Institution: University of Glasgow

Unit of Assessment: Unit 1; Clinical Medicine

Title of case study: Personalisation of in-vitro fertilisation therapy

1. Summary of the impact

The ultimate goal of in-vitro fertilisation (IVF) therapy is the live birth of a single, healthy child. However, issues of treatment failure, complications and multiple births (twins or triplets) continue to persist and have a major impact on patient quality of life. Pioneering research at the University of Glasgow has driven the concept of personalised IVF therapy and outcome prediction, reforming clinical guidelines and defining criteria for access to funded IVF therapy. This research has stimulated revision of UK regulatory policy on the number of embryos transferred during IVF. These strategies underpin the recommended practice for the 48,000 women undergoing IVF in the UK each year. In addition, the Glasgow team's online, personalised 'IVFpredict' calculator, which women can use to predict their success of a live birth, has been completed by more than 5 million users worldwide.

2. Underpinning research

The process of in-vitro fertilisation (IVF) has revolutionised human reproductive biology since it was first successfully performed in the 1970s, allowing many thousands of women with reduced fertility to conceive. Women undergoing IVF first receive drugs to stimulate ovulation, the process by which eggs are released from specialised structures (follicles) in the ovary. One or more eggs are then harvested in the clinic, fertilised by sperm outside the body and grown under laboratory conditions to establish viable embryos. These embryos are transferred to the patient's uterus with the aim of establishing a normal pregnancy.

Development of IVFpredict, a personalised predictor of IVF outcome success

Collaborative work between University of Glasgow clinical researcher Professor Scott Nelson and Professor Debbie Lawlor (University of Bristol) led to the development of a model that predicts live birth outcome following IVF treatment. Published in 2011, this carefully designed research involved a prospective analysis of data collected by the UK independent IVF regulatory body, the Human Fertilisation and Embryology Authority (HFEA), on all IVF treatment cycles (163,425) and outcomes in the UK from 2003 to 2007.[1] The resultant model offered substantial advances upon other predictor models with improved calibration, inclusion of updated clinical techniques and data on the use of donor eggs, IVF cycle number and previous successful live birth history. Consequently, the ability to predict live births using couple-specific and treatment-specific factors was significantly improved. Nelson and Lawlor subsequently named the model 'IVFpredict' and Nelson developed an IVFpredict website with Dr Tom Kelsey (University of St Andrews) in 2011.

Transfer of three embryos does not improve outcomes in any maternal age group

The number of embryos transferred into the uterus during IVF therapy can affect the success of the pregnancy. An extension of the above-mentioned 2011 study used the same dataset to analyse more than 124,000 IVF cycles, yielding vital information on outcomes with the additional prognostic indicator of maternal age. Results showed that overall, live births are more likely to occur among women aged under 40 years than those aged 40 years or above, regardless of the number of embryos transferred. Nevertheless, the analysis revealed that the transfer of three embryos does not result in a higher live birth rate in either age group compared with the transfer of two embryos; in fact, transfer of three embryos was associated with a significantly increased risk of adverse outcomes (multiple births, preterm birth and low birth weight). As a result, Nelson and Lawlor's findings advised against the transfer of three embryos for women of all ages undergoing IVF therapy.[2] Nelson and Lawlor provided equal contributions to this study which was published in *The Lancet* in 2012.

Anti-Müllerian hormone as a biomarker to stratify patients for IVF therapy

A pioneering research project conducted by Nelson and fellow University of Glasgow researcher Professor Richard Fleming revealed that the outcome of IVF could be predicted before treatment

was started by measuring the concentration of anti-Müllerian hormone (AMH) in the blood. AMH is produced by growing follicles and levels of this hormone are indicative of the magnitude of a woman's remaining supply of eggs. Nelson and Fleming (2007) analysed blood AMH levels among 340 women and found a strong positive correlation between this measure and the woman's subsequent response to ovarian stimulation and her live birth rate.[3] Notably, AMH was shown to be a sufficiently sensitive predictor that it could identify the risk of either an excessive ovarian response (ovarian hyperstimulation syndrome; OHSS) or a poor response to treatment. The effectiveness of personalised treatment regimens designed according to AMH levels was validated in 2009.[4] This study showed that women in the 'excessive response' category (AMH level greater than 15 pmol/L) who received conventional IVF treatment had a pregnancy rate of 40% (with a 20% rate of hospitalisation for OHSS). By contrast, women using personalised IVF protocols experienced a shorter duration of treatment, but with significantly greater pregnancy rates (more than 60%) and no OHSS-related hospital admissions. These results were followed by the development of a commercially-available AMH assay (AMH Gen II) in 2011.[5]

Key University of Glasgow researchers: Scott Nelson (Clinical Lecturer [2005–2008], Muirhead Chair of Reproductive and Maternal Medicine [2008–present]); Richard Fleming (Honorary Professor of Reproductive Medicine, 2006–present).
Key external collaborators: Professor Debbie Lawlor (Professor of Epidemiology, University of Bristol);[1,2] Tom Kelsey (Senior Lecturer, University of St Andrews);[1,2] Dr Sherry Faye (Beckman Coulter UK Ltd., High Wycombe).[5]

3. References to the research

1. Nelson S. M. & Lawlor D. A. Predicting live birth, preterm delivery, and low birth weight in infants born from in vitro fertilisation: a prospective study of 144,018 treatment cycles. *PLoS Med* 2011; 8: e1000386 doi:10.1371/journal.pmed.1000386.
2. Lawlor D. A. & Nelson S. M. Effect of age on decisions about the numbers of embryos to transfer in assisted conception: a prospective study. *Lancet* 2012; 379: 521–527 doi:10.1016/S0140-6736(11)61267-1.
3. Nelson S. M. *et al.* Serum anti-Müllerian hormone and FSH: prediction of live birth and extremes of response in stimulated cycles – implications for individualization of therapy. *Hum. Reprod.* 2007; 22: 2414–2421 doi:10.1093/humrep/dem204.
4. Nelson S. M. *et al.* Anti-Müllerian hormone-based approach to controlled ovarian stimulation for assisted conception. *Hum. Reprod.* 2009; 24: 867–875 doi:10.1093/humrep/den480.
5. Wallace A. M. *et al.* A multicentre evaluation of the new Beckman Coulter anti-Müllerian hormone immunoassay (AMH Gen II). *Ann. Clin. Biochem.* 2011; 48: 370–373 doi:10.1258/acb.2011.010172

4. Details of the impact

IVFpredict informs National Institute for Health and Care Excellence (NICE) guidelines on fertility

Improved prediction of IVF success allows women to be better informed about the procedure, as well as to cope with emotional pressures and the demanding treatment regimens. The IVFpredict model was used to develop best practice on prediction of IVF success and provision of patient information in the NICE "*Fertility: assessment and treatment for people with fertility problems*" guidelines published in February 2013.[a] Nelson acted as external advisor during the development of these guidelines. In Chapter 13, "*Prediction of IVF success*", Nelson's 2011 *PLoS Medicine* paper[1] was cited as one of four studies used to define the factors that predict live birth success from IVF therapy, which underpin recommendations 120–122 of the guidelines:

- Recommendation 120: *"Inform women that the chance of a live birth following IVF treatment falls with rising female age."*
- Recommendation 121: *"Inform people that the overall chance of a live birth following IVF treatment falls as the number of unsuccessful cycles increases."*
- Recommendation 122: *"People should be informed that IVF treatment is more effective in women who have previously been pregnant and/or had a live birth."*

A great deal of controversy exists surrounding which groups of women should be eligible to receive

NHS-funded IVF treatment. Chapter 14 of the NICE guidelines, "*Access criteria for IVF*", used the IVFpredict model as one of two calculators to develop the NICE economic costing model, which produced recommendations for access to NHS-funded IVF for women aged 23–39 years. The model defined estimates of IVF costs by age and treatment strategy. Furthermore, a total of 198 patient scenarios, modelled for cost-effectiveness, are provided in the guideline appendix, thereby providing a detailed reference for clinical decisions on access to free treatment.[b]

Stimulating HFEA policy debate on embryo transfer number

The most significant risk of IVF therapy is the high probability of multiple births, which is associated with increased rates of miscarriage, premature birth, low birth weight and perinatal mortality (infant death immediately before or after birth). Approximately 20–30% of all IVF pregnancies are multiple births, resulting from the transfer of multiple embryos during treatment (intended to increase the chance of a successful pregnancy). HFEA imposes strict multiple birth targets on all licenced IVF centres in the UK (set at 10% in October 2012), permitting the transfer of three embryos only to women above 40 years (since 2009). Shortly after the publication of Nelson and Lawlor's 2012 *Lancet* paper,[2] HFEA released a public statement acknowledging the value of their findings,[c] which were subsequently reviewed by the HFEA Multiple Birth Stakeholder Group and brought to the attention of the HFEA Authority – the overarching committee determining HFEA Code of Practice for IVF unit regulation – at their June 2013 meeting. Key findings and data from Nelson and Lawlor's 2012 *Lancet* paper[2] were presented at this meeting and consequently members agreed the following decision to:

> *"Develop guidance for the Code of Practice which discouraged centres from carrying out three-embryo transfers"* (recorded in the meeting minutes, 9.11, page 11)[d]

The revised HEFA Code of Conduct came into force on 1 October 2013.

According to 2011 data, around 48,000 women undergo IVF in the UK each year. Through influencing the development of evidence-based clinical guidelines and stimulating revision to regulatory codes of practice, University of Glasgow research has contributed to recommendations on information and clinical treatment delivered to patients, and defined the criteria for access to NHS-funded IVF therapy for all patients in the UK.

IVFpredict helps patients to understand their options and manage expectations

The freely-available online IVFpredict calculator is a simple questionnaire (nine questions) providing women with rapid (approximately 1 minute), accurate, evidence-based estimates of their percentage chance of having a successful pregnancy and live birth following IVF treatment. Armed with this information, women can make informed treatment choices and have realistic expectations of the outcome. The questionnaire is also available via a smartphone application (at a small cost).[f] Shortly after its release online in January 2011, IVFpredict received extensive media coverage and promotion both nationally and worldwide, including a 5-minute feature on ABC News in the USA (May 2011).[g] Since then, more than 5 million individuals have accessed the IVFpredict website (predominantly from Europe [39%], North America [24%] and Asia [19%]), according to site traffic data), and over 700 people have purchased the IVFPredict app providing them with a simple and accessible way to obtain information about their treatment choices and outcomes.[h]

Recognition of the University of Glasgow work on personalised IVF

The impacts described above formed the basis of a University of Glasgow submission to the Times Higher Education 'Research Project of the Year' awards (a category showcasing '*significant economic, social, cultural or other public benefit*') and was one of only six entries shortlisted. The awards recognise '*the excellence and amazing achievements of UK higher education institutions'* (winner to be announced on 28 November 2013).[i]

Influencing patient access and prioritisation of IVF therapy

University of Glasgow researchers were the first in the world to demonstrate that AMH levels could predict ovarian response before commencement of IVF therapy. This strategy has rapidly become recognised as a leading mechanism by which to classify patients for treatment. The AMH Gen II

assay was subsequently developed by Beckman Coulter, a multinational company supporting innovations in biomedical testing. The EMEAI Scientific Manager Immunoassay, Beckman Coulter UK Ltd.,[j] states: "*The measurement of anti-Müllerian hormone (AMH) is just starting to become accepted into routine clinical practice in fertility centres throughout the world. Professor Nelson's work has clearly established the benefit of the measurement of AMH in this setting by demonstrating that use of AMH levels to individualise therapy results in increased pregnancy rates and reduced complications*." Before any new diagnostic test can become established in the healthcare pathway, clear evidence is required that it both improves patient outcomes and reduces the cost of care. University of Glasgow research enabled Beckman Coulter to establish this evidence base for the AMH Gen II assay and Nelson's published papers are used as key proof and guidance for healthcare workers who are unfamiliar with the use of the assay. As such, "*it is integral to and underpins our whole marketing strategy which has resulted in the transition of the measurement of AMH from a research tool into routine clinical practice. AMH is a premium product for Beckman Coulter and one of our flagship immunoassays – European sales have trebled from 2008 to 2009*."

The University of Glasgow research also formed the evidence basis for inclusion of an AMH criterion in the NHS Scotland Pre-Implantation Genetic Diagnosis and Screening Service framework (2011)[j] and has therefore been instrumental in the access decisions and prioritisation of women for IVF therapy across Scotland. As a consequence, all women in Scotland are required to meet a threshold level of circulating AMH levels (of greater than 6 pmol/L) in order to be referred for IVF treatment.

5. Sources to corroborate the impact

a. NICE CG156 "*Fertility: assessment and treatment for people with fertility problems*" guidelines, February 2013. Chapter 13 (p224); Chapter 14 (*Access criteria to IVF*, p237); recommendations 120, 121 and 122 (p230–231)
b. NICE CG156 Appendix M – Cost-effective treatment of IVF analyses
c. HFEA 'Statement on embryo transfer study', 12 January 2012
d. HFEA Authority meeting 13 June 2013, Multiple Births update
e. HFEA Minutes of Authority meeting, 13 June 2013. Sections 9.7 and 9.11 (p11)
f. IVFpredict website including link to IVFpredict app
g. Examples of media coverage of IVFpredict:
   • UK: The Daily Mail, 5 January, 2011(article)
   • USA: ABC News, 1 May, 2011 (video clip)
   • Australia: ABC radio interview with Professor Scott Nelson, 15 August, 2011(recording)
h. IVFpredict website download data – available on request
i. The Times Higher Research Project of the Year Shortlist, 2013
j. Statement from EMEAI Scientific Manager Immunoassay, Beckman Coulter UK Ltd. – available on request
k. NHS Scotland National Services Division guidelines, "*A Framework for Decision Making for the Scottish Pre-Implantation Genetic Diagnosis and Screening Service*", April 2011 (p12)