Institution: The University of Edinburgh		
Unit of Assessment: UoA5 Biological Sciences		
Title of case study: Fertility preservation – informing policy and practice for female and male cancer patients.		
Period when the underpinning research was undertaken: 2008 - 2020		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s):	**Role(s) (e.g. job title):**	**Period(s) employed by submitting HEI:**
Prof Evelyn Telfer	Professor of Reproductive Biology	1992- present
Prof Richard Anderson	Elsie Inglis Professor of Clinical Reproductive Science	2005- present
Prof Hamish Wallace	Consultant Paediatric Oncologist and Honorary Professor	2013- 2014 & 2017- 2020
Dr Rod Mitchell	Reader / Honorary Consultant Paediatric Endocrinologist	2010- present
Period when the claimed impact occurred: Aug 2013- Dec 2020		
Is this case study continued from a case study submitted in 2014? Y/N No		

1. Summary of the impact

Attribution: Research at the University of Edinburgh (UoE) on the preservation and maturation of ovarian and testicular tissue has opened up new possibilities for cancer patients to retain their fertility.

Impact on health & welfare: The NHS and its patients (male and female cancer patients) have benefitted from the opportunity for long-term storage of ovary/testicular tissue. This option is available to patients (via referral from local centre) across the UK.

Specific impacts include:

i) The UK's first birth of a healthy baby following re-implantation of ovarian tissue that was frozen eleven years prior.
ii) Establishment of the UK's first testis cryopreservation service in 2014 for pre-pubertal boys and support of the development of other cryopreservation services in the UK.
iii) Girls and women in the UK and Australia with cancer and their families are counselled on fertility preservation programmes with the research findings in mind.
iv) Development of fertility preservation services in Oxford, UK and Sydney, Australia, based on the NHS Edinburgh Fertility Centre practices, which were developed following Telfer, Anderson and Mitchell's research.

Impact on patient care and policy: Improved patient care through a process of consultation and counselling. Fertility preservation through the cryopreservation of ovarian and testis tissue has been integrated into guideline documents worldwide and been adopted into clinical practice internationally.

Beneficiaries: The NHS, its patients and their families (including male and female cancer patients); clinicians advising cancer survivors on their fertility options; tissue services.

Significance and Reach: Fertility preservation is of huge significance to cancer patients. Initially this impact has been delivered through the NHS to the UK population but has global reach with take-up in the USA (Chicago, Oncofertility Consortium) and Australia (Sydney and Melbourne, FUTuRE Fertility).

2. Underpinning research

Telfer's research focuses on female fertility preservation and in understanding the mechanisms underpinning egg development. Her work on culture systems supporting the development of oocytes [3.1] has led to human immature oocytes being grown to maturity *in vitro* for the first time [3.2]. The development of oocytes entirely *in vitro* opens up possibilities for young patients who are having their ovarian tissue stored now as the culture systems give them more options. Patients who previously would not have considered tissue storage, because of the risks of re-introducing malignant cells after re-implantation, are now choosing to store tissue because of the prospect of developing their immature eggs outside the body. Telfer's work has also demonstrated the differences in oocyte morphology in the pre-pubertal human ovary compared with the adult human ovary, which had been previously unknown [3.3]. Research modelling the number of eggs in the human ovary and age-related decline formed the basis of studies to compare the effect of different chemotherapeutic regimes on the human ovary and potential infertility [3.4].

Mitchell's research on male fertility preservation [3.5] [3.6] focusses on the pre-pubertal testis. His group are developing strategies for removing and storing testis tissue, protocols which are now routine for female fertility preservation based on Telfer's work, from patients prior to potentially sterilizing treatments in order that germ cell development can be achieved using *in vitro* or *in vivo* techniques.

3. References to the research

[3.1] Telfer, EE, McLaughlin, M, Ding, C & Thong, KJ. 2008, 'A two-step serum-free culture system supports development of human oocytes from primordial follicles in the presence of activin' Human Reproduction, vol 23, no. 5, pp. 1151-1158. DOI: https://doi.org/10.1093/humrep/den070

[3.2] McLaughlin, M, Albertini, DF, Wallace, WHB, Anderson, R & Telfer, E 2018, 'Metaphase II oocytes from human unilaminar follicles grown in a multi-step culture system' Molecular Human Reproduction, vol 24, no. 3, pp. 135–142. DOI: https://doi.org/10.1093/molehr/gay002

[3.3] R.A. Anderson, M. McLaughlin, W.H.B. Wallace, D.F. Albertini, E.E. Telfer; 2013 'The immature human ovary shows loss of abnormal follicles and increasing follicle developmental competence through childhood and adolescence', Human Reproduction, Volume 29, Issue 1, 2013, https://doi.org/10.1093/humrep/det388

[3.4] M. McLaughlin, T.W. Kelsey, W.H.B. Wallace, R.A. Anderson, E.E. Telfer; Non-growing follicle density is increased following adriamycin, bleomycin, vinblastine and dacarbazine (ABVD) chemotherapy in the adult human ovary, Human Reproduction, Volume 32, Issue 1, 1 January 2017, Pages 165–174, https://doi.org/10.1093/humrep/dew260

[3.5] Smart E, Lopes F, Rice S, et al. Chemotherapy drugs cyclophosphamide, cisplatin and doxorubicin induce germ cell loss in an in vitro model of the prepubertal testis. Sci Rep 2018; 8:1773, https://doi.org/10.1038/s41598-018-19761-9

[3.6] Anderson RA, Mitchell RT, Kelsey TW, Spears N, Telfer EE, Wallace WH. Cancer treatment and gonadal function: experimental and established strategies for fertility preservation in children and young adults. Lancet Diabetes Endocrinol. 2015 Jul;3(7):556-67, https://doi.org/10.1016/S2213-8587(15)00039-X

4. Details of the impact

Impact on health & welfare:

First baby born in UK following transplant of cryopreserved ovarian tissue in 2016: Transplantation of cryopreserved ovarian tissue is now used worldwide to restore fertility in women rendered infertile following chemotherapy and over 200 babies have been born following this procedure. Edinburgh's research and clinical team performed an ovarian transplant from cryopreserved ovarian tissue, which had been frozen following Telfer's guidelines, which resulted in the UK's first baby born after the procedure. The mother had a section of ovary frozen eleven years earlier, after a cancer diagnosis and prior to chemotherapy. Following the ovarian transplant, a natural conception resulted and a healthy baby was born in 2016 [5.1].

Establishment of the UK's first testis cryopreservation service in 2014 for pre-pubertal boys and have supported the development of other similar services in the UK: Fertility in men requires the constant production of sperm. Sperm freezing is not possible for males who have not undergone puberty, such as childhood cancer patients. Dr Mitchell's research focusses on developing strategies for removing and storing testis tissue from patients prior to potentially sterilizing treatments in order that germ cell development can be achieved using *in vitro* or *in vivo* techniques. Edinburgh has recently become the first UK centre to establish a fertility preservation programme to store testicular tissue from young cancer patients prior to their treatment. This programme in males, combined with our well-established fertility preservation programme for females, has resulted in the establishment of a collaboration of scientists and clinicians working as part of the 'Edinburgh Fertility Preservation service'. This unique collaboration combines clinical and laboratory research aimed at optimising fertility for children and young adults with cancer [5.2], [5.3].

Tissue services: use the research described in [3.1], [3.2] to inform how to prepare and store tissue. The Scottish National Blood Transfusion Service (SNBTS) cryogenically freeze and store tissue from the reproductive organs of girls as young as one, which can potentially be re-implanted once they reach adulthood. Key to this protocol is that tissue is frozen by a process known as vitrification rather than using traditional cryopreservation techniques. Chemotherapy and radiotherapy can have serious side effects on reproductive organs, which can render patients infertile if the treatment takes place before they reach puberty. By removing the tissue from children before they undergo cancer treatment, it is possible to protect it from side effects that can render patients infertile [5.4i], [5.4ii].

Counselling and fertility preservation practices informed by research: More than 8,000 women aged 15-39 in the UK are diagnosed with cancer annually. Of these, approximately half receive treatment that could adversely affect their fertility. Since 2013, numbers of patients being treated in the Oxford Clinical Programme, have increased from 4 ovarian tissue cases to a total of 281 in 2019 (159 ovarian tissue cases and 122 testicular tissue cases) [5.5i]. The New South Wales Fertility Research Centre [5.5ii], set up with considerable input from Anderson and Wallace, has also been able to offer fertility preservation to an increasing number of patients.

> *"Professors Anderson and Wallace had established eligibility criteria for the Edinburgh Ovarian Research Programme and kindly allowed us to use these to draw up similar criteria for the Oxford Clinical Programme. The Edinburgh Eligibility Criteria were validated and results published in Lancet 2014"* [5.5i]

> *"In 2019, we did 98 cases of fertility preservation and so far, in 2020, we have undertaken fertility preservation procedures in 226 patients."* [5.5ii]

As a result of research carried out at the UoE on the mechanisms underpinning egg development, clinicians have changed their approach to counselling girls with their parents, and young women who may enter fertility preservation programmes after *e.g.* a cancer diagnosis [3.1], [3.2]. In Scotland, weekly multi-disciplinary team meetings happen to discuss holistic issues for new cancer patients. Fertility preservation is discussed with every young patient as a result of this research.

In addition, the advances in egg maturation *in vitro* would circumvent clinicians re-implanting ovarian tissue that may contain residual cancer cells. Whilst treatment using these *in vitro* matured eggs is not yet approved in the U.K. it is being considered in the U.S.A and, younger girls and women with cancer considering ovarian tissue cryopreservation are counselled with these developments in mind for their fertility restoration [3.3].

Impact on patient care and policy:

Enhancements to patient care following **NICE clinical guidance [CG156],** "Fertility problems: assessment and treatment" which was last updated in September 2017 [5.6]. These guidelines have made fertility preservation part of mainstream care **and have been in practice for the whole of the REF2021 impact period**. Especially relevant to the research are points:

1.16.1.3 When deciding to offer fertility preservation to people diagnosed with cancer, take into account the following factors: diagnosis; treatment plan; expected outcome of subsequent fertility treatment; prognosis of the cancer treatment and; viability of stored/post-thawed material.

1.16.1.7 When using cryopreservation to preserve fertility in people diagnosed with cancer, use sperm, embryos or oocytes.

1.16.1.11 In cryopreservation of oocytes and embryos, use vitrification instead of controlled-rate freezing if the necessary equipment and expertise is available.

Published and in practice since February 2014, the NICE quality standard guidance [QS55] "Cancer services for children and young people" contains quality statement 7: Fertility support – "*Children and young people (aged 0–24 years) with cancer are assessed for potential future fertility problems and advised about their options for fertility preservation before treatment is started"* [5.7]. **The guidelines influenced by Telfer's, Anderson's and Wallace's work impacted patient care throughout the current REF period.**

The Scottish National clinical guidelines SIGN 132 'Long term follow up of survivors of childhood cancer' states that specialist referral should be considered where there is patient or professional concern around fertility in survivors of childhood cancer. They encourage good links between paediatric and adolescent oncology units and fertility services to promote rapid referral and pre-treatment assessment of young patients who may benefit from fertility preservation and state that cryopreservation of ovarian tissue (within the context of a clinical trial) should be considered in girls at high risk of premature ovarian insufficiency [5.8i]. **The guidelines influenced by Telfer's, Anderson's and Wallace's work impacted patient care throughout the current REF period.**

> *"The SIGN guidelines from the Scottish Intercollegiate Network are in my opinion the single most useful guidance for late effects, being evidence based, pragmatic, and helpful on the clinical shop floor. These were informed by the Edinburgh team."* [5.8ii]

The European Society of Human Reproduction and Embryology (ESHRE) is the leading clinical and scientific group across Europe and worldwide on fertility preservation. Professor Anderson chairs the ESHRE Special Interest Group on Fertility Preservation (https://www.eshre.eu/Specialty-groups/Special-Interest-Groups/Fertility-Preservation). The group have finalised guidelines on fertility preservation and have recently published a comprehensive document detailing all aspects of female fertility preservation and care highlighting 78 recommendations on information provision and support, pre-FP assessment, FP intervention and after treatment care. This policy document discusses Professors Telfer, Anderson, Mitchell and Wallace's research [5.9 & 5.10].

The British Fertility Society published policy and practice guidelines in 2018. Anderson was a member of the group that produced these guidelines that feature the Edinburgh research [5.11]. Prof Anderson chairs the Scottish Government working group establishing fertility preservation for adult men and women in NHS Scotland. This group has produced guidelines that will be agreed by The Scottish National Infertility Group and put into practice soon. These guidelines are based on the UoE research and are important for patients with leukaemias.

Between 2016 and 2019, a family of international patents have been approved and put in place to protect the protocol for growing human immature oocytes to maturity *in vitro* [5.12].

5. Sources to corroborate the impact

[5.1] Dunlop et al. J Assist Reprod Genet. 2016;33(12):1615–1620. doi: https://doi.org/10.1007/s10815-016-0805-2
[5.2] Preserving fertility for boys treated for cancer before puberty https://www.childrenwithcancer.org.uk/research/projects/fertility-preservation/
[5.3] https://www.heraldscotland.com/news/15582189.boy-aged-one-youngest-in-scotland-to-have-testicle-frozen-to-preserve-fertility-amid-chemo-battle/
[5.4] Scottish National Blood Transfusion Service (SNBTS) i) Blog 18/07/2016 from https://nhsnss.org/blog-news/articles/frozen-tissue-service-offers-fertility-hope-for-children-with-cancer/ ii) Testimonial- SNBTS, Consultant and Clinical Lead, Tissue and Cells.
[5.5] i) Testimonial- Pg2 Consultant Paediatric Oncologist, Oxford Reproductive Tissue Cryo Service. ii) Testimonial- Pg 5 Paediatric and Adolescent Oncologist, Sydney Children's Hospital and Prince of Wales Hospital.
[5.6] NICE guidance - Fertility problems: assessment and treatment. https://www.nice.org.uk/guidance/cg156/chapter/Recommendations#principles-of-care
[5.7] NICE guidance - Cancer services for children and young people (Pg 31 of 43). https://www.nice.org.uk/guidance/qs55/resources/cancer-services-for-children-and-young-people-pdf-2098728855493
[5.8] i) Pg2 SIGN 132 – Long term follow up of survivors of childhood cancer https://www.sign.ac.uk/media/1070/sign132.pdf ii) Testimonial Pg71 Chair, Fertility Preservation UK
[5.9] ESHRE guidelines 2020 (Pg 84,109,126,171) https://www.eshre.eu/Guidelines-and-Legal/Guidelines/Female-fertility-preservation
[5.10] Interest Group on Fertility Preservation (https://www.eshre.eu/Specialty-groups/Special-Interest-Groups/Fertility-Preservation).
[5.11] British Fertility Society. Yasmin et al, (2018) Human Fertility, 21:1, 3-2 DOI: https://doi.org/10.1080/14647273.2017.1422297
[5.12] International patents family i)-vi)