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Original Research Article

Is the cumulative live birth rate following in vitro fertilization (IVF) lower with government coverage than prior to coverage?

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ABSTRACT

Background: Most studies conclude that the cumulative pregnancy rate depends on embryo quality and quantity, which is directly related to patient's age. In the best-case scenario, the cumulative pregnancy rate reaches 79% when the number of embryos reaches 15. Other studies reported 75% probability of live birth after 6 cycles of controlled ovarian stimulation and IVF.
Methods: Retrospective cohort study comparing IVF cycles between January 2008 to December 2009 (before governmental coverage), and between January 2012 to December 2013. University-affiliated private IVF clinic. 298 good prognosis IVF patients from 2008-2009 and 610 patients from 2012-2013 were included. The cumulative LBR per IVF cycle was the main outcome measure; the secondary outcome measures were the type of protocol used, percentage of ICSI cycles, fertilization rate, proportion of day 3 versus (vs) day 5 embryo transfers, average number of embryos transferred, average number of frozen embryos, the clinical pregnancy rate and the multiple pregnancy.
Results: no statistically significant difference in the cumulative LBR; it was 44.8% in 2008-2009 but 40.3% in 2012-2013. p: 0.134. The long agonist protocol was used the most 2008-2009 (75.5% of the cycles) compared to antagonist protocol in 2012-2013 (77.2%) p <0.01. There was no difference in the use of ICSI, but the fertilization rate in 2012-2013 (60.9% vs 65.9%, p=0.001). The proportion of day 3 embryos transferred in 2008-2009 (82.2%) and 2012-2013 (43.9%), p=0.005, and the proportion of day 5 embryos transferred is 3.7% in 2008-2009 but 54.9% in 2012-2013, p<0.001. The average number of embryos transferred in 2008-2009 was 1.96 vs 1.08 in 2012-2013. The average number of frozen embryos per cycle was not significantly different. The clinical pregnancy rate was not significantly different (56.8% vs 54.3%). The multiple pregnancy rate is 19.4% in 2008-2009 and 0.5% in 2012-2013.
Conclusions: In good prognosis IVF patients, the cumulative LBR per cycle started was not significantly different after IVF provincial coverage and the move towards eSET on day 3 or day 5. No advantage of transferring multiple embryos in this group of patients, and that transferring one at a time reduces significantly the multiple pregnancy rate and its complications.

Keywords: Cumulative pregnancy rate (CPR), Frozen embryo, ICSI, IVF, LBR, Number of embryo transfer

INTRODUCTION

The first childbirth resulting from an IVF treatment cycle occurred in 1978 when Louise Brown was born in the United Kingdom. The success of this operation has since given hope to infertile couples and even to women who have reached menopause because a combination of IVF and egg donation can still assist in developing a pregnancy (Wong et al).[1]

Since then, this scientific breakthrough has been undergoing various developments through a combination of intellectual and financial resources from different stakeholders in the health sector (Garrido et al).[2] For

instance, the operation has resulted in high rates of twin pregnancies making it an important medical factor to the public health.

By so doing, most governments have responded by creating legislative policies that encourage or mandate the widespread use of the single-embryo transfer (SET). Out of this concern, this paper analyses whether the cumulative live birth rate resulting from In Vitro Fertilization (IVF) is lower with provincial government involvement as compared to before.

The Quebec provincial government decided to cover IVF through public funding and thereby assuring equality in accessing this medical practice. It is the only province that covers the universal cost of IVF (Doherty et al).[3] Eventually, this action decreases the associated expenses which result from multiple pregnancies arising from the assisted reproductive technology (ART). The prevalent SET policy usually commissions the free IVF programs which turn out as the most efficient way of reducing cases of multiple pregnancies right after the ART. Moreover, the practice is widely encouraged in many nations through the public funding (McLernon et al).[4] Nonetheless, there are global differences concerning the safe number and the most appropriate means of transferring the embryos in addition to the best laboratory standards.

The primary concern of this analysis is about the benefits to be gained by the infertile couples undergoing the IVF treatment in addition to checking whether the treatment will yield successful pregnancies either by using the cryopreserved embryos or fresh ones.

As a matter of fact, it is noted that the rate of cumulative pregnancy is an explicit representation of the likelihood of a pregnancy after the IVF treatment (Elizur et al).[5] This rate is calculated from the data of all the successfully used embryos both fresh and frozen from the same cycle of IVF/ICSI (Cai et al).[6]

Lately, there have been impressive improvements in the quality of maternal health services provided to patients, boosted by the advancement in the vitrification standards and the survival of the embryos (Drakopoulos et al).[7]

In this paper, the supposition rested on a similarity of the cumulative pregnancy rate both before and after the IVF coverage despite the fact that fewer embryos were being transferred. Since 2010, most of the treatments were done with a single embryo transferred. Therefore, the study was meant to analyze the effects of the Quebec IVF coverage on cumulative pregnancy rates.

Medical researchers have confirmed that the age of a woman, which greatly dictates the quality and quantity of embryos produced, determines the rate of cumulative impacts (Ninimaki et al).[8] Medical disorders also affect the quality and availability of the embryos (De Vos et al).[9] The observations show that the rate of cumulative pregnancy may go as high as 79% with an availability of 15 embryos (Garrido).[2] In other studies, the chances of giving a live birth after six cycles combining the IVF and ovarian stimulation stands at 75% **(**Garrido).[2]

METHODS

A retrospective case study approved by the local Institutional Review Board (IRB) was conducted in a university associated private IVF clinic to ascertain the analysis above.

Inclusion criteria

- The chosen participants were 37 years of age and below, had already achieved a successful 1st or undergoing a 2nd IVF cycle, in addition to having more than five oocytes during the time of egg collection.

The analysis centered on the outcomes of the successive transfers of both fresh and frozen embryos obtained from one stimulated IVF cycle. The test compared patients from the 2008-2009 period (before government coverage) to those from the 2012-2013 period (during government coverage). Patients had various ovarian stimulation protocols for IVF; these included the antagonist, long, smart, short, and ovulation induction for Intrauterine insemination converted to IVF.

Exclusion criteria

- To avoid bias and increase the chances of accuracy, the study excluded all the patients who were older than 37 years and had cases of modified or natural cycles and both egg and sperm donation.

Other variables included causes and duration of infertility, the number of collected oocytes including the mature ones, and finally the rate of fertilization. Embryologists carried out the transfer of fresh embryos and cryopreservation of surnumerary embryos either three days after retrieving the oocytes, or at the blastocyst stage.

Table 1 shows the essential characteristics as demonstrated by the various patients used in the research.

Statistical analysis

Differences between groups were assessed using the Chi-Square statistics for categorical variables and the independent student's test for continuous variables.

Table 1a: Baseline demographic and patient characteristics.

	Year		
Parameter	**2008-2009 N=309**	**2012-2013 N=646**	**P-value**
PT age, years, mean (SD)	31.96 (3.05)	31.95 (3.62)	0.895
95% CI for mean (upper, lower)	(31.575, 32.257)	(31.67, 32.23)	
Attempts (number of IVF cycles), mean (SD)	1.17 (0.38)	1.68 (1.29)	<0.001
95% CI for mean (upper, lower)	(1.13, 1.21)	(1.58, 1.78)	
Attempts, n (%)			
1	256 (83.1)	443 (68.6)	
2	52 (16.9)	97 (15.0)	
3	0 (0.0)	42 (6.5)	<0.001
4	0 (0.0)	25 (3.9)	
5	0 (0.0)	16 (2.5)	
6	0 (0.0)	19 (2.9)	
7	0 (0.0)	4 (0.6)	
Type of procedure, n (%)			
IVF standard	87 (28.2)	190 (29.4)	0.711
ICSI	222 (71.8)	456 (70.6)	
Number of oocytes, mean (SD)	14.50 (6.30)	14.80 (6.20)	0.440
95% CI for mean (upper, lower)	(13.79,15.20)	(14.35, 15.31)	
Number of viable oocytes, mean (SD)	13.49 (5.79)	13.74 (5.64)	0.510
95% CI for mean (upper, lower)	(12.84, 14.13)	(13.31, 14.18)	
IVF			
% of fertilization by IVF, mean (SD)	64.87 (23.28)	64.42 (26.39)	0.871
95% CI for mean (upper, lower)	(60.72, 69.03)	(61.27, 67.58)	
2PN IVF, mean (SD)	6.64 (5.09)	6.78 (4.13)	0.783
95% CI for mean (upper, lower)	(5.74, 7.55)	(6.28, 7.28)	
ICSI			
% of fertilization by ICSI, mean (SD)	59.34 (21.65)	64.30 (21.77)	0.005
95% CI for mean (upper, lower)	(56.50,62.19)	(62.29,66.30)	
2PN ICSI, mean (SD)	5.92 (3.82)	6.58 (3.64)	0.030
95% CI for mean (upper, lower)	(5.42, 6.47)	(6.27, 6.92)	
% Fertilization, mean (SD)	60.76 (20.93)	65.40 (21.15)	0.002
95% CI for mean (upper, lower)	(63.77, 67.03)	(63.77, 67.03)	
Day of ET, n (All transfers)			
2	59 (13.2)	18 (1.5)	<0.001
3	373 (83.4)	495 (41.2)	
5	13 (2.9)	651 (54.2)	
6	2 (0.4)	36 (3.0)	
Total transfers	447 (100.0)	1200 (100.0)	
Day of ET, n (%) (all fresh transfers)			
2	56 (18.2)	18 (2.8)	<0.001
3	250 (81.2)	281 (44.1)	
5	2 (0.6)	330 (51.8)	
6	0	8 (1.3)	
Total fresh transfers	308 (100.0)	637 (100.0)	
Day of ET, n (all frozen transfers)			
2	3 (2.2)	0 (0.0)	<0.001
3	123 (88.5)	214 (38.0)	
5	11 (7.9)	321 (57.0)	
6	2 (1.4)	28 (5.0)	
Total frozen transfers	139 (100.0)	563 (100.0)	
Total frozen embryos, n	600	1357	-
Frozen embryo available per patient, mean (SD)	1.94 (3.09)	2.10 (1.68)	0.324

Table 1b: Baseline demographic and patient characteristics.

	Year		
Parameter	**2008-2009 N=309**	**2012-2013 N=646**	**P-value**
Diagnosis of infertility, n (%)			
Ovarian dysfunction	10 (3.2)	51 (7.9)	< 0.001
Endometriosis	10 (3.2)	25 (3.9)	
Implantation failure	1 (0.3)	4 (0.6)	
Low ovarian reserve	3 (1.0)	19 (2.9)	
Male factor	153 (49.5)	234 (36.2)	
Mixed factors	17(5.5)	123 (19.0)	
Repeated miscarriages	1 (0.3)	3 (0.5)	
TD	34 (11.0)	49 (7.9)	
Unexplained-donor sperm	0 (0.0)	19 (2.9)	
Unexplained	79 (25.6)	119 (18.4)	
Type of stimulation, n (%)			
Antagonist	37 (12.0)	493 (76.3)	< 0.001
Converted IUI	15 (4.9)	22 (3.4)	
Long	231 (74.8)	69 (10.7)	
Short	21 (6.8)	45 (7.0)	
Smart	4 (1.3)	17 (2.6)	
Unknown	1 (0.3)	0(0.0)	

RESULTS

The patients' characteristics were similar between the 2 groups of patients regarding their mean age and the reasons for infertility. There were slightly more patients with low ovarian reserve in the second period probably linked to the gratuity of the procedure. For the same reason, further cycles were attempted under government coverage than before.

The types of IVF protocols were different between the 2 periods. In 2008, the majority (74.8%) were long agonist protocols, compared to mostly antagonist protocols (76.3%) in 2012, with p<0.001. There were no differences in the use of standard IVF vs ICSI, fertilization rate and number of mature oocytes obtained at the egg collection between the 2 periods. The main difference was in the day of the embryo transfer. In 2008, 83.4% of the transfers were on day 3 of the embryos. In 2012, it was split 41% on day 3 and 54.2% on day 5. In the end, there was the same number of available embryos for freezing and further use. The number of embryos transferred per patient per cycle (day 3 and day 5) was significantly less with the enforcement of the eSET policy: 1.95 per patient in 2008 compared to 1.07 in 2012. The cumulative clinical pregnancy rate, meaning the percentage of patients experiencing at least one clinical pregnancy was not significantly different 62.1% in 2008 vs 66.7% on 2012. The clinical pregnancy rate per cycle was less with the government coverage and the eSET policy, 60.7% in 2008 vs 42.5% in 2012. The same is seen with the live birth rate. The cumulative LBR was not different between the 2 periods, 52.4% in 2008 vs 55.1% in 2012, but the LBR per cycle was slightly lower with the coverage, 38.8% in 2008 vs 31.3% in 2012, p<0.002.

Table 2a: Procedural and clinical outcomes.

	Year		
	2008-2009 N=309	**2012-2013 N=646**	**P-value**
Embryos day 3 transferred			
Cumulative number of embryos transferred, n	846	592	
Number of embryos transferred per patient, mean (SD)	2.74 (1.63)	0.92 (1.17)	<0.001
95% CI for mean (upper, lower)	(2.55, 2.92)	(0.82, 1.01)	
Blastocysts transferred			
Cumulative number of blastocysts transferred, n	17	691	
Number of blastocysts transferred per patient, mean (SD)	0.20 (0.51)	1.40 (1.28)	<0.001
95% CI for mean (upper, lower)	(0.09, 0.32)	(1.29, 1.51)	

Table 2b: Procedural and clinical outcomes.

	Year		
	2008-2009 N=309	**2012-2013 N=646**	**P-value**
Embryos + blastocysts transferred			
Cumulative number transferred, n	863	1283	
Number transferred per patient, mean (SD)	2.80 (1.72)	2.00 (1.09)	<0.001
95% CI for mean (upper, lower)	(2.60, 2.99)	(1.91, 2.09)	
Cycles started (fresh transfer cycle + all TECs)			
Cumulative number of cycles started, n	448	1209	
Number of cycles started per patient, mean (SD)	1.45 (0.91)	1.87 (0.96)	<0.001
95% CI for mean (upper, lower)	(1.35, 1.56)	(1.80, 1.94)	
Embryos + blastocysts transferred			
Per cycle, n	863/488	1283/1209	<0.001
Per patient, per cycle, mean (SD)	1.95 (0.44)	1.07 (0.21)	
95% CI for mean (upper, lower)	(1.90, 2.00)	(1.04, 1.08)	
Clinical Pregnancy			
Cumulative clinical pregnancy events (positive fetal heart), n	272	514	0.179
Patients experiencing at least one clinical pregnancy event, n, (%)	192 (62.1)	430 (66.7)	
Number of clinical pregnancies per patient, mean (SD)	0.88 (0.83)	0.80 (0.66)	0.080
95% CI for mean (upper, lower)	(0.79, 0.98)	(0.74, 0.85)	
Clinical pregnancy events/cycle, n	272/448	514/1209	<0.001
Rate of clinical pregnancy per cycle, %	60.7	42.5	
Clinical pregnancy events, n (%)			
Patient reporting 0 clinical pregnancy events	117 (37.9)	216 (33.4)	<0.001
Patients with 1 clinical pregnancy event	120 (38.8)	351 (54.6)	
Patients with 2 clinical pregnancy events	65 (21.0)	74 (11.5)	
Patients with 3 clinical pregnancy events	6 (1.9)	5 (0.8)	
Patients with 4 clinical pregnancy events	1 (0.3)	0 (0.0)	
Total	309 (100.0)	646 (100.0)	
Patients reporting multiple clinical pregnancy events (2 or more), n (%)	72 (23.3)	79 (12.2)	<0.001
Live Births			
Cumulative live birth events, n	174	378	0.437
Patients experiencing at least 1 live birth, n (%)	162 (52.4)	356 (55.1)	
Number of live births per patient, mean (SD)	0.56 (0.57)	0.58 (0.56)	0.572
95% CI for mean (upper, lower)	(0.50, 0.63)	(0.54, 0.63)	
Live births/cycle, n	174/448	378/1209	0.002
Rate of live births per cycle, %	38.8	31.3	

DISCUSSION

The study will give the patient an estimate of what can be expected from IVF and yield a strong basis on which to provide individual counseling to infertile couples regarding what they can expect from a treatment, when they should continue treatment, The models have been developed that may be used by clinicians at two different time points to estimate a couple's chances of having a live birth over one or more complete cycles of IVF. At these particular times points (before IVF and after first transfer of a fresh embryo) only information on the couple and treatment available at those times can be used to make predictions.

There was a total of 309 IVF patients from the 2008-2009 period compared to 646 from the 2012-2013 period. The primary outcome measure was the cumulative LBR per IVF cycle started. Other results analyzed were the patient characteristics, the protocols used, the number of mature oocytes, the fertilization rate, the number of embryos available and the day of the transfer. The patient characteristics were pretty similar between the 2 groups. Authors were interested to see if the government coverage and the strict eSET policy would decrease the LBR per cycle started. Authors waited until all the frozen embryos were transferred to draw conclusions on this provincial politic which actually ended in November 2015. There were two major changes over the years. First, the change in IVF protocol from the long agonist to the antagonist protocol, which is a worldwide tendency for patient-friendly treatment and also better response in low ovarian reserve patients. Second, the move from day 3 embryo transfer to blastocyst transfer. It is a reflection

of the improvements at the laboratory level, culture media and vitrification capacity. Also, the treatment year was highly associated with live birth, signifying improvements in technology over time.

Compared with other similar works, present data is the largest series of cases in a single facility, which allows present analysis to overcome several of the flaws present in other studies, specially adding frozen ETs and the report of live births rather than pregnancies. As a matter of fact, it is noted that the rate of cumulative pregnancy is an explicit representation of the likelihood of a pregnancy after the IVF treatment (Velez MP et al).[10]

Many studies have reported the chance of a live birth after IVF or ICS.[11,12] However, for different reasons they do not predict cumulative live birth over multiple complete cycles of IVF or ICSI. They either make predictions for the first transfer of a fresh embryo only, make predictions for individual embryo transfer episodes but with no linkage between cycle and woman (a necessary requirement for calculating cumulative outcomes over multiple cycles).[12]

Authors obtained the same number of mature oocytes, same number of embryos available for freezing, and similar cumulative clinical pregnancy rate and live birth rate per cycle started including all the transfers before and during government coverage. The policy enforcing routine single embryo transfer did not decrease the cumulative CPR per cycle started and greatly reduced the multiple pregnancy rate, in present group of good prognosis patients as stated in a previous study by Cai.[6] The data collected in this study can make it a reasonable option for couples wishing to avoid multiple pregnancies and to the health policies deciders.

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