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The Fertility Crossroad: Navigating the Divide between Unexplained and Age-Related Infertility; Where is the Cliff?

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Abstract

Unexplained infertility (UEI) and advanced maternal age (AMA) provide considerable obstacles to reproductive treatment. Unexplained infertility is a diagnosis of exclusion; nonetheless, therapies like intrauterine insemination (IUI) and in vitro fertilization (IVF) can enhance outcomes. Age-related infertility is mainly caused by decreased oocyte number and quality and increased aneuploidy rate. The decline in fertility associated with ageing is predominantly permanent, highlighting the necessity of early intervention and fertility preservation. There are crossroads between these two entities. We should know where the cliff is so we can intervene early before the prognosis becomes poor. Expectant management and intrauterine insemination are viable initial approaches for younger women; maternal age necessitates a shift toward ovarian reserve assessment and prognosis-based interventions. Preimplantation genetic testing for aneuploidy (PGT-A) may enhance reproductive success, though it remains debated due to cost and variable efficacy. The outcomes of assisted reproductive techniques (ART) decline significantly beyond the age of 40, with live birth rates becoming negligible after 44. A strategic, individualized approach balancing natural conception, fertility preservation, and assisted reproduction is essential for optimizing reproductive success in UEI and ARI cases.

Keywords: Age-related infertility, advanced maternal age, unexplained infertility and PGT-A

Introduction

Unexplained infertility (UEI, subfertility) is a diagnosis of exclusion for couples who are unable to conceive despite having regular unprotected intercourse and who do not meet the criteria for male factor infertility, oligo/anovulatory infertility, or anatomical abnormalities such as obstructed fallopian tubes, endometriosis, uterine cavity

anomalies, or cervical/vaginal obstruction (1). Consequently, they may go through a range of diagnostic and therapeutic procedures even though we don't fully understand the physiological mechanisms that cause their diminished fertility (2). The existing guidelines vary markedly in their inclusion criteria and management strategies.

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We must take into account the impact of maternal age on both embryo aneuploidy and oocytes. So the unexplained infertility could be considered true until a certain maternal age. It was reported that the prevalence of meiotic aneuploidies varies from approximately 25% in embryos from women under 35 years of age to over 50% in embryos from women over 35 years (3).

The divide between unexplained infertility (UEI) and age-related infertility (ARI)

There are crossroads between a diagnosis based on exclusion of four main entities and a "condition" related mainly to biological decline in the quality of oocytes, the hallmark of which is high rate of aneuploidy (4). It is a divide between a condition where ovarian reserve testing is not an essential prerequisite and a condition where ovarian reserve is the cornerstone for prognosis-based management.

The crossroads between orderly biological functions with cost-effective procedures on one hand and disordered chromosomal segregation with cytoplasmic ageing ending in high aneuploidy, high miscarriage rates, low live birth rates and controversial, debatable and expensive strategies on the other hand (5).

Age of 40 is a divide between a clinical scenario where investigations and guidelines (societies) determine the therapeutic algorithms shared with the couple and a decision determined by ovarian reserve, age brackets, and "debatable strategies" essential for shared "tailored" decision (6, 7).

There are crossroads between UEI, where the transition between therapeutic modalities is determined by "what is considered an adequate trial", using expectant management (12 months, for example), or controlled ovarian stimulation combined with intrauterine insemination (COS+ IUI) for 6cycles, for example and ARI, where prediction of time to menopause, menopausal transition and resistant infertility determine when to limit chances of in vitro-fertilization (IVF) success (8).

Aneuploidy in oocytes from women of advanced maternal age

Limited research has utilised complete chromosomal screening in polar bodies (PBs) and oocytes or zygotes, with an even smaller number addressing PBs from younger women (9).

Aneuploidies in oocytes may arise from errors that

occur during the first meiotic division (MI), the second meiotic division (MII), or in both phases. The hypothesis that non-disjunction (ND) of entire chromosomes during meiosis I is the predominant cause of aneuploidy (10) has been questioned upon the availability of polar bodies, with or without the corresponding oocyte for analysis, revealing that nearly all errors in meiosis I are attributable to precocious separation of sister chromatids (PSSC) (5).

Current evidence suggests that most aneuploidies occur de novo during the resumption of meiosis in the final stages of folliculogenesis, rather than being inherited from primordial follicles (11). This makes earlier fertility preservation more reasonable.

Would pre-implantation genetic testing for aneuploidy (PGT-A) be a reasonable solution?

The majority of embryos from patients with advanced maternal age, recurrent pregnancy loss, and implantation failure are aneuploidy (12). The results led to a logical yet inadequately established hypothesis that selecting euploid embryos based on a specific set of chromosomes would enhance reproductive success while decreasing the incidence of miscarriages or pregnancy terminations due to aneuploidy (13).

At the 40 crossroads, PGT-A could emerge as a last chance despite criticism, controversies and debates with escalating costs and tremendous emotional stresses leaning on strategies like embryo pooling. Before navigating this divide, techniques like elective oocyte cryopreservation could save a lot of trouble (14-20).

The Single Embryo Transfer of Euploid Embryo (STAR) trial demonstrated that among women over 35 years of age who responded well to ovarian stimulation, the application of PGT-A, in contrast to mere morphological selection of embryos for transfer, resulted in a higher ongoing pregnancy rate (OPR) per embryo transfer (51% vs. 37%, p = 0.0349) (16). A study assessing the costeffectiveness of PGT-A in women less than 42 years old undergoing IVF with multiple embryos indicated that PGT-A is cost-effective, diminishes the risk of clinical miscarriage and implantation failure, and reduces treatment duration (21). Additional research is necessary to precisely identify the population that would most benefit from PGT-A; however, evidence suggests that women with advanced maternal age are likely to be included (4, 14, 16, 19, 20).

Where is the cliff?

However, couples with unexplained infertility have the chance of natural conception; they are usually considered as less fertile. One randomized trial reported that the chance of spontaneous pregnancy in couples with unexplained infertility was 32% when compared to intrauterine insemination (IUI), but the women who were included were less than 39 years old (22). So, it is reasonable to wait for expectant management in these couples for six months.

All over the journey of unexplained infertility, there is renewal of hope even after failure of IUI or IVF. On the other hand, at the end of the downhill road of ARI, there is a cliff almost ending the chance of (own genetic child)! Futile treatment seems to reside at station 45-46 (Figure 1).

In their meta-analysis, Chua et al. found that for women at the age of 35 years or more, the natural conception rate remained clinically meaningful, and it was substantially greater for women experiencing unexplained infertility than for women with other medical diagnoses (23).

The Society for Assisted Reproductive Technology (SART) Clinic Outcome Reporting System (CORS) database had studied data from 246,740 women, with 471,208 cycles and 140,859 live births. About 47% of women were younger than 35 years old, and 15% were older than 40 years. They found that with increasing maternal age and the number of cycles using autologous oocytes, as opposed to donor oocytes, the live-birth rate declined. This was more obvious in women aged more than 41 years in comparison to women aged 31 years (24).

Klipstein et al. have studied the success of assisted reproductive technology in 1263 women who underwent 2,705 cycles at age 40 or above and found that the live birth rate was 8% per cycle and 10% per 3 cycles. They stated that ART has a reasonable success rate of up to 5% till the age of 43 years, so after 44 years, the treatment is almost futile (25).

Devesa et al. did a retrospective analysis for 4570 infertile women aged ≥38 years and reported that the most clinically relevant fertility decline was observed at 42–43 years old; cumulative live birth rate (CLBR) was 25.9% at 38–39 years, 16.4% at 40–41 years, 7% at 42–43 years and 1.2% from 44 years onwards. So they concluded that CLBR increases with the number of the retrieved oocytes in women of age up to 41 years old; however, the added value is negligible in women more than 41 years and futile in women \geq 44 years (26)



Figure 1. Crossroads and cliff between UEI/ARI

The green colour for UEI represents a wide landscape where there are guidelines and evidence-based investigations. The yellow colour is a river tributary ending in waterfall, so you have to coast earlier, as the chances for expectant management and IUI will be decreasing. While the orange colour is ARI downhill uncharted territory ending in a cliff, so walk during this downhill; there are a lot of debatable procedures of unproven efficacy that can be used or not. However, the outcome is poor (27-35). Apparently the cliff is at 44 or 45, where the expected therapeutic efficacy is below 1%, as indicated by the American Society of Reproductive Medicine (ASRM) (36).

Conclusion

Advanced maternal age (\geq 35 years) will affect the prognosis of previously diagnosed unexplained infertility, as fertility will start to decline at the age of 35 years. However, there are crossroads between unexplained and age-related infertility is at the age of 40 years. Earlier intervention may be needed till the age of 43 years, and more than that, treatment is futile. So we emphasize the need for individualization of management in couples with unexplained infertility according to maternal age with earlier intervention after the age of 37 years.

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