

## The Concepts and Consequences of Early Ovarian Ageing: A Caveat to Women's Health

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### Abstract

Apparent rise in the incidence of infertility in females and the trend shifting towards delayed child bearing brought up the concept of ovarian ageing. Women in their early thirties show poor ovarian reserve which is an entity named as early ovarian ageing. Early ovarian ageing is mostly genetically determined, but acquired modifiable factors like smoking, or ovarian surgery have some roles. Infertility and subfertility are the only clinical recognizable sequelae in the early ovarian ageing. The worrisome fact is that the outcome of assisted reproductive techniques is also not that much encouraging. Even if ovarian priming with DHEA has raised hope in the assisted reproductive techniques for these patients, but more randomized trials are needed to support this. Screening of these women with antimullerian hormone, antral follicle count and genetic analysis may be useful for recommendation at appropriate biological time regarding conception or fertility preservation.

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### Introduction

A recent contribution of assisted reproductive technology has been the better understanding of reproductive ageing. Results of *in vitro* fertilization (IVF) cycles showed accelerated decline infertility and onset of early menopause. Faddy et al. (1) showed that this accelerated decline is triggered by a number of ovarian follicles falling below a threshold value (25000 follicles). At this follicle number, the exponential rate of follicle decline changes from -0.097 to -0.237 by age. This mathematical model shows this accelerated decline of fertility nearly takes 13 years to result in menopause. Therefore, women who become menopausal by the age of 45 years will have begun accelerated decline of fertility at the age of 32 (when the threshold 25000 follicle is reached). The caveat is that these women will be asymptomatic with regular menstrual cycles, making it more difficult to diagnose. Although initially taken as an IVF headache, these women should be classified as women with early ovarian ageing (EOA).

Also known as premature ovarian ageing or primary occult insufficiency. This represents a shift to the left of the normal ageing process. Epidemiologically, 10% of women undergo into early menopause before the age of 46, and it is estimated that 10% of women in the general population might be at risk of early ovarian ageing (2).

**Criteria to define early ovarian ageing:** Due to lack of a uniform criterion, poor response to ovarian stimulation was taken as a sign of EOA, making this entity as a retrospective diagnosis. Recently, the European Society of Human Reproduction and Embryology issued a consensus on the definition of poor ovarian reserve for ovarian stimulation during IVF process as the Bologna criteria for poor ovarian response (3). At least two out of the three criteria are needed to define poor ovarian reserve (POR).

1- Advanced maternal age (>40 years) or any other risk factor for POR.

2- A previous POR (<3 oocytes with a conven

tional stimulation protocol).

3- An abnormal ovarian reserve test (*ie.* AFC, 5–7 follicles or antimullerian hormone (AMH).

This poor ovarian reserve in early thirties is synonymous with EOA.

**Early ovarian ageing to premature ovarian failure: A continuous process:** EOA is associated with a number of predictable sequel, as in terms of fertility prognosis, reproduction and general health. Due to its long latent period, screening for EOA might be possible among asymptomatic young women in the general population or in high risk groups, using tests that were initially developed to predict the outcome of IVF, especially the AMH and antral follicle count (4, 5). The same epidemiological factors that determine the age of menopause are likely to determine the risk of EOA. The main risk factors are:

1- Genetic: a family history of premature menopause; x chromosome derangements: mosaics, deletions, inversions and translocations; FMR1 (fragile x) gene; gene polymorphisms of AMH and AMH receptor genes and trisomy 21 (6, 7).

2- Autoimmune factors: thyroid autoimmunity, autoimmune oophoritis

3- Acquired modifiable factors: chemotherapy, radiotherapy, pelvic surgery (8, 9), pelvic infections or tubal disease (10, 11), severe endometriosis (12) and heavy smoking (13).

Premature ovarian failure (POF) is the end point of an extreme form of EOA and affects 1% of the general population (14). It is associated with irregular menses or secondary amenorrhoea and menopausal symptoms, as well as abnormally high baseline FSH (15). There is no effective fertility treatment for POF other than egg donation (16), while EOA is much more common (10%) in the general population and the individual is young and asymptomatic. Their baseline FSH may be within normal limits. They are fertile and will remain fertile for a few years following the diagnosis (17). Apart from reduced likelihood of conception both naturally and through IVF, they will have higher incidence of aneuploidy, miscarriage and dizygotic twinning (17, 18). Therefore, EOA is a public health issue but it is amenable to prevention of childlessness through screening and early intervention.

**Does EOA affect conception by quantitative decline of oocytes only or by affecting both quality as well as quantity?** The rapid decline of pregnancy rates in late thirties both naturally and with IVF is accompanied by an increasing rate of spontaneous mis-

carriages, and chromosomal abnormalities in the embryos, which mainly contribute to a deterioration of oocyte quality (19). The main cause of deterioration of oocyte quality is meiotic non-disjunction (20). It is caused by an accumulation of damage in the DNA of the women growing older. Another theory is that differentiation of oocyte quality is already established to some degree during foetal life and the best oocytes are simply recruited and selected first, therefore oocytes of inferior quality remain and are found at a more advanced age (21). The two hit models of non-disjunction appear to combine all the theories of oocyte ageing. The overall impact of the second hit, which is the effect of the environment on the quality of oocyte pool, depends upon the duration of environmental exposure and therefore age (22).

On the basis of this two hit theory, the quantitative decline is faster than the qualitative decline (23, 24). Young women with EOA are not infertile. Women undergoing EOA process are fertile in their mid-thirties, are asymptomatic and have regular periods. Reasons behind this condition are possession of adequate follicles and more importantly the good quality of their oocytes as it may depend on their chronological age. This is reflected in the better IVF success rates of poor responder who are chronologically young, compared to extremely poor IVF outcome of older poor responders (25). As with best oocytes, poor responders have lower follicle development (<4) and lower live birth rates than women of the same age with normal IVF response (26). This suggests young women with EOA have reduced fertility potentials.

**Cosequence of EOA:** Most young women with EOA who are still in their thirties, will remain completely asymptomatic and will have normal menstrual cycles and normal endocrine function a few more years following the early diagnosis. However, their fertility will be less than that of their peers with normal ovarian ageing and will gradually reach extremely low levels of fertility than expected for comparable age. They will eventually go through menopause before the age of 46 (1). In the years following the diagnosis, they may take longer to conceive or present with unexplained infertility. During IVF cycles they may behave as poor responders to ovarian stimulation and will need higher doses of gonadotrophins. They may also have tendency towards adverse lipid profiles and an increased cardiovascular risk (28, 29).

Elevated FSH concentration in early follicular phase has been shown to be associated with trisomy 21 and other aneuploidies (30). Women with unexplained recurrent pregnancy loss had a greater incidence of elevated day-3 FSH and estradiol levels. Premenopausal women with serum FSH > 7 mIU/ml had significantly elevated total serum cholesterol and LDL levels (31). Patients with accelerated ageing syndromes such as Werner syndrome, ataxia telangiectasia, Hutchinson-Gilford progeria and Down syndrome are either infertile or have an early menopause (32). There is an association between early menopause and shorter life expectancy (33).

**Clinician's role; prevention, evaluation, informed decision and treatment individualisation:** On the basis of Te-Valde's hypothesis that the time interval between major reproductive events is fixed and the factors determining the age at menopause also affect the age of all reproductive events, it can be speculated that the main cause of EOA are genetic. Family history of early menopause is a high risk factor for EOA and it is not preventable either. Smoking is a preventable factor that can cause an early menopause and a poor ovarian response to exogenous stimulation. Pelvic inflammatory diseases are associated with a poor ovarian response but are potentially preventable. Endometriosis is associated with poor ovarian response which is not a preventable factor although progress of endometriosis may be modified by drugs. Chemotherapy and pelvic surgeries- and not just ovarian surgery- are obvious important causes of EOA. Therefore, surgeons should look into this subject during such surgeries. Few tests like genome-wide linkage analysis and genome-wide association studies to detect genes associated with ovarian ageing have been applied to predict ovarian ageing in some studies (34), but the task is far from being accomplished.

In the twenty-first century, couples postpone childbearing because of their busy schedules and career orientation by the use of reliable contraception. Therefore, trying to become pregnant at a more advanced age contributes considerably to an increase in the incidence of infertility carrier oriented women. This trend is definitely avoidable. Women are unaware of the fact that fertility declines after early thirties in some individuals. Significant achievements in ART have created the false impression that fertility can be safely postponed.

With conventional ART protocols, women with early ovarian ageing get depressing results. Some additional modification like, ovarian stimulation protocols adjusted for decreased ovarian reserve, additional medications to control contributing factors, such as autoimmune abnormalities, which sometimes present in patients with EOA and ovarian priming with oral dihydroepiandrosterone (DHEA) are desirable for increasing conception rate of ART in these women (35). Ovarian priming not only increases IVF pregnancy rate and reduces risk of miscarriage it but also increases spontaneous conception rate in these patients. Management of certain antenatal conditions such as growth restriction could influence the size of ovarian reserve at birth, (36, 37). Chemotherapy that will limit the extent of ovarian reserve should not be used unsparingly. The same approach should be kept in mind during radiotherapy.

There is ongoing research into the possibilities of altering ovarian reserve decline rate but currently little can be offered in routine clinical practices. Currently good quality embryo freezing is an option. Improvement of oocyte cryopreservation techniques and research in the area of stem cells may open new possibilities in future (38, 39). The option of ovarian transplant is not much encouraging and for autotransplants it requires only monozygotic twins, although it is still in research stage (38).

### Conclusion

Postponement of child bearing to late thirties is a gamble. Proper assessment and detection of ovarian ageing, employment of current or development of predictors of ovarian reserve may enable the health care providers to recommend, at an appropriate time, early pregnancy achievements or fertility preservation in women at risk.

### Conflict of Interest

Authors declare no conflict of interest.

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