Analysis of 2386 consecutive cycles of in vitro fertilization or intracytoplasmic sperm injection using autologous oocytes in women aged 40 years and above

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Objective: To estimate the live-birth and miscarriage rates in 1-year age increments for women aged ≥40 years undergoing in vitro fertilization or intracytoplasmic sperm injection (ICSI–IVF) with autologous oocytes.
Design: Retrospective database and chart analysis.
Setting: Egyptian IVF and embryo transfer center.
Patient(s): 1645 women aged ≥40 years undergoing 2004 fresh nondonor IVF–ICSI cycles.
Intervention(s): ICSI–IVF using ejaculate or surgically retrieved sperm.
Main Outcome Measure(s): Pregnancy and live-birth rates per initiated cycle based on 1-year age increments.
Result(s): The overall live-birth rate per initiated cycle was 6.7% (range: 10% to 0.5%). The pregnancy loss rate was 44.8% (range: 39.0% to 75.0%). The cutoff age was 43 years, when the pregnancy rate became statistically significantly lower. The live-birth rate per initiated cycle was statistically significantly higher for women <43 years old, 132 out of 1766 (7.4%) compared with women ≥43 years old, 7 out of 620 (1.1%). The miscarriage rate was 127 out of 295 (43.1%) compared with 15 out of 23 (65.2%) for the two age groups, respectively.
Conclusion(s): The success rate of ICSI–IVF as measured by live-birth rate per initiated cycle was statistically significantly higher for women aged <43 years as compared with women aged ≥43 years. Once women have attained age 43 years, alternative methods such as oocyte donation cycles or previously cryopreserved embryos are likely to be more effective. (Fertil Steril® 2009;■:■–■. ©2009 by American Society for Reproductive Medicine.)

Key Words: ART, autologous oocytes, ICSI, IVF, live birth, multiple pregnancy rates, spontaneous miscarriage, women aged ≥40

There has been great interest in the reproductive capacity of women in their late reproductive years. The number of women delaying childbearing into their fifth decade of life has markedly increased, and 50% of them will have some difficulty in their attempt to have children (1). In the United States, births for women between 40 and 44 years of age nearly doubled between 1990 and 2002. In women 45 to 49 years of age, the birth rate increased to reach 0.5 birth per 1000 women, but the majority of these births were likely attributable to the use of egg donation (2). In assisted reproductive technology (ART) programs, 19% of all women using ART in the United States are ≥40 years of age (3). In Europe during the year 2005, the percentage of women aged ≥40 years undergoing ART was 15.4% and 13% for in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) cycles, respectively (4). In the Middle East, 9.3% of all IVF–ICSI cycles performed during the year 2001 were for women aged ≥40 years (5). In one clinic in Israel, where the government covers most infertility treatment including IVF for the first two children with no limit to the number of treatment cycles up to the age of 45 years, 31% of patients undergoing oocyte retrieval were older than 40 years (6).

Both fecundity for spontaneous conception and ART success rates are markedly reduced with advanced maternal age (7, 8). The decline of fertility is mainly attributed to a decrease in egg quality. Fluorescence in situ hybridization (FISH) studies of oocyte aneuploidy have found that advanced maternal age is linked to a loss of sister chromatid cohesion, leading to a single chromatid abnormality (9). There is little evidence that uterine factors have a significant impact on age related infertility (10).

The declining fertility of women aged ≥40 years who are using their autologous oocytes is an individual event that cannot be predicted accurately before an ART cycle is undertaken. All available ovarian reserve tests (ORTs) detect the quantity rather than the quality of the follicular pool (11). Although an ORT may predict ovarian response to stimulation in older patients, and help in determining the dose of human menopausal gonadotropin (hMG) or follicle-stimulating hormone (FSH) and the protocol of stimulation to be used in these patients, it is a poor predictor of the pregnancy rate (12).

Though ART with donated oocytes has achieved a high pregnancy and childbirth rate for many women in their fifth and sixth decades of life (13), the procedure is associated with legal, ethical, cultural, religious, and logistic problems that have limited its universal acceptability in societies around the world (14, 15).

Alternative methods of fertility preservation such as vitrification of oocytes, embryos, or ovarian cortical tissues with subsequent

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transplantation (16, 17) for postponing childbirth until a later period are not yet widely practiced; they lack data on long-term consequences, and there are emerging ethical and social questions (18).

The Egyptian IVF and Embryo Transfer (ET) Center in Cairo provides ART services to married couples from Egypt, the Middle East, and a few other countries. A retrospective analysis of 2386 consecutive IVF–ICSI cycles performed at the center initiated in women aged ≥40 years who were using autologous oocytes has provided valuable information when counseling these patients.

MATERIAL AND METHODS

Our retrospective study used data from IVF–ICSI cycles using either ejaculated or surgically retrieved sperm, regardless of the infertility type or cause, performed in women aged ≥40 years at the Egyptian IVF-ET center during the period January 1, 2003, to September 30, 2008. The study was approved by the Egyptian IVF-ET Center institutional review board on September 15, 2008, and there were no conflicts of interest for any of the authors.

Total number of oocyte pickups (OPUs) performed was 21,002. We performed 2004 consecutive OPUs in 1645 women aged ≥40 years (9.5%). All cycles were fresh nondonor IVF–ICSI cycles. In the patients assessed, the cycle day 3 (CD3) FSH and E_2 levels were ≤20 mIU/mL and ≤50 pg/mL, respectively, and the antimüllerian hormone (AMH) level was ≥0.6 ng/mL.

Ovarian Stimulation

Controlled ovarian hyperstimulation (COH) was applied using long down-regulation or short flare-up protocols with gonadotropin-releasing hormone (GnRH) agonist and hMG or GnRH antagonist/hMG protocol, as previously described elsewhere (19, 20). The choice of the protocol and the hMG/FSH dose were based on the patient's previous response to gonadotropins; the levels of FSH, E_2, and AMH, if available; the patient's age at cycle initiation, body mass index, and previous ovarian surgery; and the physician's preference. The most common starting dosage of hMG was 300 mIU/day. Monitoring was started on day 6 of hMG stimulation with E_2 measurements and vaginal ultrasonography. Cancellation of the cycle was based on a combination of factors, such as the age of the patient, her previous response, the dosage of hMG/FSH administered, the E_2 level, and the number of follicles before hCG administration. Except in a few cycles, cancellation was considered when fewer than two follicles sized 18 to 21 mm developed and/or the E_2 level was <150 pg/mL before hCG administration.

Oocyte Pickup

Transvaginal ultrasound guided OPU was performed 36 hours after hCG administration. We performed IVF or ICSI with either ejaculated sperm or surgically retrieved sperm.

Zona Drilling and Oocytes Electrical Activation

In 98 cycles with poor prognosis, zona drilling or removal was performed. Electrical activation of oocytes after ICSI was performed in 56 cycles in patients who had severe oligoasthenospermia or nonobstructive azoospermia and had reported total failure or poor fertilization rate in previous cycles, as previously described elsewhere (21).

Embryo Transfer and Luteal Support

Embryo transfer was performed on cleavage-stage day 2 or 3. The number of embryos transferred was guided by the available number and quality of embryos, outcome of ET in previous cycles (if available), and the guidelines of the institution and American Society for Reproductive Medicine (22). All available good quality embryos (with a maximum of five embryos) were transferred in 1700 ET (94.8%). Cryopreservation was performed in 83 cycles (5.2%) when more than five good quality embryos were available on the day of ET. All patients received daily luteal phase support, as previously described elsewhere (23), in the form of 50 mg/IM of progesterone in oil (prontogest; Nile Company, Cairo, Egypt) or 400 mg of vaginal progesterone (cyclogest; Multipharma, Cairo, Egypt) beginning the day after OPU and continued for 3 weeks after a positive β human chorionic gonadotropin (β-hCG) test.

TABLE 1

Patient characteristics and overall cycle outcomes in 2386 initiated cycles in women aged ≥40 years.

Characteristic	Outcome
No. of patients	1645
Age of patients	40–48 years (41.38 ± 1.2)
Year of infertility	11.46 ± 3.9
No. of cycles initiated	2386
Cancellation rate	16% (382)
hMG ampules	55.09 ± 21.6
Days of stimulation	11.21 ± 3.6
No. of oocytes retrieved	6.6 ± 2
2 pronuclei (2PN)	3.9 ± 1.1
E_2 on day of hCG	243.61 ± 980.75
Embryo transfer cancellation rate	11% (221)
No. of embryos transferred	3.6 ± 1.3
No. of cryoembryos	3.6 ± 0.2
Positive β-hCG/embryo transfer	23.9% (425)
Pregnancy rate/initiated cycle	13.4% (318)
Miscarriage rate	44.8% (113)
Live-birth rate/initiated cycle	144 (6.7%)

Serour. 2386 IVF/ICSI cycles in women ≥40 years. Fertil Steril 2009.

Follow Up

Follow up was accomplished by chart review, mailed questionnaires, and telephone communication for additional information. Patients who got pregnant and delivered a live birth received follow-up evaluations up to 1 month after delivery. The live-birth rate per initiated cycle based on 1-year age increments was the primary outcome measure.

The overall pregnancy rate stratified by 1-year age increments and the rate of spontaneous abortion, ectopic pregnancy, and multiple pregnancies was also calculated.

Statistical Analysis

Statistical analysis was performed according to the intention-to-treat principle. All analyses of significance were two sided and tested at the 5% level; $P<.05$ was considered statistically significant.

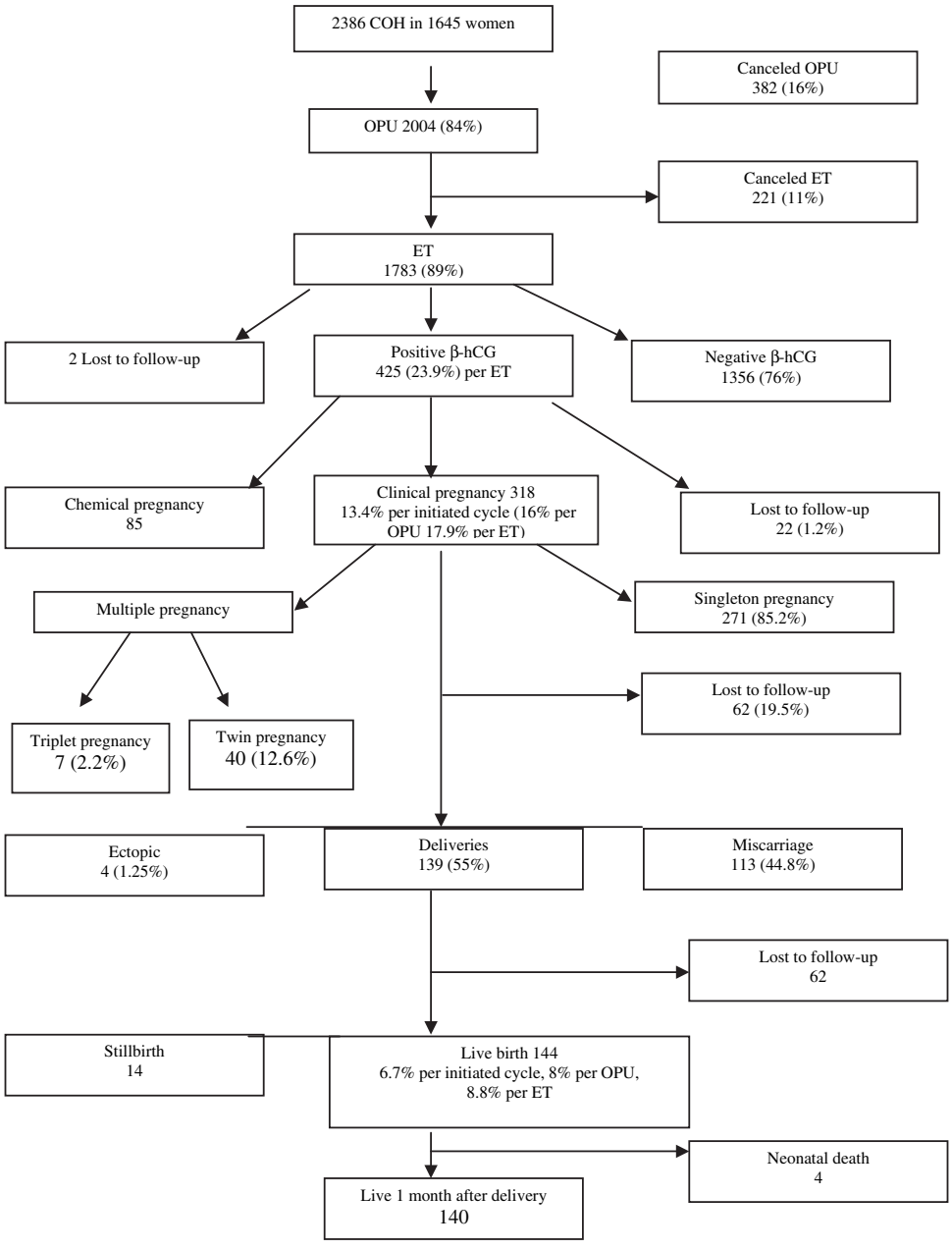
Qualitative variables were compared with chi-square test with Yates correction or Fisher's exact test, when necessary, and the 95% confidence intervals (95% CI), using the Woolf (logit) approximation. The odds ratio (OR) and 95% CI were calculated to examine the odds of improving clinical outcomes. Statistical analysis was performed using the computer statistical package StatsDirect (StatsDirect Ltd, Cheshire, United Kingdom).

RESULTS

We initiated 2386 cycles in 1645 infertile women aged ≥40 years. The indications for ART in these 1645 women were male infertility, tubal factor infertility, endometriosis, unexplained infertility, or combined factors. Only 2004 cycles proceeded to OPU. In 382 cycles (16%), OPUs were canceled due to poor response. The age of the patient in these 2004 OPUs at cycle initiation ranged from 40 to 48 years (mean 41.38 ± 1.2 years). Of these, 1588 cycles (79%) were in women aged 40 to 42 years, and 99 cycles (4.9%) were in women aged ≥45 years. In 950 cycles (47.9%), data on CD3 FSH levels were available, including all women aged ≥42

FIGURE 1

Flowchart of outcomes for 2386 initiated cycles in women aged ≥40 years.



Serour. 2386 IVF/ICSI cycles in women ≥40 years. Fertil Steril 2009.

years and women <42 years if they had a history of irregular cycles, previous poor response, or ovarian surgery. The CD3 FSH levels varied between 6.4 mIU/mL and 20 mIU/mL (normal range in the assay used: 2.5–10.2 mIU/mL). In 14% of cycles, the CD3 FSH level was above the upper range of normal. The median CD3 FSH level was 8.9 mIU/mL. Data on the AMH level was available for 214 cycles (10.6%), and it varied between 0.6 ng/mL and 2 ng/mL (normal range in the assay used: 1–10 ng/mL). In 5.6% of cycles, the AMH level was below 0.6 ng/mL. The median AMH level was 1.2 ng/mL. The patients' characteristics and overall cycle outcomes are shown in Table 1.

Figure 1 shows the flowchart of the outcome of the 2386 initiated cycles up to 1 month after delivery. The 318 clinical pregnancies resulted in 271 (85.2%) singleton, 40 (12.6%) twin, and 7 (2.2%) triplet pregnancies. In the singleton pregnancies, the live-birth rate was 45%, miscarriage rate 49%, and stillbirth rate 6%. In twin pregnancies, the miscarriage rate was 20%, and the live-birth rate was 80%. In the seven triplet pregnancies, multifetal pregnancy

TABLE 2

Cycle outcomes based on 1-year age increments for women aged ≥40 in 2386 IVF/ICSI cycles.

Outcome	Age (years)						Total
	40	41	42	43	44	≥45	
No. of initiated cycles	742	595	429	251	150	219	2386
Number of pickup cycles	673	536	379	206	111	99	2004
Cancellation rate	9.3%	10%	12%	18%	26%	55%	16%
No. of embryo transfer cycles	601	480	337	178	101	86	1783
Positive β-hCG	190	125	61	32	12	5	425
No. of clinical pregnancies	148	92	55	16	4	3	318
Clinical pregnancy rate per pickup	22.4%	17.2%	14%	7.8%	3.6%	3	17.9
Miscarriage rate	39%	44.4%	51.3%	64.3%	75%	67%	44.8%
No. of deliveries	72	40	20	5	1	1	139
Live birth per initiated cycle	10%	7%	5%	2%	0.7%	0.5%	6.7%
Live birth rate per oocyte pickup	11%	7.5%	5.3%	2.4%	0.9%	0.5%	8%
Live birth per embryo transfer	12%	8.5%	5.9%	2.8%	1%	1.1%	8.8%

Serour. 2386 IVF/ICSI cycles in women ≥40 years. Fertil Steril 2009.

reduction was performed at 6 to 7 weeks' gestation after counseling the couple.

Data generated from all 2004 OPUs subdivided by 1-year age increments for the women aged ≥40 years are presented in Table 2. The cancellation rate increased from 9.3% at age 40 years to 55% at age ≥45 years. Younger age at cycle initiation was associated with an increased pregnancy and live-birth rate per initiated cycle, OPU, and ET. The live-birth rate was statistically significantly higher for ages below 43 years than ≥43 years ($P<.0001$) (Table 3).

DISCUSSION

Despite the low pregnancy and live-birth rates in women aged ≥40 years who were using autologous oocytes, the percentage of these infertile women asking for this line of treatment in IVF programs is increasing, particularly in countries where egg donation is a cultural, religious, or ethical issue that limits or prohibits its application. However, access to innovative techniques for vitrification of oocytes or ovarian tissue with subsequent transplantation (16, 17, 24) is still limited to carefully designed research settings where efficacy and outcomes can be assessed (25), and thus it is not offered to women to preserve their fertility potential when there is no immediate threat to their fertility (25–27).

Age of the woman is the most important factor in determining pregnancy success rates, whether in natural conception or after ART. For example, in an isolated community of Hutterites, the average age of last birth was 40.9 years in women who attempted pregnancy until it was no longer possible (28). In a relatively isolated ultraorthodox Jewish community in Jerusalem where there is

TABLE 3

Age cutoff value selected as 43 years for delivery and miscarriage rates.

Item	40–43 years	≥43 years	Significance
Miscarriage	127/295 (43.1%)	15/23 (65.2%)	Odds ratio 2.48 95% CI (logit method), 1.02–6.03 $P=.04$
Live birth per initiated cycle	132/1766 (7.4%)	7/620 (1.1%)	Odds ratio 7.14 95% CI (logit method), 3.32–15.36 $P<.0001$
40 vs. 41	72/742 = 10%	40/595 = 7%	Odds ratio 1.49 95% CI, 0.99–2.23 $P=.06$
41 vs. 42	40/595 = 7%	20/429 = 5%	Odds ratio = 1.47 95% CI, 0.84–2.55 $P=.17$
40 vs. 42	72/742 = 10%	20/429 = 5%	Odds ratio 2.08 95% CI, 1.25–3.46 $P=.004$

Note: $P<.05$ was considered statistically significant.

Serour. 2386 IVF/ICSI cycles in women ≥40 years. Fertil Steril 2009.

a strong societal pressure to reproduce for as long as possible, only 0.2% women spontaneously conceived and delivered on or after the age of 45 years (29). Although pregnancy and childbirth at older ages may occur in natural conception after repeated and prolonged exposure for many cycles, it cannot be compared to ART cycles, where fertility is tested in one cycle or a few cycles at most. Furthermore the physical, emotional, and financial burdens of ART on the couple cannot be ignored.

Most data on ART outcome in women aged ≥40 years are derived from multicentric studies, or national or regional registries which by nature include disparate data, different selection criteria, variable protocols and techniques, and often are not stratified by year (3–5). A few large studies have been published (6, 30, 31). Our study is one of the largest studies, a single center experience in 2386 initiated cycles of IVF–ICSI in 1645 women aged ≥40 years that resulted in 2004 consecutive OPUs. The cancellation rate was 16% per initiated cycle, which is similar to the 16.6% in 1217 cycles reported by Tsafrir et al. (6). Klipstein et al. (31) reported a higher cancellation rate of 19.9% in 2705 cycles. Our study showed that there was a linear increase in the cancellation rate at 1-year age increments, with a sharp rise of cancellation rate at age 45 and above.

Our overall clinical pregnancy rate was 13.4%, and the live-birth rate was 6.7% per initiated cycle. Klipstein et al. (31) reported a pregnancy rate of 14.8% and a live birth rate of 9.7% per initiated cycle. The high live-birth rate in the Klipstein study could be explained by the lower median value of CD3 FSH of 7.5 mIU/mL, compared with 8.9 mIU/mL in our study. Not a single pregnancy occurred in our study when the CD3 FSH level was more than 19.8 mIU/mL. Among those who got pregnant, the median CD3 FSH was 7.55, 7.1, 7.5, 9.1, 6.7, and 10.7 mIU/mL for women aged 40, 41, 42, 43, 44, and ≥45, respectively. In all these patients, the CD3 E_2 level was ≤50 pg/mL. Tsafrir et al. (6) reported a lower pregnancy rate of 7.3% and a live-birth rate of 4.7% per initiated cycle. This could be explained by the higher percentage of patients aged >42 years (45.5%) in their study as compared with only 21% in our study.

The overall pregnancy loss rate in our study was 44.8%. The pregnancy loss increased with the increase in maternal age at initiation of the cycle, reaching 75% at 44 years of age. Klipstein et al. (31) reported a lower overall pregnancy loss rate of 32.6%.

In the Klipstein study, low CD3 FSH values were associated with a higher live-birth rate ($P<.01$) and a lower pregnancy loss rate ($P=.03$), adjusting for the woman's age at cycle start (31). The median CD3 FSH value in our study, as measured in 47.9% of cycles, was higher (8.9 mIU/mL) than in the Klipstein study (7.5 mIU/mL), where it was measured in 53% of cycles. Klipstein's group found a trend toward increased loss rate with rising CD3 FSH values, and the pregnancy loss rate tended to be lower when the CD3 FSH was below 8 mIU/mL, compared with higher values of 10–12 mIU/mL ($P=.07$) or FSH >12 mIU/mL ($P=.07$).

The miscarriage rate in our study for the multiple pregnancies was 20%, which was statistically significantly lower than the miscarriage rate of 49% in the singleton pregnancies. Pregnancies after multiple implantations or cycles with a large number of embryos available for transfer were more likely to deliver at least one liveborn infant when compared with age-matched controls who had a singleton pregnancy, as documented by fetal cardiac activity at the 7-week vaginal ultrasound examination (6, 31). The relatively high multiple pregnancy rate in our study (12% for twins and 2.2% for triplets) was due to the transfer of three or more embryos in 47% of cycles.

Our study clearly shows that women aged ≥40 years are not a homogenous group when it comes to ART outcomes. One-year increments in the women's age at initiation of the IVF/ICSI cycles markedly increased the cancellation rate and pregnancy loss rate, and decreased the live-birth rate; the cutoff age was 43 years when the pregnancy rate became statistically significantly lower. Wang et al. (32) had shown that in women aged ≤42 years the proportion of delivery was higher than the proportion of spontaneous abortion, while from age of 43 onward, proportionally more spontaneous abortions (66.7%) than deliveries (29.5%) were observed.

The outcome of the IVF–ICSI cycles in our study showed that it is not clinically appropriate to initiate an IVF–ICSI cycle once the patient is 43 years old. In our study, five live births resulted from the 251 initiated cycles at age 43, one live birth from the 150 initiated cycles at age 44, and one live birth from 219 initiated cycles at age ≥45. Considering that the average cost of an IVF–ICSI cycle is U.S.$2000 in most of the private centers in Egypt, the cost of one live birth at ages 43, 44, and ≥45 is approximately U.S.$100,000, 300,000, and 438,000, respectively. This equals 20-fold to 90-fold the gross national income per capita of U.S.$4940 for the year 2006 in Egypt (33). Henne et al. (34) have shown that, in the United States at a live-birth rate <5%, the cost of ART is high and greatly exceeds the cost of donor cycles. The cost rose exponentially at lower probabilities of live birth.

Although storage of embryos to postpone childbirth is possible for a small proportion of women who are married or have a stable relationship, the increasing success of oocytes and ovarian tissue cryopreservation and transplantation offers the potential for a broader range of options in the future to (16, 24). However, based on all available data, oocyte cryopreservation is still not clinically applicable except with institutional review board approval and is not to be used socially for fertility preservation because of concerns as to its efficacy and safety (25–27). Recently, Homburg et al. (35) argued that we do need to readdress female fertility preservation for delaying childbirth to an older age now that we have the technology to do so (35). Until this new technology becomes widely available, our study has shown a reasonable live-birth rate (7.4%) per initiated cycle is possible for women up to ages 40 to 43 years. Clinics should not turn these patients away and should counsel them properly. Couples will have to make their own informed decisions based on the detailed information provided to them. If the physician has a conscientious objection to alternative treatments such as egg donation, it is his or her obligation to refer the couple to other clinics where they may obtain this evidence-based treatment (36).

The chances of women ≥40 years becoming pregnant via ART decline every year, especially after the age of 43 years. For physicians to refuse treatment on the arbitrary basis of age alone in women younger than 43 years is illogical. Patients who have a good response in their first attempt should be encouraged to have repeat cycles. Women aged ≥43 years should be discouraged from undergoing IVF in favor of egg donation if it is ethically and culturally acceptable. Use of the woman's own vitrified oocytes or transplantation of cryopreserved, thawed ovarian cortical tissues are promising future alternatives.

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