Introduction

Infertility is the failure of a couple to conceive (regardless of cause) after 1 year of unprotected sexual intercourse - using no birth control methods. Infertility affects approximately 10-15% of reproductive age couples. Its overall prevalence has been stable during the past 50 years; however a shift in etiology and patient age has occurred.

New and advanced technologies to overcome the problem of infertility have resulted in improved pregnancy rates using assisted reproductive technologies (ART) ***(Elizabeth & Terri Lynn, 2009).***

The concept of ovarian reserve is loosely defined as the size and quality of the remaining ovarian follicular pool. The number of oocytes in any given women is genetically determined and inexorably declines throughout life, from approximately 1-2 million at birth to about 300 ,000 at puberty, 25,000 at age 37-38 (when the pace of follicular depletion accelerates), and fewer than 1000 at menopause. The evaluation of ovarian reserve has been and still the focus of substantial clinical research. The assessment of ovarian reserve is valuable for determining stimulation protocols and predicting ART outcome ***(Bukman & Heineman, 2002).***

Poor response in IVF cycles is a cause of cycle cancellation and to repeated attempts for a better response in

subsequent cycles. Treatment cancellation because of poor ovarian response is a significant problem. The prevalence of poor response is estimated to be 9-24% of the ART population ***(Vladimirov et al., 2005).***

A poor ovarian response is a reflection of reduced total ovarian follicular capacity (reserve). Identification of women with a markedly reduced ovarian reserve, likely to lead to cycle cancellation, is paramount prior to embarking on expensive and invasive treatment such as IVF ***(Akande et al., 2004).***

Ovarian reserve tests (ORT) help to predict the response to exogenous gonadotrophin stimulation and the likelihood of success with IVF and are widely accepted as an essential element of the evaluation of IVF candidates. Considering the associated costs, logistics, and risks, accurate prognostic information is very helpful to couples who may be considering IVF. (ORT) are generally reliable, but not infallible. A number of methods for measuring ovarian reserve have been described ***(Speroff & Fritz, 2005).*** The goal of these tests is to provide information regarding oocyte quality and quantity ***(Vladimirov et al., 2005).***

ORT can roughly be divided into three groups: ***(Haadsma et al., 2007). A-Passive Tests:*** These tests measure early follicular phase hormones level and they include: Female age; Cycle day 3 serum FSH concentration; Cycle day 3 serum estradiol (E2) concentration; Cycle day 10 serum progesterone

(P) concentration; Cycle day 3 serum Inhibin B concentration; Serum Anti-Mullerian Hormone (AMH) concentration and Ovarian biopsies.

B- Dynamic Tests: These tests assess the endocrine response of the ovaries to exogenous stimuli and they include: Clomiphene Citrate Challenge Test (CCCT); Gonadotrophin releasing hormone (GnRH) Agonist Stimulation Test (GAST); and exogenous FSH ovarian reserve test (EFORT).

C- Transvaginal Ultrasound (TUS): This is used for measuring Mean Ovarian Volume (MOV), Antral Follicle Counts (AFC), and Ovarian Stromal Blood Flow.

Most of the studies concerning biochemical markers of ovarian responsiveness have been directed towards identification of poor responders. But as all these tests lack sensitivity and specificity, the use of ratios of interacting markers rather than absolute values, seems to be more informative, more sensitive, and more specific. ***(Abd El Maeboud.2006).***

In reproductive endocrinology, the relative imbalance of hormonal or receptor ratios is sometimes more informative than the absolute concentrations ***(Tarlatiz et al., 1995).***

The gonadal steroid E2:FSH ratio and the gonadal peptide inhibin-B: FSH ratio were likely to reflect more closely the degree of readiness of the follicular cohort and enhanced the

ability to predict the outcome before initiating ovarian stimulation in assisted reproduction as seen in several studies ***(Ismail et al., 1997).***

In 1999, ***Ismail*** evaluated the potential role of the basal E2: basal FSH (E2:FSH) ratio as a predictor of ovarian response to HMG stimulation based on the hypothesis that the balance between both hormones during the early follicular phase reflect the ovarian reserve ***(Ismail, 1999).***

In 2004 another study pointed out the importance of the E2:FSH ratio in prediction of ART success indepentntly of age and other clinical progonostic factors ***(Frazier et al., 2004).***

Aim of the Work

The aim of the work was to assess basal serum Estradiol/Follicle-Stimulating Hormone (E2/FSH) ratio as a predictor of ovarian response in patients undergoing Intracytoplasmic Sperm Injection (ICSI).

Anatomical Basics

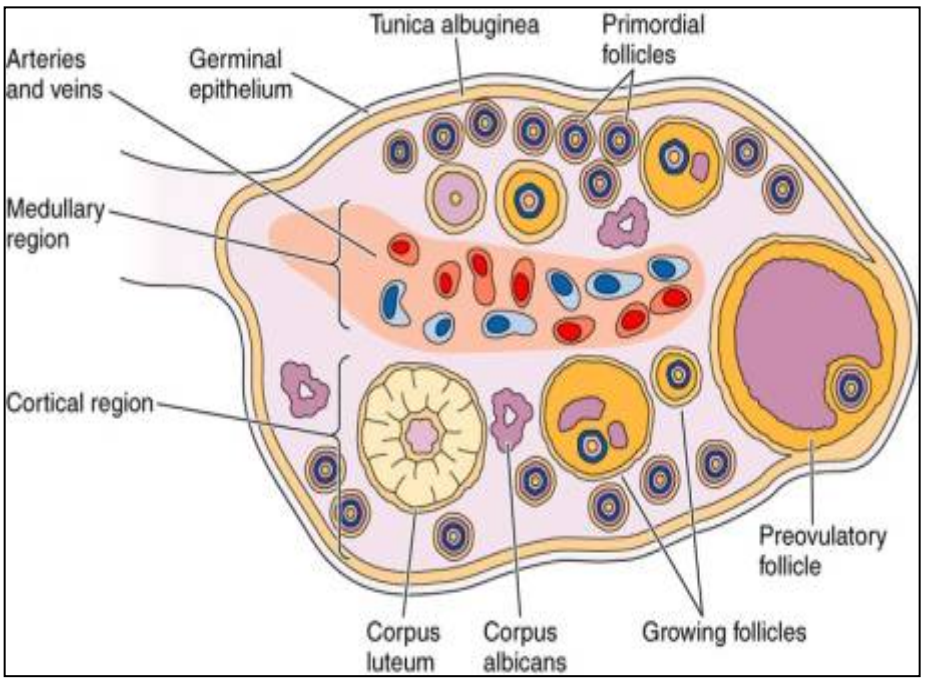

Figure (1): *Diagramatic section in the ovary.*

The human ovary contains a fixed pool of primordial follicles, maximal at five months of intrauterine life, and numbering around 701,000 at the time of birth. From this number, the pool reduces to 250,000-300,000 at the time of menarche and then declines. With increasing age, at 37-38 years, it contains about 25,000 follicles. and at this number, the follicular depletion accelerates, and menopause is estimated to be about 12-14 years away occurring at a mean age of 50-51 years, when only a few hundred or thousand follicles remain.

This age may vary in different populations ***(Wallace and Kelsey, 2004)***.

Follicular depletion occurs largely due to atresia, and is accompanied by a reduction in ovarian volume, which is thus also related to age ***(Santoro et al., 2003)***.

It has been suggested that the normal rate of oocyte depletion follows a biphasic pattern, accelerating below a number of 25 000 at a mean age of 37–38 years based on histological analyses of ovaries. This suggested midlife acceleration in oocyte loss is of great interest ***(Tufan et al., 2004)***.

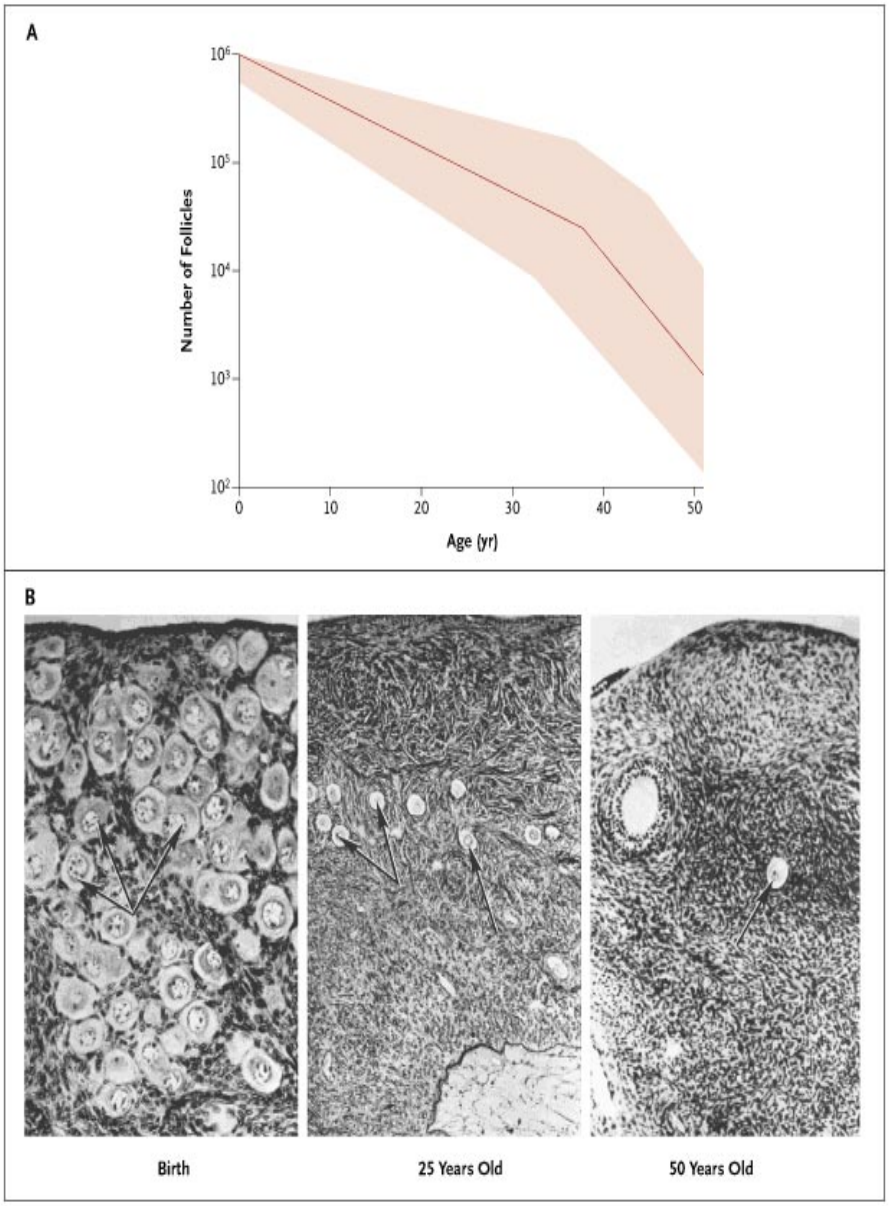

Figure (2): *Decline in the Number of Oocytes from Birth to Menopause* ***(Lobo, 2005).***

Physiology of Ovulation

In the embryo, germ cells migrate from the urogenital ridge to the primitive ovary where they proliferate to form 3.5 x 10^6 oocytes in each ovary by about 20 weeks of intrauterine life. Most of these germ cells are destroyed through apoptosis. The ovary is endowed with a fixed number of primordial follicles at the time of birth, about 1 x 106 in each ovary. This number steadily dwindles throughout life as a result of atresia and recruitment towards ovulation. Fewer than 500 of the original 7 x10^6 (0.007%) oocytes are released in the entire reproductive life span of a woman ***(Goswami and Conway, 2005).***

Ovarian folliculogenesis is a lengthy developmental process which involves a prolonged period of cellular proliferation followed by rapid cellular differentiation in selected follicles that respond to stimulation by the pituitary gonadotrophins. At any one time during the reproductive life of a woman, the paired ovaries will contain a heterogenous population of follicles at different developmental stages including a resting reserve of primordial follicles, pre-antral and early antral follicles (0.2–2.0 mm) which are largely gonadotrophin-independent, small antral follicles (1–5 mm) that are gonadotrophin-responsive or selectable, and a few larger

antral follicles (>5 mm) that are gonadotrophin-dependent ***(Jayaprakasan et al., 2007).***

There are four events involving the hypothalamic-pituitary-ovarian axis that control the human menstrual cycle: (1) the secretion of FSH, responsible for the development of ovarian follicles and production of estradiol. Throughout the cycle, estrogen maintains low gonadotropin levels via its negative feedback effect on hypothalamic gonadotropin-releasing hormone and consequently LH and FSH secretion. (2) The FSH-induced increase in ovarian estrogen secretion to levels of sufficient strength and duration triggering an LH surge (positive feedback). (3) The LH surge, a hypothalamic-pituitary response to the estrogen stimulus. This positive feedback response of estrogen on LH secretion has been used as a test of hypothalamic-pituitary function. (4) Ovulation and luteinization of the follicle, triggered by the LH surge, forming a corpus luteum. This is an ovarian response that results in progesterone secretion necessary for the establishment of a pregnancy ***(Weiss et al., 2004).***

Unlike sperms, which men produce throughout their life adult lives, women are born with a finite supply of oocytes. A woman makes all the oocytes they ever have before they are born, this supply begins to be depleted even before birth and continue until menopause with accelerated rate of loss roughly at age 37years ***(Wallace et al., 2003).***

Ovarian organogenesis starts with the formation of the sexually indifferent gonadal analogue, followed by sex differentiation, with the formation of the primitive ovary. Finally, with definitive histogenesis oogonia enter meiosis and oocytes are incorporated into primordial follicles. The perinatal pool of primordial follicles, which later grow and mature, is established by a poorly understood mechanism whereby oocyte nests are coordinately intercalated by somatic cells and fragment into single follicles ***(Uda et al., 2004).***

Ovarian follicular development is a continuous process throughout the reproductive lifespan. It is estimated that in a young woman ~10–20 follicles leave the pool of resting primordial follicles each day and start to develop as growing follicles. Since only one follicle is destined to complete maturation and undergo ovulation during each menstrual cycle, the vast majority of oocytes will become atretic. The number of growing follicles at any time-point is believed to be related to the total number of follicles present in the ovary, although the proportion growing increases as the pool of primordial follicles falls approaching the menopause ***(Yong et al., 2003).***

In the normal state the hypothalamus secretes gonadotrophin-releasing hormone GnRH in pulsatile manner. The pituitary gland responds to GnRH by releasing LH and FSH in the same cycle. In the follicular phase of the menstrual cycle, LH acts primarily on the theca cells of the ovary to

increase the production of androgenic precursors. Concurrently, FSH acts on the granulosa cells to promotes conversion of the androgen into estrogen, particularly estradiol, which assist in follicular development during the follicular phase, increasing levels of estradiol leads to an LH surge which leads to ovulation. In a complex interaction, the LH surge, the elevated levels of oestradiol and an increase in the circulating progesterone level trigger the midcycle surge of FSH ***(Marinan, et al., 2005).***

The final population of oocytes in the adult female has historically been believed to be established during a stage in embryogenesis in which the primordial germ cells undergo a multitude of mitotic divisions and formation of oogonia. Cells enter meiotic prophase and remain arrested in the cell cycle as primary oocytes until puberty and exposure to appropriate levels of gonadotropins ***(Julie et al., 2005).***

During the peripubertal phase, development of gonadotropin-dependent granulosa cells mediate oocyte growth. Depending on the species, some preantral follicles are recruited, and one or more antral follicles are selected for ovulation. At this point, the recruited oocyte waits signals from the pituitary for ovulation and resumption of meiosis. Follicular cells in the recruited oocytes undergo functional changes resulting in production of progesterone and preparation for fertilization ***(Julie et al., 2005).***

The prolonged cell cycle arrest just described is a unique feature of female vertebrate gonadal development. Thus, the follicular or ovarian reserve provides an exhaustible resource of oocytes and follicles that is established at or around the time of birth. Reported the age-related biexponential decline in follicles. There is debate, however, regarding the accuracy of those data. Arguments suggest the biexponential decline is an artifact of the log-linear transformation and that follicle depletion is in fact monophasic In any event, the ovarian follicular reserve declines during aging and the majority of follicles are lost in atretic processes It becomes very interesting to examine not only the fundamental biology of this process but also the potential for extending ovarian function with interventions known to affect overall life span ***(Julie et al., 2005).***

Ovarian Stimulation

Ovulation induction is a process of promotion of follicular growth and development culminating in ovulation. It is a frequently utilized therapeutic procedure for the management of infertility ***(Guttam et al., 2004).***

Indications of ovarian stimulation:

Ovarian stimulation with fertility drugs is used for:

1. Various types of ovarian dysfunction:

Approximately 40% of all female infertility problems are results of ovulatory dysfunction ***(Baired, 2003).*** According to the World Health Organization ovulatory dysfunction is classified into: ***(Baired, 2002).***

Group (1): Hypothalamic pituitary failure with lack of endogenous estrogen activity and fail to experience progesterone withdrawal bleeding.

Group (2): Hypothalamic pituitary dysfunction with oligomenorrhea, amenorrhea, hyperandrogenism and luteal phase disorders.

Group (3): Ovarian failure with various degree hypergonadotropic hypogonadal dysfunction.