Fertility Treatment in the Forty and Older Woman¹

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Purpose: To determine the outcomes and logical progression of fertility treatment in women forty years and older using their own oocytes.

Methods: This was a retrospective study in which 401 completed treatment cycles in 152 women aged forty and older were reviewed.

Results: Assisted reproductive technology (ART) cycles (n = 58) were reviewed, comprising both in vitro fertilization (IVF) and gamete intrafallopian transfer (GIFT). Intrauterine insemination (IUI) cycles (n = 343) were reviewed, consisting of 38 unstimulated natural cycle-IUI (NC-IUI), 194 clomiphene citrate-IUI (CC-IUI), and 111 injectable gonadotropins-IUI (INJ-IUI) cycles.

The live birth rate of 15.5% for ART cycles was significantly higher than the live birth rate of 3.2% seen for all IUI cycles ($p = 0.0007$). There were no differences among treatment groups in spontaneous abortion, preterm delivery, or ectopic pregnancy rates.

Conclusions: For women ≥ 40 years of age who wish to use their own eggs, ART offers the best chances for conception and delivery.

KEY WORDS: advanced reproductive age; assisted reproductive technology; intrauterine insemination; ovulation induction.

INTRODUCTION

It is well-known that advancing age has a negative effect on the success of fertility treatment in women.

There is a marked decline in fecundity that occurs many years before menopause (1), beginning around age 35 and becoming more marked at age 38–40. With increasing age, there is a decrease in oocyte quality (2,3), follicular response to gonadotropins and implantation rate (4), and an increase in the spontaneous abortion rate (5). These effects are more pronounced in the patient who is 40 or older. In the absence of bilateral tubal occlusion, treatment in the younger patient can begin with empiric therapy consisting of intrauterine insemination (IUI) coupled with ovarian stimulation. This may start with the less expensive clomiphene citrate (CC), followed by controlled ovarian hyperstimulation (COH) using injectable gonadotropins (INJ), and finally progresses to assisted reproductive technologies (ART). Previous studies (6–8) have evaluated these treatments individually in the >40-year-old patient population, demonstrating a significant reduction in pregnancy rates compared with younger patients. However, the effectiveness of these treatments in the 40 and older population have not been evaluated in a single comprehensive study.

This study was performed to compare the results of different fertility treatments in women 40 years of age and older. The primary aim of this study is to generate evidence to determine the most effective progression of therapy for this patient population.

MATERIALS AND METHODS

This was a retrospective study that evaluated women who were treated in the Division of Reproductive Endocrinology, at the Washington University School of Medicine between January 1992 and June 1998. The medical records of those patients who were without pregnancy for 6 or more months at the initial consultation, and who were 40 years and older at the time of IUI or embryo transfer (ET) were reviewed.

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The treatments that they received were unstimulated natural cycle–IUI (NC-IUI), clomiphene citrate–IUI (CC-IUI), injectable gonadotropins–IUI (INJ-IUI), and assisted reproductive technologies (ART) comprising gamete intrafallopian tube transfer (GIFT) and in vitro fertilization (IVF). This study was exempt from institutional review board approval as it was retrospective and it was not possible to trace data collected back to individual patients.

Exclusion Factors

For IUI cycles, those patients with independent factors for decreased pregnancy were excluded. These factors were tubal disease, uterine cavity anomalies, unilateral ovary or tube, AFS stage III or IV endometriosis (9), and uncorrected male factor. Regardless of whether the sperm sample was fresh or frozen, IUI cycles in which there were <10 million motile sperm inseminated were excluded. Failed ART cycles that were converted to IUI were also excluded. For the ART cycles, intracytoplasmic sperm injection (ICSI), donor oocyte and donor embryo cycles were excluded. By excluding cycles with donor oocytes and embryos, the patients' reproductive capacity with their own oocytes were examined. Intracytoplasmic sperm injection cycles were excluded because of the possibility of skewed results from the few cycles that were initially performed early in our experience with the technique.

Data were collected from those patient cycles meeting study criteria. Key parameters that were recorded include the following: patient's age, gravidity, parity, infertility diagnosis, early follicular phase levels FSH, number and types of treatment cycles, clinical pregnancies and outcomes. Serum levels of FSH and estradiol (E2) were measured using the IMx® system FSH and Estradiol assays (Abbott Laboratories, Abbott Park, IL), respectively. Progesterone levels were measured with the Coat-A-Count® Progesterone radioimmunoassay (Diagnostic Products Corporation, Los Angeles).

Treatment Protocols

In unstimulated NC-IUI cycles, patients were instructed to test their urine daily for a luteinizing hormone (LH) surge using commercially available kits, starting at 2–3 days prior to the day of expected ovulation until a positive test. Cycles with no detectable LH surge were cancelled. Ovulation was usually confirmed with a midluteal phase serum progesterone level ≥ 10 ng/mL.

Cycles stimulated with CC used a 5-day protocol, starting on cycle Day 3 or 5. The daily dose was determined empirically or by the patient's prior response. The maximal CC dose used was 250 mg daily. Urinary LH testing was started 3–5 days after the last dose of CC. In the absence of a detectable LH surge 10 days after the last dose of CC, transvaginal sonography (TVS) was performed in some patients to assess follicular growth. In the presence of a dominant follicle measuring ≥ 18 mm in diameter and no evidence of spontaneous ovulation, 10,000 IU of human chorionic gonadotropin (hCG; Profasi, Serono Laboratories) was given by intramuscular (IM) injection to induce ovulation.

For INJ-IUI cycles, a Day 2 or 3 baseline TVS showing no follicles >10 mm and serum estradiol (E2) <100 pg/mL were required prior to treatment. Most patients were stimulated with human menopausal gonadotropins (hMG) (Pergonal® or Metrodin®, Serono Laboratories; Humegon, Organon), while a small number used highly purified urinary FSH (Fertinex®, Serono Laboratories) or recombinant human FSH (Gonal-F®, Serono Laboratories; Follistim®, Organon). Ovarian response was monitored through serial TVS and serum E2. Administration of hCG 10,000 IU i.m.; occurred when 1 or more follicles were ≥ 18 mm in the presence of an appropriate E2 level.

For all IUI cycles, insemination was performed on the day following the LH surge or 36–40 h after the hCG injection.

In ART cycles, COH was achieved using the same gonadotropins as for INJ-IUI cycles, with the addition of a gonadotropin-releasing hormone agonist (GnRHa) (Lupron®, TAP Pharmaceuticals) at varying doses to achieve pituitary down-regulation. The treatment of patients started with 2–3 ampoules of gonadotropin for the first 3–4 days of stimulation. Ovarian response was monitored by serial TVS and serum E2 levels, and subsequent gonadotropin doses were adjusted accordingly. Ten thousand IU of hCG were injected intramuscular when two or more follicles attained a diameter of ≥ 18 mm and serum E2 reached a minimum of 500 pg/mL; transvaginal oocyte aspiration was performed 36 h after hCG injection. In IVF cycles, an average of 3–4 and a maximum of 6 embryos were transferred 2–3 days later. In GIFT cycles, 3–4 oocytes along with 500,000 sperm in 0.5 mL were transferred to the fallopian tubes via laparoscopy. A number of patients were offered assisted hatching (AH) with acid Tyrode's medium, beginning in 1998; embryo transfers (ET)

Table I. Primary Diagnoses of the Two Treatment Groups

	Total no. of patients	Cervical factor	Endometriosis	Male factor	Ovulatory dysfunction	Tubal factor	Unexplained	Others ^a
ART	45	3 (6.7)	3 (6.7)	7 (15.6)	11 (24.4)	12 (26.7)	7 (15.6)	2 (4.4)
IUI	119	8 (6.7)	9 (7.6)	43 (36.1)	48 (40.3)	0 (0)	5 (4.2)	6 (5.0)

Note. Values are number of patients in each treatment group, with percentages in parentheses.

^a This group includes Asherman's syndrome, luteal phase defect, and pelvic adhesions.

in AH cycles were performed on Day 3 after oocyte retrieval. Progesterone support was provided by progesterone in oil injections (Steris Laboratory Inc., Phoenix, AZ), 25–50-mg i.m.; on the day of ET, followed by 50–100-mg i.m.; daily. The latter dose of progesterone was continued until an ultrasound at the 10th gestational week confirmed pregnancy.

In both IUI and ART groups, patient cycles with an early follicular FSH of ≥ 15 mIU/mL were strongly discouraged from proceeding with treatment (10). Nonstarters comprised approximately 20% of all cycles; the cancellation rate for poor response was approximately 15% (data not shown).

Outcome

Clinical pregnancy was defined as a rising serum hCG and evidence of one or more gestational sacs seen on TVS 3 weeks after IUI or ET. Pregnancy rate as defined as the number of clinical pregnancies per completed cycle of IUI or ET. The live birth rate was defined as the number of live-born pregnancies per completed cycle of treatment. Spontaneous abortion, ectopic pregnancy, term and preterm delivery rates were calculated as percentages of pregnancies.

Statistics

Pregnancy rates and outcomes were analyzed with Fisher's exact test. Age differences between the different IUI and ART groups were tested using one-way ANOVA and Tukey's post hoc test. The two-tailed unpaired *t*-test was also used to assess differences in continuous variables, including age, gravidity, and the number of cycles needed to achieve pregnancy. Results were considered significant at $p < 0.05$.

A number of parameters analyzed showed significantly different standard deviations between groups, suggesting that the populations being compared were not equal or normally distributed. These raw data were either log-transformed and the analyses repeated, or nonparametric tests were performed, with no significant differences in the results (data not presented). This confirmed that the groups being compared were in fact statistically equivalent.

RESULTS

One hundred and fifty-two patients and 401 cycles met the inclusion criteria. One hundred and nineteen patients completed 343 cycles of IUI comprising 38 NC-IUI, 194 CC-IUI, and 111 INJ-IUI cycles. Forty-five patients completed 58 ART cycles comprising 11 GIFT and 47 IVF cycles. Statistical analysis showed no difference between GIFT and IVF cycles, so these were grouped together. There were differences in primary diagnoses between the two groups as dictated by the inclusion and exclusion criteria (Table I). Tubal factor, ovulatory dysfunction, and male factor accounted for approximately 67% of the ART primary diagnoses, whereas ovulatory dysfunction and male factor were the primary diagnoses for approximately 75% of the IUI patients.

The mean age ($\pm$ SD) of all patients was 41.8 (± 1.5) years, and the oldest patient was above 48.5 years old. There were no differences in age between the ART and IUI treatment groups (Table II). The average IUI patient completed 2.9 cycles (range 1–8). Intrauterine insemination patients who conceived required 2.8 ± 1.3 (mean $\pm$ SD) cycles to achieve pregnancy. The average ART patient

Table II. Age Related Parameters of the Two Treatment Groups

	Age (years)	Follicular FSH (mIU/mL)	No. completed cycles/patient	Age at pregnancy	No. cycles to pregnancy
ART	41.9 (± 1.8)	7.0 (± 2.5)	1.3 (± 0.6)*	41.4 (± 1.5)	1.1 (± 0.3)*
IUI	41.8 (± 1.4)	7.9 (± 3.0)	2.9 (± 1.8)	41.4 (± 1.1)	2.8 (± 1.3)

Note. Values are mean ($\pm$ standard deviation) unless otherwise indicated.

* $p = 0.0003$.

completed only 1.3 cycles (range 1–4) while those who conceived required an average of 1.1 ± 0.1 cycles ($p = 0.0003$). Patients who conceived in each treatment group did not differ significantly in age.

One hundred and thirteen patients (73.3%) completing 282 cycles (70.3%) had measured early follicular phase serum FSH levels. Mean FSH ($\pm$ SD) was $7.7 (\pm 3.1)$ mIU/mL, with a range of 2.3–17.8. There were no differences in FSH levels between the ART and IUI groups (Table II). Two hundred and seventy cycles with an early follicular FSH of <15 mIU/mL resulted in 22 pregnancies. No differences in FSH were found between pregnant and nonpregnant cycles.

There were 11 pregnancies in 58 ART cycles for a PR of 19.0%/cycle; 19 pregnancies resulted from 343 IUI cycles, for a PR of 5.5%/cycle ($p = 0.0014$) (Table III). There were no differences in PR between the three IUI groups. A history of one or more prior pregnancies, regardless of outcome, had no effect on pregnancy rates. There was one set of twins in the ART group, and none in the IUI group; no higher order pregnancies occurred. In addition, the IUI group had one molar pregnancy and a fetal death in utero. There were no differences in the rates of spontaneous abortion, ectopic pregnancy, preterm and term deliveries between ART and IUI (Table III). No differences in patient age were found between pregnant and nonpregnant cycles (41.4 ± 1.2 years vs. 41.8 ± 1.5 years). Similarly, no age differences were found between pregnant and nonpregnant cycles within each of the ART and IUI groups. The oldest patient to have a live birth was 45 years and 3 months old at the time of embryo transfer. Although the live birth rates for IUI cycles ranged from 0 to 5.4%, no significant differences were found between NC-IUI, CC-IUI, and INJ-IUI. However, the total IUI live birth rate of 3.2% is nearly five times less than the 15.5% from ART cycles ($p = 0.0007$) (Table III).

Fig. 1. Clinical pregnancy rates per cycle in IUI vs. ART treatment based on patient age (* $p < 0.05$).

Figure 1 graphically demonstrates clinical pregnancy rates per cycle between IUI and ART groups, based on female age. Significantly higher pregnancy rates per cycle were seen in the ART group at ages 40 and 41, but statistically significant differences were not seen in patients ≥ 43 years of age.

DISCUSSION

Many prior studies have compared the success of the older patient to her younger counterpart undergoing the same fertility treatment. This study focused on the older woman, defined as one who is 40 years or older at the time of treatment, and compared the outcomes of commonly offered empiric IUI treatment and ART. The age of the woman has an inverse relationship to and is the primary determining factor in the successful outcome of fertility treatment (4,11,12). This decrease in female fecundity with age takes a marked down turn at about age 37 to 38, coincident with an accelerated loss of oocytes (13), and reaches almost zero by 45 years (1). The cause of this decrease has been shown to be primarily dependent on the age of the oocyte and not the uterus (2,14,15). In our study design, we excluded numerous factors such as low motile sperm numbers at the time of IUI

Table III. Pregnancy Rates in ART and IUI Treatment Cycles

Treatment group (No. of patients)	No. of cycles	PR	LB	Ectopic (%)	SAB (%)	Preterm (%)	Term (%)
ART (45)	58	19.0 ^a	15.5 ^b	1 (9.1)	1 (9.1)	1 (9.1)	8 (72.7)
IUI (119)	343	5.5	3.2	2 (10.5)	3 (15.8)	0	11 (57.9)
NC-IUI (14)	38	5.3	0.0	0	2 (5.3)	0	0
CC-IUI (78)	194	5.2	2.6	2 (1.0)	1 (0.5)	0	5 (2.6)
INJ-IUI (47)	111	6.3	5.4	0	0	0	6 (5.4)

Note. PR and LB values are percentage of cycles. Values for ectopic pregnancies, spontaneous abortions (SAB), preterm, and term deliveries are actual numbers, with percentage of pregnancies in parentheses.

^a Pregnancy rates between ART and all IUI cycles, $p = 0.0014$.

^b Live birth rates between ART and all IUI cycles, $p = 0.0007$.

and unilateral tubal obstruction so that only the aging woman and her ovaries would determine the outcome of therapy. However, it should be noted that the two treatment groups were not entirely equivalent: a significant number of patients in the ART group had previously failed with IUI, thereby potentially biasing against a successful outcome with ART. In addition, the diagnoses between the two groups were of necessity different: patients with tubal factor were clearly not represented in the IUI group for reasons stated under "exclusion factors."

A search of the literature found only one study that partly addressed this question in the ≥ 40 -year-old (8). That study included a control group of patients who were less than 30 years old as well as donor oocyte cycles for comparison, but suffers from having only 36 patients ≥ 40 years completing 67 cycles of both IUI and IVF. Our findings of IUI PR in the range of 5–6% and a live birth rate of 3.2% are consistent with values reported for this age group by other investigators (6,7,16–18). A number of studies have demonstrated a definite benefit of combining superovulation with IUI compared to either treatment alone (19–22). In their 1998 study, Guzick and coworkers (20) performed a retrospective analysis of the literature from 1985 to 1995. They examined various treatments for unexplained infertility and found that the combined pregnancy rates per initiated cycle were 1.3–4.1% (untreated), 3.8% (IUI alone), 5.6% (CC alone), 8.3% (CC-IUI), 7.7% (hMG alone), 17.1% (hMG-IUI), 20% (IVF), and 27% (GIFT). They also concluded that CC-IUI was a cost-effective initial treatment in the younger patient with unexplained infertility. However, this may not be appropriate for the older patient. Even in the younger patient population, IUI without ovarian stimulation resulted in a PR of only 18% compared to 33% with INJ-IUI (19). The lack of differences in PR between NC-IUI, CC-IUI, and INJ-IUI in the present study suggests that ovulation stimulation have only a marginal effect on pregnancy success in this age group.

A study by Lass *et al.* (23) reported on 702 cycles of IVF in women ≥ 40 years of age who reached the stage of embryo transfer. They found a maximal cumulative PR of 33.6% and a cumulative delivery rate of 25.5% after 4 cycles. The 1996 national report on ART success rates in women >39 years of age reveal ART delivery rates per retrieval of 11.3%. The 1998 national report on ART success rates reveal little improvement, with live birth rates of 10.7% per retrieval in woman >40 years of age. Our ART PR of 19.0% and live birth rate of 15.5% are consistent

with these reports. Indeed, studies reporting on either IUI or IVF separately indicate that ART success rates are 3–5 times that of IUI in this age group (6,7,16,17,23–25). Furthermore, in our study, fewer ART cycles (1.1) than IUI cycles (2.8) were needed to achieve pregnancy. Since time is a limiting factor in these patients, ART has a distinct advantage over IUI. With their large number of IVF cycles, Lass *et al.* (23) were able to show a progressive decrease in PR and increase in miscarriage rates with increasing age over 40. Interestingly, we did not detect any differences in age between pregnant and nonpregnant ART cycles.

Several results were different from literature reports. Contrary to 1996 SART registry data (24), prior pregnancy did not increase the chances of pregnancy with either IUI or ART in our patients. This may be the result of patient selection in this study: factors other than ovarian age that could have affected implantation and pregnancy were excluded by design. The miscarriage rates of 9.1% for ART and 15.8% for IUI in our study are significantly lower than the approximately 30–60% reported for the ≥ 40 -year-old woman (5,7,17). In addition, the cancellation rate of approximately 15% (unpublished) in this age group is slightly lower than the 20+ percent commonly reported in the literature (23,24). One explanation for these differences is patient selection based on the early follicular FSH level. It is now standard in our practice for a Day 3 FSH level to be drawn for all patients ≥ 38 years of age prior to ovulation stimulation or COH. Those with a Day 3 FSH ≥ 15 mIU/mL are actively discouraged from pursuing IVF therapy. It has been shown that an elevated early follicular phase FSH is predictive of a poor response in that treatment cycle (17,26) as well as in subsequent cycles (27,28). The exclusion of patients with diminished ovarian reserve and other factors that could negatively affect pregnancy outcome might explain the lower cycle cancellation and miscarriage rates seen in this study.

Due to the cost of ART, as well as the time factor, a prospective, randomized controlled trial to determine the best course of therapy for the ≥ 40 woman wishing to conceive with her own oocytes probably will never be done. Although this study is limited by its retrospective design and modest patient numbers, our data strongly support the use of ART over IUI in the ≥ 40 woman who chooses to use her own oocytes. Those patients who conceive with ART appear to do so within 1–2 cycles, after which continued therapy may not be beneficial. Starting with CC-IUI or even INJ-IUI may not be optimal strategies in this patient population.

CONCLUSIONS

In the carefully chosen patient who is ≥ 40 years old who does not wish to use donor eggs, ART appears to be the most effective therapy available to achieve a successful outcome. With continued improvements in ART techniques, it is possible that even better results will be achieved in the near future.

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