themselves. Full implementation of the 2013 NICE guideline on management of the infertile couple,\(^2\) which recommended government funding for three full IVF cycles (including the related frozen transfer cycles), would provide a greater incentive for IVF centres and patients alike to adopt eSET more freely. Therefore, developing a far-sighted equitable national commissioning policy is needed to remove the current variation in IVF funding around the country and significantly increase the uptake of eSET to realise the potential gains to maternal, neonatal and child health, and the national economic advantage of reducing multiple pregnancies after IVF treatment.

References


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