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EDITORIAL

Getting Older Women Pregnant: Contemporary Thoughts

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About the Author

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Abstract For women of advanced age with abnormally increased FSH levels, standardized hormonal stimulation often represents a cost-intensive procedure with a low success rate. It is well established now that with mild ovarian stimulation, there is a greater percentage of good-quality eggs (although a smaller number) than with higher-dose conventional stimulation. Mild stimulation protocols reduce the mean number of days of stimulation, the total amount of gonadotropins used and the mean number of oocytes retrieved. The proportion of high-quality and euploid embryos seems to be higher compared with conventional stimulation protocols, and the pregnancy rate per embryo transfer is comparable. Moreover, the reduced costs, the better tolerability for patients and the less time needed to complete an IVF cycle make mild approaches clinically and cost-effective over a given period of time. The low number of embryos available for transfer poses a great challenge in the management of older women going in for IVF. A potential management of these older women is to create a sufficient pool of embryos by accumulating

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vitrified good-grade embryos over several minimal stimulation and natural cycles. At the end of the accumulation process, these embryos can be subjected to a preimplantation genetic screening using next-generation sequencing and then the pool would have only chromosomal normal embryos with maximal chances of implantation. This would potentially make the chances of success for older women similar to normal responders. This management, however, is unthinkable without an outstanding vitrification program. The option of accumulating embryos has become a promising reality with the advent of vitrification technologies.

Keywords AMH · Older patients · IVF · IUI · Vitrification · NGS · Trophectoderm biopsy · PGS · Preimplantation genetic screening · PGD · Preimplantation genetic diagnosis · IVF lite · Minimal stimulation IVF

Introduction

Iglesias et al. [1] investigated differences in ovarian reserve markers [antimüllerian hormone (AMH) and antral follicle count (AFC)] in Indian and Spanish women. The mean age of women undergoing their first or second IVF cycle was significantly higher in Spanish than in Indian women (37.5 ± 3.3 vs. 31.5 ± 3.8 years). Despite this 6-year age gap, AFCs were similar (9.5 ± 4.7 vs. 9.9 ± 4.6), as were day-3 FSH levels (7.5 ± 4.5 vs. 6.9 ± 2.3 IU/L). AMH levels were slightly lower in Spanish women (1.6 ± 1.7 vs. 2.5 ± 1.6 ng/mL). Multivariate regression analysis showed that being Indian decreased AFC by 2.3, such that AFC in Indian women was similar to that in Spanish women 6.3 years older (95 % CI 3.39–1.10). Similar ovarian reserve markers and ovarian response were observed in women with a 6-year age difference in favor of the Spanish, suggesting ethnic differences in ovarian aging. Further research is needed to understand whether these differences are genetically induced or are caused by other variables, such as nutrition [1]. The number of women attempting to conceive between the ages of 36 and 44 has increased significantly in the last decade. While it is well established that women's reproductive success dramatically declines with age, the underlying physiological changes responsible for this phenomenon are not well understood. With assisted reproductive technologies, it is clear that oocyte quality is a likely cause since women over 40 undergoing in vitro fertilization (IVF) with oocytes donated by younger women have success rates comparable to young patients. Till a few years ago, apart from oocyte donation, there was no known intervention to improve the pregnancy outcome of older patients. Today, with the widespread use of the IVF Lite protocol [2–4] and the advent of next-generation sequencing (NGS) technology to screen embryos [5, 6], we have pregnancy rates that have almost doubled in older women from a decade back.

Goldman et al. [7] set up a randomized clinical trial to determine the optimal infertility therapy for women at the end of their reproductive potential. The study included couples with ≥6 months of unexplained infertility; female partner aged 38–42 years, who were randomized to treatment with two cycles of clomiphene citrate (CC) and intrauterine insemination (IUI), follicle stimulating hormone (FSH)/IUI or immediate IVF, followed by IVF if not pregnant. They randomized 154 couples to receive CC/IUI ($N = 51$), FSH/IUI ($N = 52$) or immediate IVF ($N = 51$); 140 (90.9 %) couples initiated treatment. The cumulative clinical pregnancy rates per couple after the first two cycles of CC/IUI, FSH/IUI or immediate IVF were 21.6, 17.3 and 49.0 %, respectively. After all treatments, 110 (71.4 %) of 154 couples had conceived a clinically recognized pregnancy and 46.1 % had delivered at least one live-born baby; 84.2 % of all live-born infants resulting from treatment were achieved via IVF. There were 36 % fewer treatment cycles in the IVF arm compared with either COH/IUI arm, and the couples conceived leading to a live birth after fewer treatment cycles. This randomized controlled trial in older women with unexplained infertility to compare treatment initiated with two cycles of controlled ovarian hyperstimulation/IUI versus immediate IVF demonstrated superior pregnancy rates with fewer treatment cycles in the immediate IVF 7). Success rates for women aged 40 or over with clomiphene, IUI, IUI with FSH are all extremely low, at <1 % live birth per cycle. However, IVF offers a success rate of around 13.7 % per cycle. Attempting treatments other than IVF will delay conception unnecessarily [8].

In many IVF centers, it is a common practice to consider the day-3 FSH value as an end marker for the patient selection procedure. Most centers hold a day-3 FSH value of 10–15 IU/L as the upper limit to decide whether to provide IVF treatment or not, since one of the large-scale studies evaluated a day-3 FSH >15 IU/L and demonstrated a decrease in pregnancy rate [9]. Many patients having high day-3 FSH are denied IVF treatment quoting reduced ovarian reserve and low success rate and pushed toward donor egg IVF. The high base-line FSH concentration that is usually observed with older women due to lower ovarian reserve simply indicates the need for an IVF Lite protocol with no down-regulation and banking of embryos with back-to-back mild stimulation alternating with natural IVF cycles. In Zhang's series, patients were not denied treatment based on their day-3 FSH value or ovarian reserve [10]. Yet very acceptable pregnancy rates were achieved (20 % for fresh

embryo transfers (ETs) and 41 % for cryopreserved ETs). These results strengthen the argument for an IVF Lite protocol [2–4, 11, 12] as an alternative to standard conventional IVF stimulation protocols.

Discussion

In the era before vitrification, Weghofer et al. [13] reported on 84 IVF cycles using minimal ovarian stimulation and 85 cycles with a standard long-stimulation protocol in women aged 40 and above who had slightly increased FSH levels. Minimal stimulation cycles resulted in a clinical pregnancy rate of 8.2 % per started cycle and 10 % per ET, whereas the control group yielded a clinical pregnancy rate of 10.6 % per started cycle and of 10.7 % per ET (not statistically significant). In women aged 40 and above with abnormal FSH levels, minimal stimulation protocol achieves similar pregnancy rates to a standard protocol, and thus represents a cost-effective alternative [13].

A retrospective, cohort study was performed in private infertility center to evaluate the embryological and clinical results of a large exclusive SET program according to patient age (lower or equal 29, 30–34, 35–39, 40–44 and equal to or higher than 45 years) [14]. A total of 7,244 infertile patients underwent 20,244 cycles with a clomiphene-based minimal stimulation or natural-cycle IVF protocol during 2008. Following oocyte retrieval, fertilization and embryo culture, a total of 10,401 fresh or frozen single-ET procedures were performed involving cleavage-stage embryos or blastocysts. Successful oocyte retrieval rate (78.0 %) showed no age-dependent decrease until 45 years. Fertilization (80.3 %) and cleavage (91.1 %) rates were not significantly different between age groups. Blastocyst formation (70.1–22.8 %) and overall live birth rates (LBR) (35.9–2 %) showed an age-dependent decrease. Vitrified frozen-thawed blastocyst transfer (BT) cycles gave the highest chance of live birth per ET (41.3–6.1 %). High fertilization and cleavage rates were obtained regardless of age, whereas blastocyst formation and LBR showed an age-dependent decrease. An elective single-ET program based on a minimal ovarian stimulation protocol yielded acceptable LBR per ET in infertile patients up until their mid-40s [14]. However, in very advanced age patients (equal to or higher than 45 years old) success rates fall below 1 %.

IVF–ET with intracytoplasmic sperm injection (ICSI) was performed for a 45-year-old woman with a peak serum FSH level of 29 mIU/mL and a history of failing to conceive in five previous IVF–ET cycles at a younger age. A minimal FSH stimulation protocol was used [15]. A fresh transfer of a seven-cell embryo was performed on day 3. A successful pregnancy and delivery ensued. This case report establishes a precedent that a successful pregnancy following IVF–ET is possible in a woman whose serum FSH is >15 mIU/mL and age is 45. Of course, there is no implication that accomplishing this again in another woman with similar circumstances would be likely [15].

Zhu et al. [16] compared the clinical outcome of fresh versus vitrified-warmed BT cycles. In 110 fresh BT cycles versus 136 vitrified-warmed BT cycles performed from January 2007 to March 2010, the IR and CPR of vitrified-warmed BT cycles were 37.0 and 55.1 %, respectively, which were statistically significantly higher than the corresponding values of 25.2 and 36.4 % obtained for fresh BT cycles. Vitrified-warmed BT cycles resulted in statistically significantly higher CPR and IR compared with fresh BT cycles. A new ET strategy was therefore proposed whereby fresh BT would be avoided in the initial ovarian stimulation cycle. Instead, all the patient's available blastocysts would be vitrified-warmed and transferred in subsequent cycles [16]. Kalampokas et al. [17] did a systematic review to determine whether IVF, frozen replacement cycles offer better outcomes than fresh cycles in order to support, or not, a possible shift toward total replacement of fresh IVF/ICSI cycles from frozen elective transfers (FETs). Initial results seem to support a shift in current practice toward frozen cycles. Initial results may support replacement of all fresh IVF/ICSI cycles with FETs, as this could be a safer and equally effective strategy [17]. Also, vitrification of mature oocytes and embryos obtained better clinical outcomes and did not increase the risks of DNA damage, spindle configuration, embryonic aneuploidy, and genomic imprinting as compared to fresh and slow-freezing procedures, respectively [18]. This is the global trend now, and especially for older women, poor responders and now even for hyper-responders, a deferred or remote ET is preferred [3, 4, 11, 12].

Zhang et al. [19] performed a randomized non-inferiority controlled trial with a prespecified border of −10 % comparing one cycle of mini-IVF with single ET to one cycle of conventional IVF with double ET. Five hundred and sixty-four couples were randomly assigned between February 2009 and August 2013 with 285 allocated to mini-IVF and 279 to conventional IVF. The cumulative live birth rate was 49 % (140/285) for mini-IVF and 63 % (176/279) for conventional IVF (RR 0.76, 95 % CI 0.64–0.89). There were no cases of OHSS after mini-IVF compared to 16 (5.7 %) moderate/severe OHSS cases after conventional IVF. The multiple pregnancy rates were 6.4 % in mini-IVF compared to 32 % in conventional IVF (RR 0.25, 95 % CI 0.14–0.46). Gonadotropin consumption was significantly lower with mini-IVF compared to conventional IVF (459 ± 131 vs. 2079 ± 389 IU, $p < 0.0001$). Compared to conventional IVF with double ET, mini-IVF with single ET lowers live birth rate,

completely eliminates OHSS, reduces multiple pregnancy rates and reduces gonadotropin consumption [19].

A 3-year, retrospective, single-center cohort study was conducted in a private infertility center to determine cumulative LBR per scheduled oocyte retrieval following minimal ovarian stimulation/natural-cycle IVF in unselected infertile patients [20]. A total of 727 consecutive infertile patients were analyzed who underwent 2,876 (median 4) cycles. Natural-cycle IVF or clomiphene-based minimal ovarian stimulation was coupled with single ET and increased use of delayed vitrified-warmed BT. Crude cumulative LBR were 65, 60, 39, 15 and 5 % in patients aged 26–34, 35–37, 38–40, 41–42 and 43–44 years, respectively. Acceptable cumulative LBR are reached with an exclusive minimal ovarian stimulation/single-ET policy especially in patients aged <38 years but also in intermediate aged patients (38–40 years) [20].

Recent Advances

Mersereau et al. [5] compared the strategy of traditional IVF with prenatal diagnosis versus IVF with preimplantation genetic screening (IVF/PGS) to prevent aneuploid births in women with advanced maternal age. A decision tree analytic model was created to compare IVF alone versus IVF/PGS to evaluate which strategy is the least costly per healthy (euploid) infant. Using base-case estimates of costs and probabilities in women aged 38–40 years, after a maximum of two fresh IVF cycles and two frozen cycles, the chance of having a healthy infant was 37.8 % with IVF alone versus 21.7 % with IVF/PGS. The average cost for each strategy is $25,700, but the cost per healthy infant is substantially higher when IVF/PGS is applied as opposed to IVF alone ($118,713 vs. $68,026). To assess the robustness of the model, all probabilities were varied simultaneously in a Monte Carlo simulation, and in 96.2 % of trials, IVF alone proved to be the most cost-effective option. Conversely, our data demonstrate that in women aged >40, IVF and IVF/PGS are essentially equal in terms of cost-effectiveness ($122,000 vs. $118,713) [5].

Conclusions

Different strategies of investigation and management are proposed to patients over 40 in order to overcome their infertility and improve the live birth rate in these patients. Intrauterine insemination (IUI) in women over 40 is associated with a low rate of ongoing pregnancy, and IUI should not therefore be offered always as the first line of treatment. As best demonstrated by the 2004 US National Summary and Fertility Clinic Report, which for the first time reported pregnancies and births above age 45 year, IVF in women of advanced reproductive age represents a cutting edge area of interest for improving current IVF outcomes. Access to IVF should, therefore, not be withheld based on female age and/or baseline FSH levels [21]. Furthermore, evidence has shown that, by these avant-garde techniques (minimal stimulation, trophectoderm biopsy, vitrification and NGS), older infertile women with the help of eSET may have an opportunity to increase the success of their LBR approaching those reported in younger infertility patients [6].

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