

## The Effect Of Controlled Ovarian Hyperstimulation On Iron Status In Infertile Women

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### Abstract:

Non randomized clinical trial study done in the fertility center at AL-Sadder teaching hospital in AL-Najaf city from the period of February 2012 to August 2012. This study included 40 ICSI cycle to determine the effect of the controlled ovarian hyper stimulation (COHS) on iron status ( serum iron and serum ferritin ). The protocol used was short protocol. The results showed significant decrease ( $p \leq 0.05$ ) in serum ferritin after (COHS).

### Introduction:

Infertility commonly defined as at least 12 months of unprotected intercourse without conception (1) Approximately 10-16 % of couples will meet this definition based on observational study (2 and 3). Up to half of those couples reaching the 12month threshold may conceive within the next 36 months (2), finding borne out in clinical trials, where 4-5% of subjects may conceive spontaneously between enrollment and the beginning of treatment (4 and 5). Because a large number of couples meeting the definition of infertility are actually capable of conceiving and simply represent one end of the distribution of fecundity, many particularly in Europe, prefer the term “subfertility.” (6).

Infertility may be due to problems in the female, the male or combination of both. In some cases, the cause is not known (unexplained infertility). Treatment of infertility different according to the cause. All couples trying for a pregnancy will benefit from some general advice such as cessation of smoking and limiting alcohol intake. Pre-treatment counseling should include advice about general lifestyle measures including the need to achieve an optimum BMI. This will involve weight loss in women with a BMI of over 30, but may require some women with weight related amenorrhea and an ovulation to gain weight. Regardless of the diagnosis, prolonged infertility refractory to conventional treatment is treated by *in vitro* fertilization. Assisted conception broadly refers to procedures where by treated or manipulated sperm are brought into proximity with oocytes. It includes: Intrauterine insemination (IUI) with partner or donor sperm (in natural or stimulated cycles). Gamete intra- fallopian transfer (GIFT) *invitro* fertilization and embryo transfer (IVF-ET) Intracytoplasmic sperm injection (ICSI) (7).

### Materials And Methods:

#### Study population:

This study included 40 women aged between (19-40) years, their body mass index (BMI) range (24.6-40.6). These women are infertile of different duration and different etiology.

#### Syringes and tubes for blood collection:

Syringes of 5 cc used to draw blood which collected in plain non coagulated test tube (AFCO-DISPO) put in a centrifuge for 5 minutes with centrifugal force at a rate of 5000 RPM (round per minute) to get better precipitation of blood cells and the

supernatant serum was aspirated by a micropipette to be used for estimation of serum iron and serum ferritin.

#### kit for determination of serum iron (fortress diagnostic).

**kit for determination of serum ferritin (VIDAS Ferritin, FER):** used for determination of human ferritin in human serum or plasma using the EIFA( Enzyme Linked Fluorescent Assay).

#### Method:

Careful history was obtained from each woman including: name, address, age, type of infertility whether primary or secondary, cause of infertility, menstrual history, previous medical and surgical history .

#### Procedures:

First sample of blood drawn from the patient before she started to receive ovarian stimulation drugs in the second day of menstrual cycle after measuring of their height and weight and after hormonal study for FSH, LH, Prolactin, and E2. The patient received Decapeptyle (0.1mg short acting triptorelin, its manufacturing site IPSEN PHARMA BIOTECH-FRANCE), it is gonadotrophin-releasing hormone analogue. It was injected daily to patient from day two of menstrual cycle till follicular maturation. It is given together with Gonad-f (follitropin alfa), it similar to the human hormone 'follicle stimulating hormone. It is manufactured for: EMD Serono, Inc., Rockland, MA 02370 U.S.A. The dose of decapeptyle and gonad-f increased gradually according to patient response checked by estradiol (E2) level and ultrasound. When good number about (8-15) of mature follicles of size more than 15mm in diameter, 6500 IU of human chorionic gonadotropine (HCG) given to her to induce ovulation, then about 34-36 hours the second sample of blood draw from the patient to measure serum iron and serum ferritin.

#### Results:

Results were expressed as mean $\pm$ SD. The data were analyzed using t test considering  $p \leq 0.05$  as lowest limit of significance. The comparison between serum iron and serum ferritin before (COHS) with those after (COHS) show significant decrease in serum ferritin, with non-significant change of serum iron after (COHS).

The following table shows significant decrease of serum ferritin after COHS.

#### Effect of COHS on serum iron and serum ferritin

	Before Mean $\pm$ Deviation	COHS Std.	After COHS Mean $\pm$ Std. Deviation	P value	Significance
<b>Serum Iron</b>	97.5950 $\pm$ 45.19031		88.4425 $\pm$ 33.70804	.283	N.s
<b>Serum Ferritin</b>	41.2775 $\pm$ 43.86397		23.2085 $\pm$ 17.21034	.004	Sig.*

N.s=No significant changes of serum iron after COHS ( $p > 0.05$ ).

Sig.\*=significant decrease of serum ferritin after COHS ( $p < 0.05$ )

#### Discussion:

This result can be attributed to IL-6 which increase in serum of patient with IVF cycle(7), it was found that it induce hypoferraemia (8).

Other explanation may be related to the Estradiol (E2). Estradiol levels gradually rise as the follicles grow and mature during the IVF cycle. The follicle is

lined by granulosa cells which produce the hormone estrogen. As the follicle matures, these cells produce increasing quantities of estrogen. Rising levels suggest that the granulosa cells are of good quality. In certain study it has been found that erythropoietin hormone (Epo) and its mRNA were produced in an E<sub>2</sub>-dependent manner. E<sub>2</sub> has been reported to influence Epo production in the uterus (9). In contrast, the E<sub>2</sub>-induced increase of Epo mRNA in the uterus is very rapid. Furthermore, Epo production in uterus is not induced by hypoxia. E<sub>2</sub> does not induce Epo production in the kidney and brain (3). The finding of the immunochemical detection of erythropoietin receptors (EpoR) in uterine endothelial cells suggest that Epo directly acts on these cells. Epo is one of the E<sub>2</sub>-regulated signal molecules that is required for execution of the cyclic angiogenesis in the uterus. This affects serum ferritin which regulates vascular remodeling and angiogenesis which is regulated through the cleavage of kininogen (HK)(a 120-kDa single-chain plasma glycoprotein) by activation of the plasma protease kallikrein leads to cleavage of HK and the production of 2 cleavage products bradykinin (BK) which is angiogenesis stimulator, and cleaved HKa which is angiogenesis inhibitor, ferritin reverses the HKa-mediated inhibition of angiogenesis by its binding to 22-aa region in domain 5 of HKa which mediate inhibition of angiogenesis (6). These events may lead to change of serum ferritin level by its binding to HKa.

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**الخلاصة:**

في دراسة سريرية غير عشوائية اجريت في مركز الخصوبة في مستشفى الصدر التعليمي في مدينة النجف للمدة من شهر شباط 2012 ولغاية شهر اب 2012 شملت 40 دورة حقن مجهري (ICSI), تناولت تأثير تحفيز المبايض المسيطر عليه على حالة الحديد في الجسم المتضمن فيرتين المصل والحديد في المصل. تم سحب العينة الاولى من الدم في اليوم الثاني للدورة الشهرية قبل البدء بتحفيز المبايض المسيطر عليه بالبرنامج القصير. ثم تم سحب العينة الثانية من الدم عند نضج البويض بعد زرق المريضة بهرمون HCG (هرمون الحمل) ب34-36 ساعة تقريباً لقياس فيرتين المصل والحديد في المصل. اظهرت النتائج نقصان ذو قيمة احصائية معنوية ( $p \leq 0.05$ ) بفيرتين المصل.