Maturitas xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Maturitas

journal homepage: www.elsevier.com/locate/maturitas

Testing ovarian reserve in pre-menopausal women: why, whom and how?

Agnieszka Podfigurna[a], Krzysztof Lukaszuk[b,c,d,e], Adam Czyzyk[a], Michal Kunicki[c], Marzena Maciejewska-Jeske[a], Grzegorz Jakiel[c,f], Blazej Meczekalski[a,*]

[a] Department of Gynecological Endocrinology, Poznan University of Medical Sciences, Poznan, Poland
[b] INVICTA Fertility and Reproductive Center, Gdańsk, Poland
[c] INVICTA Fertility and Reproductive Center, Warsaw, Poland
[d] Department of Gynecological Endocrinology, Medical University of Warsaw, Warsaw, Poland
[e] Department of Obstetrics and Gynecological Nursing, Faculty of Health Sciences, Medical University of Gdansk, Gdańsk, Poland
[f] Department of Obstetrics and Gynecology, Center of Postgraduate Education, Warsaw, Poland

ARTICLE INFO

Keywords:
Ovarian reserve
premenopausal women
anti-Müllerian hormone

ABSTRACT

Numerous social and environmental factors (environmental hazards, social factors such as education and career, higher economic status desired before the decision is made to have children) influence a women's decision to postpone pregnancy until late reproductive age. In turn, age is related to a fall in ovarian reserve. The main goal of testing ovarian reserve is the identification of women with so-called diminished ovarian reserve (DOR). Additionally, it provides assistance in the counselling of women who are planning to use assisted reproductive techniques (ART). This review examines current methods of testing ovarian reserve and their application. The most useful methods of assessing ovarian reserve are ultrasonographic count of ovarian antral follicles (AFC) and serum tests of both the anti-Müllerian hormone (AMH) level and the third-day level of follicle stimulating hormone (FSH). However, there are limitations to the currently used methods of testing ovarian reserve, especially in relation to their specificity and sensitivity. It is also difficult to predict egg quality based on these tests. The value of screening programmes of ovarian reserve is yet to be determined.

1. Introduction

The introduction of the oral contraceptive pill in the 1960s initiated a trend towards delayed parenthood. Reliable contraceptive methods allowed women to avoid pregnancy and invest in their careers [1]. Connected trends were longer education, higher rate of participation in the workforce and delayed marriage. Delayed motherhood is observed mainly in Europe, the United States and Australia, but also in other regions [2–5]. This complex phenomenon results not only from the introduction of the contraceptive pill but also from other lifestyle and socioeconomic factors [6]. Women's educational attainment has increased over the last several decades. In 1960, among the member states of the OECD (Organisation for Economic Co-operation and Development), 11.7% of women aged 24–54 had secondary or higher education, whereas in 2010 this rate was 54.4% [7]. Along with the increased access to education, women's participation in the labour force has also been growing. In the OECD countries, it rose from an average of 54% in 1980–71% in 2010 [8]. Women are now more educated and can plan their career paths to a greater extent than their mothers. Higher levels of education and access to professions previously reserved for men have resulted in higher incomes and more stable economic positions for women. However, women who have their first child while they are still studying generally have to postpone their career, as they temporarily withdraw from the labour market [9]. When they do wish to return to work, many young mothers seek part-time employment [10,11]. Waldenstrom concluded that the main factors responsible for delaying parenthood are connected to 'place to live, financial security and completion of education'. In addition, growing up in a large city, having well-educated parents and having no siblings have been reported to be associated with delayed parenthood [12]. Many women who have delayed motherhood refer to difficulties in finding an optimal partner and personal feelings of being insufficiently 'mature' for parenthood.

Finally, not to be underestimated is the low level of awareness among women in general that fertility reduces with age. Unfortunately, media portraits of celebrities having children later in life increase the perception that delayed parenthood is safe and natural [13].

Postponement of parenthood can increases the time needed to achieve pregnancy, due to the diminished fertility of older women [14]. In general, the term 'ovarian reserve' reflects both the quantity and

* Corresponding author at: Department of Gynecological Endocrinology, Poznan University of Medical Sciences, Ul. Polna 33, 60-535, Poznan, Poland.
E-mail address: blazejmeczekalski@yahoo.com (B. Meczekalski).

https://doi.org/10.1016/j.maturitas.2017.11.014
Received 11 September 2017; Received in revised form 8 November 2017; Accepted 20 November 2017

quality of eggs in the ovaries, which in turn reflect reproductive potential [15]. Good markers of ovarian reserve are required so that women of older reproductive age can be appropriately counselled. Age is the primary marker of ovarian reserve, but there is a high variability between different individuals of similar age.

In this context, we undertook a narrative review of important studies of the pathophysiology, epidemiology and methods used for the assessment of ovarian reserve in women of late reproductive age.

2. Methods

PubMed was searched using following the terms: ovarian reserve, late reproductive age, premenopause, fertility, antral follicle count, anti-Müllerian hormone, ovulation and premature ovarian insufficiency. The reference lists of relevant papers were then searched for further relevant sources.

3. Pathophysiology

The gradual decline in fertility with increasing age is supported by strong scientific data. A significant decrease in female fertility begins as early as the fourth decade of life. Shwartz et al. [16] reported the cumulative pregnancy rate in a cohort of women undergoing up to 12 artificial inseminations. Pregnancy was achieved by 74% of the women under 31 years old, 62% of those aged 31–35 and 54% of women aged over 35. The natural capacity to conceive may end before the menopause, but there is a wide variation as to when this occurs [17].

However, decline in fertility does not correlate with changes in the prevalence of anovulation with age. A study assessing ovulation (based on serum progesterone levels in 3168 regularly menstruating women aged 20–49.9 years) found that overall anovulation occurred in over one-third of clinically normal menstrual cycles. Ovulation occurred in 50.5% of cycles in women aged under 30 and 61.2% of those aged 45–49 [18].

Other data show that a longer menstrual cycle in perimenopausal women is not always associated with anovulatory cycles. In women aged 40–55 years (N = 139) ovulation was present in 93% of those with 21–35 day menstrual cycles, in 55% of those with 36–50 day cycles, in 40% of those with 51–75 day cycles and in 17% of those with cycles of over 76 days [19].

Considering the large discrepancy between incidence of infertility and ovulation abnormalities, other factors should be considered as causative for the decline in fertility with age. Several mechanisms have been proposed, among them the age-related decline in the quality and quantity of oocytes.

3.1. Oocyte-dependent causes

The number of oocytes decreases continuously, from fetal life, when the pool of germinal cells is established, until the menopause. Based on histological data and mathematical models, the fetal number of oocytes is estimated to be 6–7 million in the second trimester of pregnancy, 1–2 million in the newborn, and only 0.3–0.5 million at puberty. Western women of reproductive age ovulate about 500 times, but as the vast majority of germ cells undergo atresia, perimenopausal women's ovaries contain only approximately 1000 oocytes [20]. It has been shown that not only the number of germ cells but also their quality is strongly impaired with advanced age.

Through studies of assisted reproductive techniques (ARTs), we can compare the number of live births in different age groups with homologous and donated oocytes. The main predictor of live birth is the age of the egg donor, not the host. In groups of advanced age, up to 60 years old, the success rate was high if the age of donor was younger (20–30 years) [21]. The 2014 National Summary Report of Society of Assisted Reproduction (SART) found that among patients using their own eggs the cumulative live birth rate was much higher for younger than for older women: 41.2% for those under 35 years old, 11.7% for those aged 41–42 and 3.7% for women aged over 42 [22].

In line with these data, the rate of oocyte aneuploidy increases with age. Women aged less than 35 had a 53% rate of aneuploidy among their embryos obtained in in vitro fertilisation (IVF) procedures, whereas in older groups it was significantly higher (74% among patients aged 41–42 and 93% in women older than 42) [23]. The high prevalence of aneuploidy seems to be related to meiotic errors and abnormal chromatin division spindles [24].

3.2. Other possible causes

Even though oocyte-dependent causes of decreasing fertility with age seem to be most relevant (as shown above), some data support the involvement of other factors [24,26].

Impaired angiogenesis has been found in cumulus cells surrounding the oocyte. Abnormal angiogenesis in turn may cause hypoxia, which is known to interfere with chromatin division [25]. Other proposed causes have related to placental function, uterine pathology (fibroids, adenomyosis) and endometrial pathology (implantation failure, polyps). Their significance, however, seems to be low, since epidemiological studies have revealed only a weak link between women's age and stillbirth [26].

Environmental and exogenous factors have also been examined but most of these studies have used only surrogate indices (hormonal levels, ovulation rate) rather than clinical end-points, and many of the conclusions are based on relatively small cohorts [27–31].

Micro- and macro-nutrient intake in the diet is related to ovarian function. Higher ovulation rates are found among women who consume greater amounts of folic acid, docosapentaenoic acid, and caffeine [27–29], and lower rates among groups consuming larger amounts of dairy foods (cream and yogurt) [30]. Also, the contamination of food with metals (cadmium, lead, mercury) has been shown to interfere with hormone levels (follicle stimulating hormone, FSH, and progesterone), but not ovulation [31]. Use of common analgesic medicines (ibuprofen, acetaminophen, aspirin, naproxen) is also associated with a decreased rate of ovulation [32]. The role of endocrine-disrupting chemicals (EDCs) in human reproduction has also been looked at. Data regarding fertility in women of late reproductive age is still lacking, but evidence suggests that EDCs can lower the ovulation rate and impair the hormonal milieu in women of reproductive age [33,34].

4. Why test?

The incidence of spontaneous primary ovarian insufficiency (POI) appears to have remained stable in recent decades. It is estimated to affect approximately 1% of women by the age of 40 and 0.1% by 30 [35,36]. Such factors as late menarche, irregularity of menses or longer breastfeeding are said to protect ovarian reserve [44].

Because of the improvement in the treatment of childhood malignancies and the consequent increased survival rates, the incidence of iatrogenic POI has risen. Islam et al. [37] estimated the incidence of both spontaneous and iatrogenic POI among almost 5000 women born in 1958 in the UK and assessed various risk factors for POI. The prevalence of both spontaneous and iatrogenic POI was reported to be 7.4% [37].

Age at menopause shows strong heritability. Nearly 15% of women with the diagnosis of POI have a first-degree relative also affected by POI. [38]. Morris et al. evaluated the genetic and environmental causes of POI. They studied more than 2000 first-degree relatives and confirmed that early menopause aggregates within families, and estimated that 42% of the variation in age at menopause can be explained by genetic and 14% by environmental factors common to siblings. The study also showed that women whose mother or sister experienced early menopause were themselves approximately six times more likely to be affected by early menopause (for mothers – odds ratio [OR]: 6.2,