Luteal phase support with estradiol in poor responders undergoing In Vitro Fertilization / Intra-cytoplasmic Sperm Injection using gonadotropin releasing hormone antagonist protocol: a double blind randomized controlled trial

Thesis

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By

Sara Osama Mohamed

M.B.B.Ch., (2013) Zagazig University
Resident of obstetrics and gynecology
Kafr el-Shikh University hospital

Under supervision of

Professor/Gasser Mohamed Adly Elbishry

Professor of Obstetrics and Gynecology
Faculty of Medicine
Ain Shams University

Dr. Mostafa Fouad Gomaa

Assistant Professor of Obstetrics and Gynecology
Faculty of Medicine
Ain Shams University

Dr. Radwa Rasheedy Ali

Lecturer of Obstetrics and Gynecology
Faculty of Medicine
Ain Shams University

Faculty of Medicine

Ain Shams University

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List of Abbreviations

Abb.	Full term
AFC	Antral follicular count
AMH	Anti-mullerian hormone
anti-ZP3	Anti zona pellucida
ARR	Absolute risk reduction
ART	Assisted reproductive technology
BMI	Body mass index
CL	Corpus luteum
COS	Controlled Ovarian Stimulation
DG	Dydrogesterone
E_2	Estradiol
ESHRE	European Society for Human Reproduction and Embryology
ET	Embryo transfer
FGF-2	Fibroblast growth factor type 2
FSH	Follicle stimulating hormone
FSHR	Follicle stimulating hormone receptor
GA	Gestational age
GnRH	Gonadotropin releasing hormone
HCG	Human chorionic gonadotropin
HGH	Human growth hormone
HP-HMG	Highly purified human menopausal gonadotropin
ICSI	Intra-cytoplasmic sperm injection
IGF-1	Insulin-like growth factor 1
ITT	Intention to treat
IUI	Intrauterine insemination
IVF	In vitro fertilization
LH	Luteinizing hormone

LPD	Luteal phase deficiency
LPS	Luteal phase support
NNT	Number needed to treat
OHSS	Ovarian hyper-stimulation syndrome
OP	Ovum pickup
P_4	Progesterone
POR	Poor ovarian response
PR	Pregnancy rate
rFSH	Recombinant follicle-stimulating hormone
RR	Relative risk
RRR	Relative risk reduction
RCT	Randomized controlled trial
VEGF-A	Vascular endothelial growth factor A

Introduction

Although progesterone therapy is the most widely accepted luteal phase support (LPS) and its role is well established, the role of estradiol (E_2) supplementation during the luteal phase in in vitro fertilization (IVF)/intra-cytoplasmic sperm injection cycles(ICSI) remains controversial despite the decreased mid-luteal estradiol levels ***(Fauser and Devroey, 2003).***

Although, previous researches for evaluating the use of E_2 in addition to progesterone as LPS lead to inconclusive results, a meta-analysis showed no benefit of E_2 supplementation ***(Van der linden et al., 2011).*** However, the importance of E_2 supplementation is not adequately studied in subgroups of IVF patients like poor ovarian responders ***(Kutlusoy* et al., 2014).**

There are a variety of definitions for poor ovarian response in different studies but the European Society for Human Reproduction and Embryology (ESHRE) specified poor ovarian response (POR) with at least two of the following three criteria; advanced maternal age or other risk factor causing POR (for example; ovarian surgery, chronic smoking, unexplained infertility, autoimmune

disorders and single ovary), a previous poor ovarian response with development of 3 oocytes or fewer in the former cycle by controlled ovarian stimulation (COS) protocol and any abnormality in ovarian reserve tests **(Rehman et al., 2017).**

The use of gonadotropin releasing hormone (GnRH) antagonist protocols in IVF cycles has shown premature luteolysis, resulting in a significant reduction in the length of the luteal phase ***(Fauser and Devroey, 2003).*** As well as GnRH antagonist causes more profound luteinizing hormone (LH) than follicle-stimulating hormone (FSH) blockage, thereby reducing the follicular fluid E_2 level compared to GnRH agonist protocols **(Wang et al., 2017).** In addition, women treated using the GnRH antagonist protocol have a thinner endometrium and lower pregnancy rates **(Orvieto et al., 2008).**

The present study is the first one to evaluate the use of estradiol in addition to progesterone as LPS in poor responder women undergoing IVF /ICSI cycle with the use of GnRH antagonist protocol.

Aim of the work

This study aimed at evaluating the efficacy of estradiol with progesterone as a luteal phase support in poor responders undergoing IVF/ ICSI using GnRH antagonist protocol.

-Research question:

In poor responder women undergoing IVF/ ICSI, will adding estradiol to progesterone as a luteal phase support increase clinical pregnancy rates compared to placebo?

-Research hypothesis:

Null hypothesis: adding estradiol to progesterone as a luteal phase support in poor responder women undergoing IVF and ICSI will not increase clinical pregnancy rate compared to placebo.

Poor Responders & IVF

Infertile couples make up approximately 10% of the worldwide population of reproductive age, and assisted reproductive technology (ART) currently accounts for 1.2% of total United States' live births, and up to 4% in some European countries ***(Oehninger, 2011).***

In the field of IVF, the term 'poor responder' refers to a subpopulation of patients, typically with diminished ovarian reserve, that experience heightened problems in conceiving with IVF. The identification of poor responders is important to determine the patient's appropriateness for IVF and select an appropriate protocol to increase ovarian response; however, there is no standard definition of a 'poor responder' ***(Ferraretti et al., 2011).***

According to ESHRE, POR is designated with at least two of the following three features; "advanced maternal age or any other risk factor for POR, a previous POR with maturation of 3 oocytes in the previous cycle by COS protocol and an abnormal ovarian reserve test ***(Rehman et al., 2017)***.

Assessment of the ovarian reserve

Jones et al. in 1985 pioneered the use of gonadotropins for COS in IVF therapy. The response category was based on the assessment of the resulting serum estradiol curve (E_2 pattern) and the consequent accompanying follicular response as monitored by ultrasonography.

Muasher et al. in 1988 first reported that the measurement of serum levels of FSH, LH and E_2 on day 3 of the basal menstrual cycle was a predictor of COS response and IVF outcome, however; the combined use of age and basal FSH in counseling women improves the accuracy of prognosis, and provide an index of functional ovarian reserve**.**

Since then, many other tests have been introduced as candidates for the examination of the ovarian reserve, include the clomiphene citrate challenge test (CCCT), GnRH agonist test, measurement of serum inhibin B and anti-mullerian hormone (AMH), and ultrasound examination of basal cycle ovarian volume, antral follicular count (AFC) and ovarian stromal blood flow ***(Broer et al., 2011).***

AMH is considered the most accurate predictor of excessive response to ovarian hyper-stimulation as AMH is produced solely by the granulosa cells of the growing pre-antral and small antral ovarian follicles ***(Broer et al., 2011).***

In further work, ***Riggs et al.*** in 2011 showed that AMH was superior to other biomarkers of ovarian reserve in predicting low and high response in young women selected as oocyte donors, but that it was not predictive of embryo morphology or pregnancy outcome in the recipient population. For that reason, the determination of basal cycle day 3 serum FSH, LH and E_2 levels, measurement of AMH, and the estimation of the basal AFC, are the preferred screening tests for ovarian reserve in all IVF patients, and together with the woman's age, determine the COS regimen to be chosen for the cycle treatment.

The etiologies of poor ovarian response

- ***Poor response associated with advanced maternal age***

Although neuroendocrine and uterine factors may reduce fertility with age, progressive depletion of the size of the pool of ovarian follicles is thought to be the major

cause of this problem. Decline in primordial follicle number with ageing has been linked to an equivalent decline in oocytes quality with anomalies of their zona pellucida ***(Broekmans et al., 2009).***

- ***Poor response in younger women***

As mentioned above, poor ovarian response to stimulation may be a consequence of advancing chronological age although it may also occur unexpectedly in relatively young patients. The true pathogenesis of the poor ovarian response is unknown in a large proportion of these cases, although "ovarian failure" may be due to an immunological origin in some. Occasionally, a low ovarian reserve is secondary to previous ovarian surgery, severe endometriosis, pelvic adhesive disease, iatrogenic (post-chemo- or radiotherapy), associated with high body mass index or heavy smoking ***(Buyuk et al., 2011).***

A few endocrine-related abnormalities have been observed in these cases which include; a decreased number of FSH receptors (FSHR) in granulosa cells, defective signal transduction after FSHR binding, and FSHR polymorphisms ***(Sudo et al., 2002).***

Despite the heterogeneity of this patient group, there are some characteristics and needs that are common to many poor responders, such as synchronization of early follicular development, IVF protocols tailored to poor responders, guidelines for the use of alternative medicine and nutritional supplements, and suggestions for the successful management of patient distress and anxiety. Addressing these needs through a holistic approach may help to improve the overall management of poor responders ***(Gonda et al., 2018).***

IVF protocols for poor responders

Follicle development is a complex process that involves the regulated expression and interaction of multiple reproductive hormones at different stages of the development timeline. Poor responders may benefit from the synchronization of basal antral follicles with dehydro-epiandrostrone (DHEA) supplementation for a few weeks or months prior to initiating their IVF cycle ***(Gonda et al., 2018).***

It is recommended that subsequent ovarian stimulation protocols for poor responders should try to mimic and enhance the natural developmental process of