A Novel Approach For Prevention Of Severe Ovarian Hyperstimulation Syndrome (Ohss) In Highly Suspected Cases

Thesis

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Presented by

Noha Ramadan Seddek Mohammad

M.B.B.CH 2009

Family planning resident at Om Elmisryeen general hospital

Supervised by

Prof. Dr. Ahmad Hussieny Salama

Assistant Professor of Obstetrics & Gynecology

Faculty of Medicine-Ain Shams University

Dr. Dina Yahia Mansour

Lecturer of Obstetrics & Gynecology

Faculty of Medicine-Ain Shams University

Faculty of Medicine

Ain Shams University

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تحت إشراف

أ.د/ أحمد حسينى سلامة

أستاذ التوليد وأمراض النساء المساعد

كلية الطب-جامعة عين شمس

د/ دينا يحيى منصور

مدرس التوليد و أمراض النساء

كلية الطب-جامعة عين شمس

كليـة الطب

جامعة عين شمـس

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Contents

List of Abbreviations

(ACS)	Abdominal compartment syndrome.
(AMH)	Anti-mullarian hormone.
(Ang-II)	Angiotensin II.
(ART)	Assisted reproductive technique.
(Cb2)	Cabergoline.
(CBC)	Complete blood count.
(COS)	Controlled ovarian stimulation.
(E_2)	Estradiol.
(ET)	Embryo Transfer.
(FSH)	Follicle stimulating hormone.
(FSHR)	Follicle stimulating hormone receptor.
(GnRH)	Gonadotropin releasing hormone.
(GnRH-a)	Gonadotropin-releasing hormone agonist.
(GV)	Germinal-vesicle.
(hCG)	Human chorionic gonadotropin.
(HES)	Hydroxyethyl starch.
(HIV)	Human immunodeficiency virus.
(HMG)	Human Menopausal Gonadotropin.
(ICSI)	Intra-cytoplasmic sperm injection.
(ICU)	Intensive care unit.
(IL-18)	Interleukin-18.
(IL1-b)	Interleukin-1b.
(IL-6)	Interleukin-6.
(IL8)	Interleukin-8.
(IVF)	In-vitro fertilization.
(LH)	Luteinizing hormone.
(LMWH)	Low-molecular-weight heparin.
(MI)	Metaphase-I.
(MII)	Metaphase-II.
(NSAIDs)	Nonsteroidal anti-inflammatory drugs.
(OHSS)	Ovarian hyperstimulation syndrome.
(OPU day)	Ovum pick-up day.
(PCOS)	Polycystic ovary syndrome.
(PEDF)	Pigment Epithelium Derived Factor.

(RAAS) Renin Angiotensin Aldosterone System.
(TFF) Total failed fertilization.
(TNF-a) Tumor necrosis factor a.
(TSH) Thyroid stimulating hormone.
(VEGF) Vascular endothelial growth factor.
(VEGFR) Vascular endothelial growth factor receptor.
(WBC) White blood cells.

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Abstract

BACKGROUND: Ovarian hyperstimulation syndrome (OHSS) is the most serious and potentially life-threatening iatrogenic complication associated with ovarian stimulation during assisted reproductive technology protocols. The moderate and severe forms may occur in 3% to 10% of all assisted reproductive technique (ART) cycles, and the incidence may reach 20% among high-risk women This study was performed to evaluate the effect of single puncture to retrieve 6 or 7 eggs only to prevent severe Ovarian hyperstimulation syndrome in women at high risk in in vitro fertilization/intracytoplasmic sperm injection (IVF/ICSI) treatment cycles.

METHODS: Thirty women at risk to develop severe OHSS undergoing IVF/ICSI treatment cycle were included in this prospective study grouped into two groups, each group contains fifteen patients. The study group, single ovarian puncture retrieving about 7 eggs only was done in comparison to the control group who undergo retrieval of all eggs. The prevention of severe OHSS was the primary outcome.

RESULTS: The incidence of severe OHSS was 13.3% in the study group and 73.3% in the control group. Thus, the incidence of OHSS was significantly reduced, in the study group in comparison with the control group.

CONCLUSION: Single puncture retrieving about 7 eggs only, reduces the incidence of OHSS in women at high risk undergoing IVF/ICSI treatment.

Key Words: Prevention, Ovarian Hyperstimulation Syndrome (Ohss)

INTRODUCTION

Ovarian hyperstimulation syndrome (OHSS) was first described by Muller in 1962 ***(Muller P, 1962).***

OHSS is defined as an exaggerated systemic response to ovarian stimulation with a broad spectrum of clinical and laboratory findings ***(Golan A and Weissman A, 2009).***The moderate and severe forms may occur in 3% to 10% of all assisted reproductive technique (ART) cycles, and the incidence may reach 20% among high-risk women ***(Li H et al., 2014) (Nastri C et al., 2010).***

The main characteristics of OHSS are increased vascular permeability and ovarian enlargement ***(Nastri C et al., 2010).***The generalized capillary leak and acute shift of protein-rich fluid from the intravascular compartment into the third space (ascites, hydrothorax, hydro pericardium) lead to hypoproteinemia, oliguria, acute renal failure and increased blood viscosity with changes in coagulation parameters resulting in thromboembolic events ***(Lamazou F et al., 2011).***

Early OHSS refers to patients whose symptoms occur within 9 days following ovum pick-up day (OPU), while late OHSS refers to patients whose symptoms began at least 10 days after OPU day ***(Mathur R et al., 2000).***

AIM OF THE WORK

In highly suspected cases of severe ovarian hyper-stimulation syndrome on the day of egg collection; the aim of this study was to compare:

- Aspiration of all follicles available bilaterally versus
- Aspiration of 7 follicles only from a single ovarian puncture unilaterally in order to prevent the establishment of severe ovarian hyperstimulation syndrome.

PATHOPHYSIOLOGY

Pathophysiology of Ovarian hyperstimulation syndrome is difficult to understand and it has been extensively studied by investigators ***(Naredi N et al., 2014).***

The main characteristics of OHSS are increased vascular permeability and ovarian enlargement ***(Nastri C et al., 2010),***but the exact cause of OHSS is currently unknown and subject of controversy; however, the ovarian response is directly correlated with the risk of OHSS ***(Ji J et al., 2013).***

The onset of this iatrogenic complication usually occurs during luteal phase in ovulation stimulation or during early pregnancy ***(Andersen A et al., 2009) (de Mouzon J et al., 2010).***It is almost exclusively associated with exogenous gonadotropin stimulation and is only rarely observed after clomiphene citrate treatment or spontaneous ovulation ***(Mathur R et al., 2007).***

The roles of estradiol, luteinizing hormone, human chorionic gonadotropin (hCG), inflammatory mediators, the renin–angiotensin system, vascular endothelial growth factor (VEGF), follicle stimulating hormone (FSH) receptor variability ***(Alper M et al., 2009)***and genetic predisposition ***(Papanikolaou E et al., 2010)***are already discussed in the pathophysiology of OHSS ***(Papanikolaou E et al., 2011) (Nastri C et al., 2010).***

1- Estradiol:

Serum estradiol concentration is frequently used for monitoring controlled ovarian stimulation (COS); one of the reasons is to assess the risk of OHSS ***(Martins W et al., 2014).***Although estradiol alone is not capable of inducing OHSS ***(Nastri C et al., 2010) (Martins W et al., 2014),*** it is considered a marker of increased granulosa cell activity ***(Soares S et al., 2008)***. Absolute high or rapidly rising values may potentially predict OHSS as at risk women demonstrate high absolute (>2,500 pg/mL) or rapidly rising serum estradiol levels ***(ASRM, 2008).***

In the presence of human chorionic gonadotropin (hCG), high estradiol levels may increase the expression of cystic fibrosis transmembrane conductance regulator leading to a massive shift in body fluids through epithelial ion channels***(Ajonuma L, 2008) (Ajonuma L et al., 2011) (Evbuomwan I, 2000).***

2- Human Chorionic Gonadotrophin (HCG):

Human chorionic gonadotropin (hCG) triggering is used as a surrogate for the midcycle luteinizing hormone (LH) surge ***(Youssef M et al., 2014).***Unlike the physiological midcycle surge of LH, terminating 48 hours after its onset, the half-life of hCG is considerably longer and spans several days into the luteal phase ***(Kol S and Humaidan P, 2013).***

HCG stimulates similar periovulatory events, including softening of the connective tissue of follicle, which allows easy detachment of oocyte cumulus complex from the follicle wall, enabling aspiration during oocyte retrieval ***(Bjercke S et al., 2000).***

The use of human chorionic gonadotropin is most strongly associated with the development of OHSS ***(Alper M et al., 2009).***This is based on the findings that OHSS does not develop when hCG is withheld as an ovulatory trigger during COS and also that increased hCG exposure is associated with an increased risk of OHSS ***(Aboulghar M and Mansour R, 2003) (Mathur R et al., 2000)***.

HCG causes the stimulated enlarged ovaries to produce the angiogenic molecule Vascular Endothelial Growth Factor (VEGF) ***(Humaidan P et al., 2010).***Studies confirmed in humans have shown that vascular permeability, VEGF and VEGF receptor (VEGFR) levels are already elevated during the gonadotropin stimulation phase, preceding hCG injection ***(Wang T et al., 2002)***. Preceding stimulation, VEGFR may be found only in the corpus luteum vessels, but after hCG stimulation these receptors may be found throughout the corpus luteum ***(Wang T et al., 2002).***Also, peak expression for both VEGF and VEGFR occurs approximately 48 h after hCG injection ***(Gomez R et al., 2003).***