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ASSISTED REPRODUCTION TECHNOLOGIES

Is intrauterine insemination a viable treatment option for women over 43 years old? An analysis by ovarian stimulation protocol and sperm source

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Abstract

Purpose The aim of this study was to determine how female age at the end of the reproductive spectrum effects success of natural cycle intrauterine insemination (IUI) or IUI in combination with ovarian stimulation.

Methods We performed a retrospective cohort study of women 43 years of age and older at the time of IUI in a single academic fertility center between January 2011 and March 2018. Primary outcomes were both pregnancies and live births per cycle of IUI. Data are presented as percentage or mean ± SD. Fisher exact and chi-squared analyses were performed.

Results There were 9334 IUI cycles conducted during the study period. Of these cycles, 325 IUIs (3.5%) were for women aged 43 years and over at the time of insemination (43.6 ± 0.8, range 43 to 47 years). Analysis of these 325 IUI cycles revealed 5 biochemical pregnancies (1.5%) and only 1 live birth (0.3%). The pregnancy rate did not differ between IUIs using donor sperm ($N = 1/49$, 2.0%) compared to IUIs with partner sperm ($N = 4/276$, 1.4%). The pregnancy rate did not differ between IUIs with gonadotropins ($N = 2/211$, 0.9%), clomiphene or letrozole ($N = 2/78$, 2.6%), or natural cycle ($N = 1/36$, 2.8%).

Conclusions The use of intrauterine inseminations in women 43 years of age and older is an ineffective treatment strategy. This is irrespective of the use of ovarian stimulation or donor sperm. Costly gonadotropin injections did not increase the chance of pregnancy nor did oral medication when compared to natural cycle IUIs.

Keywords Intrauterine insemination (IUI) · Ovarian stimulation · Older women · Infertility

Key messages The use of intrauterine inseminations in women 43 years of age and older is an ineffective treatment strategy. This is irrespective of the use of ovarian stimulation or donor sperm.

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Introduction

Trends toward delayed childbearing and the subsequent increasing maternal age at first birth have been documented across many societies [1–4]. Over the last 25 years, birthrates for women ages 40 to 44 years have almost doubled across North America [5, 6]. Unfortunately, there is a lack of awareness of the effects of age on fertility on the part of patients. This leads to misconceptions about the success of assisted reproductive technologies to overcome age-related fertility decline [7–9]. Age-related decline in female fecundity begins at approximately age 30 years and progresses more rapidly after age 35 years [10]. This is primarily due to declines in the quantity and quality of oocytes with advancing age as well as increasing miscarriage rates, which can reach over 50% after the age of forty [2, 10]. While the IVF success rates are increasing over time, the average live birth per cycle start is only 3% in women 43 years of age and < 2% in women over 44 in the USA [2]. The success of intrauterine insemination (IUI) similarly is effected by female age [11–15]. IUI is a

common first-line treatment for patients with ovulatory disorders, unexplained infertility, and those using donor sperm [15]. However, data regarding IUI success for women at the end of the reproductive spectrum is lacking. The Forty and Over Treatment Trial, which randomized women over 40 years of age to Clomid or folliclep-stimulating hormone (FSH) with IUI to immediate IVF, found that while immediate IVF demonstrated superior pregnancy rates, the IUI group had a pregnancy rate of 21.6% for clomiphene citrate and 17.3% for FSH [16]. Most studies on IUI do not specifically address women over 43 years of age or include a limited number of these patients in their analysis. A Canadian study published in 2002 found that for 89 women aged 40–42 years, the live birth rate was 9.8% per insemination. For the 24 women over the age of 43 in the study, the authors reported only one live birth was achieved after insemination [11]. A German study of the effect of maternal age on IUI success reported a per-patient pregnancy rate of 8.3% for over the age of 43 but did not include data on live birth and only represented one pregnancy in a group of twelve women [13].

An accurate accounting of success rates and pregnancy outcomes across reproductive technologies will allow patients to make informed choices about their family planning and fertility treatments. The aim of this study is to determine how female age at the end of the reproductive spectrum, i.e., over 43 years, effects the success of IUI alone or in combination with ovarian stimulation.

Material and methods

We performed a retrospective cohort study of women 43 years of age and older at the time of intrauterine insemination in a single academic fertility center between January 2011 and March 2018. Primary outcomes were both pregnancies (defined by a HCG > 10 mIU/ml) and live births per insemination. All IUI cycles conducted after the age of 43 were analyzed regardless of prior fertility treatments. We included IUI's completed in unstimulated natural cycles as well as oral stimulation medications which included clomiphene or letrozole and gonadotropin-stimulated cycles. Doses used were clomiphene citrate 50 or 100 mg, letrozole 5 mg, and injectable FSH 50–300 IU daily.

In natural cycles, patients were screened for ovulation with a luteinizing hormone (LH) level and ultrasound. If the serum LH was positive (≥ 20 IU/L), the IUI was scheduled 24 h later. If a follicle greater than 17 mm in diameter was present and serum LH was negative, the patient would receive HCG and the IUI would be scheduled 24–36 h later. Patients using clomiphene citrate or letrozole took their medication on days 2–6 of the cycle and had an ultrasound on day 10 to monitor follicle growth. Patients planning to use gonadotropins would have a baseline ultrasound on days 2 or 3 of the cycle. If the ultrasound was normal (endometrial thickness less than 5 mm and no ovarian cysts), the patient would begin gonadotropin stimulation and return for ultrasound monitoring. If the leading follicle is greater than 17 mm in diameter, the patient would receive HCG and the IUI would be scheduled 24 to 36 h later. Luteal support with vaginal progesterone was started the day after insemination for all gonadotropin-stimulated cycles.

Cycles were canceled if (a) an ovarian cyst or endometrial polyp was present at baseline scan, (b) if no dominant follicle was recruited, (c) if there was no sperm sample for insemination, (d) if the ovulation was missed, or (e) if the patient requested cancelation for personal reasons.

All inseminations for women over the age of 43 years at the time of insemination were included. Canceled cycles were excluded from our analysis. Cycles were also excluded if they were converted to IVF.

Donor sperm was used for women in same-sex relationships, single women, and women with azoospermic partners. Both partner sperm and commercially available donor sperm insemination cycles were included in the study. When partner sperm was used, the partner was instructed to abstain from ejaculation for 48 h before IUI. Samples were produced on-site and processed within 30 min of production. A basic wash and a density gradient centrifugation were performed on all semen samples. The concentrated pellet was reconstituted to a volume of 0.5 ml with tubal media (Ferticult, Beemm, Belgium). All samples were inseminated into the uterus using a Cook catheter (Indiana, USA). Patients were instructed to ambulate immediately post-insemination or to remain recumbent if experiencing pain or at patient request.

A serum HCG pregnancy test was performed 16 days after IUI. If it was positive (HCG > 10 mmol/L), a viability scan was booked at 5–6-week gestation. All patients with a positive HCG after IUI had a chart review to assess live birth outcomes. All data are presented as percentage of IUIs or mean ± SD. Categorical data were compared using chi-squared. Internal institutional review board approval was obtained for this study.

Results

There were 9334 IUI cycles conducted during the study period between January 2011 and March 2018. Of these cycles, 325 IUIs (3.5%) were for women 43 years and over at the time of insemination and are included in this analysis. The average age was 43.6 ± 0.8 years, range 43 to 47 years. These inseminations were performed for a total of 152 women (125 women using partner sperm and 27 women using donor sperm). The average number of inseminations per patient was 2.1. Sixty-eight women underwent a single insemination (68/152, 44.7%), 40/152 (26.3%) completed two inseminations,

Table 1 Number of insemination cycles completed per patient and the pregnancy rates and live birth rate at each completed cycle

Total number of inseminations completed	1	2	3	4	5	6	7	8	9
Number and percentage of women	68/152 (44.7%)	40/152 (26.3%)	23/152 (15.1%)	11/152 (7.2%)	7/152 (4.6%)	1/152 (< 1%)	-	1/152 (< 1%)	1/152 (< 1%)
Number of pregnancies	4/152 (2.6%)	1/152 (< 1%)	-	-	-	-	-	-	-
Life births	0/152 (0%)	1/152 (< 1%)	-	-	-	-	-	-	-

23/152 (15.1%) completed three inseminations, and 21/152 (13.8%) completed four or more inseminations (Table 1). Of the IUI cycles, 36 (11.1%) cycles were performed in a natural cycle with IUI alone, 78 (24%) cycles in combination with clomiphene or letrozole, and 211 (64.9%) with gonadotropin stimulation. Analysis of these 325 IUI cycles revealed 5 biochemical pregnancies (1.5%) and 1 live birth (0.3%). The pregnancy rate did not differ between IUIs with gonadotropins ($N = 2$, 0.9%), clomiphene/letrozole ($N = 2$, 2.6%), or natural cycle ($N = 1$, 2.8%), ($p = 0.51$) (Table 2). For those using partner sperm, the average partner age was 45 ± 6 years (range 28 to 69 years old). For all partner-produced specimens, the average post-wash total motile sperm count was 23.6 ± 18.9 million (range 50,000 to 95 million sperm). For donor sperm samples, the average post-wash total motile sperm count was 13.0 ± 6.5 million (range 3.1 to 30.0 million sperm). The pregnancy rate did not differ between IUIs using donor sperm ($N = 1$, 2.0%) compared to IUIs with partner sperm ($N = 4$, 1.4%): $p = 0.55$; Table 3 (68/152, 44.7%). The single live birth occurred in a 43-year old patient stimulated with letrozole using partner sperm.

Discussion

The effect of age-related fertility decline on the success of ART procedures has been widely reported [2, 10–12, 17–20]. Published literature has both supported [11] and discouraged [1, 15, 16, 18, 21, 22] the use of IUI in women over the age of 40. It was the purpose of this retrospective cohort study to determine how female age at the end of the reproductive spectrum, specifically in women over the age of 43, effects the success of IUI procedures in combination with various stimulation techniques.

As anticipated, the pregnancy rate and live birth rate were extremely low in this cohort. However, with only five pregnancies and one live birth in over one hundred women completing over 300 inseminations, our results were worse than expected. The live birth rate was 0.03% per cycle and 0.7% per patient. The pregnancy rate did not differ between IUIs using donor sperm compared to IUIs with partner sperm. Donor sperm was used for women in same-sex relationships, single women, and women with azoospermic partners. At our clinic, we previously believed that women using donor sperm would fare better with IUI compared to those using partner sperm due to the fact that they did not carry a subfertility diagnosis, other than advanced age. Yet, the single live birth in this cohort resulted from partner sperm. There is no evidence that a lack of exposure to sperm confers a higher chance of IUI success nor constitutes an indication to try IUI for women over 43 years.

Pregnancy rates did not differ depending on the type of IUI preparation protocol. The pregnancy rates per cycle for gonadotropins ($N = 2/211$, 0.9%), clomiphene/letrozole ($N = 2/78$, 2.6%), or natural cycle ($N = 1/36$, 2.8%) were not significantly different ($p = 0.51$), though this may be due to the small number of pregnancies in this cohort. A study by Dimond et al. randomized women 18–40 years with unexplained infertility found that ovarian stimulation with letrozole resulted in a significantly lower frequency of multiple gestations but also a lower frequency of live birth, as compared with gonadotropin but not as compared with clomiphene [23]. The single live birth in our cohort occurred in a letrozole-stimulated cycle.

Our study does not address the role of mature follicle count on pregnancy rates for women with advanced reproductive

Table 2 Stimulation used for insemination cycles completed

	Unstimulated/natural cycle	Letrozole or clomiphene citrate	Gonadotropin	*p* value	Total for all cycles
No. of insemination cycles*	36 (11.1%)	78 (24%)	211 (64.9%)		325 (100%)
No. of pregnancies**	1 (2.8%)	2 (2.6%)	2 (0.9%)	0.51	5 (1.5%)
No. of live births**	0	1 (1.2%)	0		1. (0.3%)

*% of all cycles

**% per type of cycle

Table 3 Sperm source used for insemination cycles completed

	Partner sperm	Donor sperm	*p* value	Total for all cycles	Total for each woman
No. of insemination cycles*	276 (84.9%)	49 (15.1%)		325 (100%)	325/127, average of 2.6 IUIs per patient
No. of pregnancies**	4 (1.4%)	1 (2.0%)	0.55	5 (1.5%)	5/127 (3.9%)
No. of live births**	1 (0.36%)	0		1 (0.3%)	1/127 (0.8%)

*% of all cycles

**% per type of sperm

age. A study by Evans et al. found that in patients older than age 40 years, increasing the follicle number increased clinical pregnancy without increasing the risk of multiple gestations. Specifically, increasing from one up to five follicles increased the clinical pregnancy per IUI rate from 4.1 to 13.5% [24]. It is unclear if treating to a goal of up to five mature follicles per IUI would have been possible in our cohort. In our cohort, over two hundred insemination cycles were completed using upwards of 300 IUI of gonadotropins daily for 10 or more days. These costly medications failed to improve the pregnancy rate and they did not result in any live births in this cohort. While IUI can be a cost-effective treatment strategy in certain populations [15, 25, 26], our results suggest that this is not true for women over 43 years of age. If attempted, the ineffectiveness of IUI procedures and ovulation medications in women over age 43 will add significantly to the mean cost per pregnancy in the majority of cases.

With an overall treatment success rate of less than 1% per patient, IUI in women over 43 meets the ASRM ethics committee definition of futility [27]. Additionally, continuing IUI attempts after repeated failure can become a source of emotional and psychological distress [19]. In the jurisdiction where the study was conducted, the provincial health authority covers up to nine inseminations per patient at zero cost to the patient. Only one of the 152 patients in the cohort completed a full 9 inseminations.

Our study is limited by the lack of patient demographic information such as smoking status, BMI, AMH or FSH levels, and number of prior children. This study does not account for the duration of infertility or treatments received prior to age 43. These results are biased in that canceled cycles were excluded from the analysis. Furthermore, patients that converted to IVF were omitted, though this was likely a rare event. The missing demographic data points, canceled cycles, and conversions to IVF were unlikely to effect our primary outcome given the overall low pregnancy and live birth rate found. Thus, our results represent an unselected sample and our data can be applied to all comers over 43 years old who proceed through IUI.

In conclusion, IUI for women 43 years of age or older is considered an ineffective treatment strategy. This study included women without diagnosed subfertility using donor sperm as well as women using various super ovulation techniques.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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