Institution: The University of Edinburgh

Unit of Assessment: 1

Title of case study: H: Ovarian cryopreservation can restore fertility in women following cancer treatment that would otherwise irreversibly deny them children

1. Summary of the impact (indicative maximum 100 words)

Impact: Health and welfare; policy and guidelines. Anderson and colleagues demonstrated that cryopreservation of ovarian tissue could be used for preservation of fertility following cancer therapy. This step-change has been incorporated into guideline documents internationally and has been adopted into clinical practice world-wide.

Significance: Ovarian tissue has been preserved from many hundreds of women; this is now translating into a growing number of babies born worldwide (currently 24 in nine countries).

Beneficiaries: Women at risk of fertility loss including pre-pubertal girls newly diagnosed with cancer; clinicians; the NHS and healthcare delivery organisations.

Attribution: The underpinning research was performed entirely at UoE.

Reach: Worldwide: UK, Europe, US, Australia.

2. Underpinning research (indicative maximum 500 words)

Professors Richard Anderson (UoE, 1994–1997, Professor of Clinical Reproductive Science, 2005–present), David Baird (Professor of Reproductive Endocrinology, UoE, 1977–2000; now Emeritus) and W Hamish Wallace (Honorary Professor of Paediatric Oncology, UoE, 2007–present) were the first to show that ovarian tissue obtained laparoscopically could be cryopreserved and used for fertility preservation in the context of cancer therapy; leading ultimately to successful conception. This is a step-change of profound significance to female survivors of cancer therapy who would otherwise face a childless future.

The current use of cryopreservation of ovarian tissue to restore fertility in women following cancer can be traced directly to the studies carried out in Edinburgh by Dr Roger Gosden (Reader in Physiology, UoE, 1976–1994), Baird and colleagues using sheep as a model for human ovarian function. The first publication of this approach in 1994 [3.1] demonstrated that spontaneous ovarian cycles and fertility could be restored by autotransplantation of ovarian cortex. Subsequent studies (1994–1999) by Baird [3.2] investigated the long-term function of frozen/thawed grafts up to 2 years after auto-transplantation, highlighting the survival of primordial oocytes as key to success. This procedure was introduced into clinical practice in Edinburgh in collaboration with the Tissue Services directorate of Scottish National Blood Transfusion Service (SNBTS) in 1997: the first clinical application of this in the world.

Anderson, Baird and Wallace first demonstrated that this procedure using minimally invasive laparoscopic surgery is also appropriate in pre-pubertal girls and introduced this into clinical practice in a research-based programme approach and decade-long case experience described in [3.3, 3.4]. Their approach and criteria for patient selection [3.3, 3.5] set an international standard.

Restoration of fertility by replacement of cryopreserved ovarian tissue is not always appropriate, particularly if there are safety concerns regarding malignant contamination of the tissue. This requires the development of techniques for in vitro growth of early human ovarian follicles, which has been pioneered by Professor Evelyn Telfer (Professor of Reproductive Biology, UoE, 1992–present) and colleagues since 2005 [3.6]. Recent developments have demonstrated that follicles can be grown from primordial stages right through to large antral stages, with oocytes then matured further in vitro to metaphase II of meiosis (i.e., to a stage at which they can be fertilised).

This multi-stage protocol is world-leading (reflected in numerous invitations of the researchers to international meetings) and is being developed further with £610K MRC funding. Safety in all aspects of assisted reproduction remains a key concern: Wallace and colleagues recently demonstrated that children born from assisted conception are not at increased risk of childhood cancer.

3. References to the research (indicative maximum of six references)

3.1 Gosden R, Baird D, Wade J, Webb R. Restoration of fertility to oophorectomized sheep by ovarian autografts stored at -196°C. Hum Reprod. 1994;9:597–603. URL: http://www.humrep.oxfordjournals.org/content/9/4/597.long

3.2 Baird D, Webb R, Campbell B, Harkness L, Gosden R. Long term ovarian function in sheep after ovariectomy and transplantation of autografts stored at -196°C. Endocrinology. 1999;140:462–71. DOI: 10.1210/en.140.1.462.

3.3 Wallace W, Anderson R, Irvine D. Fertility preservation for young patients with cancer: who is at risk and what can be offered? Lancet Oncol. 2005;6:209–18. DOI: 10.1016/S1470-2045(05)70092-9.

3.4 Anderson R, Wallace W, Baird D. Ovarian cryopreservation for fertility preservation: indications and outcomes. Reproduction. 2008;136:681–9. DOI: 10.1530/REP-08-0097.

3.5 Wallace W, Critchley H, Anderson R. Optimizing reproductive outcome in children and young people with cancer. J Clin Oncol. 2012;30:3–5. DOI: 10.1200/JCO.2011.38.3877.

3.6 Telfer E, McLaughlin M, Ding C, Thong K. A two step serum free culture system supports development of human oocytes form primordial follicles in the presence of activin. Hum Reprod. 2008;23:1151–8. DOI: 10.1093/humrep/den070.

Example Grant:

Telfer E, Anderson R, Thong, K. Activation of human ovarian follicles and derivation of competent oocytes. MRC grant G0901839 July 2010 to Oct 2013; £610,000.

4. Details of the impact (indicative maximum 750 words)

Impact on clinical practice

The first clinical application of transplanted frozen ovarian tissue was in Edinburgh in 1993 and this led to an explosion of interest and activity in this field around the world. The first human live birth was reported in 2004 from Belgium [5.1], using a procedure that exactly replicated the one first validated in Edinburgh.

Since 2008, ovarian cryopreservation has become widespread in clinical practice world-wide, and the term ‘oncofertility’ is now in general use to describe this developing clinical specialty, linking fertility preservation and cancer treatment. Major centres of expertise and national programmes operate in Europe (Denmark, Belgium, France, Spain, Israel and Germany) and elsewhere (US, Australia). Ovarian tissue cryopreservation is now regarded as a standard of care in the UK and elsewhere.

Clinical practice recommendations were published by the American Society of Clinical Oncology (and updated in 2013 [5.2]) — on which guideline group Wallace was the only UK representative — and led to the rapid development of the field in the US. Both Anderson and Wallace have been keynote guest speakers at the Oncofertility Consortium, founded in 2008 with funding from the National Institutes of Health to establish US clinical care pathways and promote research in fertility preservation and now covering 50 centres across the US.

While most of the impact has been in adult oncology, prepubertal and adolescent girls have made up approximately one third of the patients for whom ovarian tissue has been stored in Edinburgh and UoE remains the only centre in the UK offering this clinical service. The UoE contribution in paediatric oncology is widely recognised internationally with centres in France and Denmark (and

probably elsewhere) now offering this clinically (e.g., [5.3]) with the team's approach widely adopted as indicated by 347 citations of reference [3.3].

Impact on public policy
Anderson and colleagues' pioneering contribution in this field is recognised in Scottish (Scottish Intercollegiate Guidelines Network (SIGN), 2013), UK (National Institute for Health and Care Excellence, 2013), Europe, and US (American Society for Reproductive Medicine, 2008) guideline documents [5.4–5.6], all of which cite the work of the Edinburgh group. The importance of ovarian cryopreservation in girls is recognised in the current SIGN guidance (2013), which states: 'Cryopreservation of ovarian tissue (within the context of a clinical trial) should be considered in girls at high risk of premature ovarian insufficiency' [5.5].

Anderson and Wallace were instrumental in establishing, and are key members of, the International Society for Fertility Preservation (2009) [5.7] and a task force for fertility preservation by the European Society for Human Reproduction and Embryology (2010) [5.8], whose aims are to develop ovarian tissue cryopreservation for much wider access to women across Europe and worldwide.

In the UK, ovarian tissue storage requires a license from both the Human Tissue Authority and the Human Fertilisation and Embryology Authority (HFEA). The Tissue and Cells Directorate of the Scottish National Blood Transfusion Service in Edinburgh is currently the only tissue bank in the UK with these licenses, although other centres (Oxford, Southampton) are developing this. The UoE team's interactions with the HFEA helped develop the latter's approach.

Impact on health and welfare
The cryopreservation of ovarian tissue has now been performed in many hundreds of women and girls, initially in Europe and subsequently in the USA, Australia and South Africa. Despite the time lag required to ensure survival from their cancer, ovarian tissue has now been replaced in 60 women in three leading European centres (Denmark, Belgium and Spain) and more elsewhere, and has resulted in a rapidly growing number of babies. Twenty-four babies have now been born in nine countries around the world since 2008 (Belgium, Denmark, Spain, Israel, France, Italy, Germany, USA, Australia) [5.9, 5.10] and an increasing number of successful pregnancies and new centres are reported every year.

5. Sources to corroborate the impact (indicative maximum of 10 references)

5.1 Donnez J, Dolmans M, Demylle D, et al. Livebirth after orthotopic transplantation of cryopreserved ovarian tissue. Lancet. 2004;364:1405–10. DOI: 10.1016/S0140-6736(12)61172-6.

5.2 Loren A, Mangu P, Beck L, et al. Fertility preservation for patients with cancer: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol. 2013;31:2500–10. DOI: 10.1200/JCO.2013.49.2678.

5.3 Poirot C, Abirached F, Prades M, Coussieu C, Bernaudin F, Piver P. Induction of puberty by autograft of cryopreserved ovarian tissue. Lancet. 2012;379:588. DOI: 10.1016/S0140-6736(11)61781-9.

5.4 NICE (2013): Assessment and treatment for people with fertility problems. http://www.nice.org.uk/nicemedia/live/14078/62769/62769.pdf. *[Makes fertility preservation part of UK mainstream care (section 1.16).]*

5.5 SIGN 132 (2013). Long term follow up of survivors of childhood cancer. http://www.sign.ac.uk/pdf/sign132.pdf. Summarised by UoE authors in: Wallace W, Thompson L, Anderson R. Long term follow-up of survivors of childhood cancer: summary of updated SIGN guidance. BMJ. 2013;346:f1190. DOI: 10.1136/bmj.f1190.

5.6 American Society for Reproductive Medicine (ASRM Committee Opinion No. 405: ovarian tissue and oocyte cryopreservation; 2008). Fertil Steril. 2008;90:S241–6. DOI: 10.1016/j.fertnstert2008.08.039.

5.7 International Society for Fertility Preservation. http://www.isfp-fertility.org/.

5.8 ESHRE Task Force in Fertility Preservation. http://www.eshre.eu/Specialty-Groups/Task-forces/TF-Fertility-preservation.aspx.

5.9 Monash IVF, Australia (November 2012). “Monash IVF announces first pregnancy in Australia from ovarian tissue freezing”. http://monashivf.com/first-pregnancy-in-australia-from-ovarian-tissue-freezing/.

5.10 Donnez J, Dolmans M, Pellicer A, et al. Restoration of ovarian activity and pregnancy after transplantation of cryopreserved ovarian tissue: a review of 60 cases of reimplantation. Fertil Steril. 2013;99:1503–13. DOI: 10.1016/j.fertnstert2013.03.030.