The initial impact of the Ontario Fertility Program

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Introduction

Globally, the majority of fertility treatments are uninsured and paid by the patient. While Ontario has historically funded IVF for women with bilateral tubal obstruction, in December 2015, Ontario began funding a fixed number of IVF cycles for Ontario residents who were <43 years, regardless of reason for treatment.[1] The objective of this study was to examine the demographic differences and clinical outcomes of patients seeking IVF in Ontario after the implementation of the Ontario Fertility Program (OFP).

Material & methods

This was a population retrospective cohort study that used Ontario data from CARTR Plus and BORN Ontario. The pre-funding group (PreFG) contained cycle starts prior to 2016; the funded post-funding group (PostFG) were funded through the OFP; and the self-pay post-funding group (SPG) by the patient (January and December 2016). Descriptive statistics were preformed using chi square tests and ANOVAs.

Results

There were 33,567 embryo transfer (ET) cycles included (PreFG-total (2013-2015): 24,567; PreFG-2015:7,874; PostFG: 5,624; SPG: 5,376). An ET cycle was defined as a fresh or frozen transfer using autologous or donor oocytes. The majority of cycles were fresh cycles that used autologous oocytes (PreFG: 52.5%; PostFG: 58.7%; SPG: 44.2%). The mean oocyte provider age (PreFG: 34.6 (SD:5.1); PostFG: 35.0 (SD:4.6); SPG: 34.3 (SD:5.4)) and the mean BMI (PreFG: 24.5 (SD:5.1); PostFG: 25.0 (SD:4.9); SPG: 24.8 (SD:5.2)) were significantly different ($p<0.01$). The proportion of patients in the highest education (PreFG: 30.7%; PostFG: 25.6%; SPG: 30.6%) and income (PreFG: 26.7%; PostFG: 21.6%; SPG: 27.2%) quintiles were significantly different between the groups ($p<0.001$).

There was an increase in the total number of clinical pregnancies (PreFG-2015: 3,017; PostFG: 2,007; SPG: 2,064), and the corresponding live births (PreFG-2015: 2,283; PostFG: 1,519; SPG: 1,577). The multiple birth rate per ET decreased in 2016 compared to 2015 for both the PostFG and SPG (PreFG-2015: 3.66%; PostFG: 1.14%; SPG: 2.66%).

Conclusions

The first year of funding from the OFP provided access to IVF for patients that may not have been able to afford treatment. There was an increase of 1,054 clinical pregnancies and 813 live births in 2016 compare to 2015, while there was a decrease in the multiple birth rate.

Reference

1. Government of Ontario. Get fertility treatments. Queen's Printer for Ontario. https://www.ontario.ca/page/get-fertility-treatments. Published 2018. Accessed Nov 20, 2018.

Investigating the uptake of prenatal screening among IVF conceptions in Ontario

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Introduction
In Ontario, various modalities of prenatal aneuploidy screening are offered to pregnant women. Among IVF conceptions, pre-implantation genetic testing for aneuploidy (PGT-A) is offered to detect aneuploidy before the embryo transfer. This study assessed the utilization of prenatal screening modalities among IVF conceptions compared to spontaneous conceptions in Ontario.

Methods
This population-based cohort study used data from BORN Ontario and CARTR Plus. We included all singleton IVF pregnancies in Ontario with a fresh or frozen treatment cycle in CARTR Plus (cycle start between Nov 15, 2015-Dec 31, 2017); the spontaneous group was identified through prenatal screening records in BORN (estimated date of birth between Sep 1, 2016-Aug 31, 2017). IVF conceptions were further grouped by PGT-A use. Propensity-score matching was used to match each IVF pregnancy to 4 spontaneous pregnancies by oocyte age.

Results
Of the 2,881 IVF cycle records, 326 (11.3%) had PGT-A. The mean oocyte age was 33.4 years (SD=4.4). Mean gestation at both multiple marker screening and cell-free fetal DNA testing was lower among IVF conceptions compared to spontaneous conceptions (14.96 weeks *vs* 15.34 weeks, $P<0.001$; 13.9 weeks *vs* 15.2 weeks, $P<0.001$). The mean fetal fraction was lower among IVF compared to spontaneous conceptions (10.7% *vs* 12.0%, $P<0.001$). The odds of utilizing prenatal screening were 1.21 (95% CI: 1.05-1.39) times greater in IVF compared to spontaneous conceptions. Among IVF conceptions, the odds of utilizing prenatal screening was 1.68 (95% CI: 1.19-2.36) times greater in the PGT-A group than in No PGT-A. The odds of utilizing a prenatal diagnostic procedure was 2.27 (95% CI: 1.72-3.03) times greater in spontaneous conceptions than in IVF and comparable between PGT-A and No PGT-A.

Conclusions
IVF pregnancies are associated with higher use of prenatal screening than spontaneous pregnancies. IVF pregnancies following PGT-A are associated with higher use of prenatal screening than those without PGT-A. This finding has important health policy implications, as the relative yield of further screening for age-based aneuploidy following PGT-A is expected to be extremely low.

New algorithm to increase the number of utilizable blastocysts using a mixed protocol of HP-hMG and follitropin delta

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Introduction:

This study aims to evaluate the number of utilizable blastocysts and the safety profile of controlled ovarian stimulation (COS) with mixed protocol of HP-hMG (Menopur®) and follitropin delta (Rekovelle®).

Methods:

This multi-center, open label, exploratory study enrolled 110 subjects aged 18-40 yrs undergoing their first IVF/ICSI cycle. COS was performed with a mixed antagonist protocol of follitropin delta, dosed according to an established algorithm based on AMH and body weight, and HP-hMG; dosed as 1, 2 or 3 vials, based on Rekovelle dose (< or =12 µg) and body weight (< or ≥100 kg). Ovulation was triggered using GnRH-agonist or hCG when ≥3 follicles reached 17 mm. In cases of hyper response (E2 ≥15,000 pmol/L on the day of trigger or ≥20 follicles of ≥12 mm) a freeze-all strategy was employed. Oocyte retrieval was performed 36±2 hours after triggering and IVF or ICSI was completed with either partner or donor sperm. All embryos were cultured to day 5 or 6 and graded with Gardner's modified scoring system.

Results:

The mean age of subjects was 34.05 years (SD 3.47) and weight 71.65 kg (SD 14.61). Mean AMH was 15.07 pmol/L (AMH varied from 0.6 to 34 pmol/L) and antral follicle count 16.10 (SD 8.89). Participants were stratified by age into 3 groups: 18-34 years (50%), 35-36 years (21.81%) and 37-40 years (28.18%). Mean number of oocytes obtained was 14.55 (SD 7.69), mature oocytes 11.28 (SD 6.04), day 3 embryos 8.3 (SD 4.96) and good-quality blastocysts 4.91 (SD 3.97). The rate of good-quality blastocysts in this study was significantly higher than observed in ESTHER where follitropin delta was used alone (4.91±3.87 vs. 2.0±2.2 P<0.001), even when stratified by age. Fresh embryo transfer was performed in 35 (32.71%) cases, freeze-all in 68 (63.55%) and 4 participants (3.74%) did not have a transfer. There were 10 cases of mild OHSS (9.26%) (grade 1). No late or severe OHSS was observed.

Conclusion:

Mixed protocol of HP-hMG and follitropin delta yielded more utilizable blastocysts on day 5-6 of embryo culture without increasing the OHSS rate than follitropin delta alone.

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Standard insemination versus intracytoplasmic sperm injection (ICSI): Assessing the impact on preimplantation genetic testing – aneuploidy results

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Introduction:
The impact of fertilization method on the results of Preimplantation Genetic Testing - Aneuploidy (PGT-A) has not been comprehensively studied. With improved resolution of current PGT-A platforms, standard insemination is considered an acceptable approach, which many patients choose to mitigate the theoretical risks of ICSI (1-3). Our objective is to determine whether a difference exists in rates of mosaicism or aneuploidy between embryos that have undergone ICSI versus standard insemination.

Materials and Methods:
This was a retrospective cohort study examining 1420 embryos that underwent PGT-A testing over a 3-year period. Data on chromosomal status and mosaicism were collected and cross-referenced to method of insemination.

T-test was used for comparisons of continuous variables. Categorical outcomes were compared using chi-square test. Generalized linear models were applied to compare outcomes adjusted for co-variables.

Results:
This analysis included 1335 embryos that underwent PGT-A testing. 65 embryos were excluded due to incomplete data. Standard insemination was completed in 16.0% of embryos (n=213) and ICSI in 84.0% (n=1122). The relative proportion of abnormal embryos (aneuploid and/or unbalanced) was 47.1% (n=629), euploidy was 37.9% (n=506), and mosaicism was 13.2% (n=176). The remaining embryos either had inconclusive results (1.3%, n=17) or technical failure (0.5%, n=7).

When comparing results by method of insemination, ICSI embryos were more likely to be definitively abnormal (aneuploid and/or unbalanced) compared to those from standard insemination ((51.4% (n=566) vs 30.1% (n=209), $P<0.0001$). Embryos were also more likely to be euploid with standard insemination vs ICSI (50.7% (106/209) vs. 36.3% (400/1102), $P<0.0001$).

Of those initially categorized as mosaic, 58.8% of ICSI embryos and 57.5% of standard insemination embryos were “definitive” mosaic (80/136 and 23/40 respectively, p=0.881). The remainder were equivocal and related to aberrant signaling. Of definitive mosaics, multiple mosaicism and segmental mosaicism was found in 11.7% (n=12) and 38.8% (n=40) respectively. There was no difference in probability of definitive mosaicism based on embryo sex (56.3% in females, 59.5% in males (p=0.679)).

Conclusions:
ICSI resulted in a higher rate of chromosomal abnormalities in embryos undergoing PGT-A. Method of insemination or embryo sex had no impact on rate of mosaicism. Although preliminary, this study provides impetus to avoid unnecessary ICSI for PGT-A in the absence of indications.

References:

(1) Practice Committees of the American Society for Reproductive Medicine and Society for Assisted Reproductive Technology. Intracytoplasmic sperm injection (ICSI) for non-male factor infertility: a committee opinion. Fertility and Sterility. 2012;98(6):1395–1399.

(2) Davies, M. J., Moore, V. M., Willson, K. J., Van Essen, P., Priest, K., Scott, H., et al. Reproductive technologies and the risk of birth defects. The New England Journal of Medicine. 2012;366(19), 1803–1813.

(3) Esteves SC, Roque M, Bedoschi G, Haahr T, Humaidan P. Intracytoplasmic sperm injection for male infertility and consequences for offspring. Nat Rev Urol. 2018 Sep;15(9):535–62.

(4) PGDIS Position Statement on Chromosome Mosaicism and Preimplantation Aneuploidy Testing at the Blastocyst Stage. PGDIS Newsletter [Internet]. 2016 July 19 [cited 2019 April 8]: [2p.]. Available from: https://www.pgdis.org/docs/newsletter_071816.html

(5) Palmerola KL, Vitez SF, Amrane S, Fischer CP, Forman EJ. Minimizing mosaicism: assessing the impact of fertilization method on rate of mosaicism after next-generation sequencing (NGS) preimplantation genetic testing for aneuploidy (PGT-A). J Assist Reprod Genet. 2018 Oct 25;350:g7611.

Identification, isolation and genetic analysis of rare spermatozoa.

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Introduction: The absence of spermatozoa in ejaculate affects up to 10% of men with infertility with majority attributed to non-obstructive azoospermia (NOA). Extended labor-intensive search though ejaculate on men with NOA samples has been shown to identify some rare spermatozoa in 30% of cases. However, the genetic quality of these rare spermatozoa is not well studied. The purpose of our study was to improve identification of spermatozoa in NOA by investigating the suitability of RareCyte® technology followed by isolation of rare spermatozoa for single cell next-generation sequencing (NGS).

Materials and Methods: Immunofluorescence (IF) using antibodies to sperm-specific proteins ACRV1 (intra-acrosomal) and AKAP4 (sperm flagella) was performed on a sample with NOA and normozoospermic control. Anti-CD45 was used as an exclusionary marker to further differentiate somatic cells from sperm cells. Stained slides were automatically scanned with the CyteFinder® instrument, and ACRV1/AKAP4-positive, CD45-negative sperm cell candidates were automatically identified and presented to the reviewer for visual confirmation. Objects with flagella and morphology characteristics of spermatozoa were isolated with the integrated CytePicker® module for NGS ploidy analysis. Single cell whole genome amplification (WGA) and NGS were performed.

Results: RareCyte® technology identified 7 spermatozoa in the sample that was confirmed to be azoospermic by extended search. NGS revealed that none of spermatozoa from NOA sample were haploid, 72% were diploid (failure of the second meiotic division), while 28% were aneuploid. In comparison, the control sample had 86% haploid spermatozoa while 14% were aneuploid.

Conclusion: We were able successfully identify, retrieve, and sequence single spermatozoa from a patient with NOA using two sperm markers, RareCyte® technology, and NGS. Single spermatozoon NGS offers a novel approach for analysis of aneuploidy and meiotic errors in patients with NOA or with unexplained male infertility in general.

A systematic review of the ethical issues identified in the normative bioethics literature about select assisted reproductive technologies: 1978-2017

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Introduction

Since IVF brought assisted reproductive technologies (ART) to the public's consciousness over forty years ago, this class of health technologies has been at the centre of moral conflicts between social groups; conflicts about what kind of society we should create and what role these technologies have in it.[1] Formal bioethics input into these conflicts and questions informs clinical practice, health policy and law with respect to ART and related health techologies.[2] This systematic review of ARTs in the bioethics literature is the first to provide a descriptive acccount of the ethical issues, debates, and positions of concern to ART clinicians and policymakers.

Methods

Our systematic review used the search strategy of McCullough et al (2007) to identify ethical issues about all treatments or procedures that include the in vitro handling of both human oocytes and sperm or embryos for the purpose of establishing a pregnancy (i.e., ET, IVF, ICSI, PGD, ovarian stimulation/induction). Documents included were published in English from January 1978 to December 2017. Our review yielded 1913 records of which 274 met inclusion criteria. Data capture and synthesis was followed by thematic coding.

Results

Three themes were identified: (1) ARTs and their environments of practice (2) Impact of ARTs on the patient-clinician relationship; (3) PGD now and in future. General findings taken within the themes include the following: distrust with the validity and goal of clinic success metrics and the lack of empirical research available to support them warrants re-conceptualizing ARTs' effectiveness as more than simply quantifying ARTs' biotechnical performance. Regulation and policy can provide solutions to problems about which uses of ARTs are medically and ethically appropriate, and can help ensure patients receive more reliable information about them, but there is no consensus on who should be in involved in determining this and how much proscription is needed. Policymakers share a primary, if not the ultimate, goal as patients - to create children - and believe that funding this technology is an ethically sound way to achieve it.

Conclusion

The study suggests that despite the lack of consensus on key moral questions, a diversity of analytical perspectives and products has greater value to and influence on clinicians, professional bodies, and policy developers tasked with implementing and regulating these technologies to diverse populations in complex contexts.

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1 Grunwald A. Technology assessment. Encyclopedia of Information Science and Technology, Third Edition: IGI Global; 2015. p. 3998-4006.

2 Giacomini M, Kenny N, DeJean D. Ethics frameworks in Canadian health policies: foundation, scaffolding, or window dressing? Health Policy. 2009;89(1):58-71.