Chapter 21
Cost-Effectiveness of Single Embryo Transfers Relative to Higher Embryo Transfer Policies in Clinical Practice: A Population-Based Analysis

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Introduction

An in vitro fertilisation (IVF) treatment cycle can lead to a single live birth, multiple births, or, in most instances, no birth at all. Considerable debate surrounds the issue of whether, after how many treatment cycles, and for whom, certain embryo transfer (ET) policies are cost-effective. Although a mandatory single ET (SET) policy may be inappropriate for all patients, an excessive ET policy will lead to a higher

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proportion of multiple births that are born prematurely and carry significant perinatal and neurological risks. This chapter presents a population-based retrospective analysis using nationwide IVF data from across the United Kingdom (UK) from 1 July 1991 to 31 December 1998. This work aimed to test the hypothesis that the cost-effectiveness of any IVF policy depends not only upon maternal age and number of transferred embryos [1, 2], but also upon the number of IVF treatment attempts.

Persuasive movement towards a SET approach in clinical IVF practice is best facilitated by a correct reckoning of the full economic costs associated with the current clinical practice entailing transfer of multiple embryos per cycle. Accordingly, this chapter estimates the cost-effectiveness of each ET policy for clinically relevant subgroups of women undergoing treatment cycles of IVF and captures data during a very specific phase in the life cycle of IVF patients. For this study, our inclusive time horizon begins with the attempts to achieve pregnancy with IVF and concludes at the end of the fifth year of life for the children ultimately delivered following ET. The analysis embraces all hospital costs for the mother during IVF and delivery and for the child to the end of the fifth year of life. Not included are specific costs related to disability should a child suffer from a condition requiring services that are not provided in a hospital setting.

As the current National Institute for Health and Care Excellence (NICE) guidelines suggest a maximum of two embryos transferred per cycle, it is important to know for each subgroup of women (i.e. older vs. younger women; first-time users vs. repeat users) whether an alternative policy such as SET after molecular screening may be more cost-effective. Central to this debate are the questions: (a) what is the cost-effectiveness of each ET policy, and (b) what would be the cost to achieve an additional live birth event for each group of women, if an additional embryo were offered on a given cycle? Hence a traditional incremental cost-effectiveness analysis was constructed to determine whether improved live birth rates and avoided multiples following SET or alternative ET policies, for that matter, justify their additional costs.

Cost-effectiveness planes were constructed from the incremental cost and marginal effect data presented and combined in Figs. 21.1 and 21.2 of this chapter. These graphical representations show the within-cycle incremental cost-effectiveness of moving between three changes to the number of transferred embryos on the final treatment cycle: from SET to 2ET, from SET to 3ET, and from 2ET to 3ET.

Methods

Data on IVF clinics in the UK were provided by the Human Fertilisation & Embryology Authority (HFEA) to calculate the cost-effectiveness for each ET policy (1 embryo, 2 embryos, and 3 embryos) and treatment history category (1 cycle, 2 cycles, ≥3 cycles). Within-cycle cost-effectiveness was calculated for two age groups (<38 vs. ≥38 years) and compared between three embryo transfer shifts: from SET to 2ET, from 2ET to 3ET, and from SET to 3ET. The incremental cost-effectiveness between cycle groups was not compared in the same way, because patients in different cycle categories are assumed to have different levels of baseline fertility.

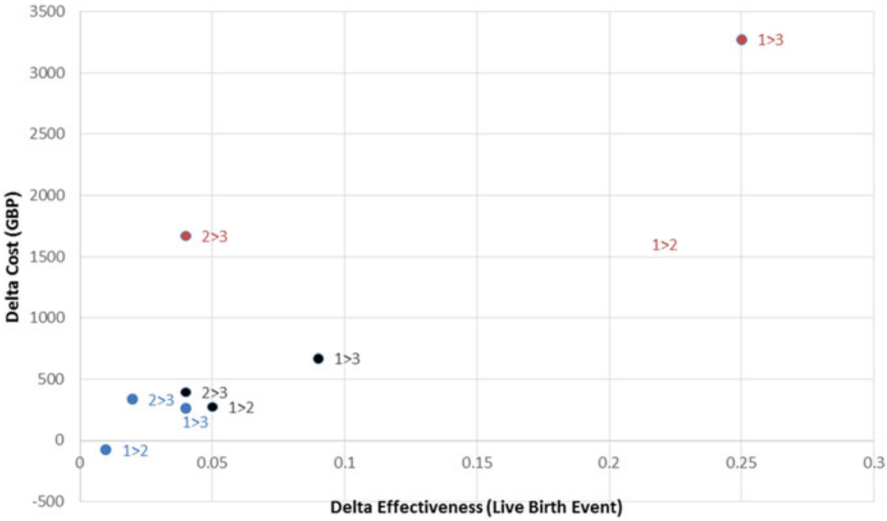

Fig. 21.1 Incremental cost-effectiveness ratios of embryo transfer policies for women <38. *Notes*: Whereas adjustments for inflation would move the ICER ratios upward on the y-axis, the relative difference in the ICERs between alternative embryo transfer policies would likely remain the same. As such, a standard healthcare inflation adjustment (based on published annual healthcare inflation for the UK) can be applied to the final ICER estimates, as well as the "willingness-to-pay' thresholds

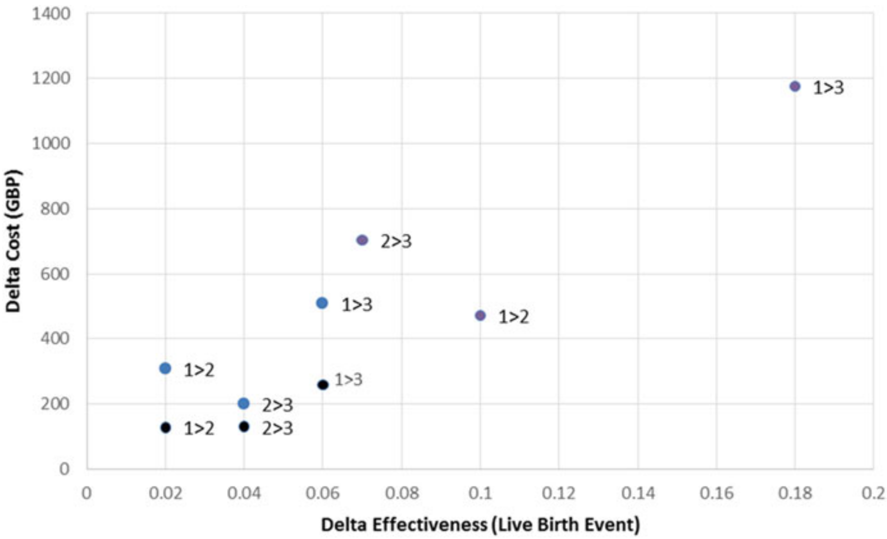

Fig. 21.2 Incremental cost-effectiveness ratios of embryo transfer policies for women 38 years and older. *Notes*: Whereas adjustments for inflation would move the ICER ratios upward on the y-axis, the relative difference in the ICERs between alternative embryo transfer policies would likely remain the same. As such, a standard healthcare inflation adjustment (based on published annual healthcare inflation for the UK) can be applied to the final ICER estimates, as well as the 'willingness-to-pay' thresholds

Study Population

A total of 68 clinics contributed comprehensive data to the HFEA under what can be described as a legislative mandate. The study population comprised all women undergoing at least one IVF treatment cycle with ET in the UK between 1 July 1991 and 31 December 1998 ($n = 174,418$). All IVF treatment cycles (with and without ICSI; fresh and frozen sperm/eggs/embryos; donor and partner's gametes) and outcomes registered during this time were retrospectively reviewed in a non-identifiable, anonymous manner. Cases excluded from this research were all women who received a fertility therapy other than IVF with ET, all women older than 44 years of age at cycle start, and quadruplet deliveries ($n = 4$ sets). We based our calculations on IVF treatments involving only SET, 2ET, or 3ET (higher-order ETs were not tabulated). Accordingly, a total of 74,755 women undergoing 137,307 cycles (79 % of registered cases) met our inclusion criteria. Patients were next stratified by age, number of transferred embryos on their final cycle, and number of treatment cycles.

A health economic evaluation was performed in the form of an incremental cost-effectiveness analysis. Costs included all treatment costs, antenatal costs, and pregnancy and birth costs from parturition to the first 5 years of childhood life (inclusive). Costs were reported according to the period over which the treatments occurred, with subsequent adjustment to 2012–2013 levels using standard healthcare inflationary corrections.

Definitions: Live Birth Rate and Multiple Birth Rate

Our investigation used the standard HFEA definition of a live birth event: a maternity in which the child(ren) survive(s) 27 completed days post-delivery. Because the HFEA dataset does not distinguish between stillbirth and neonatal death, infants who died in utero or who did not survive through 27 competed days post-delivery per pregnancy were not included for analysis.

The live birth rate (LBR) as used in this study includes most cases familiar to clinicians, but the 'average live birth rate per IVF patient' is used here to normalise the live birth rates between increasing cycle categories. This form of LBR is often referred to as the 'take-home' baby rate.

Two forms of measuring the multiple birth rate (MBR) were used: the first is calculated as the MBR divided by the total number of IVF cycles, and the second method is the MBR divided by the total number of live birth events. The former statistic represents the per cycle incidence of multiple births. The latter estimation is more useful, since it represents the proportional incidence of multiple births as a function of all live births.

Sensitivity Analysis

There was uncertainty regarding values of several estimated parameters in our analysis. Sensitivity analysis allows assessment of robustness of conclusions to changes in key parameters by assigning varying ranges to uncertain parameters over realistic ranges and re-evaluating the conclusions for different combinations. This can be accomplished by using a one-way sensitivity analysis, where only one variable is changed at a time. In probabilistic sensitivity analysis, parameter ranges are used to estimate likelihood of cost-effectiveness. In multi-way sensitivity analysis, several variables are changed concurrently. Finally, in the extreme scenario analysis a nominal estimate of cost-effectiveness is determined, and uncertain parameters are varied using their extreme 'maximum' and 'minimum' values. This latter approach was utilised for the present analyses (i.e. low cost/low resource use vs. high cost/high resource use) to estimate the extent to which the conclusions in this chapter may change with maximum and minimum variations in the cost and resource assumptions.

Data organisation and Presentation of Statistical Significance

Our initial analysis was confined to records of IVF patients who completed no more than three treatment cycles because >90 % of the national study population underwent only one, two, or three treatment cycles. All results are reported as exact (or mean) values. Differences in live birth rates and multiple birth rates between subgroups of women were compared by Student's *t*-test, with differences considered significant if two-tailed *p*-values were ≤0.05.

Sources of Cost Estimations

For purposes of this analysis, the estimated average cost per IVF cycle is £2,876.26 (±681.63) excluding medications. This estimate was derived from the author's (CAJ) 2003 telephone survey of charges in the 70 UK clinics that provided IVF services [3]. The number of treatment cycles (and thus cycle costs) will change for different patient populations (1 cycle, 2 cycles, and ≥3 cycles).

Average antenatal bed days were estimated by Henderson et al. [4] at 1.09 days (SE=0.01) for women expecting a singleton child, 8.35 days (SE=0.51) for those expecting twins, and 32 days (SE=11.22) for those expecting triplets. A cost per bed day of £277.40 (±41.53) was based on figures provided by the Oxford Radcliffe Hospitals NHS Trust (www.orh.nhs.uk) multiplied by the average number of bed days reported by Henderson et al. [4]. This cost per bed day was compared to a national estimate of £318.93 in the sensitivity analysis. Resulting antenatal costs were calculated at £302.37 (SE=2.77) per singleton delivery, £2,316.28 (SE=141.47) per twin delivery, and £8,876.77 (SE=3,112.41) per triplet delivery.

'Cost of the first 5 years of child life' was adapted from a report on long-term health service costs for hospital stays associated with singleton, twin, and triplet births up to 5 years of age [4] . That computation was derived from the Oxford Record Linkage Study (ORLS), which recorded health data on all women and infants who lived and delivered in Oxfordshire or West Berkshire between January 1, 1970, and December 31, 1993. Their study included all delivery costs for the mother, as well as hospital service utilisation costs from birth through baby's first 5 years of life. These costs were adjusted for inflation estimated at £2,345.69 (±12.50) per singleton delivery, £11,715.88 (±80.46) per twin delivery, and £37,462.66 (±467.13) per triplet delivery.

For each IVF case, the hospital costs described above were added to IVF treatment costs to generate a total cost. To bring these historical economic figures in line with current levels, all costs were inflated by £2,004 using NHS Hospital and Community Health Services pay and price deflators provided by the UK Department of Health (www.statistics.gov.uk/statbase). This total cost included the cost of IVF treatment (without gonadotropins and other medications), hospital visits during the antenatal period, intrapartum care, and any paediatric hospitalisation from birth through the first 5 years of life. Mode of delivery was included neither in the HFEA dataset nor in the report by Henderson et al. [4]. Accordingly, delivery costs were excluded from our analysis.

Measuring Incremental Cost-Effectiveness

Here, effectiveness is defined as the average number of live birth events per woman in each category as classified by age, cycle, and number of transferred embryos. The incremental cost-effectiveness ratio (ICER) is calculated for each group of women as the cost of achieving an additional live birth event in a higher embryo category. ICERs are expressed in terms of (a) maternal age (<38 vs. ≥38 years), (b) number of treatment cycles (1, 2, or ≥3 cycles), and (c) number of transferred embryos (1, 2, or 3 embryos) on the final treatment cycle. The average live birth rate per woman was chosen for effectiveness to normalise the data with respect to differences in the number of women in each age, ET, and cycle populations.

In summary, the variables included in the analysis comprise (a) the respective number of singleton, twin, and triplet live birth events; (b) antenatal cost of each plurality; (c) cost from delivery to the first 5 years of life; (d) total cost for each plurality; (e) total cost of each ET policy; (f) total effectiveness of each ET policy; (g) incremental cost of achieving an additional live birth event in a higher ET policy; (h) incremental effectiveness at achieving an additional live birth event with a higher ET policy; and (i) incremental cost-effectiveness expressed as the incremental cost to achieve an additional live birth event in comparative ET policies. Effectiveness ratios were expressed as the number of live birth events per woman. ICERs were subsequently mapped onto cost-effectiveness planes to graphically illustrate the within-cycle cost-effectiveness of each intervention.

Results

A total of 174,418 IVF treatment cycles occurred in the UK between 1 July 1991 and 31 December 1998. After application of exclusion criteria, 74,755 women undergoing 137,307 cycles (79 % of those registered) were analysed. These 74,755 fertility patients underwent between 1 and 23 IVF cycles where ET occurred. A total of 41,033 women underwent one cycle only, 18,275 two cycles only, and 15,447 three or more cycles. Of these 61,284 were less than 38 years of age and 13,471 were greater than 38 years of age.

SET Versus 2ET Policy

One Prior IVF Cycle

Among 3,089 women aged <38 years who underwent SET after one prior IVF cycle, there were 463 live birth events comprising 450 singletons, 11 sets of twins and 2 sets of triplets. A policy of 2ET was noted to increase the live birth rate by a factor of 2.4 (0.15 vs. 0.36 births/woman; $p<0.05$), although this came at the expense of tenfold rise in multiple births (2.81 % vs. 27.32 %; $p<0.05$). Correspondingly, the incremental cost per additional live birth associated with a 2ET policy was £7,728 in the nominal scenario. This value ranged from £7,450 to £8,023 in minimum and maximum scenarios, respectively.

In 1,270 women aged ≥38 years having SET after one prior IVF cycle, there were 71 live births comprising 69 singletons, 1 set of twins, and 1 set of triplets. In this group, moving from SET to 2ET increased the live birth rate by a factor of 2.7 (0.06 vs. 0.16; $p<0.05$) at the expense of a fivefold increase in the incidence of multiple births (2.82 % vs. 13.89 %). The incremental cost per additional live birth in moving to a 2ET policy in the one prior cycle population was £4,663 in the nominal scenario. This value ranged from £4,537 to £4,794 in minimum and maximum scenarios, respectively.

Two Prior IVF Cycles

In 1,451 women aged <38 years with SET and two prior IVF cycles, there were 64 live births comprising 63 singletons and 1 twin delivery. A policy of 2ET increased the live birth rate by more than twofold (0.04 vs. 0.09; $p<0.05$), accompanied by a ninefold increase in the risk of multiple births (1.56 vs. 14.23; $p<0.05$). Whilst the proportion of multiple births to total births was slightly lower than the younger, one-cycle patients, the live birth rate was almost four times lower for two-cycle compared to one-cycle patients (0.04 vs. 0.15; $p<0.05$). The incremental cost per additional live birth event in moving to a 2ET policy in this population was £5,662 in the nominal scenario, ranging from £5,464 to £5,874 in minimum and maximum scenarios, respectively.

There were 460 women aged ≥38 years who underwent SET after two prior IVF cycles, from which 10 live birth events resulted (all singleton deliveries). A policy of 2ET doubled the live birth rate (0.02 vs. 0.04; $p<0.05$) at the expense of an increase in the incidence of multiple births (0 % vs. 11.76 %) including three sets of twins and one set of triplets. There were no multiple gestations in the SET group with two prior IVF cycles. The live birth rate was three times lower for women undergoing two cycles as compared to women undergoing only one cycle (0.02 vs. 0.06; $p<0.05$). The incremental cost per additional live birth event in moving to a 2ET policy in this population was £8,001 in the nominal scenario. This value ranged from £7,538 to £8,535 in minimum and maximum scenarios, respectively.

Three or More Prior IVF Cycles

There were 49 live births comprising 48 singletons and 1 set of twins in 1,274 women aged <38 years with SET after ≥3 prior IVF cycles. A policy of 2ET accomplished a moderate increase in the live birth rate (0.04 vs. 0.05; $p>0.05$) at the expense of a fourfold increased risk of multiple births (2.04 vs. 7.29; $p<0.05$). Whilst the proportion of multiple births to total births was 30 % higher in comparison to women undergoing only two cycle attempts, the live birth rate was identical. There is an incremental cost savings (indicated by a minus sign) of (–)£6,340 in the nominal scenario per additional live birth event in moving to a 2ET policy in this population. This value ranged from (–)£3,751 to (–)£8,920 in minimum and maximum savings scenarios, respectively.

In 288 women aged ≥38 years with SET and ≥3 prior IVF cycles, there were two live births, both singletons. In this subgroup, a policy of 2ET doubled the very low live birth rate from 0.01 to 0.02. This came at the expense of an increase in the proportion of multiple births with the extra embryo, although it is important to note that there were no multiple births observed among women undergoing SET in this category. The live birth rate was six times lower for women undergoing three or more cycles compared to women undergoing only one cycle attempt (0.01 vs. 0.06; $p<0.05$). The live birth rate was half the rate for women undergoing two IVF cycles compared to those undergoing three or more IVF cycles (0.01 vs. 0.02; $p<0.05$). The incremental cost per additional live birth event in moving to a 2ET policy in this population was £20,906 in the nominal scenario. This value ranged from £16,980 to £24,840 in minimum and maximum scenarios, respectively.

Two Versus Three ET Policy

One Prior IVF Cycle

Four thousand seven hundred ninety-five live births occurred among 13,260 women aged <38 years with 2ET and one prior IVF cycle, comprising of 3,485 singletons, 1,302 sets of twins, and 8 sets of triplets. A policy of 3ET increased the live birth rate by 10 % (0.36 vs. 0.40; $p < 0.05$) at the expense of a 50 % increase in the proportion of multiple births (27.32 vs. 40.97 %; $p < 0.05$). Correspondingly, the incremental cost per additional live birth event in moving to a 3ET policy in this population was £45,964 in the nominal scenario. This value ranged from £42,218 to £50,430 in minimum and maximum scenarios, respectively.

Among 2,258 women aged ≥38 years with 2ET and one prior IVF cycle, there were 360 live births comprising 310 singletons and 50 twin sets. A policy of 3ET increased the live birth rate by a factor of 1.4 (0.16 vs. 0.23; $p < 0.05$) at the expense of a 1.7-fold increase in the proportion of multiple births (13.89 % vs. 23.87 %; $p < 0.05$). The incremental cost per additional live birth event in moving to a 3ET policy in this population was £10,045 in the nominal scenario. This value ranged from £9,501 to £10,668 in minimum and maximum scenarios, respectively.

Two Prior IVF Cycles

Amidst 5,925 women aged <38 years with 2ET and two prior IVF cycles, there were 555 live births consisting of 476 singletons, 78 sets of twins, and 1 set of triplets. In this group, a policy of 3ET increased the live birth rate by approximately 50 % (0.09 vs. 0.14; $p < 0.05$) at the expense of 40 % increased proportion of multiple births (14.23 % vs. 19.91 %; $p < 0.05$). Whilst the proportion of multiple births to total live birth events was approximately half the value for <38 years/1 cycle patients, the live birth rate was four times lower for two- compared to one-cycle patients (0.09 vs. 0.36; $p < 0.05$). The incremental cost per additional live birth event in moving to a 3ET policy in this population was £8,943 in the nominal scenario. This value ranged respectively from £8,406 to £9,570 in minimum and maximum scenarios.

In 895 women aged ≥38 years with 2ET and two prior IVF cycles, there were 34 live birth events comprising 30 singletons, 3 sets of twins, and 1 set of triplets. A policy of 3ET doubled the live birth rate (0.04 vs. 0.08; $p < 0.05$) with a slight decrease in the proportion of multiple births in the higher embryo category (11.76 % vs. 10.07 %). The proportion of multiple births to total births was slightly less than the value for one-cycle patients, but the twin delivery rate was higher in women receiving 3ET compared to those receiving 2ET. The live birth rate was four times lower for women with only two cycles compared with those having only one cycle (0.04 vs. 0.16; $p < 0.05$). The incremental cost per additional live birth event in moving to a 3ET policy in this population was £3,173 in the nominal scenario. This value ranged from £3,214 to £3,125 in the minimum and maximum scenarios, respectively.

Three or More Prior IVF Cycles

IVF for 4,853 women aged <38 with 2ET and ≥3 prior cycles resulted in 247 live births comprising 229 singletons and 18 sets of twins. A policy of 3ET increased the live birth rate by 60 % (0.05 vs. 0.08; $p < 0.05$) with surprisingly fewer multiple births in the higher embryo category (7.29 % vs. 6.44 %, respectively). The proportion of multiple births to total births was approximately 25 % of the value for women who received three or more cycles compared to those who received only one cycle. The proportion of multiple births was approximately half the value for women who received three or more cycles compared to those who received only two cycles. The live birth rate was approximately seven times lower for women who received three or more cycles compared to women who received only one cycle (0.05 vs. 0.36; $p < 0.05$), and approximately half the live birth rate of women who received only two cycles (0.05 vs. 0.09; $p < 0.05$). The incremental cost per additional live birth event in moving to a 3ET policy in this population was £14,016 in the nominal scenario, and ranged from £11,431 to £16,619 in minimum and maximum scenarios, respectively.

In 636 women aged ≥38 with 2ET and ≥3 prior cycles, there were 14 live birth events comprising 12 singletons and 2 twin sets. A policy of 3ET trebled the live birth rate (0.02 vs. 0.06; $p < 0.05$) with four times fewer multiple births in the higher embryo category (14.29 % vs. 3.41 %, respectively; $p < 0.05$). The proportion of multiple births to total births was slightly higher for women who received three or more cycles compared to those who underwent only one or two cycles ($p > 0.05$). The live birth rate was eight times lower for women who received three or more cycles compared to those who received only one cycle (0.02 vs. 0.16 births per woman; $p < 0.05$), and half that of women who received only two cycles (0.02 vs. 0.04 births per woman; $p < 0.05$). The incremental cost per additional live birth event in moving to a 3ET policy in this population was £4,969 in the nominal scenario. This value ranged from £4,304 to £5,632 in minimum and maximum scenarios, respectively.

One Versus Three ET Policy

One Prior Cycle

Sixteen thousand seven hundred fifty women aged <38 underwent IVF with 3ET after one prior cycle. There were 6,680 live births from this group comprising of 3,943 singletons, 2,273 sets of twins, and 464 sets of triplets. A policy of 3ET increased the live birth rate by a factor of 2.7 (0.15 vs. 0.40; $p < 0.05$), although this was accompanied by a 15-fold increase in the proportion of multiple births in the 3ET category (2.81 % vs. 40.97 %; $p < 0.05$). The incremental cost per additional live birth event in moving from SET to 3ET in this population was £13,440 in the nominal scenario. This value ranged from £12,645 to £14,359 in minimum and maximum scenarios, respectively.

Among 4,406 women aged ≥38 who completed IVF with 3ET after only one prior IVF cycle, there were 1,018 live birth events comprising 775 singletons, 222 sets of twins, and 21 sets of triplets. For this subgroup, a 3ET policy increased the live birth rate by a factor of 3.8 (0.06 vs. 0.23; $p < 0.05$) with an eightfold increase in the proportion of multiple births after 3ET (2.82 % vs. 23.87 %; $p < 0.05$). The incremental cost per additional live birth event in moving from SET to 3ET for this subgroup of IVF patients was £6,864 in the nominal scenario. This value ranged from £6,566 to £7,196 in minimum and maximum scenarios, respectively.

Two Prior IVF Cycles

Among 7,682 women aged <38 who underwent IVF and 3ET after two prior IVF cycles, there were 1,065 live births comprising 853 singletons, 182 sets of twins, and 30 sets of triplets. Here, a policy of 3ET increased the live birth rate by a factor of 3.5 (0.04 vs. 0.14; $p < 0.05$), accompanied by 13 times more multiple births in the higher embryo category (1.56 % multiples in the 2ET group vs. 19.91 % in the 3ET group). The proportion of multiple births to total births was approximately half the value for women who underwent only two cycles compared to those who underwent only one cycle. The live birth rate was approximately three times lower for populations undergoing two cycles compared to populations undergoing only one cycle (0.14 vs. 0.40; $p < 0.05$). The incremental cost per additional live birth in moving from SET to 3ET in this population was £7,223 in the nominal scenario and ranged from £6,864 to £7,632 in minimum and maximum scenarios, respectively.

In 1,862 women aged ≥38 years who received 3ET after two prior IVF cycles, there were 149 live births comprising 134 singletons, 14 sets of twins, and 1 set of triplets. A policy of 3ET increased the live birth rate by a factor of 4 (0.02 vs. 0.08; $p < 0.05$) at the expense of a tenfold increase in the proportion of multiple births in the higher embryo category (0.0 % vs. 10.07 %; $p < 0.05$). The proportion of multiple births to total births was approximately half the value for women with two prior IVF cycles compared to those with only one prior cycle. The live birth rate was approximately three times lower for women with two previous IVF cycles compared to those who had only one prior IVF cycle (0.08 vs. 0.23; $p < 0.05$). The incremental cost per additional live birth event in moving from SET to 3ET in this population was £4,519 in the nominal scenario and ranged from £4,356 to £4,697 in minimum and maximum scenarios, respectively.

Three or More Prior IVF Cycles

Among 7,000 women aged <38 who underwent IVF and 3ET after three or more previous IVF cycles, there were 528 live birth events comprising 494 singletons, 31 sets of twins, and 3 sets of triplets. Here, a 3ET policy doubled the live birth rate (0.04 vs. 0.08; $p < 0.05$) at the expense of a threefold increase in multiple births in the higher embryo category (2.04 % vs. 6.44 %; $p < 0.05$). The proportion of multiple births to total live births for women who had completed three or more IVF cycles was approximately one-sixth that of women who had completed only one prior IVF cycle (6.44 % vs. 40.97 %; $p < 0.05$). The proportion of multiple births to live births for patients with a history of three or more IVF cycles was approximately one-third that of the proportion for women who received two cycles (6.44 % vs. 40.97 %; $p < 0.05$). The live birth rate was five times lower for women with three or more prior IVF cycles compared to women with only one prior cycle (0.08 vs. 0.40; $p < 0.05$), and 43 % lower than the live birth rate of women with only two prior IVF cycles (0.08 vs. 0.14; $p < 0.05$). Again, this indicates that patients entering treatment with a history of three or more prior IVF cycles are significantly less likely to conceive than patients with only one or two prior IVF cycle attempts. The incremental cost per additional live birth event in moving from SET to 3ET in this population was £7,169 in the nominal scenario, ranging from £6,324 to £8,028 in minimum and maximum scenarios, respectively.

There were 1,396 women aged ≥38 years who completed IVF with 3ET after three or more prior IVF cycles. Within this group, 88 live births were recorded, comprising 85 singletons and 3 sets of twins. A policy of 3ET increased the live birth rate by a factor of 6 (0.01 vs. 0.06; $p<0.05$) with the result of three sets of twins. The live birth rate for patients with three or more IVF cycles was approximately one-fourth that of women who had completed only one prior IVF cycle (0.06 vs. 0.23; $p<0.05$), and approximately 33 % of the live birth rate of women who received two cycles (0.06 vs. 0.08; $p>0.05$). The incremental cost per additional live birth event in moving from SET to 3ET in this population was £9,249 in the nominal scenario, ranging from £7,710 to £10,793 in minimum and maximum scenarios, respectively (Table 21.1).

Comparisons of Incremental Cost-Effectiveness Ratio as a Function of Patient Age

In evaluating a policy move from SET to 2ET for IVF patients <38 years of age, the ICER for women who had completed two prior IVF cycles was 27 % less than the ICER for those with only one prior IVF cycle. For women who received one or two cycles where SET was performed, the cost of achieving an additional live birth by moving to a policy of 2ET was less than £8,160. However, the ICER comparing SET to 2ET was negative for women with three or more prior IVF cycles, suggesting that it is actually cost saving to offer this particular population of IVF patients an extra embryo for transfer. The total cost per patient with a history of three or more prior IVF cycles was £6,078 less with 2ET compared to SET. This unexpected finding is the topic of further investigation.

In the case of moving from SET to 2ET for IVF patients 38 years and older, the ICER increased precipitously with increasing IVF cycle attempts. This suggests that for IVF patients aged ≥38, it may be more cost-effective to offer 2ET to those with shorter and less complex treatment histories. Offering 2ET to women who were in the one prior IVF cycle category with SET yielded an ICER of £4,663 per additional live birth event. This ICER doubled (to £8,001) in the case of two prior cycles/SET women and quadrupled (to £20,906) in the case of women who underwent SET with three or more IVF cycle attempts.

2ET to 3ET ICER Comparison

For patients age <38 years who had completed two prior IVF cycles, the ICER was approximately one-fifth the value estimated for those who underwent only one prior IVF cycle and 67 % of that estimated for those with three or more previous IVF cycles.

Table 21.1 Fiscal impact of advancing to a higher embryo transfer policy (i.e. moving from SET to 2ET, and 2ET to 3ET)

	<38 years of age				≥38 years of age			
	ΔLBR	ΔMBR	LBR comparisons	ICER	ΔLBR	ΔMBR	LBR comparison	ICER in nominal scenario
1ET + 1Cycle	2.4× increase (0.15 vs. 0.36, $p<0.05$)	10× increase (2.81 % vs. 27.32 %, $p<0.05$)		£7,728 in the nominal scenario	2.7× increase (0.06 vs. 0.16, $p<0.05$)	5× increase (2.82 % vs. 13.89 %)		£4,663
1ET + 2Cycle	2× increase (0.04 vs. 0.09, $p<0.05$)	9× increase (1.56 vs. 14.23, $p<0.05$)	LBR almost 4× lower for 2-cycle vs. 1-cycle (0.04 vs. 0.15, $p<0.05$)	£5,662 in the nominal scenario	2× increase (0.02 vs. 0.04, $p<0.05$)	Increased (0 % vs. 11.76 %)	LBR almost 3× lower for 2-cycle vs. 1-cycle (0.02 vs. 0.06, $p<0.05$)	£8,001
1ET + ≥3Cycle	Moderate increase (0.04 vs. 0.05, $p=$NS)	4× increase (2.04 vs. 7.29, $p<0.05$)	MBR 30 % higher than 2-cycle with identical LBR	(–)£6,340 in the nominal scenario	2× very low LBR (0.01–0.02)	Increased	6× lower for 3-cycle vs. 1-cycle (0.01 vs. 0.06, $p<0.05$) and 0.5× 3-cycle vs. 2-cycle (0.01 vs. 0.02, $p<0.05$)	£20,906
2ET + 1Cycle	10 % increase (0.36 vs. 0.40, $p<0.05$)	50 % increase (27.32 % vs. 40.97 %, $p<0.05$)		£45,964 in the nominal scenario	1.4× increase (0.16 vs. 0.23, $p<0.05$)	1.7× increase (13.89 % vs. 23.87 %, $p<0.05$)		£10,045
2ET + 2Cycle	50 % increase (0.09 vs. 0.14, $p<0.05$)	40 % increase (14.23 % vs. 19.91 %, $p<0.05$)	LBR 4× lower for 2-cycle vs 1-cycle (0.09 vs. 0.36, $p<0.05$)	£8,943 in the nominal scenario	2× increase (0.04 vs. 0.08, $p<0.05$)	Slight decrease (11.76 % vs. 10.07 %)	LBR 4× lower for 2-cycle vs. 1-cycle (0.04 vs. 0.16, $p<0.05$)	£3,173
2ET + ≥3Cycle	60 % increase (0.05 vs. 0.08, $p<0.05$)	Decreased (7.29 % vs. 6.44 %)	LBR 7× lower for 3-cycle vs 1-cycle (0.05 vs. 0.36, $p<0.05$) and 0.5× lower for 3-cycle vs. 2-cycle (0.05 vs. 0.09, $p<0.05$)	£14,016 in the nominal scenario	3× increase (0.02 vs. 0.06, $p<0.05$)	4× decrease (14.29 % vs. 3.41 %, $p<0.05$)	LBR 8× lower for 3-cycle vs. 1-cycle (0.02 vs. 0.16, $p<0.05$) and 0.5× lower for 3-cycle vs. 2-cycle (0.02 vs. 0.04, $p<0.05$)	£4,969

(continued)

Table 21.1 (continued)

	<38 years of age				≥38 years of age			
	ΔLBR	ΔMBR	LBR comparisons	ICER	ΔLBR	ΔMBR	LBR comparison	ICER in nominal scenario
3ET + 1Cycle	2.7× increase (0.15 vs. 0.40, $p < 0.05$)	15× increase (2.81 % vs. 40.97 %, $p < 0.05$).		£13,440 in the nominal scenario	3.8× increase (0.06 vs. 0.23, $p < 0.05$)	8× increase (2.82 % vs. 23.87 %, $p < 0.05$)		£6,864
3ET + 2Cycle	3.5× increase (0.04 vs. 0.14, $p < 0.05$)	13× increase (1.56 % vs. 19.91 %)	LBR 3× lower for 2-cycle vs. 1-cycle (0.14 vs. 0.40, $p < 0.05$)	£7,223 in the nominal scenario	4× increase (0.02 vs. 0.08, $p < 0.05$)	10× increase (0.0 % vs. 10.07 %, $p < 0.05$)	LBR 3× lower for 2-cycle vs. 1-cycle (0.08 vs. 0.23, $p < 0.05$)	£4,519
3ET + ≥3Cycle	2× increase (0.04 vs. 0.08, $p < 0.05$)	3× increase (2.04 % vs. 6.44 %)	LBR 5× lower for 3-cycle vs. 1-cycle (0.08 vs. 0.40, $p < 0.05$); and 0.43× lower than the 2-cycle (0.08 vs. 0.14, $p < 0.05$)	£7,169 in the nominal scenario	6× increase (0.01 vs. 0.06, $p < 0.05$)	3 sets of twins born	LBR 4× lower for 3-cycle vs. 1-cycle (0.06 vs. 0.23, $p < 0.05$) and 0.33× lower for 3-cycle vs. 2-cycle (0.06 vs. 0.08, p = N/S)	£9,249

Note: ET = embryo transfer; ΔLBR = change in live birth rate; ΔMBR = change in multiple birth rate; ICER = incremental cost-effectiveness ratio; (–)£ = cost savings

In women aged ≥38 years with two prior cycles, the ICER was approximately one-third the value compared to those who received one IVF cycle and 65 % of the value estimated for those who received three or more IVF cycles.

SET to 3ET ICER Comparison

In moving from SET to 3ET in women aged <38 years, the ICER for women who received only one IVF cycle was twice the ICER values of women who underwent two and three or more IVF cycles (£13,440 vs. £7,223 and £7,169, respectively). Among IVF patients age ≥38, moving from SET to 3ET created an ICER of £6,864 per additional live birth for women who received one IVF cycle. This value declined to £4,519 for women who received two cycles, but then increased to £9,249 for women who received three or more IVF cycles. For women ≥38 who received one IVF cycle, the move from SET to 2ET was more cost-effective than a move from SET to 3ET (£4,663 vs. £6,864, respectively).

Of note, moving from SET to 3ET in ≥38-year-old IVF patients was approximately twice as cost-effective as the move from SET to 2ET in the case of women who received either two or three or more IVF cycles. In the case of women who received two cycles, the ICER for the move from SET to 3ET was £4,519. The corresponding ICER for SET to 2ET was £8,001. In the case of IVF patients who received three or more cycles, the incremental cost to achieve an additional child with a move from SET to 3ET was £9,249. The corresponding ICER for SET to 2ET was £20,906.

Discussion

Trends with Increasing Treatment Cycles

The findings in this investigation are in parallel with those reported earlier by Templeton et al. [5], who analysed the HFEA dataset from August 1991 to April 1994. For IVF patients undergoing SET, we noted that the LBR is observed to decline precipitously with increasing treatment cycles, from 0.15 live births per patient in the <38/SET/1 cycle group to only 0.04 live births per patient in both the <38/SET/2 cycle and <38/SET/≥3 cycle populations (0.15 vs. 0.04; $p<0.01$). In the case of the 2ET population, as with the SET population, the live birth rate declines precipitously with increasing IVF cycle attempts. However, this live birth rate is higher than in the case of the SET population, at 0.36 births per patient in the <38/2ET/1 cycle group. This rate declines by a factor of 4—from 0.36 to 0.09—when comparing <38 one-cycle to <38 two-cycle women. It declines even further from 0.09 to 0.05 in comparing <38 two-cycle women to the <38 women who receive three or more IVF cycles. This indicates that women who received two IVF cycles were significantly less likely to conceive than women who underwent only one IVF cycle attempt and women who received three or more IVF cycles were significantly less likely to conceive than women after one or two IVF attempts.

Trends with Increasing Age

In the case of IVF patients having 3ET who received only one treatment cycle, those age <38 years compared to those age ≥38 achieved twice the live birth rate (0.40 vs. 0.23; $p<0.001$), although this was accompanied by an essentially doubled rate of multiple births (0.41 vs. 0.24; $p<0.001$). This doubled chance of a live birth for younger women was not observed in the 2- and ≥3-cycle populations of 3ET, however.

For IVF patients undergoing 2ET, those aged <38 years compared to women aged ≥38 were more than twice as likely to deliver a live birth. However, this often resulted in multiple births and in the case of patients undergoing IVF with 2ET, the multiple birth rate ratios between mothers <38 years and those age ≥38 declined as the number of IVF cycles increased. Stated another way, the ratio of multiple births in 2ET patients who are <38 years compared to the ratio of multiple births in 2ET women who are age ≥38 declines with increasing IVF cycle attempts.

Incremental Cost-Effectiveness

This study created a novel way of comparing total cost as a function of optimizing live birth events while minimizing and bringing awareness to the risk of multiples. For women aged ≥38, our analysis suggests that the most cost-effective ICER occurs in the setting of 2ET treatments for patients who received two IVF cycles. Here a policy change from 2ET to 3ET presents an additional cost of £3,173 per additional live birth. For women <38 years of age; the least cost-effective ICER occurred in the first IVF cycle population of women, when changing policy from 2ET to 3ET. For this latter group, a third embryo at transfer yielded an ICER of an additional £45,964 per additional live birth event.

A paradox was observed in that the most cost-effective and least cost-effective scenarios occurred, respectively, with <38-year-old and ≥38-year-old patients who underwent three or more IVF cycles, in the move from SET to 2ET. In the case of patients age <38 with at least three IVF cycles, 2ET in comparison to SET yielded an incremental cost savings of approximately £6,392 per additional live birth. This occurred because, in women aged <38 years who had at least three IVF cycles, the SET group had fractionally fewer IVF cycles compared to the 2ET group (3.88 vs. 3.83 cycles). In contrast, for women aged ≥38 years who underwent ≥3 IVF cycles, a policy move from SET to 2ET yielded an ICER of approximately £20,944 per additional live birth.

Importantly, this analysis shows that moving from 2ET to 3ET is not cost-effective in any cycle group of patients age <38. For women with one or two prior IVF cycles only, allocating 3ET to those who received SET on their last cycle is cost-effective if the willingness to pay is at least £13,600 and £8,160, respectively. For women aged <38 who have undergone three or more IVF cycles, a move from SET to 3ET is cost-effective if the willingness-to-pay is at least £6,800. Further, a

Table 21.2 Recommendations based on cost-effectiveness (arbitrary values used for willingness to pay)

Willingness to pay GBP 20k		Willingness to pay GBP 10k	
<38 years	≥38 years	<38 years	≥38 years
All policies moving to a higher embryo transfer category (2ET or 3ET) would be cost-effective except:	All policies moving to a higher embryo transfer category (2ET or 3ET) would be cost-effective except:	A policy move from 1ET to 2ET would be cost-effective *only* for women undergoing 1ET who have had two or more prior treatment cycles	A policy move to a higher embryo transfer category would be cost-effective especially for those who have undergone two or more prior treatment cycles
(a) Policy move to 3ET for women who are on their first treatment cycle	(a) Policy move to 2ET in a women ≥38 years with 1ET and history of having undergone ≥3 prior treatment cycles		
(b) Policy move to 3ET for women who are on their third or higher treatment cycle that would otherwise receive 2ET			

move from SET to 2ET is cost saving in this patient population. For those age ≥38 with only one prior IVF cycle, a move from 2ET to 3ET is not cost-effective. However, a move from SET to 3ET in this group of women is cost-effective to the extent that the willingness-to-pay is at least £6,800. For patients age ≥38 who have undergone two IVF cycles only, a move from SET to 3ET (compared to the move from 2ET to 3ET) is cost-effective if the willingness-to-pay is within the above range. Compared to the move from SET to 2ET, a shift from 2ET to 3ET is also cost-effective and within a relatively small willingness-to-pay threshold. A move from SET to 3ET is cost-effective if the willingness-to-pay is at least £8,840. However, a move from SET to 2ET is not cost-effective in this group of women.

The cost-effectiveness planes used to generate this cost analysis are based on baseline assumptions of incremental cost-effectiveness. These may be subject to uncertainty introduced by the omission of certain values (such as neonatal mortality costs) or the inclusion of non-homogeneous patients who have intrinsically different clinical profiles. As such, the above statements should serve only as a guide (Table 21.2).

Conclusion

As clinical reproductive medicine practice has become more conservative in the last decade with respect to number of embryos transferred in IVF, the HFEA national dataset is well suited to allow for a timely evaluation of ET cost-effectiveness for specific populations of patients. Our investigation shows that the live birth rate declines precipitously with increasing IVF attempts, highlighting that for this refractory subgroup of IVF patients the likelihood to achieve pregnancy and deliver is very limited. Similarly, with one notable exception (women aged <38 having SET, undergoing ≥3 IVF cycles), additional embryos for transfer are more costly in facilitating an ever valued increase in the live birth rate.

The population-based findings reported in this chapter show that IVF is more likely to lead to twins and triplets among fertility patients undergoing their first IVF cycle. Since triplets have been shown to have higher mortality rates [6], contribute disproportionately to hospital inpatient costs [4], and require antenatal and NICU services that are higher than the cost of corresponding singletons and twins [7], their incidence must be regarded as a major health risk.

Much of the advocacy for fewer embryo transfers (and especially SET) is based upon the well-known risks of cerebral palsy [8], epilepsy [9], congenital malformations [10], and other neurological sequelae [11] that accompany multiple births, rather than the iatrogenic complications of IVF. Studies on growth and physical outcomes show no differences between children conceived by IVF or by natural conception, at least on the measures of major dysmorphism and organ abnormalities during the first 2 years of life [12]. While IVF may not cause unreasonable harm when successful, a more fundamental problem is that it very seldom yields a live birth for the patients who receive more than three IVF treatments.

During pretreatment counselling, IVF patients are sometimes informed that women experience the same chance of delivering a live birth irrespective of the number of previous cycle attempts. Our analysis gives a starkly different view, indicating that an IVF patient's best outcome is achieved with her first treatment attempt where appropriate embryo transfer policies should be encouraged. Indeed, these data show the refractory nature of infertility encountered over three or more IVF attempts presages a bleak reproductive outcome for these 'repeat' patients.

Nevertheless, the forecast for IVF patients with a failed first cycle who seek a second opinion (and another IVF attempt) need not be dismal. While the treatment data used for our calculations were collected from a large number of IVF cycles, these treatments were completed before molecular testing of embryos was widely available. This means that embryo selection for these cases was based on conventional morphologic criteria, rather than comprehensive chromosomal screening. Incorporating genetic assessment of embryos is one way to individualise patient care during IVF to improve live birth rate and reduce incidence of multiple gestation. Indeed, personalised treatment guidelines for specific populations are urgently needed in order to maximise the effectiveness of IVF with respect to its long-term costs. Patients attending for reproductive endocrinology consultation should have treatments tailored to their specific age and IVF histories which can help estimate their treatment response and reproductive outcome. The data presented here suggest that maternal age and number of prior IVF cycles are highly informative in estimating the cost-effectiveness of IVF.

Can improvements in the live birth rate from transferring additional embryos be justified by the additional cost associated with a higher incidence of multiple gestation? Whether an ET policy is estimated to be cost-effective or not, patients should be entitled to make informed decisions based on the facts, which include the short- and long-term costs and short- and long-term willingness-to-pay for treatments and outcomes;,views which will change between populations and over time. It is also important to keep in mind that the majority of cost burden due to multiples stems from patients age <38 and, more particularly, from younger women who are on their first IVF cycle. This analysis strengthens the impression that SET would be cost-effective from the vantage point of insurance companies or health authorities which must absorb the additional cost of multiple births.

At present an absolute limit on number of embryos to transfer based on cost-effectiveness theory may miss the mark, however. Analysis of cost-effectiveness is discriminatory by nature. In this investigation, the central question is whether SET is a policy where a threshold will be ignored for societal preferences to help particular patients have children. By not offering more embryos to older patients with poor fertility prognosis, any absolute SET (or 2ET) limit may be viewed as an unacceptable discriminatory practice that unfairly prevents some patients from delivering progeny. Thus, any cost-effectiveness analysis should not be the sole factor for consideration in determining the role for public support for IVF coverage in general, and ET policy in particular.

This analysis had sufficient sample size to arrive at conclusions that are both meaningful and immediately relevant to decision-makers. With the exception of women aged <38/1ET/≥3 cycles, a SET policy appears to be the best value for money across the population. This is particularly the case for younger women who are on their first IVF cycle attempt. Table 21.1 summarises the conclusions made regarding embryo transfer policy with willingness to pay thresholds adjusted for inflation to 2012–2013 based on published annual healthcare inflation for the UK.

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Conflict of Interest Dr. Jones has an ownership interest in a proprietary predictive counselling tool developed from this research, marketed by ForMyOdds LLC.

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