Relation between Progesterone Level on the Day of HCG Administration and the Clinical Pregnancy Rate in Intracytoplasmic Sperm Injection Patients

Thesis

Submitted for partial fulfillment of Master Degree
In Obstetrics and Gynecology

Submitted by

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2019

Acknowledgments

First and foremost, I feel always indebted to Allah, the Most Beneficent and Merciful. I can do nothing without Him.

I would like to express my deep thanks and appreciation to **Dr. Tarek Aly Raafat,** *Assistant Professor of Obstetrics and Gynecology, Faculty of Medicine – Ain Shams University, for his outstanding help, valuable instructions constant support and close supervision through revising each part of the thesis. I really have the honor to complete this work under his great supervision.*

My deep gratitude goes to **Dr. Hayam Fathy Mohammad,** *Lecturer of Obstetrics and Gynecology, Faculty of Medicine – Ain Shams University, for her great support, tireless guidance and meticulous supervision throughout this work.*

I can't forget to thank with all appreciation **Prof. Dr. Azza Awad,** *Consultant & Embryology Laboratory Director, ART Unit, Ain Shams University, for her support and aid during the whole work.*

***Finally**, I wish to express all my feelings of love and appreciation to **my lovely family** who give me never ending support, understanding, love and care throughout my graduate study.*

Enas Ibrahim Hassan Hassan

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List of Abbreviations

Abbr.	Full-term
AFC RT	: Antral follicle count (right side)
AFC LT	: Antral follicle count (left side)
ART	: Assisted reprodutive technology
bcl2	: B cell lymphoma/leukemia 2
BMI	: Body mass index
C	: Colesterol
CC	: Clomiphene citrate
CL	: Corpus luteum
CNS	: Central nervous system
COH	: Controlled ovarian hyperstimulation
COS	: Controlled ovarian stimulation
COX-2	: Cyclo-oxygenase
DCs	: Dendritic cells
E	: Estrogen
E2	: Estradiol
EAE	: Experimental allergic encephalomyelitis
ECM	: Extracellular matrix
ET	: Embryo transfer
FSH	: Follice-stimulating hormone
GnRH	: Gonadotropin-releasing hormone
hCG	: Human chorionic gonadotropin

HDL : High-density lipoprotein
HMG : Human menopausal gonadotrophine
ICSI : Intracytoplasmic sperm injection
IGBP-1 : Insulin-like growth factor binding protein-1
IGFBP : Insulin growth factor binding protein 2
IL : Interleukin
IM : Intramuscular
IQR : Interquartile range
IU : International unit
IVF : In vitro fertilization
LDL : Low-density lipoprotein
LH : Luteinzing hormone
mL : Milliliter
MII : Metaphase II oocyte
MMPs : Matrixmetalloproteinases
MPA : Medroxy progesterone acetate
MS : Multiple sclerosis
ng : Nanogram
OHSS : Ovarian hyperstimultion syndrome
P : Progesterone
PCOS : Polycystic ovary syndrome
PE : Progesterone elevation
PEP : Progesterone-associated endometrial protein
PG : Prostaglandins
PGD : Pre-implantation genetic diagnosis

PKA : Protein kinase A

PPR : Premature progesterone rising

PR : Progesterone receptors

ROC : Receiver-operating characteristic

SD : Standard deviation

SPSS : Statistical package for social science

TIMP-1 : Tissue inhibitor metalloprotienase

TSH : Thyroid-stimulating hormone

VLDL : Very Low-density lipoprotein

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Relation between Progesterone Level on the Day of HCG Administration and the Clinical Pregnancy Rate in Intracytoplasmic Sperm Injection Patients

Abstract

Background: Infertility is an illness clinically defined as failure to achieve a clinical conception after 12 months of regular and unprotected normal sexual intercourse. It affects around 8 -12% of child bearing-aged couples globally. Premature progesterone elevation is considered for a long time a cornerstone factor to endometrial implantation failure. Although the extensive usage of GnRH analogues for down-regulation of pituitary, rise in progesterone serum levels, still occur at various levels on the day of administration of hCG for ultimate oocyte maturity in fresh IVF management cycles. **Aim** to investigate and evaluate the correlation between serum progesterone level on the day of HCG administration and the clinical pregnancy rate as a primary outcome, quality of embryo, quality of oocyte, fertilization rate and chemical pregnancy assessed by B-HCG level 2 weeks after embryo transfer as secondary outcomes. **Methodology:** This prospective non interventional study was conducted at Assisted Reproduction Unit, Ain Shams University Maternity Hospital, Cairo, Egypt, starting from December 2015 till March 2017. The study included 240 women scheduled for ICSI presented with primary or secondary infertility, the causes of infertility in this study were male factor, tubal factor and unexplained infertility. **Results:** the current research study displayed that there was unfavorable statistical correlation between serum progesterone elevation at the day of HCG trigger and the clinical pregnancy rates which was 34.2%, the cut off value of serum progesterone was 1.09 ng/ml; above this value the serum pregnancy rates were negatively influenced. Additionally premature rise of serum progesterone levels reduced the embryonic quality, oocyte quality and fertilization rate. **Conclusion:** serum progesterone level equal to or above 1.09 ng/ml at the day of HCG trigger unfavorably influences on the clinical pregnancy rates in ICSI cycles. **Recommendations:** All embryos should be cryopreserved when serum progesterone on the day of HCG trigger equals to or above 1.09 ng/ml during ICSI cycle to be transferred in subsequent cycle to avoid implantation failure.

Keywords: Progesterone, HCG, ICSI

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Introduction

Infertility is the inability of a sexually active, non-contracepting couple to achieve spontaneous pregnancy in one year (WHO, 2000). About 15% of couples do not achieve pregnancy within one year and seek medical treatment for infertility. Infertility classified as primary, when there is no history of pregnancy having occurred, or secondary, when inability to conceive occurs after one or more successful pregnancies ***(Mokhtar, et al., 2006).***

Infertility is a widespread problem. For about one in five infertile couples the problem lies solely in the male partner. In about one in four couples, there are problems with both male and female partners, and in about one in seven infertile couples, the cause of the problem cannot be found (idiopathic infertility). It is estimated that one in 20 men has some kind of fertility problem with low numbers of sperm in his ejaculate. However, only about one in every 100 men has no sperm in his ejaculate ***(Andrology Australia, 2004).***Micro-assisted fertilization in the form of intracytoplasmic sperm injection (ICSI) has truly revolutionised the treatment options for couples with impaired semen quality, and those with both obstructive and non-obstructive azoospermia. Its main use is for significant male infertility cases ***(Campbell, et al., 2000).***

The first human pregnancies resulting from ICSI being described by the Brussels group in 1992. This approach involves injection of a single spermatozoon directly into the cytoplasm of the oocyte through the intact zonapellucida, with pregnancy rates of 22% per started

cycle being reported ***(Campbell, et al., 2000; Elnashar, 2010).***

During controlled ovarian hyperstimulation premature luteinization, as detected by elevated serum progesterone (P) level, is generally prevented by suppression of LH secretion with GnRh analogues ***(Elnashar, 2010).***

Despite the widespread use of gonadotropin-releasing hormone (GnRH) analogues for pituitary down-regulation, progesterone elevation (PE), which refers to an increase in serum progesterone concentrations, still occurs at different frequencies on the day of human chorionic gonadotropin (hCG) administration for final oocyte maturation in fresh in vitro fertilization (IVF) cycles ***(Venetis, et al., 2013; Huang, et al., 2015).***

Progesterone isa 21-carbon steroid which is a precursor molecule for steroids biosynthesis.Progesterone is primarily produced by the granulosa-lutein cells of the corpus luteum (CL) during the luteal phase of the menstrual cycle and the syncytiotrophoblast of the placenta during pregnancy***(Al-Asmakh, 2007)***.The major physiological actions of progesterone are: a) in the uterus and ovary: induction of ovulation,facilitation of implantation, and maintenance of early pregnancy. The follicular phase of the menstrual cycle is estrogen dominated, while the luteal phase of the menstrual cycle is progesterone dominated***(Al-Asmakh, 2007)***. Secretion of progesterone converts an estrogen primed proliferative endometrium into a secretory one, which is receptive to the blastocyst. For the issue of

oocytes fertilization, most literatures have found the presence of a negative association between P elevation and fertilization. They suggested that P elevation may only influence the endometrium, leading to impaired endometrial receptivity, recently it is found that elevated P had an adverse effect on the oocytes fertilization too, especially if the P concentration >1.50 ng/mL ***(Huang, 2014).***

In primates, luteinization and follicular rupture occur 36–38 h after the onset of midcycle gonadotropin surge. During this preovulatory phase, granulosa cells undergo changes in response to the ovulatory stimulus that result in terminally differentiated luteal cells. While differentiating (luteinizing) granulosa cells secrete large amounts of progesterone. The discovery that these cells express the progesterone receptor led to the hypothesis that progesterone acts in a local manner to mediate ovulation and luteinization ***(Suzuki, et al., 1994; Al-Asmakh, 2007).***

Premature luteinization invitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) was a common event before the introduction of Gonadotropin-releasing hormone (GnRH) analogues ***(Huang, et al., 2012).*** This situation associated with poor oocyte quality, low fertilization rate, and adverse pregnancy outcome and is thought to be induced by inappropriate Luteinizing hormone (LH) elevation ***(Hamori, et al., 1987; Saharkhiz, et al., 2015)***. Incidence of premature progesterone rising (PPR) has high levels approximately 35% in GnRH agonist cycles and 38% in GnRH antagonist cycles ***(Ochsenkuhn, et al., 2012; Saharkhiz, et al., 2015).***

Moreover, the question of whether Progestrone Elevation on the day of hCG administration affects the outcomes of IVF is still being debated ***(Xu, et al., 2012; Huang, et al., 2015).*** Some studies have indicated that PE does not affect the probability of pregnancy in IVF(Saharkhiz, et al., 2015); however, other studies have concluded that Progestrone Elevation resulted in a decreasedprobability of pregnancy ***(Huang, 2014; Huang, et al., 2015).***