

Obligatory Versus Elective Single Embryo Transfer in in Vitro Fertilization

A Population-based Analysis of Data from the U.K. Human Fertilisation and Embryology Authority

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OBJECTIVE: To determine how obligatory single embryo transfer (SET) and elective SET influence pregnancy outcome.

STUDY DESIGN: We compared women who underwent obligatory and elective SET using data from a comprehensive, population-based register from the United Kingdom Human Fertilisation and Embryology Authority, which contained all in vitro fertilization (IVF) treatments administered between 1991 and 1998. Generalized estimating equations were used to generate adjusted odds ratios (ORs) and 95% confidence intervals (CIs) to compare clinical pregnancy, live birth, and multiple birth rates.

RESULTS: Obligatory and elective SET had similar clinical pregnancy and live birth rates and comparable multiple birth rates. Obligatory and elective SET were equally likely to end in a live birth (OR = 1.08; 95% CI = 0.90, 1.30). Similar results were found after restricting the data to women without previous IVF births (OR =

1.18; 95% CI = 0.98, 1.42) and without previous naturally conceived live births (OR = 1.16; 95% CI = 0.95, 1.43).

CONCLUSION: This study suggests that obligatory SET can achieve pregnancy and live birth rates that are at least as good as elective SET. Equally important is the low multiple birth rate which was maintained in both forms of SET. More studies comparing elective versus obligatory SET can

Our results suggest that similar pregnancy and live birth rates can be achieved with obligatory and elective SET.

assist with achieving optimal pregnancy rates while preventing multiple births. (J Reprod Med 2013;58:95–100)

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Historically, in vitro fertilization (IVF) has been associated with an increased incidence of multiple births as well as increasing maternal and neonatal

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health risks. More recently, efforts have been made to prevent the occurrence of multiple pregnancies by eliminating excessive embryo transfers and replacing these with single embryo transfer (SET) techniques.¹⁻⁵ Of late, some publications have noted increased risks of adverse birth outcomes among SET singleton births as compared to spontaneously conceived neonates.^{6,7} Compared to double embryo transfer (DET), SET often decreases the rate of clinical pregnancy, although some studies suggest that the live birth rate remains unchanged under certain conditions, particularly, when embryos can be cryopreserved and a second (or third) round of IVF performed.^{2,5} When elective SET is used with both fresh and frozen embryo transfers, elective SET and DET have similar cumulative pregnancy rates (55.7% vs. 51.8%, $p=0.10$) and similar cumulative live birth rates (48.7% vs. 45.0%, $p=0.20$).⁸ Similarly, Ryan et al⁹ reported no change in pregnancy rate and decreased multiple gestation rates after adopting a policy of mandatory SET for women at highest risk of multiple gestations and an educational program designed to explain the risks of twin gestations.

Pregnancies resulting from SET actually comprise two distinct populations: obligatory SET and elective SET. Obligatory SET occurs when there is at once only one embryo available for transfer. The term *elective SET* is used to describe the selection of the highest quality embryo from among all those that are available, and its use as the sole option at the time of embryo replacement. Elective SET is well known to occur more often in recent years because of advances in hyperstimulation and the recent changes in approach to IVF that prioritize singleton births. With obligatory SET, on the other hand, embryo quality may be suboptimal, a factor which impacts early pregnancy loss.¹⁰ To our knowledge, only one study has compared and examined pregnancy outcomes in elective versus obligatory SET.⁵ The authors found that clinical pregnancy rates were lower in women with obligatory SET, and, unlike elective SET, the pregnancy rate was not affected by maternal age.⁵ However, it is unclear whether the differences in clinical pregnancy rates were statistically significant as these data were not presented.⁵

The prevention of multiple births is as important for medical as it is for social reasons, not the least of which is the additional cost associated with multiples in terms of added maternal hospital days, antenatal care, and prolonged neonatal intensive care

unit stays for many if not most of the preterm neonates associated with twin pregnancy.¹¹ Under these circumstances a better understanding of the pregnancy and live birth rates that accompany both types of SET may further demonstrate why either type of SET may be preferable to multiple embryo transfers and whether or not one type of SET is preferable over the other. Accordingly, we sought to compare the clinical pregnancy rate and birth outcomes of women who underwent obligatory and elective SET using data that were derived from the most comprehensive, population-based register currently in existence.¹¹ Data analyzed by one of our authors (C.J.) over the course of 6 years (1999–2005) from this United Kingdom (U.K.) Human Fertilisation and Embryology Authority (HFEA) registry contained plurality outcomes for all treatments of IVF administered in the U.K. from 1991 to 1998.¹¹ The HFEA became operational in August 1991 after it was created by the Human Fertilisation and Embryology Act of 1990.¹² It is tasked with regulating fertility treatments and related activities, providing information about treatments and services to patients, governmental agencies, and the general public while maintaining a register of all patients, treatments, and births that are the result of fertility treatments.¹²

Materials and Methods

All treatments occurring between July 1, 1991, and December 31, 1998, were eligible for inclusion. The data which formed the national dataset (analyzed here) were provided by 68 separate clinics working under the HFEA guidelines of the time. Permission was granted by the then-chairperson of the HFEA to the senior author (C.J.), not only to use for his doctoral thesis but to allow for the population-based IVF data to be analyzed in a new light and disseminated in the public domain. Since we sought to differentiate between outcomes of obligatory (only 1 embryo available for transfer) and elective (1 embryo out of several selected for transfer) SET, the study population was accordingly classified into 2 groups (obligatory versus elective). Birth outcomes, IVF treatment characteristics, and characteristics of mothers who had obligatory and elective SET procedures were compared using χ^2 tests. Confounders and covariates examined in this study include maternal age (<35 and ≥ 35), presence of endometriosis (yes or no), tubal disease (yes or no), miscarriage (yes or no), ectopic pregnancy (yes or no), number of years infertile (<5 or ≥ 5), gravidity

(0 or ≥ 1), previous IVF live births (yes or no), and previous natural live births (yes or no). The analysis also included IVF-related factors, such as use of cryoembryos (yes or no), gamete type (0 = partner sperm, partner egg; 1 = donor sperm, partner egg; 2 = partner sperm, donor egg; 3 = donor sperm, donor egg [i.e., donor embryo]) and the use of hormone stimulation (yes or no). Egg donor information (clinical and epidemiologic profiles) was not recorded in the HFEA dataset. Clinical pregnancy was defined by ultrasound examination.

Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were generated using logistic regression. Intraclass correlations were corrected using the generalized estimating equations framework.¹³ SAS (SAS Institute, Inc., Cary, North Carolina) was used to conduct all analyses. Tests of hypotheses were two-tailed with a type 1 error rate fixed at 5%. This study was approved by the Institutional Review Board at the University of South Florida. Publications resulting from this original sampling of data from the HFEA, London, were exempt from the current data acquisition process but approved by that body for analysis, dissertation, and publication.

Results

A summary of the number of embryos transferred for women with at least 1 egg available for fertilization and transfer is presented in Table I. In women who had only 1 egg collected and available for fertilization, only 49.5% of them ultimately had a successful embryo transfer and the remaining women did not have any embryos transferred. On the other hand, among women who had multiple eggs collected and available for fertilization, only 8.2% underwent SET. Most women underwent the transfer of 2 (31.0%) or 3 (48.1%) embryos. After excluding incomplete cycles in which no embryos were trans-

ferred (18.2%) and an additional 5.4% of cycles with an unknown number of eggs available for fertilization, 134,924 IVF cycles (77.4%) were available for inclusion in the study. Of the 14,509 single embryo transfers that were made during the study period, fully 86.1% were elective and 13.9% obligatory.

The definition of a live birth by the HFEA was a baby who was born alive and survived through 28 completed days postdelivery. Using this uncommon but conservative definition, a live birth resulted from 7.8% and 6.9% of obligatory and elective SETs, respectively (Table II). The majority of births were live singletons, regardless of embryo transfer type. Clinical pregnancy resulted from 8.8% of elective transfers and 10.1% of obligatory transfers ($p = 0.05$). The rate of multiple birth for obligatory transfer was twice the rate for elective transfer (0.2% [18 sets of multiples] vs. 0.1% [3 sets of multiples]), but the difference was not statistically significant ($p = 0.96$). The risk that multiple births can occur from a single embryo is well known to be elevated in the case of IVF versus natural conceptions.¹⁴ As shown in Table III, the 2 subpopulations had similar rates of miscarriages and ectopic pregnancies. However, women with obligatory SETs were more likely to have endometriosis (51.8% vs. 36.0%, $p < 0.001$), less likely to have undergone hormonal stimulation (60.7% vs. 79.2%, $p < 0.001$), and less likely to have used cryopreserved embryos (3.4% vs. 20.1%, $p < 0.001$). Of note, the proportion of live births was slightly higher for women who underwent natural cycle IVF (10.3%) in comparison to those who underwent cycles of IVF following hormone stimulation (6.9%).

Table I Proportion of Harvested Eggs Available for Transfer Versus Embryos Transferred, United Kingdom, 1991–1998

Transfer data	No.	%
Single egg harvested		
0 Embryos transferred	2,064	50.5
1 Embryo transferred	2,024	49.5
Multiple eggs harvested		
0 Embryos transferred	19,309	12.7
1 Embryo transferred	12,485	8.2
2 Embryos transferred	47,211	31.0
3 Embryos transferred	73,204	48.1

Table II Distribution of Maternal Factors and Pregnancy Success Rates by Obligatory Transfer Status

Maternal factor	Elective	Obligatory	p Value ^a
	N = 12,485 (86.1%)	N = 2,024 (13.9%)	
Maternal age (yr)			
< 35	49.6	43.1	< 0.001
Parity			
0	81.8	74.5	< 0.001
≥ 1	18.3	25.5	
Gravidity			
0	58.0	48.4	< 0.001
≥ 1	42.0	51.6	
Clinical pregnancy rate	8.8	10.1	0.05
Live birth	6.9	7.8	0.40
Multiple birth	0.1	0.2	

^aBased on χ^2 tests.

Table III IVF Treatment Characteristics by Type of Single Embryo Transfer (Obligatory Verses Elective), United Kingdom, 1991–1998

	Elective	Obligatory	p Value ^a
	N = 12,485 (86.1%) %	N = 2,024 (13.9%) %	
Years infertile			
< 5	40.4	44.6	< 0.001
≥ 5	59.6	55.4	
Endometriosis	36.0	51.8	< 0.001
Tubal disease	10.6	12.3	0.03
Ectopic pregnancy	0.2	0.4	0.10
Miscarriage	1.2	1.4	0.27
Cryoembryo used	20.1	3.4	< 0.001
Hormone stimulation	79.2	60.7	< 0.001
Gamete type			
Partner sperm/partner egg	88.9	93.4	< 0.001
Donor sperm/partner egg	2.7	0.9	
Partner sperm/donor egg	8.1	5.5	
Donor sperm/donor egg	0.3	0.2	

^aTested using χ^2 tests.

Adjusted models (Table IV) show that obligatory and elective SETs had similar likelihoods of achieving a live birth (OR = 1.08; 95% CI = 0.90, 1.30). Similar results were found after restricting the study population to women without previous IVF births (OR = 1.18; 95% CI = 0.98, 1.42) or women without previous live births conceived naturally (OR = 1.16; 95% CI = 0.95, 1.43). There were no differences in the chance of achieving a singleton birth between elective and obligatory SET procedures. Few multiple births (3 sets of triplets and 18 sets of twins) occurred in the study population, but there were still no differences in the risk of multiple birth (OR = 1.10; 95% CI = 0.31, 3.90) between the 2 SET types.

Discussion

When comparing obligatory to elective SET, no sta-

tistically significant differences were observed in either clinical pregnancy (10.1% and 8.8%, respectively) or live birth rates (7.8% and 6.9%, respectively). Further, the comparable likelihood of having a singleton live birth following obligatory SET and elective SET was maintained even after adjusting for covariates (OR = 1.08; 95% CI = 0.90, 1.30). Although we initially examined the impact of gamete type and cryopreservation in our models, only cryopreservation had a significant impact on the effect estimates. Most cycles did not use donor eggs or sperm. Although Vilska et al⁵ reported different pregnancy rates for obligatory and elective SET, it is unclear whether the difference was statistically significant, thus it is difficult to compare findings from the two studies. When compared to ours, that study may have differences with regard to embryo quality and population age distribution, thus accounting for the apparent inconsistency.

In our study only 49.5% of embryos were transferred from a single available egg, whereas in situations in which multiple eggs were available for transfer, 87.3% of resultant embryos were subsequently transferred ($p < 0.0001$). Since embryo quality is an important predictor of pregnancy success, this finding probably reflects the desire to transfer only the highest quality embryos.^{10,15} Stated another way, it is possible that a greater percentage of the embryos available for obligatory SET were not transferred because they were suboptimal. Supporting this hypothesis are the findings from one study which found an association between pregnancy outcome and the number of embryos available for transfer.¹⁶ In that study obligatory SET had more than a threefold increased risk of early pregnancy loss as compared to elective SET or DET (OR = 3.26; 95% CI = 1.46, 7.26).¹⁶ However, the sample size in the obligatory SET group was small ($n = 53$). A previous analysis using an expanded

Table IV Odds Ratios and 95% Confidence Intervals for the Association Between Obligatory Single Embryo Transfer and Elective Single Embryo Transfer (Referent) and Birth Outcome in All Women Included in the Study, Women Without Previous IVF Births, and in Women Without Previous Natural Live Births

	Birth outcome					
	All live births		Singleton		Multiple	
	OR	95% CI	OR	95% CI	OR	95% CI
All women ^a	1.08	0.90, 1.30	1.08	0.90, 1.30	1.10	0.31, 3.90
Women without previous IVF births ^a	1.18	0.98, 1.42	1.18	0.98, 1.42	1.20	0.34, 4.27
Women without previous natural live birth ^b	1.16	0.95, 1.43	1.16	0.94, 1.42	1.45	0.42, 5.05

^aAdjusted estimates were generated after controlling for the following covariates: maternal age, parity, and use of cryopreserved embryos.

^bUnadjusted odds ratios. Adjusted estimates could not be generated because of limited sample size.

dataset for a subset of the population examined here evaluated the number of eggs fertilized and the number of embryos transferred in relation to the odds of a birth.¹⁷ The authors found that there was a greater likelihood of a birth when multiple eggs were fertilized and available for transfer.¹⁷ The author did not examine SET as was done in this analysis, but the results suggest that embryo quality may play an important role in IVF success measures.

Misclassification may have occurred in our study among women who had multiple eggs available but had only 1 egg become fertilized. Therefore, it is possible that some of the elective SET cases described here were actually obligatory, possibly contributing to the low pregnancy rate. However, previous studies of the same study population have reported low live birth rates per embryo transferred, especially with advanced maternal age.¹⁸ On average, the study population examined was 35 years of age at the time of treatment, thus advanced maternal age may have contributed to the low pregnancy rates. We did not have data on the proportion of eggs that were successfully fertilized, thus this potential source of misclassification could not be further evaluated.

In our study the rates of ectopic pregnancy were higher in the obligatory group (3.46/1,000 cycles) than for the elective group (0.96/1,000), although there was a small number of cases ($n=7$ and $n=21$ for the obligatory and elective groups, respectively) and these differences were not statistically significant ($p=0.10$). Additionally, similar rates of miscarriage were observed (1.43/100 and 1.15/100 cycles in the obligatory and elective groups, respectively).

At present, and unfortunately, no international consensus exists regarding the validity of measuring embryo quality. Information on embryo quality was unavailable for the present analysis, as were other maternal factors that are known to negatively impact IVF outcomes, such as body mass index (BMI),^{16,19-21} although the relationship between BMI and IVF outcomes remains poorly understood.^{20,21} Given that obligatory and elective SET have similar live birth rates, it is likely that the transferred embryos were of similar quality. While we acknowledge the dataset is from 1991–1998, many policy changes were implemented in 1991 that are captured, and multiple national analyses over time (HFEA and the Society for Assisted Reproductive Technology, to report but the major ones) have verified that SETs remain scarce in most settings. Furthermore, prior to 2009 most policy

changes focused on 2 and 3 embryo transfers, thus the proportion of SETs has remained relatively stable, especially when compared to 2 and 3 embryo transfers. Data from the HFEA underscores this point as the SET live birth rate has remained relatively constant between 1992 and 2006.²² We further evaluated this in our dataset and found no difference in clinical pregnancy rate ($p=0.16$) or live birth rate ($p=0.06$) over time. As such, we feel the dataset remains prescient and its statistical power useful in highlighting SET practices that existed in the 1990s and have held steady in both the U.K. and United States to the present day.

Despite these limitations that exist even today, our study is strengthened by its large, population-based sample size and its ability to clearly differentiate pregnancy rates and outcomes. To our knowledge only one previous study addressed or defined obligatory and elective embryo transfer. That study found slightly lower pregnancy rates in obligatory as opposed to elective SET, but it is unknown whether the difference was statistically significant as test statistics were not reported.⁵ The low multiple birth rate achieved from both forms of SET is of importance given the current efforts to prevent complications resulting from multiple births. Most importantly, our results suggest that similar pregnancy and live birth rates can be achieved with obligatory and elective SET. More studies comparing elective versus obligatory SET in large population-based datasets would inform patients and clinical decision makers on how to formulate evidence-based embryo transfer practices and policies that achieve optimal live birth rates with respect to the risk of multiple births.

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