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Research Article

A Decade of Social Fertility Preservation

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Abstract

The global phenomenon of deferment of conception has led to an increase in the age of sub fertile community and a growing demand for assisted reproductive techniques. Social fertility preservation can be considered a hedge against age-related decline in fertility and is considered as a form of elective self-donation; where healthy females collect then freeze their oocytes for autologous use at a later stage in life. From August 2005 to July 2014, 67 women presented for social fertility preservation at our institution. The mean age was 38.6±3.6 years. They were mostly single, nulliparous and professionals. They underwent a total of 128 cycles of *In Vitro Fertilization* (IVF) and 4 cycles of *In Vitro Maturation* (IVM). The number of oocytes frozen was 11.3±7.1. Only 5 women returned to achieve a pregnancy (7.5%). Embryo transfer of 4 patients did not reveal any live birth. It suggests that social fertility preservation after the age of 35 years is associated with a poor outcome. Social fertility preservation should be considered at an early reproductive age.

Introduction

The global phenomenon of deferment of conception is due to a variety of reasons including increased opportunities for women in education and careers, high divorce rate and economic instability [1]. With this growing tendency toward delayed reproduction, there is an increase in the age of the sub fertile community and a growing demand for Assisted Reproductive Techniques (ART) [2] by women who falsely assume that it can restore their fertility at any age. Subsequently more women in their late thirties and older are requiring fertility services [3], increasing the treatment demands worldwide. For instance in the USA in the year 2011, women 35-40 years of age represented 41.2% of the total IVF cycles volume, where as those older than 40 years represented 14.5% suggesting that most of the treated population in the United States were women older than 35 years of age [4].

Traditionally, fertility preservation was for women with malignancy treated with gonadotoxic treatment that might lead to sterility [5]. It is considered as a form of elective self-donation [6]. The available options in females range from established techniques such as embryo and oocyte cryopreservation to experimental techniques such as ovarian tissue cryopreservation [7-9]. Hundreds of live births have been reported with oocyte cryopreservation and it has the unique advantage of avoiding the need for sperms at the time of collection. Therefore, it is highly desired by single women who might reject the use of donor sperm due to religious, ethical, future relationship and cultural concerns [10].

The European Society for Human Reproduction and Embryology (ESHRE) task force stated that oocyte vitrification should also be obtainable for non-medical purposes [11]. Subsequently, the American Society of Reproductive Medicine (ASRM) lifted the "Experimental" label from the oocyte freezing technique [7]. Unfortunately, data on reasons behind "Anticipated Gamete Exhaustion (AGE) banking" are scarce [3,6]. It is known that the recipient age does not affect success; implicating that the oocyte is the primary determinant of reproductive aging [12,13]. Indeed, the age of the woman at the time of oocyte collection impacts the fertility outcome [14].

The purpose of our study was to describe the demographics, motivations, treatment protocols and outcome achieved by women who chose to socially preserve their fertility by means of oocyte or embryo cryopreservation and who returned to our center aiming for a pregnancy.

Materials and Methods

We define social fertility preservation as an attempt to increase the likelihood of conception, where healthy females collect then freeze their gametes for autologous use at a later stage in life. During the period from August 2005 to July 2014, 67 women were referred to us for social fertility preservation. They underwent a total of 128 cycles of *In Vitro Fertilization* (IVF) and 4 cycles of *In Vitro Maturation* (IVM). We included all cycles independent whether they resulted in oocyte or embryo cryopreservation. Data were obtained from the database of the reproductive unit of the McGill University Health Center (MUHC) and cross-checked with the medical files. The Research and Ethics Board of MUHC (13-360-SDR) approved the study.

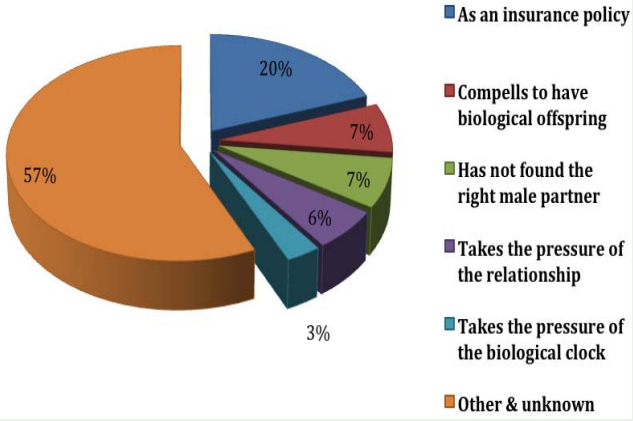

Figure 1: Motivation for undergoing social fertility preservation.

The data evaluated included patient demography, serum baseline hormone levels, Antral Follicle Count (AFC), treatment protocol, number of cycles, duration of stimulation, dose of gonadotropins used, estradiol (E2) level on the day of trigger, number of oocytes retrieved, the number of frozen metaphase 2 oocytes, and the number of frozen embryos.

We also evaluated their motive and willingness of becoming a mother. Five patients returned to attempt a pregnancy; the data on the duration between the freezing and use for pregnancy, use of donor or partner sperms, protocol type, oocyte or embryo freezing, number of embryo(s) transferred and the pregnancy outcome were collected. Payment history of annual storage fees was checked to appraise their interest in continuous storage for future use.

All patients underwent controlled ovarian hyper stimulation with either one of 4 protocols: a fixed antagonist protocol (gonadotropin from day 2-3 of the cycle and GnRH antagonist on the sixth day of stimulation) (63 cycles) [15], a long agonist protocol (GnRH agonist started in the mid-luteal phase and gonadotropin after 2 weeks of down-regulation) (41cycles) [16], a micro dose flare protocol (initiation of GnRH agonist on day 2-3 of the cycle and gonadotropin on the third day of the GnRH agonist) (25cycles) [17] or IVM (without preceding stimulation, 10,000 IU HCG trigger was given when the dominant follicle reaches 10-12mm and the endometrial thickness becomes 6-8mm) (4 cycles) [18]. The protocol used and the initial dose of gonadotropins were decided by the patient's treating physician according to the patient's age, the serum FSH level on day 3 of the cycle, and the AFC at baseline ultrasound.

Table 1: Demography of 67 women who underwent social fertility preservation.

No. patients	67
Age (years)	38.6±3.6
Day 2-3 FSH (mIU/ml)	6.9 (5.6-8.4)
Day 2-3 AFC	14 (9-19)
Parity: • Nulliparous • Primiparous	 66 (98.5%) 1 (1.5%)
Marital status: • Single • Married • Divorced • In a relation	 58 (86.6%) 1 (1.5%) 6 (9 %) 2 (3%)
Ethnic group: • Caucasian • Asians	 58 (86.6%) 9 (13.4%)
Occupation: • Professionals • Others	 55 (82.1%) 12 (17.9%)

For IVF cycles, 3,300 to 10,000 units of human Chorionic Gonadotropin (hCG) or 250mcg recombinant-hCG (choriogonadotropin alfa injection) was administered when the leading follicle mean diameter was ≥18 mm on Trans Vaginal Scanning (TVS). Transvaginal oocyte pickup was performed 36-38 hours after hCG administration. For IVM cycles, oocytes were collected 38 hours after triggering [19]. Oocyte and embryo vitrification were performed as previously described [20,21].

Embryo Transfer (ET) was performed after preparing the endometrium with 17β-estradiol 6 mg daily starting on day 2-3 of the menstrual cycle until the endometrial thickness reached 8mm and trilaminar on TVS. Embryos were transferred if they retained ≥50% of the blastomeres after thawing. The luteal phase was supplemented with either 200 mg of micronized progesterone capsules vaginally, 3 times per day, progesterone gel 8% vaginally 2 times a day, effervescent progesterone tablets 100 mg vaginally 3 times per day or intramuscular progesterone in oil 50 mg daily.

A positive pregnancy test was defined as a serum β-hCG level of >10 IU/L, measured 11 days after blastocyst transfer or 14 days after cleavage stage embryo transfer. A viability scan was performed two weeks after a positive pregnancy test. A clinical pregnancy was defined as a pregnancy with an intrauterine gestational sac at 6 weeks gestation.

Results

The total number of women who underwent fertility preservation for social reasons was 67 (Table 1). They underwent 132 treatment cycles. Motivations to preserve their fertility are described in Figure 1. Twenty six women stated their desire to become future single mothers (38.8%) if they do not find a partner, 12 would only use their gametes in a couple situation (17.9%), and the remainder 29 women (43.2%) were not sure of their future intentions.

In the IVF group (128 cycles), the mean age of the women was 37.9±3.6 years, serum FSH 8.2±4.0mIU/ml and AFC 12.7±7.4 follicles. The duration of stimulation was 8.7±2.0days. The mean dose of gonadotropin used were 3078.2±1578.5 IU. The mean E2 levels on

Table 2: Clinical stimulation parameters among women who underwent social fertility preservation.

No. of attempts/patient	2 (1-9)
Dose of gonadotropins (IU)	3078.2±1578.5
Days of stimulation	8.7±2
E2 level on day of HCG trigger (pmol/L)	6937.2±4923.4
Dose of triggering medication • Chorio-gonadotropin alfa (mcg) • HCG (IU) • GnRHa (IU)	 250 7810±3229.7 1000
No. of oocytes collected/patient	11.3±7.1
No. of frozen MII oocyte/patient	9.4±5.9
No. of frozen embryos	10

Table 3: Clinical outcomes of 5 women who returned to achieve a pregnancy after social fertility preservation.

Case	Age at freezing (years)	Number of oocytes	Age at return (years)	Outcome
1	35	10	42.6	10 oocytes thawed, 1 survived and fertilized, day 2 embryo transfer grade 3, no pregnancy
2	37	4	42.3	Transfer to another clinic
3	38.7	31	43.1	15 oocytes thawed, 5 survived, 3 embryos grade 3 transferred, not pregnant
4	40	16	44.3	1st cycle: 16 oocytes thawed, 14 survived, 9 fertilized, 2 blastocysts grade 2, 1 transferred and 1 frozen, no pregnancy 2nd cycle: Frozen-thawed blastocyst transfer, miscarriage at 8 weeks gestation
5	42.2	39	43.1	1st cycle: 14 oocytes thawed,12 fertilized with donor sperms, 4 grade 2 embryos transferred, not pregnant 2nd cycle: 16 oocytes thawed, 14 fertilized, embryos transferred, no pregnancy

the day of triggering was 6937.2±4923.4pmol/L. In the IVM group (4 cycles) the average age of the patients was 40.8 years, FSH 6.0mIU/ml and AFC 14 follicles. Most of the patients (n=65) opted to freeze oocytes only. Using frozen donor sperm from a bank, 2 patients froze both oocytes and embryos, but did not return for a transfer. After IVF and IVM, a total of 1486 oocytes were obtained; of which 1259 MII oocytes were vitrified (84.7%) (Table 2).

Five patients (7/5%) returned to the clinic to achieve a pregnancy. We obtained the outcome of 4 patients. Another had her oocytes transferred to another clinic and was lost from follow up. The outcome is demonstrated in Table 3. One of the 4 patients achieved a pregnancy, but ended in a miscarriage.

Discussion

Social fertility preservation offers an opportunity to conceive to a various psychosocial and single status groups of women. The most widely technique to retain the option for future children bearing the genetics of both spouses in a couple is oocyte cryopreservation. Although, embryo vitrification is the most established fertility preservation method, its use is confined to women who have male partners, or who are willing to use donor sperm [7,22-26].

In the past two decades, the advancement of vitrification technique has played a major role in ART and oocyte cryopreservation outcomes. It yields comparable pregnancy results to that achieved with fresh oocytes [27-29]. As previously reported [30,31], the number of patients returning to try to conceive with their cryopreserved oocytes was very low (7.5%). The reasons are unclear. Perhaps, those who attempt a pregnancy first prefer to exhaust all other resources before utilizing the cryopreserved eggs [32].

In agreement with previous reports [33-36], the mean age at cryopreservation was 38.6±3.6 years. This is fairly advanced for optimal results. Ideally, women considering social oocyte cryopreservation should do it in the late twenties or early thirties [37]. This will boost their chances of a biological motherhood. Stoop et al reported that 96.1% of oocyte bankers would recommend the procedure to their peers; and three quarter of them (76%) would prefer to do it at a younger age [32].

It seems likely that women in their 20s or early 30s are still optimistic about finding a partner and focusing their efforts on relationship building as opposed to family building. The primary motivation for fertility preservation is the women's single status, and they become aware of their biological clock at around the age of 38 years [38]. Due to the marked decrease in fertility and the quality of oocytes from the age 35 years, women should be counseled that cryopreserved oocytes after age of 35 years may not yield the desired outcome and that is a live, healthy baby. Before offering oocyte cryopreservation, women should be counseled thoroughly to mitigate a false sense of hope. Surveys addressing the acceptance of "AGE banking", showed that experts and younger population were more in favor of the procedure as compared to the greater level of ambivalence expressed by the older general population [3,39].

As Leridon suggested, after 2 to 4 years attempting to conceive without success, ART can only make up for half of the births lost by deferring attempts of pregnancy from age 30 to 35 years, and less than 30% of the loss after postponing from 35 to 40 years [40]. ART certainly does not overcome the decline in fecundity by age [40]. Age-related infertility should be seen as a medical issue and its prevention is the responsibility of health care professionals [4]. First line physicians including family doctors and general gynecologists should be discussing this option with their young female patients. Similarly, medical organizations must be proactive and are advised to encourage educational programs promoting fertility at an age of 20-35 years [31].

The motivation for egg freezing in our study is in agreement with others [32,40]. In our cohort, 38.8% of women expressed their desire to become future single mothers if they do not find a partner, and 17.9% would only use their gametes in a couple situation. Gold et al evaluated 20 women who electively cryopreserved their oocytes. They were all highly educated professionals, single and wanting to take the pressure off their relationships and their biological clock. Around a half of them showed desire to become future single mothers [40]. Stoop et al. found that among 86 oocyte banker, 50.8% would use their oocytes at some point, while 29.2% were less likely considering, compared to the time of oocyte retrieval [32].

To the best of our knowledge, this is one of the largest published report on social fertility preservation from a single institution. Other reports evaluated diverse indications or methods of fertility preservation and were for shorter periods of follow up [41-43]. We conclude that social fertility preservation after the age of 35 years is associated with poor outcome. Social fertility preservation should be considered at an early reproductive age.

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