Role of Ratio of Progesterone to Number of Follicles as a Prognostic Tool for Intracytoplasmic Sperm Injection Outcome

Thesis

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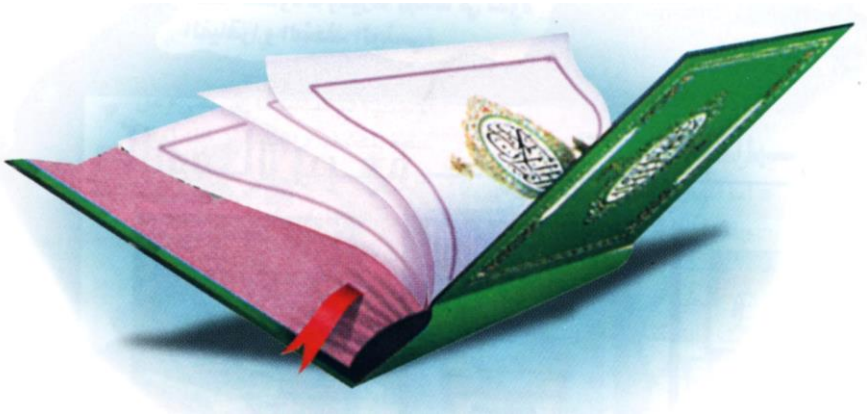
بسم الله الرحمن الرحيم

وَقُلِ اعْمَلُوا فَسَيَرَى اللَّهُ
عَمَلَكُمْ وَرَسُولُهُ وَالْمُؤْمِنُونَ



صدق الله العظيم

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Ahmed Nasr Ali Etman

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List of Abbreviations

Abb.	Full term
AFC	*Antral follicle concentration*
ART	*Assisted reproductive technology*
ASRM	*American Society for Reproductive Medicine*
AZF	*Azoospermia factor*
BMI	*Body mass index*
CC	*Clomiphene citrate*
CFTR	*Cystic fibrosis transmembrane conductance*
COH	*Controlled ovarian hyperstimulation*
E2	*Estradiol*
ESHRE	*European society for human reproduction*
ET	*Embryo transfer*
FSH	*Follicle stimulating hormone*
GIFT	*Gamete intrafallopian transfer*
GnRH	*Gonadotrphine releasing hormone*
HCG	*Human chorionic gonadotrophin*
HH	*Hypergonadotrophine hypogonadism*
hMG	*Human menopausal gonadtrophine*
ICSI	*Intracytoplasmic sperm injection*
IVF	*Invitro fertilization*
LH	*Leutinizing hormone*
LNV	*Large nuclear vacuoles*
MESA	*Microsurgical epididymal sperm aspiration*
OHSS	*Ovarian hyperstimulation syndrome*

List of Abbreviations cont...

Abb.	Full term
P4	*Progesterone*
PCOS	*Polycystic ovarian syndrome*
PGD	*Preimplantation genetic diagnosis*
PID	*Pelvic inflammatory disease*
POF	*Premature ovarian failure*
PR	*Pregnancy rate*
rFSH	*Recombinant FSH*
ROS	*Reactive oxygen species*
SART	*Society for Assisted Reproductive Technology*
UI	*Unexplained infertility*
ZIFT	*Zygote intrafallopian transfer*

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INTRODUCTION

Progesterone elevation (PE) has been observed during controlled ovarian stimulation (COS) using gonadotropins and gonadotropin-releasing hormone (GnRH) analogs, occurring mainly at the end of the follicular phase and on the day of human chorionic gonadotropin (hCG) administration. Its frequency varies, but it occurs in up to 35 % of cycles in patients treated with a GnRH agonist and in up to 38 % of cycles in those treated with a GnRH antagonist ***(Bosch et al., 2010).***

A recent meta-analysis has suggested that PE during COS is associated with a decreased probability of pregnancy following fresh embryo transfer (ET), but this elevation is not associated with the outcome of frozen–thawed transfer (FET) ***(Venetis et al., 2013).***

These data suggest that PE may be associated with adverse effects on the endometrium (specifically, advanced endometrial histological maturation and altered gene expression) and that it does not negatively impact embryo quality ***(Papanikolaou et al., 2012).***

Thus, patients with PE during a fresh cycle would benefit from elective FET, for which the entire cohort of embryos is cryopreserved and the embryo transfer is performed later in a natural cycle or in a cycle with hormonal replacement for endometrial priming ***(Roque et al., 2013).***

However, deleterious progesterone (P) levels may vary according to ovarian response ***(Griesinger et al., 2013)***. Thus, it would be better to define a ratio between P level and ovarian response instead of using a single P level as a prognostic tool.

AIM OF THE WORK

This study aims to assess the accuracy of progesterone to follicle number ratio for predicting pregnancy outcome in women under going ICSI.

Research hypothesis:

In women under going ICSI, the ratio between progesterone to the number of follicles may predict the clinical pregnancy rate or outcome accurately.

Research question:

In women undergoing ICSI, does the ratio of progesterone at day of HCG injection and number of follicles predict the pregnancy rate accurately.

Chapter 1:

THE OVARY

The ovaries develop from the incorporation of primordial germ cells into coelomic epithelium of the mesonephric (wolffian) duct. The embryologic ovaries migrate caudad to the true pelvis. Primordial ovarian follicles develop but remain dormant until stimulation in adolescence by gonadotropins ***(Rey et al., 2016).***

Ovarian follicular development begins while the female fetus is in-utero. During the fifth week of pregnancy, a female fetus's ovary contains about 500 to 1300 primordial germ cells. The primordial germ cells undergo mitosis, and by the twentieth week of pregnancy, the female fetus has approximately 6 to 7 million germ cells. Once mitosis is complete, the germ cells enter meiosis and arrest in meiotic prophase I forming germ cell cysts ***(Sun et al., 2017).***

Many germ cells are lost during this process, and the female is born with one to two million primordial follicles. By the time she reaches puberty, approximately 400,000 to 500,000 primordial follicles remain. After menarche, approximately 1000 follicles are lost monthly. After 35 years of age, the rate of follicular loss increases ***(Sun et al., 2017).***

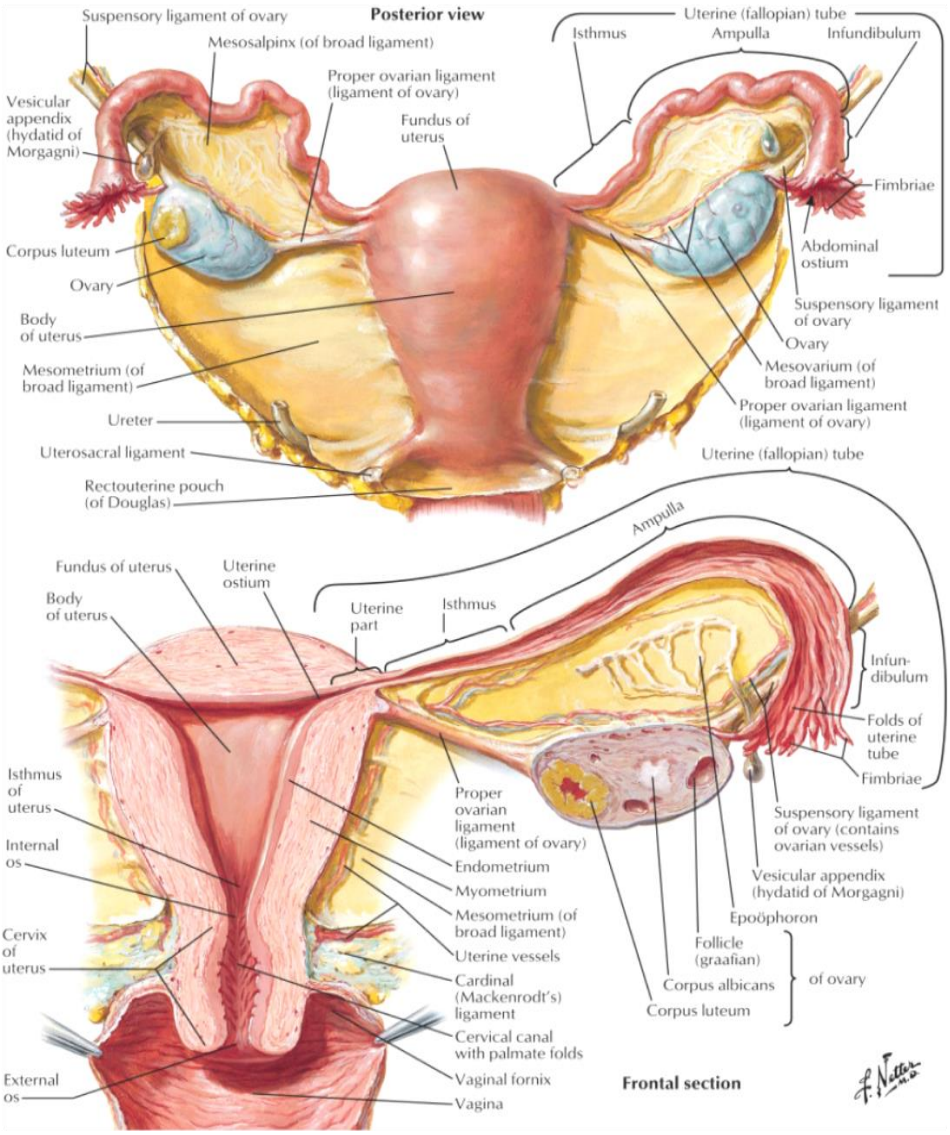

Figure (1): Frontal section in the female reproductive system (Atlas of human anatomy, F.Netter 2011 edition).

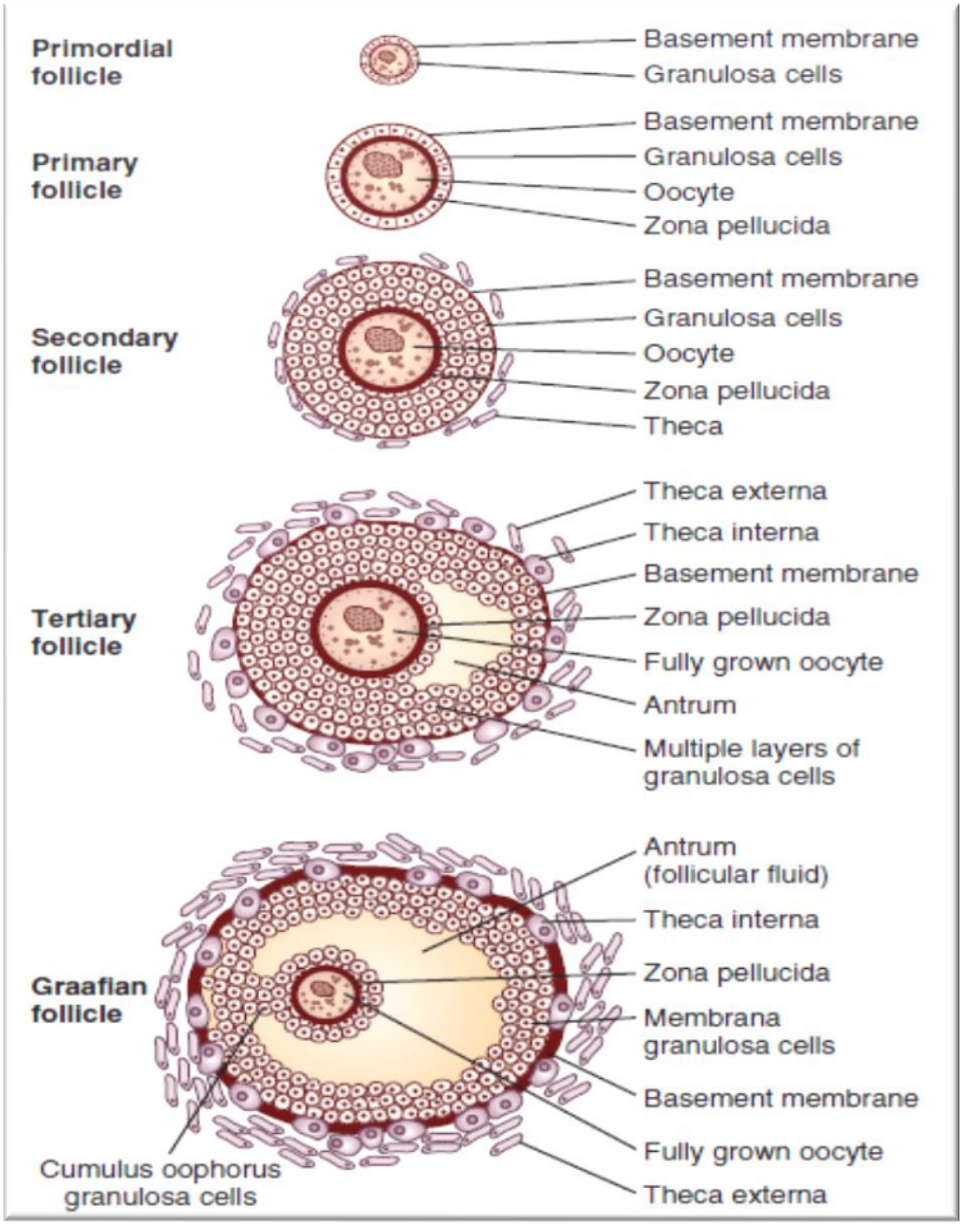

Figure (2): Stage of oocyte maturation.

In the adult, non-pregnant state, the ovaries lie on each side of the uterus close to the lateralpelvic wall. They are dull white in color and consist of dense fibrous tissue, in which ova

are embedded. Before regular ovulation begins, they have a smooth surface but, thereafter, their surfaces are distorted by scarring that follows the degeneration of successive corpora lutea. Their average dimensions are $4 \times 2 \times 3$ cm in reproductively mature women. In the neonate, their dimensions are $1.3 \times 0.6 \times 0.4$ cm ***(Summer et al., 2016).***

The ovary is essential for periodic release of oocytes and production of the steroid hormones, estradiol and progesterone. These activities are integrated into the cyclic repetitive process of follicular maturation, ovulation, and formation and regression of the corpus luteum. The ovary fulfills two major objectives: generation of a fertilizable ovum and preparation of the endometrium for implantation through the sequential secretion of estradiol and progesterone ***(Brendan Van Iten, 2016).***

The ovarian follicle comprising the egg and surrounding granulosa and theca cells constitutes the fundamental functional unit of the ovary. Adult human ovaries are oval bodies with a length of 2 to 5 cm, a width of 1.5 to 3 cm, and a thickness of 0.5 to 1.5 cm. The ovaries lie near the posterior and lateral pelvic wall and are attached to the posterior surface of the broad ligament by the peritoneal fold, called the *mesovarium* ***(Edson et al., 2009).***

The ovary consists of three structurally distinct regions: an outer cortex containing the surface germinal epithelium and the