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Quebec public funding facilitates fertility preservation for male cancer patients

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ABSTRACT

Background Sperm cryopreservation remains the only clinically feasible option to preserve male fertility. The quality of counselling provided by the treating physicians and the cost of sperm cryopreservation can both influence a patient's decision about whether to preserve sperm. On 5 August 2010, the Quebec government introduced provincial coverage of assisted reproductive technologies, with sperm cryopreservation included as a covered service. The aim of the present study was to evaluate whether and how such a program affects the behaviour of cancer patients with respect to sperm cryopreservation.

Methods We analyzed the database derived from male patients undergoing sperm cryopreservation from August 2008 to August 2012 at our centre. The retrieved data included patient age, male infertility or oncologic diagnosis, sperm quality parameters, and details about the number of visits for sperm cryopreservation.

Results The number of cancer patients who cryopreserved sperm before and after the policy change did not differ significantly, but a marked increase in the number of non-cancer patients was observed. Further analysis revealed that, after implementation of the public funding program, the total number of sperm cryopreservation sessions per patient increased significantly in cancer patients but not in non-cancer patients.

Conclusions It appears that cancer patients who are willing to freeze sperm are keen to return for more sessions of sperm banking when no fees are associated with the service. Those findings suggest that cost reduction is an important factor for improving delivery of fertility preservation services to male cancer patients.

Key Words Male fertility preservation, costs, assisted reproductive technologies

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INTRODUCTION

Approximately 10%–15% of childbearing-age couples experience infertility. This condition also affects the couples emotionally and financially[1–3]. The *Diagnostic and Statistical Manual of Mental Disorders* states that approximately 30% of women and 10% of men using assisted reproductive technology (ART) fulfil the criteria for a depressive or anxiety disorder[4]. The National Survey of Family Growth in the United States demonstrated that the choice to pursue expensive treatments such as ART is highly influenced by income[5].

Since the early 2000s, provincial and regional health plans in Canada have covered the cost of infertility investigations. In the province of Quebec, the cost of fertility treatment—including *in vitro* fertilization (IVF)—was covered entirely by patients, who afterwards received a 50% tax rebate. However, on 5 August 2010, Quebec became the first North American jurisdiction to offer full funding for assisted reproduction, including IVF treatments and related services[6]. Under the provincial program, all costs related to IVF were covered by Quebec's universal health insurance plan. The coverage also extended to other related evaluation or management procedures such as semen analysis and sperm cryopreservation, two fertility care procedures specifically relevant to the male partners. On 10 November 2015, after submission of this manuscript, the Quebec public funding program for assisted reproduction was modified; however, sperm cryopreservation and sperm storage for 5 years remain covered for cancer patients[7].

Sperm banking with cryopreservation of ejaculated semen or testicular sperm remains the only clinically feasible

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option to preserve male fertility for cancer patients and for infertile non-cancer patients. Sperm cryopreservation is indicated in male patients undergoing surgical or cytotoxic therapies such as radiation or chemotherapy that can lead to impaired reproductive function—for example, ejaculatory disorders and reduced capacity for spermatogenesis. Sperm cryopreservation is also indicated for non-malignancy patients, including infertile men with progressive and severe deterioration of sperm count or motility, men with ejaculatory disorders leading to inconsistency in the capacity to produce semen voluntarily, and men for whom only surgical sperm retrieval can obtain sperm for freezing and future use in ART procedures[8,9].

We previously demonstrated that fertility outcomes in male cancer survivors are comparable to those in non-cancer patients undergoing IVF treatment, supporting the notion that sperm banking for cancer patients is a highly valued service that should be encouraged before gonadotoxic cancer treatment[10]. The aim of the present study was to evaluate whether the implementation of Quebec provincial coverage of assisted reproductive care influenced the service of sperm cryopreservation for cancer patients.

METHODS

Study Design

We retrospectively analyzed database-derived records of patients undergoing sperm cryopreservation at the McGill University Health Centre from August 2008 to August 2012. The Research Ethics Board of the McGill University Health Centre approved the study (protocol number 12-471-PSY). Data were obtained from the files in the sperm banking archives and from the medical records in the computerized fertility database system. The retrieved data for the male patients included age, type of infertility or oncologic diagnosis, semen analysis parameters, and details about the number of visits for sperm banking.

Patients

All male patients undergoing sperm cryopreservation were newly diagnosed with cancer or were choosing fertility preservation for non-cancer-related reasons. We categorized the cancer patients based on the type of cancer being treated. All cancer patients were referred by their treating oncologist. Non-cancer infertile patients were all referred by their fertility specialists. They were stratified into 3 categories: patients with abnormal semen parameters, patients with inconsistent capacity to ejaculate voluntarily, and azoospermic patients with surplus samples of surgically retrieved sperm after completion of IVF treatment.

Semen Collection and Sperm Cryopreservation

Ejaculated semen samples were collected by masturbation on the day of cryopreservation. Semen analysis was performed according to World Health Organization (WHO) guidelines[11]. Seminiferous tubules obtained surgically by testicular sperm extraction were mechanically teased to release spermatozoa and processed as previously described[12].

Ejaculated and testicular sperm extraction samples were both diluted in Sperm Maintenance Medium (Irvine Scientific, Santa Ana, CA, U.S.A.). After equilibration at room temperature for 10 minutes, sperm samples were loaded into 0.5 mL CBS High Security straws (Cryo Bio System, Santa Ana, CA, U.S.A.). Samples were then frozen for 30 minutes in liquid nitrogen vapor, followed by a final plunge into liquid nitrogen[10].

Outcome Measures

For both cancer and non-cancer patients, we analyzed the number of sperm cryopreservation sessions for each patient as well as details of their age, diagnoses, and semen parameters. Evaluation of semen parameters involves the measurement of sperm concentration, sperm motility, and sperm morphology. We adopted the reference values of the 2010 WHO guidelines for the entire study. Because our semen analysis protocols before 2010 met the standards of the 2010 edition of the WHO guidelines, the adoption of one set of reference values allowed us to standardize the comparison of semen parameters for all samples in the study. According to the 2010 WHO guidelines, the reference values for a semen sample meeting the lowest 5th percentile of fertile men are a sperm concentration of 15 million/mL or more, sperm motility of 32% or more, and 4% or more normal sperm forms[11]. To simplify the interpretation of semen quantity and quality for the present work, we report the motile sperm index for each sample, which was determined as the product of the sperm concentration and percentage of total motility plus 1%, as described in a previous study[10]. The WHO parameters were taken as a reference value to establish a cut-off motile sperm index of 5.8. Measurements in the present study included the frequency of sperm cryopreservation by patients overall and the number of sperm cryopreservation sessions per patient.

Statistical Analysis

We used the Shapiro–Wilk test to evaluate the data distribution. Continuous variables were analyzed using the Student t-test or the Mann–Whitney U-test, as appropriate. Proportions were compared using the chi-square test or Fisher exact test. Results are expressed as means with standard deviation, medians with range, or percentages, as appropriate. All comparisons between groups were performed using a two-sided test at an alpha level of 5% unless otherwise specified. Analysis of covariance was used to explore the effect of policy change on the number of visits per patient for cancer patients and non-cancer patients separately after accounting for the influence of age and semen profile (reflecting sperm quantity and quality).

RESULTS

Of the 568 patients analyzed, 272 (47.9%) had been diagnosed with cancer, and 296 were non-cancer patients (52.1%). Patients in the cancer cohort were significantly younger than those in the non-cancer group (median age: 30.4 years vs. 40.0 years; $p < 0.0005$). Most men in the cancer cohort (82.4%) were between 19 and 40 years of age. Only 5.5% of the cancer patients were less than 18 years of age; 12.1% were between 41 and 62 years of age. In contrast, 57.6% of the patients in the non-cancer cohort were between 22 and 40 years of age, and 42.4% were between

41 and 65 years of age. The proportion of patients with a motile sperm index above 5.8 was significantly larger in the cancer cohort than in the non-cancer cohort (57.7% vs. 48%, $p = 0.04$; 95% confidence interval for the difference in proportion: 0.002 to 0.190).

The most prevalent types of malignancies in the cancer cohort were lymphoma (25.5%), testicular cancer (19.2%), and leukemia (8.1%). Other diagnoses in the cancer cohort (47.2%) included sarcoma and gastrointestinal and central nervous system malignancies. Among the non-cancer patients, 33.8% had low sperm count and motility (motile sperm index below 5.8), 29.7% had surplus samples of surgically retrieved sperm, and 36.5% had normal semen parameters (motile sperm index above 5.8).

The distribution of cancer types in the cancer cohort remained comparable before and after public funding for ART (Table I). However, within the non-cancer cohort seeking fertility preservation after 5 August 2010, we observed a significant increase in the percentage of subjects with poor semen parameters (oligoasthenospermia: $p = 0.03$; 95% confidence interval for difference in proportions: 0.02 to 0.246) and a significant decrease in the percentage of azoospermic patients requiring surgical sperm retrieval ($p = 0.01$; 95% confidence interval for difference in proportions: 0.03 to 0.265; Table I).

Table II presents the number of patients and the number of visits per patient before and after public funding for ART. The total number of cancer patients managed by our fertility centre was similar before and after implementation of the ART public funding program. However, after 5 August 2010, a significant increase occurred in the number of sessions of sperm banking per cancer patient. Among the non-cancer patients, a significant increase in patient numbers, but not in the number of sessions per patient, occurred after 5 August 2010.

Because the age distribution within the cancer cohort before and after the implementation of public funding for ART was similar (Table II), we further evaluated whether the increase in the number of visits per cancer patient was associated with the quantity and quality of the sperm sample. We found that the increase in the number of sperm banking visits per patient with cancer after the ART coverage was similar for patients with motile sperm indexes greater than and less than 5.8 [Figure 1(A,B)]. The extent of the "right shift" of the curves in the frequency of sperm banking indicate that the increase in the number of sessions per patient after the implementation of ART coverage was similar for cancer patients with a motile sperm index greater and less than 5.8. Figure 2(A,B) highlights the finding that, even though the number of sessions in the non-cancer cohort remained constant before and after public funding for ART, banking tended to be more frequent among non-cancer patients with poor semen parameters [Figure 2(B)] than among those with normal semen parameters [Figure 2(A)].

DISCUSSION

We evaluated two study periods of equal length before and after the implementation of a provincially-funded assisted reproduction program and found that the number of cancer patients who used fertility preservation services before and after the policy change did not differ significantly. On the other hand, a marked increase occurred in the number of non-cancer patients using sperm cryopreservation services. Further analysis revealed that, after implementation of the provincially-funded ART program, the total number of sessions of sperm banking per patient increased significantly only among cancer patients.

Several explanations could be applied to our observations. First, the increase in the volume of non-cancer patients was understandably a direct result of the increase in the overall volume of couples seeking fertility care once the treatment cost was covered provincially[13]. Second, physicians referring the non-cancer infertile patients were typically fertility practitioners who were fully aware of the availability and coverage of sperm cryopreservation. They were in an ideal position to counsel about sperm banking to avoid the possibility of failing to have an adequate quantity and quality of sperm at the time of assisted reproduction

TABLE I Proportions of cancer and non-cancer patients who cryopreserved sperm before and after provincial funding of assisted reproductive technology (ART)

Patient type	Users (%) relative to start of provincial funding for ART		*p* Value
	24 Months before	24 Months after	
Cancer patients with ...			
Testicular cancer	19.8	18.6	NS
Lymphoma	27.0	24.1	NS
Leukemia	7.1	9.0	NS
Other cancers	46.1	48.3	NS
Non-cancer patients with ...			
Normospermia	35.4	37.2	NS
Oligoasthenospermia	25.7	38.8	0.03
Azoospermia requiring surgical sperm retrieval	38.9	24.0	0.01

NS = nonsignificant.

TABLE II Patient types and visits per patient before and after provincial funding of assisted reproductive technology (ART)

Patient type	Users relative to start of provincial funding for ART		*p* Value
	24 Months before	24 Months after	
Cancer patients [*n* (%)]	127 (46.7)	145 (53.3)	NS
Median age (years)	30.9	30.0	NS
Median sessions per patient (*n*)	1.30	1.70	0.0005
Non-cancer patients [*n* (%)]	114 (38.5)	182 (61.5)	0.001
Median age (years)	40.0	40.0	NS
Median sessions per patient (*n*)	1.20	1.33	0.216

NS = nonsignificant.

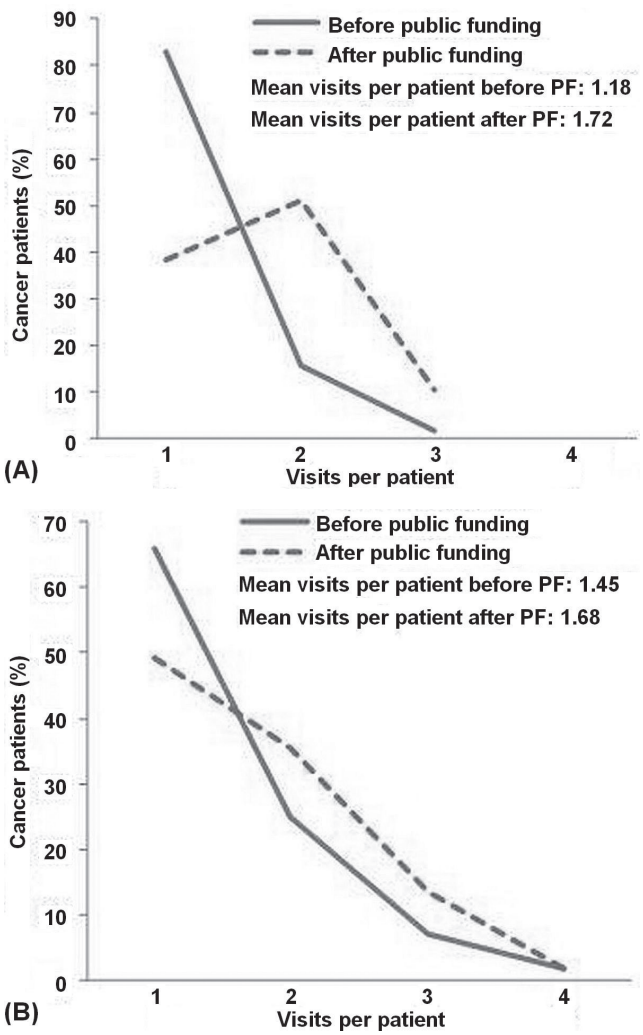

FIGURE 1 Visits per cancer patient according to sperm quality. (A) Motile sperm index 5.8 or greater. (B) Motile sperm index less than 5.8. PF = public funding.

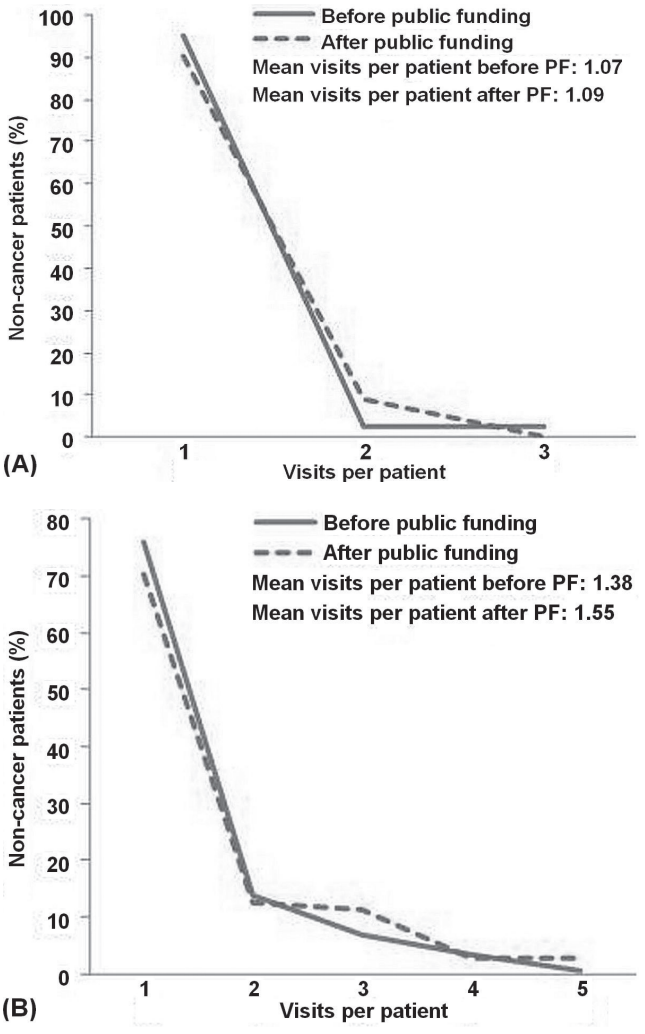

FIGURE 2 Visits per non-cancer patient according to sperm quality. (A) Motile sperm index 5.8 or greater. (B) Motile sperm index less than 5.8. PF = public funding.

management. Because those men were actively pursuing fatherhood, they were obviously motivated to use sperm cryopreservation—particularly those with subnormal semen parameters, as seen in our results. Our findings support earlier reports suggesting that, in addition to a patient's own agenda, the attitude and the quality of

counselling provided by health care providers can strongly influence the intention to cryopreserve sperm[14,15].

For cancer patients and oncology care professionals, the immediate priority is to manage the cancer; the need for fertility preservation is secondary[15,16]. We previously reported that a cancer diagnosis can indeed have an overwhelming psychological effect on patient priorities at various times in their life agenda[15]. As suggested by Yee *et al.*[14,17], an understanding of cancer-related infertility and fertility preservation resources is lacking among oncology practitioners. Additionally, cancer patients and their treating physicians might not be fully aware that sperm cryopreservation is covered as of 5 August 2010. Because the number of cancer patients managed at our centre for sperm cryopreservation were comparable before and after the implementation of the provincially funded ART program, it is reasonable to assume that neither the cancer patient volume managed by oncologists nor the pattern of counselling about male fertility preservation provided by oncology care professionals changed after implementation of the policy.

Our finding that, after policy implementation, cancer patients who might not have considered fertility preservation to be a high priority and who might not have received information on coverage of those costs when they were referred by their oncology care professionals for fertility preservation were willing to return for additional sperm banking sessions was surprising. Obviously, the number of sessions of sperm banking before cancer therapy depends on several factors, including the cancer diagnosis, the urgency to start cancer therapy, and the health and fertility status of the patient. Assuming that those factors were unchanged before and after the ART policy implementation, our observation can logically be attributed to the reduction in the cost for sperm cryopreservation after implementation of service coverage.

In assisted reproduction, even with the most advanced technology of IVF using intracytoplasmic sperm injection, the success rate per trial leading to a live birth is only about 25%[18]. Hence, multiple cycles of intracytoplasmic sperm injection are often required before a live birth is achieved, and for those who desire more children, repeated attempts must be made. Although sperm freezing is currently the only feasible option for male fertility preservation, sperm that are cryopreserved are of finite quantity. Once they are used up, if the patient cannot produce fresh sperm, there is no further hope to produce genetically related children. Thus, the more sessions of sperm cryopreservation, the better the chance of avoiding sperm quantity being the limitation to success during future use of assisted reproduction—a situation that is particularly true for patients who will likely experience a decline in spermatogenesis capacity in the future, as occurs in cancer patients undergoing gonadotoxic treatment.

The Canadian study of the provision of oncology sperm banking services reported that 42% of the clinics provide financial subsidies through charitable organizations and that 54% offer a case-by-case assessment for financial aid[14]. The mean initial sperm banking fee (Canadian dollars) was $304 (range: $0–$500), and the subsequent mean fees for additional sessions of sperm banking were in the $0–$350 range. The mean annual storage fee after the first year for all clinics was $235 (range: $100–$350). At our centre, before implementation of provincial coverage for ART, a fee of $250 was applied to pre-chemotherapy sperm banking procedures; the subsequent annual cryopreservation storage fee was $150. At the time of writing, cryopreservation fees ranged between $150 and $500 (based on the Web site prices listed by 8 fertility clinics in Western Canada, 4 fertility clinics in Ontario, and 1 fertility centre in Eastern Canada). In Quebec, the cost is currently nil (Table III).

Given that the practice pattern of oncologists appeared to be constant, our data show a significant increase in the number of sperm banking sessions per cancer patient after provincial implementation of ART coverage. That observation suggests that, once cancer patients are aware of the option to freeze sperm, and when cost is no longer a barrier, they are keen on banking sperm. It has been speculated that young cancer patients could have a strong desire for fatherhood, but that cost could be a barrier to the pursuit of fertility preservation before cancer therapy[19–21]. Taken together, our findings support the importance of both awareness and knowledge on the part of oncology care providers about the availability and accessibility of and the obstacles to fertility preservation options. Because oncology care providers are the first to counsel cancer patients, the information reported here can potentially improve the quality of the cancer management counselling delivered to those patients.

The main strength of our study is its experimental model. The introduction of provincial coverage for ART provided a unique opportunity to study the sole impact of cost on the behavior of cancer and non-cancer patients with respect to sperm banking. Limitations of our study include its retrospective nature and our inability to account for the patients who might have been referred by their practitioners but who chose not to proceed with sperm banking. However, because the proportion of such patients could be assumed to have remained constant during the entire study period, the possible bias thus represented should not have any significant impact on the validity of the study.

CONCLUSIONS

We conclude that, as a result of the implementation of a provincially-funded ART program, cancer and non-cancer patients in need of fertility preservation are more willing to bank sperm. The result is that a greater quantity of sperm would be expected to be available for future use, potentially leading to a higher chance of procreation success. We believe that the provincially-funded ART program improves the quality of care in fertility preservation, benefiting male patients facing infertility.

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CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare that we have none.

TABLE III Current sperm cryopreservation fees for cancer patients in Canada

Variable	Western Canada	Atlantic provinces	Ontario	Quebec
Facilities sampled (*n*)	8	1	4	7
Freezing fee (CA$)	150–380	500	175–350	0
Annual storage fee (CA$)	175–300	225	250–300	0 (first 5 years)

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REFERENCES

1. Cousineau TM, Domar AD. Psychological impact of infertility. *Best Pract Res Clin Obstet Gynaecol* 2007;21:293–308.
2. Mosalanejad L, Khodabakshi Koolee A. Looking at infertility treatment through the lens of the meaning of life: the effect of group logotherapy on psychological distress in infertile women. *Int J Fertil Steril* 2013;6:224–31.
3. Connolly MP, Hoorens S, Chambers GM on behalf of the ESHRE Reproduction and Society Task Force. The costs and consequences of assisted reproductive technology: an economic perspective. *Hum Reprod Update* 2010;16:603–13.
4. Volgsten H, Skoog Svanberg A, Ekselius L, Lundkvist O, Sundstrom Poromaa I. Prevalence of psychiatric disorders in infertile women and men undergoing *in vitro* fertilization treatment. *Hum Reprod* 2008;23:2056–63.
5. Farley Ordovensky Staniec J, Webb NJ. Utilization of infertility services: how much does money matter? *Health Serv Res* 2007;42:971–89.
6. Tulandi T, King L, Zelkowitz P. Public funding of and access to *in vitro* fertilization. *N Engl J Med* 2013;368:1948–9.
7. Government of Quebec. Wellness portal. Assisted reproduction program [Web page, French]. Quebec, QC: Government of Quebec; 2015. [Available at: http://sante.gouv.qc.ca/programmes-et-mesures-daide/services-de-procreation-assistee/; cited 21 December 2015]
8. Anger JT, Gilbert BR, Goldstein M. Cryopreservation of sperm: indications, methods and results. *J Urol* 2003;170:1079–84.
9. Shufaro Y, Schenker JG. Cryopreservation of human genetic material. *Ann N Y Acad Sci* 2010;1205:220–4.
10. Garcia A, Herrero MB, Holzer H, Tulandi T, Chan P. Assisted reproductive outcomes of male cancer survivors. *J Cancer Surviv* 2015;9:208–14.
11. World Health Organization (WHO). *WHO Laboratory Manual for the Examination and Processing of Human Semen*. 5th ed. Cambridge, U.K.: Cambridge University Press; 2010.
12. Son WY, Chung JT, Henderson S, *et al*. Fertilization and embryo development with spermatozoa obtained from testicular sperm extraction into oocytes generated from human chorionic gonadotropin-primed *in vitro* maturation cycles. *Fertil Steril* 2013;100:989–93.
13. Velez MP, Connolly MP, Kadoch IJ, Phillips S, Bissonnette F. Universal coverage of IVF pays off. *Hum Reprod* 2014;29:1313–19.
14. Yee S, Buckett W, Campbell S, Yanofsky RA, Barr RD. A national study of the provision of oncology sperm banking services among Canadian fertility clinics. *Eur J Cancer Care (Engl)* 2013;22:440–9.
15. Achille MA, Rosberger Z, Robitaille R, *et al*. Facilitators and obstacles to sperm banking in young men receiving gonadotoxic chemotherapy for cancer: the perspective of survivors and health care professionals. *Hum Reprod* 2006;21:3206–16.
16. Schover LR, Brey K, Lichtin A, Lipshultz LI, Jeha S. Oncologists' attitudes and practices regarding banking sperm before cancer treatment. *J Clin Oncol* 2002;20:1890–7.
17. Yee S, Fuller-Thomson E, Lau A, Greenblatt EM. Fertility preservation practices among Ontario oncologists. *J Cancer Educ* 2012;27:362–8.
18. Human Fertilisation and Embryology Authority. IVF – chance of success [Web page]. London, U.K.: Human Fertilisation and Embryology Authority; 2014. [Available at: http://www.hfea.gov.uk/ivf-success-rate.html; cited 5 August 2014]
19. Huyghe E, Martinetti P, Sui D, Schover LR. Banking on Fatherhood: pilot studies of a computerized educational tool on sperm banking before cancer treatment. *Psychooncology* 2009;18:1011–14.
20. Schover LR, Brey K, Lichtin A, Lipshultz LI, Jeha S. Knowledge and experience regarding cancer, infertility, and sperm banking in younger male survivors. *J Clin Oncol* 2002;20:1880–9.
21. Schover LR. Patient attitudes toward fertility preservation. *Pediatr Blood Cancer* 2009;53:281–4.