

Ovarian aging and infertility

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Summary

Ovarian aging is expressed with altered menstrual cyclicity, endocrine and biochemical profiles and impaired fertility. Shortening of the menstrual cycle may be the first signal of diminished ovarian reserve. Hormonal interplay in the aging ovary is manifested as a monotropic FSH rise, decreased inhibin B concentrations and fluctuating estradiol concentrations.

Due to social changes, childbearing has been delayed, thus the group of women in their late thirties seeking infertility treatment has been increasing. Intrauterine insemination (IUI) usually precedes more sophisticated assisted reproductive technology (ART) treatments such as *in vitro* fertilization-embryo transfer (IVF-ET) and intracytoplasmic sperm injection (ICSI). We present the outcomes of ART treatments achieved in our institution in women over 38 compared to younger women. The pregnancy rate after IUI was 3.7% in women over 38 years, and 28.6% in women less than 38 years; after IVF-ET the cumulative pregnancy rate was 16% (the miscarriage rate 21%) in women over 38, and 28% (13%) in women less than 38 years; the cumulative pregnancy rate after ICSI was 9% (the miscarriage rate 26%) in women over 38, and 27% (the miscarriage rate 14%) in women younger than 38 years. Women in advanced age should therefore be properly counselled and informed about poor success rates, and about the high cost of infertility treatment.

Key words: Ovarian aging; Impaired fertility; Infertility treatment; Menstrual cyclicity; FSH; Inhibin B.

Introduction

Ovarian aging and age-related changes in the female reproductive life have become more actual and significant due to changes in social development and altered attitudes that have resulted in delayed pregnancy planning in developed countries [1].

Progressive decline in fertility with advanced age has created a new population of women presenting in infertility centres for further investigations and treatment. The knowledge of physiology of the reproductive function is therefore required of health care providers to be able to give the most adequate counselling about the outcome of infertility treatments in women aged over 38.

Hypothalamic-pituitary ovarian axis is the first organ system in the body that ages to a state of non-function at a time when the function of most other organ systems in women is not impaired. There are two competing hypotheses in regard to aging in the female reproductive system, yet they both consider that the rise of monotropic follicle stimulating hormone (FSH) promotes further follicular depletion [2]. Women are born with a finite number of primordial follicles in the ovaries. There is a progressive loss of primordial follicles throughout life, but the loss starts accelerating approximately at the age of 38. The total loss of primordial follicles in the ovaries occurs several years after menopause.

From the clinical point of view the changes in menstrual cyclicity, endocrine and biochemical profiles, and fertility are important in predicting ovarian aging and should therefore be carefully considered.

Menstrual cyclicity

The chronological age does not always cope with the biological age. The women with apparently normal cycles can have a rather variable ovarian reserve. Shortening of the menstrual cycle may be the first signal of diminished ovarian reserve.

Follicular recruitment usually begins during the late luteal phase, after the corpus luteum secretion of progesterone, E₂ and inhibin has started to decline. FSH levels show an inverse pattern to E₂ levels and have an acute elevation unaccompanied by LH for five days before the onset of menses, reaching the plateau two

days after the onset of menses. Consequently, rising FSH levels stimulate a new cohort of ovarian follicles to grow [3]. An explanation for shortening of the menstrual cycle has been suggested by Batista *et al.* [4] who have found that in cycling women over 40 inhibin levels at the time of follicular recruitment are decreased, implying a primary abnormality in the cohort of follicles that begin to grow in the luteal-follicular transition. Reduced inhibin concentrations may be related to a gradual decline in the number and quality of oocytes in the aging ovary. Due to decreased inhibin levels a disruption in follicular recruitment can occur with consequent impaired length of the follicular phase and different timing of ovulation and corpus luteum formation.

Endocrine and biomedical profile

The authors who published the first major study of serum gonadotropin and sex steroid levels in women both early and late in their reproductive lives were Sherman and Korenman [5]. They registered a striking selective increase in the levels of serum FSH in older regularly cycling women, and significantly lower levels of serum E_2 , LH and progesterone than in younger women. They proposed a regulatory hormone, an inhibin, to be responsible for a negative feedback control over FSH secretion, reduced in the years before the menopause due to a diminished number of follicles.

Both E_2 and inhibin are important components of gonadal influence on FSH. E_2 alone is not sufficient to account for gonadal feedback, as illustrated by the failure of physiological levels of E_2 to suppress FSH into the normal range in women with ovarian failure [6]. This explanation has been confirmed in the study on women evaluated for idiopathic infertility; they were found to have elevated basal FSH and diminished serum inhibin levels without a corresponding fall in serum E_2 levels [7]. Additionally, this explanation has been confirmed by Klein *et al.* who found that aging women with elevated FSH levels have E_2 levels similar to or higher than younger women, and significantly reduced inhibin B levels [8]. Therefore in women continuing to cycle regularly with increasing age the variations in serum E_2 allow the suggestion that E_2 itself may not be a reliable marker of follicular number [9].

In premenopausal period FSH levels vary considerably; several years before the menopause FSH levels gradually increase, the variability is high and it would be exceedingly difficult to identify meaningful cut-off levels in cycling women.

Inhibins

Inhibins are dimeric, disulfide-linked glycoproteins, consisting of an alpha subunit and either beta (A) or beta (B) subunit. Inhibin is synthesized in various tissues including brain, bone marrow, placenta, pituitary, testes and ovary. Its primary role is the suppression of the pituitary secretion of FSH.

Circulating inhibin B is primarily a product of small follicles, whereas inhibin A is a product of the dominant follicle and the corpus luteum. Inhibin B concentrations in the early follicular phase have been suggested to reflect the ovarian reserve. As the woman approaches the menopause, serum inhibin B in the follicular phase falls and this is accompanied by a rise in FSH. During the process of ovarian aging, the levels of inhibin B during the follicular phase decrease earlier than those of inhibin A [10-12].

The aim of our previous study was to investigate the role of inhibins by assessing whether inhibin B is increased in women that do not respond to gonadotropin stimulation. Therefore, we determined FSH, inhibin B and E_2 levels in postmenopausal women, in women with premature ovarian failure, in poor responders to gonadotropin, and in women with normal menstrual cycles and found that the interplay of FSH, inhibin B and E_2 is of little, if of any value in predicting the ovarian reserve in women unresponsive to gonadotropin stimulation. Only in menopausal women and in those with premature ovarian failure has their interaction been defined [13].

Fertility

For approximately ten years it has been known that FSH levels measured on day 2, 3 or 4 of the menstrual period are highly predictive of future fertility. An FSH level > 14 IU/l is associated with only a 5-percent chance of achieving a pregnancy; also, normal FSH and high estrogen levels on day 3 are not promising for predicting fertility. This paradoxical finding suggests that the estrogen level is too high early in the cycle, which in turn suppresses FSH and further follicular growth.

The loss of fertility is the first sign of reproductive aging, usually associated with a monotropic FSH rise and changes in menstrual cyclicality. It appears that a single elevated FSH level represents severely diminished ovarian reserve and a poor prognosis for pregnancy even if the FSH levels in subsequent months are normal.

A clomiphene-citrate challenge test is one of the options to test ovarian reserve; in fact it is a screening test that predicts fertility options. Clomiphene citrate is administered from day 5 to 9 of the menstrual cycle in a daily dose of 100 mg. Levels of FSH are determined on days 3 and 10. The FSH level < 10 IU/l on days 3 and 10 is considered normal and represents the normal ovarian reserve. The levels between 11 and 15 IU/l on day 10 are intermediate and are associated with lower fertility and higher miscarriage rate [14-16].

Infertility treatment in women with advanced age

To many women deferring their reproduction, the options to treat their infertility have been offered by assisted reproduction technologies (ART). However, the age-related decline in pregnancy rates and a markedly elevated incidence of spontaneous abortion rates are observed also in ART [17]. Advanced maternal age is connected to chromosomal abnormalities, found in 50% of all first trimester abortions, most of them being autosomal trisomic defects [18].

Intrauterine insemination (IUI) is generally considered to be an intermediate step of low complexity before the application of more sophisticated ART, such as *in vitro* fertilization (IVF) or intracytoplasmic sperm injection (ICSI). According to the literature [19] there is a sharp contrast to the pregnancy rates in patients less than 39 years old (21% pregnancy rate per patient, 10% per cycle) than in older women (14% pregnancy rate per patient, 5% per cycle) that also exhibited an extremely high pregnancy wastage rate (73%).

The results of IUI performed at our department also clearly demonstrate the influence of age on the success of the procedure (Table 1).

Table 1. — *Pregnancy rates achieved by intrauterine insemination in the period 1999-2000 in women over 38 and in those less than 38 years old.*

	Age	
	> 38 years	< 38 years
No. of patients	27	260
No. of cycles	67	757
Cycles/patient	2.48	2.91
No. of pregnancies	1	75
Pregnancy rate/patient	3.7%	28.6%
Pregnancy rate/cycle	1.5%	9.9%

The data on miscarriage rates are lacking because of incomplete follow-up of the patients.

Besides maternal age the outcome of IUI is strongly connected to the patient's history of pelvic inflammation that seems to decrease the likelihood of conception by IUI. On the contrary, unexplained and anovulatory causes of infertility are etiologies with a relatively better prognostic value for pregnancy [20]. However, the outcome of IUI depends on the quality of semen; the presence of severe male factor infertility demands more sophisticated treatment modalities such as IVF or ICSI.

It has been generally accepted that IUI is a useful and cost-effective treatment modality for some infertility etiologies. Since the woman's age is one of the factors having a great influence on the outcome of IUI, it is of utmost importance that the procedure is not repeated more than two to three times. The patients should very soon thereafter be counselled on the IVF-ET procedure. The outcomes of IVF-ET treatment in women over 38 and in women less than 38 years old, registered at our Department, are shown in Table 2.

Table 2. — *Pregnancy rates achieved by IVF-ET in the period 1996-2001 in women over 38 and in those less than 38 years old.*

	Age	
	> 38 years	< 38 years
No. of patients	526	2733
No. of cycles	598	3.157
Cycles/patient	1.1	1.1
No. of pregnancies	98	882
Pregnancy rate/patient	16%	28%
Pregnancy rate/cycle	14%	25%
Cumulative pregnancy rate	16%	28%
Ectopic pregnancy rate	—	2%
Miscarriage rate	21%	13%

Women with advanced reproductive age have by far smaller chances to achieve a successful pregnancy with IVF-ET than those who are younger. Considering a high miscarriage rate and a low pregnancy rate it seems reasonable to highlight the fact that the cost of a delivery per an initiated cycle is 3.6 times higher than in younger women [21]. In case of male infertility ICSI procedures are effective in younger women, while in those over 38 years of age the results are not encouraging.

Table 3. — Pregnancy rates achieved by ICSI in the period 1996-2001 in women over 38 and in those less than 38 years old.

	Age	
	> 38 years	< 38 years
No. of patients	280	1878
No. of cycles	353	2156
Cycles/patient	1.2	1.1
No. of pregnancies	33	466
Pregnancy rate/patient	11%	25%
Pregnancy rate/cycle	9%	22%
Cumulative pregnancy rate	9%	27%
Ectopic pregnancy rate	6%	2%
Miscarriage rate	26%	14%

It is obvious that in patients with advanced age there is a significant decline in success rates obtained by IVF-ET and ICSI. Besides poor ovarian response and high percentage of cancelled cycles, oocyte factors seem to be most importantly responsible for poor outcomes. Some efforts, including special stimulation protocols, zona pellucida micromanipulation and preimplantation genetic diagnostic procedures could improve the success rate, although not substantially. It is of utmost importance that women with advanced age undergoing ART procedures are properly informed and counselled about the poor success and high costs of their infertility treatment.

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