Monitoring gonadotropin therapy of anovulatory infertility by ultrasound alone.

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الملخص

في الدراسة الحالية تم مسح طريقة العلاج بهرمونات المناسل بواسطة الامواج فوق الصوتية بسبب ان Serum oestradiolغير متوفر في البصرة والكشف عن ما اذا كانت الامواج فوق الصوتية لمنطقة الحوض كافية للسيطرة لوحدها على استجابة المبايض لهذا العلاج وحثها على التبويض.استخدم جهاز المسح للامواج فوق الصوتية نوع Real time للكشف عن نمو وتطور حويصلات المبايض لـ 35 مريضا اظهرت النتائج ان الامواج فوق الصوتية لوحدها يمكن استخدامها بكفاءة للسيطرة على العلاج بهرمونات المناسل في معظم الحالات.

Abstract

In our study we monitor the gonadotopin therapy by ultrasound because serum oestradiol is not available in Basrah, and we investigate whether pelvic ultrasound alone suffices to control ovarian response to gonadotropin to induce ovulation.

Real time ultrasound scanning of follicular development was performed for 35 patients receiving metrodin during 113 cycle. Twenty pregnancies were obtained resulting in a pregnancy rate of (57.1%); with (16) patients singletons, set of twins 4 (20%), with abortions 6(30%) and about patients 2 (5%) develops mild ovarian hyperstimulation syndrome (OHSS).

So ultrasound alone can be used effectively to control gonadotropin therapy in the majority of cases.

Introduction

Ovulation induction is aimed at the development of more than one mature follicle in a woman who is anovulatory so that more oocytes are available for fertilization [(1)].

Human menopausal gonadotropin (hMG) and human chorionic gonadotropin (hCG) are used in the treatment of anovulatroy infertility for induction of ovulation and to establish pregnancy [(2)].

Metrodin which contains a highly purified hormone obtained from human menopausal urine, having only (FSH) activity, two strengths are available 75 I.U., 150 I.U. each ampoule contains urofollitrophin.

Metrodin acts directly on the ovary to stimulate granulose cell function and have three primary functions they are :

1- **Replication of granulose cell and increase FSH receptors concentration.**
2- **Induction of aromatization (conversion of thecaly derived androgen to osteogens).**
3- **Generation of LH receptors [3] .**

Metrodim can be given daily intramuscularly or subcutaneously with an increase in dose each time, or alternate daily injections from early follicular phase until follicular maturation is confirmed followed by intramuscular injection of 5000 I.U of (hCG) to induce ovulation [4,5] .

The most common complications of gonadotropin therapy are multiple pregnancy and ovarian hyperstimulation syndrome (OHSS) [6,7] .

Many indirect Methods have been described to monitor the ovarian response to gonadotropin, these include [8,9] :

1- **Serial vaginal smears and fern test.**
2- **Cervical scoring, measurement of total urinary oestrogens.**
3- **Daily measurement of total urinary oestrogens.**
4- **Serial estimation of oestradiol in peripheral venous plasma.**

However, these procedures have considerable short-coming, such as being costly, time consuming, unreliable and fewer specifics [9] .

5- **Serial ultrasound monitoring.**

Ultrasound, on the contrary, has the advantage of providing direct investigation of follicular development, ovulation and corpus luteum formation in both spontaneous and induced cycles and endometrial thickness measurement [10], so that ultrasound monitoring appear to be useful Methods of timing hCG administration and preventing multiple birth and (OHSS) [6,7].

Aim of the study

The aim of this study is to investigate whether pelvic ultrasound alone suffices to control ovarian response to gonadotropin stimulation and the time of administration of hCG to induce ovulation.

Area of particular interest included :-

- **Pregnancy rate.**
- **Number of cycle required to achieve pregnancy.**
- **Incidence of multiple pregnancies and other complication.**

Materials and Methods

Thirty five patients with history of infertility of >2 years duration because of anovulation were included in this study and they were reviewed prospectively from the period of January 2000 till August 2001 in Basrah. The couples were assessed thoroughly including a full history positive test of tubal patency were obtained preferably by laparoscopy (20 out of 35) and hysterosalpingography (15 out of 35), hormonal measurement of FSH, LH, oestradiol of third day of the cycle and progesterone and prolactin in the twenty first day of the cycle was sent for all patients. In all male partners, a complete semen analysis was obtained in two separate occasions 2-6 weeks apart. All the couples a positive postcoital test was obtained. Patients received sequential intramuscular injections of metrodin 751 U on day 3,4,5 and 6th of the cycle [(11)] .On day 7th ovarian response was investigated with the use of ultrasound, the number and the size of detected follicles recorded, adjustments of treatment regimen were made in the following manner, if one or two active follicle of 7-8 mm in diameter were observed, the previous average metrodin dosage was continued, the dosage was increased in the next cycle to five ampoules, then after 3-4 days another ultrasound was taken and the follicles were considered pre-ovulatory when they reached a mean diameter of (20±1) mm.

Endomelerial thickness was checked if it reaches 7-8mm. Ovulation was then induced by intramuscular administration of 5000 I.U. of hCG [(12)]. The hCG was withheld though if more than three follicles reached maturity (20-25)mm in diameter [(13)]. If two or three preovulatory follicles were present, thus increasing the likelihood of multiple gestation [(14)].Sexual intercourse was recommended the day of hCG administration and on the following days, further follow up examination was not an integral part of the study.

The patients would report either after menstral bleeding for another treatment cycle or with amenorrhea to have their pregnancy confirmed.

Results

The clinical data are summarized in table no. 1, out of 35 treated patients only 20 patients conceived within 61 cycles, with a mean three cycles treatment for each patients, resulting in a cumulative pregnancy rate (57.1%).

In 16 patients singleton pregnancy were obtained, in the remainder there were four set of twin (20%), three ended by spontaneous abortion and the fourth set ended by caesarian section at 37 weeks.

Table no.2 shows seven pregnancies ended prematurely; there were four spontaneous abortion, including three set of twin and one singleton pregnancy, two ectopic tubal pregnancy were treated by salpingectomy, one pregnancy ended at 35 weeks by caesarian section because of premature rupture of membrane.

Five patients were ended by normal vaginal delivery, and four by term size caesarian section, two of them due to pre-eclampsia and two because of malpresentation, there were two cases of mild ovanan hyperstimulation, but no case of moderate to severe hyper stimulation.

Table no.1:Clinical and ultrasound data during 20 conceptions cycles after metodin injection

patients	Age	Infertility In years	Treatment cycle	Ampoule of metro din	No./size of preovulatoy follicles	Endometrial thickness In(mm)	Results
1	27	2	3	4	19,17	8	Singleton, spontaneous abortion at 8wks.
2	29	3	2	4	20.19	9	Twin spontaneous abortion at 10wks.
3	23	4	3	3	18,20,19	11	Twin spontaneous abortion at 16 wks.
4	24	2	4	5	20,20	9	Twin spontaneous abortion at 25 wks.
5	30	2	5	4	23,17,19	10	Singleton, ectopic 8wks.
6	28	3	2	2	21,20	8	Singleton ectopic 9wks.
7	28	6	6	3	22,18	10	Singleton, term NVD.
8	20	2	2	4	18,20	9	Singleton, term NVD.
9	18	2	4	4	19,21	8	Singleton, caesarean section 35wks.
10	21	4	3	5	21,18	7	Singleton, term NVD
11	31	4	5	3	20.17,19	8	Singleton term NVD.
12	19	2	1	3	20,18	11	Singleton term NVD.
13	32	5	3	4	21,20	8	Singleton caesarean section
14	25	3	2	4	19,20	10	Twin, term caesarean section
15	25	2	4	2	20,22	9	Singleton term CS.
16	17	2	2	4	21,19	8	Singleton term CS.
17	26	4	2	4	21,19	8	Singleton, on going pregnancy at 32wk.
18	33	5	4	4	19,22	8	Singleton, on going pregnancy at 30 wk.
19	26	4	3	3	22,19	10	Singleton, on going pregnancy at 28 wk.
20	27	2	1	4	20	9	Singleton, on going pregnancy at 15 wk.

NVD: normal vaginal delivery
Wk : week

Table no.2 :Results of the conception

Results	No.	%
Singleton spontaneous abortion.	1	5
Twin spontaneous abortion.	3	15
Ectopic pregnancy.	2	10
Normal vaginal delivery.	5	25
Preterm cesarean section.	1	5
Term cesarean section.	4	20
Ongoing pregnancy.	4	20
Total	20	100%

Table no.3 :Results of different monitoring Methods of gondatropin therapy

Authors	Methods	Pregnancies /patient	%	Twin	%
Kurachi 1984[15]	Cervical score	498/2166	23	93/361	26
Zimmermann1982[16]	Plasma E_2	119/392	30	26/119	22
Pittaway 1983[17]	Plasma E_2	12/25	48	3/12	25
West 1984[18]	Plasma E_2	33/46	72	10/46	22
Bessis 1981[19]	Plasma E_2/ ultrasound	6/27	22	2/6	33
Fink 1982[20]	Plasma E_2/ ultrasound	21		2/21	10
Marrs [21]	Plasma E_2/ ultrasound	6/18	33	0	
Haning 1983 [22]	Plasma E_2/ ultrasound	22/28	79	3/22	14
Lunefeld 1985 [23]	Plasma E_2/ ultrasound	384/1000	38	115/384	30
Sallam 1982 [12]	Ultrasound alone	12/22	55	4/21	25

Discussion

Although serial measurements of hormones in peripheral plasma or their metabolites in urine offer useful Methods of monitoring therapy with gonadotropins, this approach has many disadvantages, for example, it`s time consuming for the patient, special laboratory facilities are required and there is at least a six hours delay between sampling and treatment.

It also remains an indirect Methods of following follicular growth. Moreover, patients differ in their body weights composition and build, and follicles of the same size may not secret the same amount of hormone in different patients, and plasma oestradiol levels are often not good indicator of follicle maturing, specially in cases where more than one follicle is nearing maturation [12,24] . While real timed scannes were used to reduce the time of the procedure to less than 5 minutes for

each examination. So ultrasound measurement provide direct Methods of following follicle growth in both spontaneous and induced ovulation [22] .In this study the result demonstrate that ovarian response to both gonadotropin and hCG timing of ovulation could be predict accurately using ultrasound measurements of the number, size of follicle induced and endometrial thickness. The procedure resulted in accumulative conception rate (57.1) which is a good conception rate in comparison with other studies as shown in table no.3, thus ultrasound alone can be used successfully to monitor gonadotropins induction of ovulation without use of additional monitoring measures.In our study, there were four cases of multiple pregnancies all were twin so the rate of multiple pregnancy was (20%) in any cases hCG is given in the presence of two mature follicles as determined by number and size of mature follicle by ultrasound. Therefore, it appears that ultrasound could predict multiple ovulation and gestation by accurately assessing the number and the size of mature follicles during gonadotropin therapy, so a treatment modality, restricting the number of preovulatory follicle to one should render multiple an exception to the rule as in the normal cycle.In our study patients, monitored by ultrasound, were thought to have been overstimulated with gonadotropin. One developed about four follicles of 20-25 mm diameters, the other patients developed five follicles.Both patients, however, were mild symptom and on manual examination the ovaries were tender and detectable, although in these patients hCG injection was withhold and intercourse was abounded, thus management of gonadotropin therapy with ultrasound alone was sufficient to prevent severe ovarian hyperstimulation [12] .Increased risk of abortion is another complication associated with gonadotropin therapy [23]. In our study, we found that abortion rate was (30%), three after twin pregnancy (15%) and two ectopic abortion (10%) and one following singleton pregnancy (5%), so the risk of abortion increased following multiple pregnancy [23]. So treatment regimen approaching the normal cycle as closely as possible should in turn reduce the incidence of abortions to approximately that following spontaneous conceptions [23, 24, 25].

Conclusions

Ultrasound alone can be used effectively to control gonadotropin therapy for induction of ovulation in a routine infertility clinic in the majority of cases, and can help to induce ovulation at the best moment of follicular growth, the follicle reach a certain diameter to be able to rupture and lead to normal ovulation . Also it might predict the risk of OHSS, and it can reduce the risk of multiple pregnancy and abortion.

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