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Impact of in vitro fertilization-preimplantation genetic testing (IVF-PGT) funding policy on clinical outcome: An issue that stems beyond effectiveness of treatment

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ABSTRACT

Objective(s): The aim of this study was to compare the patient characteristics, type of genetic disease and inheritance, volume of activity, practice patterns and pregnancy outcomes, in private versus publically funded IVF pre-implantation genetic testing (PGT) for translocation (IVF-PGT-SR) and aneuploidy (PGT-A) periods.

Study design: This study retrospectively analyzed data during both privately funded period (PRP) and publically funded period (PUP) of assisted reproductive technology (ART) for a total of 275 patients. 83 patients underwent IVF-PGT-SR and 192 patients underwent IVF-PGT-A. Given that PGT-SR is a chromosomal abnormality hereditary in nature, whereas PGT-A is sporadic in addition to the contrasting funding policies, the two cohorts were analyzed separately. To achieve the proposed objective, the two groups under analysis were grouped in accordance with their respective coverage systems for infertility.

Results: Among translocation patients, 94 normal/balanced embryos were obtained from 47 IVF-PGT cycles in PRP whereas 145 embryos were obtained from 92 IVF-PGT cycles in PUP. The average number of embryos transferred per embryo transfer cycle was significantly lower in PUP in comparison to PRP (1.13 vs. 1.74, $p < 0.0001$). 13 singletons and 2 sets of twins were conceived in PRP. 14 singletons were conceived in PUP. Regardless of funding period, there were more reciprocal translocation carriers (79.4% in PRP and 76.4% in PUP) and more male carriers (82.4% in PRP and 60% in PUP), of which the majority had abnormal sperm parameters. Among aneuploidy patients, on average 2.5 embryos in PRP and 1.4 embryos in PUP were transferred per ET cycle ($p = 0.05$). There was a 13.3% increase in number of IVF-PGT-A attempts per patient in PRP compared to PUP. Live birth rate per IVF-PGT-A was higher in PRP (29.7% vs. 15%, $P = 0.02$), which consisted of 48 singletons and 18 multiparous pregnancies in PRP and 9 singletons in PUP.

Conclusion(s): Public coverage of ART is associated with a greater utilization ART, as well as a reduced number in embryo transfer (ET) per cycle, a lower proportion of cycles resulting in successful pregnancy and a lower multiple birth rate. Our study ultimately shines light on the effect of providers' and patients' monetary conscious on pregnancy outcome.

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Introduction

In recent years, pre-implantation genetics testing (PGT) was developed with the aim to prevent the inheritance of genetic diseases and to diagnose frequently occurring chromosomal aneuploidies [1,2]. Advancing technology and techniques simultaneously raised the concern regarding healthcare expenditure. Specifically, whether the population should be covered by national health plans, private insurance companies or solely on a fee-for-service basis [1,3].

Previously, a number of studies were conducted to evaluate the effects of publically versus privately funded ART on their outcomes [4–7]. However, a lack in uniformity in policies worldwide has prevented the formation of a consensus. In the Province of Quebec, prior to August 5th 2010, the cost of all ART procedures were covered by the patient and partially reimbursed as tax rebate. There did not exist government regulations on the number of embryos transferred, nor was there a limit to number of treatment

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cycles. Between August 5th 2010 and November 10th 2015, the government of Quebec applied a public IVF program, in which the cost of all medical procedures related to IVF for three stimulated cycles or up to six modified natural cycles were covered by Quebec's universal health insurance plan. Patients who had excess embryos cryopreserved were obliged to thaw those embryos for transfer before embarking on another ovarian stimulation cycle, but frozen ET (FET) did not count as part of their three attempts. The new policy further stated that only one embryo could be transferred at a time, but the law allowed for clinicians to transfer a maximum of two embryos when the woman is 36 years old and a maximum of three embryos or two blastocysts could be transferred when the woman is 37 years old or older [8,9]. During these 5 years, IVF-PGT for translation (PGT-SR) patients were financially covered during this period, but IVF- PGT for aneuploidy (PGT-A) patients were not covered. However, the Quebec government cut coverage for the entire Assisted Reproduction program on November 10th, 2015 under Bill 20 and it has remained privately funded to this day.

The aim of this study was to compare the patient characteristics, type of genetic disease and inheritance, volume of activity, practice patterns and pregnancy outcomes, in private versus publically funded IVF-PGT-SR and IVF-PGT-A periods [10]. The goal was to positively impact the decisions of future policy makers regarding the risks and benefits of each system.

Materials and methods

Patient details

This study retrospectively analyzed data during both privately funded period (PRP) and publically funded period (PUP) of ART for a total of 275 patients. Among the 83 patients who underwent IVF PGT-SR for chromosome translocation and 192 IVF PGT-A. To achieve the proposed objective, the two groups under analysis were grouped in accordance with their respective coverage systems for infertility.

Among patients who underwent IVF-PGT-SR, 34 were during PRP and 5 of those later enrolled in the PUP as well. 55 patients attempted during PUP, 3 of which later attempted IVF-PGT-SR after November 10, 2015. Among those 3 couples, 2 had also attempted during the 1st privately funded IVF-PGT-SR period (prior to August 5th 2010). Among patients who underwent IVF-PGT-A, 148 attempted during PRP and 45 attempted in the PUP. 1 patient had attempted both in PRP and PUP.

All patients were referred to the McGill University Health Centre – Reproductive Center (MUHC-RC) in Montreal, Quebec, Canada. The data was collected from March 1998 to June 2016. The project was approved by the Royal Victoria Hospital – MUHC Office of Research Ethics.

Definitions

The term "cycle" here is clarified as either an IVF-PGT-SR or IVF-PGT-A treatment cycle. Embryo transfer (ET) cycle is defined as an IVF-PGT-SR or IVF-PGT-A cycle in which at least 1 embryo was transferred, including frozen embryo replacement cycle (FERC). Clinical pregnancy rate (CPR) was defined as the number of IVF-PGT-SR or IVF-PGT-A cycles with at least one gestational sac divided by the total number of IVF-PGT-SR or IVF-PGT-A cycles. Implantation rate was obtained by dividing the total number of gestational sacs obtained in all IVF-PGT-SR or IVF-PGT-A cycles by the total number of embryos transferred.

Genetic analysis

Genetic analysis was performed using multicolor FISH for PGT and specific probes for translocations. FISH was performed in two rounds using probes specific for certain chromosomes in aneuploidy and translocation cases [11]. Only Telemere and CEP probes from translocated chromosomes were included in the analysis of reciprocal translocations cases [12].

Statistical analysis

Statistical analysis was performed using chi-squared test with statistical significance level set at $p = 0.05$.

Results

We analyzed data obtained from a total of 275 patients who were separated into either IVF-PGT-SR or IVF-PGT-A and their embryological, diagnostic and clinical aspects are listed in Tables 1 and 4.

Regardless of the type of ART (IVF-PGT-SR or IVF-PGT-A), the average female age in PRP and PUP did not differ significantly, and likewise for the number of cumulus-oocyte complexes, zygotes with two pronuclei, number of embryos biopsied, number of embryos with valid results and number of normal or balanced embryos.

Table 1
Embryological, diagnostic and clinical aspects of IVF-PGT for chromosome translocation patients.

Variants	Privately funded	Publically funded	P-value
Number of patients	34	55	
Average female age ± SD	33.3 ± 3.2	35.2 ± 4.0	
Number of PGT cycles (per patient)	47 (1.4)	92 (1.7)	
Number of Cumulus-oocyte complexes (per cycle)	748 (15.9)	1348 (14.7)	
Number of zygotes with two pronuclei (per cycle)	438 (9.3)	807 (8.7)	
Number of embryos biopsied	400	747	
Number of embryos with valid results	370	710	
Normal/ Balanced embryos (%)	94 (27.8%)	145 (20.4%)	
Number of fresh embryos transferred	67	65	
Number of frozen embryos transferred (# clinical pregnancies)	6 (3)	15 (6)	
Total number of embryos transferred	73	80	
Number of cycles without ET (%)	5 (10.6 %)	21 (22.8%)	
Average number of embryos transferred per ET*	1.74*	1.13*	< 0.0001
Number of PGT cycles with ≥ 1 sac (No.of sacs)	20 (23)	23 (23)	
Implantation rate %	31.5%	28.8%	
Clinical pregnancy rate per PGT cycle*	42.6%*	25%*	0.03
Total number of live birth	17 (13 singleton - 1 by FERC, 2 sets of twins)	14 singleton	

* p value ≤ 0.05.

With a test efficiency of 93%, 94 normal or balanced embryos (27.8%) were obtained from 47 IVF-PGT-SR patients in PRP group. 73 embryos were transferred, of which 67 were fresh and 6 were frozen. In PUP, 145 (20.4%) normal or balanced embryos obtained from a test with an efficiency of 95%. 92 IVF-PGT-SR cycles were performed and 80 embryos were transferred, of which 65 were fresh and 15 were frozen. In PRP there were less IVF-PGT-SR cycles that did not result in ET than in PUP (10.6% vs. 22.8%, not statistically significant). The average number of embryos transferred per ET was significantly lower in PUP versus PRP (1.13 vs. 1.74, $p < 0.0001$). When comparing implantation rate, fertilization rate, CPR or miscarriage rate per IVF-PGT-SR cycle in PRP versus PUP, the difference was not statistically significant. Of all live births in PRP, the majority were singleton pregnancies (n = 13) and the remaining 4 were 2 sets of twins. In PUP, 14 singleton babies were conceived and 0 multiple pregnancies (Table1).

Among the patients with known reciprocal (REC) and Robertsonian (ROB) translocation carrier status, there were similar numbers of male carrier patients for both REC and ROB translocation. In PRP there is a significant increase in the percent of male carriers (82.4% vs. 60%, $p = 0.03$) and significantly less female carriers (17.6% vs. 40%, $p = 0.03$). Interestingly, there are consistently higher numbers of REC translocation carriers (79.4% in PRP and 76.4% in PRP) versus ROB carriers (20.6% in PRP and 23.6% PUP), regardless of which funding period (Table 2).

Sperm parameters and reproductive history of male translocations carriers were further analyzed (Table 3). In both groups, the majority of patients had abnormal sperm parameters and only 32.1% in PRP and 30.3% in PUP had normal sperm parameters. Among all male translocation carriers with normal sperm parameters, 43.8% of couples had primary infertility and 37.5% had multiple miscarriages.

There is a contrast in trend when analyzing number of IVF-PGT-SR attempts and number of IVF-PGT-A attempts in the two periods. Among chromosomal translocation carrier patients, there was a 34.8% increase in IVF-PGT-SR attempts per patient in PUP. Among patients with aneuploidies, there was a 13.3% increase in number of IVF-PGT-A attempts in PRP.

Of statistical significance ($p = 0.05$), there were on average of 2.5 embryos transferred per ET cycle in PRP for IVF-PGT-A patients in contrast to average of 1.4 embryos transferred per ET cycle in PUP. Similarly, the live birth rate per IVF-PGT-A cycle was higher in PRP (29.7% vs. 15%, $p = 0.02$). There was no significant difference in miscarriage rate per IVF-PGT-A cycle (9.9% in PRP vs. 8.3% in PUP). However, when comparing singleton and multiparous pregnancies, there were significant differences in PUP and PRP. In total there were 48 singleton live births and 18 live births from multiparous pregnancy in PRP, in contrast to 9 singleton live births in PUP without any multiparous pregnancies.

Discussion

This retrospective study aimed to compare IVF-PGT-SR and IVF-PGT-A patients in PRP and PUP, in terms of patient characteristics, practice patterns and treatment outcomes in a single clinic.

IVF-PGT-SR patients

Among carriers of chromosome translocations, more patients attempted IVF-PGT-SR and each patient had more attempts in the PUP. This increase in demand is expected given the relief of financial burden [13].

More embryos were transferred per ET cycle during the PRP likely as a result of patients' awareness of the cost of IVF-PGT-SR, which decreased their threshold for a failed procedure. Likewise, there is an increased pressure on physicians to minimize the cost while maximizing the chance of conception with each attempt, after having disclosed the probable increased chance of multiparous pregnancy [14]. Additionally, PGT-SR is a hereditary chromosomal abnormality, which has been found to produce more abnormal embryos than PGT-A [15]. Consequently, the idea of mandatory single blastocyst transfer (mSBT) has been raised [16,17]. In 2007, Ryan et al. showed excellent pregnancy rates (66.2% vs. 63%) with markedly decreased twin rates (41% vs 2%) [18]. However, in 2013, while Esinler et al.'s study further supported mSET's effect on decreasing multiple pregnancy rates, day-3 ETs decreased pregnancy rates as a whole and this detrimental effect was not observed in day-5 ETs [19]. Therefore, the selection of good quality embryos is critical.

A 12.2% increase in number of cycles without ET was noted in publically funded period for PGT-SR patients. Comparing PRP and PUP CPR per patient (58.8% vs. 41.8%), no statistically significant difference was noted. However, the CPR per PGT cycle was noted to be statistically significant (42.6% vs. 25%, $p = 0.03$, Table 1). The recurrently returning poor prognosis patients likely had fewer embryos retrieved then tested, and once poor quality embryo was confirmed, it was less likely to be transferred in PUP than in PRP, given that the policy allowed them to return for a subsequent trial without additional cost.

The higher CPR per patient in PRP needs to be interpreted cautiously. First, it is evident that the more embryos transferred would lead to a higher pregnancy rate but it has also directly led to

Table 2
Types of chromosome translocation and number of male and female carrier patients who underwent PGT.

Variants	Privately funded	Publically funded	P-value
% Male carriers*	82.4%*	60%*	0.03
% Female carriers*	17.6%*	40%*	0.03
% Reciprocal translocation carriers	79.4%	76.4%	
% Robertsoninan translocation carriers	20.6%	23.6%	

* p value $\leq$ 0.05.

Table 3
Sperm parameters and reproductive history of the male translocation carriers.

Variants	Privately funded	Publically funded
Male carriers	28	33
Normal Sperm (%)	9 (32.1%)	10 (30.3%)
Oligospermia ± asthenospermia ± teratozoospermia with primary infertility (%)	13 (46.4%)	12 (36.4%)
Oligospermia ± asthenospermia ± teratozoospermia with secondary infertility (%)	1 (3.6%)	2 (6.1%)
Oligoasthenoteratozoospermia with miscarriages or Termination of pregnancy (%)	5 (17.9%)	9 (27.2%)

Table 4
Embryological, diagnostic and clinical aspects of IVF-PGT for aneuploidy patients.

Variants	Privately funded	Publically funded	P-value
Number of patients	148	45	
Number of IVF-PGT cycles (per patient)	222 (1.5)	60 (1.3)	
Average female age ± SD [range]	38.3 ± 4.3 [24-44]	38.9 ± 3.6 [27-43]	
Number of previous IVF attempts - prior to referral for PGT (per patient)	467 (3.2)	89 (2.0)	
Number COC (per cycle)	3599 (16.2)	855 (14.6)	
Number of 2 PN embryos (per cycle)	2371 (10.7)	508 (8.5)	
Number embryos biopsied (per cycle)	2106 (9.5)	454 (8.0)	
Number embryos with results (per cycle)	1833 (8.3)	410 (7.2)	
Number of diploid embryos (% diploid)	631 (34.3%)	104 (25.4 %)	
Number embryos transferred (per ET cycle)*	536 (2.5)*	78 (1.4)*	0.05
Number of cycles with no ET	10	6	
Fresh embryos transferred	499	65	
Frozen embryos transferred (#clinical pregnancy)	37 (2)	13 (1)	
Clinical pregnancy rate per PGT cycle	39.60%	29.6%	
Number of PGT cycles with ≥ 1 sac (No.of sacs)	79 (88)	14 (16)	
Implantation rate %	16.40%	20.50%	
Total number of live birth*	66 (48 singleton, 18 from multiparous pregnancy)*	9 (9 singleton, 0 multiparous)*	0.003

* p value ≤ 0.05.

significant increases in multiple birth rates [20–22]. Secondly, patients who underwent IVF-PGT-SR during the PRP can be postulated to have had a better prognosis to begin with. These patients underwent less IVF-PGT-SR cycles and resulted in higher CPRs (47 IVF-PGT-SR cycles and 58.8% CPR per couple), whereas patients in PUP underwent more IVF-PGT-SR cycles per couple and ultimately had less success (92 IVF-PGT-SR cycles, 41.8% pregnancy rate per couple). Notably, there is a trend showing higher CPR in PRP [23,24].

Comparing male carrier and female carrier proportions in PRP and PUP, male translocation carriers remain the most frequent problem. In both funding periods, more than 30% of males carriers had normal sperm parameters, whereas the majority suffered from oligospermia, asthenospermia and/or tertozoospermia resulting in primary infertility, secondary infertility, miscarriage or termination of pregnancy (Table 3). In couples with male translocation carriers, the poor sperm parameters make spontaneous pregnancy essentially non-achievable. Thus, in order to conceive, they necessitate professional investigation and financial issues would play less of a role in their incentive to seek medical assistance. Our results are comparable to those of Keymolen et al's in 2012, in which the majority of patients with poor sperm parameters experience primary infertility. Meanwhile, female carriers are more likely to attain pregnancy, albeit after multiple miscarriages [25]. According to our study, in PRP 83.3% of female carriers and in PUP 76.2% of female carriers experienced miscarriages or termination of pregnancy, but the difference was not statistically significant.

A current theory to explain this phenomenon is such the sex of the carrier parent has an effect on chromosome segregation and perhaps, spermatogenesis is severely compromised in male carriers, whereas oogenesis is less affected in female translocation carriers [26]. Female carriers are more likely to produce a higher rate of balanced gametes and have a higher chance of a balanced good quality embryo during IVF-PGT-SR [27–30]. Once normal or balanced embryos were transferred, there was no statistically significant difference in CPR. Given the higher probability of spontaneous pregnancy, couples with female carriers are less likely to seek investigation in PRP. However, after many miscarriages, women are more inclined to seek medical investigation during PUP. Notably, this raises the question of whether or not these patients would have had a birth in the absence of treatment.

Consistently more than ¾ of patients were REC translocation carriers, regardless of PUP or PRP and this population underwent the majority of IVF-PGT-SR cycles. As per Yilmaz et al. chromosome segregation analysis in human embryos obtained from couples involving male carriers of both REC and ROB translocation, ROB carriers produce more normal or balanced embryos (27.1% vs. 55.1%), which provide more options to select morphologically better quality embryos for transfer [12,31].

IVF-PGT-A patients

In the second group of IVF-PGT-A patients, there were more patients in the PRP in contrast to the PUP. This is due to the longer inclusion period of 12 years versus 5 year PUP. The political issue of IVF-PGT-A treatment not being covered by the Québec healthcare plan, "Regie de l'assurance maladie du Quebec" (RAMQ), in PUP also played a role in the drop from 148 IVF-PGT-A patients in PRP to only 45 in PUP. While patients who were treated in the transition period from PRP to PUP were still willing to pay for PGT to optimize their successful pregnancy outcome after IVF, after the implementation of publically funded IVF-PGT-SR, the financial mentality likely shifted and patients opted to try more IVF cycles rather than pay for IVF-PGT-A out of pocket. Importantly, to be eligible for IVF-PGT-A there exists stringent criteria, one being repeated spontaneous miscarriages and repeated unsuccessful ET (European Society of Human Reproduction and Embryology – ESHRE). While this explains the high number of prior IVF attempts (3.2 attempts per patient in PRP and 2.0 per patient in PUP), this also highlights the significant emotional burden on patients, playing an important role in the decreasing number of IVF-PGT-A patients over time. In PRP, patients attempted more IVF-PGT-A compared to PUP (1.5 vs. 1.3). Among the highly selective patient population with many risk factors, IVF-PGT-A often represents their final stretch in attempt to conceive. As such, older couples are more willing to try more than once [32,33]. Finally, for similar reasons explained for IVF-PGT-SR, more embryos were transferred per ET cycle in IVF-PGT-A patients.

There are some limitations to our study. Notably, the sample size was small, complicating the comparative statistical analysis, but given that all patients were from the same institution and treated by the same expert team, our study allowed for a better-controlled setting. Bitler and Schmidt found little evidence that financial coverage reduced disparities in access to treatment by race, ethnicity or socioeconomic status, which then raises the question of whether financial coverage targets the intended beneficiaries [34]. Our data does not directly analyze what types of patients benefitted from the increase in access, thus for subsequent studies it would be beneficial to stratify patients based on good and poor prognosis and observe difference in use of

resources. Finally, FISH technique was the prevailing technique used at the time of data collection; however, we acknowledge that it is no longer as widely used and comprehensive chromosome analysis (CCS) has taken over as techniques, including SNIP array and NGS [35,36]. However, in terms of the results of our study since both groups were subject to the same technique, the differences observed cannot be explained by the technique used.

In summary, our results corroborate the existence of differences in ART practices and outcomes in relation to public or private coverage. Our study further supports the first North American publicly funded IVF program with SET policy, in that a greater utilization ART, a reduced number in ET per cycle, and a lower multiple birth rate was appreciable [9]. However, our results differ in terms of the lower proportion of cycles resulting in successful pregnancy. Our study elucidates important implications surrounding policy changes. As such, future policies concerning access to ART must take into consideration the desired balance between the effectiveness of treatments but also be cognizant of acceptable risks.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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