

Dose individualization of ovarian stimulants: A comparative study of different ovulation enhancing modalities and their effect on reproductive hormones

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الخلاصة

لسنين عديدة اعتمد الأطباء في علاجهم لحالات العقم على استخدام أدوية لتحفيز عملية الإباضة محاولين زيادة قدرة المرأة على الإنجاب من خلال زيادة فعالية هرموناتها التناسلية. كان الهدف من الدراسة هو معرفة الاختلافات في مستويات هرمونات التكاثر في ثلاث أنواع من البرامج المحفزة للإباضة.

اشتركت في هذا البحث خمسة و أربعون مريضة بعانين من حالات العقم الأولي تم تقسيمهم إلى ثلاث مجاميع عشوائية تضام كل منها خمسة عشر مريضة. تخدمت المجموعة الأولى الكلويميد فقط لتحفيز الإباضة بينما استخدمت المجموعة الثانية الحقن بعلاج الهرمون المنشط للجريب HMG فقط واستخدمت المجموعة الثالثة كل من الكلويميد بالإضافة إلى الحقن بعلاج الهرمون المنشط للجريب HMG.

نتائج الدراسة أوضحت زيادة بمس تويات الهرمونات (FSH) و (LH) في المجموعة الثالثة وبدلالة إحصائية معنوية ($P < 0.05$) كما كانت نسبة النض وجمالية للبرنجام الثاني وبدلالة إحصائية معنوية ($P < 0.05$) وكانت مستويات كل من هرمون الاستروجين و البروجسترون عالية في البرنامج الأول وبدلالة إحصائية معنوية ($P < 0.05$). النتائج في هذا البحث أهميتها نوعية العلاج المسخدم وكميته على مس تويات النض وجمالية حدوث الحمل.

مفاتيح الكلمات برامج تحفيز المبايض، الهرمون المنشط للجريب، الهرمون اللوتيني، الكلويميد!!!!!!

Abstract

Background:- Many years ago, clinicians treating couples for infertility by using ovarian stimulants drugs, which produce their action on reproductive hormones, a variety of medications can temporarily correct ovulatory problems and increase a woman's ability to become pregnant.

Objectives:- To identify the effect of different type of ovarian stimulents modalities on serum level of reproductive hormone which will eventually affect the out come of the cycle (follicular maturation and ovulation).

Methods:- Forty-five patients were enrolled in this study all of them suffer from primary infertility, the patients were randomized into three groups.

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The first group consist of fifteen patient they use clomiphene only as ovulation stimulant drug (starting from cycle day two and for five days), the second group also fifteen patient they use human menopausal gonadotropins injection (HMG) as ovulation induction drug(starting from cycle day two), and the third group also fifteen patient use both drugs for ovulation induction(first they took clomiphene from cycle day two and for five days followed by HMG injection from cycle day seven).

Results:- Showed a significant increase in the serum concentration of follicular stimulating hormone and Luteinizing hormone in the third group more than the first and second groups. The rates of the follicular maturation were significantly higher in the second group more than the first and third groups. The serum concentrations of the progesterone and estrogen hormones were significantly higher in the first group more than the second and third groups.

Conclusion:-Careful selection of treatment modality, dosing combined with appropriate levels of monitoring may result in excellent maturation rate.

Key words:-folliculogenesis, ovulation induction, gonadotropin hormones, clomiphene citrate.

Introduction

Infertility is a relatively common problem, it is estimated that approximately 10% of those who wish to have children can be considered infertile and about 30 to 40% of them present with ovarian dysfunction⁽¹⁾

Ovarian stimulants involve drugs that stimulate development of one or more mature follicles in the ovaries of women who have anovulation and infertility. These women do not regularly develop mature follicles without the help of ovulation enhancing drugs⁽²⁾.

There are different types of ovarian stimulants that are used to induce ovulation⁽³⁾. Treatment with these drugs has the potential to result in pregnancy if the women has mature follicles and if other causes of infertility are not present^(4,5).

Clomiphene is the first line drug in the treatment for anovulation in infertile women⁽⁶⁾. Clomiphene citrate has been the gold standard treatment for induction of ovulation. It is a selective estrogen-receptor

modulator that antagonizes the negative feedback of endogenous estrogen on the hypothalamic–pituitary axis. Treatment with Clomiphene should return luteinizing hormone (LH) to normal and increase FSH secretion, thereby stimulating follicle growth and ovulation⁽⁷⁾.

The dose titration of Clomiphene is effective as an initial dose of one tablet (50 mg) per day for five days and if this is not successful in causing ovulation the dose is increased in the next cycle to 2 tablets per day and for five days⁽⁸⁾. If two tablets a day are not successful in causing ovulation we would either try 3 tablets a day⁽⁹⁾.

In addition gonadotropins contain follicle stimulating hormone (FSH) was also designed for use in women as an ovarian stimulant where it stimulates the ovaries to produce multiple follicles thus making them more fertile^(10,11).

The gonadotropic follicle stimulating hormone and luteinizing hormone which are produced and secreted by anterior pituitary gland in response to the hypothalamic gonadotropin releasing hormone stimulate the synthesis and secretion of estrogen and progesterone hormones⁽¹²⁾. The rising level of estrogen causes the endometrium to be thicker and more richly supplied with blood vessels and gland, a rising level of LH causes the developing egg within the follicle to complete the first meiotic division forming a secondary oocyte. LH also triggers ovulation and formation of corpus luteum which will secrete progesterone⁽¹³⁾ and in order to increase ovulation a human chorionic gonadotropins (HCG) is given⁽¹⁴⁾.

The aim of the present study was to evaluate the variable effect of clomiphene on the level of follicular maturation and the effect of different ovarian stimulant modalities on serum level of reproductive hormones and their relation with follicular maturation.

Subject and methods

Forty-five volunteers patient were enrolled in this study. Their age range from 23-30 years old and their body mass index range (24 – 28)Kglm². All of the patients suffer from primary infertility and attended the Maternity and Pediatric Teaching Hospital in Al-Qadisiah (from

December 2006 to July 2007).they were free from other cause of infertility (they have problem in ovulation only).

They were randomized into three groups each group included fifteen patients. The first group treated with clomiphene citrate (clomid, patheon France S.A) in a dose of 100mg/day starting from cycle day two and for five days. The second group treated with the human menopausal gonadotropins (HMG, Menopur Germany 75 IU FSH 75IU LH) i.m injection in a dose of 150 IU/day from cycle day two of menstruation every other day till day 10 of cycle. Ultrasound was performed to asses the follicular size. follicular size reach to more than 17mm was regarded as mature follicles, in order to induce final maturation of ovarian follicles subcutaneous injection of(10 000 IU) human chorionic gonadotropins (HCG)(patheon France S.A) were given to patient who have mature follicles. The third group was treated with 100 mg/day clomiphene tablets from cycle day 2 and for five days followed by HMG i.m injection (150 IU/day) daily from cycle day seven till day 10 of cycle and when the follicle size reach to >17mm a (10 000 IU) of HCG injection was given.

Base line assessments of ultrasound and blood sampling were performed on cycle day 2, then it repeted at day 12 and 21 of cycle to detect any ovarian cyst that later may be confused by follicle and to detect hormonal level.

Enzyme link fluorescent assay kits were used to determine the serum concentration of FSH, E2, LH and P hormones (Biomerieux, France). Using the minividas instrument.

Results are expressed as mean \pm SD. Data were analyzed by using t-test and chi-square test. A P- value less than 0.05 were considered statistically significant.

Results

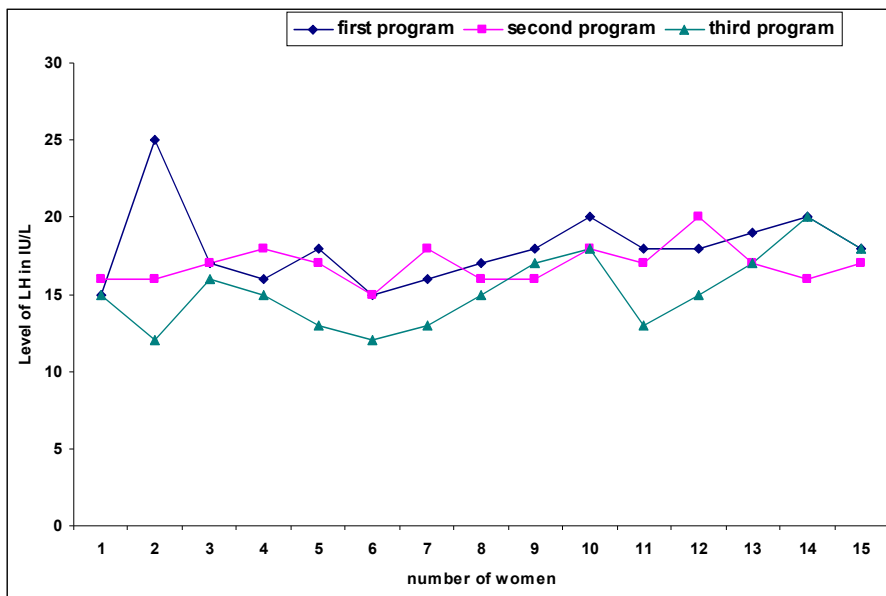
The measurement of serum concentration of LH, FSH and E2 hormone in the second day of the cycle shows no significant difference in the three groups of patients figure (1),(3),(5) and (table 1).While in the twelve day of the cycle after administration of three different ovulation induction programs the serum concentration of LH and FSH were significantly higher(P<0.05) in the third groups than the first and second

groups figure(2),(4)and (table 1).E2 hormone measurement in the twelve day of the cycle shows a significantly higher concentration($P<0.05$) in the first group than second or third groups figure (6) and (table 1).

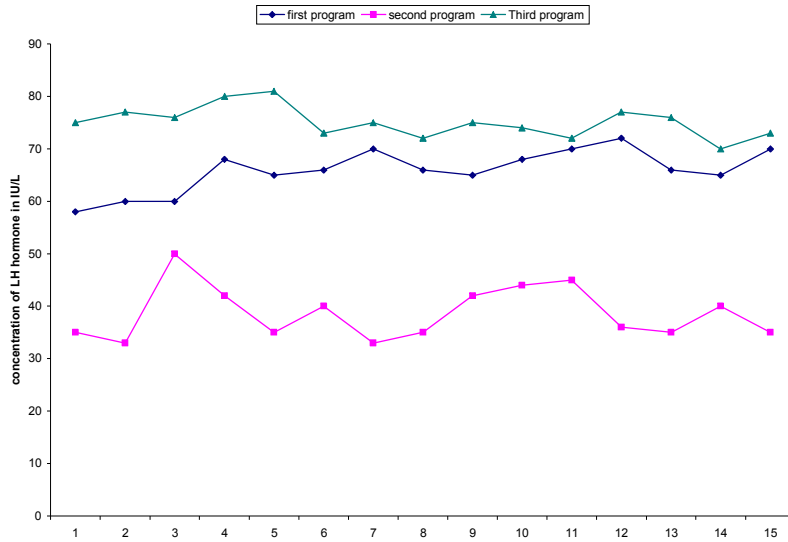
The measurement of serum progesterone hormone concentration in the twenty-one day of the cycle shows a significant higher concentration ($P<0.05$) in the first group more than second or third groups figure (7) and (table 1).

The number and the level of oocyte maturation within the same modality are variable, patient develop follicles ranging from 1 mm to 27 mm with considerably effective level of hormone reaching after induction.

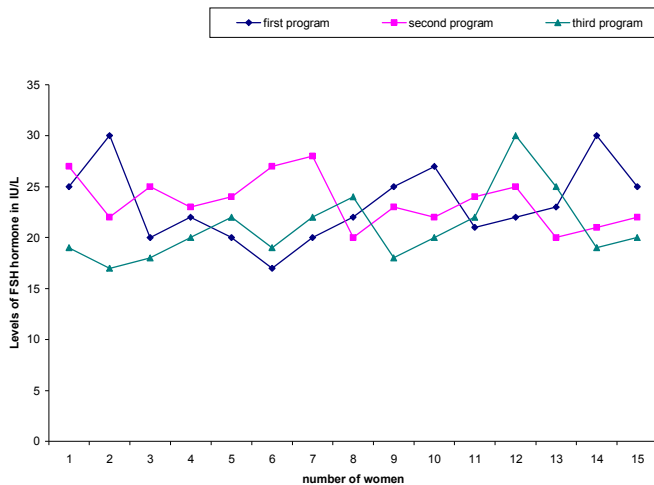
The percentage of mature oocyte were significantly higher in the second program ($P<0.05$) more than first or third groups(table 2).



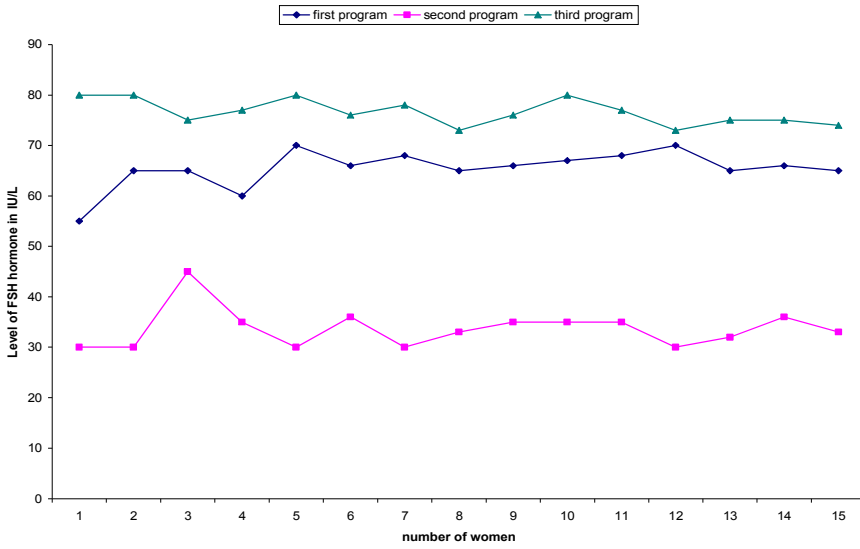
Figure(1) The concentration of luteinizing hormone in the second day of the cycle.



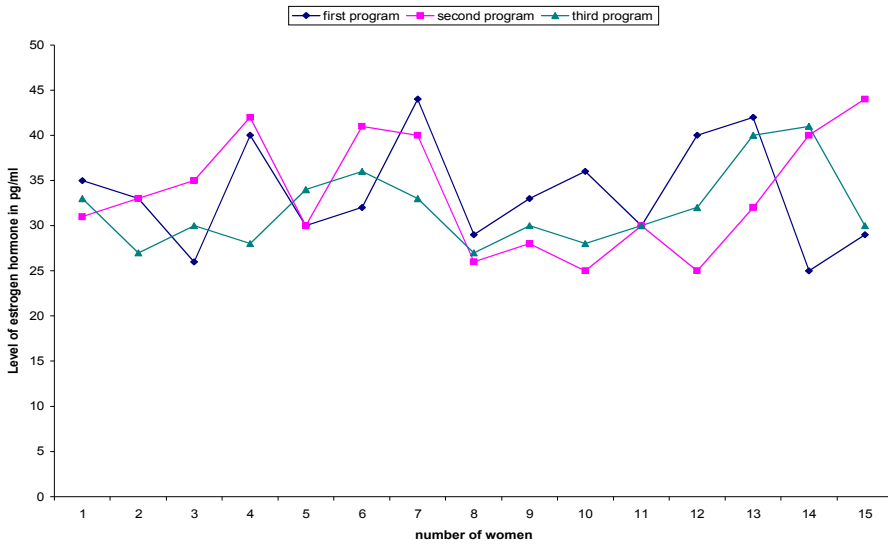
Figure(2)The concentration of luteinizing hormone in the twelve day of thecycle.



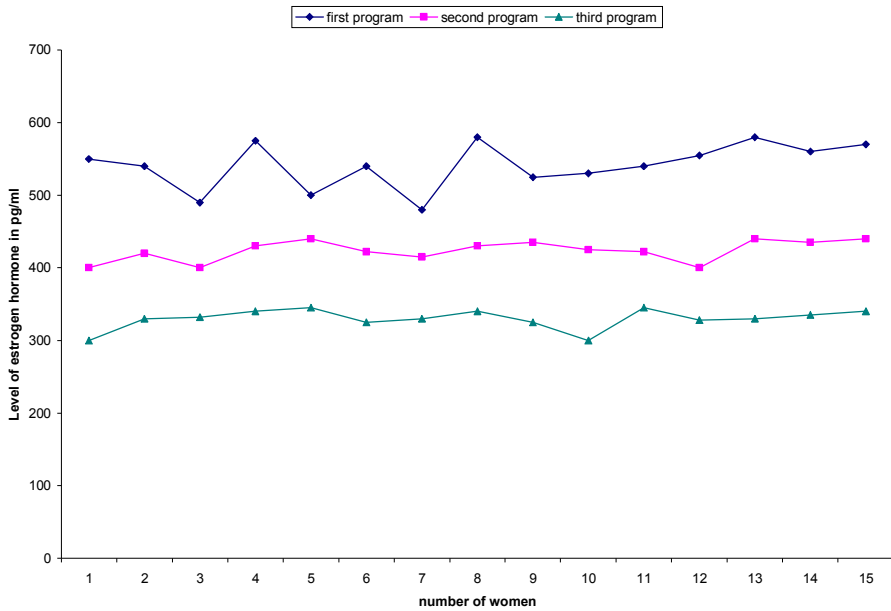
Figure(3)The serum concentration of follicle stimulating hormone in the second day of the cycle.



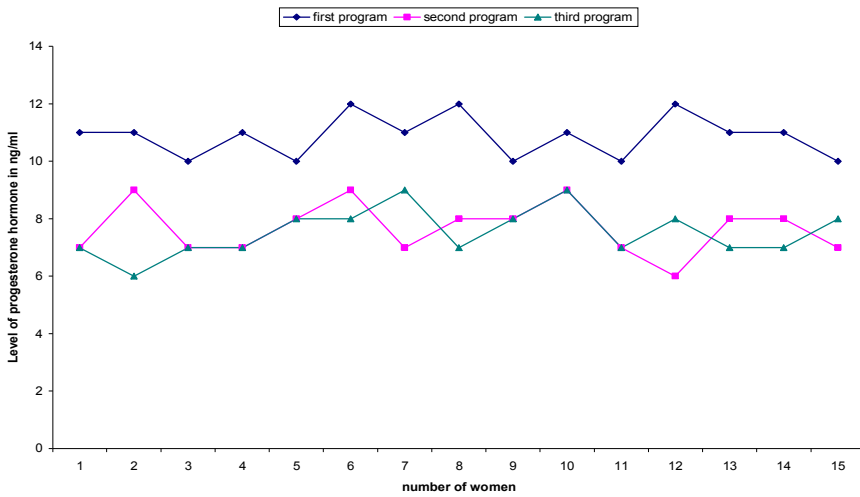
Figure(4)The serum concentration of follicle stimulating hormone in the twelve day of the cycle.



Figure(5)The serum concentration of estrogen hormone in the second day of the cycle.



Figure(6)The serum concentration of estrogen hormone in the twelve day of the cycle.



Figure(7)The serum concentration of progesterone hormone in the twenty-one day of cycle.

Table(1) The mean concentration of reproductive hormones in the three groups (M ± SD)

Cycle day	Hormones	First group	Second group	Third group	P < 0.05
Second day	E2 pg/ml	33.6±5.8	33.4 ± 6.5	31.9 ± 4.3	NS
	FSH IU/L	23 ± 3.7	23.5 ± 2.5	21 ± 3.3	NS
	LH IU/L	18 ± 2.4	16.9 ± 1.2	15.2 ± 2.4	NS
Twelve day	E2 pg/ml	539 ± 39.6	423.6 ±14.4	329.6 ±13.7	S
	FSH IU/L	65.4 ± 3.7	33.6 ± 3.9	76.6 ± 2.5	S
	LH IU/L	65.9 ± 4.1	40.6 ± 10.6	75 ± 2.9	S
Twenty-one day	P ng/ml	10.9 ± 0.7	7.7 ± 0.9	7.5 ± 0.8	S

Table (2) The percent of oocyte maturation in the three groups

	Number of mature oocyte	%of maturation
First program	16	28.6%
Second program	26	46.4%
Third program	14	25%

Significantly higher maturation rate in second group(P<0.05)than in other groups.

Discussion

Some studies confirm that about 50-80% of anovulatory women would be able to have ovulation induced by clomiphene medication with a pregnancy rate of approximately half of the ovulation rate (15) .

In this study use only clomiphene for induction of ovulation (first group) have a lower and variable maturation rate as compared to the second group. Three women in the first group became pregnant inspite the fact that this group have a significant higher levels of estrogen and progesterone hormones than the other groups which is necessary to maintain pregnancy(16). This probably due either to a decrease in the quality of the follicles with clomiphene , the negative impact of the clomiphene on the quantity and quality of cervical mucus, and a negative impact on the quantity and/or quality of the endometrial lining (17) .

Anovulatory women could have induced ovulation with human menopausal gonadotropins therapy with a better pregnancy rates per month than those with clomid therapy (18) .

In this study women who used only HMG (second group) showed a significant rise in rate of follicular maturation than the first or third groups and even one woman achieved pregnancy. This could be related to the proper level of hormones that is required for the good quality of eggs and endometrial lining (19).

Combination of two drugs is a third choice for anovulatory women. Many studies reported a higher ovulatory rate of over 90% with a pregnancy rate of about 50%(20). In this study women who used the clomiphene plus HMG (third group) showed a rise in the levels of FSH and LH hormones but a lower E2 hormone concentration and a lower follicular maturation than the other groups. The reason is unclear although Gurnee DH and Crystal L suggested that increase aromatase activity result in a lower maturation rate (21).

Some studies reported a complication associated with the use of this program due to the hyperstimulation that lead to enlarged ovaries, abdominal pain fluid build-up within the abdomen, and may require hospitalization in extreme cases to control pain or manage the syndrome(22).

In this study no complication were observed and again most of women fail to become pregnant. The reason could be related to the lower level of estrogen hormone in the twelve day of cycle which is necessary to build the lining of the endometrium to receive the fertilized ova (23). Further more the reduced level of progesterone hormone in the twenty one day of cycle will effect the maintenance of pregnancy since it is important for the placenta formation and maintenance (24).

In conclusion this study indicate that the specific dose and type of medication used for each patient to induce ovulation have a great effect on the outcome of the cycle further pharmacogenetic studies that focus on the doses of the drugs needed to produce specific size of ova that become laible for fertilization for each woman , and luteal phase support are needed.

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