Cumulative pregnancy and live birth rates through assisted reproduction in women 44–45 years of age: is there any hope?

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Abstract

Purpose The purpose of the study is to calculate the cumulative pregnancy rate and cumulative live birth rate in women undergoing in vitro fertilization (IVF) at ages 44–45.

Methods The study calculated cumulative live pregnancy rate and cumulative live birth rate of 124 women aged 44 to 45 years old who commenced IVF treatment.

Main outcome measures The main outcome measures are cumulative live pregnancy rate and cumulative live birth rate.

Results Cumulative live pregnancy rates following 1, 2, 3, and 4 cycles were 5.6, 11, 17, and 20%, respectively, with no additional pregnancies in further cycles. Cumulative live birth rates following 1, 2, and 3 cycles were 1.6, 3, and 7%, respectively, with no additional live births in further cycles.

Conclusions The cumulative pregnancy rate rises during the first 4 cycles and cumulative live birth rate rises during the first 3 cycles, with no additional rise in pregnancies or deliveries thereafter, suggesting that it is futile to offer more than 3 cycles of treatment to 44–45-year-old women.

Keywords Assisted reproductive technology · Low ovarian reserve · Cumulative pregnancy rate · Cumulative live birth rate

Background

The average women's age at child bearing shows a trend of increasing in Western countries. Accordingly, the treatment of women at advanced maternal age is one of the challenges of reproductive medicine today. The upper age limit for in vitro fertilization (IVF) treatments differs from one country to

another and is influenced not only by medical reasons but also by financial and ethical ones [1, 2].

Most studies focusing on maternal age and assisted reproductive technology (ART) supply crude data on clinical pregnancy rates per cycle.

Hourvitz et al. [3] reported on clinical pregnancy rates per cycle of 7.7, 5.4, and 1.9% for 42, 43, and 44 years old,

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respectively. These data reflect the retrospective overall IVF results of clinical pregnancies at advanced maternal age in a specific medical center.

Smith et al. [4] retrospectively showed that for women aged 40–42, the live birth rate for the first IVF cycle was 12.3% with 6 cycles achieving a pregnancy-adjusted live birth rate of 31.5%. For women older than 42 years, all rates within each cycle were less than 4%.

Most studies on ART examine live birth rate per cycle. However, this data fails to predict the probability of successful pregnancies in successive cycles after failure of a previous treatment, which could show cumulative pregnancy and live birth rates. For patients, data on the cumulative probability of pregnancy/live birth are highly informative [5], yet there is not enough data on cumulative live birth rate [4, 6–8].

Fertility treatments in Israel are publicly funded till the age of 45, and the debate on proper age cutoff for publicly funded IVF treatments is ongoing.

The aim of this study was to determine, solely on medical considerations, the extent to which repeated IVF cycles continue to increase the likelihood of pregnancies and live births and thus to better counsel our patients on whether to continue ART treatment or to seek for other treatment options.

Materials and methods

Study design, setting, and participants

This retrospective, single-center cohort study reviewed women aged 44–45 years old, who attended the Wolfson Medical Center IVF unit from March 1997 to December 2015 (with outcomes assessed up to June 2016).

All patients underwent a thorough infertility investigation for autologous IVF treatments. All patients who underwent egg donation cycles or used gestational carriers were excluded.

Stimulation protocols for the induction of follicular growth were used in the majority of patients. A long protocol of gonadotrophin-releasing hormone analogue (GnRHa) followed by recombinant FSH (rFSH) or menotropins was used in 66 cycles (22.6%). A short “flair up” protocol of GnRHa followed by rFSH or menotropins was used in 86 cycles (29.5%). GnRH antagonist protocol was used in 88 cycles (30.1%). Thirteen cycles (4.4%) were natural cycles, 35 cycles (12%) were modified natural cycles, and 4 cycles (1.4%) were other protocol cycles. The stimulated cycles were individually adjusted according to ultrasonographic measurements of follicles combined with hormonal levels of estradiol and progesterone.

Human chorionic gonadotropin (hCG) was administered when an 18-mm follicle or more was observed by transvaginal ultrasound. Approximately 36 h after hCG administration,

harvesting of oocytes was achieved by transvaginal ultrasound-guided follicular puncture. Conventional insemination or intracytoplasmic sperm injection (ICSI) was performed as indicated. Most embryos were transferred on days 2–3 (cleaved embryos). Only five patients had a blastocyst transfer on day 5. Progesterone supplementation was given to all women either by vaginal ovules of Utrogestan (*Besins Healthcare, Belgium*) 200 mg, or Endometrin (Ferring, Switzerland) 100 mg daily, 3 times per day.

Pregnancy was defined as a serum hCG concentration above 100 IU/l on day 14 after transfer. The visualization of fetal heart beat by ultrasound defined a clinical pregnancy.

Ethical approval

Ethical approval for this study was provided by a local Helsinki committee at Wolfson Medical Center.

Study outcomes

The following patient and cycle criteria were studied: gynecologic and obstetric history, infertility history (total number of IVF trials, number of IVF trials since last IVF pregnancy, years of infertility, reason for infertility), FSH, AFC, and cycle characteristics (protocol type, gonadotropin dose, E2/progesterone and endometrial thickness on hCG administration day, number of oocytes retrieved/fertilized, fertilization method IVF/ICSI, number of embryos transferred, day of transfer, number of abortions and deliveries).

Statistics

Data were analyzed using SQL queries software version 11.0.5058.0, SPSS and GraphPad software. For values not normally distributed, we used the Mann-Whitney *U* test calculator.

The pregnancy rate and live birth rate were calculated as the proportion of cycles resulting in pregnancy or live birth, respectively, out of all cycles.

Pregnancy/live birth rate per cycle was calculated by dividing the number of patients who achieved pregnancy/live birth in each cycle by the number of patients who initiated that cycle.

Cumulative pregnancy/live birth rate per cycle is the number of pregnancies/live births that had been achieved from the first to the current cycle divided by the initial number of patients, assuming no patient dropout. Calculating the cumulative pregnancy/live birth rates of all cycles up to and including the calculated cycle was challenging, since there is no actual data about patients dropping out of ART. In order to estimate the potential success rates of these dropout patients, we used two assumption methods (optimal and conservative, as previously described by Andrew Smith et al. [7]), regarding women

who discontinue IVF without a pregnancy/live birth, up to the sixth cycle, using the Kaplan-Meier method.

The optimal assumption suggests that the pregnancy/live birth rate of the dropout patients is similar to that of patients who continued to the successive cycle, while the conservative assumption suggests that the pregnancy/live birth rate of dropout patients was 0, i.e., all the dropout patients had poor prognosis in ART.

There were various reasons for dropout such as cultural reasons, psychological reasons, estimated poor prognosis, and others. The optimal estimation assumes that the pregnancy/live birth rate in women who discontinued an IVF cycle without achieving pregnancy would have been equal to the pregnancy/live birth rate in women who continued to the next IVF cycle, if they in fact had continued—this would in turn give favorable results. The conservative estimation assumes that the pregnancy/live birth rate in women who discontinue IVF without a pregnancy would have been 0, if they in fact had continued. The conservative assumption thus assumes that the reason for discontinuation of treatment was poor prognosis.

Results are presented as mean $\pm$ standard deviation; $p < 0.05$ was considered significant.

Further follow-up of patients' pregnancy outcomes was performed by phone.

Results

During the period March 1997 to December 2015, a total of 292 treatment cycles at age 44–45 were performed in 124 patients. Table 1 shows the preliminary ovarian reserve estimation and the cycle characteristics in conceptus and non-

conceptus women. As seen in this table, cycle characteristics were similar in conceptus and non-conceptus cycles.

One third of embryo transfer cycles were with sperm donation. In all these cases, donor sperm was used starting with the first cycle, i.e., there were no cases of partner sperm switch to donor sperm.

In patients who underwent embryo transfer, we did not demonstrate a statistically significant difference between conceptus and non-conceptus cycles in any of the patient/cycle characteristics (gonadotropin units, length of stimulation, peak E2 and *P* levels on day of hCG, number of oocytes retrieved, fertilization rate, number of embryos transferred).

Table 2 shows patient characteristics and outcome of the in vitro fertilization cycles: 16 pregnancies and 5 live births. The clinical pregnancy rate and live birth rate per started cycle were 5.5 and 1.7%, respectively. The clinical pregnancy rate and live birth rate per patient in this age group were 13 and 4%, respectively. The miscarriage rate was 69%.

It is interesting to note that out of 16 successful pregnancies, only four occurred following a single embryo transfer while 12 were achieved by ET of more than one embryo.

Five women delivered in this study, four as a result of a day 3 ET and one as a result of a day 2 ET. All deliveries were singleton. Four were delivered via uncomplicated cesarean section and one was an uncomplicated vaginal delivery. Four deliveries were at term and the remaining one was at 36 weeks of gestation. Birth weights ranged between 2635 and 3380 g.

Out of the 11 pregnancies that ended in abortions, five were chemical, five ended in the first trimester, and one was a blighted ovum. None of the abortions occurred beyond the first trimester.

Table 1 Ovarian reserve estimation and cycle characteristics of ART in 44–45-year-old women: conceptus or non-conceptus cycles

	Conceptus <i>n</i> = 16	Non-conceptus <i>n</i> = 179	<i>p</i> value
Preliminary AFC (number)	5.25 $\pm$ 1.83	5.15 $\pm$ 2.6	0.72
Preliminary FSH (IU/l)	9.1 $\pm$ 5.9	9.2 $\pm$ 3.3	0.4
Number of gonadotropin units used	4500 $\pm$ 1196	4158.6 $\pm$ 1639	0.21
Duration of stimulation (days)	8 $\pm$ 2.4	10.4 $\pm$ 3.5	0.35
Peak E2 levels on day of hCG administration (pmol/l)	2318 $\pm$ 2391	2497 $\pm$ 2679	0.43
Progesterone levels on day of hCG administration (nmol/l)	1.1 $\pm$ 1.18	1.4 $\pm$ 1.47	0.13
Number of oocytes retrieved	5.4 $\pm$ 13.6	5 $\pm$ 13.6	0.48
Fertilization rate (%)	77 $\pm$ 24	71 $\pm$ 25	0.48
Number of embryos transferred	2.5 $\pm$ 1.2	2.4 $\pm$ 1.2	0.79

Data presented as mean $\pm$ SD

Data in this table is calculated out of all cycles with embryo transfer

Table 2 Patient characteristics, IVF performance, and pregnancy outcome of 44–45-year-old women

Characteristic	Value
Number of patients	124
Number of cycles	292
Average duration of infertility (years)	
All cohort	6.5 (0.4–24)
Achieved pregnancy	5.3 (0.5–16)
Achieved delivery	6.8 (0.5–16)
Cause of infertility	
Low ovarian reserve only	79/292 (27%)
LOR combined with other causes of infertility	41/292 (14%)
Male factor only	52/292 (18%)
Mechanical factor only	41/292 (14%)
Unexplained infertility	32/292 (11%)
Mechanical + MF	18/292 (6%)
Other (uterine, thrombophilia, immune, recurrent abortion, RIF) (10%).	29/292 (10%)
Cancellation rate	45/292 (15.4%)
Low ovarian response	21/292 (7.2%)
Early luteinization	16/292 (5.5%)
Patient request/patient low compliance	8/292 (2.7%)
Pregnancy rate	
Per cycle	16/292 (5.5%)
Per embryo transfer cycles	16/195 (8.2%)
Live birth rate	
per cycle	5/292 (1.7%)
per embryo transfer cycles	5/195 (2.56%)

Data presented as mean $\pm$ SD and ratio (percentage) as appropriate

Table 3 and Fig. 1 show the cumulative pregnancy rate of women at age 44–45 in IVF, and Table 4 and Fig. 2 show the cumulative live birth rate of the same age group in IVF.

Discussion

It is well known that the pregnancy rate for IVF patients aged 44–45 is low and that the live birth rate is even lower. It is also

Table 3 Cumulative pregnancy of 44–45-year-old women across IVF treatment cycles

Cycle number	Number of patients treated per cycle	Number of pregnancies per cycle	Pregnancy rate per cycle [%]	Cumulative pregnancy rate across all cycles using different estimates	
				Optimal estimation ^a	Conservative estimation ^b
1st	124	7	5.6	5.6	5.6
2nd	81	5	6.2	11.4	9.7
3rd	47	3	6.4	17.1	12.1
4th	28	1	3.6	20.1	12.9
5th	9	0	0	20.1	12.9
6th	3	0	0	20.1	12.9

^a Optimal estimation: Takes into consideration that the cumulative pregnancy rate in women, who discontinue IVF without a pregnancy, would have been equal to the rate in women who continued to further IVF, if they had continued. Thus, the reason for discontinuation was personal decision rather than poor prognosis

^b Conservative estimation: Takes into consideration that the cumulative pregnancy rate in women, who discontinue IVF without a pregnancy, would have been zero, if they had continued. Thus, the reason for continuation was poor prognosis

Fig. 1 Cumulative pregnancy rate of 44–45-year-old women across IVF treatment cycles

known that the live birth rate by the alternative treatment—egg donation—is prominently higher. Without considering cost of the IVF cycles, we tried to find the cutoff IVF cycle number beyond which no additional live births were achieved.

We found that in 44–45-year-old women undergoing IVF, the pregnancy rate was 5.5%, the live birth rate was 1.7%, and the miscarriage rate was 69%. Similar outcomes were demonstrated in a previous article by Orvieto et al. [9].

We found that the optimal cumulative pregnancy rate in this age group rises to 20% after 4 cycles and the cumulative live birth rate rises to 7% after 3 cycles. There is no additional rise with further cycles.

The conclusions of Smith et al. [4] in a recent publication support the extension of the number of IVF cycles beyond 3 or 4; however, the median age of their patients was 35. The smallest group in the study was those patients aged over 42, in which all rates were less than 4%. Thus, there is no real contradiction between our conclusions, since we evaluated a subgroup with a worse prognosis than the patients participating in Smith's study.

We showed that in the first 3 cycles, the pregnancy rate was quite similar (5.6–6.4%) while out of 28 women who underwent a fourth cycle, only one achieved a pregnancy (3.6%) which ended in an abortion with no further pregnancies in later treatments.

We conclude that the chance of conceiving after the third treatment is dramatically low. We speculate that the similar rates in the first 3 cycles represent variable treatment regimens that might achieve better results while cycles beyond the third cycle actually represent the patient's poor personal profile and poor prognosis.

If a similar trend appears in larger studies, it might be logical to recommend that patients who have not conceived after three IVF cycles at age 44–45 years should turn to egg donation as the only option.

Hourvitz et al. [3] studied a group of 87 (154 cycles) women aged 44 in which 5 conceptions (3.2) and only 1 delivery (0.6%) were achieved. They concluded that IVF treatment should be limited to patients not older than 43 with adequate

Table 4 Cumulative live birth rate of 44–45-year-old women across IVF treatment cycles

Cycle number	Number of patients treated per cycle	Number of live birth per cycle	Live birth rate per cycle [%]	Cumulative live birth rate across all cycles using different estimates	
				Optimal estimation ^a	Conservative estimation ^b
1st	124	2	1.6	1.6	1.6
2nd	81	1	1.2	2.8	2.4
3rd	47	2	4.2	7	4
4th	28	0	0	7	4
5th	9	0	0	7	4
6th	3	0	0	7	4

^a Optimal estimation: Takes into consideration that the cumulative pregnancy rate in women, who discontinue IVF without a pregnancy, would have been equal to the rate in women who continued to further IVF, if they had continued. Thus, the reason for discontinuation was personal decision rather than poor prognosis

^b Conservative estimation: Takes into consideration that the cumulative pregnancy rate in women, who discontinue IVF without a pregnancy, would have been zero, if they had continued. Thus, the reason for continuation was poor prognosis

Fig. 2 Cumulative live birth rate of 44–45-year-old women across IVF treatment cycles

ovarian response, and noted the marked decline in clinical pregnancy rates, delivery rates, and the increase of abortions with advanced woman age. Our data suggests a different perspective based on cumulative rates, demonstrating a cumulative pregnancy rate of 13–20% (adjusted-optimal) and live birth rate of 4–7%, despite a pregnancy rate of 5.5% and live birth rate of 1.7%. This demonstrates the benefit of up to 3 cycles in 44–45-year-old women. We are aware that the percentages are low and better alternative treatments exist. However, if the patient's request is to continue IVF treatments with autologous eggs, our data may better counsel our patients when to move forward to alternative treatments rather than accede to our patients' demand for an additional treatment.

There are several possible reasons for discontinuation of treatment in women who have not achieved pregnancy and live birth: a poor prognosis as explained by the consulting physician, emotional reasons, relationship problems within the family, low compliance, and financial reasons (not common in Israel where IVF treatments are free at this age up to 2 children). This is the reason why we calculated optimal and conservative values, as suggested by Smith et al. [4]. Though it might seem surprising that the optimal cumulative pregnancy rate is 20% after 4 cycles and cumulative live birth rate is 7% after 3 cycles, it is important to emphasize that the calculation of optimal cumulative pregnancy rate is based on the assumption that had all the women who discontinued IVF without a live birth continued treatments, their pregnancy/live birth rate would be equal to those women who actually continued treatment. The conservative cumulative pregnancy rate and live birth rate (4 and 13%, respectively) are based on the assumption that had all the women who discontinued IVF without a live birth continued treatments, they would have achieved no pregnancies/live births.

In fact, the group of patients who discontinued treatment is heterogeneous (including a mixture of patients with relatively good and bad prognoses). Thus, the correct cumulative live pregnancy rate and cumulative live birth rates are in between the conservative and the optimal cumulative values (4–7 and 13–20%, respectively).

Conclusions

In the present study, we conclude that the chance of conceiving in the population of 44–45-year-old patients undergoing ART treatments, after the third treatment, is very low and most probably additional treatments are futile. This allows us to better counsel our patients when to move forward to alternative treatments, especially if our patient's demand an additional treatment. Our findings support limiting the number of IVF cycles in the population of 44–45-year-old patients to 3 cycles. These findings may impact the counseling of couples considering IVF treatment.

The study strengths include a relatively large number of 44–45-year-old cycles. The study was conducted in one center only, with uniform treatment policies and laboratory protocols. Universal compensation for IVF treatments almost excludes financial consideration as a factor in continuing treatment and a cultural influence toward high fecundity encourages women to continue treatments. Sixty one of embryo transfer cycles were with sperm donation (31%) reducing the effect of male factor infertility on the results.

The study's limitations include its being a retrospective study of a relatively long duration of data accumulation. These limitations indicate the need for more studies on 44–45-year-old women undergoing ART treatments.

Compliance with ethical standards Ethical approval for this study was provided by a local Helsinki committee at Wolfson Medical Center.

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