The correlation between the pregnancy outcomes and serial progesterone levels in the follicular phase of ICSI cycles

Thesis

Submitted for Partial Fulfillment of Master Degree
in Obstetrics & Gynecology

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2017

Acknowledgement

*First of all, I would like to express my deepest gratitude and thankfulness to **Allah,** for giving me the strength and will to fulfill this work.*

*I wish to express my deepest gratitude to **Prof. Karim Hassanin Abd Elmaeboud,** Professor of Obstetrics and Gynecology, Faculty of Medicine, Cairo University, for his valuable advice, encouragement, guidance, great support and continuous help.*

*Many thanks to **Dr. Ahmed Elsayed Hassan Elbohoty,** Assist. Professor of Obstetrics and Gynecology, Ain Shams University, for his generous help, very kind assistance, honest guidance and continuous support.*

*I would like to thank **Dr. Amr Helmy Yehia,** Assist. Professor of Obstetrics and Gynecology, Faculty of Medicine-Ain Shams University, for his precious advice and continuouse ncouragement.*

Finally, I would like to thank my family for their support and care

Rasha Mohamed Ahmed Elkholy

List of Contents

List of Abbreviations

ART	Assisted reproductive technology
ASRM	American Society for Reproductive Medicine
BMI	Body mass index
CC	Clomiphene citrate
COH	Controlled ovarian hyperstimulation
E2	Estradiol
ERC	Ethics Research Committee
ET	Embryo transfer
FSH	Follicle stimulating hormone
GIFT	Gamete intrafallopian transfer
GnRH	Gonadotrphine releasing hormone
HCG	Human chorionic gonadotrophin
hMG	Human menopausal gonadtrophine
ICSI	Intracytoplasmic sperm injection
IVF	Invitro fertilization
LH	Leutinizing hormone
MBH	Mediobasal hypothalamus
OHSS	Ovarian hyperstimulation syndrome
PCOS	Polycystic ovarian syndrome
PID	Pelvic inflammatory disease
PL	Premature luteinization
POA	Preoptic area
PR	Pregnancy rate
rFSH	Recombinant FSH
TV U/S	Transvaginal ultrasound
ZIFT	Zygote intrafallopian transfer

List of Tables

List of Figures

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INTRODUCTION

The introduction of gonadotrophin-releasing hormone (GnRH) analogues for pituitary suppression in vitro fertilization (IVF) significantly decreased the incidence of premature luteinizing hormone (LH) surge (premature luteinization PL) **(*Elnashar, A. M. 2010*) ,** this refers to a rise in serum progesterone levels on the day of human chorionic gonadotrophin (hCG) administration **(*Venetis et al., 2007*) .**

Some authors **(*Papanikolaou et al. 2009*)** have reported decreased implantation and pregnancy rates with this phenomenon. Its pathogenesis is still poorly understood. Its impact on pregnancy outcome is still controversial **(*Elnashar, A. M. 2010*)**. One of the major reasons for the controversy has been the diverse definitions of PL in previous literature **(*Ou, Yu-Che, et al., 2008).***

The absolute cutoff value of serum progesterone concentration on the hCG day to define premature elevation, with ranges from0.8 to 2 ng/ml ***(Huang et al., 2012)***. ***Younis et al. (2001)*** proposed a progesterone/estradiol (P/E2) ratio >1 as the definition of pre-hCG progesterone rise in order to differentiate between its secretion from dysmature follicles and physiologic secretion from multiple healthy mature follicles **(*Huang et al., 2012*)**. A P/E2 ratio>1 was associated with lower

ovarian reserve and poorer pregnancy outcomes ***(Fatemi 2013; Younis et al., 2001)*.** However, this definition is not universally accepted.

Using different definitions, some studies reported no association between pre-hCG progesterone rise and the pregnancy rate **(*Ubaldi et al., 1995; Venetis et al., 2007; Andersen et al., 2011*),** while other studies including a recent meta-analysis showed that a pre-hCG Prise is associated with poorer pregnancy outcomes **(*Venetis et al., 2013, Griesinger 2013؛ Fanchin et al., 1997a; Bosch et al., 2003, 2010; Kolibianakis et al., 2012).***

There is a marked variation in the incidence of PL. Previous literature reported incidence varying from 13% to 71%, using progesterone only to define PL **(*Ou, Yu-Che, et al.,2008*).**The incidence of PL using the definition of P/E2 ratio >1 was 41% in the report of **(*Younis et al.,2001*).**

Several hypotheses have been proposed to explain the possible pathophysiology of PL, such as precocious elevation of follicular LH levels, serum accumulation of hCG or LH from hMG, and increased sensitivity of granulosa cell LH receptors to gonadotrophin **(*Lai et al., 2009; Elnashar, 2010*)**. Furthermore, recent studies have demonstrated that prematurely elevated serum progesterone may cause an advanced

endometrial secretory transformation resulting in the early closure of the implantation window **(*Labarta et al., 2011*).**

The majority of the previous studies only analysed the serum progesterone concentration on the day of hCG administration for oocyte maturation ***(Huang et al., 2012*).** Since the implantation window has been proposed to range from postovulatory Day 6 to Day 10, evaluating only 1 day of absolute serum P4 concentration might not accurately reflect the chronological change in the implantation window **(*Huang et al., 2012*).** Therefore, the **aim** of our study is to investigate the correlation between the pregnancy outcomes and serum progesterone level in the follicular phase of **ICSI** cycles by serial measures of serum progesterone level.

Aim of the Work:

To establish whether there is a correlation between the pregnancy outcomes and serum progesterone levels in the follicular phase of **ICSI** cycles or not.

Research Question:

In women undergoing **ICSI** cycle is there correlation between the pregnancy outcomes and serum progesterone levels in the follicular phase**?**

Research hypothesis**:**

In women undergoing ICSI cycles there may be an association between the pregnancy outcomes and progesterone levels in the follicular phase.

Study Design: This is a prospective cohort study that includes patients who will undergo Intra-Cytoplasmic Sperm Injection (ICSI).

Population:

Eighty eight infertile women undergoing controlled ovarian stimulation (COS) with human menopausal Gonadotrophin (hmG) for Intra-Cytoplasmic Sperm Injection (ICSI) at Ain shams University hospital (ART Unit).

Comparison:

Compare pregnancy rates in patients with normal or elevated serum progesterone level in follicular phase of **ICSI** cycles.

Outcome:

1ry Outcome:

Clinical pregnancy rates.

2ry Outcome:

1-Number of MII oocytes.

2-Endometrial thickness at day of HCG injection

Intervention

The subject population will be divided into 2 groups according to progesterone level:

- **Group I:** normal progesterone level<1.0 ng/ml in follicular phase.
- **Group II:** elevated progesterone level> 1.0 ng/ml in follicular phase.

The pregnancy rate will be compared between the two groups.

The subjects – as routinely- will be subjected to:

1. Explanation of the nature of the study and signed written consent will be obtained.
2. Full history taking including past medical, surgical history and past history of induction of ovulation.
3. General and abdominal examination for signs of disturbed endocrinological function (e.g.: hyper-androgenism etc.).
4. Base-line Transvaginal ultrasound measurement will be performed to detect morphological changes in ovary and uterus.

Inclusion Criteria:

1. Age between: 20-35 years.
2. Body mass index (BMI) between 20-35.
3. Eligible indications for ovarian stimulation before **ICSI**.

Exclusion Criteria:

1. Signs or symptoms of disturbed endocrinological functions (as hyperandrogenism, hypo- or hyperthyroidism, hyperprolactinemia).
2. Known allergic reaction against one of the ingredient of the medications used during the study.
3. Canceled cycles which didn't reach embryo transfer

IVF protocol: (Long acting protocol+HMG)

On day 2-3 of spontaneous cycles all planed women to have super ovulation will have basal hormonal profile FSH, LH and E_2. Ovarian hyper stimulation protocol will be performed according to long protocol, on day 18 of the preceding cycle to superovulation, GnRh agonist injection of (Decapeptyl 0.1mg, triptorelin, Ferring and Switzerland) will be started daily till the day of HCG , on day 2-3 of the cycle (day 0 in the protocol) ovarian hyper stimulation will be started by daily injection of gonadotrophins (Mengon 75mg, menotrophin, Ferring and Switzerland) after confirming the suppression of the ovaries by measuring E_2 and endometrial thickness.

Serum progesterone level will be measured on days 0, 7 and day of (hCG) administration. The starting dose of gonadotrophin will be prescribed according to age, BMI of the subjects and FSH, the dose will be adjusted according to sonographic response of the ovaries.

Ovarian response will be assessed by TV folliculometry to be done on cycle day 7.According to the ovarian response, day after day TV U/S will be performed and at the moment where the leading follicle reach 15 mm daily TV U/S will be performed till the largest follicle reach a diameter > 18 mm with good count of secondary follicles when HCG (Pregnyl