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Editorial

Is 45 years-of-age the cut-off for using autologous oocytes?

A case report published in this issue of *RBMO* (Gleicher et al., 2018) invites a philosophical debate around two women, both aged 47 years, who became pregnant from autologous oocytes, one progressing to a pre-term livebirth at 35 weeks, by which time the mother was 48 years old. Each woman received adjuvants, either dehydroepiandrosterone (DHEA) or growth hormone (GH). The case report also notes two further livebirths in 2016 in women aged 45 years.

Advanced age and IVF

The assisted reproductive technology (ART) journey has progressed steadily towards improved outcomes from each oocyte retrieval procedure – by this we mean a better chance of achieving a live healthy infant, at term, without significant risk to the mother (avoiding ovarian hyperstimulation syndrome, ovarian torsion, ectopic and heterotopic pregnancies) and without significant risk to the infant (avoiding multiple pregnancy, intrauterine growth restriction and severe preterm). This year the first IVF 'child' celebrates her 40th birthday and will be among an estimated 7 million such offspring. However, this glowing picture can be subdivided into favourable or unfavourable prognostic groups governed by the woman's age and ovarian reserve, the latter measured by the antral follicle count (AFC) in the ovaries and/or the serum level of anti-Mullerian hormone (AMH). A recent report (Mustafa et al., 2017) shows the productivity rate (for fresh and frozen transfers from a single autologous oocyte retrieval cycle) combined with the cumulative livebirth rate (CLBR) from repeated cycles ranges from 45.5% with PIVET Algorithm Group A (AFC ≥20 antral follicles or AMH ≥20 pmol/l) steadily declining through the grades to 18.4% for Group E (AFC <5 antral follicles or AMH ≤5 pmol/l). Focussing on older women (≥40 years) with Group E, the CLBR across 4 retrieval cycles was 13.6%. Whilst this appears satisfactory at first glance, a closer breakdown showed that no livebirths (from 29 cycles) were obtained after age 44 years. It is of interest to note that younger women with Group E showed a 30% livebirth rate across 4 retrieval cycles. It was concluded that when financial concerns are not a deciding factor, fully informed women aged <45 years should not be deprived of the opportunity to undergo repeated autologous IVF attempts. In that study the chance of livebirth was often higher in the fourth retrieval cycle, hence it is not clear at which point a woman should be advised to desist from further autologous attempts. Certainly, for those who will accept the proposal, donor oocytes from younger women can provide a higher chance of livebirth and this is probably best undertaken at the 'youngish' age of 45–49 years, prior to established menopause.

Advanced age data from authorities

Data from the most recent annual report of the Australia and New Zealand Assisted Reproduction Database (Fitzgerald et al., 2017) for procedures conducted during the year 2015 show that live births per initiated cycle for women aged ≥45 years using autologous fresh cycle was 0.3%, whilst autologous frozen cycle was 7.0%, oocytes having been cryopreserved at a younger age (<45 years). The most recent national clinical summary report published by the Society for Assisted Reproductive Technology (SART, 2017), an affiliated body of the American Society for Reproductive Medicine (ASRM), indicates a 3.2% live birth rate from autologous cycles for women >42 years, but no data are provided for specific years in this older age range, although the SART website does enable potential patients to calculate their chance of livebirth. Entering age 51 years, height 1.7 meters, BMI 24.3 kg/m^2 using own eggs showed a cumulative livebirth chance from one cycle as 1% and 2% after three cycles. The comparable rates for age 48 years is shown as 2% after one cycle, 3% after two cycles and 4% after three cycles. It is not clear whether these estimates are based on real experience in ART or generated from spontaneous pregnancy data. The European Society for Human Reproduction and Embryology (ESHRE) reporting on the year 2013 (Calhaz-Jorge et al, 2017) provides livebirth data for an age range of 15–45 years but nil documented thereafter.

Of interest is birth data for 2016 published in the National Vital Statistics Report (Martin et al., 2018) from the United States Department of Health and Human Services showing birth rates for women >45 years as 0.9 per thousand women, with 786 of these births occurring in women aged ≥50 years, being 0.7 per ten thousand women in the age range 50–54 years. The nature of these pregnancies (natural or assisted) is not described. Perhaps the oldest woman achieving a livebirth from autologous oocytes utilising IVF is aged 50 years, documented in the journal *Fertility and Sterility* by authors from West Bengal, India as a rare case (Rani et al., 2015). However, given the

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rarity of such pregnancies from ART, the report could be treated sceptically given that 50% of births in India still occur at home; birth certificates may not be generated in real time; and the reported case relied on a government-issued voter's card to indicate the woman's age. Gleicher and colleagues ignored this report from Kolkata and we concur that the case is not worthy for consideration here given the circumstances surrounding the purported age of the woman.

The largest single centre report (Gunnala et al., 2017) shows live birth rates per initiated autologous cycle of 2.9% for the 679 cycles in women age 45 years; 0.5% for the 198 cycles in women age 46 years; nil for the 19 cycles in women age 48 years; and nil for the 5 cycles in women age 49 years. Among the entire group of women age ≥ 45 years it was noted that a minimum of 4 mature oocytes was required to generate any pregnancy.

Adjuvants for advanced age

The question of whether adjuvants can assist women of advanced age or those with low ovarian reserve to join the ranks of success with autologous cycles has only recently started to become clearer. Two of the authors of this editorial have been exploring the relevance of GH and DHEA, with recent publications reporting the most current knowledge, albeit with the caveat that these studies have identifiable weaknesses, mainly related to being retrospective. When GH was used for the first time in women classified as poor prognosis for one or more of four reasons (advanced age, poor egg numbers, poor embryo development or repetitive failed implantations), GH improved the chance of livebirth by 6-fold overall and the effect was most marked in the age range 35–39 years (almost 15-fold benefit) but with diminishing benefit after 40 years, and no detectable benefit at ≥42 years (Keane et al., 2017). A further study which examined the effects of DHEA with or without GH showed no clear benefit for DHEA alone or any modifying or potentiating effect on live birth chance to the GH benefit (Keane et al., 2018). These studies covered the initiated fresh cycle outcomes. Analysis of the outcomes of GH-generated or DHEA-generated embryos that have been cryopreserved has yet to be undertaken, hence the biological mechanism for the GH benefit as embryo-mediated or endometrium-mediated has yet to be determined.

Ethical considerations

There are three ethical considerations in advanced age ART. The first is the welfare or best interests of the child. There is no indication from the evidence above that the use of autologous oocytes in women seeking to achieve a pregnancy at or after 45 is associated with a significantly increased risk of non-lethal abnormalities. The main effects appear to be failure to implant or miscarriage.

The second consideration is the autonomy of the woman. Women in public or private must be informed of the latest reliable statistics of success and failure, as tailored as possible to their subgroup. Provided women are presented with the evidence above, as well as the risks and costs of ART, and not coerced into choosing ART, their choice should be respected, even if the chances of success are low. A 1/100 chance of a healthy live birth can still be worth taking if the costs are low.

Lastly, distributive justice will determine whether advanced age ART should be offered within a public health system. Whether it is cost effective at low probabilities (1/100 or less) will depend on how the metric is constructed: if the quality-adjusted life years of the newborn created by ART are included, it will almost certainly be cost-effective. However, if relief of maternal psychological symptoms and improved quality of life is the only positive outcome, it will probably be of marginal or poor cost-effectiveness. None of these arguments would apply in private where a patient is meeting the full costs of ART.

Conclusions

The 40-year success story of ART has been accompanied by new knowledge in reproductive medicine enabling conception, pregnancy and ensuing livebirth in previously infertile circumstances. However, we have also learnt about some of the limitations, the main one being that related to the age of the female when using autologous oocytes. Best evidence does imply that subfertile women have almost no (<1.0%) chance of livebirth undertaking autologous fresh ART procedures after 45 years of age. They can conceive using donor oocytes from younger women or even using autologous oocytes or embryos cryopreserved at younger ages. Whilst women over 45 years who are prepared to cover all costs should be enabled to undertake a treatment cycle attempting to achieve pregnancy with autologous oocytes in order to 'come to terms' with their infertility status, they need to be given the best available advice, as contained within this Editorial.

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