ICSI in the management of age-related infertility (ARI); reality or mirage?

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Advanced maternal age (AMA) is associated with a decline in ovarian reserve, an increase in the number of genetically abnormal embryos, and an increased risk of genetically abnormal pregnancy (1, 2). This phenomenon starts from the mid-thirties and when the age exceeds 43 AMH declines below 0.1 and the number of oocytes becomes less than 5000 (3). It is estimated that for 95% of women by the age of 30 years only 12% of their maximum pre-birth non-growing follicles (NGF) population is present and by the age of 40 years only 3% remain 3. In age-related infertility (ARI) the poor oocyte quality and high rate of aneuploidy decrease the cost-effectiveness of conventional ICSI and entail modifications of clinical and laboratory protocols (4). In women over 40 ICSI pregnancy rate is 10% after all embryos fresh and frozen are transferred from one cycle, and this poor figure does not improve even if ICSI was repeated 3 times (5). At age 42-43 ICSI pregnancy rate per cycle is 6% and drops to 2% at age 44 and above. This figure does not improve after 3 completed ICSI cycles (6). Since the cumulative live birth rate is less than 2% at 45 years using standard ICSI, PGTA, and social freezing are logical alternatives providing a higher probability of success in age-related infertility (ARI). The high cost may limit access to such alternatives. PGTA is not a straightforward alternative, the evidence is contradictory, the cost is high and the number of oocytes needed to produce one euploid blast is difficult to obtain in such an age group (7, 8). The recent improvement of oocyte vitrification has introduced social freezing at a younger age as an irreplaceable game changer in the management of age-related infertility (9, 10). Cost, availability of service, and age-related pregnancy complications limit the wider application of social freezing (11). Although controversial and lacking solid evidence adds on like Q10, vitamin D, and growth hormone represent a viable non-costly, almost risk-free option in this desperate situation (12).
With advancing maternal age oocyte mRNA stores and efficiency of DNA repair decrease (13), adds on could be viewed as a "safe haven" because the practice is currently at an impasse. Last but not least the chances of spontaneous conception should be an integral part of counseling, surprisingly expectant management offers the same chances of success as conventional ICSI in this age group (14, 15). In summary, conventional ICSI, with no clinical or laboratory adds on is not a good treatment option for infertile women over 40 (ARI). Social freezing at a young age preserves fertility and avoids ineffective treatment in later years. In the absence of social freezing modification of laboratory (eg PGTA) or clinical protocols (adds on) may be carefully offered when possible. Chances of natural conception are realistic and have to be properly presented to the couples before they choose their treatment or after the failure of ICSI attempt. The proper action plan can be only determined based on a well-designed RCT which is definitely needed to solve the current limitation of practice.

**Keywords**

Advanced maternal age (AMA), age related infertility (ARI), infertility over 40 years of age, ICSI, aneuploidy, oocyte quality, PGTA, social freezing, add on.

**References**


