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Application of a Validated Prediction Model for in Vitro Fertilization: Comparison of Live Birth Rates and Multiple Birth Rates with One Embryo Transferred over Two Cycles versus Two Embryos in One Cycle

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Abstract

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Condensation: Cumulative live birth rates with one embryo transferred over two cycles versus two embryos in one cycle were comparable, while greatly reducing the probability of a multiple birth.

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Objective—To use a validated prediction model to examine whether single embryo transfer (SET) over two cycles results in live birth rates (LBR) comparable to two embryos transferred (DET) in one cycle, while reducing the probability of a multiple birth (i.e., multiple birth rate, MBR).

Study Design—Prediction models of LBR and MBR for a woman considering ART developed from linked cycles from the Society for Assisted Reproductive Technology Clinic Outcome Reporting System (SART CORS) for 2006-2012 was used to compare SET over two cycles with DET in one cycle. The prediction model is based on a woman's age, body mass index (BMI), gravidity, prior full-term births, infertility diagnoses, embryo state, number of embryos transferred, and number of cycles.

Results—To demonstrate the effect of number of embryos transferred (1 or 2), the LBRs and MBRs were estimated for women with a single infertility diagnosis (male factor, ovulation disorders, diminished ovarian reserve, and unexplained); nulligravid; BMI of 20, 25, 30, and 35; and ages 25, 35, and 40 by cycle (1^{st} or 2^{nd}). The cumulative LBR over two cycles with SET was similar to or better than the LBR with DET in a single cycle. For example, for women with the diagnosis of ovulation disorders, age 35, BMI 30: 54.4% versus 46.5%; for women age 40, BMI 30: 31.3% versus 28.9%. The MBR with DET in one cycle was 32.8% for women age 35 and 20.9% for women age 40; with SET the cumulative MBR was 2.7% and 1.6%, respectively.

Conclusions—Applying this validated predictive model demonstrated that the cumulative LBR is as good as or better with SET over two cycles than with DET in one cycle, while greatly reducing the probability of a multiple birth.

Keywords

assisted reproductive technology; multiple births; live births; prediction model

Introduction

Since the birth of the first child from in vitro fertilization (IVF) over 35 years ago, more than five million babies have been born from this technology [1]. Worldwide, more than one million IVF cycles resulting in the birth of more than 250,000 babies occur annually [2]. In 2012 in the United States, there were more than 65,000 babies born from IVF, accounting for 1.6% of all births, a proportion which has doubled over the past decade [3-7].

Multiple births are one of the primary acknowledged adverse outcomes of IVF [8-10]. In 2010 in the United States, multiple-birth deliveries accounted for nearly 30% of all IVF births and 44.5% of all IVF infants [9]. On a national basis, IVF infants account for 0.8% of all singletons, but 43.4% of twins and 32.5% of all triplet and higher-order multiples [9]. Although infants of multiple births comprise only 3% of all live births, they account for 13% of all preterm births (<37 weeks), 15% of all early preterm births (<32 weeks), 21% of all low birthweight infants (LBW, <2,500 g), and 25% of all very low birthweight infants (VLBW, <1,500 g) [11-16]. The average birthweight and gestational age is 3,296 g at 38.7 weeks for singletons, compared to 2,336 g at 35.3 weeks for twins, 1,660 g at 31.9 weeks for triplets, and 1,291 g at 29.5 weeks for quadruplets, and 1,002 g at 26.6 weeks for quintuplets [15]. The two most important factors affecting perinatal mortality are gestational age and

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relative birthweight [16, 17]; with each additional fetus both of these factors are compromised [18, 19]. As a consequence, the risk of dying before their first birthday is nearly seven times greater for twins and almost twenty times greater for triplets and quadruplets, and the survivors are at continued higher risk of perinatally-related mental and physical handicaps [20-24]. It is estimated that twin pregnancies produce a child with cerebral palsy twelve times more often than do singleton pregnancies and that one-fifth of all triplet pregnancies and one-half of all quadruplet pregnancies result in at least one child with a major handicap [25, 26]. Even when matched for gestational age, at one year of age, children of multifetal pregnancies have nearly three times the risk for cerebral palsy [27].

Historically, multiple embryos have been transferred to compensate for low implantation rates which in turn, increased the likelihood of a multiple pregnancy, a known complication of IVF [28, 29]. In an effort to reduce the multiple birth rate with IVF, the Society for Assisted Reproductive Technology issued the first clinical guidelines on the number of embryos to transfer in 1998; these guidelines have been revised downward in 1999, 2004, 2006, 2008, 2009, and most recently in 2013 [30-36]. The effect in clinical practice has been a reduction in the number of embryos transferred, as well as a dramatic decrease in the higher-order multiple rate (triplets, quadruplets, and higher) due to IVF [37, 38]. Analyses of IVF cycles in the US from 1996 to 2002 indicated a progressive trend of transferring fewer embryos [39]. Data from the Society for Assisted Reproductive Technology Clinic Outcome Reporting System (SART CORS) from 2004-2012 shows that the proportions of single embryo transfer (SET) and double embryo transfer (DET) have increased from 7.0% to 23.1%, and 32.9% to 49.8%, respectively, while the transfer of three or more embryos has decreased from 60.1% to 27.1%.. During this same time period, the proportion of singleton births from IVF increased from 67.9% to 73.8%, while twin and triplet and higher-order births decreased from 29.7% to 25.4%, and 2.4% to 0.8%, respectively. Single embryo transfer is recommended in the most recent guidelines for women under age 35 with a favorable prognosis (first cycle of IVF, good embryo quality, excess embryos available for cryopreservation, or previous successful IVF cycle) [36].

We developed validated prediction models for LBR and MBR using the SART CORS data from 2004-2011 [40]. We have subsequently revised the model to include data from 2006-2012; this revised model is implemented on the Society for Assisted Reproductive Technology website (www.sart.org) [40]. The goal of this analysis is to compare the estimates of LBR and MBR when two embryos are transferred, either (1) both in one cycle (double embryo transfer, DET), or (2) in two successive cycles, each with a single embryo (i.e., SET).

Materials and Methods

Development and validation of the original model has been described previously [40]. This analysis was based on de-identified data, and was therefore deemed exempt by IRB review at Michigan State University (as defined in 45 CFR 46.l02(f). We only describe changes between the current and original model. Data for this model used cycles reported between 2006-2012. Instead of categorizing age and BMI and fitting the model to the categorical data, we included both a linear and quadratic term for both age and BMI in the model. In

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addition, we included an indicator variable for reporting year. We developed separate models for the LBRs when one and two embryos are transferred. Since the rate of multiple births is very low when one embryo is transferred, we modeled MBR simultaneously for both one and two embryos transferred with an indicator variable to denote the number of embryos transferred. The other variables included in the modeling were number of prior full term births (0, 1, ≥2), number of infertility diagnoses (1, >1), infertility diagnosis (male factor, endometriosis, ovulation disorders, diminished ovarian reserve, tubal ligation, tubal hydrosalpinx, tubal other, uterine factor, other factor, and unexplained).

Logistic regression modeling was performed, using a backward-stepping algorithm, eliminating variables until those remaining were all significant at $p<0.05$. In this application of the prediction model, we estimated the LBRs and MBRs for women with: 1) a single infertility diagnosis of male factor, ovulation disorders, diminished ovarian reserve, or unexplained; 2) no prior conceptions or live births (nulligravid); 3) cycles using only, autologous oocytes; 4) cycle 1 used only fresh embryos.. The model for SET at cycle 1 included data from 33,065 cycles; for DET at cycle 1 it included 126,921 cycles, and for fresh SET at cycle 2 it included 8,682 cycles and thawed SET at cycle 2 it included 6,747 cycles. Estimates are reported for ages 25, 35, and 40 years and for BMIs of 20, 25, 30, and 35. Since the LBR improved with reporting year, all estimates are calibrated to 2012 (the most recent year with data).

Live birth rates and multiple birth rates

The cumulative LBR at cycle 2 is equal to LBR at cycle 1 + LBR at cycle 2 * (1 – LBR at cycle 1). This assumes that there is no contraindication during cycle 1 to continuing into cycle 2. The cumulative MBR at cycle 2 is equal to MBR at cycle 1 + MBR at cycle 2 * (1 – LBR at cycle 1).

Results

The LBR and MBR at cycle 1 and the cumulative LBR and MBR over two cycles when one embryo is transferred are presented in Table 1 for combinations of four infertility diagnoses (male factor, ovulation disorders, diminished ovarian reserve, and unexplained), three ages (25, 35, and 40 years), and four BMI levels (20, 25, 30, and 35) for women without a prior birth, a single infertility diagnosis, using fresh, autologous oocytes in cycle 1 and separately for fresh SET in cycle 2 and thawed SET in cycle 2. The cumulative LBR at cycle 2 with fresh SET in both cycles is greater or equal to the LBR at cycle 1 with DET, ranging from 23.0 – 63.9% compared to 21.8 – 53.4%. The cumulative MBR at cycle 2 with SET is between 1.4 - 3.0% compared to 18.3 – 39.8% with DET in cycle 1. The largest difference in LBR are among the women with the youngest ages, 17-20% improvement in LBR when two cycles with SET are used compared to one cycle with DET. This reduces to a 4-6% improvement at age 40. The MBR with two cycles of SET is reduced by 92-94% from the MBR with DET.

Among women with the same diagnosis and age, an increase in BMI from 20 to 35 is associated with a reduction in LBRs by about 6-7 percentage points for women age 25,

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about 5-6 percentage points for women age 35, and about 3-4 percentage points for women age 40. Among women with the same diagnosis and BMI, an increase in age from 25 to 35 is associated with a reduction in LBRs by about 4-6 percentage points; an increase in age from 35 to 40 is associated with a reduction in LBRs by about 18-24 percentage points.

We also developed a model where the second cycle used a thawed embryo. These models were based on the assumption that there were additional embryos of adequate quality to freeze in cycle 1. The cumulative LBRs and MBRs did not differ significantly from those reported in Table 1 for women aged 20 to 30 with fresh SET in both cycle 1 and cycle 2. However, because there were relatively few cases of SET with thawed embryos in cycle 2 for older women, the LBRs for women over age 30 should be viewed with caution.

Discussion

Contemporary challenges of ART include a need to shift from achieving a pregnancy to achieving a successful outcome and narrowing the gap in perinatal outcomes between assisted versus spontaneous pregnancies [41]. Success for modern IVF is defined as a singleton pregnancy resulting in a healthy singleton infant born at term [42-44]. While prior prediction models have been proposed, ranging from 642 to 12,003 cycles [45-48], the current models have the advantage of much larger numbers [33,065 (SET cycle 1), 126,921 (DET cycle 1) and 8,682 cycles (SET cycle 2)]. This model also accounts for the effect of the woman's BMI, which has been shown in prior studies to adversely affect live birth rates, even with the use of donor oocytes [49-52]. These results provide valuable information for patients, practitioners, and insurance companies.

Since this analysis used a clinical database, cycles where SET was used may not be representative of all cycles. SET is more likely to be used when the treating physician believes that the conditions are optimal (i.e., good embryo development and uterine environment). Therefore, the probabilities estimated by the model should be viewed as appropriate when there are no factors, such as increased age or diagnosis, that are indicative of a negative prognosis.

Prevention of twin pregnancies after IVF with SET has been advocated for more than a decade, with results from clinical studies and trials demonstrating comparable live birth rates and greatly reduced multiple birth rates with repeated cycles of SET versus one cycle of DET [53-60]. In addition, transferring excess embryos has been shown to have a negative effect on the embryos that subsequently develop, including subtle reductions in birthweight and birthweight-for-gestation even when plurality at six weeks gestation and at birth are the same [61]. Others have shown greater risks for prematurity and low birthweight with DET vs SET [62, 63]. Fetal loss early in pregnancy is associated with lowered birthweight, shortened gestation, and reduced birthweight-for-age, whereas losses after eight weeks' gestation are associated with adverse neurological sequelae for the survivors [64-67]. Perinatal outcomes with SET is associated with decreased risks of preterm birth and low birth weight compared with DET, but higher risks compared to spontaneously-conceived singletons [68].

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In spite of evidence supporting the use of single embryo transfer, there has been resistance among patients. Numerous factors contribute to this resistance including the increased cost of additional cycles, lack of insurance coverage, additional time commitment required to continue treatment for a second or third cycle, and concern regarding overall success rates. In regard to cost, several studies have demonstrated that fewer embryos are transferred in States with mandated insurance coverage [69-71]. On an international basis, the affordability of IVF was independently and negatively associated with the number of embryos transferred: the decrease in the cost of a cycle of 10 percentage points of disposable income predicted a 5.1% increase in single-embryo transfer cycles [72]. Regardless of the cost, however, some patients still see birth of twins as a more positive outcome than birth of a singleton in that two babies born at once can constitute a completed family, and patients will no longer have to return to the rigors and time commitments of fertility treatment [73]. Again, education is key to ensuring that patients understand the long term medical, financial and social risks they assume in embarking on a twin gestation.

Although studies have demonstrated patient support for single embryo transfer, this requires that the provider be committed to spending time and energy on extensive patient education regarding the perinatal and childhood risks associated with multiples [74, 75]. As a part of this education process, patients must be comfortable with the comparative rate of achieving a live birth with transfer of a single embryo rather than two embryos at the specific clinic at which they are being treated. As clearly demonstrated on the national SART website (www.sart.org), success rates can vary with marked variability added by success of embryo freezing and thawing. Our study summarizes results for national data.

Policies that encourage SET will lead to significant savings to the healthcare system, including insurance companies. A recent study compared the costs of twins versus singleton pregnancy by calculating the total all-cause healthcare cost for mothers from 27 weeks before delivery to 30 days after delivery and for infants up to age one [76]. This study found that for IVF-conceived pregnancies, the average costs were $26,922 for singletons and $115,238 for twins. The average cost for higher order multiples was $434,669. Thus, on a per infant basis, healthcare costs were more than double for twins compared to having two singleton births. Covering IVF while encouraging SET may well be a cost-effective strategy for the health insurance industry to avoid the high costs associated with prematurity and twins.

In summary, these analyses demonstrate that cumulative live birth rates achieved with two cycles of SET are as good as or better than one cycle of DET, while reducing the probability of a multiple birth by more than 90%. This analysis examines outcomes based on sequential fresh ART treatment cycles. The choice between two SET cycles and one DET cycle should consider the total cost of the procedures (two SET versus one DET) and hospitalization (singleton birth versus multiple birth) and the reduction in long-term complications (singleton versus multiple birth). Future analyses will refine this model to include other treatment paradigms. Information provided may not only assist patients with decisions on the number of embryos to transfer, but also may also inform practitioners and insurance companies.

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Table 1

Live Birth Rates and Multiple Birth Rates by Maternal Age, BMI, Diagnosis, and Single Embryo Transfer (SET) and Double Embryo Transfer (DET)*

			Live Birth Rates (%)				Multiple Birth Rates (%)			
			SET			DET	SET			DET
			Cycle 1	Cumulative, Cycle 2		Cycle 1	Cycle 1	Cumulative, Cycle 2		Cycle 1
Diagnosis	Age	BMI	Fresh cycle 1	Fresh cycle 1, Fresh cycle 2	Fresh cycle 1, Thawed cycle 2	Fresh cycle 1	Fresh cycle 1	Fresh cycle 1, Fresh cycle 2	Fresh cycle 1, Thawed cycle 2	Fresh cycle 1
Male factor	25	20	45.9	62.7	63.4	53.4	2.1	3.0	3.2	39.8
		25	45.2	61.4	62.0	52.3	2.1	3.0	3.2	39.8
		30	43.2	59.2	59.8	50.3	2.1	3.0	3.3	39.8
		35	40.0	56.0	56.8	47.1	2.1	3.1	3.4	39.8
	35	20	39.7	56.7	59.3	49.6	1.5	2.5	2.5	32.8
		25	39.0	55.4	57.8	48.6	1.5	2.5	2.5	32.8
		30	37.0	53.1	55.3	46.5	1.5	2.5	2.6	32.8
		35	34.0	50.0	51.8	43.4	1.5	2.6	2.6	32.8
	40	20	22.3	33.1	40.0	31.5	0.8	1.4	1.6	20.9
		25	21.8	32.0	38.3	30.6	0.8	1.4	1.6	20.9
		30	20.4	30.2	36.0	28.9	0.8	1.5	1.6	20.9
		35	18.3	27.7	33.1	26.4	0.8	1.5	1.6	20.9
Ovulation	25	20	47.8	63.9	64.1	53.4	2.1	3.1	3.1	39.8
disorders		25	47.0	62.7	62.8	52.3	2.1	3.1	3.2	39.8
		30	45.0	60.5	60.6	50.3	2.1	3.2	3.2	39.8
		35	41.8	57.3	57.6	47.1	2.1	3.2	3.3	39.8
	35	20	41.5	58.0	60.1	49.6	1.5	2.6	2.5	32.8
		25	40.7	56.7	58.6	48.6	1.5	2.6	2.5	32.8
		30	38.8	54.4	56.4	46.5	1.5	2.7	2.5	32.8
		35	35.7	51.3	53.2	43.4	1.5	2.7	2.6	32.8
	40	20	23.7	34.2	41.3	31.5	0.8	1.5	1.6	20.9
		25	23.1	33.1	39.6	30.6	0.8	1.5	1.6	20.9
		30	21.7	31.3	37.3	28.9	0.8	1.6	1.6	20.9

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			Live Birth Rates (%)				Multiple Birth Rates (%)			
			SET			DET	SET			DET
			Cycle 1	Cumulative, Cycle 2		Cycle 1	Cycle 1	Cumulative, Cycle 2		Cycle 1
Diagnosis	Age	BMI	Fresh cycle 1	Fresh cycle 1, Fresh cycle 2	Fresh cycle 1, Thawed cycle 2	Fresh cycle 1	Fresh cycle 1	Fresh cycle 1, Fresh cycle 2	Fresh cycle 1, Thawed cycle 2	Fresh cycle 1
		35	19.5	28.8	34.3	26.4	0.8	1.6	1.6	20.9
Diminished	25	20	40.4	56.0	60.5	47.2	1.8	2.8	3.1	36.0
Ovarian		25	39.7	54.7	58.8	46.2	1.8	2.8	3.1	36.0
Reserve		30	37.7	52.5	56.2	44.1	1.8	2.8	3.1	36.0
		35	34.7	49.3	52.7	41.0	1.8	2.9	3.2	36.0
	35	20	34.4	50.0	54.9	43.5	1.3	2.3	2.3	29.4
		25	33.7	48.7	53.1	42.5	1.3	2.3	2.3	29.4
		30	31.9	46.5	50.5	40.4	1.3	2.4	2.4	29.4
		35	29.1	43.4	47.2	37.5	1.3	2.4	2.4	29.4
	40	20	18.6	27.8	35.2	26.4	0.7	1.4	1.4	18.3
		25	18.1	26.8	33.6	25.6	0.7	1.4	1.4	18.3
		30	16.9	25.2	31.5	24.1	0.7	1.4	1.4	18.3
		35	15.1	23.0	28.9	21.8	0.7	1.4	1.4	18.3
Unexplained	25	20	46.3	62.9	63.6	53.4	2.1	3.0	3.2	39.8
		25	45.5	61.6	62.2	52.3	2.1	3.0	3.2	39.8
		30	43.5	59.4	60.1	50.3	2.1	3.0	3.3	39.8
		35	40.3	56.3	57.0	47.1	2.1	3.1	3.4	39.8
	35	20	40.0	57.0	59.5	49.6	1.5	2.5	2.5	32.8
		25	39.3	55.6	58.0	48.6	1.5	2.5	2.5	32.8
		30	37.3	53.4	55.5	46.5	1.5	2.5	2.6	32.8
		35	34.3	50.3	52.1	43.4	1.5	2.6	2.6	32.8
	40	20	22.6	33.3	40.2	31.5	0.8	1.4	1.6	20.9
		25	22.0	32.2	38.5	30.6	0.8	1.4	1.6	20.9
		30	20.6	30.4	36.2	28.9	0.8	1.5	1.6	20.9
		35	18.5	27.9	33.2	26.4	0.8	1.5	1.6	20.9

* Models adjusted for all of the factors included in the table, assuming no prior births, a single infertility diagnosis, and the use of autologous oocytes.