Institution: University of Aberdeen

Unit of Assessment: 2 - Public Health, Health Services and Primary Care

Title of case study: Making *in-vitro* fertilisation (IVF) safer: a strategy of elective single embryo transfer to minimise the risk of perinatal complications associated with multiple pregnancy

1. Summary of the impact

Multiple births following *in-vitro* fertilisation (IVF) treatment leads to serious health risks in the mother and offspring. It is caused by replacing multiple embryos within the uterus. Concerns about reduced success rates have deterred patients and practitioners from transplanting a single embryo. A programme of research led from the University of Aberdeen established that a policy of replacing one embryo at a time minimises the risk of twins without compromising livebirth rates. This work has received international media coverage, influenced clinical guidance and resulted in an increased uptake of single embryo transfer in the United Kingdom and beyond.

The claimed impact, as defined by REF guidance, is therefore on *public policy and services; practitioners and professional services* and *health and welfare.*

2. Underpinning research

Researchers from the University of Aberdeen have led a programme of research on single embryo transfer in IVF since 2002. The work has been led by Siladitya Bhattacharya (Senior Lecturer/Professor from 2000) together with Zabeena Pandian (Research Fellow, 2001-3), Allan Templeton (Professor, 1985 – 2011), Graham Scotland (Senior Research Fellow, 2004-date), Abha Maheshwari (Clinical Senior Lecturer, 2010-13) and David McLernon (Research Fellow, 2008-date). The research has been funded by Wellcome Trust and the Chief Scientist Office for Scotland. Initial work involved exploring patient and service providers' views on risks of multiple pregnancy in IVF and the level of equipoise regarding a strategy of elective single (eSET) versus double embryo transfer [1]. This was accompanied by a Cochrane review of randomised trials of eSET versus double embryo transfer in IVF [2] conducted by the Aberdeen group and a widely cited updated version of this review published in 2005 [3]. Pooled results showed that multiple pregnancy rates were significantly higher following transfer of two embryos. Although double embryo transfer led to a higher live birth rate in a single fresh IVF treatment in a fresh IVF cycle, comparable results were obtained by subsequent transfer of a frozen embryo.

Dr McLernon and Professor Bhattacharya subsequently conducted an individual patient data (IPD) meta-analysis [4] of all randomised trials (including unpublished data from two additional trials in the United Kingdom and Australia). This individual patient meta-analysis included data on more than 1300 women. This study showed that eSET in a fresh IVF cycle (even without the need for an additional frozen embryo) resulted in a 5-fold increase in the odds of having a healthy baby (i.e. a singleton baby after 37 weeks) in comparison with double embryo transfer (odds ratio 4.93, 95% confidence intervals 2.98 to 8.18) [4].

Further research conducted by the Aberdeen researchers [5] used data from Scottish IVF units to model the cost effectiveness of eSET and double embryo transfer in women of different age groups with varying prognoses for livebirth. The results demonstrated that eSET was particularly useful in younger women but not in those who were older and/or had a poorer chance of achieving pregnancy through IVF. Finally, a systematic review of worldwide implementation of eSET conducted by the Aberdeen researchers provided much needed data on why certain countries were able to use eSET successfully in order to reduce IVF risks without compromising livebirth rates [6] but not others. This study also identified the personal, organisational and societal barriers to the uptake of an eSET policy and provided information relevant to patients, clinicians, regulators and policy makers.

In summary, University of Aberdeen researchers led the first systematic review and meta-analysis

of eSET versus double embryo transfer. They led the only individual patient data meta-analysis ever undertaken in this field. They were also the first and only group to model the cost effectiveness of an individualised age-based policy of eSET. Finally the Aberdeen team have explored factors affecting the global uptake of eSET - the output of which has informed guideline development groups in other countries.

3. References to the research

[1] Porter M, Bhattacharya S. Investigation of staff and patients' opinions of a proposed trial of elective single embryo transfer. Human Reproduction (2005); 20(9): 2523 - 2530.
Paper by two Aberdeen researchers exploring attitudes to single embryo transfer and levels of equipoise as regards a proposed randomised trial of this policy versus double embryo transfer in IVF.

[2] Pandian Z, Bhattacharya S, Ozturk O, Serour GI, Templeton A. Number of embryos for transfer following in-vitro fertilisation or intra-cytoplasmic sperm injection. Cochrane Database Syst Rev. 2004 Oct 18;(4):CD003416.
Initial Cochrane review of aggregated data from published trials showing significantly lower twin rate but also reduced livebirth rate after eSET. First, second, third and last author are from Aberdeen. (Cited 103 times, Google Scholar at 12/8/13).

[3] Pandian Z, Templeton A, Serour G, Bhattacharya, S. Number of embryos for transfer after in-vitro fertilisation and intra-cytoplasmic sperm injection: a systematic review. Human Reproduction (2005); 20 910): 2681 - 2687.
Paper publication based on updated Cochrane review by the same group of authors, which included a new trial showing that cumulative live birth rates following fresh + frozen single embryo transfer are similar to those after double embryo transfer. (Cited 127 times, Google Scholar at 12/8/13)

[4] McLernon DJ, Harrild K, Bergh C, Davies MJ, de Neubourg D, Dumoulin JCM, Gerris J, Kremer JAM, Martikainen H, Mol BW, Norman RJ, Thurin-Kjellberg A, Tiitinen A, van Montfoort APA, van Peperstraten AM, van Royen E, Bhattacharya S. Clinical effectiveness of elective single versus double embryo transfer: meta-analysis of individual patient data from randomised trials. BMJ. 2010;341:c6945.
Most comprehensive systematic review undertaken in the field to date. The review included individual data meta-analysis based on all published and unpublished randomised trials. It showed that eSET led to a fivefold increase in the odds of having a single baby born at term. The first and last authors from Aberdeen; the secretariat for handling all data was based in Aberdeen; and all methodological work was undertaken in Aberdeen. The results were widely publicised by the media /professional organisations and were influential in converting increased numbers of stakeholders to eSET. (Cited 67 *times, Google Scholar at 12/8/13)*

[5] Scotland G, McLernon D, Kurinczuk J, McNamee P, Harrild K, Lyall H, Rajkhowa M, Hamilton M, Bhattacharya S. Minimising twins in in-vitro fertilisation: a modelling study assessing the costs, consequences and cost-utility of elective single versus double embryo transfer over a 20-year time horizon. BJOG. 2011; 118(9):1073-1083.
Study using Scottish IVF data to model cost effectiveness of single and double embryo transfer policies. First, second and last author (CI) were from Aberdeen, where all the analysis and methodological work was done. This was the first study to investigate fertility outcomes in different age groups of women in terms of QALYs. The study was quoted by NICE in its fertility guideline in the context of recommendations on number of embryos to transfer in IVF.

[6] Maheshwari A, Griffiths S, Bhattacharya S. Global variations in the update of single embryo transfer. Human Reproduction Update. 2010; 17(1):107-120.
All authors based in Aberdeen. First and only study to describe global uptake of eSET and explored barriers to wider implementation of this strategy.

Key grant funding associated with the research (which all underwent rigorous peer review):

- Effective treatment of Infertility. Research Leave Award. Bhattacharya S. Wellcome Trust (2002) £775,757.
- ECOSSE: Efficacy and cost effectiveness of selective single embryo transfer. Bhattacharya S, Templeton A, Harrold, A, Lieberman B, Brison D, Gazvani R, Braude P. Bertarelli Foundation. CHF (2004) £240,030.
- Clinical and Cost-Effectiveness of Elective Single Embryo versus Double Embryo Transfer Policy in Assisted Reproduction. Bhattacharya S, Scotland G, Harrild K, Rajkhowa M, Harold A, Lyall H. Chief Scientist Office for Scotland (2008-9) £45,638.

4. Details of the impact

The results of this research programme have demonstrated that, in younger women undergoing IVF replacing one embryo at a time (ie. eSET), results in livebirth rates are comparable to the usual policy of double embryo transfer. This research also established that eSET leads to higher rates of term singleton liveborn babies i.e. healthy babies in comparison with double embryo transfer.

The Aberdeen research group's Cochrane systematic review [2] and subsequent print publication [3] was influential in informing policy within the United Kingdom, where the Human Fertilisation and Embryology Authority (HFEA) - the IVF regulatory body for the UK - set up an expert group to advise on Multiple Births after IVF. This Group referenced the Aberdeen review in its recommendation, which advised eSET (with transfer of a second frozen embryo) and set targets for twin rates after IVF [a]. This resulted in an increase in the uptake of eSET from 4.8% in 2008 to 14.7% in 2010 and a corresponding decrease in multiple pregnancy rates [b]. The implementation of eSET has been particularly noticeable in younger women who have the best chance of achieving a livebirth, but the overall success rate has not been affected as a consequence of this policy.

Although the results of the initial Cochrane systematic review led to a degree of change in the IVF sector, many practitioners remained unconvinced until the publication of the individual patient data meta-analysis of all relevant randomised trials [4]. This meta-analysis showed that eSET in a fresh IVF treatment cycle (without an additional frozen embryo replacement) resulted in a higher chance of a single healthy baby (live baby born at full term). This work was widely publicised by the national and international media, the NHS and the global professional organisation for Obstetricians and Gynaecologists [c,d,e] and highlighted by the HFEA on its website [a]. It was also promoted by the "One at a time" website - a professionally-led website in the UK aimed at reducing the risks of multiple pregnancies associated with fertility treatment. This meta-analysis was also cited in the updated NICE guideline [f] on infertility published in 2013 as clear evidence of the benefit of eSET to mothers and their babies. Along with the paper from the Aberdeen group on the cost effectiveness of alternative embryo transfer strategies (eSET versus DET) in IVF in women of different ages, it also served to inform NICE guidance on selective use of eSET in women of different ages [f]. In the UK, the impact of the research directly and indirectly through HFEA recommendations is evident from national data published by HFEA [b]. Between 2008 and 2011, HFEA data show that rates of eSET have increased from 4% to 18% (25% in women aged 18-34 years) in all IVF cycles in the UK and twin rates have fallen from 27% to just under 20% [a,b]. There is no evidence of any compromise in livebirth rates per IVF treatment in the UK over this period with perhaps even a modest increase from 26% to 32%.

Results of the Aberdeen research group's individual patient data meta-analysis on eSET, which included data from over 1300 women, has also informed clinical guidelines on IVF embryo transfer policies internationally in countries such as Canada and South Africa [g,h]. Most recently, the United States, which has also used our research as evidence to inform its eSET policy [i] has also witnessed an increase in eSET in women under 35 years of age - from 4.5% in 2007 to 11.75% in 2011 [j].

In summary, the initial impact in the UK occurred just after the Cochrane review and received a further boost after the publication of the IPD meta-analysis and health economic papers prompting

policy changes within the regulators, HFEA, [a] and NICE [f]. Countries more initially resistant to eSET (Canada, South Africa and USA) have now developed guidance [g,h,i] and have cited the Aberdeen work. The effects of these more recent changes on international guidance on eSET are already apparent with evidence continuing to accrue.

The claimed impact as defined by REF guidance is, therefore on *public policy and services; practitioners and professional services* and *health and welfare* in the UK and internationally.

5. Sources to corroborate the impact

[a] http://www.hfea.gov.uk/6211.html
This is the Human Fertilisation Embryology Authority website which highlights their expert group on Multiple Births after IVF. This Group referenced the Aberdeen review in their recommendation, which advised elective single embryo transfer (with transfer of a second frozen embryo) and set targets for twin rates after IVF.

[b] http://www.hfea.gov.uk/docs/2011-12-01_-_Multiple_Births_Publication_2011_-_Rationalising_Register_Data_-_FINAL_1.2.DOC.pdf
This report shows the increase in the uptake of eSET from 4.8% in 2008 to 14.7% in 2010 and the corresponding decrease in multiple pregnancy rates.

The three references [c-e] below are examples of the extensive media coverage of Aberdeen's large individual data meta-analysis showing that single embryo transfer led to a fivefold increase in the odds of having a single baby born at term:
[c] http://www.guardian.co.uk/society/2010/dec/22/ivf-researchers-single-embryo-treatment

[d] http://abcnews.go.com/Health/WomensHealth/single-embryo-transfer-effective-safer-double-embryo-transfer/story?id=12451473

[e] http://www.figo.org/news/single-embryo-transfer-ivf-increases-chance-delivering-full-term-baby-003151

[f] http://guidance.nice.org.uk/CG156/Guidance
This is the NICE guidance on the management of infertility, published in 2013. It cites the Aberdeen research as clear evidence of the benefit of eSET to mothers and their babies.

[g] Min JK, Hughes E, Young D, Gysler M, Hemmings R, Cheung AP, Goodrow GJ, Senikas V, Wong BC, Sierra S, Carranza-Mamane B, Case A, Dwyer C, Graham J, Havelock J, Lee F, Liu K, Vause T; Joint Society of Obstetricians and Gynaecologists of Canada-Canadian Fertility and Andrology Society Clinical Practice Guidelines Committee. Elective single embryo transfer following in vitro fertilization. J Obstet Gynaecol Can. 2010 Apr;32(4):363-77.
This summarises Canada's guidance on the management of infertility and cites the Aberdeen research as evidence of benefit of eSET.

[h] http://www.fertilitysa.org.za/Guidelines/ReproductiveMedicine/SASREGEmbryoTransferRecommendations.asp
This summarises South Africa's guidance on the management of infertility and cites the Aberdeen research as evidence of benefit of eSET.

[i] Elective single embryo transfer. Practice Committee of the Society for Assisted Reproduction and Practice Committee of American Society for Reproductive Medicine. Fertility and Sterility 2012; 97:835-42
This summarises the US guidance on the management of infertility and cites the Aberdeen research as evidence of benefit of eSET.

[j] http://www.sart.org/frame/detail.aspx?id=3893
This reports US registry data on eSET and shows an increase in eSET in women under 35 years of age from 4.5% in 2007 to 11.75% in 2011.