

## Impact case study (REF3)

<b>Institution:</b> University of Bristol		
<b>Unit of Assessment:</b> 2) Public Health, Health Services and Primary Care		
<b>Title of case study:</b> Improving outcomes and minimising harm with in vitro fertilisation (IVF)		
<b>Period when the underpinning research was undertaken:</b> 2010 - 2015		
<b>Details of staff conducting the underpinning research from the submitting unit:</b>		
<b>Name(s):</b>	<b>Role(s) (e.g. job title):</b>	<b>Period(s) employed by submitting HEI:</b>
Deborah Lawlor Kate Tilling Andrew Smith	Professor of Epidemiology Professor of Medical Statistics Senior Research Associate	2000 - present 2002 - present 2013 - 2015
<b>Period when the claimed impact occurred:</b> 1 <sup>st</sup> August 2013 - 2020		
<b>Is this case study continued from a case study submitted in 2014?</b> No		

### 1. Summary of the impact

As the global use of in vitro fertilisation (IVF) increased, it was crucial to determine which IVF treatments work best in which circumstances, to inform couples, funders and stakeholders. To address these challenges, Lawlor and colleagues implemented novel analytical approaches in the Human Fertilisation and Embryology Authority (HFEA) register data, working with key stakeholders to enhance the evidence underpinning IVF treatment, and this research has led to substantial changes in clinical practice. The research helped to stimulate a 15 percentage point increase in the number of single embryo transfers in the UK over the period 2013-2016 (from 45% to 60%), with associated reductions in multiple pregnancies and preterm births. Furthermore, the work supported NHS Scotland's decision to increase NHS-funded IVF cycles from two to three and reduce variation in IVF provision in Scotland.

### 2. Underpinning research

One in six couples are infertile. In vitro fertilisation (IVF) is a routine treatment for most forms of infertility. However, it is time consuming and emotionally demanding for couples, with rates of livebirth per cycle in high income countries of 25-40% (depending on prognostic factors, in particular a woman's age). Costs per cycle are relatively high, and NHS provision is limited; across the UK, 60% of cycles are couple-funded, though with considerable geographic variation. Providers often use surrogate markers of success (including fertilisation or pregnancy rate) in marketing to couples. Hence couples, funders and stakeholders have identified the need to determine which IVF treatments work best and in which circumstances. Randomised controlled trials (RCTs) in reproductive medicine rarely, if ever, have adequate power to detect reasonable target differences in the key outcome of live-birth rates; indeed, only 2% of meta-analyses of such RCTs have been shown to have sufficient power in this respect. Moreover, no previous observational studies had explored whether the associations between the number of embryo transfers and various outcomes differed according to maternal age.

To address these research challenges, Lawlor and colleagues have undertaken a series of analyses using a comprehensive UK-wide dataset of all IVF cycles taking place since 2003. This body of research has demonstrated the following.

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**Determined the effect of single, two or three embryo transfers** on live-birth success and perinatal outcomes [1]. Multiple embryo transfer increases clinical pregnancy rates, incentivising providers and patients. Yet, multiple pregnancy arising from multiple embryo transfer is associated with adverse outcomes for the baby. Lack of evidence on the balance between live-birth success and adverse perinatal outcomes with different numbers of embryos transferred in one treatment led to widespread variation in embryo transfer practice nationally and globally. By 2010 it was recognised (by couples, clinicians and funders) that the question of whether it was best to transfer one or more embryos was of paramount importance and two large RCTs were funded (one in the UK and one in Australia). Both of these RCTs were stopped early because of failure to recruit. The UK trial recruited just 23 of a planned 700 participants, and the Australian trial just 27 of a planned 1000 participants. Recruitment was poor because of couple treatment preferences – for double embryo transfer in the UK and single in Australia. In any case, neither trial would have addressed the best practice for women aged over 37 years, since they were excluded. Previous observational studies also lacked power to detect effects in women over the age of 40 years, for whom a double transfer may be the last opportunity to complete a family of two children.

Using data on 124,148 IVF cycles, which resulted in 33,514 live-births, Lawlor and colleagues showed that in women younger than 40 years, a single fresh embryo transfer, followed by subsequent single frozen transfer, resulted in an equivalent live-birth rate and lower risk of harm (fewer multiple births, preterm births and small for gestational age babies), compared with those occurring following a double embryo transfer. Furthermore, for the first time, they showed that in women aged 40 years or older, double embryo transfer resulted in a higher live-birth rate and lower risk of harm than single embryo transfers [1]. In both age groups, transfer of three embryos reduced live-birth rates and increased adverse outcomes [1]. It was recommended that single embryo transfer should be the routine approach in women younger than 40 years and a double embryo transfer the norm in those older than 40 years, with triple transfers phased out.

**Determined the benefit of repeat treatment cycles**, including how many cycles were required to obtain a live-birth rate similar to that in couples conceiving naturally, and whether it was worth continuing with further cycles if an initial cycle failed to yield oocytes [2]. Using prospectively collected UK-wide data on over 150,000 women collected over nearly a decade from 2003, Lawlor and colleagues showed that the cumulative live-birth rate in all women continued to increase up to nine cycles. In women younger than 40 years (and of any age using donor eggs), couples could achieve a cumulative live-birth rate (68%) similar to that of couples conceiving naturally with six cycles [2]. This provided the evidence for funding more than one or two cycles and has made demonstrable differences in Scotland where up to three cycles per couple are now NHS-funded. The research also challenged traditional assumptions that low or zero egg retrievals in a cycle implied that further cycles should be limited as live-birth was unlikely. Contrary to these assumptions, Lawlor's team found that egg retrieval for each cycle was independent; in other words, zero retrieval in one cycle did not influence live-birth success in subsequent cycles [2].

**Identified accurate predictors of live-birth success** using data from 144,018 IVF cycles. Lawlor and colleagues identified key characteristics associated with live-birth rates relating to couples (e.g. woman's age, nature and duration of infertility) and treatments (e.g. use of donor eggs and intracytoplasmic sperm injection (ICSI)). In addition, they elucidated how these factors interacted with each other – for example, the increased live-birth rates with donor eggs were apparent at all ages but strongest at older ages, and ICSI increased live-birth rates in those with male-related infertility [3]. The prediction model these researchers developed was found to

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predict outcomes with greater accuracy than the existing model, not just in their original research but also in an external validation study they carried out on 130,960 cycles in the UK[4]. They have also produced an online tool and smart phone app based on their prediction model, for use by couples and clinicians.

### 3. References to the research

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1. **Lawlor DA**, Nelson SM. 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](https://doi.org/10.1016/S0140-6736(11)61267-1)
2. **Smith ADAC**, **Tilling K**, Nelson SM, **Lawlor DA**. Live-birth rate associated with repeat in vitro fertilization treatment cycles. *JAMA*, 2015; 314: 2654-2662. DOI:[10.1001/jama.2015.17296](https://doi.org/10.1001/jama.2015.17296)
3. Nelson SM, **Lawlor DA**. 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 Medicine*, 2011; 8(1): e1000386. DOI:[10.1371/journal.pmed.1000386](https://doi.org/10.1371/journal.pmed.1000386)
4. **Smith AD**, **Tilling K**, **Lawlor DA**, Nelson SN. External validation and calibration of IVFpredict: a national prospective cohort study of 130,960 in vitro fertilisation cycles. *PLoS One*, 2015; 8;10(4):e0121357. DOI:[10.1371/journal.pone.0121357](https://doi.org/10.1371/journal.pone.0121357)

### 4. Details of the impact

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#### Reduced IVF related multiple birth rate in the UK

Lawlor and colleagues' research demonstrating the benefit of single embryo transfer in women younger than 40 years, and of a double transfer in older women, has enhanced the efforts of the HFEA to increase single embryo transfer and hence reduce harm associated with IVF [A-D].

Between 2008 and 2012, single embryo transfer in the UK increased from 18% to 45%, and multiple birth rates decreased from 25% to 15% by 2011 [A]. These improvements became static from 2011 and transfer of three embryos was more common in the UK than most European countries [A]. The HFEA used findings from Lawlor and colleagues' research [1] to promote single embryo transfers in younger women and double transfer in older women. This has led to a further increase in single embryo transfers (45% to 60% from 2013 to 2016) and associated decreases in multiple pregnancies and multiple births [B, C]. The Chief Executive of HFEA describes the importance of the research in '*providing continued momentum for our campaign to promote 'one at a time' embryo transfers and see IVF related multiple births, with their associated risk of preterm birth and low birth weight, reduced.*' [D]. The statement further confirms the continued declines in multiple births, with HFEA's target of a maximum 10% of live-births being multiple births achieved by 2017 and further declining to 8% by 2018 [D].

#### Changing practice in relation to repeat treatment cycles

Prior to work by Lawlor and colleagues, governments and insurance companies internationally limited the number of IVF cycles they would fund. In the UK there was variation across countries, and by clinical commissioning groups (CCG) within England, with no country/CCG providing NHS funding for more than two cycles. Clinicians and funders cautioned against further cycles (even when couple-funded) following a cycle where no eggs were retrieved. Lawlor and colleagues' research, showing that live-birth rates continued to increase with successive IVF

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cycles, regardless of the number of oocytes retrieved [2], was cited by the Scottish National Infertility Group in their 2016 government report to request an increase in the number of NHS-funded treatment cycles [E (p.17)]. This resulted in Scotland changing its guidelines to recommend up to three (from the previous limit of two) full cycles for eligible patients to be funded by the NHS from 2017 [F]. As a result of these changes, equity of access to IVF and the number of cycles funded by the NHS in Scotland increased, such that by 1<sup>st</sup> April 2017, all newly referred couples who were eligible were provided with up to three NHS-funded cycles [F]. Since publication of this response to Lawlor and colleagues' research, the proportion of all IVF cycles in Scotland funded by the NHS has increased from 56% to 62% [G]. The action by Scotland was welcomed by patient support groups, '*We commend the Scottish Government both for recognising the importance of treating this medical condition, and for taking action to help the one-in-six couples affected by infertility*' [H].

Lawlor and colleagues' research made a major contribution to NICE (supported by the HFEA, the Royal College of Obstetrics and Gynaecology (RCOG) and patient groups) increasing pressure on CCGs to implement NICE guidelines. Lawlor and colleagues' research [3, 4] and bespoke analyses undertaken by Lawlor for NICE, contributed to the economic evaluation used by NICE Fertility guidance (CG156) on access criteria for IVF (Chapter 14) (2013). On the basis of that economic evaluation NICE recommended, for the first time, that funding be provided by the NHS for up to three IVF cycles. In subsequent revisions of those NICE guidelines (in 2015 and 2017) presentation of Lawlor's economic evaluation remained, and there is greater emphasis on the recommendation that up to three cycles be NHS-funded [li]. Lawlor and colleagues more recent (2015) research, showing continued increases in live-birth success with repeat cycles [2], has been used by NICE to further emphasize to CCGs in England why funding three cycles is important [liii]. In conjunction with the RCOG and patient groups, the HFEA have directly issued guidance to each CCG in England, notifying them of the strong evidence and NICE guidelines, meaning it is imperative that they support up to three IVF cycles [D, J]. The Chief Executive of HFEA notes that '*As an authority with a remit to support equitable and fair access to infertility treatments, we value research, such as this by Prof Lawlor and colleagues, that we have been able to use in our guidance to commissioning groups in England.*' [D].

## 5. Sources to corroborate the impact

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- A. HFEA (2015). [Improving outcomes for fertility patients: multiple births](#) [accessed 30.10.20]. *Report and associated data for download were used to estimate changes in single embryo transfers and multiple births from 2008 to mid-2013 – i.e. to provide a baseline against which our research subsequently influenced change.*
- B. HFEA (2018). [Fertility treatment 2014 – 2016 trends and figures](#) [downloaded 30.12.20]. *HFEA registry data used to analyse change in use of single embryo transfers and multiple births with IVF from 2013 to 2016 (for comparison with baseline data obtained from A above).*
- C. HFEA (2020). [Fertility treatment 2018: trends and figures](#) [accessed 30.12.20]. *UK statistics for IVF and DI treatment, storage, and donation. Human Fertilisation and Embryology Authority. Providing data on SET and multiple pregnancy rates for 2017.*
- D. HFEA (2020). Submitted testimony from the Chief Executive of the HFEA.
- E. National Infertility Group (2016). [National Infertility Group Report](#) [accessed 30.12.20]. *Report to the Scottish Government recommending that they increase the number of NHS-funded IVF cycles agreed by them and implemented in 2017. Cites Figure 2 [2] (p.17).*

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- F. NHS Scotland (2018). [Chief Executive's Annual Report 2017/18](#) [accessed 30.12.20].
- G. HEFA (2019). [Fertility treatment 2017: trends and figures](#) [accessed 30.12.20].  
*Used to obtain data on changes in the proportion of cycles funded by the NHS in devolved UK countries between 2015 and 2017.*
- H. i) BBC (2017). [Scottish government to fund three IVF cycles on NHS](#) [accessed 30.12.20].  
*Action of the Scottish government widely reported in the media.*
- ii) Fertility Fairness (2017). [Gold standard: Scotland the first country to provide 3 NHS-funded IVF cycles for all eligible couples](#) [accessed 30.12.20].  
*Action also praised by patient groups.*
- I. i) NICE (2013, 2015, 2017). [CG156 Fertility problems: assessment and treatment](#)  
*Health economic model and recommendations in chapter 14, on NHS funded access to IVF and has remained in place in 2015 and 2017 revisions.*
- ii) NICE (2014). News: [The importance of 3 full cycles of IVF](#) [accessed 30.12.20].  
*Use of Lawlor's research by NICE to re-emphasise the importance of funding three rather than two IVF cycles on the NHS.*
- J. HFEA (2019). [Commissioning guidance for fertility treatment](#) [accessed 30.12.20].  
*Commissioning guidance regarding funding three cycles of IVF.*