The Use of ICSI for Non-Male Factor Infertility (NMFI): A Multi-Centre Study

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Introduction

In 1992, intracytoplasmic sperm injection (ICSI) was introduced to improve fertilization in patients with severe male factor infertility or suboptimal fertilization in a previous IVF cycle despite having a normal semen analysis. However, the widespread application of ICSI for other indications has increased dramatically over the past 20 years despite the lack of evidence to support its use. In 2018, 78% of IVF cycles in Canada used ICSI despite male factor infertility only accounting for 31% of all diagnoses. Large prospective, randomized controlled trials are still lacking. To date, there has only been one large RCT has been published in the literature[1].

Objective(s)

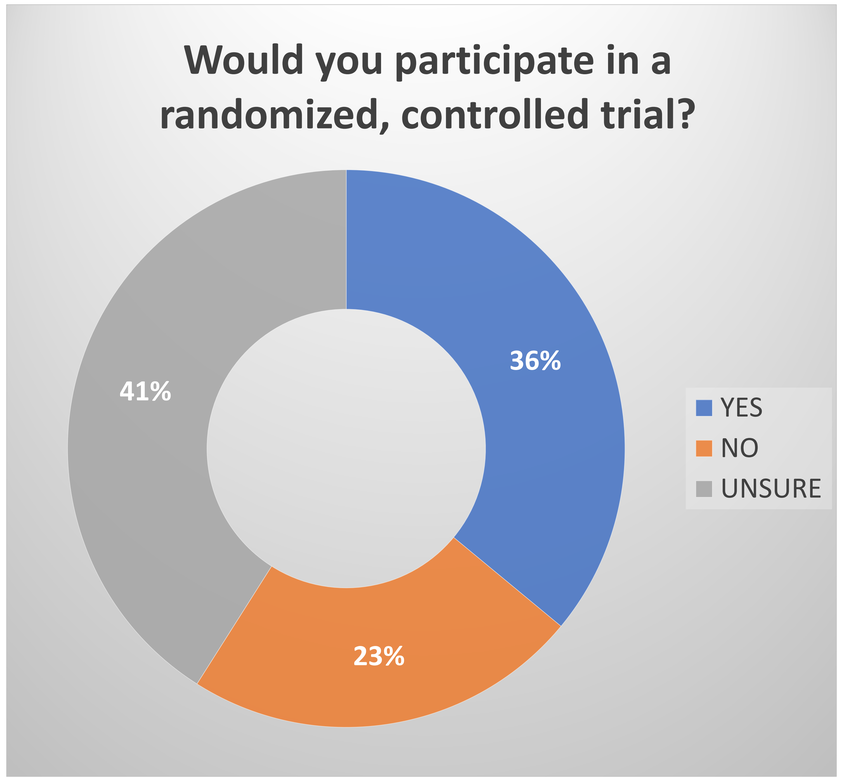
This study aims to examine challenges and barriers in conducting a large, RTC comparing conventional IVF versus ICSI for couples with NMFI within Canada.

Method(s)

The present study is a multi-centre, feasibility study using a standardized, online questionnaire. There were a total of 2 centres included in the study - both within the province of Ontario. All patients undergoing IVF treatment for NMFI were included. Our exclusion criteria included: abnormal semen parameters (based on concentration and/or motility according to WHO 2010 criteria); donor sperm; surgically retrieved sperm; frozen/thawed sperm; frozen/thawed oocytes; a previous history of suboptimal or total fertilization failure; and/or a history of testicular cancer requiring chemo/radiation therapy. Couples were approached by a clinical research assistant prior to speaking to their physician about their IVF cycle. This study was supported by the CFAS SEED grant.

Result(s)

A total of 90 patients (n = 90) agreed to participate prior to meeting with their physician to discuss their IVF treatment cycle. 66% of participants were planning an OFP Funded IVF cycle. Our results showed that 36% of participants would agree to participate in a RCT, while 41% were unsured and 23% would decline to participate. Based on these findings, we calculated a total of 8 years to complete our RCT in order to demonstrate a 10% difference in live birth rates (power 0.90, two-sided alpha 5%). The most common reason for declining to participate was having concerns about the potential risks associated with ICSI (47%). 60% of participants believed IVF to be the “more natural approach” and most respondents (37%) were not sure which method of fertilization provided them the best chances of conception. 55% of respondents would prefer to use the fertilization technique recommended by their physician.



Discussion(s)

The use of ICSI for NMFI continues to persist in Canada despite evidence to demonstrate no improvement in clinical outcomes in patients undergoing IVF treatment. The liberal use of ICSI could result in unintended and potentially harmful consequences. ICSI has been previously associated with an increased risk in chromosomal abnormalities, imprinting disorders and birth defects – albeit these risks have been predominantly studied in couples with male factor infertility.

To date, there has only been one large, randomized, controlled trial published in the literature by Bhattacharya et al. (Lancet, 2001). This study included a total of 435 treatment cycles (IVF 224 and ICSI 221). The primary outcome of interest was implantation rate (number of gestation sacs per embryo replaced expressed as a percentage). Their findings actually demonstrated a higher implantation rate in the IVF group (30%) compared to ICSI (22%). Their results also demonstrated a higher pregnancy rate per cycle (33% vs. 26%, respectively. More recently, Li et al. (Human Reproduction, 2018) examined a population-based cohort of 14, 693 women undergoing IVF treatment between July 2009 and June 2014. Their findings demonstrated similar cumulative, live birth rates compared to ICSI in couples with NMFI. However, in 20 years, there has been no other large, RCTs published in the literature replicating the results of Bhattacharya et al.

Conclusion(s)

Evaluating the benefits of ICSI for NMFI, through a proper RCT, can present significant challenges. Reproductive specialists play a key role in the patient’s decision-making process and should be encouraged to provide evidence-based counselling.

Reference(s)

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Live birth rates after resolution of endometrial cavity fluid in frozen embryo transfer cycles

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Introduction

- The presence of endometrial cavity fluid (ECF) is known to be detrimental to clinical pregnancy rates.[1]
- Fluid in the endometrial cavity detected in any given cycle may resolve spontaneously by the time of embryo transfer.
- Many centres opt to continue with embryo transfer if ECF has resolved, however there is a paucity of evidence to support this practice.
- The objective of this study was to evaluate whether live birth rates are equivalent between patients who had ECF which resolved spontaneously compared to those who never had ECF to begin with.

Methods

- The first cycle of reproductive aged women who underwent frozen blastocyst transfer between January 1st, 2016 and December 31st, 2019 were included in this retrospective cohort study at an academic fertility center.
- The presence or absence of endometrial cavity fluid detected on initial ultrasound and at time of transfer was recorded.
- The primary outcome was live birth rates in the group with resolved ECF and the group without ECF.

Results

- A total of 1711 frozen embryo transfer cycles were eligible for inclusion in this study. Of these, 1083 were the first cycle within the time period of the study.
- Of the 1083 eligible cycles, 49 patients met exclusion criteria (uterine anomaly, hydrosalpinx, persistent endometrial cavity fluid, controlled ovarian stimulation protocol, and cycles using PGT-A). Thus, 1034 cycles were included in final analysis.
- Similar baseline patient characteristics between the study and control group – age, BMI and number of prior pregnancies were similar between both groups.
- Tubal factor infertility was similar among both groups (ECF 11.1% vs. 10.6% without ECF). PCOS was more predominant in the ECF group (20.4% vs. 10.2%).
- Live birth rates were 35.2% and 34.2%, adjusted risk ratio 1.00 [95% CI 0.70-1.50] in the two groups, respectively.

Outcome	Fluid resolved (N=54)	No fluid (N=984)	RR	aRR*
Live birth rate	19 (35.2)	335 (34.2)	1.0 (0.8-1.2)	1.0 (0.7-1.5)
+BhCG	26 (48.2)	548 (55.9)	0.9 (0.7-1.1)	0.9 (0.7-1.2)
Clinical intrauterine	21 (38.9)	460 (46.9)	0.9 (0.7-1.1)	0.8 (0.6-1.2)
Miscarriage	2/26 (7.7)	109/548 (19.9)	0.9 (0.8-1.0)	DNC
Ectopic	0 (0)	19 (1.9)	---	---

*All analyses performed using log binomial regression adjusted for age at the time of retrieval, body mass index, number of prior pregnancies, diagnosis of PCOS, other ovulatory disorder, tubal factor, endometriosis and number of embryos transferred.
RR=risk ratio; aRR = adjusted risk ratio; CI = confidence interval; hCG = human chorionic gonadotropin; DNC = did not converge

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Discussion

- Limited studies have been conducted to elucidate the etiology of ECF and its effects on clinical pregnancy rates.[2]
- ECF has been predominantly associated with tubal factor infertility and hydrosalpinx[3], however our study shows similar prevalence between ECF and no ECF groups.
- Current literature emphasizes transient self-limiting ECF in response to stimulation as non-threatening to pregnancy rates[4]. Our study in FET cycles corroborates that ECF does not leave lasting deleterious effects for subsequent embryo transfer.

Conclusions

- Live birth rates in frozen embryo transfer cycles are equivalent between patients with resolved endometrial cavity fluid compared to those who never had endometrial cavity fluid to begin with.
- The presence of endometrial cavity fluid likely does not pose a threat if the fluid spontaneously resolves by the time of embryo transfer.

Reduced live birth rates after embryo transfer in patients with prior cesarean delivery: A retrospective cohort study

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Introduction

Cesarean delivery rates are on the rise. In 2017 the Canadian cesarean delivery rate was 28.8%, compared to 18.7% in 1997[1]. Recent studies suggest a possible association between cesarean delivery and subsequent subfertility. A 2013 meta-analysis found a 9% lower pregnancy rate and 11% lower live birth rate relative to patients with only prior vaginal delivery[2]. Few studies have evaluated outcomes among patients with prior cesarean delivery after embryo transfer (ET)– three studies suggest prior CD is associated with reduced pregnancy outcomes and one found no association[3-6].

We present a cohort study evaluating live birth rates after the first embryo transfer among patients with prior cesarean delivery compared to prior vaginal delivery only, with sub-group analysis according to whether cesarean was done in labour.

Methods

- Single-centre retrospective cohort study at the Ottawa Fertility Centre (OFC) including patients who underwent first ET after prior delivery between January 1 2013 - September 1 2019, using BORN-CARTR data
- REB approval protocol number 20170813-01H
- Inclusion criteria: prior delivery >20 weeks gestation, with first ET occurring at OFC
- Exclusion criteria: PGT, day 2 embryo transfer, hydrosalpinx, gestational carrier
- We fit multivariable logistic regression models. Primary outcome was live birth rate.
- We conducted a subgroup analysis evaluating outcomes based on whether the patient's caesarean delivery was done in active labour

Results

- Total of 962 met inclusion criteria: 351 caesarean delivery (CD) group and 611 vaginal delivery (VD) group.
- Similar baseline demographics – Age, number of prior deliveries and miscarriages was similar between the two groups. Patients in VD group had a slightly longer time interval from last delivery to ET (4.4 ± 4.2 years vs 3.8 ± 2.9 years) and male factor as the indication for IVF was more prevalent (66.6% vs 55.8%)
- Indications for prior CD:
  - Failure to progress in labour (92/351; 26.2%)
  - Fetal malpresentation (52/351; 14.8%)
  - Fetal distress (26/351; 7.4%)
  - Placenta previa (14/351; 4.0%)
  - Elective (5/351; 1.4%)
  - Other maternal or fetal indications (72/351; 20.5%)
  - Unavailable 90/351 (25.6%)

Table 1. Primary and secondary outcomes

Outcome	Prior VD (n = 611)	Prior CD (n = 351)	aRR [95% CI]	P value
Live birth rate	223 (36.5)*	105 (29.9)*	0.81 [0.67-0.98]	0.029
Clinical IUP	277 (45.3)	136 (38.8)	0.85 [0.73-0.99]	0.040
Positive hCG	338 (55.3)	161 (45.9)	0.82 [0.72-0.94]	0.004
Biochemical loss	58 (17.3)	23 (14.5)	0.82 [0.51-1.24]	0.306
Miscarriage	48 (7.9)	31 (8.8)	1.07 [0.70-1.66]	0.748
Ectopic	3 (0.5)	2 (0.6)	---	---
Stillbirth	0	3 (0.9)	---	---

Data are *n or proportion* (%).
VD, vaginal delivery; CD, cesarean delivery; aRR, adjusted risk ratio; CI, confidence interval; IUP, intrauterine pregnancy; hCG, human chorionic gonadotropin; IUP, intra-uterine pregnancy
*Live birth data missing from BORN Ontario for 6 patients in the prior vaginal delivery group and 1 patient within the prior cesarean delivery group.

Results

Within the "active labour" cesarean delivery group, 29/118 patients (24.6%) had a live birth, vs 223/605 patients (36.9%) in the vaginal delivery group. This difference was statistically significant after adjusted log binomial regression analysis (aRR = 0.67, 95% CI [0.49-0.92], p=0.015).

Within the "no active labour" cesarean delivery group, 35/117 patients (29.9%) had a live birth vs 223/605 patients (36.9%) in the prior VD group. This difference was not statistically significant after adjusted log binomial regression analysis (aRR = 0.84, 95% CI [0.64-1.11], p=0.221).

Conclusions

History of a prior cesarean delivery was associated with lower live birth rates after embryo transfer relative to patients with prior vaginal delivery only. These findings may be largely attributable to a subgroup of patients with prior cesarean delivery in active labour, who may be at particular risk of impaired embryo implantation and subfertility.

This study highlights the importance of further research evaluating the association of active labour cesarean delivery with future fertility and exploring possible etiologies if this subset of patients with an inferior prognosis is confirmed.

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Effect of parental origin of Robertsonian and reciprocal translocation carriers on the outcome of day 3 and day 5/6 PGT-SR embryos

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Introduction

Carriers of balanced reciprocal translocations are at higher risk of producing chromosomally abnormal embryos due to the chromosomal imbalances from segregation during meiosis, leading to recurrent pregnancy loss or birth of affected offspring. Sandalinas et al. illustrated an increase in normal/balanced embryos observed as a result of the development of an embryo from day 3 to day 5/6.[1] Whereas, Fragouli et al. commented on the effect of translocation carrier gender on the modes of segregation patterns.[2] However, no further investigation has been done on the effect of translocation carrier gender and segregation pattern in relation to the negative development of an embryo.

Objective: To determine the effect of gender on chromosome segregation patterns of robertsonian (ROB) and reciprocal (REC) translocation carriers between day 3 cleavage stage and blastocyst stage embryos.

Material & Methods

A total of **74 translocation carrier patients** (26 ROB patients - 18 male and 8 female; 51 REC patients with 32 male and 19 female) underwent 143 PGT-SR cycles (55 ROB and 88 REC) at the MUHC Reproductive Center. Overall**, 1160 day 3 embryos** were successfully analyzed by FISH after embryo biopsy, with abnormal embryos re-examined on day 5. The **ROB group** consisted of 365 day 3 embryos and 98 reexamined abnormal day 5 embryos. The **REC group** consisted of 795 day 3 embryos and 384 reexamined abnormal day 5 embryos. A comparison of sperm quality between male carriers with ROB and REC also performed. Statistical analysis of the results was performed using the Fisher exact test, with a P value of <0.05 considered statistically significant.

Results & Discussion

Table 1: Sperm quality comparison between male carriers with ROB vs. REC translocations

Patients	O	OA	T	AT	OAT	N
Robertsonian	5	2	1	1	4	5
Reciprocal	3	5	1	4	3	16

O: oligozoospermia, OA: oligoasthenozoospermia, T: teratospermia, AT: asthenoteratozoospermia, OAT: oligoasthenoteratospermia ; N: normal

❖ There was a significantly greater percentage of abnormal sperm parameters observed in the ROB group in comparison to the REC group (72% vs. 50%, P < 0.5).

Results & Discussion

Table 2: Comparison of day 3 cleavage stage vs. day 5/6 blastocyst stage embryos from male and female ROB translocation carriers.

ROB Carriers Segregation Pattern	Male Day 3	Male Day5/6	Female Day3	Female Day5/6
Adjacent 1	56 (50%)	14 (30%)	66 (50%) **	36 (69%) **
Adjacent 2	34 (30%) **	18 (40%) **	28 (21%)	10 (19%)
3:1	4 (3%)	0 (0%)	6 (5%)	2 (4%)
Chaotic	18 (17%) **	14 (30%) **	32 (24%)	4 (8%)
Total	112	46	132	52

*** Shows Significant Changes in Percentages*

❖ For male and female ROB carriers, a significant reduction in the number of abnormal embryo production was noted from day 3 to day 5/6 (59%, and 60%, respectively; P < 0.05).

❖ For male ROB carriers, Adjacent 2 and chaotic segregation patterns significantly increased from day 3 to day 5/6 (P < 0.05).

❖ For female ROB carriers, Adjacent 1 segregation pattern significantly increased from day 3 to day 5/6 (P < 0.05).

Table 3: Comparison of day 3 cleavage stage vs. day 5/6 blastocyst stage embryos from male and female REC translocation carriers

❖ For male and female REC carrier groups, a reduction in abnormal embryos reaching day 5/6 blastocyst stage from day 3 cleavage stage was seen for all types of abnormal segregation patterns.

❖ No specific segregation pattern abundance was noted in relation to the gender of the translocation carrier.

REC Carriers Segregation pattern	Male Day 3	Male Day5/6	Female Day3	Female Day5/6
Adjacent 1	136(32%)	110(24%)	50(24%)	34(18%)
Adjacent 2	76(18%)	42(10%)	22(10%)	14(7%)
S 3:1	109(25%)	56(13%)	72(35%)	32(17%)
S 4:0	6(1%)	0(0%)	4(2%)	0(0%)
Chaotic	101(24%)	48(11%)	58(28%)	48(26%)
Total	428	256	206	128

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Discussion

Day 3 cleavage → Day 5/6 blastocyst: Abnormal Segregation Pattern

❖ A reduction in number of abnormal embryos was observed from day 3 to day 5/6 in both ROB and REC carriers. This confirms the existence of natural selection against chromosomally abnormal embryos.

Robertsonian Translocation Observations

❖ Both Adjacent 2 and chaotic segregation patterns for male ROB carriers and Adjacent 1 segregation pattern for female ROB carriers significantly increased from day 3 to day 5/6 (P < 0.05). (Table 2) Embryos with these segregation patterns can be associated with an increased likelihood of reaching the blastocyst stage.

❖ Overall, the proportion of translocated chromosomal abnormalities in day 5/6 embryos from Robertsonian carriers was significantly higher than that in carriers with reciprocal translocation.

Reciprocal Translocation Observations

❖ No increase in any specific segregation pattern was noted in either male or female REC carriers from day 3 to day 5/6.

❖ An overall reduction of abnormal embryos reaching the day 5/6 blastocyst stage irrespective of gender or segregation patterns was noted for REC carriers. (Table 3) This developmental arrest may be associated with the embryonic genome of reciprocal carriers that regulate the cell cycle, resulting in a reduction of cells with chromosomal abnormalities at the blastomere stage. [3]

Conclusion

❖ Carrier gender and translocation type influence the abnormal segregation patterns changes from day 3 cleavage stage to day 5/6 blastocyst stage. Additionally, specific segregation patterns for ROB carriers have been noted to increase from day 3 to day 5/6 (Adjacent 2 and chaotic for males; Adjacent 1 for females)

❖ As well, our study depicted the elimination of many complex aneuploidies from day 3 embryo biopsies before the formation of day 5/6 blastocysts secondary to the natural selection process of embryos.

❖ **Limits:** The small sample size and inherent possibility of human error with the utilization of FISH procedures were two limitations observed in this study. Further research with larger sample sizes is required to further affirm the correlations.

Comparative Embryo Outcomes following Extending Embryo Culture to Day 6: A Retrospective Cohort Study

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Introduction

Human embryos can display variable developmental rates. The blastocyst stage is typically achieved on day 5 after fertilization, but can be reached on day 6 or 7 in extended culture[1]. It is estimated that 30% of embryos can be slow-growing, with some that never reach the blastocyst stage.

At our clinic, prior to June 2020, good-quality early (B1, B2) and expanded (B3, B4, B5) blastocysts were cryopreserved on day 5. Embryos that did not reach the blastocyst stage by day 5 were usually discarded if not transferred fresh. Recent evidence demonstrates that culturing slow-growing day 5 embryos to day 6 may increase blastocyst yield[2, 3]. Therefore, as of June 1, 2020, our centre changed its embryo cryopreservation policy to extend culture of slow-growing day 5 embryos to day 6. Good-quality expanded blastocysts were then frozen on either day 5 or day 6, but early blastocysts were discarded.

This study aims to evaluate if this change in embryo culture and cryopreservation policy resulted in a difference in the proportion of embryos eligible for cryopreservation, and to identify factors that are predictive of the potential for a day 5 embryo to becoming a good-quality expanded blastocyst on day 6. We hypothesized that the policy change will result in an increase in the proportion of embryos eligible for cryopreservation.

Methods

- Retrospective cohort study.
- Inclusion criteria: autologous fresh IVF cycles with viable day 5 embryos.
- Exclusion criteria: donor oocyte, frozen oocyte, preimplantation genetic testing, surrogacy cycles.
- Study groups:
  - Group 1, prior to policy change, Sept. 2019-March 2020
  - Group 2, after policy change, June 2020-Dec. 2020
- Primary outcome:
  - Proportion of embryos eligible for cryopreservation, whether or not they were transferred fresh, defined in Group 1 as the number of good-quality blastocysts (B1-B5) over the total number of viable day 5 embryos; and defined in Group 2 as the number of good-quality expanded blastocysts (B3-B5) over the total number of viable day 5 or day 6 embryos.
- Secondary outcomes:
  - Factors predictive of day 6 blastulation.
- Embryos derived from eligible cycles were evaluated by trained embryologists and selected for cryopreservation on either day 5 or day 6 based on their Gardner morphological scoring.
- Comparative and descriptive statistical analyses were done.

Results

Figure 1. Proportion of embryos eligible for cryopreservation between Groups 1 and 2.

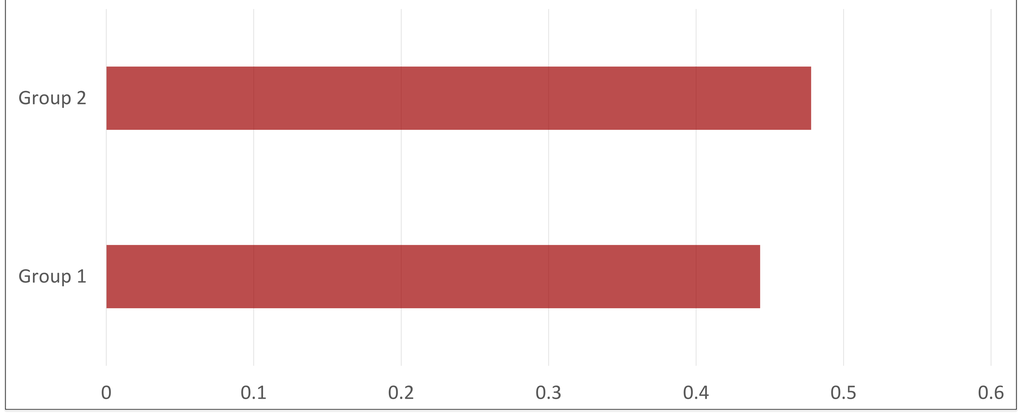

Table 1. Baseline patient and cycle characteristics between patients in Groups 1 and 2.

	Group 1 (N = 341)	Group 2 (N = 338)	P-value
Age at cycle start (years)	35.2 (4.1)	35.3 (4.1)	0.73
Gravidity	0.8 (1.1)	0.9 (1.4)	0.09
Parity	0.2 (0.03)	0.3 (0.03)	0.30
FSH (IU/L)	7.5 (2.2)	7.6 (2.2)	0.66
AFC	24.8 (12.5)	24.9 (12.6)	0.88
AMH (pmol/L)	24.4 (16.4)	24.2 (20.4)	0.93
BMI (kg/m^2)	26.5 (5.6)	27.0 (5.5)	0.25
Cause of infertility (%):			0.36
-male factor	144 (31.7)	133 (29.6)	
-decreased ovarian reserve/advanced maternal age	106 (23.3)	109 (24.2)	
-unexplained	52 (11.5)	56 (12.4)	
-endometriosis	41 (9.0)	31 (6.9)	
-tubal factor/peritoneal	41 (9.0)	40 (8.9)	
-ovulatory disorder/PCOS	35 (7.7)	50 (11.1)	
-other	35 (7.7)	31 (7.0)	
Type of IVF Protocol (%):			0.92
-antagonist	276 (80.9)	296 (87.5)	
-agonist	22 (6.5)	10 (3.0)	
-microdose flare	43 (12.6)	32 (9.5)	
Total FSH Dose (IU)	2743.2 (1395.1)	2749.8 (1423.3)	0.95
Number of COCs retrieved	12.2 (6.3)	12.2 (7.0)	0.95
Number of MIIs retrieved	9.6 (5.1)	9.8 (5.5)	0.71
Number of fertilized oocytes	6.8 (3.8)	7.1 (4.6)	0.31
Method of fertilization (%)			0.08
-standard IVF	134 (39.3)	157 (46.6)	
-ICSI	207 (60.7)	180 (53.4)	

Abbreviations: AFC = antral follicle count, AMH = antimullerian hormone, BMI = body mass index, COC = cumulus oocyte complex, FSH = follicle-stimulating hormone, G = gravidity, ICSI = intracytoplasmic sperm injection, IVF = in vitro fertilization, P = parity, PCOS = polycystic ovarian syndrome. Presented mean (standard deviation).

Table 2. Comparison of embryos between patients in Groups 1 and 2.

	Group 1	Group 2	P-value
Total number of viable embryos on Day 5	1667	1771	-
Total number of viable embryos on Day 6	0	740	-
Mean number of fresh embryos transferred on Day 5 per retrieval (SD)	1.5 (0.6)	1.4 (0.6)	0.25
Total number of vitrified blastocysts	598	753	-
Mean number of vitrified blastocysts per retrieval (SD)	1.7 (2.0)	2.1 (2.2)	0.007
Mean number of vitrified expanded Day 5 blastocysts per retrieval (SD)	1.6 (1.9)	2.2 (2.4)	0.0001
Mean number of vitrified expanded Day 6 blastocysts per retrieval (SD)	N/A	0.2	-
Proportion of blastocysts eligible for cryopreservation per retrieval	0.44	0.47	0.28

Results

Table 4. Impact of various factors on embryo progression on Day 6.

	Freezable D5 Embryos	Non-Freezable D5 Embryos	Freezable D6 Embryos	% Progression to Day 6
Total	772	999	70	7.0%
Age (years)				
-<35	426	475	42	8.8%
-35-37	201	247	16	6.5%
-38-40	102	167	7	4.2%
-41-42	23	70	4	5.7%
-≥43	20	40	1	2.5%
Method of fertilization:	399	529	42	7.9%
-Standard IVF	373	470	28	6.0%
-ICSI				
Multi/binucleation:				
-Yes	208	323	21	6.5%
-No	564	676	49	7.2%
Embryo progression:				
-M1	N/A	87	1	1.1%
-M2		148	9	0.6%
-B1		220	21	9.5%
-B2		159	19	11.9%
-B3-BC/CC/CB		134	8	6.0%
-B4-BC/CC/CB		188	11	5.9%
-B5-BC/CC/CB		57	2	3.5%
Sperm origin:	N/A			
-PESA/TESE		27	4	14.8%
-Ejaculate		944	71	7.5%

Abbreviations: B = blastocyst. ICSI = intracystoplasmic sperm injection, IVF = in vitro fertilization, M = morula, PESA = percutaneous epididymal sperm aspiration, TESE = testicular sperm extraction.

- The mean proportion of blastocysts eligible for cryopreservation per retrieval was comparable before and after the policy change (Figure 1, 46.9 vs. 44.4%, mean difference 0.025, 95% confidence interval -0.021 to 0.071, p = 0.28).
- Only 7.0% of slow-growing day 5 embryos progressed to good-quality expanded blastocysts on day 6. Predictors of increased day 6 embryo blastulation included younger age of egg provider, presence of an early blastocyst on day 5 (B1/B2), and cycles involving surgically-retrieved sperm.

Conclusions

The results of our study suggest that changing our cryopreservation policy to include good-quality expanded day 6 blastocysts while eliminating early blastocysts yielded comparable proportions of embryos eligible for cryopreservation per retrieval, and that factors such as maternal age, stage of embryo development on day 5, and surgically-retrieved sperm, are most predictive of embryo blastulation potential on day 6. Further research into the implantation potential of these day 6 embryos will be performed.

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Outcomes of Mosaic Embryo Transfers from a Canadian Private Fertility Centre

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OLIVE fertility centre

INTRODUCTION

Mosaic results on PGT-A first occurred with the introduction of NGS testing of embryos approximately 5 years ago. There was hesitation world-wide to transfer embryos with known abnormal cells. After thorough counselling, some patients chose to transfer mosaic embryos. The purpose of this study is to review the outcomes following mosaic embryo transfers at a private IVF center.

METHODS

Retrospective analysis of embryo transfer outcomes was performed at a private fertility center from September 2016 to May 2021 for embryos determined to be mosaic on PGT-A using NGS testing.

RESULTS

- 41 mosaic embryo transfers among 40 patients
- 38 single embryo transfers (SET); 3 double embryo transfers (DET)

Single Embryo Transfers (n=38)

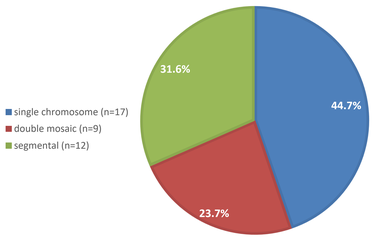


Figure 1a. Type of Mosaicism in SET

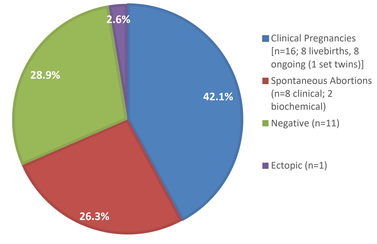


Figure 1b. SET Outcomes

Double Embryo Transfers (n=3)

- 1 mosaic monosomy/euploid (pregnant)
- 1 double mosaic monosomy (SA)
- 1 mosaic segmental/mosaic trisomy (negative beta)

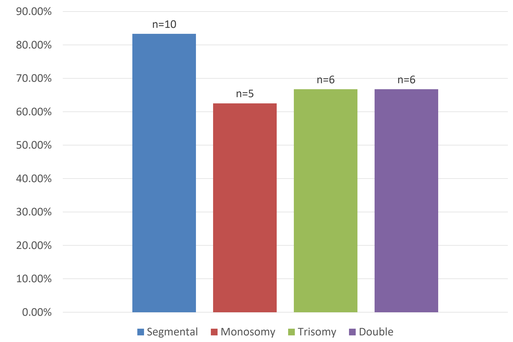


Figure 1c. Implantation Rate by Subtype. Mosaic segmental embryos implanted more frequently (10/12; 83.3%) than monosomies (5/8; 62.5%), trisomies (6/9; 66.7%) or double mosaics (6/9; 66.7%).

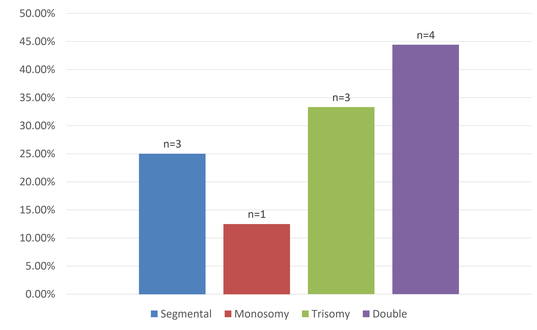


Figure 1d. Miscarriage Rates by Subtype. Double mosaic embryos were the most likely to miscarry (44.4%), followed by trisomies (33.3%), segmentals (25.0%), and monosomies (12.5%).

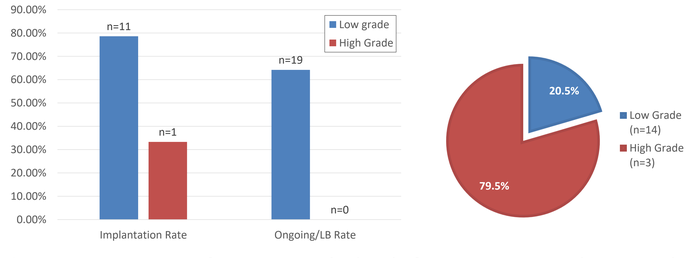


Figure 1e. Percentage of Mosaicism. The level of mosaicism was only reported after May 2019 and includes 17 cases. Low grade mosaics (i.e., <50%) implanted more frequently (n=11; 78.6%) and had a higher ongoing pregnancy/delivery rate (n=19; 64.2%) than high grade mosaic (i.e., >50%) embryos (n=1; 33.3% and n=0; 0%, respectively).

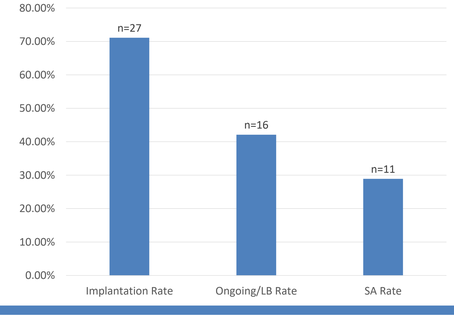
Adverse Outcome:

- Duodenal atresia was identified in a pregnancy subsequent to transfer of an embryo affected with mosaic monosomy 8.
- Amniocentesis RAD and chromosome microarray were normal.
- Findings were not associated with mosaicism according to diagnostic testing.
- No other abnormalities have been identified in ongoing pregnancies or livebirths to our knowledge.

SUMMARY

Subsequent to a SET with a mosaic embryo, the following outcomes were observed:

- Implantation rate 71.1% (n=27)
- Ongoing/live birth rate 42.1% (n=16)
- SA rate 28.9% (n=11)



CONCLUSION

Transfer of mosaic embryos led to many successful pregnancies and livebirths at our clinic. One congenital anomaly was identified, but was not associated with mosaicism according to diagnostic testing. Given the reasonable healthy live birth rates, transfer of mosaic embryos can be considered with proper counselling. The current data set comprises the largest series of mosaic embryo transfers in Canada.

Eugin experience of expanded screening for genetic diseases prior to ART

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Background

Expanded carrier screening is genetic testing in healthy individuals without family history of hereditary illness. It screens for genetic diseases with X-linked or autosomal recessive inheritance.

Genetic counselling then allows an informed decision regarding reproductive options (IVF + PGT-M, prenatal diagnostic testing, gamete donation, adoption, not having children, seeking a new partner).

If the ART involves a donor, reproductive risks can be reduced by "genetic matching".

The 'recipient' thus receives gametes from a donor with whom they do not share any pathogenic variants.

However, zero risk does not exist, there is always a residual reproductive risk due to germinal mosaicism, de novo mutations, deletions/ duplications and chromosomal mutations.

Patients and methods

Retrospective consecutive cohort study. MicroArrays (CarrierMap) were carried out between March 2015 and July 2018. NGS (qCarrier plus) were carried out between August 2018 and July 2020.

CarrierMap studies 314 diseases (25 linked to X chromosome, 2692 mutations, 302 genes).

QCarrier plus studies 329 diseases (57 linked to X chromosome), sequencing 303 genes.

Results

7644 CarrierMap tests were performed. 3524 (46.1%) were found to be carriers of at least one mutation. 13% carried more than one mutation.

Disorder	Gene	N=7644
Biotinidase deficiency	*BTD*	1:14
Mucoviscidosis	*CFTR*	1:27
Pseudocholinesterase deficiency	*BCHE*	1:29
Non-syndromic hearing loss	*GJB2*	1:33
Smith–Lemli–Opitz syndrome	*DHCR7*	1:35
Fragile X syndrome (FXS)	*FMR1*	1:43
Alpha-1 antitrypsin deficiency	*SERPINA1*	1:45
Spinal muscular atrophy (SMA)	*SMN1*	1:49
21-hydroxylase deficiency	*CYP21A2*	1:58
Beta thalassemias + Hb S	*HBB*	1:58
Familial Mediterranean fever (FMF)	MEFV	1:66

Results

3179 qCarrier plus genetic tests were carried out in total. 2598 (81.7%) were found to be carriers of at least one mutation. 49% were carriers of more than one mutation.

Disorder	Gene	N=3179
Mucoviscidosis	*CFTR*	1:6
Non-syndromic hearing loss	*GJB2*	1:17
Stargardt disease	*ABCA4*	1:18
Alpha-thalassemia	*HBA2*	1:21
21-hydroxylase deficiency	*CYP21A2*	1:27
Phenylketonuria (PKU)	*PAH*	1:31
Acid maltase deficiency (AMD)	*GAA*	1:31
M. Wilson	*ATP7B*	1:31
Alpha-1 antitrypsin deficiency	*SERPINA1*	1:32
Polycystic kidney disease AR	*PKHD1*	1:35
Retinitis pigmentosa	*EYS y USH2A*	1:36

Conclusion

More than 80% of our patients will be carriers of pathogenic variants. It is recommended that couples are offered genetic matching. It is vital that the reproductive risk is established in each case and that the limits of our screening panels are well understood.

Comparison of Obstetrical and Neonatal Outcomes of women with polycystic ovarian syndrome with controls when both have had bariatric surgery: A Population Based Study.

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INTRODUCTION

- Patients with polycystic ovarian syndrome (PCOS) are felt to be at risk for adverse obstetrical and neonatal outcomes as compared to women without PCOS.
- This is felt to be due to the increased insulin resistance seen in PCOS, which is primarily modulated by obesity.
- Bariatric surgery (BS) can decrease insulin resistance in morbidly obese patients.

OBJECTIVE

▪This study was done to assess the pregnancy risks in women with PCOS who have undergone BS as compared to controls who have also had weight reduction surgery

MATERIALS AND METHODS

- This is a retrospective study using the Health Care Cost and Utilization Project-Nationwide Inpatient Sample (HCUP-NIS) database from 2004-2014.
- We compared women with PCOS who underwent BS with a control group consisting of pregnant patients without PCOS who had also had weight reduction operations, regarding; pregnancy, delivery, and neonatal outcomes.
- Data was compared using multivariate logistic regression analysis to control for confounding effects.

Figure 1. Prevalence of PCOS / 1000 women underwent Bariatric surgery who gave birth between 2004 and 2014

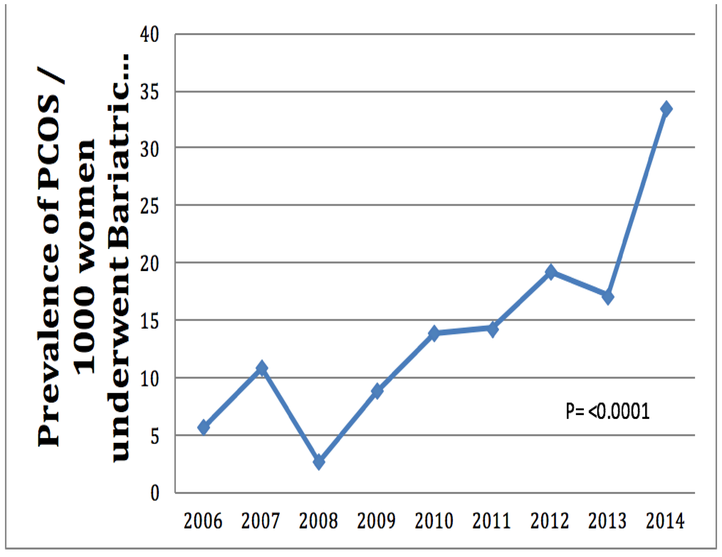

TABLE I: Table 1 Maternal Characteristics

Characteristics	PCOS N= 141	No PCOS N= 9197	P-value
Age (years)			
<25	12 (8.5%)	714 (7.8%)	0.34
25-34	69 (48.9%)	5066 (55.1%)	
≥35	60 (42.6%)	3414 (37.1%)	
Race			
White	73 (56.9%)	5085 (63.8%)	0.33
Black	22 (17.5%)	1258 (15.8%)	
Hispanic	24 (19.0%)	1275 (16.0%)	
Asian and Pacific	3 (2.4%)	67(0.8%)	
Native American	0 (0%)	46 (0.6%)	
Other	4 (3.2%)	243 (3.0%)	
Income quartiles			
Less than 39.000	21 (16.3%)	1693 (21.3%)	0.50
$39.000-47.999	33 (25.6%)	2023 (25.4%)	
$48.000-62.999	43 (33.3%)	2298 (28.9%)	
$63.000 or more	32 (24.8%)	1949 (24.5%)	
Plan type			
Medicare	2 (1.4%)	275 (3%)	0.15
Medicaid	26 (18.4%)	2360 (25.7%)	
Private including HMO	109 (77.3%)	6139 (66.9%)	
Self Pay	2 (1.4%)	93 (1.0%)	
No charge	0 (0%)	8 (0.1%)	
other	2 (1.4%)	305 (3.3%)	
Hospital type			
Rural	9 (15.0%)	269 (11.6%)	0.41
Urban	51 (85.0%)	2058 (88.4%)	
BMI			
Obese	62 (44%)	2344 (25.5%)	<0.0001
Previous CS	35 (24.8%)	2570 (27.9%)	0.45
IVF	1 (0.7%)	66 (0.7%)	1.00
Smoking during pregnancy	6 (4.3%)	599 (6.5%)	0.28
Chronic HTN	17 (12.1%)	733 (8 %)	0.09
Pregestational DM	10 (7.1%)	339 (3.7%)	0.03
Illicit Drug use	2 (1.4%)	172(1.9%)	0..69
Thyroid disease	762 (8.3%)	13 (9.2%)	0.65
HIV	0 (0.0%)	2(0.0%)	1.00
Multiple gestation	5 (3.5%)	328 (3.6%)	1.00

RESULTS

▪We identified 9,096,788 unique pregnancies during the study period. 141 patients had a history of PCOS and underwent BS. The control group was composed of 9 197 subjects who were not diagnosed with PCOS and underwent BS.
▪Patients with PCOS who underwent BS were more likely to be obese when compared to the control group (44% vs. 25.5%, p<0.0001)
▪Rates of pre-gestational diabetes were higher in the PCOS group (7.1% vs. 3.7%, p=0.03).
▪Both groups had comparable in vitro fertilization (IVF) rates (0.7% vs. 0.7%, P=1) and histories of previous cesarean sections (CS) (24.8% vs. 27.9%, p=0.45).
▪Both groups had similar rates of pregnancy induced hypertension (PIH) (aOR-0.79, 95%CI-0.44-1.41, p=0.43), gestational hypertension (aOR-0.71, 95%CI 0.29-1.74, p=0.45) and gestational diabetes mellitus (GDM) (aOR-1.09, 95%CI-0.62-1.92, p=0.76).
▪Rates of spontaneous vaginal delivery (aOR-0.69, 95%CI 0.49-0.99, p=0.04) and Cesarean Section (aOR-1.48, 95%CI 1.05-2.09, p=0.03) were unfavorable among patients with PCOS.
▪With regards to neonatal outcomes; small for gestational age babies (aOR-0.52, 95%CI-0.19-1.41, p=0.20), and congenital anomalies (aOR-0.89, 95%CI-0.12-6.46, p=0.91) were similar between both groups.

TABLE II: Pregnancy and delivery outcomes.

Table 2 Pregnancy and delivery outcomes

Outcomes	PCOS (%)	No PCOS (%)	Crude OR (95% CI)	Adjusted OR (95% CI)	Adjusted p-value
Pregnancy outcomes [a]					
Pregnancy induced hypertension	13 (9.2%)	924 (10%)	0.91 (0.51 – 1.62)	0.79 (0.44 – 1.41)	0.43
Gestational hypertension	5 (3.5%)	421 (4.6%)	0.77 (0.31 - 1.88)	0.71 (0.29 - 1.74)	0.45
Preeclampsia	7 (5.0%)	358 (3.9%)	1.29 (0.60 -2.78)	1.14 (0.53 -2.47)	0.73
Eclampsia	0 (0.0%)	5 (0.1%)	0 (0 -)	0 (0 -)	0.997
Preeclampsia and Eclampsia superimposed HTN	3 (2.1%)	150 (1.6 %)	1.31 (0.41 - 4.16)	1.01 (0.31 - 3.22)	0.99
GDM	14 (9.9%)	777 (8.4%)	1.20 (0.69 - 2.09)	1.09 (0.62 – 1.92)	0.76
Placenta previa	1 (0.7%)	63 (0.7%)	1.04 (0.14 -7.52)	1.03 (0.14 - 7.47)	0.98
Delivery outcomes b					
PPROM	4 (2.8%)	153 (1.7 %)	1.73 (0.63 – 4.72)	1.79 (0.65 – 4.91)	0.26
Preterm delivery	19 (13.5%)	974 (10.6 %)	1.31 (0.81 - 2.14)	1.35 (0.83 – 2.20)	0.23
Abruptio placenta	2 (1.4%)	130 (1.4%)	1.00 (0.25 - 4.10)	1.10 (0.27 – 4.51)	0.89
Chorioamnionitis	3 (2.1%)	128 (1.4 %)	1.54 (0.48 - 4.90)	1.52 (0.48 - 4.84)	0.48
Operative vaginal delivery	6 (4.3%)	451 (4.9 %)	0.86 (0.38 - 1.96)	0.84 (0.37 - 1.92)	0.68
CS	87 (61.7%)	4523 (49.2%)	1.67 (1.18 - 2.34)	1.48 (1.05 – 2.09)	0.03
SVD	51 (36.2%)	4390 (47.7) %	0.62 (0.44 – 0.88)	0.69 (0.49 – 0.99)	0.04
Hysterectomy	0 (0.0%)	26 (0.3%)	0 (0 -)	0 (0 -)	0.997
PPH	3 (2.1%)	233 (2.5%)	0.84 (0.27 - 2.65)	0.85 (0.27 – 2.70)	0.78
Wound complications	1 (0.7%)	96 (1 %)	0.68 (0.09 – 4.89)	0.60 (0.08 - 4.33)	0.61
Maternal Death	0 (0.0%)	3 (0.0%)	0 (0 -)	0 (0 -)	0.997
Transfusion	2 (1.4%)	267 (2.9 %)	0.48 (0.12 – 1.94)	0.48 (0.12 - 1.94)	0.30
Others					
Maternal infection	4 (2.8%)	166 (1.8%)	1.59 (0.58 - 4.34)	1.53 (0.56 – 4.19)	0.41
DVT	0 (0.0%)	15 (0.2%)	0 (0 -)	0 (0 -)	0.997
Pulmonary embolism	0 (0.0%)	4 (0.0%)	0 (0 -)	0 (0 -)	0.997
VTE	0 (0.0%)	19 (0.2%)	0 (0 -)	0 (0 -)	0.997
DIC	0 (0.0%)	25 (0.3%)	0 (0 -)	0 (0 -)	0.997

a- Pregnancy outcomes: Adjust for for obesity and pregestational DM
b- Delivery Outcomes: Adjust for for obesity and pregestational DM

TABLE III: Neonatal outcomes [a]

Table 3 Neonatal outcomes [a]

Outcomes	PCOS (%)	No PCOS (%)	Crude OR (95% CI)	Adjusted OR (95% CI)	Adjusted p-value
SGA	4 (2.8%)	503 (5.5%)	0.51 (0.19 – 1.37)	0.52 (0.19 -1.41)	0.20
IUFD	0 (0.0%)	49 (0.5%)	0 (0 -)	0 (0 -)	0.996
Congenital Anomalies	1 (0.7%)	76 (0.8%)	0.88 (0.12 – 6.21)	0.89 (0.12 – 6.46)	0.91

Neonatal Outcomes: Adjust for obesity and pregestational DM

CONCLUSIONS

- Bariatric surgery seems efficient at reducing most risks during pregnancy in women with PCOS into the normal range. Further study should be directed to understand why C/S were increased in the PCOS subjects.

Retrospective study comparing IVF antagonist protocols utilizing highly purified human menopausal gonadotropin and three different recombinant FSH preparations

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INTRODUCTION

This retrospective study compares clinical and laboratory outcomes of 3 antagonist mixed protocols for IVF (In vitro fertilization) utilizing:

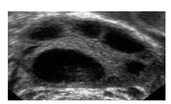
A = HP-hMG; Menopur® + follitropin alfa (Gonal-F®)
B = HP-hMG; Menopur® + follitropin beta (Puregon®)
D = HP-hMG; Menopur® + follitropin delta (Rekovelle®)

METHODS

Study Design:
Retrospective study conducted at **Clinique Ovo** and **Olive Fertility Centre** from January 2018 to September 2019.

Study Participants:
Women aged 18-42 years.
Total of subjects: 267 (89 subjects per group).

Procedures:
Enrollment of patients undergoing controlled ovarian stimulation for in vitro fertilization (IVF) using a mixed antagonist protocol.



Triggering criteria:
At least 3 follicles ≥ 17mm at ultrasound.
Embryos cultured until day 5 or 6.

Study Outcomes:
Clinical and laboratory outcomes were evaluated

Statistical Methods:
A single-way ANOVA with post-hoc Tukey multiple comparison test was used.

RESULTS

The mean age of all subjects was 34.62 years (SD 3.74) and weight 71.65 kg (SD 14.61). No significant differences were observed in age (p=0.19) or weight (p=0.78) among groups.

	GROUP A	GROUP B	GROUP D [&]	*P-value*
OVARIAN STIMULATION				
Total dose HP-hMG (IU)	2109 +/- 811	1567 +/-687	1918 +/-928	< 0.01 *
Total dose rFSH (IU)	2160 +/-909	2380 +/-620	1794 +/-522	< 0.01 *
Total dose FSH (IU)	4269 +/-1217	3947 +/-1110	3713 +/-1353	0.01 *
Duration of stimulation (days)	11.6 +/-1.5	10.6 +/-1.37	11.4 +/-1.3	< 0.01 *
LABORATORY OUTCOMES				
MII oocytes	11.5 +/-7.1	10.28 +/-5.1	10.9 +/-7.4	0.46
Fertilized oocytes	8.18 +/-5.41	6.96 +/-3.77	8.56 +/-5.32	0.07
Utilizable blastocysts	3.9 +/-3.1	3.6 +/-2.5	4.8 +/-3.5	0.029 *
FSH/Blastocyst ratio **	541.69	653.78	370.56	0.034 *

[&] Follitropin delta is administered in micrograms. The dose equivalence used was 10 µg of follitropin delta = 150 IU of follitropin alpha and beta
* Statistically Significant
** Calculated as FSH total dose (IU) per number of utilizable blastocysts obtained

The results shown in the table above demonstrate that group D used less gonadotropins despite a longer stimulation. No statistically significant differences were observed in the number of MII or fertilized oocytes. However, the **number of good quality utilizable blastocysts was significantly higher** in group D than in group A or B. The FSH/blastocyst ratio was significantly lower in group D than in the other groups, showing the need for **less gonadotropins per embryo obtained** in this group.

CONCLUSION

Mixed protocol of HP-hMG and follitropin delta (group D) yielded a significantly higher number of good quality, utilizable blastocysts even though MII and fertilized oocytes were comparable between the groups. The total dose of FSH required to obtain utilizable blastocyst was significantly lower in group D compared to the other groups, which gives this group an advantage in terms of cost effectiveness.

Genetic Counselling on Mosaic Embryos: Patient Concerns and a Genetic Counsellor's Perspective

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INTRODUCTION

Preimplantation genetic testing for aneuploidies (PGT-A), is a genetic test designed to improve IVF success rates by providing information about embryos' chromosomal health. Selection of single euploid embryos for transfer have improved pregnancy rate per transfer and reduced multiple pregnancy rate. However, recent advances in PGT-A technology (next generation sequencing) have increased the proportion of embryos diagnosed as mosaic that contain a mix of normal and abnormal cells. Whereas the occurrence of aneuploid embryos increases with maternal age, the occurrence of mosaic embryos is consistent at ~20% across age groups. Current recommendations are to consider mosaic embryos for transfer as a second-tier option if no euploid embryos are available. Although initial data on pregnancy outcomes of mosaic transfers are encouraging, it is still limited and scarce.

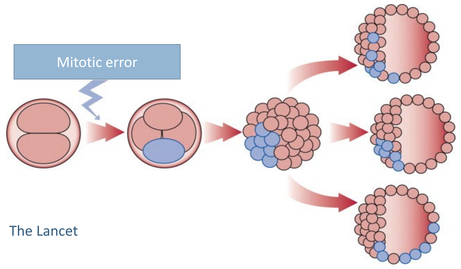

Figure 1: Mosaicism in embryos. Presence of two or more cell lines of different genotype within the same embryo occurring as a result of mitotic error in cell divisions. Extend and degree of mosaicism depend on timepoint of defective event and type of error.

OBJECTIVE

The aim of this single centre retrospective cohort study is to summarize the concerns that patients have facing the decision of mosaic embryo transfer.

MATERIALS AND METHODS

Over the last 20 months, 113 patients received genetic counselling on mosaic embryo transfer. All patients have been referred to genetic counselling after their Reproductive Endocrinologist at the CReATe Fertility Centre, has informed them on their PGT-A results and the patient feels that they need more information on mosaic embryos and the outcomes of their specific embryo.
The PGT-A testing was performed using NGS at CReATe's Reproductive Genetics Lab. The sensitivity for mosaicism detection was established at 20%, and aberrations considered clinically relevant were ≥10Mb in size and with ≥30% mosaicism. The counselling was done following the PGDIS guidelines (2106 and 2019) on the priority of mosaic transfers based on chromosome(s) involved, as well as the level of mosaicism.

RESULTS

Prior to counselling, the most common questions were:	
What are the chances that I will have a healthy baby if we transfer this mosaic embryo?	37% of patients
I need more information on this topic; I googled and need more; I consulted a Facebook group but need more information.	27% of patients
These embryos are our only hope, can we transfer them?	22% of patients

Comments received after the completion of a genetic counselling session
I had decided not to transfer this embryo but now that I have spoken to you, I am going to consider it
This information was so helpful
That was a lot of information, but it makes sense now
We need sometime to think about this
We are going to attempt another IVF cycle
What can I do differently next time? Are there supplements that I can take? Dietary changes I can make?

Points that are covered in a mosaic embryo genetic counselling session
This is not your fault (or the fault of the egg donor). This was a random event that happened after the time of fertilization.
When we give recommendations on transferring a mosaic embryo, we consider the chromosome involved and the level of mosaicism
Recent studies have reported normal prenatal diagnostic results, pregnancy and birth outcomes with mosaic embryo transfers. (Madjunkov et al, 2021; Viotti et al, 2021). There is a considerable potential for these embryos

- The genetic counselling sessions ranged from 20 to 45 minutes and with longer sessions if counselling is for several embryos with more complex findings.
- 6.7% of patients needed a second session to review the information a few months later, often after the unsuccessful transfer of a euploid embryo.
- 15% of cases required a follow up email to clarify one point or another.

Future Directions:
Assessment of patient's questions and concerns prior to a counselling session and again after the counselling session. This will be done in a questionnaire format.
Further studies are needed to fully determine the impact of genetic counselling on client's decision-making process.

CONCLUSION

Genetic counselling and evidence-based information on mosaic embryos and transfer outcomes after mosaic transfers with an approach that gives patients time to discuss their concerns and potential outcomes, helps inform these patients and can change their perspective of mosaic embryos from when they came into the session. Most leave with a better understanding of mosaic embryos and that these embryos have a good potential for a successful live birth. This is a preliminary study that demonstrates that a more comprehensive study on the needs of patients from genetic counsellors is needed and identifies the burning questions that can be addressed with enhanced patient information packages about PGT during IVF treatment.

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