Time-lapse KIDScore Day 5 can be used as a primary marker to predict embryo pregnancy potential in fresh and frozen single embryo transfers

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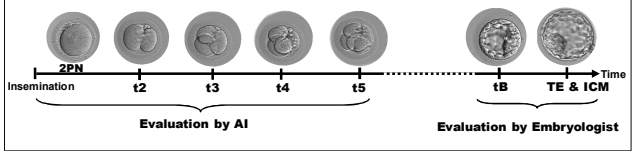
Introduction

Time-lapse (TL) studies and the recent introduction of Artificial Intelligence (AI) to conduct complex multi-parameter analyses of embryo development, eliminate human subjectivity and streamline the selection decision for the embryo with best potential for pregnancy. Utilization of KIDScore Day 5 (KIDS5), an AI generated multi-variable morphokinetic score (1 to 10, 10 being best), has shown promise in decreasing the number of embryo transfer attempts and the time to pregnancy.

Variables included in the morphokinetic score KIDS5



Aim of the study: Determine whether the KIDS5 can be used as a primary marker for selecting the best embryo for fresh and frozen single embryo transfers.

Methods

- Retrospective cohort study of consecutive cycles conducted between May 2019 and April 2021.
- Single embryo transfer cycles with either fresh or frozen expanded Day 5 blastocysts.
- Embryo culture in TL incubator EmbryoScope Plus (Vitrolife, Sweden).
- The morphokinetic analysis of embryos achieved by assessing the images captured by the EmbryoScope Plus (Vitrolife, Sweden), every 10 min in seven focal planes.
- Selection for transfer or cryopreservation based on Gardner morphological scoring system.
- Embryo annotation and computation of the KIDS5 v3 score (Vitrolife, Sweden) performed retrospectively (corresponding to the time of transfer for fresh ET and corresponding to the time of freezing for frozen ET).
- Exclusion criteria: cycles with surgically retrieved sperm, endometrial factors, PGT.
- Clinical outcomes measured: implantation rate, viable pregnancy rate.
- Statistical tests: Pearson correlation coefficient (ρ), Area Under the Curve (AUC).

Results

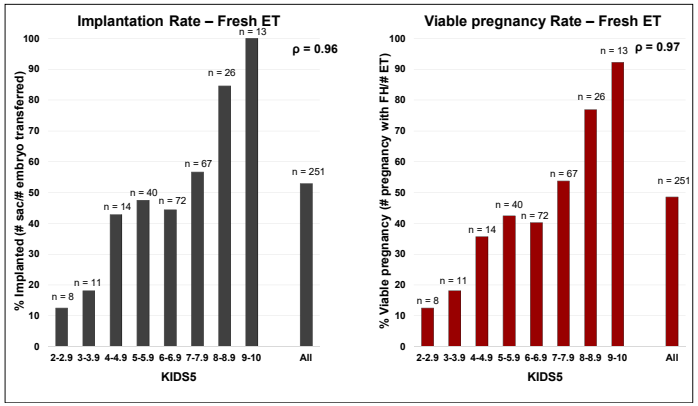


Figure 1. KIDS5 positively correlates with Implantation and Viable pregnancy rates for fresh ET

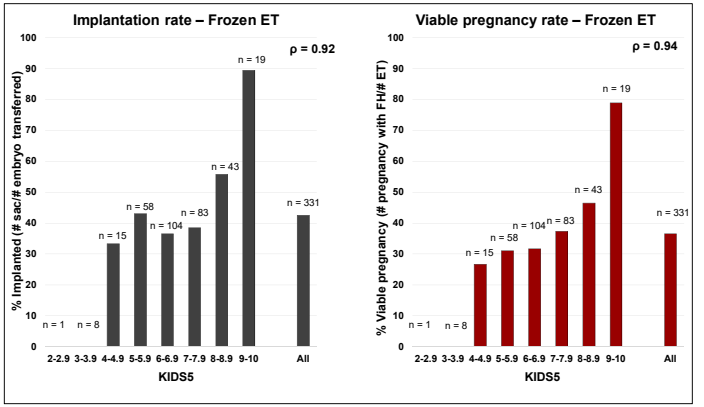


Figure 2. KIDS5 positively correlates with Implantation and Viable pregnancy rates for frozen ET

Outcome tested	Implantation - Fresh ET	Viable pregnancy - Fresh ET	Implantation - Frozen ET	Viable pregnancy - Frozen ET
AUC	0.7	0.7	0.6	0.6

Table 1. KIDS5 performance in predicting implantation and viable pregnancy for fresh and frozen ET cycles

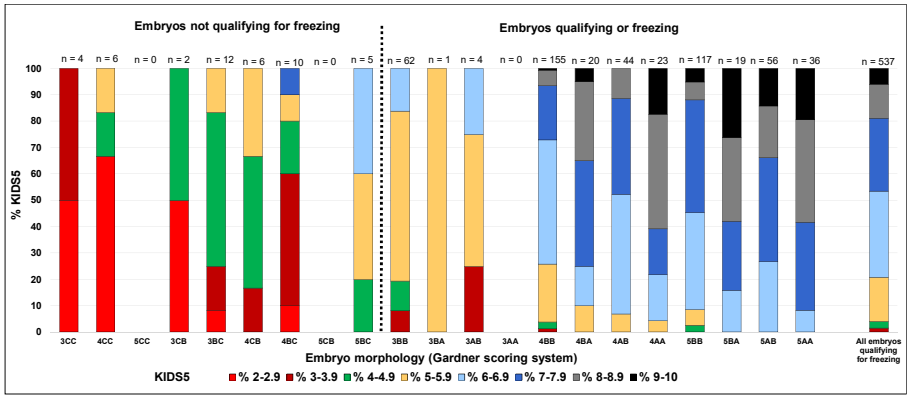


Figure 3. Lack of concordance between KIDS5 and blastocyst morphology

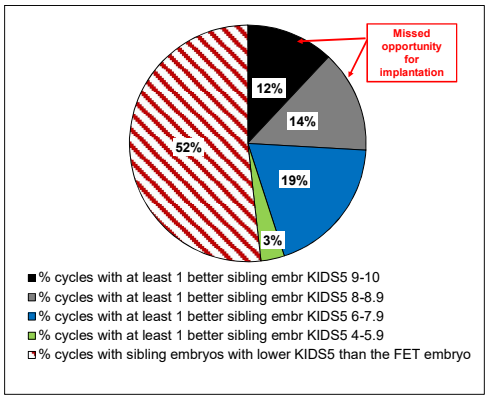


Figure 4. Many frozen ET cycles had at least one better sibling frozen embryo available and not warmed

Conclusions

- KIDS5 is a good predictor of embryo implantation and viable pregnancy in both fresh and frozen ET cycles.
- A lack of concordance was observed between embryo morphology and KIDS5.
- For many frozen ET cycles, a sibling embryo with a better KIDS5 was not selected for transfer, suggesting a missed opportunity for potential implantation.

Static Morphology of Mosaic Embryos is a Prognostic Factor of Transfer Outcome

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INTRODUCTION

Preimplantation genetic testing for chromosomal aberrations (PGT-A) using NGS in IVF has increased rates of implantation per transfer, but at the same time has increased mosaic embryo detection to ~20% of all tested embryos. The current recommendation is to consider mosaic embryos for transfer if there are no euploid embryos remaining. Evidence is still limited on the developmental potential, implantation and birth outcomes of mosaic embryos. Some studies suggested that level and type (segmental or all chromosome aberrations) may determine the implantation potential of mosaic embryos.

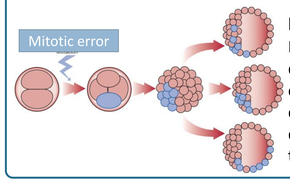


Figure 1: Mosaicism in embryos. Presence of two or more cell lines of different genotype within the same embryo occurring as a result of mitotic error in cell divisions. Extend and degree of mosaicism depend on timepoint of defective event and type of error.

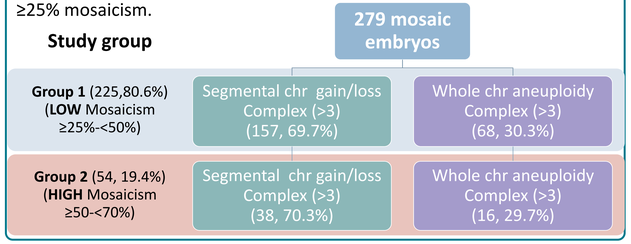
OBJECTIVE

To evaluate the implantation and pregnancy outcomes after mosaic embryo transfer detected at NGS resolution and relationship between the static morphology and implantation/ongoing pregnancy of mosaic

MATERIALS AND METHODS

This is a single centre retrospective cohort study where we analysed the PGT-A results from 13,336 TE biopsies and clinical outcomes from 279 single mosaic embryo transfers.

NGS analysis was performed using VeriSeq (Illumina) kits with BlueFuse software. The sensitivity for mosaicism detection was established at 20%, and aberrations considered clinically relevant were ≥10Mb in size and with ≥25% mosaicism.



RESULTS

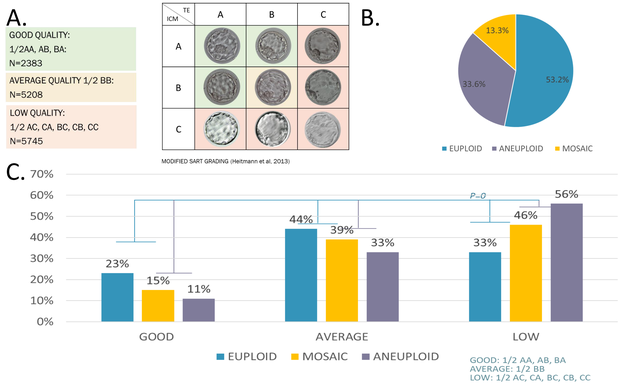


Figure 2: Static morphology grading and PGT-A results of 13336 analyzed embryos. A. Modified SART grading was used and embryos were grouped in 3 groups as described. B. PGT-A results using NGS. C. Distribution of ploidy by embryo grade.

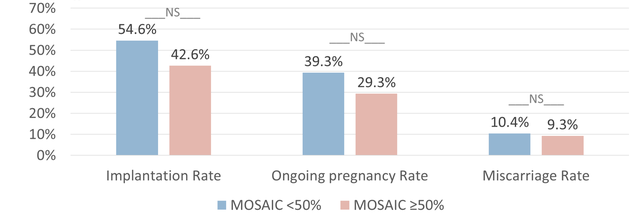


Figure 3: Level of mosaicism is not associated with pregnancy outcomes of 279 mosaic embryo transfers. Overall implantation rate for mosaic embryos was 52.3%. There was no statistical difference between Group 1 (Low mosaicism) and Group 2 (HIGH mosaicism) in embryo implantation rate, ongoing pregnancy rate or miscarriage rate. Healthy babies were delivered from 72 available birth outcomes.

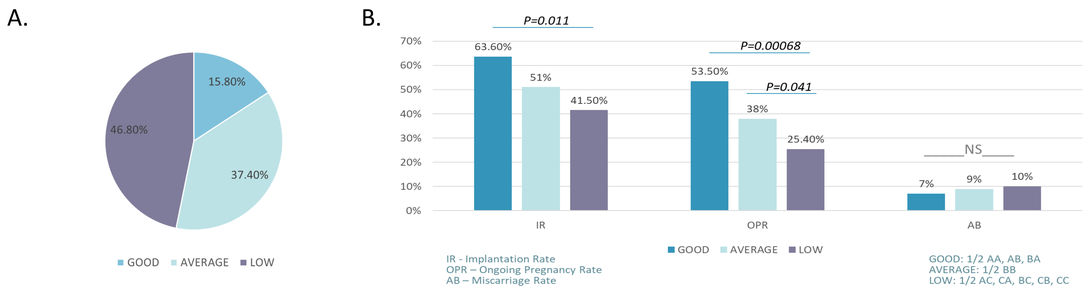


Figure 4: A. Morphology grade of 279 transferred mosaic embryos. B. Pregnancy outcomes by static morphology grade. Mosaic embryos with Good morphology grade had higher implantation rate (IR) and ongoing pregnancy rate (OPR) compared to mosaic embryos with Poor morphology (IR, p=0.011, OR 2.4, 95%CI[1.2-4.9]; OPR p=0.000687, OR 3.378, 95%CI[1.642-6.948]).

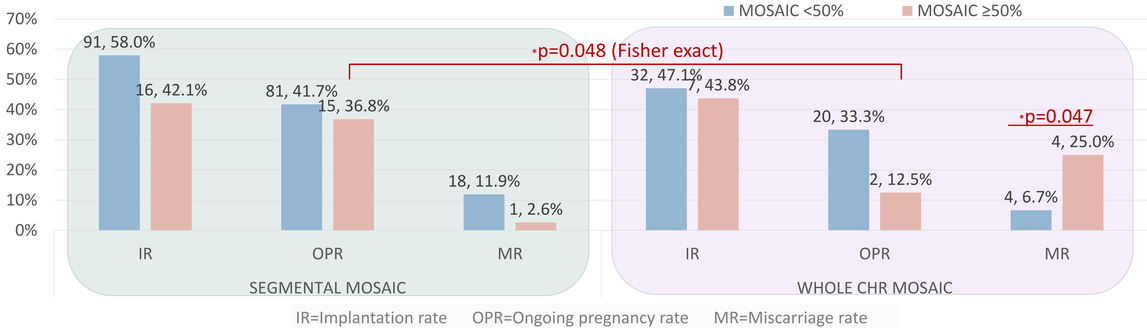


Figure 5: Pregnancy outcomes by level and type of mosaicism. Whole chromosome ≥50% mosaicism (Group 2) is associated with higher miscarriage rate (p=0.047). Segmental chr mosaics ≥50% (Group 2) have higher ongoing pregnancy rate compared to whole chr mosaicism ≥50% (Group 2). There was no statistical difference between pregnancy outcomes of segmental chr aberrations in Group 1 and Group 2.

CONCLUSION

Good static morphological grade is associated with higher IR and OPR of mosaic embryos.

Our results indicate that static morphological grade should be considered in selection of mosaic embryos for transfer. Our findings provide evidence that the majority of mosaic embryos that implant will develop into healthy babies and supports the hypothesis that low level mosaicism in early embryonic development may be a physiological phenomena.

Future Directions:

- Assessment of morphokinetic parameters of mosaic embryos is currently in progress to complement this study.
- Further studies are needed to fully determine the impact of specific mosaic chromosomal aberrations on pregnancy outcome and birth outcome.

ACKNOWLEDGEMENTS

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Thanks to ALL CReTAe Fertility Staff and Patients

Authors have no conflict of interest to declare.

NATIONAL SURVEY ON THE MANAGEMENT OF NON-EUPLOID EMBYROS

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Introduction :

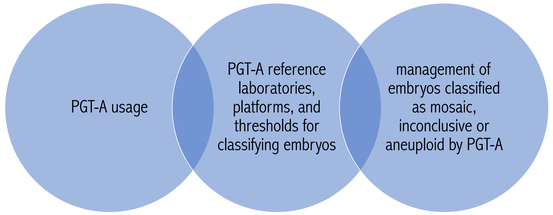
- Up to 36% of IVF cycles in Canada are initiated with the intention of performing PGT-A[1]
- PGT-A is a screening test with limitations such as technical errors, embryonic mosaicism and sampling bias[2]
- PGT-A results include euploid, mosaic, aneuploid and inconclusive
- No consensus on management of non-euploid embryos

Aim:

- Comprehensively describe current PGT-A practices and management of screened non-euploid embryos in Canada

Materials and Methods

- cross-sectional survey with unique access link sent by email to medical directors of all Canadian fertility clinics with an independent IVF embryology laboratory
- Hosted on SimpleSurvey and available online from June to August 2020
- Designed to determine practice patterns with respect to



Statistical Analysis

- Number of participants who provided consent was used to determine the response rate
- Fisher's exact tests were performed to examine the associations between clinical and laboratory factors and transferring of non-euploid embryos
- Wilcoxon rank sum tests or Kruskal-Wallist tests were used to compare continuous variables between groups

Demographics :

- Survey sent to 37 IVF clinics, with 2 clinics being represented by the same medical director
- 25 participated in the survey, response rate of 69%
- 22 completed the survey, completion rate of 88%
- 20 clinics performed PGT-A
- 18 clinics received mosaicism data

Characteristic	n	%
Province of Practice		
- Ontario	10	45
- Manitoba	1	5
- Nova Scotia	1	5
- Quebec	4	18
- British Columbia	4	18
- Saskatchewan	1	5
- Alberta	1	5
Practice Type		
- Academic	4	18
- University-affiliated	7	32
- Private	11	50
Annual number of IVF cycles for clinics performing PGT-A		
- Under 500	9	45
- 500-999	3	15
- 1000-1499	7	35
- No response	1	5
Percentage of cycles including PGT-A		
- Less than 10%	3	15
- 10-29%	7	35
- 30-49%	7	35
- 50% or more	2	10
- No response	1	5

TABLE 1: DEMOGRAPHICS OF PARTICIPANTS

Conclusions:

- High utilization rate of PGT-A
- Most commonly offered for RPL, RIF; 45% offer routinely to all patients
- Majority of clinics have or would consider mosaic embryo transfer
- Prenatal screening (NIPT) often recommended after mosaic embryo transfer; diagnostic genetic testing recommended less often

References

1. 2019 Canadian Fertility and Andrology Society (CFAS) Report on Canadian Assisted Reproduction Registry (CARTR) Outcomes. https://cfas.ca/_Library/CARTR/2019_CARTR_Press_Release_PDFpdf; 2019.
2. Chan C, Ryu M, Zwingerman R. Preimplantation genetic testing for aneuploidy: A Canadian Fertility and Andrology Society Guideline. Reprod Biomed Online. 2020.
3. Kim TG, Neblett MF, Shandley LM, Omurtag K, Hipp HS, Kawwass JF. National mosaic embryo transfer practices: a survey. Am J Obstet Gynecol. 2018;219(6):602 e1- e7.

Results :

61% of clinics have transferred at least one mosaic embryo
94% of clinics would consider transfer of a mosaic embryo
50% of clinics have transferred at least one inconclusive embryo
5% of clinics have transferred at least one aneuploid embryo
15% of clinics would consider transfer of an aneuploid embryo

Clinics who performed **more than 1000 cycles** were **more likely** to have transferred a mosaic embryo

Clinics who used **less PGT-A per cycle** were more likely to have transferred a mosaic embryo

Figure 1. INDICATIONS FOR PGT-A TESTING

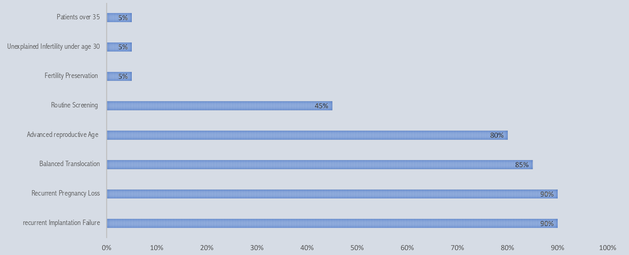


FIGURE 2: RECCOMENDED MANAGEMENT OPTION PROVIDED TO PATIENT BY CLINICS ACCORDING TO PGT-A BIOPSY RESULTS

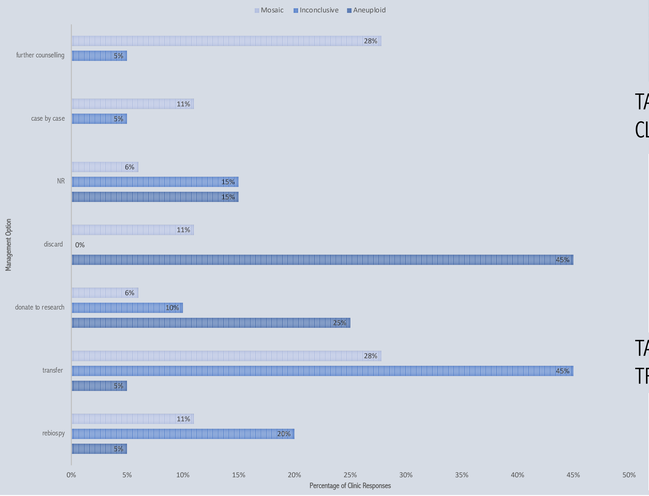


TABLE 2: THE ASSOCIATIONS BETWEEN CLINICAL AND LABORATORY FACTORS AND THE TRANSFER OF MOSAIC EMBRYOS

	Transfer of mosaic embryos		*P value
	Yes (n=11)	No (n=6)	
Threshold for diagnosis of mosaicism			0.440
20-80%	6 (85.7)	1 (14.3)	
30-70%	3 (50.0)	3 (50.0)	
Unknown	2 (50.0)	2 (50.0)	
Annual IVF cycles			0.043
<1000	5 (45.5)	6 (54.5)	
≥1000	6 (100)	0 (0)	
Percentage of IVF cycles using PGT-A (%)			
Mean±SD	12.3±9.77	30.4±20.1	0.033
Practice type			0.661
University affiliated	4 (66.7)	2 (33.3)	
Academic	1 (33.3)	2 (66.7)	
Private	6 (75.0)	2 (25.0)	
Testing facility			0.099
Reference lab	10 (76.9)	3 (23.1)	
In house lab	1 (25.0)	3 (75.0)	
PGT-A routine screening			0.335
No	4 (50.0)	4 (50.0)	
Yes	7 (77.8)	2 (22.2)	

TABLE 3: ALL MANAGEMENT OPTIONS PROVIDED TO PATIENT BY CLINICS ACCORDING TO PGT-A BIOPSY RESULTS

	Biopsy Result		
Management Option	Aneuploid	Inconclusive	Mosaic
Discard	75%	15%	28%
Donate	50%	10%	11%
Rebiopsy	15%	45%	22%
Transfer	10%	60%	39%

TABLE 4: FOLLOW-UP GENETIC TESTING AFTER MOSAIC EMBRYO TRANSFER

Follow-up genetic testing recommended	83%
NIPT	73%
CVS	33%
Amniocentesis	53%

Positive Patients and Healthcare Providers*

E.S. Dason, MD, L. Drost, E.M. Greenblatt MD, A.S Scheer MD, J. Han BSc, MD, M. Sobel, MSc, MD, L. Allen, MD, M. Jacobson MD, T. Doshi, E. Wolff, E. McMahon, RN, MN, C.A. Jones MD

INTRODUCTION

- Women carrying the BRCA mutation are usually offered a risk-reducing salpingo-oophorectomy at age 35-40 to reduce their risk of breast and ovarian cancer
- Choosing amongst reproductive options in the context of a BRCA mutation discovery is a shared decision between patient and provider

* This article refers to "women" as people with internal reproductive organs; however we understand that not everyone with internal reproductive organs identifies as a woman and acknowledge that this information is relevant for anyone assigned female at birth irrespective of their gender identity

RATIONALE

- Prior studies have reported that patients feel unsupported in reproductive decision-making by their provider highlighting the potential role for improved decision support

AIM

- Assess decision-making needs of patients and providers when discussing reproductive options with female BRCA genetic mutation carriers prior to RRSO

METHODS

Email recruitment of providers at FOCC, FBCC, and MSF (November 2018 - October 2020) → Semi-structured interviews guided by the Ottawa Decision Support Framework → Audio-recorded and transcribed → thematic analysis using NVIVO 12

RESULTS

Demographics :

- 15 providers : REI physicians (4/15), REI fellows (3/15), general OB/GYNs (3/15), a gynecological oncologist (1/15), a nurse practitioner specializing in fertility preservation (1/15), a registered nurse at the FOCC (1/15), a genetic counsellor specializing in PGT (pre-implantation genetic testing) (1/15), and a genetic counsellor at FBCC specializing in BRCA genetic testing (1/15)

Key Points :

- This is a complex decision due to inherent decision elements, modifiable decisional needs and voiced uncertainty (Figure 1)
- There were three major reproductive decisions (Box 1) with varied patient considerations impacting decision-making (Figure 2)
- Proposed decisional supports are identified in Figure 3

Conclusion

- Highly complex decision requiring tailored decision support for both providers and patients
- Would not be well suited to a patient decision aid
- Decision Support Options :
  - Population-specific informational material for both patients and providers developed (available upon request)
  - Implementable clinical practice changes identified

Selected References

Quinn, G. P. *et al.* BRCA carriers' thoughts on risk management in relation to preimplantation genetic diagnosis and childbearing: when too many choices are just as difficult as none. *Fertility and Sterility* **94**, 2473–2475 (2010).

Kim, J., Skrzynia, C. & Mersereau, J. E. A Pilot Study of BRCA Mutation Carriers' Knowledge About the Clinical Impact of Prophylactic-oophorectomy and Views on Fertility Consultation: A Single-Center Pilot Study. *Journal of Genetic Counseling* **24**, 149–157 (2015).

Poprzeczny, A. J., Stocking, K., Showell, M. & Duffy, J. M. N. Patient Decision Aids to Facilitate Shared Decision Making in Obstetrics and Gynecology: A Systematic Review and Meta-analysis. *Obstetrics & Gynecology* **135**, 444–451 (2020).

Hoefel, L. *et al.* 20th Anniversary Update of the Ottawa Decision Support Framework Part I: A Systematic Review of the Decisional Needs of People Making Health or Social Decisions. *Med Decis Making* 0272989X2093620 (2020) doi:10.1177/0272989X20936209.

Three Major Reproductive Decisions :

Do I want to have children?
Do I want to take the chance of passing on this mutation?
Do I want to carry a child?

Box 1 : Major Reproductive Decisions

Figure 1 : Patient Considerations Impacting Reproductive Decision-Making

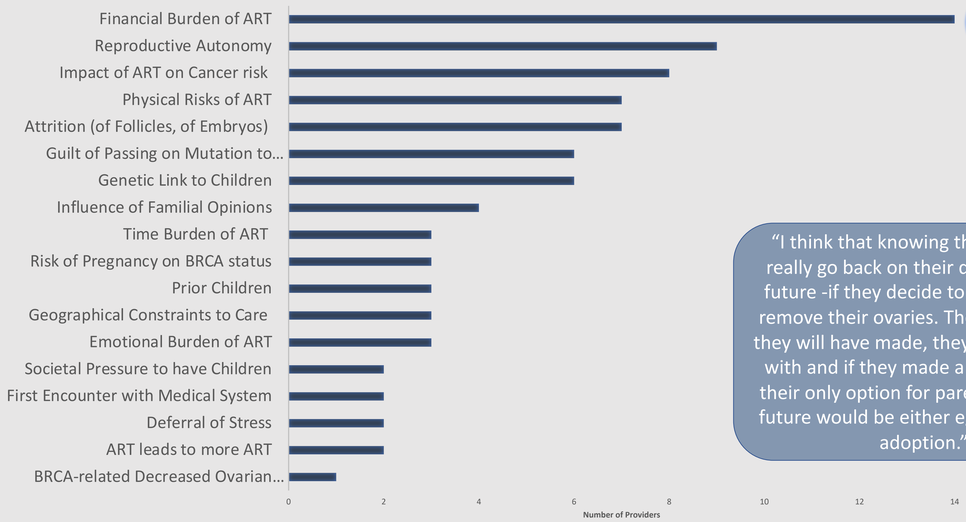
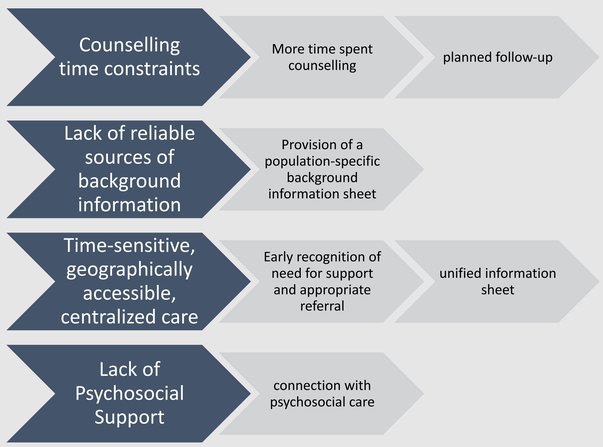


Figure 2 : Clinical Gaps and Suggested Clinical Modifications



"I think that knowing that they can't really go back on their decision in the future -if they decide to go ahead and remove their ovaries. The decision that they will have made, they'll have to stick with and if they made a mistake, then their only option for parenthood in the future would be either egg donation or adoption."

"People do like to know 'what have most people in my situation done'. How many people have come back to use what they've frozen, and how successful were they? We don't have a huge number of data or information for them on that... Certainly clinic specific freeze and thaw pregnancy rate data would be helpful. I don't have it. We have some but not enough. I don't think the numbers are great enough to make it an average to provide to patients."

"'Do I think I'll ever use these eggs?' Some of them aren't sure or you know you can't tell me these eggs will definitely result in live birth so that makes it hard for people because I'm not going to put myself through potentially risky procedure even though the risk is quite low, less than 1% for infection or bleeding, but it's not 0. And you can't guarantee that there will be live birth from these eggs so some of them, that's a hard decision for them."

"Well I think one of the things is that I always tell people just for any individual person, there's no test we can do that will act as a crystal ball to tell me whether that person will be able to conceive spontaneously in the future."

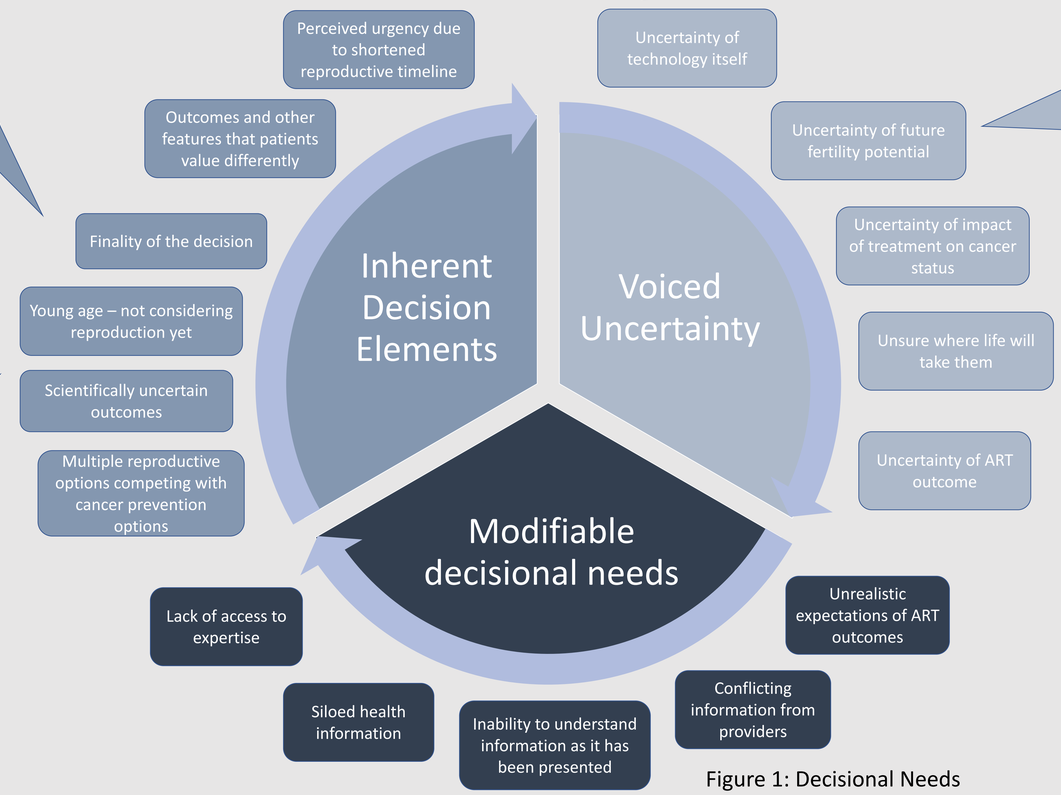


Figure 1: Decisional Needs

The clinical outcomes of older and younger patients with different indications underwent Preimplantation genetic testing for aneuploidy (PGT-A) in one center

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McGill University

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Introduction

Preimplantation genetic testing for aneuploidy (PGT-A) allows us to choose euploid embryos for transfer in order to increase live birth rates of IVF cycles, and to reduce the risks of adverse reproductive outcomes. Different group of patients with different indications may be recommended for PGT-A, such as recurrent implantation failure (RIF), recurrent miscarriages (RM), advanced maternal age (AMA), male factors and others with higher aneuploidy risks. The objective of this study was to evaluate the clinical outcomes of PGT-A in older and younger female patient groups with different indications in one center.

Material and methods

We retrospectively analyzed data obtained in 220 PGT-A cycles with older female age (38 or older, average age: 40.4), and 155 cycles with younger female age (37 or younger, average age: 34). The indications for PGT-A testing includes RM, RIF, AMA, male factor and others with higher aneuploidy risks. The PGT-A tests were done by FISH to detect 8 9 chromosomes (261 cycles) or NGS to detect all 23 sets of chromosomes (114 cycles). Embryos diagnosed as euploid were transferred on day4 or day5 after fertilization freshly for FISH testing, or frozen embryo replacement cycle (FERC) in the following month for NGS testing. The chromosome aneuploidy rate, implantation rate (IR), clinical pregnancy rate (CPR) and miscarriage rate were compared between older and younger female age groups. The study was approved by research ethics board of McGill University Health Center (MUHC).

Table 1. Clinical outcomes of female patients 37 years or younger underwent Preimplantation Genetic Testing for Aneuploidy (PGT-A)

	RM	RIF	Others (male factor, infertility, miscarrage sexing, PGT-M)
No.cycle (patient)	55(45)	49(41)	51(35)
Average age	34	33.4	34.5
No. COC (per cycle)	1017(18.5)	872(17.8)	739(14.5)
No. Fert(%)	710(86.5%)	588(86%)	496(88%)
2PN	655	557	453
No. Em tested	463 (8.4)	399 (8.14)	311
Normal(%)	209 (47%)	159 (41.6%)	137 (48%)
Abnormal (%)	239 (53%) *	223 (58.4%) *	157 (52%) *
Cycles with ET	46 (4 cycles with no available embryo for ET; 5 cycles not ET yet)	42 (4 cycles with no available embryo for ET; 4 cycles not ET yet)	33 (1 cycle with no available embryo for ET; 17 cycles not ET yet)
No.Embryo transferred	99	113	73
No. Sac (IR)	35(35.4%)	24(21.3%)	25(34.2%)
CPR/Cycle	46%	37%	37%
CPR/ET cycle	54.30%	43%	58%
Miscarrage rate	16% (4/25)	16.7% (3/18)	15.8% (3/19)

* p < 0.001 when compared: RM with younger female age vs RM+AMA; RIF with younger female age vs RIF+AMA; Others with younger female age vs AMA only

Table 2. Clinical outcomes of female patients 38 years or older underwent Preimplantation Genetic Testing for Aneuploidy (PGT-A)

	RM+AMA	RIF+AMA	AMA only
No.cycle (patient)	58(36)	53(30)	109(79)
Average age	40.45	40.3	40.67
No. COC (per cycle)	781(13.46)	869(16.4)	1859(17)
No. Fert(%)	547(83%)	641(85%)	1242(85.7%)
2PN	481	599	1143
No. Em tested	383 (6.6)	451 (8.51)	818
Normal(%)	106(29.4%)	134(31.3%)	218(27%)
Abnormal (%)	255(70.6%) *	294(68.7%) *	589(73%) *
Cycles with ET	51(7 cycles not ET yet)	45(2 cycles with no available embryo for ET; 6 cycles not ET yet)	81(16 cycles with no available embryo for ET; 12 cycles not ET yet)
No.Embryo transferred	94	123	158
No. Sac (IR)	25(26.6%)	22(17.9%)	42(26.6%)
CPR/Cycle	32.80%	25%	29.40%
CPR/ET cycle	37.30%	28.90%	40%
Miscarrage rate	31.5% (6/19)	30.7% (4/13)	15.6% (5/32)

* p < 0.001 when compared: RM with younger female age vs RM+AMA; RIF with younger female age vs RIF+AMA; Others with younger female age vs AMA only

Results

There was significantly higher aneuploidy rate in older patients with RM and RIF compared to younger patients groups (RM: 70.6% vs 53%; RIF: 68.7% vs 58%. p<0.001), however, there was no significant difference of IR in both groups (RM: 26.6% vs 35.4%, p=0.18; RIF: 17.9% vs 21.3%, p=0.51), and no significant difference of CPR/ET cycle(RM: 37.3% vs 54.3%, p=0.09; RIF: 28.9% vs 42.9%, p=0.17) and CPR/Cycle (RM: 32.8% vs 45.5%, p=0.16; RIF: 25% vs 37%, p=0.19). Similar pattern was observed when compared “AMA only” and “Others” in the younger patients group. There were more oocytes retrieved per cycle from RM patients with younger age compared to the older age patients (18.5 vs 13.4) which resulted in a similar trend in the number of embryos being tested (8.4 vs 6.6). The number of oocytes retrieved from RIF patients in different age groups was similar. (Table 1 and Table 2)

Conclusion

There was no difference in chromosome abnormality rate among RIF, RM and other groups within the younger age group. A similar result was observed in the older age group (≥38 yr.) within RIF, RM and AMA only indications. However, the aneuploidy rate was significantly higher in older age group of all indications when compared to the younger age counterpart. This suggests that this increase in aneuploidy rate is only age-related. Following PGT-A, no difference in CPR,IR, or miscarriage rate was observed in younger and older age groups of all indications suggesting that PGT-A eliminates the negative impact of maternal age on clinical outcomes.

How does advanced age interact with the requirement for IVF on pregnancy complications?

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INTRODUCTION

- Due to changing social trends, women are delaying childbearing to a more convenient time in pursuit of higher education, financial stability, and partnership formation.
- Age is a risk factor for pregnancy complications. Women at least 38 years old are at increased risk of many issues, including hypertensive disorders, gestational diabetes, placentation abnormalities, abruption, blood transfusion, cesarean section and fetal demise, among others.
- The need for IVF to conceive is also a risk factor for pregnancy complications.

OBJECTIVE

- To evaluate the risks in IVF pregnancies in women 38-43 years of age, using a retrospective population database.

MATERIALS AND METHODS

- We used the Health Care Cost and Utilization Project-Nationwide Inpatient Sample database from 2008 to 2014, inclusive to generate a list of unique deliveries in women aged 38-43 years old.
- Women who underwent IVF were compared to the rest of the cohort.
- Multivariate logistic regression analysis was performed to compare both groups regarding pregnancy, delivery, and neonatal outcomes after adjusting for plausible confounding factors

Figure 1. Prevalence of IVF among women Between 38 – 43 years old, who gave birth between 2008 and 2014.

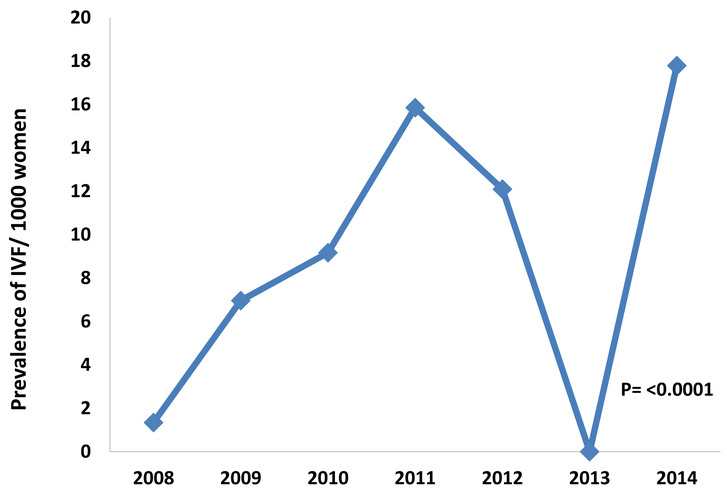

TABLE I: Table 1 Maternal Characteristics

Characteristics	Spontaneous pregnancy N= 306805	Pregnancy from assisted reproduction N= 2762	P-value
Race			<0.0001
White	151752(54.7%)	1820 (69.0%)	
Black	31528 (11.4%)	165 (6.3%)	
Hispanic	52683(19.0%)	158(6.0%)	
Asian and Pacific	25651(9.3%)	347(13.2%)	
Native American	1512(0.5%)	10(0.4%)	
Other	14103(5.1%)	138(5.2%)	
Income quartiles			<0.0001
Less than 39,000	53342(17.7%)	136(5.0%)	
$39,000-47,999	60609(20.1%)	291(10.6%)	
$48,000-62,999	76513(25.4%)	643(23.5%)	
$63,000 or more	110516(36.7%)	1664(60.9%)	
Plan type			<0.0001
Medicare	2772(0.9%)	2(0.1%)	
Medicaid	78422(25.6%)	71(2.6%)	
Private insurance	208718(68.1%)	2604(94.3%)	
self-pay	9360(3.1%)	38(1.4%)	
No charge	466(0.2%)	0(0%)	
Other	6640(2.2%)	46(1.7%)	
Previous CS	82659(26.9%)	455(16.5%)	<0.0001
Smoking during pregnancy	10295(3.4%)	12(0.4%)	<0.0001
Chronic HTN	16090(5.2%)	117(4.2%)	0.018
Pregestational DM	6193(2.0%)	43(1.6%)	0.086
Drug use	2958(1.0%)	1(0.0%)	<0.0001
Thyroid disease	18637(6.1%)	447(16.2%)	<0.0001
HIV	98(0.0%)	0(0.0%)	1.000
Obesity	159 (5.8%)	17166 (5.6%)	0.71
Multiple gestation	8024(2.6%)	753(27.3%)	<0.0001

RESULTS

- During the study period, 5,545,612 pregnant women were identified. Among these, 309,567 women were found to be 38-43 years old. The IVF group included 2,762 women, and there were 306,805 controls.
- The IVF group was more likely to have private insurance, higher incomes, thyroid diseases (16.2% vs. 6.1%) & multiple gestations (27.3% vs. 2.6%) (p<0.0001 all cases). Previous caesarean sections (16.5% vs. 26.9%, p<0.0001), diagnosis of chronic hypertension (4.2% vs. 5.2%, p=0.02), and cigarette smoking (0.4% vs. 3.4%, p<0.0001) rates were lower among the IVF. Other baseline demographics did not differ.
- After adjusting for confounding variables, the IVF group had a higher risk of: gestational diabetes (aOR 1.24, 95% CI 1.01-1.52), pregnancy-induced hypertension (aOR 1.31, 95% CI 1.06-1.62), placenta previa (aOR 2.37, 95% CI 1.55-3.61), preterm delivery (aOR 1.45, 95% CI 1.16-1.81), preterm premature rupture of membrane (aOR 2.26, 95% CI 1.57-3.25), caesarean section (aOR 1.84, 95% CI 1.55- 2.19), chorioamnionitis (aOR 2.08, 95% CI 1.41-3.08), maternal infection (aOR 1.90, 95% CI 1.31-2.77), postpartum hemorrhage (aOR 1.84, 95% CI 1.55- 2.19), and. blood transfusion (aOR 1.85, 95% CI 1.25-2.73)
- Small for gestational age (5.5% vs. 2.4%, OR 2.36, 95% CI 2.00-2.78) and congenital anomalies (1.2% vs. 0.5%, OR 2.25, 95% CI 1.60-3.17) occurred at a higher rate in women with IVF compared to controls. These did not differ when controlling for confounding effects (aOR 1.29, 95% CI 0.92-1.82) and (aOR 1.67, 95% CI 0.85-3.27). Intrauterine fetal demise did not differ between the groups (0.6% vs. 0.5%).

TABLE II: Pregnancy and delivery outcomes.

Outcomes	Spontaneous pregnancy N= 306805	Pregnancy from assisted reproduction N= 2762	Crude OR (95% CI)	Adjusted OR (95% CI)	Adjusted p-value
Pregnancy outcomes [a]					
Pregnancy induced hypertension	28583(9.3%)	429(15.5%)	1.790(1.614 - 1.985)	1.312(1.062-1.621)	0.012
GDM	40403(13.2%)	406(14.7%)	1.136(1.022-1.263)	1.236(1.006-1.518)	0.044
Placenta previa	4137(1.3%)	108(3.9%)	2.977(2.450-3.617)	2.369(1.553-3.614)	<0.0001
Delivery outcomes [b]					
PPROM	4375(1.4%)	119(4.3%)	3.112(2.584-3.749)	2.262(1.574-3.250)	<0.0001
Preterm delivery	24682(8.0%)	528(19.1%)	2.701(2.455 - 2.973)	1.446(1.156-1.810)	0.001
Abruptio placenta	4199(1.4%)	44(1.6%)	1.167(0.865-1.574)	1.121(0.625-2.010)	0.701
Chorioamnionitis	4452(1.5%)	96(3.5%)	2.445(1.991-3.004)	2.080(1.405-3.080)	<0.0001
Operative vaginal delivery	18605(6.1%)	205(7.4%)	1.242(1.076-1.433)	1.299(0.986-1.712)	0.063
CS	141451(46.1%)	1807(65.4%)	2.212(2.044-2.393)	1.844(1.553-2.189)	<0.0001
Hysterectomy	962(0.3%)	17(0.6%)	1.967(1.216-3.183)	0.617(0.149-2.548)	0.504
PPH	9826(3.2%)	213(7.7%)	2.525(2.193-2.909)	1.684(1.266-2.240)	<0.0001
Transfusion	4548(1.5%)	96(3.5%)	2.391(1.947-2.938)	1.846(1.246-2.737)	0.002
Maternal infection	5357(1.7%)	105(3.8%)	2.224(1.826-2.708)	1.904(1.310-2.766)	0.001

a- Pregnancy outcomes: adjusted by Race, Plan type, Hospital type, Income quartiles, Drug Use, previous Caesarian section, Chronic HTN, Smoking During Pregnancy, Thyroid disease and Multiple Gestation.
b- Delivery Outcomes: adjusted by Race, Plan type, Hospital type, Income quartiles, Drug Use, previous Caesarian section, Chronic HTN, Smoking during Pregnancy, Thyroid disease, Multiple Gestation, Pregnancy induce HTN, Gestation DM and Placenta Previa.

TABLE III: Neonatal outcomes [a]

Outcomes	Spontaneous pregnancy (%)	Pregnancy from assisted reproduction (%)	Crude OR (95% CI)	Adjusted OR (95% CI)	Adjusted p-value
SGA	7341(2.4%)	151(5.5%)	2.359(1.999-2.784)	1.296(0.924-1.82)	0.133
IUFD	1978(0.6%)	13(0.5%)	0.729(0.422-1.259)	0.264(0.037-1.89)	0.185
Congenital Anomalies	1686(0.5%)	34(1.2%)	2.255(1.603-3.174)	1.671(0.854-3.27)	0.134

a- Neonatal Outcomes: adjusted by Race, Plan type, Hospital type, Income quartiles, Drug Use, previous Caesarian section, Chronic HTN, Smoking during Pregnancy, Thyroid disease, Multiple Gestation, Pregnancy induce HTN, Gestation DM and Placenta Previa.

CONCLUSIONS

- Pregnancy from IVF in women 38-43 years of age induces an 80% to 120% increases in rates of many pregnancy complications.
- Increased risks of hypertensive disorders and gestational diabetes were less pronounced.
- Compared to previous published studies including younger patients, most pregnancy risks were substantially increased in the IVF patients of older age as compared to the age matched controls.

Patients' and Providers' Perspectives on Elective Egg Freezing Decision-Making

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Mount Sinai Fertility
Sinai Health

Introduction

- Although elective egg freezing (EEF) has become increasingly popular, the details of the discussion around EEF and how patients and providers should be supported has yet to be fully explored.
- Prior studies have identified that the decision to undergo EEF is complex for both patients[1] and the providers supporting them[2], however a specific analysis of contributing factors is lacking.

Methodology

Participants were part of two populations selected by purposive and convenience sampling:

Providers (n = 13)
From across Canada, included REI physicians nurse practitioners, and reproductive counsellors

Patients (n =12)
Over 18, who had attended Mount Sinai Fertility and were considering/had considered EEF

- Data collection included individual interviews with a semi-structured fluid interview guide.
- Interviews explored options and alternatives to EEF, factors influencing decision-making, decisional supports, and barriers.
- Interviews were recorded and transcribed verbatim and checked by a second investigator.
- Thematic analysis of the data included development of codes, concepts, categories and theories about the decision to undergo EEF.
- Iterative process was used until data saturation achieved.

Results

Themes

Two important themes were identified which each highlighted a disparity in how patients and providers perceive the purpose of EEF:

Elective egg freezing as a "back-up plan"

Patients:

- Patients saw egg freezing as a way to delay the decision about whether they wanted to have children at all
- Patients had come to terms with the fact that success in egg freezing does not guarantee a child

Providers:

- Providers assumed patients saw egg freezing as a way to guarantee having a child in the future
- Providers were apprehensive that patients did not put enough thought into the uncertainty of success of egg freezing

Dichotomy of ovarian reserve testing results

Patients:

- Most patients did not bring up results of ovarian reserve testing as important for their decision
- When prompted, patients felt testing to be either irrelevant or that it unnecessarily complicated their decision

Providers:

- Because providers placed emphasis on the success of live birth through EEF, ovarian reserve testing was considered essential by most providers to guide decision-making
- Providers felt this test could predict future success or futility of EEF

Both themes, while distinct, were related:

Providers desired to optimize a positive outcome of achieving a live birth.

BUT

Patients desired to preserve whatever fertility they might have, and to defer the decision about childbearing to a later time.

Demographics

Table 1. Participant Demographics

Demographic	n (%)
PATIENTS	**N = 12**
Age (years)	
30-35	3 (25.0%)
35-39	8 (66.7%)
Not asked	1 (8.3%)
Education	
University/college undergraduate	5 (41.6%)
University graduate	4 (33.3%)
Medical degree	1 (8.3%)
Medical and graduate degree	1 (8.3%)
PhD	1 (8.3%)
PROVIDERS	**N = 13**
Years in practice	
< 5	4 (30.8%)
5-10	4 (30.8%)
10-20	5 (38.5%)
Gender	
Female	7 (53.8%)
Male	6 (46.2%)
Practice role, discipline	
Physician, GREI	9 (69.2%)
Psychologist/psychotherapist, Fertility	2 (15.4%)
Nurse practitioner, Fertility	1 (7.7%)
Social worker, Fertility	1 (7.7%)
Location	
Ontario	6 (46.2%)
Nova Scotia	3 (23.1%)
Alberta	2 (15.4%)
British Columbia	2 (15.4%)

Conclusion

The decision to undergo EEF is complex and individual patient values play a significant role in the decision-making process. There is considerable disconnect between providers and patients in their views both on the goals of egg freezing and on the utility of ovarian reserve testing, and these should be addressed in discussions between providers and patients to improve shared decision-making.

References

1. Baldwin, K. et al. *Journal of Psychotsomatic Obstetrics and Gynaecology* 2019;40(2), 166-173.
2. Yu, L. et al. *Human Reproduction* 2016;31(2), 403-411.

Preimplantation genetic testing for triple repeat expansion disorders

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Background and Objective

Preimplantation genetic testing for single gene defects (PGT-M) allows couples at risk of hereditary disorders to selectively transfer unaffected embryos to the uterus, thereby to avoid the possibility of termination later in gestation. Myotonic dystrophy type 1 (DM1), Huntington's disease (HD) and Fragile X syndrome (FRAXA) are three monogenic diseases which are caused by so-called dynamic mutations. These mutations are caused by triplet repeats inside or in the vicinity of the gene which have the tendency to expand beyond the normal range thus disrupting the normal function of the gene. The objective of our study was to investigate the clinical outcome of these three triplet repeat disorders undergoing Preimplantation Genetic Testing (PGT-M) in a single fertility center.

Results

From 1998 to 2020, there were 26 PGT-M cycles carried out on 13 female patients carrier of DM expended repeats in the group of Myotonic Dystrophy, 22 PGT-M cycles carried out on 13 female patients in the group of Fragile X syndrome, and 9 PGT-M cycles carried out on 7 patients (5 male carrier and 2 female carrier) in the group of Huntington's Disease. The average age of female patients in the three groups were 33.6, 31.5 and 31.4years, respectively. The numbers of cumulus oocyte complexes (COC), MII stage oocytes, and fertilized embryos were 14.6, 11.3, 8.8 and 13.8, 11.2, 9.6, and 17.6, 13.2, 12.2 for the three groups, respectively. There was no statistically significant difference among these three groups of patients in all above categories. The successful diagnosis rates for these three diseases were 94.5%, 95.7% and 96.7%, respectively. The clinical pregnancy rate per PGT-M cycle was 34.6%, 36.4% and 44.4%, respectively; the difference is not statistically significant. In addition, IVF/IVM serial vitrification was performed in another four PGT-M cycles on three FRAX patients, of whom two patients successfully became pregnant and babies were born.

Comparison of three triple repeat expansion disorders

Disease	DM1	FraX	HD
Embryological and diagnostic aspects			
No. patients	13	13	7
No. cycles (PGD/IVF)	27/34	22/27	9/12
Female age	33.6±3.9	31.1±3.4	31.4±1.8
Range of female age	24-41	26-35	29-35
Total No. of oocytes collected	499	372	211
Average oocytes collected per IVF cycle	14.7±8.0	13.8±7.0	17.6±6.4
No. of oocytes of MII stage	388	302	159
Average oocytes of MII per IVF cycle	11.4±7.2	11.2±6.8	13.2±4.8
Oocyte maturation rate	77.8%	81.2%	75.4%
No. of fertilized oocytes	299	259	147
Average fertilized oocytes per IVF cycle	8.8±6.0	9.6±6.4	12.2±4.6
No. of embryos analyzed	191	162	91
No embryo analyzed per PGD cycle	7.1	7.4	10.1
No. of embryos successfully tested	181	155	88
Rate of embryo successfully tested	94.8%	95.7%	96.7%
No. of embryos unaffected	74	68	39
Abnormal allele transmission	58.0%	55.5%	55.7%
No. of embryos transferred	34	26	14
Clinical Outcome			
No. patients	13	13	7
No. cycles (PGD/IVF)	27/34	22/27	9/12
No. of embryos transferred	34	26	14
No. PGD cycle with clinical pregnancies	10	8	4
Clinical pregnant rate per PGD cycle	37.0%	36.4%	44.4%
No. babies live born	6	7+ 1 ongoing	5

Materials and Methods

For IVF-PGT-M cycles, all female parents underwent standard ovarian stimulation procedure as practiced in our fertility clinic. Intracytoplasmic sperm injection (ICSI) was performed for all patients undergoing PGT-M to avoid sperm contamination thereby to decrease misdiagnosis rate. Embryo biopsy was performed on day 3 (blastomere biopsy) or day 5/day 6 (blastocyst biopsy) according to the embryo development. Fluorescence-based multiplex PCR was used for mutation analysis of single gene defects. Embryos diagnosed as unaffected were transferred on day 5/6 post-fertilization or were frozen for future transfer.

Conclusions

In spite of the ovarian dysfunction of Fragile X patients, the pregnancy rate of the three groups following IVF-PGT is similar. For those FRAX patients with severe ovarian dysfunction, IVM and/or IVF with serial vitrification is an option to achieve successful clinical outcome. The effect of DM1 on ovarian reserve and outcomes of ovarian stimulation in IVF/PGT cycles is controversial in the literature. According to the experience of our center, female DM1 patients with higher doses of gonadotropins can achieve similar clinical results. The clinical result for the three monogenetic diseases with dynamic mutation is not significantly different. A further study based on only female carriers of triplet repeat disorders for HD should be carried out to compare with FRAX patients. This study is also limited by its small sample size and retrospective design over a long period.

References

Sermon K, Seneca S, De Rycke M, Goossens V, Van de Velde H, De Vos A, Platteau P, Lissens W, Van Steirteghem A, Liebaers I. PGD in the lab for triplet repeat diseases - myotonic dystrophy, Huntington's disease and Fragile-X syndrome. Mol Cell Endocrinol. 2001 Oct 22; 183 Suppl 1:S77-85.

Fernández RM, Lozano-Arana MD, Sánchez B, Peciña A, García-Lozano JC, Borrego S, Antiroll G. Preimplantation Genetic Diagnosis for Myotonic Dystrophy Type 1 and Analysis of the Effect of the Disease on the Reproductive Outcome of the Affected Female Patients. Biomed Res Int. 2017; 2017:9165363.

Prevalence of antiphospholipid syndrome and live birth rate following anti-thrombotic treatment in a cohort of 1443 patients with recurrent pregnancy loss

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Background

- Antiphospholipid syndrome (APS) is a systemic autoimmune disorder resulting from persistent antiphospholipid antibodies (aPL) including lupus anticoagulant (LA), anti-beta-2 glycoprotein I (aβ2GPI), anti-cardiolipin (aCL), and antiphosphatidylserine (aPS).[1]
- Clinical manifestations of APS include vascular thromboses and obstetrical complications including preterm birth, intrauterine growth restriction (IUGR), placental dysfunction, and recurrent pregnancy loss.[2]
- Recurrent pregnancy loss (RPL) is defined as the loss of two or more pregnancies prior to 12 weeks' gestation and occurs in approximately 1-2% of pregnant women. There are multiple etiologies of RPL, however APS and the presence of antiphospholipid antibodies has been shown to be present in up to 20% of women with recurrent miscarriages.[3,4]
- Current treatment recommendations for patients with APS and RPL is antepartum administration of low-dose aspirin (LDA) and prophylactic low-molecular weight heparin (LMWH). This has been shown to reduce miscarriage rates by 54%. Additional therapies for refractory obstetrical APS include prednisone and hydroxychloroquine (HCQ).[1,5,6]

Hypothesis

- Standard of care anti-thrombotic therapy of low-dose aspirin (LDA) and low-molecular weight heparin (LMWH) improves ongoing pregnancy beyond 10 weeks' gestation and live birth rate in women with APS and RPL.

Objectives

- The first aim of this study is to analyze the prevalence of APS and the anti-thrombotic treatment provided in a cohort of RPL patients.
- The second aim is to assess ongoing pregnancy beyond 10 weeks' gestation and live birth rate following anti-thrombotic and immunomodulatory treatments including LDA, LMWH, prednisone, and HCQ.

Study Design & Methods

- Retrospective cohort study of 1443 RPL patients.
- In order for patients to be eligible for analysis they required both a clinical and laboratory diagnosis of antiphospholipid syndrome (APS).

CLINICAL
1. Thrombosis
2. Recurrent pregnancy loss
= two or more pregnancy losses

LABORATORY
Presence of one or more antiphospholipid antibodies on initial testing and on confirmatory testing 12 weeks later
1. Lupus anticoagulant (LA)
2. Anticardiolipin antibody (aCL)
3. Anti-Beta-2 glycoprotein (aβ2GPI)
4. Antiphosphatidylserine (aPS)

Results

- Of the 1443 charts reviewed, **76 patients (5.27%)** tested positive for aPLs based on the above criteria.

Antiphospholipid Antibody (aPL)	Number of Patients	Percentage Among APS Patients (%)
Lupus Anticoagulant (LA)	59	77.6%
Anti-Cardiolipin (aCL)	17	22.4%
Anti-Beta-2 Glycoprotein I (aβ2GPI)	13	17.1%
Antiphosphatidylserine (aPS)	6	7.9%
Double Positive	11	14.5%
Triple Positive	3	3.9%

Table 1: Prevalence of antiphospholipid antibody positivity among cohort of 1443 patients diagnosed with recurrent pregnancy loss. Patients with double or triple positivity have an increased risk of thrombotic events.[2]

- Of the 76 patients who met both the clinical and laboratory criteria for APS, **39 patients (51.3%)** received anti-thrombotic treatment during pregnancy.

Anti-Thrombotic Therapy	Number of Patients	Percentage Among Treated Patients (%)
Low-Dose Aspirin (LDA)	13	33.3%
Low Molecular Weight Heparin (LMWH)	2	5.2%
LDA + LMWH	17	43.6%
LDA + Unfractionated Heparin (UFH)	3	8.0%
LDA + Hydroxychloroquine (HCQ)	1	2.6%
LDA + LMWH + UFH	1	2.6%
LDA + LMWH + HCQ	1	2.6%
LDA + LMWH + HCQ + Prednisone	1	2.6%

Table 2: Prevalence of anti-thrombotic treatment use among patients with APS and RPL. Combination of LDA and LMWH was the most common form of treatment, which is in keeping with the standard of care therapy.

- No significant differences in live birth rate (p=0.688) and pregnancy beyond 10 weeks gestational age (p=0.810) when comparing anti-thrombotic treated versus non-treated APS patients.

	Odds Ratio	CI	p
Live birth	0.82	0.31 – 2.15	0.688
Pregnancy beyond 10 weeks	0.89	0.34 – 2.29	0.810

Table 3: Logistic regression analysis of live birth rates and pregnancy beyond 10 weeks gestation when comparing treated versus non-treated patients. Odds ratio for patients who received anti-thrombotic therapy. Live birth rate (n=73) and pregnancy beyond 10 weeks gestation (n=72).

References

1. Chaturvedi, S., McCrae, K.R. (2017). *Blood Reviews*, 31(6): 406-417.
2. Garcia, D., Erkan, D. (2018). *New England Journal of Medicine,* 378(21): 2010-21.
3. American Society for Reproductive Medicine. (2012). *Fertility and Sterility,* 98(5): 1103-11.
4. Chetty, M., Duncan, W.C. (2018). *OBGYN and Reproductive Medicine,* 28(6): 164-70.
5. Empson, M., et al. (2005). *Cochrane Database Syst Rev,* 2: CD002859
6. Ford, H.B., et al. (2009). *Rev Obstet Gynecol,* 2: 76-83.
7. Uthman, I., et al. (2019). *Annals of the Rheumatic Diseases,* 78(2): 155-61.

Results

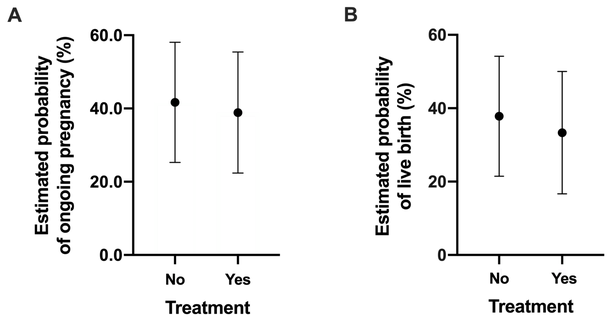

Figure 1: Anti-thrombotic treated versus non-treated APS patients. A) Predicted probability of ongoing pregnancy beyond 10 weeks gestation (n=72). B) Predicted probability of live birth (n=73). Error bars indicate 95% CI.

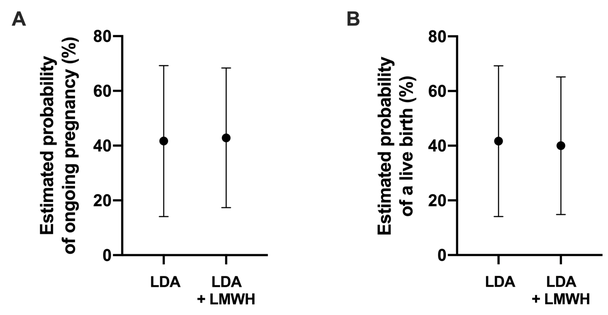

Figure 2: LDA vs LDA + LMWH treated APS patients. A) Predicted probability of ongoing pregnancy beyond 10 weeks gestation (n=30). B) Predicted probability of live birth (n=30). Error bars indicate 95% CI.

Discussion

- Prevalence of APS diagnosis in this RPL cohort to be in keeping with predicted population prevalence.
- Unfortunately, there is limited data for the use of additional therapies including HCQ and prednisone, therefore cannot be analyzed separately.

Conclusion

- 5.27% of patients met the clinical and laboratory criteria for APS diagnosis.
- 51.3% of patients received anti-thrombotic or immunomodulatory treatment during pregnancy.
- No significant differences in live birth rate and pregnancy beyond 10 weeks gestation when comparing anti-thrombotic treatment versus no treatment and when comparing LDA versus LDA and LMWH.

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Adenomyosis and pregnancy outcome in patients undergoing assisted reproductive treatment with donor oocytes

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BACKGROUND

- Adenomyosis is a benign gynecological condition where endometrial glands and stroma invade into the myometrium causing surrounding smooth muscle hyperplasia.
- Associated with multiple aspects of infertility, including recurrent pregnancy loss and implantation failure.

Diagnosis:
- Gold standard for diagnosis is by histologic assessment of uterine tissue from hysterectomy
- There is no standard definition of adenomyosis on imaging
- Morphological Uterus Sonographic Assessment (MUSA) criteria were developed in 2018 to provide a standardized assessment of the condition through ultrasound imaging

Hypothesis:
- The presence of ultrasonographic signs of adenomyosis is associated with a lower live birth rate, lower clinical pregnancy rate, and higher miscarriage rate in patients undergoing treatment with donor oocytes.

MUSA CRITERIA

The following should be reported when examining adenomyosis on ultrasound:
- Presence
- Location
- Differentiation (focal vs diffuse)
- Uterine Layer Involvement
- Extent
- Size of lesion

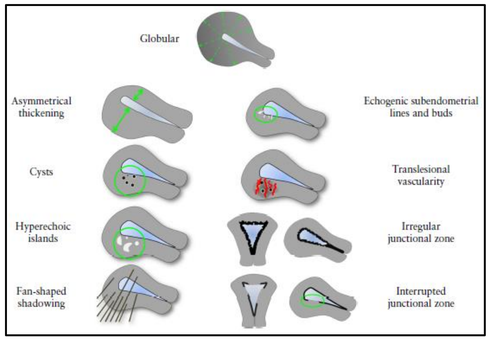

Figure 1: Morphological Uterus Sonographic Assessment (MUSA) criteria for diagnosis of adenomyosis. Taken from Van den Bosch et al. 2019.

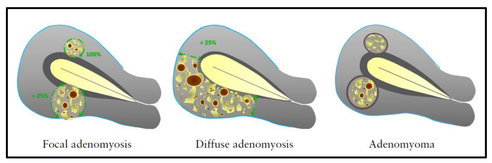

Figure 2: Differentiation between focal and diffuse adenomyosis and adenomyoma. Adenomyosis is focal if >25% of circumference of lesion is surrounded by normal myometrium Taken from Van den Bosch et al. 2019.

METHODS

- Retrospective cohort study
- Mount Sinai Fertility between Jan 1st, 2014 and Jan 1st, 2020
- Patients aged 21-55 undergoing donor oocyte embryo transfer who had previous transvaginal pelvic ultrasound
- Ultrasonographic characterization was done by an independent radiologist using MUSA criteria

Transfer outcomes were defined as follows:
- *Biochemical pregnancy* → Positive β-HCG
- *Chemical loss* → Falling β-HCG or no gestational sac on ultrasound
- *Clinical pregnancy* → Gestational sac on ultrasound
- *Miscarriage* → Clinical pregnancy loss <20W
- *Live Birth* → Infant is alive at delivery

Statistical Analysis
- Descriptive statistics including means and standard deviations for continuous data and counts and percentages for categorical data were calculated
- Univariable and multivariable generalized estimating equation (GEE) models were used to assess differences in live birth rate (LBR), biochemical pregnancy rate (BPR), clinical pregnancy rate (CPR), or rate of miscarriage (MR) between presence vs. absence of adenomyosis
- Live birth rate was the primary outcome of this study, and we achieved 80% power.

DEMOGRAPHIC INFORMATION

Demographic Information			
Subjects (n)	100	**Gravida**	1.35 (1.45)
Transfers (n)	223	**Para**	0.32 (0.65)
Age (mean (SD))	40.02 (4.84)	**Adenomyosis (%)**	170 (76.2)
BMI (mean (SD))	26.44 (6.28)	**Original Report Adenomyosis (%)**	50 (22.4)
Donor Age (mean (SD))	25.86 (3.10)		
Indication (%)			
ARA/DOR/Menopause	159 (71.3)		
RIF/RPL	37 (16.6)		
Tubal Factor	16 (7.2)		
Genetic Factor	11 (4.9)		

Table 1: Summary Table of Demographic Information (per cycle)

Transfer Outcome (N=223)	n (%)
Biochemical Pregnancy	120 (53.8)
Chemical Loss	26 (11.7)
Clinical Pregnancy	94 (42.2)
Miscarriage	27 (12.1)
Before heartbeat	10 (4.5)
After heartbeat	17 (7.6)
Live Birth	66 (29.6)
Singletons	64 (28.7)
Multiples	2 (0.9)

Table 2 : Summary Table of Transfer Outcomes (per cycle)

RESULTS

Adenomyosis (N=170)	n(%)		n(%)
Characteristics		**Disease Location**	
Globular enlarged uterus	152 (89.4)	Anterior	145 (85.9)
Adenomyoma	4 (2.6)	Posterior	146 (85.9)
Fan-shaped shadowing	1 (0.6)	Lateral Right	130 (76.5)
Asymmetrical thickening	103 (60.6)	Lateral Left	127 (74.7)
Echogenic lines/buds	2 (1.2)	Fundal	160 (94.1)
Myometrial Cysts	21 (12.4)		
Translesional Vascularity	0 (0)		
Hyperechoic/Echogenic	2 (1.2)		
Irregular/interrupted JZ	170 (100)		
Uterine Layer Involvement		**Disease Extent**	
Junctional Zone	66 (38.8)	Mild	81 (47.6)
Middle Myometrium	89 (52.4)	Moderate	73 (42.9)
Outer Myometrium	15 (8.8)	Severe	16 (9.4)

Table 3: Summary Table for patients with Adenomyosis (per cycle)

Only 22 subjects were reported to have adenomyosis prior to this study. Using MUSA criteria, 76 of the study subjects were identified to have at least one characteristic of adenomyosis on ultrasound, and these subjects represented 170 cycles **(Table 3)**. The most common features were an irregular/interrupted junctional zone (JZ), a globular enlarged uterus, and asymmetrical thickening. Mild disease that extended into the middle myometrium was most common.

PRIMARY OUTCOME: Number of features does not affect live birth

Adjusted GEE Model: Live Birth Outcomes for Adenomyosis		
	OR (2.5%, 97.5%)	P value
1 feature	0.668 (0.1, 4.449)	0.68
2 or more features	1.117 (0.457, 2.731)	0.81

Table 4: Adjusted multivariate analysis analysing live birth outcomes for patients with adenomyosis, as defined as 1 or 2 or more characteristic on ultrasound

Specific features do not affect live birth

Univariate GEE Model: Live Birth Outcomes for each feature		
	OR (2.5%, 97.5%)	P value
Globular Enlarged Uterus	0.803 (0.406,1.588)	0.53
Asymmetrical Thickening	1.183 (0.609,2.297)	0.62
Myometrial Cysts	1.067 (0.319,3.574)	0.92
Irregular JZ	0.774 (0.384,1.562)	0.47

Table 5: Univariate analysis examining live birth outcome for four features of adenomyosis.

RESULTS CONTINUED

FOCAL distribution does affect CPR and BPR

When we examined the distribution patterns of the features and locations, we did not see an effect on LBR. However, irregular JZ in the fundal or posterior uterus in a FOCAL distribution decreased CPR and BPR **(Tables 6 & 7)**.

Adjusted GEE Model: Clinical Pregnancy Outcomes for FOCAL distribution		
Irregular JZ	OR (2.5%, 97.5%)	P value
Fundal	0.419 (0.184, 0.952)	0.04
Anterior	0.571 (0.261, 1.25)	0.16
Posterior	0.404 (0.185, 0.882)	0.02

Table 6: Adjusted multivariate analysis examining clinical pregnancy outcome for Irregular JZ in a FOCAL distribution at various locations. Lateral right and Lateral left were excluded for lack of data

Adjusted GEE Model: Biochemical Pregnancy Outcomes for FOCAL distribution		
Irregular JZ	OR (2.5%, 97.5%)	P value
Fundal	0.407 (0.179,0.927)	0.03
Anterior	0.608 (0.276,1.338)	0.22
Posterior	0.402 (0.191,0.849)	0.02

Table 7: Adjusted multivariate analysis examining biochemical pregnancy outcome for Irregular JZ in a FOCAL distribution at various locations. Lateral right and Lateral left were excluded for lack of data

Increasing diameter of FOCAL lesions decreases LBR

Multivariable Logistic GEE Model: Live Birth Outcomes for largest diameter of FOCAL lesions		
	OR (2.5%, 97.5%)	P value
Largest Lesion Diameter	0.0857 (0.0117, 0.6304)	0.02

Table 8: Adjusted logistic GEE model examining outcome of live birth for increasing diameter of focal lesions.

Adjusted logistic GEE models show that for every centimeter increase in the diameter of a focal lesion there is a 91% decrease in the odds of live birth. This was also shown to be significant when controlling for the volume of the uterus.

CONCLUSIONS

- First study of its kind that analyzes the donor oocyte population using the new MUSA criteria
- Seventy-six percent (76%) of our subjects had signs of adenomyosis on ultrasound, a proportion that is much higher than any other study has reported
- Our data currently suggests that adenomyosis, as defined by 1 or more features, does not impact live birth or other pregnancy outcomes in a donor oocyte population
- The number of features does not have an impact on live birth outcomes
- Uterine factors such as adenomyosis may have less impact on outcomes when high quality embryos derived from donor oocytes are utilized.

References

1. García-Solares J, Donnez J, Donnez O, Dolmans M-M. Pathogenesis of uterine adenomyosis: invagination or metaplasia? Fertility and sterility. 2018;109(3):371-9.
2. Vercellini P, Consonni D, Dridi D, Bracco B, Frattaruolo MP, Somigliana E. Uterine adenomyosis and in vitro fertilization outcome: a systematic review and meta-analysis. Human Reproduction. 2014;29(5):964-77.
3. Van den Bosch T, de Bruijn AM, de Leeuw RA, Dueholm M, Exacoustos C, Valentin L, et al. A sonographic classification and reporting system for diagnosing adenomyosis. Ultrasound in Obstetrics & Gynecology. 2018
4. Gordts S, Grimbizis G, Campo R. Symptoms and classification of uterine adenomyosis, including the place of hysteroscopy in diagnosis. Fertil Steril. 2018 Mar;109(3):380-388.e1.
5. Chapron C, Vannuccini S, Santulli P, Abrão MS, Carmona F, Fraser IS, et al. Diagnosing adenomyosis: an integrated clinical and imaging approach. Hum Reprod Update. 2020 Apr 15;26(3):392–411.