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Evaluation of Ovarian Response Indexes as Predictors to the Outcome of Intra-Cytoplasmic Sperm Injection

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وَيَسْأَلُونَكَ عَنِ الرُّوحِ ۖ

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صدق الله العظيم

Supervisor Certificate

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DEDICATION

To …

My Lovely family for their abundant support, for their patience and understanding, and for their love.

My husband Dr. Hussein, for his unconditional support throughout the whole two years, without you, this work would probably have never come into existence.

My mother who suffer with me through these two years.

The soul of my father who prepared me for this moment.

MIAMI

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Summary

Background

Knowing predictors of pregnancy in Assistant Reproductive Technology is helpful for clinicians to individualized the treatment plans and to improve patient counseling and for the patients to decide whether to undergo infertility treatment so it is important to evaluate Ovarian reserve prediction indexes as an index to predict the response to Assistant Reproductive Technology.

Ovarian reserve is a term that used to determine the capacity of the ovary to provide oocyte cells that are capable of fertilization resulting in a healthy and successful pregnancy. With advanced maternal age, the number of oocyte cell that can successfully recruited for a possible pregnancy declines, constituting a major factor in the inverse correlation between age and female fertility.

There are several biochemical and biophysical markers for ovarian reserve, usually termed as ovarian reserve tests .Commonly ovarian reserve tests had done for a female before assisted reproductive technique(as attempt to predict their specific ovarian response. To evaluate ovarian reserve there are biochemical testes and ultra-sonography parameters. One of the biochemical markers is estimation of anti – mullerian hormone serum level, which can done at any day of the cycle antral follicular count, is one of ultrasonic parameters of ovarian reserve tests.

Most infertile patients treated with assisted reproductive techniques and among these techniques are intra cytoplasmic sperm injection, which is a common clinical assisted reproductive technique with advantage of being independent of sperm count and morphology and having a high fertilization rate

Aim of this study: is to evaluate the Ovarian reserve index (AMH*AFC/Age) in expectation of total number of oocyte retrieve, Metaphase II ,oocyte and quality of embryo obtained and pregnancy rate.

The primary outcome measured will be:

1. Total number of oocyte retrieve.

2. Number of Metaphase II oocyte

3. Number & quality of embryo obtained.

Secondary outcome: is pregnancy rate.

Study design :This study was analytic prospective cohort study and was carried out on sixty infertile women aged between 22-45 years (29.75+3.91) referred to the fertility clinic in Al-Sadder teaching hospital and underwent intracytoplasmic sperm injection throughout period from August 2022 to March 2023 Each patient undergo details history and physical examination.

Patient and method: at cycle day 2 (vaginal ultrasound and blood tests for Anti-mullerian hormone, Follicle stimulating hormone, Luteinizing hormone, estradiol , serum prolactin and thyroid function test were done.

The ovarian response prediction index values were measured by multiplying the Anti-mullerian hormone (ng/ml) serum level by the number of the antral follicles of (2-9mm) diameter and then the result was divided by the age of the subjects (years).

Results: Pregnancy rate of the studied group was 33.33% and there was a significant difference between pregnant and non-pregnant women with their Anti-mullerian hormone level, which was compatible with other study, which indicated that Anti-mullerian hormone could also independently predict pregnancy outcomes, (p value was **0.004**)

Current study demonstrated significant difference of ovarian reserve prediction index between pregnant and non-pregnant women where ovarian reserve prediction index was significantly higher in pregnant women than non-pregnant group.

There were significant correlation of ovarian reserve prediction index with Metaphase II, embryo number and number of embryo transfer.

Binary logistic regression analysis done to assess the prognostic effect of Ovarian reserve prediction index of pregnant women, there was a significant positive correlation of Ovarian Reserve Prediction Index and higher Anti-mullerian hormone, Antral follicle count, lower Body mass index, Metaphase II, oocyte and embryo number. (P value of Antral follicle count **0.03**); (Body mass index p value **0.047**).

Receiver Operating Characteristics curve analysis done to assess the validity of ovarian reserve prediction index in prediction of Intra cytoplasmic sperm injection success rate.

Ovarian reserve prediction index showed an Area Under Curve of 1.00 at a cutoff point 2, giving a sensitivity and specificity 97% and 100% respectively and AUC of 1.00 at a cutoff point 1, giving a sensitivity and specificity 100% and 95% respectively, which indicate that Ovarian Reserve Prediction Index is highly predicting factor in of Intracytoplasmic sperm injection success rate.

Conclusion:

- ORPI was significantly higher in pregnant women than non-pregnant group.
- The pregnancy rate of the studied group was 33.33%.
- The incidence of pregnancy was significant in the group of women in which the level of AMH was high compared to the group of women in which the level of the hormone was low.
- Women with higher AMH, AFC and lower BMI more likely to have higher ORPI.
- ORPI showed an AUC of 1.00 at a cutoff point 2, giving a sensitivity and specificity 97% and 100% respectively
- The overall success rate of ICSI in Iraqi fertility centers near the results of the centers of other outside fertility centers.
- The type of protocol in ICSI program had insignificant role in success rate.
- There were insignificant positive correlation between ORPI level with MII, embryo number and number of embryo transfer.
- As no single ovarian reserve marker has 100% sensitivity and specificity, a combined index of three variables depicted by ovarian response prediction index can improve ovarian response prediction.

LIST OF ABBREVIATIONS:

ABBREVIATIONS	MEANING
AMH	Anti-mullerian hormone
ART	Assistant reproductive technique
AFC	Antral follicle count
AUC	Area under curve
BMI	Body mass index
COS	Controlled ovarian stimulation
CD2	Day two cycle
DOR	Diminished ovarian reserve
E2	Estradiol
FSH	Follicle stimulating hormone
GnRH	Gonadotropin releasing hormone
hCG	human chorionic gonadotropin
LH	Luteinizing hormone
MII	Metaphase II
MC	Menstrual cycle
NOR	Number of oocyte retrieve
NG	Nano gram
ICSI	Intracytoplasmic sperm injection
IVF	In vitro fertilization
IU	International unite
SD	Standard deviation
TGF-B	Tran forming growth factor-B
TSH	Thyroid stimulating hormone
PCOS	Polycystic ovarian syndrome
PFs	primordial follicles
PGCs	primordial germ cells
OR	Ovarian reserve
OS	Ovarian stimulation
ORPI	Ovarian reserve prediction index
ORTs	Ovarian reserve tests
US	ultra sound
WHO	World health organization
ROC Curve	Receiver operating characteristic curve

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Chapter One

Introduction

Introduction

Ovarian reserve is a term that is used to determine the capacity of the ovary to provide egg cells that are capable of fertilization resulting in a healthy and successful pregnancy. With advanced maternal age, the number of egg cell that can be successfully recruited for a possible pregnancy declines, constituting a major factor in the inverse correlation between age and female fertility (Broekemans, et al.1998).

The ovarian ability to provide healthy oocyte used to describe ovarian reserve (OR) in women, which mainly determined by the number of primordial follicles in the ovary (Molhuijsen and Visser 2020; Ruth *etal* 2021). With ovarian aging, there will be decline in the OR and the Biological ovarian age (BOA) in human has a life span of about 50 years. (Molhuijsen and Visser 2020; Ruth *etal* 2021).Ovarian reserve declines when females enter their thirty ys.

There are several biochemical and biophysical markers for ovarian reserve, usually termed as ovarian reserve tests (ORTs). Commonly ORTs done for a female before artificial reproductive technique (ART), as attempt to predict their specific ovarian response.

These tests give us an indirect evaluation of female s remaining follicular reserve, the accurate ORT might give a chance to distinguish between normal and poor ovarian responders. (Kiran, 2021).

To evaluate OR there are biochemical testing and ultra-sonographic markers. One of the biochemical markers is estimation of anti – mullerian hormone (AMH) serum level, which can be done at any day of the cycle. AMH is a peptide glycoprotein consisting of two very similar sub units of glycoprotein that are bounded by a disulfide bridges (Kanakatti, *et al.* 2021). It is secreted by granulosa cells of small developing follicles in the ovaries. Serum AMH level is tightly related to the number of small and growing developing follicles, therefore Anti – mullerian hormone is consider as an important biomarker of ovarian reserve (Gupta, 2022).

Antral follicle count is one of ultra-sonographic markers of ORT (Kiran, 2021).The antral follicular count done through transvaginal ultrasound at 2 – 4 days of the menstrual cycle, so it commonly done at the early follicular phase (Gupta, 2022).

The antral follicle count (AFC) describes the number of antral follicles measuring between 2–10mm noted on early follicular phase ultrasound of the ovaries. AFC measures have a good inter-cycle and inter-observer reliability in centers with experienced sonographers (Broer, 2011; ASRM.2015; Tal 2017).

An antral follicle is a follicle that is appears as a small fluid – filled sac that contain premature oocyte. By Trans – vaginal ultrasound, do AFC estimation on D2 or D3 of the menstrual cycles. The follicles is measured in both ovaries vary in size from (2 – 10mm) AFC can be considered as an important indicator of the ovarian reserve test and antral follicular count is also could be reflected the size the remaining primordial follicular pool

Age can play an important driver in determining successful rates in the treatment of infertile cases (cedars, 2022).

The quantity and quality of female's ovarian follicular pool thoroughly bounded and correlated with their age. (Feyereisen, *et al.* 2020).

Ovarian response prediction index is calculated by multiplying AMH level (which can be measured through ELIZA kit (ng /ml) and AFC no. (Can be calculated by Trans vaginal U/S on day 2) and the result is divided by the age of the patients (years) (peluso, etal 2020).

Infertility is a clinical condition after unprotected inter course for a period of 12 months in which there is a failure to achieve pregnancy. For women aged 20-44 years old the prevalence of infertility is 8-12 %, and with 1 in 6 couples experiencing some of infertility problems (ART fact sheet, European society of human production and embryology 2020).

Most infertile patients are treated with assisted reproductive techniques and among these techniques are intra cytoplasmic sperm injection (ICSI) which is a common clinical assisted reproductive technique with advantage of being independent of sperm count and morphology and having a high fertilization rate (Esteves, *et al*. 2018).

Aim of this study: to evaluate the Ovarian reserve index (AMH*AFC/Age) in expectation to the ICSI out comes regarding the total number of oocyte retrieve MII oocyte and quality of embryo obtained and pregnancy rate.

The primary outcome measured will be:

1. Total number of oocyte retrieve.

2. Number of MII oocyte

3. Number & quality of embryo obtained.

Secondary outcome: is pregnancy rate.

Chapter Two

Review of Literature

Female reproductive tract: the female gonads are paired of intra peritoneal endocrine organs, which found in the left and right quadrant of the abdomen, respectively. The principle roles of the ovaries are reproduction of egg cells and hormones production. (Tetkova, *et al*. 2019).

The female reproductive organs consist of the uterus, fallopian tubes, and the ovaries.
Figure 2.1 (Sokol, 2011). The fallopian tubes communicates with the upper part of the uterus, while the lower part of uterus is closest through the narrow canal of the cervix with the vagina and external organs, which are collectively called the vulva (Ganong ,*et al.*,2019).

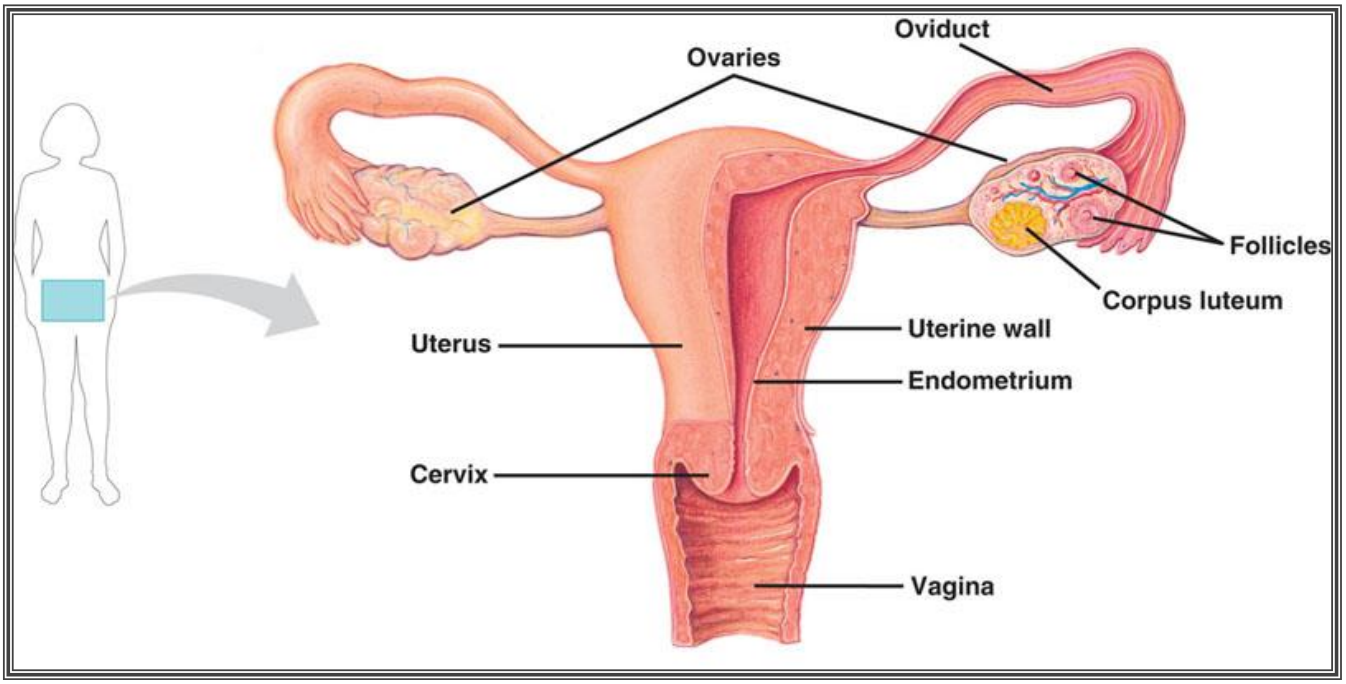


Figure 2.1: Parts of female reproductive organs (Sokol, 2011).

PART 1

2.1 Gamete Formation

2.1.1 Primordial Germ Cell:

Development begins with fertilization, the process by which male gamete, the sperm and female gamete, the oocyte, unite to give rise to a zygote.
Gametes derived from primordial germ cells (PGCs) that formed in the epiblast during the second week, move through the primitive streak during gastrulation and migrate to the wall of yolk sac. (Sadler, 2019).
During the fourth week, these PGCs begin to migrate to ward the developing gonad, where they reached by the end of the fifth week.
Mitotic division increase their number during their migration and continue as they reached to the gonads. Germ cells undergo gametogenesis as a preparation step for fertilization and this include

meiosis to reduce the number of chromosomes and cyto differentiation to complete their maturation (Sadler, 2019).

Sadler 2019

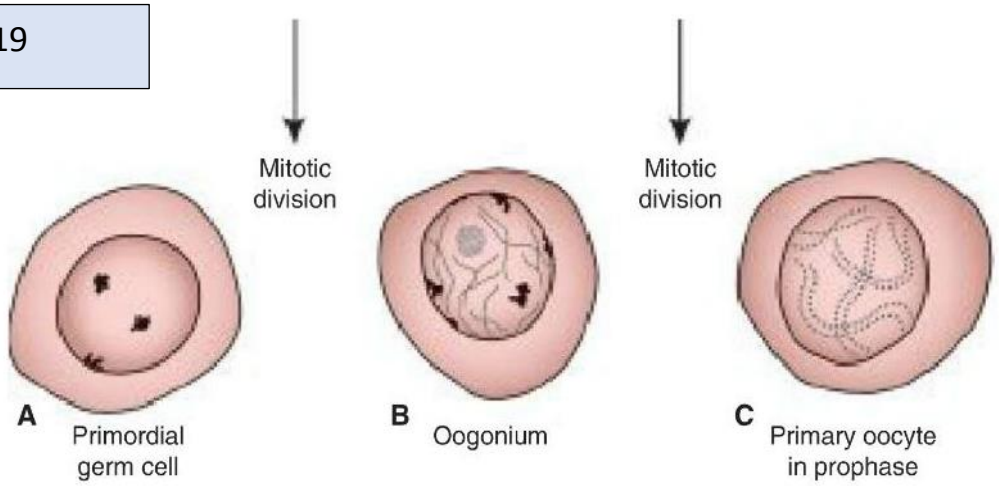


Figure 2.2 Differentiation of PGCs into oogonia begins shortly after their arrival in the ovary. By the third month of development, some oogonia give rise to primary oocytes that enter prophase of the first meiotic division. This prophase may last 40 or more years and finishes only when the cell begins its final maturation. During this period, it carries 46 double-structured chromosomes.

2.1.2 Maturation of the gametes

2.1.2.1 Oogenesis

Oogenesis is the process whereby oogonia differentiated into mature oocytes and before birth maturation of the oocyte begin.

Prenatal Maturation of Oocytes:

Once PGCs have arrived in the gonad of a genetic female, they differentiate into oogonia
These cells undergo a number of mitotic divisions, and by the end of the third month, they are arranged in clusters surrounded by a layer of flat epithelial cells and whereas all of the oogonia in one cluster are probably derived from a single cell. (Sadler ,2019).

The flat epithelial cells, known as follicular cells, originate from surface epithelium covering the ovary .The majority of oogonia continue to divide by mitosis, but some of them arrest their cell division in prophase of meiosis I and form primary oocytes.

During the next few months, oogonia increase rapidly in number, and by the fifth month of prenatal development, the total number of germ cells in the ovary reaches its maximum, estimated at 7 million. (Sadler, 2019).

At this time, cell death begins, and many oogonia as well as primary oocytes degenerate and become atretic. By the seventh month, the majority of oogonia have degenerated except for a few near the surface. All surviving primary oocytes have entered prophase of meiosis I and most of them are individually surrounded by a layer of flat follicular epithelial cells

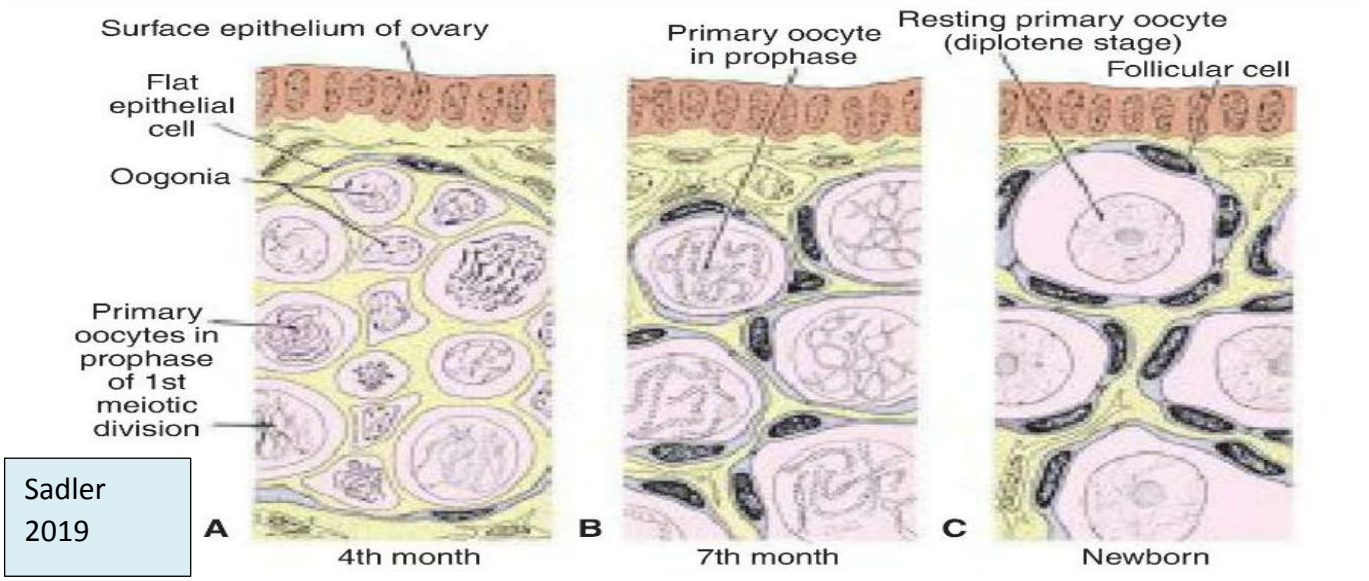
A primary oocyte, together with its surrounding flat epithelial cells, known as a primordial follicle (Sadler, 2019).

After the formation of the primary oocyte, there is a layer of a connective tissue that is covered the oocyte and this layer consist from one layer of flattened follicular cells, this primary oocyte together with flattened follicular cells will formed the primary follicle. During puberty, the primary oocyte will increase in size and so these single flattened follicular cells will convert into cuboidal cells, and then will convert into columnar cells until the formation of a primary oocyte. (Moore ,2016).

The primary oocyte later on enveloped by a blanket of amorphous, acellular, glycoproteinous materials, which known as zona pellucida.
Examining the surface layer of the zona pellucida under the electron microscopy show regular mesh like appearance with intricate rose window.
The first meiotic division of the primary oocyte will start before birth, but the finishing of the prophase dose not occur until adolescence (it start at puberty).
The follicular epithelial cells that are covering the primary oocyte release materials, which is called oocyte maturation inhibitor, which arrest oocyte meiotic process (Moore, 2016).

Postnatal maturation of oocyte

It starts at puberty, commonly only one follicle will develop and grow each month and then there will be release of the oocyte from that mature ovarian follicle .the primary oocyte stay paramount in the ovarian follicle until puberty.
When the ovarian follicle develop and grow, the primary oocyte size will increase and before the ovulation, the first meiotic division of the primary oocyte will finish to bring about a secondary oocyte and the first polar body.
The secondary oocyte will receive most of the cytoplasm due to unequal division of the cytoplasm. While the first polar body will receive very little amount of the cytoplasm. The polar body is small cell certain to decline. When ovulation occur the nucleus of the secondary oocyte starts its second meiotic division but it will pass only to metaphase where the division will be dominant. The second meiotic division will not start until the sperm enter the secondary oocyte (Moore, 2016).



Sadler 2019

Figure 2.3 Segment of the ovary at different stages of development. A. Oogonia are grouped in clusters in the cortical part of the ovary. Some show mitosis; others have differentiated into primary oocytes and entered prophase of the first meiotic division. B. Almost all oogonia are transformed into primary oocytes in prophase of the first meiotic division. C. There are no oogonia. Each primary oocyte is surrounded by a single layer of follicular cells, forming the primordial follicle. Oocytes have entered the diplotene stage of prophase, in which they remain until just before ovulation. Only then do they enter metaphase of the first meiotic division.

Primary oocytes remain arrested in prophase and do not finish their first meiotic division before puberty reached. (Sadler, 2019).

This arrested state produced by oocyte maturation inhibitor (OMI), a small peptide secreted by follicular cells. The total number of primary oocytes at birth is estimated to vary from 600,000 to 800,000. During childhood, most oocytes become atretic; only approximately 40,000 are present by the beginning of puberty, and fewer than500 will be ovulated. Some oocytes that reach maturity late in life have been dormant in the diplotene stage of the first meiotic division for40 years or more before ovulation. Whether the diplotene stage is the most suitable phase to protect the oocyte against environmental influences is unknown. The fact that the risk of having children with chromosomal abnormalities increases with maternal age indicates that primary oocytes are vulnerable to damage as they age. At puberty, a pool of growing follicles is established and continuously maintained from the supply of primordial follicles. Each month, 15 to20 follicles selected from this pool begin to mature. Some of these die, where other follicles entering the antral or vesicular stage then fluid start to accumulate in the antral space. Instantaneously before ovulation, fluid persist to accumulate and so follicles are completely swollen and called graafian follicles (mature vesicular follicles). (Sadler, 2019).

The longest stage is the antral stage while the mature vesicular stage close approximately 37 hours before to ovulation (Sadler, 2019).

Sadler 2019

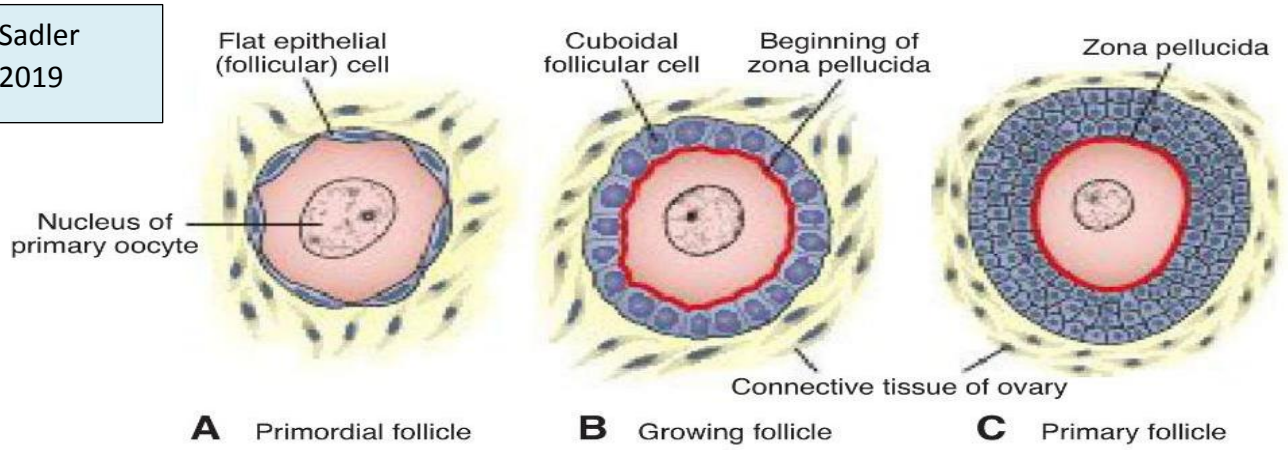


Figure 2.4 **A.** Primordial follicle consisting of a primary oocyte surrounded by a layer of flattened epithelial cells. **B.** Early primary or preantral stage follicle recruited from the pool of primordial follicles. As the follicle grows, follicular cells become cuboidal and begin to secrete the zona pellucida, which is visible in irregular patches on the surface of the oocyte. **C.** Mature primary [preantral] follicle with follicular cells forming a stratified layer of granulosa cells around the oocyte and the presence of a well-defined zona pellucida.

As primordial follicles start to grow surrounding cells transform flat epithelium to cuboidal and start to divided and their number begin to increase to produce stratified epithelium of granulosa cells and the oocyte with surrounding follicular cells are now called primary follicle. With each ovarian cycle, a number of follicles begin to develop but only one will reach to full maturation while other follicles become atretic.

When the secondary follicle is mature, a surge in luteinizing hormone (LH) induces the pre ovulatory growth phase. Meiosis I is completed, resulting in formation of two daughter cells of unequal size, each with 23 double-structured chromosomes. One cell, the secondary oocyte, receives most of the cytoplasm; the other, the first polar body, receives practically none. (Sadler, 2019).

The result of this division is one cell secondary oocyte that is contain most of the cytoplasm while the other receive no cytoplasm which known as a first polar body. (Sadler 2019).

The cell then enters meiosis II but arrests in metaphase approximately 3 hours before ovulation. Meiosis II is completed only if oocyte is fertilized; otherwise, the cell degenerates approximately 24 hours after ovulation.

At puberty, the female begins to undergo regular monthly cycles. These sexual cycles are controlled by the hypothalamus. Gonadotropin-releasing hormone (GnRH), produced by

The hypothalamus, acts on cells of the anterior lobe (adenohypophysis) of the pituitary gland, which in turn secrete gonadotropins. These hormones, follicle-stimulating hormone (FSH) and luteinizing hormone (LH) stimulate and control cyclic changes in the ovary.

At the beginning of each ovarian cycle, 15to 20 primary-stage (pre antral) follicles are stimulated to grow under the influence of FSH. (The hormone is not necessary to promote development of primordial follicles to the primary follicle stage, but without it, these primary follicles die and become atretic.) Thus, FSH rescues 15 to 20 of these cells from a pool of continuously forming primary follicles (Sadler, 2019).

Sadler
2019

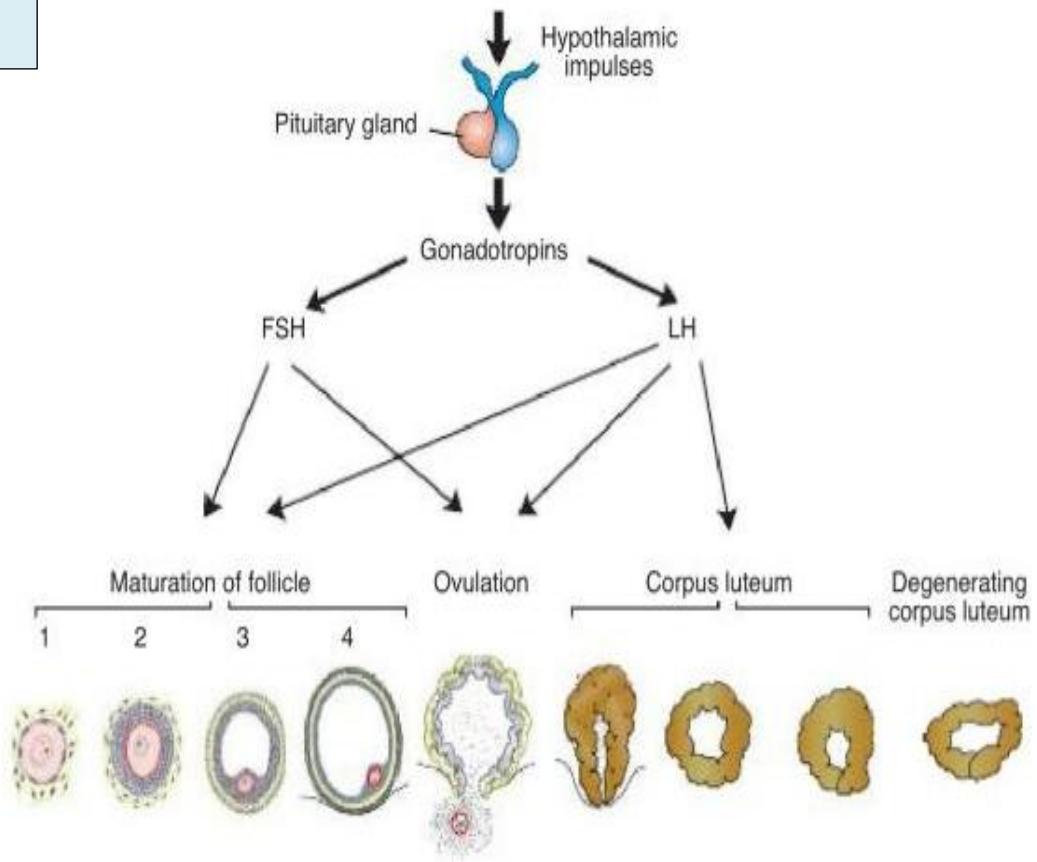


Figure 2.5 Drawing showing the role of the hypothalamus and pituitary gland in regulating the ovarian cycle. Under the influence of GnRH from the hypothalamus, the pituitary releases the gonadotropins, FSH, and LH. Follicles are stimulated to grow by FSH and to mature by FSH and LH. Ovulation occurs when concentrations of LH surge to high levels. LH also promotes development of the corpus luteum. *1*, primordial follicle; *2*, growing follicle; *3*, vesicular follicle; *4*, mature vesicular (graafian) follicle.

Under normal conditions, only one of these follicles reaches full maturity, and only one oocyte is discharged; the others degenerate and become atretic. In the next cycle, another group of primary follicles is recruited, and again, only one follicle reaches maturity. Consequently, most follicles degenerate without ever reaching full maturity.

When a follicle becomes atretic, the oocyte and surrounding follicular cells degenerate and are replaced by connective tissue, forming a corpus atreticum. FSH also stimulates

Maturation of follicular (granulosa) cells surrounding the oocyte. In turn, proliferation

Of these cells is mediated by growth differentiation factor 9, a member of the transforming growth factor-B (TGF-B) family. In cooperation, theca interna and granulosa cells produce estrogens: Theca interna cells produce androstenedione and testosterone, and granulosa cells convert these hormones to estrone and 17 B-estradiol. Because of this estrogen production:

The uterine endometrium enters the follicular or proliferative phase. Thinning of the cervical mucus occurs to allow passage of sperm. The anterior lobe of the pituitary gland is stimulated to secrete LH. At mid cycle, there is an LH surge that: Elevates concentrations of maturation promoting factor, causing oocytes to complete meiosis I and initiate meiosis II Stimulates production of progesterone by follicular stromal cells (luteinization) causes follicular rupture and ovulation (Sadler, 2019).

In the days directly before ovulation, under the effect of FSH and LH, the diameter of vesicular follicle will reach 25 mm and so it will convert into graafian follicles.

There is abrupt increase in LH that cause the primary oocyte to finish meiosis I and the follicle to pass to the pre ovulatory mature vesicular stage.
The oocyte is arrested in metaphase nearly for 3 hours before ovulation, at the same time the surface of the ovary bulge locally and a vascular spot appear (stigma,.(Sadler 2019).Collagenase activity will increase because of LH activity resulting in collagen fiber digestion. Prostaglandin level also increase , this cause contractions that are in turn will extrude oocyte with surrounding granulosa cells from the cumulus oophorus where some of them re arrange around zona pellucida to form corona radiate. (Sadler, 2019).
The rest of granulosa cells together with theca interna are vascularized and under the action of LH a yellowish pigment develop, that change into corpus luteum which secret estrogen and progesterone, if the conception not occur, corpus lutein reaches maximum development a days after ovulation.
After that it degenerate and fibrotic tissue will formed that is called corpus albicans and so progesterone secretion will decrease and menstruation will occur (Sadler, 2019).

2.2. Fertilization

Fertilization: is the fusion of the female mature oocyte and male sperm. Which is mostly occur in uterine tube. Male sperm stay viable several days in the female reproductive tract.
In the vagina 1% of male gamete will be deposited and then complete their journey into cervix where many of them survive for hours and by the effect of muscular contraction they pass up to the uterine tube. This journey occur so fast about 30 minutes or slowly for about 6 days. (Sadler, 2019).
Male sperm become less movable and its emigration stopped but when ovulation occur sperm return to its motion and this might be due to the action of chemotactic substance produced by cumulus cells surrounding oocyte.
Fertilization will not occur before sperm undergo capacitation and acrosome reactions.
Fertilization process consists of many phases: first phase is penetration of corona radiate
The second phase is penetration of zona pellucida and the last third phase is oocyte and sperm wall fusion (Sadler, 2019).

Sadler 2019

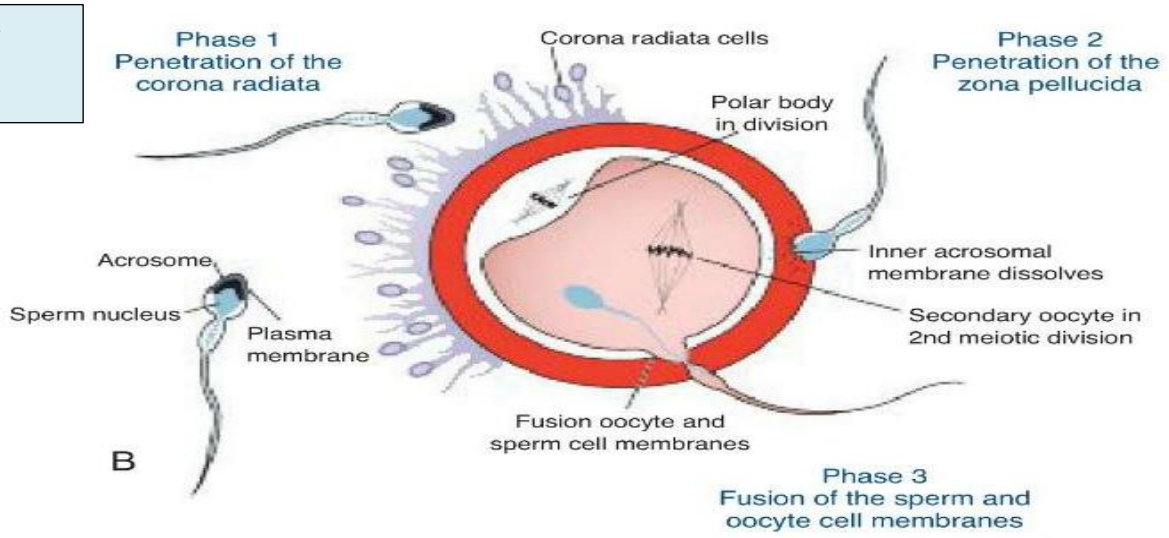


Figure 2.6 **A.** Scanning electron micrograph of sperm binding to the zona pellucida. **B.** The three phases of oocyte penetration. In phase 1, spermatozoa pass through the corona radiata barrier; in phase 2, one or more spermatozoa penetrate the zona pellucida; and in phase 3, one spermatozoon penetrates the oocyte membrane while losing its own plasma membrane. *Inset* shows normal spermatocyte with acrosomal head cap.

2.3. Cleavage:

After the zygote reach the two – cell stage, series of mitotic divisions occur and so number of cells increased. With every division; cells become smaller and this lead to the formation of what known as blastomeres. At the eight-cell stage, they are formed loosely arranged clump.

A solid ball of cells will bound or joined together after the third cleavage where blastomeres maximize their connection with each other this is also are similar to what occur in intra-cytoplasmic sperm injection(ICSI) that have been used to overcome infertility (Sadler 2019).

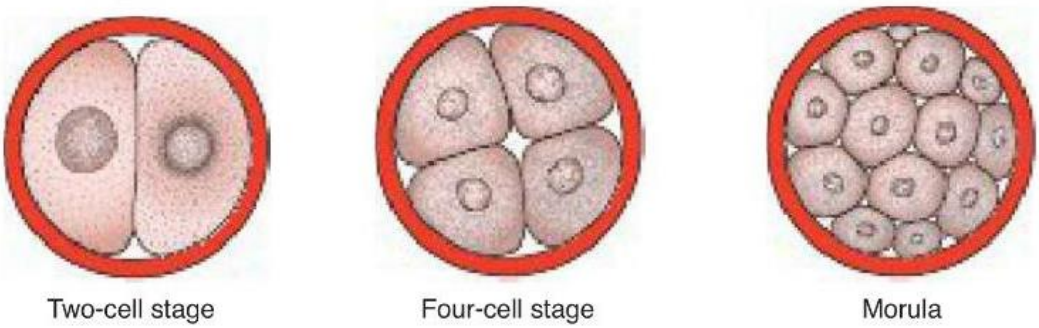


Figure 2.7 Development of the zygote from the two-cell stage to the late morula stage. The two-cell stage is reached approximately 30 hours after fertilization; the four-cell stage is reached at approximately 40 hours; the 12- to 16-cell stage is reached at approximately 3 days; and the late morula stage is reached at approximately 4 days. During this period, blastomeres are surrounded by the zona pellucida, which disappears at the end of the fourth day.

(Sadler 2019).

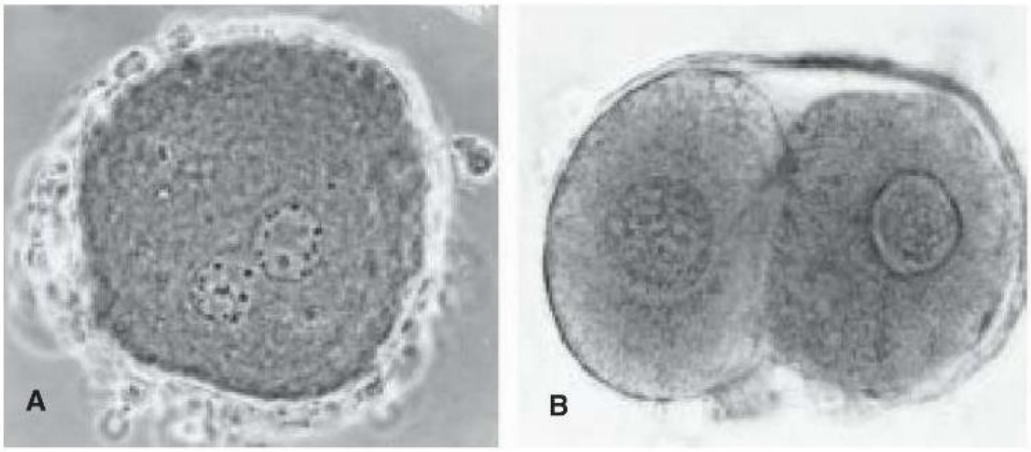


Figure 2.8 **A.** Phase contrast view of the pronuclear stage of a fertilized human oocyte with male and female pronuclei. **B.** Two-cell stage of human zygote.

PART 2: ovarian reserve indices

Generally woman's fertility begin to decline at around age of 32 years old, and after the age of 37 years old the drops off is more dramatically. ASRM 2022

Reproductive aging in female mammals is an irreversible process associated with declining oocyte quality, which is the rate-limiting factor to fertility. (Bertoldo, et al., 2020)

The number of primordial follicles in the ovaries is mainly the determination of the ovarian reserve where the number of the primordial follicles continuously depleted until ovarian senescencesec (Logan, 2022).

Ovarian reserve is a term that is used to determine the capacity of the ovary to provide egg cells that are capable of fertilization resulting in a healthy and successful pregnancy. With advanced maternal age, the number of egg cell that can be successfully recruited for a possible pregnancy declines, constituting a major factor in the inverse correlation between age and female fertility (Broekemans et al.1998). Ovarian reserve, or oocyte number, is different from oocyte quality, which relates to the potential of a fertilized oocyte to result in a live-born infant (Hansen, et al. 2008).

Ovarian reserve tests include both biochemical tests and ultrasound imaging of the ovaries. Biochemical tests of ovarian reserve can be divided further into early-follicular-phase measurements of FSH, E_2, or inhibin B ; measurement of cycle-day-independent anti- müllerian hormone (AMH) ; and provocative tests, such as the clomiphene citrate challenge test (CCCT). Biochemical measures of ovarian reserve intended to directly or indirectly measure the oocyte or follicular pool.

Ovarian reserve used to clarify and describe the ability of the ovarian function to provide viable oocytes. (Moolhuijsen, and Visser, 2020; Ruth, et al. 2020). With ovarian aging the OR declined in human life span of the biological ovarian age (BOA) is about of 50 years. (Moolhuijsen and Visser, 2020; Ruth, *et al*, 2021). Depletion of OR can accelerate by several pathological factors including chromosomal abnormalities, auto immune disorders , iatrogenic injuries which can lead to diminished ovarian reserve (Steiner, et al., 2017; Spears, et al., 2019; Takahashi , *et al*. 2021).

Functional ovarian reserve assessment hold promise in helping women make informed decisions about their future fertility and desired family size, rather than providing them
With generic age – related fertility recommendations. (Dong, *et al* 2017; Maslehi, *et al*, 2019).
Reliable assessment of OR can provide an accurate estimation of the number of oocyte retrieved be by the reliable assessment of ovarian reserves which is also provide a good quality embryos in the IVF. ICSI, cycles of the infertile women.
markers including : female age , basal follicle stimulating hormone (FSH) , Estradiol (E2) , anti – mullerian hormone (AMH) , Inhibin – B , antral follicle count (AFC) , ovarian volume are used as markers and indicators of ovarian stimulation during IVF , ICSI. (Siddiqui, et al. 2019).
To ensure safe and efficient ovarian stimulation, prediction of the ovarian response must achieved. (Maged et al., 2015).

Predicting the ovarian response helps to individualize the ovarian response, which results in decrease cancellation rate and minimized negative impact of excessive ovarian response **(Rubio**, et al.2010).

There are many blood tests used as biomarkers for ovarian reserves as AMH and other hormonal tests which are used in conjunction with medical history and ultrasound images of ovaries to visualized the number of developing ovarian follicles or antral follicle count (AFC) during single menstrual to guide treatment(Tal and Seifer, 2017) .

2.1. AGE

Gradually women s fecundity decreased but significantly decline begin approximately at age 32 years and decreased more rapidly after age of 37 years.
Education and enhanced awareness of the effect of age on fertility are essential in counseling the patient who desire pregnancy, given the anticipated age – related decline in Fertility. Woman older than 35 years should receive an expedited evaluation and undergo treatment after 6 month of failed attempts to conceive or earlier if clinically indicated.
In woman older than 40 years old more, evaluation and treatment immediately are warranted. (ARSM, 2022). Woman s fecundity known to decrease with increase chronologic age.
Follicular atresia and ovulation result in a slow depletion of oocyte number over time, and menopause subsequently ensues. Ovarian reserve correlates inversely with age, but there is considerable variation in ovarian reserve among women of the same chronologic age.

There are assumptions indicated that the relationship between age and ovarian reserve is highly variable and the potential different validity of ovarian reserve markers in woman in different age group remain to be demonstrated. (Sameh, *et al.* 2021).

Reproductive aging is characterized by a decline in oocyte quantity and quality, which is directly associated with a decline in reproductive potential, as well as poorer reproductive success and obstetrical outcomes.

Age related meiotic errors in oocyte are well established. In addition; it is also important to understand how intra ovarian regulators; change with aging. In addition, how certain treatment can lighten the effect of aging.

Individual studies have demonstrated that reproductive pathways involving : vascular endothelial growth factor (VEGF) ,AMH , insulin – like growth factor (IGF1) and mitochondrial function are critical factors for healthy egg and cumulus cell development and are change and vary with increasing age .(Ecencan , *et al*. 2022).

2.2. Biochemical test:

Historically, fertility specialist to identify women susceptible for diminished ovarian reserve (DOR) has used ovarian reserve test (ORT). ORT for woman s reproductive potential has been regarded as a general barometer and for those women whose searching advice before undergo ART.

Also ORT important for plan of treatment and ovarian stimulation protocols.

(Petersem et al., 2017).

Many direct procedures have been used to screen or estimate for ORT as FSH, antral follicular count, AMH tests.

2.2.1. Follicular stimulating hormone:

The earliest assessing test that used to check and estimate ovarian reserve is FSH test which is firmed on feedback inhibition of Follicle stimulating hormone secretion from pituitary gland in response to ovarian factors throughout the menstrual cycle, terribly FSH levels is changing and vary widely and this in turn to greatly reducing testing window and reliability for this test. (Tal and Seifer, 2017).

Follicular stimulating hormone is a gonadotropin synthesized secreted by the anterior pituitary gland regulate development, pubertal maturation and reproductive processes. (Wen – Kai Bii, *etal*, 2020).

Activin enhances biosynthesis of FSH while its synthesis down regulated by inhibin, FSH play a major a role in the regulation of the development, growth and pubertal maturation and reproductive process of the body. (Das et al. 2018*;* Coss, 2020 Wang et al., 2021).

Follicle stimulating hormone structurally is a dimeric glycoprotein of 35.5 Kilo-Dalton composed of two polypeptide units including alpha and beta subunits.

During adult life FSH stimulate follicular growth and granulosa cells and follicle growth in female .While in male FSH stimulate sertoli cells function.

There is two distinct peaks of FSH concentration during female reproductive cycle. (Coss, 2020). Surge of both LH and FSH are triggers both by a surge of GnRH during after - noon, this surge in turn result in ovulation of mature follicles in response to Luteinizing hormone.

In late luteal phase, FSH level increase. In addition, through mid-follicular phase of menstrual cycle, in addition to pre ovulatory rise – corresponding to recruitment of cohort of follicle to the growing pool.

During ovarian folliculogenesis and antral follicle development FSH plays a key role and in a combination with LH, it stimulates pre ovulatory follicular growth, and so FSH acts on woman s ovaries by stimulating granulosa cell proliferation, oocyte maturation and estrogen synthesis.

In woman undergoing fertility treatment, FSH is the most widely performed test. (Tseplidis *etal*, 2009). Basal FSH is consider as one of the commonly used test for daily practice, when the level of FSH exceeds 10 – 12 IU / L generally expected that the ovarian reserve is low. (Fang, *etal* 2015).

Basal FSH levels is more correlated to the number of follicles and number of oocytes retrieved which in turn reflected pregnancy rate .(Dua et al. , 2013).

Early follicular FSH in combination with estradiol used for more than 30 years as an indirect measure of ovarian reserve (Schuh-Huerta 2012; Tal 2017).

At the beginning of the menstrual cycle feedback inhibition from estradiol and inhibin B are at the lowest point and allow the basal, unsuppressed FSH to be measured. Women with normal ovarian reserve produce enough estradiol and inhibin B from the granulosa cells in the ovary during the early cycle to keep the FSH low. (Steiner, 2017; ASRM 2017; Schuh-Huerta, 2012)

However, as the follicular pool declines, the early follicular FSH increases due to insufficient production of estradiol and inhibin B fully inhibit FSH production. (Schuh-Huerta 2012)Therefore, when the early follicular phase FSH is elevated it is highly suggestive of diminished ovarian reserve (DOR). It is important measure the estradiol level at the same time for an accurate interpretation of the FSH. In women with DOR the incompletely suppressed FSH can drive estradiol levels higher (>60–80pg/mL), which in turn will then suppress FSH levels to normal ranges (ASRM 2015) In this case if only the FSH were measured, it could be falsely interpreted as a normal result. Therefore, a normal FSH with elevated estradiol should also prompt concern for DOR (Marcelli, 2017).

Elevated FSH values are associated with but not always predictive of poor ovarian response and failure to conceive (ASRM, 2015; Marcelli, 2017).

FSH values can also vary significantly from cycle to cycle, which can limit its reliability (ASRM, 2015; Abdalla,2005) Using FSH cut off levels of 10–20 IU/L can be somewhat specific for predicting poor response to stimulation, defined as less than 2–3 follicles or less than or equal to 4 oocytes retrieved or cycle cancellation.

However, sensitivity is poor and widely variable for poor ovarian response and failure to conceive Given that elevated FSH can suggest a poor outcome with IVF and FSH does vary between cycles, there has been some thought that repeating

FSH monthly to attempt to select a cycle when the level falls below a desired cut point before proceeding with IVF in that specific month may improve results.

However, when evaluated using an FSH of 10 IU/L or greater as an elevated value, this selection process does not improve live birth rate or ART outcomes including number of oocytes collected, oocytes fertilized, or embryos transferred. (ASRM, 2015; Marcelli, 2017).

Though the majority of young, reproductive aged women tested will not have an elevated FSH, the test is still clinically useful because it is fairly certain that a woman with an elevated FSH will have DOR However, given that there is significant variability from cycle to cycle, the positive predictive value is higher in older women (ASRM,2015).

False positives are higher when FSH tested in a low risk population of young women. Consequently, one elevated FSH level in women younger than 40 may not predict a poor response to stimulation or failure to achieve pregnancy. Currently, it is not known whether elevated FSH can predict an earlier menopause among women of reproductive age (ASRM, 2015; Marcelli, 2017).

Also in reproductive medicine, serum FSH and AFC have been widely used

FSH and AFC , beyond their general predictive value have specific disadvantages, which is FSH levels fluctuate during the inter/ intra cycle of measurements tend to increase after 35 years of age ; are dependent on the functional hypothalamic - pituitary - ovarian axis (HPO axis) have low sensitivity when the number of follicles significantly decreased . (Kim , Slaughter , Wang ,*et al.2017* ; Amer *et al* .,2020) .

2.2.2 ESTRADIOL

Estradiol (E_2) is one of the three types of estrogen found in the body.

Estradiol (E_2) is the main estrogen responsible for the female reproduction function.

The other two types are estrone (E_1), estriol (E_3). Granulosa of the ovary are produced E_2 and its production is stimulated by FSH that is secreted by the pituitary gland.

The secretion of E_2 is pulsatile as FSH secretion , at the day three of cycle serum level of E_2 is below 35 – 50pg / ml which might be indication for active follicle that produce estradiol

Because the level of both FSH and E_2 can be, vary depending on age, PCOS, hormonal contraceptive usage, presence of irregular periods and ovarian dysfunction for many other reasons.

For all what mention above E_2 and FSH should not be used as sole indicators for ovarian reserve. (Gupta, 2022).

Basal E_2 alone should not use to screen for DOR. The test has value only as an aid to the correct interpretation of a normal basal serum FSH value, as follows. An early rise in serum E_2 concentrations is a classic characteristic of reproductive aging.When the basal FSH concentration is normal but the E_2 level is elevated (>60–80 pg/mL), this may indicate ovarian dysfunction attributable to DOR (Evers**.** et al., 1998).

In human, the most potent form of naturally occurring steroid sex hormone is estradiol, which produce by ovary, placenta, testis, and in small amount by adrenal gland.

In the female organ, estradiol can bind to especial intra cellular estrogen receptors located in female organs, breast, hypothalamus, pituitary gland.

Estradiol (E_2) consider as the androgenic types from other two types, has two (- OH) groups while second type is estrone has only one (-OH) and thired type is estriol has three (-OH) groups .During pregnancy, estriol becomes the predominant. Estrone is predominant during menopause. estradiol is consider as the primary estrogen throughout the reproductive years .E_2 acts as a growth hormone for the female reproductive organs including the vaginal lining, cervical gland, lining of fallopian tubes, the endometrium and the myometrium, For maintenance the proper environment for oocytes in the ovary, for initiating and maintaining post pubescent female secondary sex hormone characteristics, estradiol plays a major role. (William Stillwell, 2016).

2.2**.3 Inhibin - B**

Inhibin b is a heterodimeric glycoprotein that consists of an alpha subunit that bind to a beta sub unit , that arise from super family of transforming growth factor – B

Inhibin – B secreted by granulosa cells of developing follicles, the non – steroidal hormone known by its characteristics of suppressing of follicle stimulating hormone (FSH).

When there is a high serum level of inhibin – b secretion, it will exert a direct negative feedback effect on the pituitary gland and intern this will lead to decrease secretion of (FSH) level (Wijayarathna and De kretser 2016).

Therefore, in order to maintain low level of serum (FSH), inhibin – B serum level should be higher in the reproductive age of female.

As with increase age of female both quality and quantity of ovarian follicle decrease , so that the inhibitory effect on FSH will be weakened , which will be also one of the important reasons for the dynamic increment of the serum level of (FSH). (Wijayarathna and De kretser 2016).

As FSH and AFC could regarded as traditional biomarkers for estimation of ovarian reserve, therefore inhibin- B may has an important role in deliberating ovarian reserve estimation.

Inhibin – B concentration can be intended as more direct indicator for the ovarian reserve and this is related to the fact that inhibin – B is secreted by the small ovarian follicle for that that reason it has been consider as direct indicators of ovarian follicular pool .(Wang etal 2020).

2.2.4. Anti – mullerian hormone (AMH)

The name of AMH derived from its role through the differentiation of male sex by stimulation the regression of mullerian duct. Anti – mullerian hormone consider as one of the members of the transforming growth factor family. It is a glycoprotein hormone when it produced by testicular sertoli cells in the male fetus, it will provoke the degeneration of the mullerian structures (including the oviduct, uterus and upper part of the vagina).

While in adult female, the production of AMH will be from the granulosa cells in the pre antral and small antral follicles in the ovary. (Jung S., *et a.l* 2017).

The production of AMH from the pre antral follicles and small follicles are gonadotropin in dependent for that reason the level of AMH stays somewhat stable within and between the menstrual cycles. (Jung S. , *et al*. 2017), in spite of that there is some small variation which has been recorded , but these variations have been noted to have a small clinical relevance and they are limited to younger woman and those with high basal level of AMH (practice committee of the American society, 2015;Liu XY., et al. 2019) .

Anti - mullerian hormone performance is as a negative paracrine in the follicles up to 6mm in size, which lead to inhibition of follicular recruitment of the follicles early in folliculogenesis, through its inhibitory role of the expression of aromatase enzyme (Tal and seifer, 2017; Liu *et al.,* 2019).

As women age increase, AMH level will decline and it strongly related to what is remained of early follicles in female gonads.

Also AMH has been consider as one of the most usually ordered tests of ovarian reserve over the last 20 years , and now is regarded as principle part of the work of the fertile couple in most centers.

Particularly beyond the age of 30 years , the important features of AMH is that its secretion is solely by ovarian follicles at nearly a constant levels from one period to another , and so AMH level can be calculated and can be taken at any stage of menstrual cycle , and due to the fact that consider AMH level is hugely independent of hypothalamic pituitary action so , its calculation produce a reliable estimation with single measurement (Bressler and Steiner, 2018).

Many team works in the field of ART suggest that AMH is strongly correlated to egg quantity (Sun X.Y., *et al.* 2020), forecasting the ovarian response for to gonadotropin stimulation (Alson et al. 2018; Najafian and Pour, 2018).

Anti – mullerian hormone has a notably higher diagnostic accuracy than FSH (Li, X, *etal* 2020 ; Gunning, M.N., , *etal*) and AFC(Bentzen , et al. 2012 ; Kushnir, et al. 2014 ; Grossman et al. 2017 ; Tal and seifer,2017) and has been the screening test of choice in estimation of ORT.

2.3. Ultrasonic tests:

2.3.1. Measurement of Antral Follicle Count (AFC):

The antral follicle count (AFC) describes the number of antral follicles measuring between 2–10mm noted on early follicular phase ultrasound of the ovaries. AFC measures have a good inter-cycle and inter-observer reliability in centers with experienced sonographers. (Broer, 2011; ASRM, 2015; Tal, 2017).

An antral follicle is a follicle that is appears as a small fluid – filled sac that contain premature oocyte. By Trans – vaginal ultrasound, do AFC estimation on D2 or D3 of the menstrual cycles. The follicles is measured in both ovaries vary in size from (2 – 10mm) , AFC can be considered as an important indicator of the ovarian reserve test and antral follicular count is also could be reflected the size the remaining primordial follicular pool
In a comparison of early follicular phase AFC using a 3-D ultrasound with FSH and ovarian volume , the AFC showed the least variability between two observed IVF cycles (Jayaprakasan ,et al., 2008)**.**

One limitation of the AFC is that it is possible that the count would overestimate the amount of follicles able to respond to FSH in a given cycle, as atretic follicles would also be included in the total number visible with ultrasound (Tal, 2017).

Antral Follicular Count has been shown to be a reliable predictor of ovarian response to stimulation for IVF, including over response. (Broer, 2011; ASRM, 2015) However, it is a generally a poor predictor of pregnancy outcomes (ASRM, 2015; Tal, 2017). Using a cut off value of 3–4 follicles in both ovaries is highly specific but less sensitive for predicting IVF cycle cancellation or a low number of oocytes retrieved (<3–4). That same cut off value is moderately specific but retains a low sensitivity for predicting failure to conceive. Furthermore, the positive and negative predictive values for predicting poor response vary widely among studies (ASRM, 2015) .AFC is also a strong predictor of those at highest risk for OHSS.

A meta-analysis included 5 studies with cut off values ranging from 9 to 18 found that AFC had a good discriminatory capacity to separate normal and excessive responders, and it can be used to help drive dosing decisions to attempt to prevent a dangerous over response to stimulation (Broer ,et al., 2011).

The authors proposed that the individual physician should determine a cut off for AFC as the results could vary based on ultrasound equipment, dedicated personnel, and systematic visualization and counting process. While this would certainly improve internal consistency, it does limit the generalizability of AFC across centers. . (Broer, et al., 2011) AFC can be a useful adjunct for evaluating a woman's overall picture of ovarian reserve given its stability across menstrual cycles and ability to predict respond to stimulation. However, AFC is limited in its ability to predict pregnancy outcomes.

Low quantity of the eggs it is a distinctive features of low fertility and it is somewhat associated with high follicular stimulating hormone level (FSH).

When forecasting IVF out come and result for a female more than 44 years of age, AFC can regarded to be more reliable than basal follicular stimulating hormone level.

On ultrasound , when fertility specialists notice an average to high number of antral follicles (eight or more) , he expected a good chance to retrieved an adequate number of oocytes and the pregnancy rates are high than average.

A poorer response is expected, if the antral follicular count is few and the IVF and ICSI cycles could be cancelled to trail better counts the next month. (Owen, 2022).

In spite of that, the AFC is essentially constant and not change much, throughout the menstrual cycles.

Ultrasound estimation and the presence or absence of follicles or cyst in the ovary can still interfere with the result of AFC.

Antral follicular counts, age and selection of treatment s protocols are affected factors on the number of retrieved eggs, which deserve attention of physician. (Xingyu , *et al* 2022).

Antral follicular counts and AMH concentration and level used as indicators of ovarian reserve and both used as a predictor of ovarian response to gonadotropins in woman undergoing ovarian stimulation (Baker , *et al.* 2018).

The response to gonadotropins may be roughly approximated by antral follicle count (AFC), estimated by vaginal ultrasound, which in turn reflects how many primordial follicles there are in reserve in the ovary. Fertility center Chicago, 2009.

Antral follicle count	Classification	Approximate expected response	Risks	Pregnancy rates[6]	Recommendation
Less than 4	Extremely low	Very poor or none	Cancelled cycle expected	0–7% with 1 oocyte	Not attempt IVF
4-7	Low	Possibly/probably poor response	Higher than average rate of IVF cycle cancellation	15%	High doses of gonadotropin likely
8-10	Reduced	Lower than average	Higher than average rate of IVF cycle cancellation	Slightly reduced	
11-14	Normal (but intermediate)	Sometimes low, but usually adequate	Slight increased risk for IVF cycle cancellation	Slightly reduced compared to the "best" group	
15-30	Normal (good)	Excellent	Very low risk for IVF cycle cancellation. Some risk for ovarian overstimulation	Best overall as a group with approx. 35%	Low doses of gonadotropins
More than 30	High	Likely high	Overstimulation and ovarian hyperstimulation syndrome	Very good overall as a group, but potential egg quality issues	Low doses of gonadotropins

Table 2.1 Antral Follicle Counts, Resting Follicles, Ovarian Volume and Ovarian Reserve. Testing of egg supply and predicting response to ovarian stimulation drugs Advanced Fertility Center of Chicago. Retrieved on October 2, 2009; Oudendijk JF, Yarde F, Eijkemans MJ, Broekmans FJ, Broer SL (2011).

The definition of "*poor ovarian response*" is the retrieval of less than four oocytes following a standard hyperstimulation protocol, that is, following maximal stimulation (La Marca A, 2013) .On the other hand, the term "*hyper response*" refers to the retrieval of more than 15 or 20 oocytes following a standard hyperstimulation protocol. The cut-offs used to predict poor responders versus normal versus hyper-responders upon vaginal ultrasonography vary in the literature, with that of likely poor response varying between an AFC under 3 and under 12, largely resulting from various definitions of the size follicles to be called antral ones. (La Marca A, 2013)

2.3.2. Ovarian volume:

Ovarian volume consist from follicles, stroma, vasculature and the percentile of each of these contents are bank on many factors like age, any coexistence Gynecological problem.
Commonly ovarian volume measured by using ultrasound.
Ovarian volume measurement is limited because OV is makeshift following any normal physiological changes such as presence of dominant follicle and also it shift in the presence of any medical case like endometriosis, also OV measurement can decrease due to usage of exogenous hormone.(Amanda Deadmond, *et al*. 2022).

Part 3.Infertility:

Infertility is a disease of the male or female reproductive system, defined by the failure to achieve a pregnancy after 12 months or more of regular unprotected sexual intercourse. In addition, there is no other reason, such as breastfeeding or postpartum amenorrhea). Primary infertility is infertility in a couple who have never had a child. Secondary infertility is failure to conceive following a previous pregnancy (Vander Borght, etal.2018). It can cause significant distress, stigma, and financial hardship, affecting people's mental and psychosocial well-being (WHO, 2023).
Large numbers of people affected by infertility in their lifetime, according to a new report published today by the World Health Organization (WHO). Around 17.5% of the adult population – roughly 1 in 6 worldwide - experience infertility, showing the urgent need to increase access to affordable, high-quality fertility care for those in need **(**WHO,2023).
The main causes of infertility: Male infertility is responsible for 20–30% of infertility cases, while 20–35% are due to female infertility, and 25–40% are due to combined problems in both parts (ESHRE, 2016; Chowdury , et al., 2017) .In 10–20% of cases, no cause is found. (ESHRE, 2016). The most common cause of female infertility are ovulation problems, usually manifested by scanty or absent menstrual periods. (National Health Service, 2017).

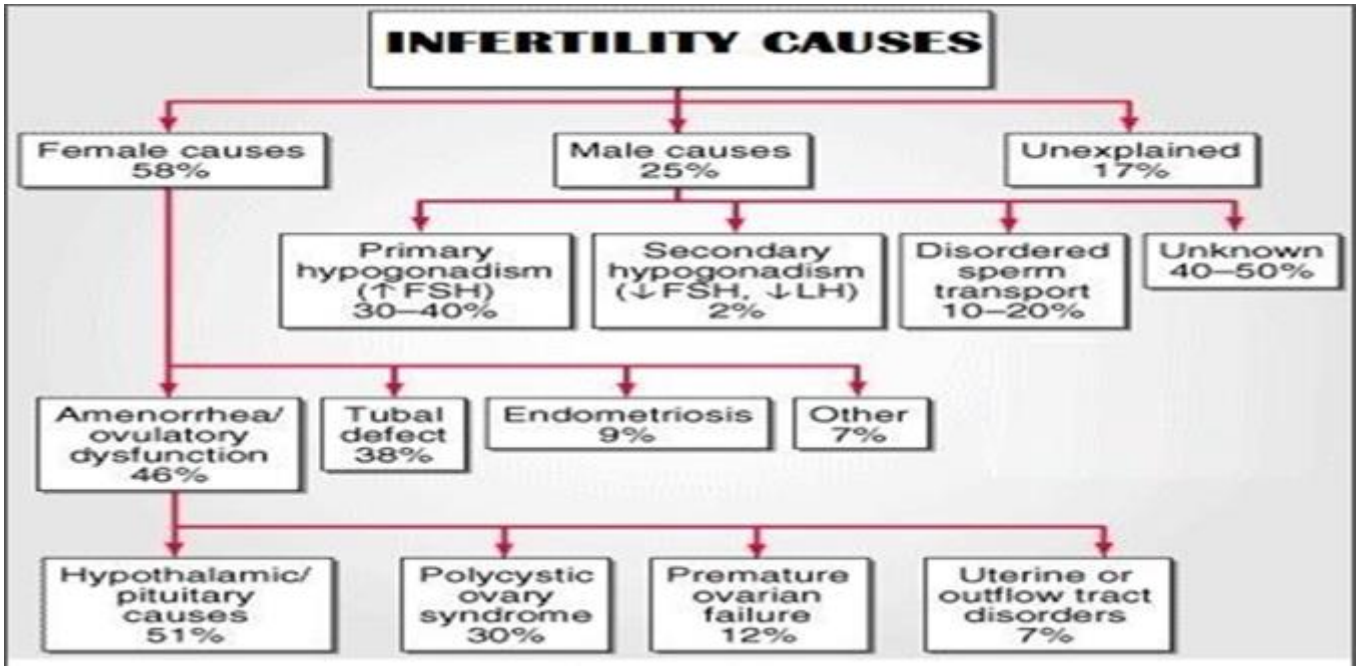


Figure 2.9 The major causes of infertility (ASRM, 2013 and Antony, *et al*., 2013).

Diagnosis of female infertility

Infertile couple should be evaluated by infertility specialist for any factor that may affect their fertility to advise them about the possible causes of their infertility and to suggest a treatment plan according to their problem (Murphy, et *al.*, 2010). Couple may have many factors affect their infertility; so, a full initial evaluation should be done to detect the most common causes of infertility, if present (Hacker, et al., 2010).

Initial assessment should involve a full medical, social history, a physical examination and initial medical tests, which include (Abdalla, 2011):

- Hormone profile: FSH, LH, Progesterone, Testosterone and Prolactin hormone should be requested from all women complaining of subfertility (ASRM, 2013).
- Blood tests: Full blood count should be checked to confirm that the woman is not anemic (ASRM, 2012a).
- Transvaginal ultrasound scan should done to identify fibroids or polyps. Other anatomical uterine anomalies, such as a uterine septum, may also be seen (Barry, *et al.*, 2012).

Seminal fluid analysis should also be done at this stage to confirm the male fertility (Abdalla, 2011).

Some patients are referred for ***further investigations*** such as tubal patency tests (figure2.10). Ahystero-salpingography carried out when there are no recognized co morbidities like pelvic inflammatory disease and previous ectopic pregnancy (Hacker, et al., 2010). A laparoscopy is done if the woman had these co morbidities (ASRM, 2012 a).

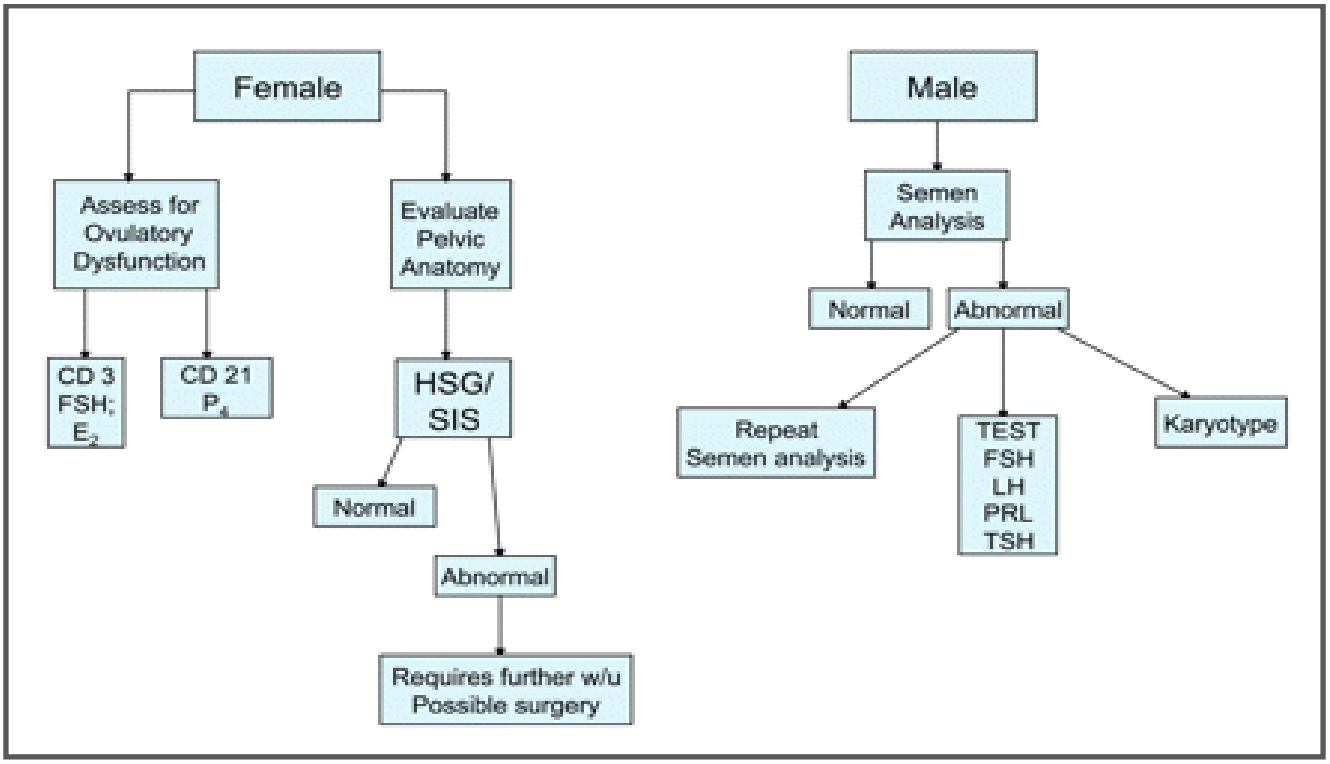


Figure (2.10): Assessment of infertile couple (Saner, 2011).

Treatment of female infertility

The treatment falls into three main types as shown in table 2.1):

1. Medical treatments.
2. Surgical treatments.
3. Assisted Reproductive Technology (NICE, 2013).

Medicine to improve fertility	Anti-oestrogens
	Gonadotrophins
	Pulsatile gonadotrophin-releasing hormone
	Gonadotrophin-releasing hormone analogs
	Dopamine agonists
	Aromatase inhibitors (experimental)
Surgical treatments	Ovarian drilling
	Fallopian tube surgery
	Uterine surgery
	Surgery for endometriosis
Assisted reproductive technology	IUI (Intrauterine Insemination)
	IVF (In Vitro Fertilisation)
	GIFT (Gamete Intrafallopian Transfer) & ZIFT (Zygote Intrafallopian Transfer)
	ICSI (Intracytoplasmic Sperm Injection)
	Donor insemination (eggs or sperm donation)
	PGD (Pre implantation Genetic Diagnosis)
	IVM (In Vitro Maturation)

Table 2.2 Infertility treatment (NICE, 2013).

Assisted Reproductive Techniques (ART)

Assisted reproductive technologies (ART), by the American Center for Disease Control (CDC) definition, are any fertility-related treatments in which eggs or embryos are manipulated. Procedures where only sperm are manipulated, such as intrauterine inseminations, are not considered under this definition. Additionally, procedures in which ovarian stimulation is performed without a plan for egg retrieval are also excluded from the definition.

About one in six couples are affected by infertility and so assisted reproductive technology (ART) is used and needed by those couples.

After the use of ART, more than eight million children have been conceived (Adamsson, *et al*. 2015; ESHRE, 2019) and up to 6% of European birth cohort is conceived by ART (range between 0.2% and 6.4%) De Gegter, et al. 2018.

In vitro fertilization (IVF) and intra cytoplasmic sperm injection (ICSI) are both involved in Assistant Reproductive Technique.

There are many indications for ART to expand because of either societal changes and increasing desire and opportunity to preserve fertility. For example and for social reasons;

In a women wishing to improve their chance of conception at older age, or for medical reasons such as preservation of eggs prior to cytotoxic anti-cancer therapy.

By the development of more efficient ovarian stimulation protocols, it was notice increasing in the usage of ART. Example of more development ovarian stimulation , is modified Luteal support after gonadotropin releasing hormone (GnRH) agonist triggers In gonadotropin releasing hormone antagonist protocol (Humaidan, 2013) .With couples, who are, suffer from difficulties in achieving conception, so they can used assisted reproductive technology to solve their problems.

Any case performed with only ovarian stimulation but without plan for oocyte retrieval are also being excluded from definition. (Meaghan Jain, Manvinder Singh, 2022).

In England in 1978, the first successful in vitro – fertilization treatment in human was performed. The most common ART procedure is IVF and associated techniques such as intra cytoplasmic sperm injection (Meaghan Jain, 2022).

By the American center for disease control (CDC) definition of assisted reproductive technologies are the treatment of fertility – related conditions in which eggs or embryos are manipulated.

INDICATIONS:

- Male factor.
- ART most frequently performing procedures in-patient with tubal factors, in vitro fertilization directly bypasses the fallopian tubes.
- UN explained causes of infertility.
- Secondary to infertility
- Diminished ovarian reserve.
- Ovarian failure.
- Ovulatory dysfunction. (Vav Eekelen, *etal* 2019).

In vitro fertilization is used also in persons who desire pre implantation genetic testing; ART can be done and used before pregnancy. (Such as those known to be carriers of certain genetic diseases)

Also prior to a gonado toxic therapy in fertility preservation, in couples planning to delay conception, in female those in a stable relationship, can have a chance to freeze their oocytes or embryos (Vav Eekelen, *etal* 2019).

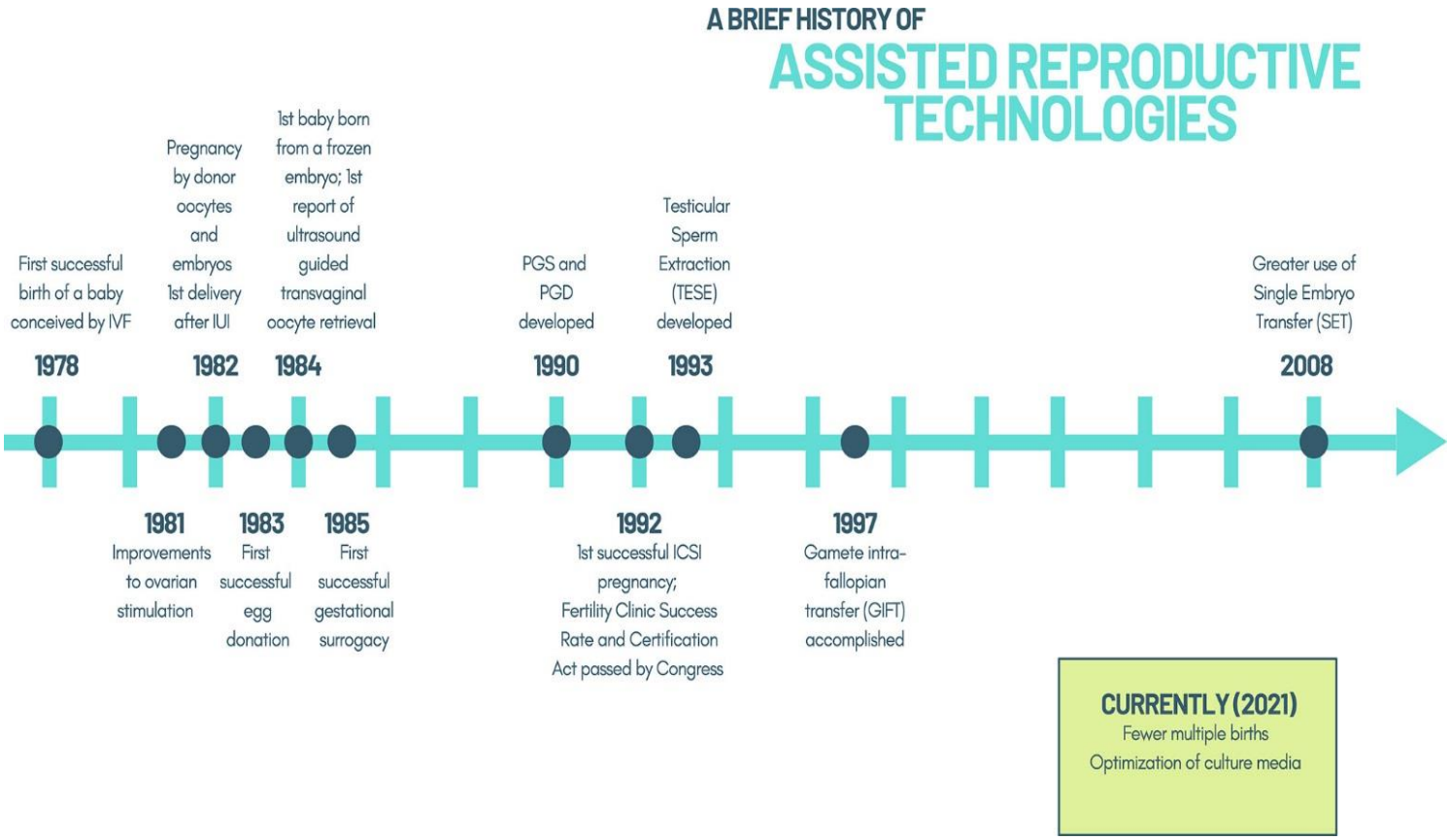


Figure 2.11 A brief history of assisted reproductive technology (ART). Since the first live birth of an infant conceived by in vitro fertilization (IVF), ARTs have continued to evolve and advance (Beal SA et al. 2012; Kamel RM, 2013; Ombelet W, et al. 2015; Ashely M et al. 2017)

Controlled ovarian stimulation

The first critical steps is controlled ovarian stimulation in most ART cycles , this step it is essential step in ART cycles and It should be monitored , the aim of monitoring is to evaluated the response of ovaries to gonadotropin hormone administration.

The first cases of IVF utilized a natural menstrual cycle where a single oocyte was retrieved. Natural cycle IVF is still in practice. However, controlled stimulation of the ovaries is now more commonly performed to maximize the number of oocytes gained per cycle. The latter also offers a much higher chance of pregnancy success

The optimal dose and the time of gonadotropin hormone administration should determine, and prevent over hyper stimulation of ovaries (OHSS). (Wikland and Hillensjö, 2017).Controlled ovarian stimulation is consist of taking of exogenous gonadotropins hormone in order to stimulate the growth of follicles.

Multiple agents and regimens exist for controlled ovarian stimulation. Selective estrogen receptor modulators (SERM) like clomiphene citrate and tamoxifen are one such avenue for this. Benefits of minimal stimulation protocols ("mini-IVF") utilizing SERMs include a decreased risk of ovarian hyper stimulation syndrome and multifetal gestation. However, it also results in a lower live birth rate (49% versus 63% birth rate between mini-IVF and conventional IVF, respectively).

Injection of exogenous gonadotropins, as follicle-stimulating hormone and luteinizing hormone, frequently used for controlled stimulation. It maximizes the number of developing follicles during a single cycle. The following gonadotropin protocols are most popular currently (Zang, etal 2016).

Beside the usage of the drugs that prevent ovulation by inhibition of the pituitary gland

Different drugs combinations might be used in COS, and these drugs vary according to the kinds of drugs that have been used to suppress pituitary gland (for examples, gonadotropin – releasing hormone {GnRH} agonist, antagonist) and ovarian stimulation (for example urinary or recombinant gonadotrophins (Melo, *etal* 2022).

Natural menstrual period had been used in the first cases of ART, where one egg was retrieved, natural regime ART is still in practice.

While now in order to increase the quantity of eggs, which are gained by cycles, controlled ovarian stimulation of the ovaries are now more commonly done.

For controlled ovarian stimulation, many drugs and protocols are used.

One of these drugs that have been used is selective estrogen receptors modulators (SERM) for example clomiphene citrate.

As a trial to decrease risk of ovarian hyper stimulation syndrome and multi fetal gestation , so minimal stimulation protocols (mini – IVF) have been used SERMs , this is also result in a lower live birth where it is about 49% in mini IVF while in conventional IVF is about 63% (Zang , etal 2016).

During only one cycle and to increase the developing follicles, it has been used exogenous gonadotrophin hormone.

1.Gonadotropin releasing hormone (GnRH) antagonist protocol

GnRH anta acts through a competitive binding to pituitary GnRH recepters and thus suppress gonadotropin secretion (Clayton, 1989). In contrast to GnRHa, suppression of gonadotropins occurs immediately after administration of the antagonist .for this reason; in controlled ovarian hyper stimulation GnRH anta administration can be limited to the period

with increased risk for premature LH surge, during the final stage of follicular development(Hodgen,1996) so they do not suppress the endogenous intercycle rise in FSH, And as a result , less exogenous FSH may be required in association with GnRH antagonist versus agonist co- treatment (Macklon et al., 2006).

The antagonist may administer as single or multiple dose protocol. It is commenced normally around day 6of gonadotropin stimulation or when the leading follicles are 12-14mm in diameter.it is continue until the day oh HCG administration and appears to be as effective as the GnRHa protocols in preventing premature LH surges.GnRH anta treatment has several advantages to GnRHa treatment the required doses of gonadotropin will probably be lower (Olivennes et al.,1994;Lindheim and Morales, 2003). Further more HCG administration for induction of ovulation can be replaced by native GnRH or GnRHa, and luteal support might be un necessary , both reducing the risk of the ovarian hyperstimulation syndrome(Emperair and Ruffie,1991).

Mixed gonadotropin medications are used through two types of injection, one with FSH activity (Recombinant FSH) and one, which has both FSH and LH activity. The premature LH surge is protected from occurring by a GnRH antagonist. These cycles can be started with menses after normal baseline parameters are confirmed with ultrasound and normal hormonal levels of FSH and estradiol levels. On many occasions, the cycle starts after pretreatment with oral contraceptives for 2-4 weeks. (Zang, etal 2016).

2. Gonadotropin releasing hormone agonist protocol

The use of GnRHa in COS is widespread. The initial stimulatory effect of GnRHa administration on pituitary gonadotropin release followed by a down regulation of GnRH Receptors and desensitization of gonadotropic cells, resulting in a suppression of gonadotropin secretion (Clayton, 1989). The half-life of GnRHa is only a few hours and have a 100-200 times higher binding affinity for GnRH receptor than does native molecules. The suppressive effect prevent the occurrence of premature luteinizing hormone surge in ovarian stimulation.

Because of the initial stimulatory effect, GnRHa treatment is usually started prior to gonadotropin treatment. In a frequently used stimulation protocol, the so-called long protocol, GnRHa administration is started in the luteal phase of preceding cycle.This protocol is associated with requirement of large doses of gonadotropin (Droessch et al., 1989). A retrospective study comparing human embryo quality in the natural versus long GnRHa stimulated IVF cycle revealed no difference in cleavage rates, development capacity(number of blastomeres) or degree of fragmentation of embryo(Zeibe et al,2004). Additionally an excessive response to ovarian stimulation was shown to have no negative impact on embryo quality as assessed by morphology (Ng et al., 2003.2006).

Mixed gonadotropins are also used through two types of injection, one with FSH activity (Recombinant FSH) and one with both FSH and LH activity. The premature LH surge is protected from occurring by a GnRH agonist. The GnRH agonist is started in the luteal phase of the cycle before the gonadotropins are started. When the gonadotropins are started, the dose of the GnRH agonist is customarily halved until a trigger is given for final maturation before egg retrieval. Pretreatment with oral contraceptives can also be used in these cycles

Transvaginal ultrasound monitoring is utilized to track the number and growth of follicles. Serum lab testing is also performed, most frequently measuring estradiol (E2) levels to track ovarian response. Once ovarian follicles are mature (typically when 2-3 follicles reach 18mm in size), final maturation is artificially triggered via exogenous human chorionic gonadotropin (hCG) or with a GnRH agonist administration. (Zang, etal 2016).

Intra- cytoplasmic sperm injection:

On April 1989 in Singapore, the first baby was born from gamete micromanipulation (IVF.ICSI).later on ICSI technique was progressed by Giannpiero Palemo at the vriie universities in the center for reproductive medicine directed by Paul Derroeq and Andre van steirteghen. Really, this finding was a production of a mistake that was done accidently. ICSI technique was done in 1987 at the first time in spite of that it passed only to pronuclear phase.

While the first trial of active embryo was production, of many trials in 1990 but the last and successful trial of ICSI, that was lead to activated embryo and birth took place on January 14, 1992 after conception that was done on April 1991. (Article Talk from Wikipedia, the free encyclopedia).

One of the widely used fertilization method is intra cytoplasmic injection which is micromanipulation procedure through there will be injection of one spermatozoon into the cytoplasm of the oocyte by using a glass of micropipette. (Esteves, *et al* 2018).
In spite of the intra cytoplasmic sperm injection was a modification procedure of conventional in vitro fertilization (IVF) in order to defeat the sever infertility of males.
In the clinical practice ICSI was insinuate (introduced) in 1992 to defeat infertility of male factor and it used in failure of conventional IVF conditions.
For the most causes of infertility, the ICSI procedure used throughout the word and ICSI usually give a high pregnancy rate.
Many researches clarify that; the ICSI out comes could improve if the sperm selected for microinjection examined under very high magnification for morphological characteristics. (Nagy and Vanderzwalmen, 2018).
In ART, ICSI regarded as the familial procedure or laboratory method That have becoming used, where it account about 70% of 2 – 8 million yearly ART cycles, according to global estimations. (De Moazon , et al. 2020).By the procedure of ICSI, there will be fertilization of the egg when a single sperm injected into interior of the egg (cytoplasm of egg) and by treatment with combining enzyme by using micro dissection that is allow the mature eggs to be release from their surrounding cells.
By using micromanipulation equipment, the eggs separately injected with only one sperm, these injected eggs placed back in the seedbed (nursery or incubator) lab and as in IVF, they are cared with ICSI attacking protein of sperm and sperm antibodies that are found in blood, seminal fluid or vaginal fluid can be treated. (ESCO Medical, 14 September 2012).

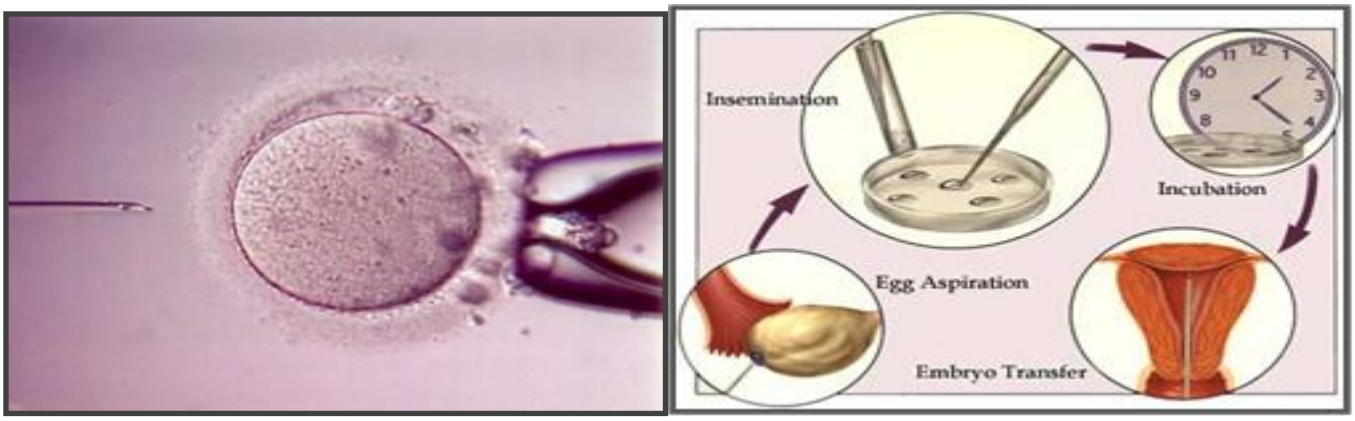


Figure 2.12 Intracytoplasmic sperm injection (SART, 2013).

Fertilization rate increased through the ICSI procedure and fertilization failure decreased. (Ferraretti, *et al*. 2017), about 15% of couples of reproductive age, sub fertility conditions have been found among those groups of couples.

Micromanipulation of gamete, such as ICSI is very useful for treating couples with compromised sperm parameters.

An alternative method of sperm selection has been described; under high magnification (over 6000x); the spermatozoa \ selected, and used for ICSI .This technique. Named intra cytoplasmic selected sperm injection (IMSI), while among couples and through the ICSI procedure there is theoretical potential to improve reproductive out comes among those couples whose undergoing assisted reproduction techniques (ART). (Danielle and Teixeeira 2020).

Until the late 1970s, there were a few treatment options for couples where subfertility, found in up to 15% of reproductive age.

About 20 – 30% of infertility conditions are compromised, semen parameters, at the least 30 million men worldwide are considered sub fertile. (Agarwal, 2015).

For ICSI, after sperm preparation, an optical magnification of 200x to 400x used to examine the sample.

The best normal looking motile spermatozoa selected, according on their major morphology, and then they have been taken and injected into the cytoplasm of the egg retrieved after controlled ovarian stimulation.

Anyhow, pregnancy rates stay low that might need for more assert (justify) the research for fiction (noval) interference as trial to improve out comes (Leicher, 2019).

Indications of intra cytoplasmic sperm injection

1. Male infertility

- There are many conditions and causes for male infertility like oligospermia, asthenospermia, teratospermia, cryospermia, azoospermia, and the combination of diseases like oligosthenozoospermia.
- An ejaculation or retrograde ejaculation, in this condition, the male sperm can be taken from urine.
- Infectious disorders for example HIV or Hepatitis.

Beneficial semen study (valuable semen analysis): throughout the usage of chemotherapy and radiotherapy and in the persons who are under go vasectomy semen might be frozen. (Marta Barranqure Gomes, et *al*. 2022)

2. Female infertility

- Egg numbers is low.
- Egg that have a characteristic thickened zona pellucida.
- Follicular puncture having low quantity of egg (Marta Barranqure Gomes, *etal* 2022)

3. Other indications

- Breeding defeat (fertilization failure).
- Defeat of last trial or cycle of IVF.
- Defeat of last artificial insemination (AI).
- Immunological sterility due to anti sperm antibodies.
- Rescue microinjection for fertilization after conventional IVF.
- Pre implantation genetic diseases is be performed.
- When donor oocytes or sperms are used.
- In the devitrification of oocytes. (Marta Barranqure Gomes , *et al*. 2022)

Factors affecting outcome of ICSI

Some factors that affect outcome of ICSI are:

1. Female age: One of the most important factor that determine of spontaneous conception and treatment related conception is female age (Maheshwari, *et al.,* 2008). Fertility begins to decrease greatly at late 30s and early 40s (ASRM, 2014).

2. *Number of treatment cycles: Researchers* found that the chance of a live birth after IVF is dependable for the first three cycles of treatment, but that the success rate after three cycles is less certain (Martin-Johnston, *et al.,* 2009).

3. *Smoking*: Smoking has a negative effect on IVF outcome, the zona pellucida become thicker, made it difficult for sperm to penetrate the oocyte , make the fertilization more difficult (Klonoff,2005).

4. *Weight*: Obesity is linked with declined pregnancy rates (Maheshwari *et al*., 2007and Chu, *et al.,* 2008). Treatment efficacy and outcomes of ART affected negatively with increase weight (Sloboda, *et al*., 2010). The best BMI between 19 – 30 kg / m^2 before starting ART, outside this range, the likelihood of the ART success is reduced (NCC WCH, 2004).

5. *Stress (anxiety/depression):* Some researchers found that anxiety and depression had no effect on pregnancy rates of a first ART treatment (Lintsen, *et al.,* 2009).Others found significant association between depression/anxiety and pregnancy rate after ART (Sohraband, *et al*., 2008). The recent research in the field of infertility focused on the free radicals, which suspected to be one of the major factors that affect ART success.

Risks and adverse effects associated with ART

Most common adverse effects associated with ART are (Permuth-Wey and Sellers, 2009 a Salehi, *et al*., 2008):

- Multiple pregnancies
- Ovarian hyperstimulation syndrome (OHSS)
- Ectopic pregnancies

- Ovarian cancer
- Other cancers like breast, endometrium and cervix has not been recognized (NCC WHC, 2004).

Chapter Three

Materials and Methods

Materials and Methods

3.1. Population: Patient groups

This study was prospective cohort study, which carried out on sixty infertile women aged between 22-45 years (5.81±2.76), referred to the Fertility center in Al-Sadder Teaching medical city and underwent intracytoplasmic sperm injection throughout the period from August 2022 to April 2023.

3.2. Calculation of ovarian response prediction index (OPRI):

The ovarian response prediction index values were measured by multiplying the AMH (ng/ml) serum level by the number of the antral follicles of (2-9mm) and then the result was divided by the age of the subjects (years), this is consider as a definition of ovarian response prediction index which clarify that the ovarian response to the stimulation had a positive correlation between the OPRI and the AMH serum level and the number of antral follicles; while OPRI was negatively correlated with the subjects age.

The PORI defined by the following equation: OPRI = {AMH (ng/ml) *AFC}/ subjects age (year).

The measured result and value of OPRI was not influenced by the regimen of treatment that have been choose during the ICSI cycle which was used for the induction of ovulation also the values was not influenced by the dose of the gonadotropin

3.3 Ethical Approval

This study approved by medical ethical committee of college of Medicine, University of Babylon, under reference no. 1-1 in 30-6-2022. All subjects involved in this work have been informed, verbal agreement have been obtained from each participants before the enrollment

Female were asked about their gynecological and medical history; underwent complete medical examination; height and weight measurements. Gynecological examination was performed; cycle day 2 (CD2) vaginal ultrasound (U/S) for AFC and blood tests for FSH. LH, AMH, estradiol (E2), serum prolactin and thyroid function test.

Below down figure 3.1 which contain the full standard questionnaire for evaluation of the 60 couples**.**

(Evaluation of the pateint)

(Female Name: Case No. :

Age: Education:

Live in: urban rural

Her Husband: Age: work place:

Smoking:

M.C. History:

Age of menarche:

Regularity Yes No

Duration:

Days of bleeding: Amount of bleeding:

Dysmenorrhea: Yes No

Subfertility History:

Type: primary secondary

Duration of subfertility:

Cause if diagnosed:

Does her husband have children from another wife? Yes No

Medical History:

Genital tract infection:

Surgical History:

Examination (Female):

Wt. Height BMI

Investigations: AMH, AFC

3.4 Baseline assessment

All women were asked to be seen at cycle day 2 or 3 of their menstrual cycle to evaluate their fitness for ICSI program.

patient information was documented in details, including age, , duration of infertility, types of infertility, residence, family history, drug history , smoking habit , menstruation history, previous infertility treatments and outcomes ,previous pregnancies and outcome and body mass index (BMI).
Calculating your body mass index (BMI) involves using a simple formula with your weight (in pounds or kilograms) and height (in inches or meters).

Metric (kilograms, meters)	**Formula: weight (kg) / height (m2)** **The formula for BMI is weight in kilograms (kg) divided by height in meters squared (m^2). (Bailey, 2023)** **Severely underweight - BMI less than 16.5kg/m^2** **Underweight - BMI under 18.5 kg/m^2** **Normal weight - BMI greater than or equal to 18.5 to 24.9 kg/m^2** **Overweight – BMI greater than or equal to 25 to 29.9 kg/m^2** **Obesity – BMI greater than or equal to 30 kg/m^2** **(Weir ,2023)**

Vaginal ultrasound scan is performed by the gynecologist of the center using real time ultrasound devise (MediSON,Serial number: A63505300001709.Sonar type: SAS000). Using vaginal probe (5-7MHZ). The scan used to check the uterus, ovaries and surrounded structures.

Blood sample usually taken from female partner at day 2 or 3 to measure hormone levels such as estradiol, FSH, prolactin LH, and AMH, to assess ovarian reserve. The levels of these hormones may give a predictable idea about the response to ovulation stimulation drugs. Also, blood test from both the male and female partners for routine screening tests including HIV , hepatitis B and hepatitis C, unless presence of a copy of the results from an qualified lab and is no more than 12 months old.

3.5 Selection criteria:

Inclusion:

1. Both ovaries are normal and visible on ultrasound
2. The cause of infertility is either unexplained or tubal factor infertility.
3. Female are with normal ovulation.
4. Screening test for hepatitis B&C as well as for HIV proved to be negative.
5. Male partner with normal semen analysis according to WHO 2010.

The exclusion criteria were:

1. Sever endometriosis.
2. History of ovarian surgery.
3. Endocrine disorders include pcos.
4. Presence of ovarian cyst that assessed by the usage of trans-vaginal ultrasound.

Once the couples have been screened and found to be eligible according to our selection criteria, they were randomized with the designed programme.

Table 3.1 : The apparatus used in this study.

Instrumental	Supplied Company
Automatic Pipette	Thermoscientific , USA
Centrifuge	Universal 16 A, German KOKUSAN
CO2 incubator	HERA,USA Galaxy HIS, New Brunswick
Digital camera	Canon IXUS 11015, Japan
Dissecting microscope	Olympus Optical Co Ltd., Japan SZ *10
Distillator	Bibby science(England)
Electrocardiograph	Germany
Electronic balance	Sartorius(Germany)
EZ-strip pipette	RI, UK GYNETICS
Holding pipette and for Injecting needle	Cook, Australia
ICSI dish	Falcon,USA
Inverted microscope	Olympus Optical Co Ltd., Japan
IVF work station	K-system ,UK
Laminar air flow hood	Gelman instrument, Germany
Modified Sphygmomanometer	Germany
PH-meter	Jenway,Germany
Spectrophotometer	Apel (Japan)

Spectrophotometer, Cecil 10ll (UV-visible)	Spectronic 303,Milton Roy(USA)
HERACELL CO2 incubator	Thermoscientific , USA
Micromanipulator Integra	INTEGRA TI
Light Microscope	GENEX
Nunc IVF Dish	Thermoscientific , USA
Nunc IVF Multi Dish	Thermoscientific , USA
Four Wail Nuclon	Thermoscientific , USA
Nunc IVF Petri dish	Thermoscientific , USA
INER TUERCUIN	CODAN
Follicle-puncture-system(Double lumen and single lumen)	REPROLINE
Embryo Transfer Catheter	GYNETICS
ICSI Injection Pipettes	SUNLIGHT
Holding Pipette	SUNLIGHT
Round Bottom Nunc Tube	Thermoscientific , USA
Nunc IVF Centrifuge tube	Thermoscientific , USA
ERA-20 Centrifuge	HETICH
Mini Vidas	Biomerieux
Vaginal ultrasound	MediSON

3.2 Methods

3.2.1 Controlled ovarian stimulation protocol and intracytoplasmic sperm injection procedure

Controlled ovarian stimulation:

All of these women underwent ovulation induction with either long (N=1) or short (N=59) protocols based on timing, hormonal conditions and ovarian reserve status of the women on the discretion of the clinician.

Gonadotrophins are administered by using of the one of following regimes or protocols according to patient result:

According to its initiation and duration , GnRH analog use was divided into three protocol: the long ,which was the best for suppression of endogenous , high tonic LH levels ,especially in polycystic syndrome and normo gonadotropic patients, And the short and ultra-short protocols which were mainly used in poorresponder to ovarian stimulation treatment , older or hypergonadotropic patients with ovarian failure .(Macklon et al., 2006)

Table 3.2 Drugs use in the study

Drug Name	Dosage	Company
Menopure (HMG)	**75IU S.C or IM , 1 vial contains HMG corresponding to 75iu FSH and 75iu LH(**	**FERRING Gmbh Wittiand 11, D-24109 Kiel, Germany**
Merional	**75 IU S.C or IM**	**IBSA institute biochimique SA Swtzeland**
Folisurge(Follitropin ALFA)	**Recombninat Human Follicle Stimulating Hormone 75 IU**	**INTAS India LG Chem Korea**
Pregnat HCG	**5000 IU S.C or IM**	**SKY PHARM LTD. London- UK.**

• **The Long protocol:** protocol has used for patient with high FSH, LH or E_2 levels or has endometrial thickness more than 5mm on day 2 of cycle. A single shot of Decapeptyl, Depot 3.75 mg/ampule, can be given on the 21st day of the previous cycle. Then a blood test for FSH, LH and estradiol hormones may be made on the 2nd or 3rd day of the next cycle or after 10-14 day of injection to confirm suppression.

Table 3.2: Drugs use in COS treatment

• **The short protocol:** If the hormones level were normal; FSH < 10 MIU/ml, LH < 8 MIU/ml and E2 < 50 pg/ml, the treatment will started on 2nd or 3rd day of cycle.

.

The Gonadotrophins are initiated from 3rd day of the menstrual cycle. Stimulation is started with one of the following drugs: HMG (Pergonal®, Menogon®) ; FSH (Follitropin®) or Recombinant FSH (Gonal F® ;Puregon®) ; and is continued in our patients for 8 to 21 days (median = 13 days), till the ovulating dose of HCG is given as Recombinant hCG (Ovitrelle® or pregnyl®).The dosage differs, depending on the age of the patient, and the response to stimulation.

During this period, the treatment cycle was monitored for checking the developing follicles and endometrial thickness by vaginal ultrasound and adjusting the dose of the drugs if required and finally timing the HCG injection. On average, the patients in our study need attend to the clinic for 4-12 visits (median = six visits).

When the ultrasound scan indicates a reasonable number of follicles and the diameter of the chief follicles is larger than 18 mm. In addition, the endometrium is of good thickness and quality. The estrogen levels (500 – 3000 pg/ml) correspond to the number of growing follicle. Both the GnRh agonist and the FSH/hMG injections were stopped and human chorionic gonadotropin (hCG) is given in a dose of 5000-10000 IU.

3.2.1.2 Sperm retrieval and Preparation

Semen specimen was obtained by masturbation after 3-5 days of sexual abstinence at day of pickup in a labeled standard sterile disposable plastic container.

Semen analysis carried out by contrast microscope. Sperm characteristics were assessed according to World Health Organization criteria (WHO, 2010).

	WHO 2010	WHO 2021
Semen volume (mL)	1.5 (1.4–1.7)	1.4 (1.3–1.5)
Total sperm number (10^6 per ejaculate)	39 (33–46)	39 (35–40)
Total motility (%)	40 (38–42)	42 (40–43)
Progressive motility (%)	32 (31–34)	30 (29–31)
Non-progressive motility (%)	1	1 (1–1)
Immotile sperm (%)	22	20 (19–20)
Vitality (%)	58 (55–63)	54 (50–56)
Normal forms (%)	4 (3–4)	4 (3.9–4)

Table 3.3. WHO 2010 (5th Edition) and WHO 2021 (6th Edition) lower fifth percentile (with 95% confidence interval) of semen parameters from men in couples starting a pregnancy within one year of unprotected sexual intercourse leading to a natural conception. (Boitrelle, et al., 2021).

Semen analysis is carried out by contrast microscope. Sperm preparation involves washing and incubation of the sperm in culture fluid by swim up from pellet.

Swim-up of Sperm from Pellet

1. Liquefaction of specimen for 30-60 min. in the incubator at 37°C before processing.

2. Mixing of semen sample by pipetting for much time.

3. Transfer 1-2 ml of the specimen (or all sample for oligozoospermia) from the plastic cup to a sterile centrifuge conical tube (15 ml).

4. Addition of an equal volume of media 1:1 to the liquefied sample.

5. Centrifuge the conical tubes at 2500 rpm for up to 10 minutes.

6. The supernatant was discarded carefully without disturbing the underlying pellet.

7. Layering the pellet gently in 0.5 ml of fresh media and incubate the tube for 30 min-lhr at 45° angle vertical rack for sperm swim-up. The uppermost layer of the medium usually gathered for IUI.

8. Checking of the count, morphology and progressive motility by

Examining a small (10 microliter) drop under a light microscope after

Spreading on a glass slide and covered by (22x22 mm) a coverslip

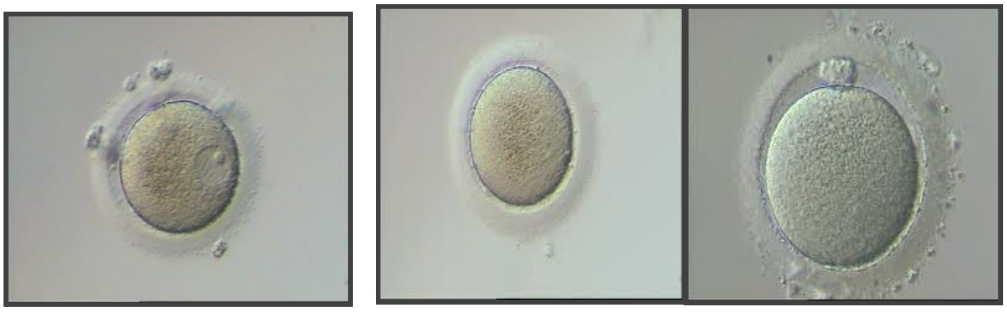
This method can help removal of chemicals (prostaglandins) that can cause uterine contraction and cramp. Also , it can help to remove sexually transmitted viruses, such as HIV and hepatitis, which could be transmitted to the woman during fertility treatment also help to remove cellular depress , round dead or gelatinous material to obtain active motile sperm which will be used for ICSI (Bausenwein and Sigman 2014).

3.2.1.3 Oocyte retrieval and preparation

Oocyte retrieval procedures are performed approximately 36 hours after HCG injection.

The oocyte retrieval done under a mild anesthetic. It was done under ultrasound guidance, by insertion a thin needle into each follicle and the follicular fluid is aspirated by applying gentle suction. This fluid is passed on to the laboratory where it is examined under a microscope by an embryologist in order to identify the oocytes.

After denudation, embryologist in the inverted microscope scores the oocytes and their maturation stages are noted. Intracytoplasmic sperm injection is carried out on all morphologically intact oocytes that have extruded the first polar body (metaphase II (MII)). Immature oocytes that include germinal vesicle (GV) and metaphase I (MI) were not injected.



Germinal vesicle (GV). Metaphase I (MI) Metaphase II (MII)

Figure (3.2): Stage of oocyte maturation.

3.2.1.4 Intracytoplasmic sperm injection

The oocyte was stabilized with a holder micropipette and injected with injection micropipette under an inverted microscope. Motile spermatozoa were initially immobilized by injection micropipette. The individual sperm cell was aspirate and directly injected in to the oocyte cytoplasm (Rao, 2014). The polar body was held at six or twelve o'clock position, then, all injected oocytes were transferred to culture dish in culture media (FertiCultTM) covered by mineral oil and incubated at (37°C, 6% CO_2).

3.2.1.5 Assessment of Fertilization and Embryo Development a quality

Fertilization results were assessed 16–18 hours after ICSI. The first signs of fertilization is the development of two round bodies in the center of the egg (presence of two pronuclei (2 PN)), after that, the two pronuclei were join, forming one nucleus of 46 chromosomes.

The fertilization rate (FR) was defined as the ratio between the numbers of diploid zygotes to the number of injected mature oocytes (Al-Taee, et al. 2014).

FR= (NO. of 2PN on day one / Whole NO. of oocytes injected) ×100

Early cleavage was evaluated hours after ICSI and embryo cleavage was assessed after a 24 hours culture. **The cleavage rate (CR)** was defined as the ratio between the numbers of embryo to the number of diploid zygotes (Al-Taee, *et al.* 2014).

CR = (NO. of cleaved embryos on day / Total NO. of 2PN) ×100.

During further embryo development (day 2, and 3 post injection), the embryo quality was evaluated, according to their percentage fragmentation. In our lab, embryologist classify embryos into grades 1 through 4 (Hazlet, 2011 and Al-Taee, *et al.* 2014). Grade 1 represents the best quality embryos as shown in table (3.4).

Grade I	Cells are of equal size; no fragmentation seen
Grade II	Cells are of equal size; minor fragmentation only (1–20%)
Grade III	Cells are of unequal size; no fragmentation to moderate fragmentation (21 - 50%)
Grade IV	Cells are of equal or unequal size; fragmentation is moderate to heavy (over 50%).

Table (3.4): Embryo grading (Hazlet, 2011).

Fertilization rates, oocyte cleavage rates, numbers of available embryos, embryo grading and number of transferred embryos were done by expert Gynecologist and embryologist.

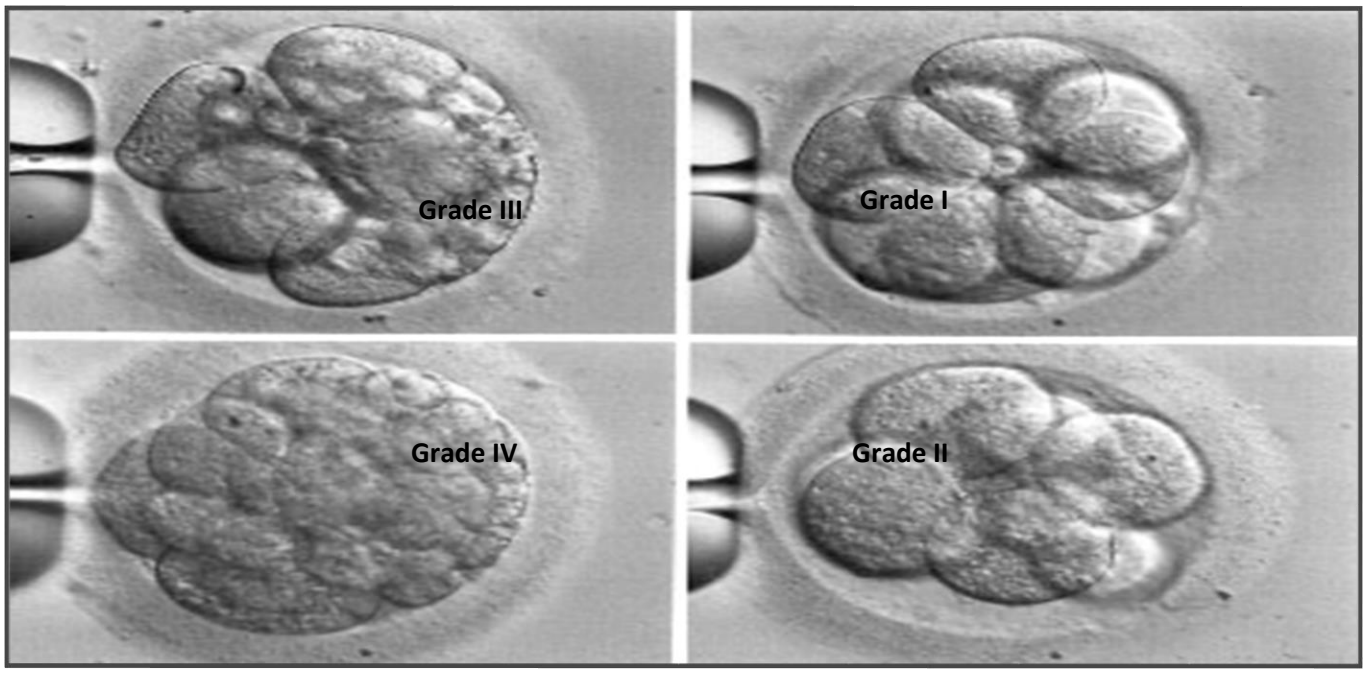


Figure (3.3): Embryo grading.

3.2.1.6. Embryo Transfer

Embryologist before embryo transfer (ET) assessed embryo quality. ET is the procedure during which one or more selected embryos are non-surgically transferred to the uterus under ultrasound guidance. Embryo transfer is most commonly done on the second or third day after oocyte collection depending on individual circumstances.

3.2.1.7 Pregnancy Evaluation

On the fourteenth day of embryo transfer serum β- HCG was performed to confirm pregnancy. By that time, pregnancy rate (PR) is stated. All pregnancies reported were, therefore, biochemical pregnancies while clinical pregnancy was confirmed with ultra-sonographic visualization of gestational sac (Al-Taee. et al.. 2014).

$$PR = \frac{\text{NO. Of pregnant ladies after ICSI}}{\text{Total NO. Of patients who underwent ICSI}} \times 100\%$$

3.2.2 Collection of blood

3.2.2.1 Collection of blood and serum preparation

About 5 ml of venous blood for specific test of markers was collected by vein puncture using 5ml disposable syringes. Blood samples were put in plain tubes and allowed to clot, then separated by centrifugation 5-10 minutes at 1000xg - 2000xg (Bishop ,*et al*.,2000). The ELISA kit that was used the Sandwich-ELISA principle and the catalog No. of the kit is E-TSEL-H0018.

Product size: 96T/48T/24T96T Elabscience Quickey Human AMH (Anti-Mullerian Hormone) ELISA Kit

3.3. Statistical Analysis:

All statistical analyses were performed using Statistical package for science SPSS software, version 23 (SPSS, IBM Company, Chicago, IL 60606, USA).

For continuous data mean ±SD were used, for categorical data we used number or percentage. An independent sample student t- test was used for comparing parameters between groups. For categorical values, Chi square test was used.

The Binary logistic regression analysis for pregnant against non-pregnant group was done to get odds ratio. ROC curve was used to detect cutoff value with sensitivity and specificity of ORPI. P value ≤ 0.05 was considered statically significant (Dnial, 1999).Continuous variables were expressed as mean SD and ranges. Categorical variables as percentage

Bivariate analysis (Pearson correlation coefficient) test was used to test the degree of association between OPRI and ICSI outcome (no. oocyte, no. MII, no. embryo).

Chapter Four

Results

THE RESULTS

Demographic characteristics of the studied groups:

There were 60 women involved in this study their demographic characteristics shown in (table 1) .Most of them lived in urban area (70%). 65% of them had primary infertility and 35% of them had secondary infertility.

Table 4.1: Demographic characteristics of the studied groups

Variable		Studied group(60)	
		No.	%
Address	Rural	18	30
	Urban	42	70
Type of infertility	Primary	39	65
	Secondary	21	35
Duration of infertility (years)		5.81±2.76	
Age (Mean ±SD) years		29.75±3.91	
BMI (kg/m²)		24.18±2.83	

BMI (body mass index)

Hormonal level at day 2 or 3 of MC was measured and showed in table 2.

Table 4.2: Hormonal level at day 2 of Menstrual cycle of the studied groups (No. =60)

Hormones	Mean ±SD
FSH (mIU/mL)	7.32±1.46
LH (IU/L)	4.90±1.22
Prolactin (ng/mL)	19.11±5.55
E2 (pg/mL)	44.63±10.40
*AMH (ng/mL)	3.64±1.22
TSH (ng/mL)	2.14±0.63

FSH (follicle stimulating hormone) , LH (luteinizing hormone) , E2 (estradiol) , AMH (anti-mullerian hormone) , TSH (thyroid stimulating hormone) , MC (Menstrual cycle)

Type of treatment protocol in studied group:

All patients undergo ICSI program were taken ovarian stimulation treatment and the type of protocol was shown in table 3. Most of them underwent antagonist protocol (71.67%).

Table 4.3: Type of protocol in studied group (No. =60)

Protocol	No.	%
Agonist	16	26.67
Antagonist	43	71.67
Prolong	1	1.66

ORPI of studied group:

The ORPI of studied group was shown in table 4. The mean of ORPI was 1.82± 1.14. Most of them had ORPI between one and three.

Table 4.4: The ORPI of studied group (No. =60)

ORPI	No.	%
<1	**19**	**31.67**
1-<2	**27**	**45**
2-3	**12**	**20**
>3	**2**	**3.33**
	60	**100%**

ICSI outcome:

The ICSI outcome of oocyte number, MII number, embryo number and embryo transferee number as mean ±SD was shown in table 5.

Table 4.5: ICSI out come in studied group (No. =60)

ICSI out come	Mean ±SD
Oocyte No.	11.03±6.02
MII No.	9.10±5.76
Embryo No.	5.73±3.78
Embryo transferee No.	2.00±0.63

MII =Meta phase II

The pregnancy rate of the studied group was 33.33% as shown in figure 1.

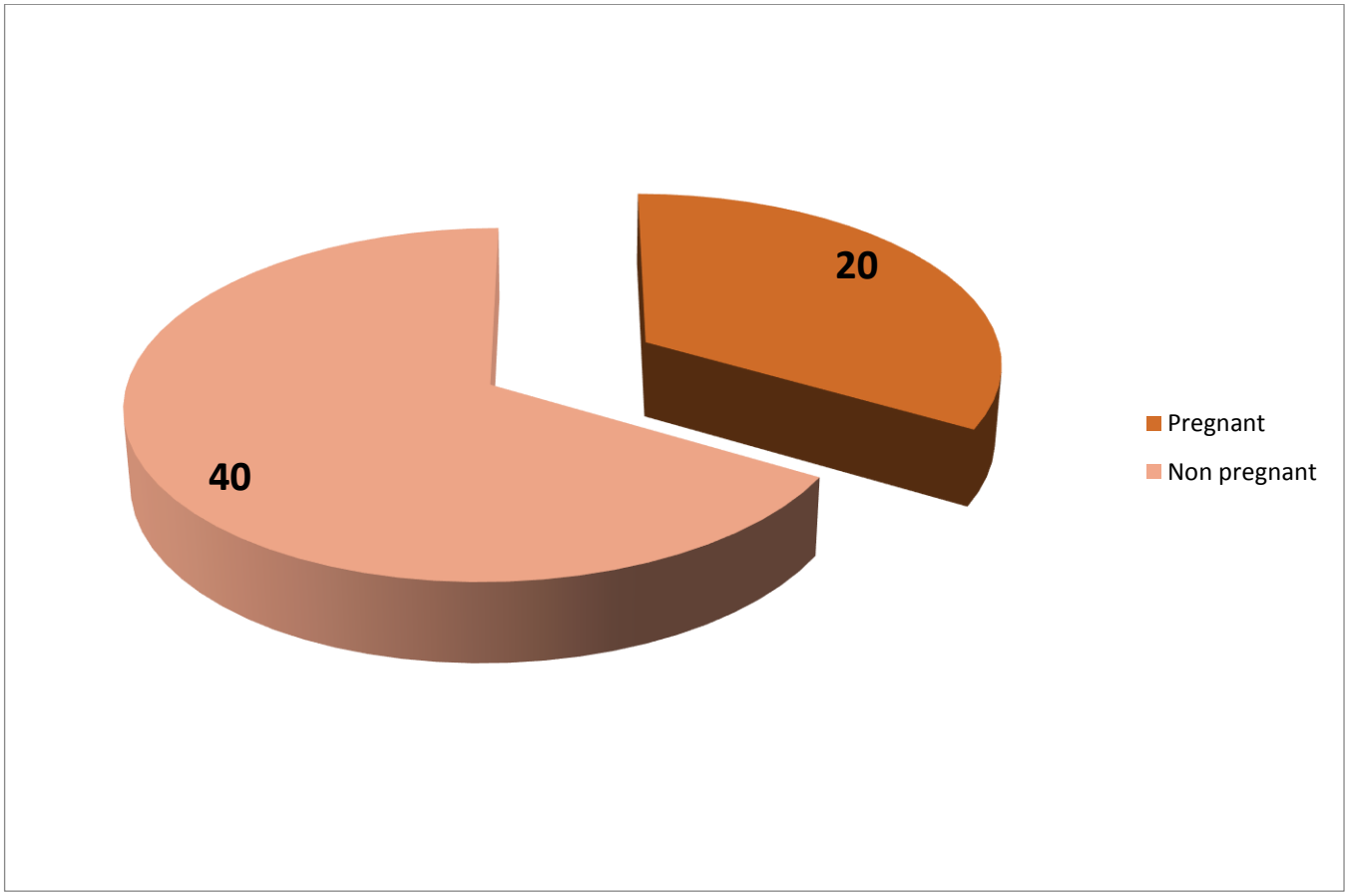


Figure 4.1: The pregnancy rate of the studied group (No. = 60)

Demographic characteristics of the pregnant and non-pregnant women:

The demographic characteristics of the pregnant and non-pregnant women was shown in table 6.4 There were insignificant difference between pregnant and non-pregnant women regarding age, BMI, type of infertility, duration of infertility and address (P>0.05).

Table 4.6: Demographic characteristics of the pregnant and non-pregnant women (studied group no. =60

Variable		Pregnant (20)		Non pregnant (40)		P value
		No.	%	No.	%	
Address	Rural	9	45	9	22.5	0.069
	Urban	11	55	31	77.5	
Type of infertility	Primary	11	55	28	70	0.194
	Secondary	9	45	12	30	
Duration of infertility (years) (Mean ±SD)		5.75±2.88		5.91±2.67		0.87
Age (Mean ±SD) years		29.78±3.05		29.70±5.33		0.20
BMI (kg/m^2) (Mean ±SD)		23.85±2.72		24.85±2.99		0.94

BMI = Body Mass Index

Hormonal level at day 2 of menstrual cycle of the pregnant and non-pregnant women:

Hormonal level at day 2 or 3 of MC was measured and showed in table 7 , AMH was significantly higher in Pregnant women than non-pregnant group, (P value <0.05).

Table 4.7: Hormonal level at day 2 of menstrual cycle of the pregnant and non-pregnant women

Hormones	**Non pregnant (40)**	**Pregnant (20)**	**P value**
FSH (mIU/mL)	6.94±1.62	7.51±1.36	0.15
LH (IU/L)	5.24±1.48	4.73±1.04	0.13
Prolactin (ng/mL)	18.26±5.25	19.54±5.72	0.41
AMH (ng/mL)	1.41±0.50	3.35±1.10	0.001
E2 (pg/mL)	43.27±11.19	45.31±10.06	0.47
TSH (ng/mL)	2.07±0.75	2.18±0.57	0.53

***P value<0.05 was significant**

FSH (follicle stimulating hormone) , LH (luteinizing hormone) , E2 (estradiol) , AMH (anti-mullerian hormone) , TSH (thyroid stimulating hormone) , MC (Menstrual cycle).

Type of protocol of the pregnant and non-pregnant women:

The type of protocol of the pregnant and non-pregnant women was shown in table 8. There was insignificant difference between pregnant and non-pregnant group, (P value >0.05).

Table 4.8: Type of protocol in of the pregnant and non-pregnant women (studied group no. =60)

Protocol	**Pregnant 20**		**Non pregnant 40**		**P value**
	No.	**%**	**No.**	**%**	
Agonist	3	15	13	21.67	**0.54**
Antagonist	16	80	27	78.33	
Prolong	1	5	0	0	

Type of protocol in of the pregnant and non-pregnant women

ORPI of the pregnant and non-pregnant women:

The ORPI of the pregnant and non-pregnant women was shown in table 9. ORPI was significantly higher in Pregnant women than non-pregnant group, (P value <0).

Table 4.9: The ORPI of the pregnant and non-pregnant women (studied group no. =60)

OPRI	**Pregnant 20**		**Non pregnant 40**		**P value**
	No.	**%**	**No.**	**%**	
<1	1	5	18	30	0.01
1-<2	10	50	17	28.33	
2-3	8	40	4	6.67	
>3	1	5	1	1.67	
Mean ±SD	2.54±0.60		0.98±0.32		0.001

ICSI out come in the pregnant and non-pregnant women:

The oocyte, MII, number of embryo and embryo transfer had insignificant difference between the pregnant and non-pregnant women (P value >0.05) as shown in table 10.

Table 4.10: ICSI out come in the pregnant and non-pregnant women (studied group no. =60)

ICSI out come	**non pregnant (40)**	**Pregnant (20)**	**P value**
Oocyte No.	9.10±5.62	12.00±6.05	0.07
MII No.	8.35±6.25	9.48±5.55	0.48
Embryo No.	5.45±3.66	5.88±3.87	0.68
Embryo transferee No.	1.80±0.76	2.10±0.54	0.08

MII =Meta phase II

ICSI= Intra Cytoplasmic Sperm Injection

Figure 2, figure 3 and figure 4 shows the correlation between ORPI and MII number, embryo number and number of embryo transfer ,there were insignificant positive correlation between ORPI level with MII, embryo number and number of embryo transfer (r=0.144 , p=0.273 ; r=0.058,p0.658 and r=0.176 ,p0.179)

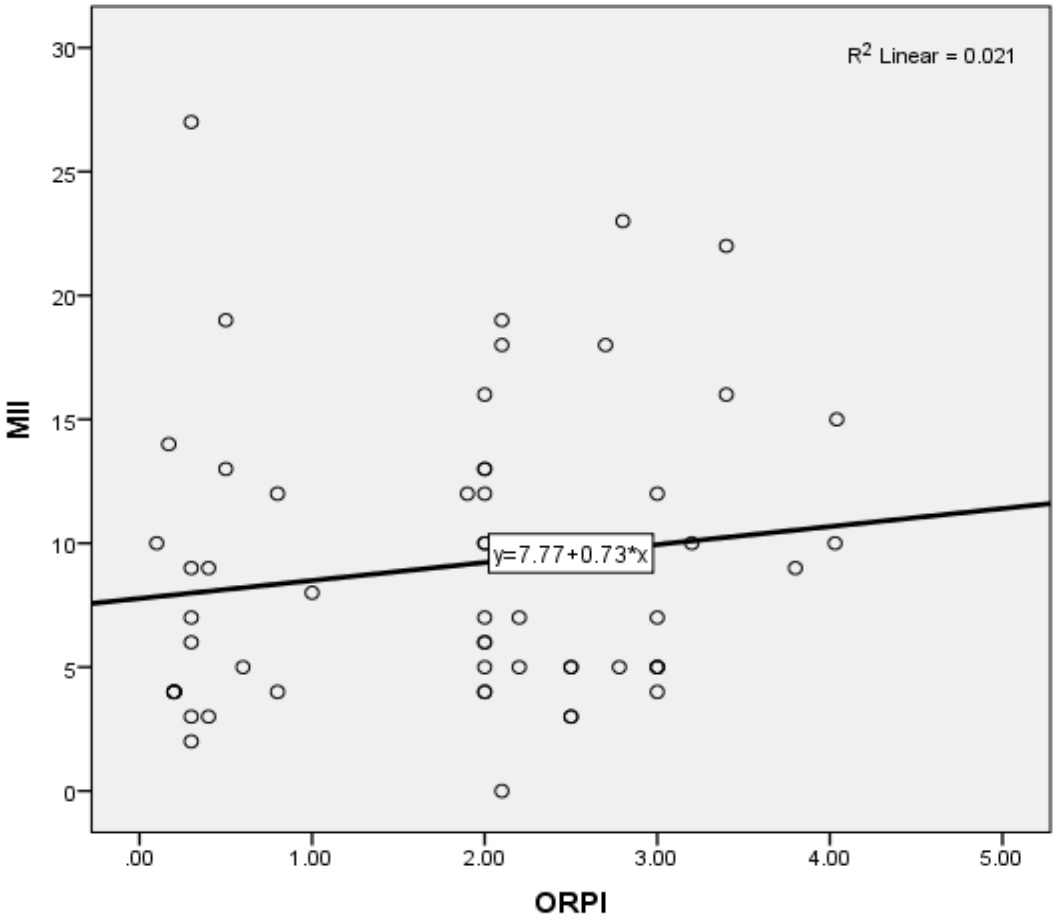


Figure 4.2: The correlation between ORPI and MII
ORPI =Ovarian Reserve Prediction Index
MII =Meta phase II

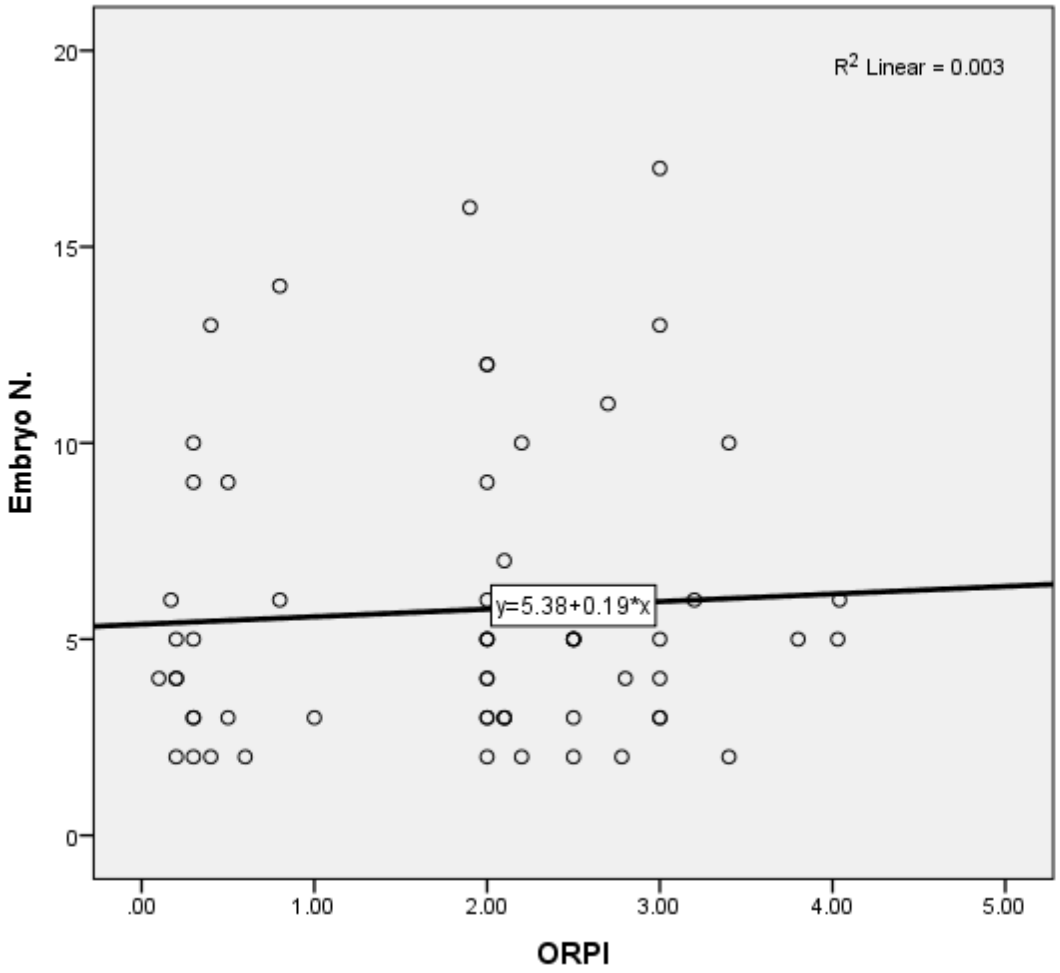


Figure 4.3: The correlation between ORPI and embryo number
ORPI =Ovarian Reserve Prediction Index

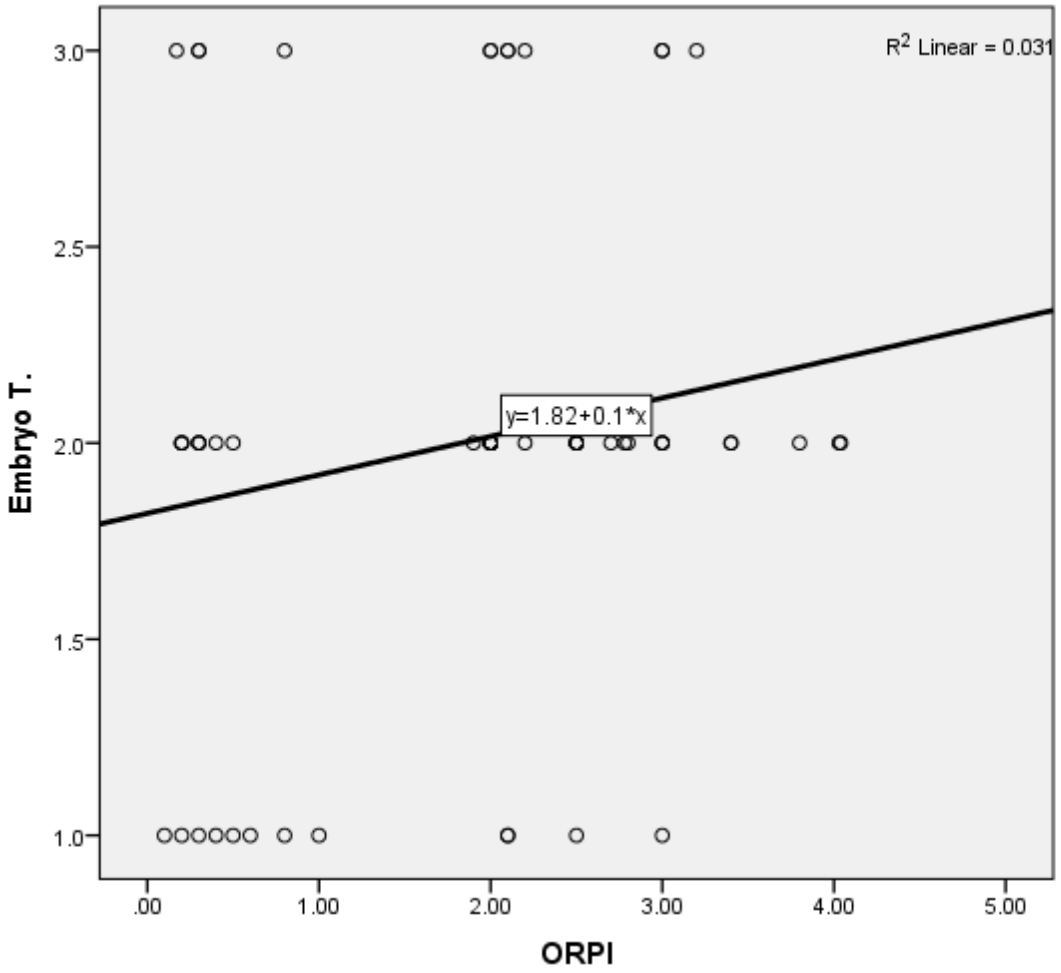


Figure 4.4: The correlation between ORPI and number of embryo transfer
ORPI =Ovarian Reserve Prediction Index

Binary logistic regression analysis was done to assess the prognostic effect of ORPI of Pregnant women compared to non-pregnant group as reference group
as shown in table 5 ,where AMH , AFC and BMI appeared to be significant affecting factor of ORPI, however, the higher odds ratio (OR) reported with AMH (Odds ratio = 2.72) and a significant ratio for AFC (odds ratio=2.34). Women with higher AMH, AFC and lower BMI more likely to have higher ORPI.

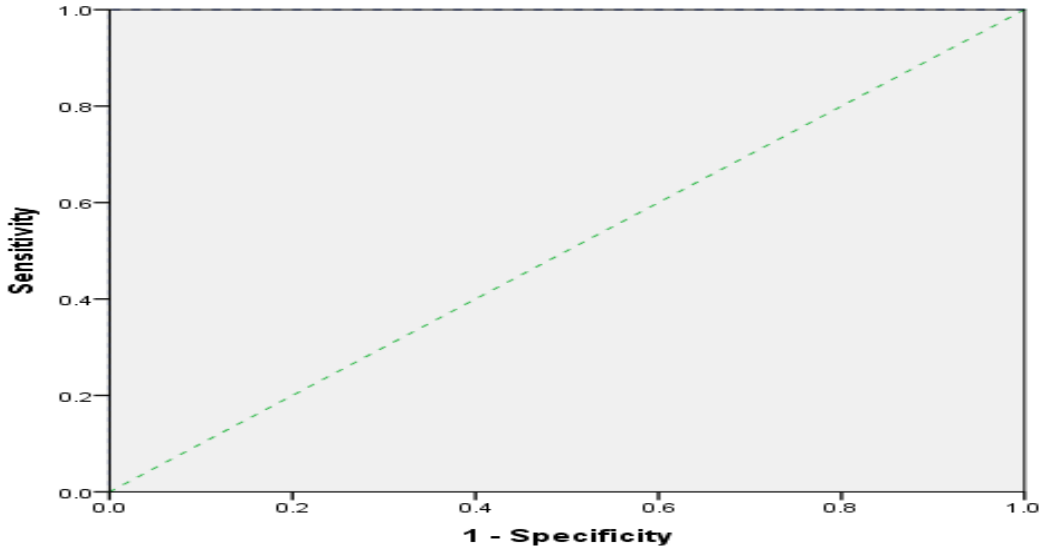
Table 4.11: Binary logistic regression analysis done to assess the prognostic effect of ORPI of Pregnant women compared to non-pregnant group as reference group

PREGNANT	P value	Odds ratio	95% Confidence Interval for odds ratio	
			Lower Bound	Upper Bound
Age	.142	0.825307	0.12	0.91
*BMI	.047	0.772	0.595	0.99
Duration	0.051	0.88	0.7808	0.97
*AMH	0.004	2.72	0.9996	3.56
*MII	0.010	1.85	0.722	4.13
*AFC	0.03	2.341	0.85	5.43
*Embryo N.	0.012	1.93	0.8731	2.34
Embryo T.	0.117	0.93	0.7067	1.40
*Oocyte	0.015	1.92	0.404	2.37

***P value<0.05 was significant**

FSH (follicle stimulating hormone) , LH (luteinizing hormone), E2 (estradiol) , AMH (anti-mullerian hormone) , TSH (thyroid stimulating hormone) , ORPI =Ovarian Reserve Prediction Index , MII =Meta phase II , BMI = Body Mass Index , AFC =Antra Follicle Count

Binary logistic regression analysis for measurement of the effect of baseline parameters and ICSI outcome in pregnant women compared to non-pregnant women as dependent variable.



AUC	Cutoff value	Sensitivity	Specificity	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
1.00	2	97%	100	1.000	1.000

Figure 4.5: Receiver Operating Characteristics (ROC) curve analysis was done to ass assess the validity of ORPI in prediction of ICSI success rate
ICSI= Intra Cytoplasmic Sperm Injection

Chapter Five

Discussion

DISCUSSION:

The advantage of combined use of more than one ovarian reserve tests to predict ovarian response more than the usage of any one of them alone have an accurate and ideal prognostication of ovarian response. (Haritha, 2020).

The aim of the present study was to explore the evaluative effectiveness ovarian response prediction index (ORPI) to determine ICSI outcome.

This research enrolled 60 infertile women who had undergone intracytoplasmic sperm injection treatments

The female have demographic characteristic and hormonal profile of study group summarized in Table (1) and (2).

Age of women was with mean age of (29.75±3.91) year; these women are still with safe zone of infertility. However even women with same age group might have different ovarian response to controlled ovarian stimulation (Muttukrishma, 2005)

The ovary, the key organ that maintains female reproductive and endocrine function, enters aging earlier and faster than other organs and attracted extensive attention from society. Ovarian aging mainly characterized by the progressive decline in the number and quality of oocytes, the regulatory mechanisms of which have yet to be systematically elucidated (Jiachen, *et al.*, 2022).

Body mass index of women of the current study was (24.18±2.83) kg/ m^2 this body mass index is with in normal weight category according to WHO criteria of obesity**.** (Weir, 2023)

In recent issue by Kloos in September 2022 as a letter to the editor in The Journal of Clinical Endocrinology & Metabolism, he concluded that: whether obesity lowers AMH levels is still controversial, as he marginalized within the publication. (Kloos, 2022)

The mean duration of infertility period in our study was (6.14±1.59) years and primary infertility was the most common type, which similar to results concluded by Ali, *et al.*, 2018

During the study period, each patient was subjected to an individualized COS protocol according to ovarian reserve testing and other characteristics. A GnRH agonist or antagonist give to prevent the premature spike of LH that would induce ovulation (Fleming, et al., 2015).

Table (4.3) illustrated the ovarian stimulation protocol of our patients, most of them (71.67%) underwent Antagonist protocol, while (26.67%) of them underwent agonist

protocol and (1.66%) prolong protocol. The chosen protocol was individualized according to the age, AMH and AFC (Warlin et al, 2020; Yaxin et al., 2021).

Women with normal AFC and low AMH may benefit from the GnRH-an ultra-long protocol. Nevertheless, for women with normal AMH and low AFC, the long GnRH-a protocol seems to be associated with better clinical outcomes (Yaxin et al., 2021).

Others concluded that flexible GnRH antagonist protocol might not be suitable for patient with low ovarian reverse AFC less than seven or patient aged over 40 years. However, flexible GnRH antagonist protocol might be strongly recommended for patients under 30 years and with ovarian reverse AFC more than 24. For the rest group of patients in their study, antagonist protocol was slightly favored because it had low OHSS in general. (Warlin and his colleges', 2020).

Table (4.4) demonstrates the ORPI of studied group, which show the mean of ORPI (1.82±1.14). Most (65 %) of them had ORPI between one and three.

ORPI is the combination of age of the woman, AMH and AFC and ORPI proposed to be a more reliable indicator of ovarian response. Previous studies have suggested that ORPI is a more precise index of ovarian response than each of the constituent parameters alone (Ashrafi, *et al.*, 2017).The result of the present study near the results get by Gupta, he found that mean ORPI was (1.34±1.41) (Gupta 2023).

ICSI outcomes regarding total number of oocytes retrieved, no. of MII oocytes, no. of embryo and no. of embryo transferred is illustrated in (table 4.5). The results of the present study are near the results get by Gupta, 2023.

Drakopoloulos, *et al.*, stated that the number of oocytes obtained after OS is a vital cornerstone of ART as an independent indicator of the probability of pregnancy, (Drakopoloulos, et al., 2016).

The pregnancy rate of the studied group was (33.33%), (figure 4.1). An Iraqi study at the fertility center in AL-Najaf province at AL-Sadder medical city, had found that clinical pregnancy rate following an ICSI procedure was 23.4%, which was less than that of present study (Hussain SS *et al*, 2018). Ahmeid, 2015 found that the pregnancy rate in Baghdad IVF fertility center following ICSI was 20.4 %. AL-Zawea and AL. Mossa, 2021, found that the rate of clinical pregnancy was 46.7 % However, a pregnancy rate of (51 %) was recorded by some Iraqi authors in a study carried out at out at the High institute for infertility diagnosis and Assisted Reproductive technologies/AL-Nahrain University and Specialist Fertility Department/ Al-Bonook hospital (Fadhil et al., 2017)

In nearby countries (Iran), the successful clinical pregnancy rate following ART's has ranged from (21.5 to 33.9 %) (Ashrafi et al., 2013) indicating that the rate of positive clinical pregnancy in the current study is one of the best an achieved rates. However, in a number of fertility centers in the United States, the rate of positive clinical pregnancy has reached relatively high level between (43.9 % and 54.2 %) (Zagadailov et al., 2017). These controversies in the results of pregnancy rate are attributed to many factors of these: age of female, baseline ovarian reserve parameters, protocol used for ovarian stimulation and o also, this difference related to the fact that that their study done in more than one ART center.

Table (4.6) showed that no significant difference between pregnant and non-pregnant women with their type of infertility, duration of infertility, address that was agreement with other study get by Ashrafi , et al., 2013.

Table (4.7) There was a significant difference between pregnant and non-pregnant women with their AMH level, which was compatible with other study, which indicated that AMH could also independently predict pregnancy outcomes (Zhao et al., 2021).

Several studies (Tobler, et al. 2015); (Peluso, et al. 2014); (Sahmay et al. 2014); (Brodin et al. 2015). Have revealed that age, antral follicle count (AFC), and serum anti-Müllerian
Hormone (AMH) levels reflect the ovarian reserve admittedly, so these factors are considered valuable predictors of the ovarian response to exogenous gonadotrophins. Furthermore, debate exists regarding whether a single parameter or a combined index
Moreover, using AMH, AFC, and age together constituted a new model for predicting poor or excessive ovarian response.
The significantly higher OPRI in pregnant than in non- pregnant women is shown in (table 4.9). Our result is similar to that of Oliveira et al., who first innovate ORPI to assess ovarian response. He stated that ORPI exhibited an excellent ability to predict poor or excessive ovarian response, a collection of greater than or equal to four metaphase II oocytes and the occurrence of pregnancy in pregnancy in infertile women (Oliveira et al., 2012).
In addition, he recommended the use of ORPI to improve the cost-benefit ratio of ovarian stimulation regimens by guiding the selection of medications and by modulating the doses and regimens according to the actual needs of the patients.
Zhou et al.2020, in their study where they compare different ovarian reserve parameters including OPRI, to evaluate their effectiveness in predicting ovarian response , he agreed that the evaluative effectiveness of a combined index exceeded that of a single parameter for evaluating the ovarian reserve and response of infertile women.
Table (4.10) show the ICSI out come in the pregnant and non-pregnant women, there were no significant difference between them .In compare to other study that showed statistically

Significant differences between pregnant and non-pregnant groups in number of MII oocytes, embryo transfer and number of embryo (Ashrafi et al., 2013).

Age has a strongly negative effect on the chances of pregnancy and ART does not compensate for basic physiological preconditions of reproductive senescence, since there is a decrease in ovarian reserve and a rise in the development of aneuploidy embryos with very low implantation rates. , Advancing female age reported to be a negative prognostic factor, and the decline in implantation rates with advancing age primarily linked to poor oocyte quality rather than uterine function, because the number of good quality embryos is significantly lower in women aged > 40 year, and less embryos are available for replacement (Leeners et al., 2013).

Therefore, the achievement of IVF can be as high as 40% at age 20 year in comparison with 5% of those with age > 40 year .Overall, it has been shown that ongoing pregnancy rates in assisted reproductive technology decreased significantly with advancing age (Leeners. Et al., 2013) American College of Obstetricians and Gynecologists Committee (ACOG) reported that the significant increase in aneuploidy and spontaneous abortion rates with advanced maternal age making age alone as detrimental impact on fertility (American Committee on Gynecologic practice and practice committee , 2014)

It is evident that various factors may influence the outcome of ICSI. Kovacs et al. showed, women who became pregnant after ART showed thicker endometrium, better quality of embryo, as well as more follicles, oocytes and embryos, as we observed other study[(Ashrafi M. et al., 2013) So variable parameters in patients with different causes of infertility and predicted pregnancy success rates following ICSI. In addition, patient characteristics, total dose of gonadotropin, endometrial thickness, number of previous cycle and quality of embryo transferred evaluated as predictors of success rates following ICSI.

Persians correlation was done to explore if there are any relation between OPRI and MII, embryo number and number of embryo transfer, (Figure 4.2, 4.3 and 4.4). There were no significant correlation between them. These results incompatible with Gupta results, who reported a significant positive correlation between them (Gupta, et al., 2023). This may be due to difference in sample size and age of women whom he included in his study.

Binary logistic regression analysis was done to assess the prognostic effect of ORPI of pregnant women compared to non-pregnant women as reference group (table 4.11).

There was a significant positive correlation of higher AMH, AFC, and lower BMI, MII, oocyte and embryo number with occurrence of pregnancy. The highest odd ratio gained by

AMH and AFC (2.72 and 2.341 respectively).our results are compatibles with many research works.

Kalpana et al., showed a significant positive correlation between pregnancy occurrence and higher AMH and AFC (Kalpana, et al., 2019). Mannem Haritha and his co- workers 2020, suggested that combination of different variables of ORPI (AMH,AFC, age) have resulted in more precise index to predict ovarian response to COS hormones, also they found a significant correlation with p value ($P < 0.001$) between ORPI and number of MII oocytes.

Ritika Gupta and team workers 2023 have similar finding in their study, where they found a positive relation between ORPI with AFC, AMH, oocytes, MI oocytes and embryo. They concluded that ORPI a novel ovarian response markers. Also Oehninger et al. 2015 concluded similar finding. Oliveria and his colleagues 2012, suggested the prognostication of ovarian response to COS hormones during ART cycles can depend on ORPI, they found a strong relation between ORPI and the number of oocytes pickup and with maturity of collected oocytes.

Zhao D. et al., 2021 indicated that AMH could independently predict pregnancy outcomes (Zhao D. et al., 2021). Although a good predictive value for both AFC and AMH is reported, but published evidence leans towards AMH level, (Fleming et al., 201; Alebic. et al., 2018).

Operating Characteristics (ROC) curve analysis was done to assess the validity of ORPI in prediction of ICSI success rate, (Figure4.5)

ORPI showed an AUC of 1.00 at a cutoff point 2, giving a sensitivity and specificity 97% and 100% respectively and AUC of 1.00 at a cutoff point 1, giving a sensitivity and specificity 100% and 95% respectively, which indicate that ORPI is highly predicting factor of pregnancy. The ROC curves also revealed good prognostic potency by (Kalpana et al., 2019) and Oliveira et al. 2012; they evaluated the predictive value of ORPI for ovarian reserve. They found that ORPI has an ideal predictive for poor ovarian response .They concluded that the use of ORPI could improve the cost benefits of ovarian induction regimens through guiding the drugs type, dose and regimen according to the real patient's needs. However, the odds ratios presented by the ORPI were always higher than those presented by all other prognostic factors were.
Zhou and teamwork in Peking University International Hospital compares different variables to predict ICSI outcome, OPRI was one of these; which presented better effectiveness in predicting excessive ovarian response. Zhou, et al. 2020
Asystemic review done by Broer etal concluded that none of the individual predictors of ovarian reserve is considered reliable for either oocytes number and quality or possibility of pregnancy after treatment. In addition, they described their accuracy as modest (Broer et al. 2009).

Ahmed M. and his teamwork, 2019 in Cairo, compare the accuracy of AMH, AFC and OPRI in predicting ovarian response to cos in patients attending IVF/ICSI programme, using ROC curve.

He concluded that the ORPI might be used to improve the cost-benefit ratio of ovarian stimulation regimens by guiding the selection of medications and by tailoring the doses and regimens to the actual needs of patients to achieve optimal response with minimal risks.

He added that OPRI might inform patients regarding their reproductive life span and menopausal timing, and aid in counseling and treatment strategy planning of young female cancer patients receiving gonad toxic therapy. In addition, it may aid in establishing the diagnosis of PCOS and provide insight into disease severity.

In our opinion the ideal ovarian reserve test should be convenient, be reproducible, display little if any intra cycle and inter cycle variability, and demonstrate high specificity to minimize the risk of wrongly diagnosing women as having DOR and accurately identify those at greatest risk of developing OHSS prior to fertility treatment.

Chapter Six

Conclusion and Recommendation

Conclusions and Recommendations

6.1. Conclusions

- ORPI was significantly higher in pregnant women than non-pregnant group.
- The pregnancy rate of the studied group was 33.33%.
- The incidence of pregnancy was significant in the group of women in which the level of AMH was high compared to the group of women in which the level of the hormone was low.
- Women with higher AMH, AFC and lower BMI more likely to have higher ORPI.
- ORPI showed an AUC of 1.00 at a cutoff point 2, giving a sensitivity and specificity 97% and 100% respectively
- The overall success rate of ICSI in Iraqi fertility centers near the results of the centers of other outside fertility centers.
- As no single ovarian reserve marker has 100% sensitivity and specificity, a combined index of three variables depicted by ovarian response prediction index can improve ovarian response prediction.

6.2. Recommendations

- The ORPI might be used to improve the cost-benefit ratio of ovarian stimulation regimens by guiding the selection of medications and by modulating the doses and regimens according to the actual needs of the patients.
- Encouraging physicians to adopt the OPRI as a marker in ICSI protocol.
- Due to the small sample size in our studies, we recommend that a meta-analysis on the factors involving in ICSI success be conducted.
- We suggest that further studies with a larger sample size from multiple centers be conducted.
- Continued research on other factors that are not well-studied in humans or that are only studied in gametes will add to the current knowledge about the best treatment options for men and women undergoing ICSI and other assisted reproduction procedures
- Encouraging physicians to adopt the OPRI as a marker in IUI.

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الخلاصة

الخلفية:

احتياطي المبيض هو مصطلح يستخدم لتحديد قدرة المبيض على توفير البويضات القادرة على الإخصاب مما يؤدي إلى حمل صحي وناجح. مع تقدم عمر الأم، ينخفض عدد البويضات التي يمكن تجنيدها بنجاح لاحتمال الحمل، مما يشكل عاملاً رئيسياً في العلاقة العكسية بين العمر وخصوبة الإناث.

قدرة المبيض على توفير بويضات قابلة للحياة تستخدم لوصف احتياطي المبيض لدى النساء والذي يتم تحديده بشكل أساسي من خلال عدد الجريبات البدائية في المبيض، مع شيخوخة المبيض سيكون هناك انخفاض في الخصوبة وعمر المبيض البيولوجي لدى الإنسان يبلغ حوالي ٥٠ سنة.

هناك العديد من العلامات البيو كيميائية والفيزيائية الحيوية لاحتياطي المبيض، والتي يطلق عليها عادة اختبارات احتياطي المبيض. تم إجراء اختبارات احتياطي المبيض الشائعة للأنثى قبل تقنية الإنجاب المساعدة (كمحاولة للتنبؤ باستجابة المبيض المحددة. ولتقييم احتياطي المبيض هناك اختبارات كيميائية حيوية وعلامات الموجات فوق الصوتية: إحدى العلامات البيوكيماوية ز

يتم تعريف عدد الجريبات الغارية على أنه جريب يظهر على شكل كيس صغير مملوء بسائل يحتوي على بويضة مبكرة. يتم تقدير عدد الجريبات الغارية في اليوم الثاني أو اليوم الثالث من الدورة الشهرية بواسطة الموجات فوق الصوتية عبر المهبل في ذلك الوقت، ويختلف حجم التي يتم قياسها في كلا المبيضين من (٢ - ١٠ ملم).

يمكن أن يلعب العمر محركًا مهمًا في تحديد معدلات النجاح في علاج حالات العقم. يتم علاج العديد من المرضى الذين يعانون من العقم باستخدام تقنيات الإنجاب المساعدة ومن بين هذه التقنيات حقن الحيوانات المنوية داخل السيتوبلازم، وهي تقنية إنجابية مساعدة سريرية شائعة تتميز بكونها مستقلة عن عدد الحيوانات المنوية وشكلها ولها معدل إخصاب مرتفع. تنخفض الخصوبة مع تقدم العمر ويزداد عدد الأزواج الذين يسعون لعلاج العقم. تعتبر اختبارات احتياطي المبيض بمثابة تقديرات غير مباشرة لتجمع الجريبات المتبقي لدى المرأة ويمكن أن تعطي فكرة عن استجابتها لتحفيز المبيض وتوقعاتها للنجاح في برنامج التخصيب في المختبر وحقن الحيوانات المنوية داخل الهيولى.

يعتبر تقدير مستوى الهرمون المضاد للمولري في المصل أحد المؤشرات البيوكيميائية القوية لمؤشر التنبؤ باحتياطي المبيض الذي يمكن إجراؤه في أي يوم من أيام الدورة كما يعد عدد الجريبات الغارية علامة مفيدة بالموجات فوق الصوتية لمؤشر التنبؤ باحتياطي المبيض.

إن معرفة تنبؤات الحمل في التكنولوجيا الإنجابية المساعدة مفيد للأطباء في تخصيص خطط العلاج وتحسين الاستشارة للمريض وللمرضى أن يقرروا ما إذا كانوا سيخضعون لعلاج العقم، لذلك من المهم تقييم مؤشرات التنبؤ باحتياطي المبيض كمؤشر للتنبؤ بالاستجابة لمساعد تكنولوجيا الإنجاب

العقم هو مرض يصيب الجهاز التناسلي الذكري أو الأنثوي ويتم تعريفه بالفشل في تحقيق الحمل بعد ١٢ شهرًا أو أكثر من الجماع الجنسي المنتظم دون وقاية. يؤثر العقم على ملايين الأشخاص في جميع أنحاء العالم، وغالبًا ما يكون له عواقب وخيمة

يتم علاج معظم المرضى الذين يعانون من العقم باستخدام تقنيات الإنجاب المساعدة ومن بين هذه التقنيات حقن الحيوانات المنوية داخل السيتوبلازم، وهي تقنية إنجابية مساعدة سريرية شائعة تتميز بكونها مستقلة عن عدد التصوير بالموجات فوق الصوتية، إحدى العلامات البيوكيميائية هي تقدير مستوى مصل الهرمون المضاد للمولري، والذي يمكن إجراؤه في أي يوم من أيام دورة تعداد الجريبات الغارية، وهي إحدى علامات الموجات فوق الصوتية لاختبارات احتياطي المبيض.

الهدف من هذه الدراســـة: تقييم مؤشـــر احتياطي المبيض (AMH*AFC/Age) توقعًا للعدد الإجمالي للبويضـــات المسترجعة، الطور الفوقي الثاني، البويضات وجودة الأجنة التي تم الحصول عليها ومعدل الحمل.

النتيجة الأولية المقاسة ستكون:

١. العدد الإجمالي لاسترجاع البويضات.

٢. عدد البويضات الطورية الثانية

٣. عدد ونوعية الأجنة التي تم الحصول عليها.

النتيجة الثانوية: هي معدل الحمل.

تصميم الدراسة: كانت هذه الدراسة دراسة الأتراب المحتملين.

المرضـــى والطريقة: أجريت هذه الدراســـة على ســـتين امرأة تعاني من العقم تتراوح أعمارهن بين ٢٢-٤٥ ســـنة (٢٩,٧٥+٣,٩١) راجعن عيادة الخصوبة في مستشفى الصدر التعليمي وخضعن لحقن الحيوانات المنوية داخل السيتوبلازم طوال الفترة من آب ٢٠٢٢ إلى آذار ٢٠٢٣ لكل مريضة. الخضوع لتفاصيل التاريخ والفحص البدني.

في اليوم الثاني من الدورة (الموجات فوق الصـــوتية المهبلية واختبارات الدم للهرمون المنبه للجريب، والهرمون الملوتن، والهرمون المضاد للمولر، والإستراديول، وبروﻻكتين المصل، واختبار وظائف الغدة الدرقية.

تم قياس قيم مؤشر توقع استجابة المبيض عن طريق ضرب مستوى مصل الهرمون المضاد للمولر (نانوغرام/مل) في عدد الجريبات الغارية التي يبلغ قطرها (٩-٢ ملم) ومن ثم قسمة النتيجة على عمر النساء (سنوات)

كان معدل الحمل للمجموعة المدروســـة ٣٣,٣٣%، وكان هناك فرق كبير بين النســـاء الحوامل وغير الحوامل في مســـتوى الهرمون المضاد للمولري، والذي كان متوافقًا مع دراسة أخرى، والتي أشارت إلى أن الهرمون المضاد للمولري يمكنه أيضًا التنبؤ بشكل مستقل بنتائج الحمل، (قيمة P كانت ٠,٠٠٤)

أظهرت الدراسة الحالية وجود اختلاف كبير في مؤشر التنبؤ باحتياطي المبيض بين النساء الحوامل وغير الحوامل حيث كان مؤشر التنبؤ باحتياطي المبيض أعلى بكثير عند النساء الحوامل منه في المجموعة غير الحوامل.

العلاقة بين مؤشـــر التنبؤ باحتياطي المبيض والطور الفوقي الثاني، عدد الأجنة وعدد الأجنة المنقولة، كانت هناك علاقة غير معنوية لمستوى مؤشر التنبؤ باحتياطي المبيض مع الطور الفوقي الثاني، عدد الأجنة وعدد الأجنة المنقولة.

تم إجراء تحليل الانحدار اللوجســـتي الثنائي لتقييم التأثير النذير لمؤشـــر التنبؤ باحتياطي المبيض لدى النســـاء الحوامل، وكان هناك ارتباط إيجابي كبير بين ORPI وارتفاع الهرمون المضـــاد للمولري، وعدد الجريبات الغارية، وانخفاض مؤشـــر كتلة الجســـم، والطور الثاني، وعدد البويضـــات والأجنة (قيمة P لعدد الجريبات الغارية ٠,٠٣)؛ (مؤشـــر كتلة الجســـم القيمة p (0.47.

وأخيراً، تم إجراء تحليل منحنى خصائص تشغيل المستقبِل (ROC) لتقييم مدى صحة مؤشر التنبؤ باحتياطي المبيض في التنبؤ بمعدل نجاح حقن الحيوانات المنوية داخل الهيولى، (الشكل ٥). أظهر مؤشر التنبؤ باحتياطي المبيض وجود AUC قدره ١,٠٠ عند نقطة القطع ٢، مما يعطي حساسية ونوعية ٩٧% و١٠٠% على التوالي و1.00 AUC عند نقطة القطع ١، مما يعطي حساسية ونوعية ١٠٠% و٩٥% على التوالي، مما يشير إلى أن ORPI يعد عامل تنبؤ كبير بمعدل نجاح حقن الحيوانات المنوية داخل السيتوبلازم

خاتمة:

• نسبة النجاح الإجمالية لحقن الحيوانات المنوية داخل الهيولى في مراكز الخصوبة العراقية قريبة من نتائج مراكز الخصوبة الخارجية الأخرى.

- بلغت نسبة الحمل للمجموعة المدروسة ٣٣,٣٣%

• كان الهرمون المضاد لمولريان أعلى بكثير في النساء الحوامل منه في المجموعة غير الحوامل

• لم يكن لنوع البروتوكول في برنامج حقن الحيوانات المنوية داخل الهيولى دور يذكر في نسبة النجاح.

• كان مؤشر التنبؤ باحتياطي المبيض أعلى بكثير لدى النساء الحوامل مقارنة بالمجموعة غير الحوامل.

• النساء اللواتي لديهن ارتفاع في الهرمون المضاد لمولر، وعدد الجريبات الغارية، وانخفاض مؤشر كتلة الجسم أكثر عرضة لارتفاع مؤشر التنبؤ باحتياطي المبيض.

• أظهر ORPI AUC بقيمة ١,٠٠ عند نقطة القطع ٢، مما يعطي حساسية ونوعية ٩٧% و١٠٠% على التوالي.

• كانت هناك علاقة إيجابية معنوية بين مستوى مؤشر التنبؤ باحتياطي المبيض مع الطور الاستوائي الثاني، وعدد الأجنة وعدد الأجنة المنقولة.

وزارة التعليم العالي والبحث العلمي
جامعة بابل-كلية الطب
فرع الفسلجة والفيزياء الطبية

تقييم مؤشرات مخزون المبيض للتنبؤ بنتائج حقن الحيوانات المنوية داخل سايتوبلازم البويضة

رسالة مقدمة الى مجلس كلية الطب-جامعة بابل وهي جزء من متطلبات نيل درجة الماجستير في العلوم | الفسلجة الطبية

من قبل

ميامي هاشم كاظم علوان العامري

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١٤٤٤ هـ ___ ٢٠٢٣ م