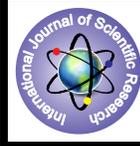


To Assess The Relationship of Ovarian Response to Stimulation after Clomiphene Citrate with Markers of Ovarian Reserve



Medical Science

KEYWORDS : clomiphene citrate, ovarian reserve, infertility.

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ABSTRACT

Objective: - To assess the relationship of ovarian response to stimulation after clomiphene citrate (100mg) with hormonal and ultrasonographic markers of ovarian reserve among women with primary infertility aged >35yrs and to find out best predictor of ovulation after induction with clomiphene.

Methodology: Fifty women with primary infertility of age >35 years having regular monthly cycles and no history of ovarian surgery were included in this cross-sectional study conducted from December 2010 until July 2011 in SMS Medical College. A transvaginal ultrasound to find out ovarian volume and antral follicles (AFC) and; blood tests for serum Follicle Stimulating Hormone (s.FSH) & serum. AntiMullerian Hormone (s.AMH) were carried out between the third and fifth day of their menstrual cycle. From day 3-7 of the cycle patient were given clomiphene citrate (100mg) and periodic Transvaginal ultrasound scan was done every alternate day from day 9-14 to find out whether ovulation occurs or not after stimulation.

Results: This study shows highly significant association of markers of ovarian reserve viz.s.FSH, s.AMH, antral follicle count, ovarian volume and ovarian blood flow; with ovulation after clomiphene citrate.

Conclusion: Patients with normal FSH, AMH, ovarian volume, antral follicle count and ovarian blood flow have higher chances of ovulation after stimulation with clomiphene citrate. Of all the markers of ovarian reserve ovarian blood flow is the best predictor of ovulation after induction

Introduction Ovarian reserve is an indication of reproductive age as opposed to chronological age and is a parameter of calculating remaining reproductive lifespan of woman. Diminished ovarian reserve is characterized by decreased number of remaining oocytes in the ovaries and impaired preantral oocytes development and recruitment.

Ovulatory disorders are common causes of subfertility and infertility in women of reproductive age. Several pharmacologic agents are available to induce or augment ovulation, with varying rates of success. These medications include clomiphene citrate (a selective estrogen receptor modulator), aromatase inhibitors, urinary and recombinant gonadotropins, gonadotropin-releasing hormone (GnRH) analogs, and insulin-sensitizing agents. Clomiphene citrate is considered a first-line treatment because of its low cost, relative ease of use, and minimal side effects.

It is a selective estrogen receptor modulator. It is known to be both an estrogen agonist and antagonist; however, its agonist properties manifest only when endogenous estrogen levels are extremely low. In general, its antagonistic effects prevail. Clomiphene citrate administration leads to depletion of estrogen receptors at the level of the pituitary and hypothalamus, interrupting the negative feedback that estrogen normally produces. As a result, GnRH secretion is improved and stimulates pituitary production of follicle-stimulating hormone (FSH), which in turn drives follicular growth and maturation with emergence of 1 or more dominant follicles.

Over the past two decades, a number of tests of ovarian reserve have been used to determine follicle number and quality; and to predict the outcome of assisted reproduction procedures. The woman's age and assays of serum FSH in the early follicular phase were amongst the earliest and most useful parameters used for evaluation of ovarian reserve. Several ultrasound parameters have been used for evaluation of ovarian reserve, including ovarian volume, ovarian blood flow and the antral follicle count, with varying degrees of reliability. Recently, serum antimüllerian hormone levels have been introduced as a novel measure of ovarian reserve. AMH is a product of the granulosa cells in preantral and antral follicles. Serum AMH levels decline with age and are correlated with the number of antral follicles and the ovarian response to hyperstimulation.

Present study is done to find relationship of ovarian response to stimulation after clomiphene citrate (100mg) with hormonal and

ultrasonographic markers of ovarian reserve among women with primary infertility aged >35yrs and to find out best predictor of ovulation after induction with clomiphene.

Methodology This study was conducted in department of Obstetrics and Gynaecology, Sawai Man Singh Medical College, Jaipur between December 2010 to July 2011 on first 50 women coming for management of primary infertility who were >35 yrs. of age with regular menstrual cycles(excluding Male factor infertility, Tubal factor, Presence of gynaecological disorders such as menorrhagia or DUB, History of ovarian surgery & other causes of infertility).The study was approved by ethical committee and research review board of Sawai Man Singh Medical College, Jaipur.

Every case gave informed written consent prior to participation in the study. Cases were called on early follicular phase of menstrual cycle (day 1-3) and underwent transvaginal USG and Blood Tests. All Transvaginal USG was carried out by Toshiba Echo C using 7.5 MHz vaginal probe. The length, height and width of each ovary was measured in sagittal and coronal plane during TVS scanning and ovarian volume was obtained using formula of ellipsoid i.e., $\pi/6 \times (\text{length} \times \text{height} \times \text{width})$. The number of antral follicles <10 mm in each ovary were counted.

Blood samples were taken for measurement of s.FSH and s.AMH. s.FSH was measured by standard MICT R FSH test kit-Magnetic Immunochromatometric test-sensitivity 0.2mIU/ml and s.AMH was measured by ELISA (B.Lal laboratories diagnostic analytical sensitivity 0.2ng/ml)

From day 3-7 of the cycle patient were given clomiphene citrate (100mg) and periodic Transvaginal ultrasound scan was done every alternate day from day 9-14 to find out whether ovulation occurs or not after stimulation

Results In this study we have taken reference values as following¹-

s.FSH <10mIU/ml- normal

s.AMH 1-3ng/ml-normal

Antral follicle count-total antral follicle count of both ovaries >6 normal

Ovarian volume- mean ovarian volume was taken >3 cc-normal ovarian volume

Present study shows 27 cases have normal FSH of which 22.2% had no ovulation and 77.8% had ovulation; 23 cases had low FSH of which 78.3% had no ovulation after clomiphene and 21.7% had ovulation. As p- value is 0.000 this difference is highly statistically significant, as shown in Table-1.

34 cases have normal AMH of which 73.5% ovulated after and 26.5% does not ovulated after clomiphene; 16 cases have low AMH of which only 6.3% ovulated and rest 93.8% not ovulated after clomiphene. This difference is highly statistically significant as shown in Table-2.

33 cases have normal ovarian volume of which 24.2% ovulated and 75.8% does not ovulated and 17 cases have poor ovarian volume of which only 5.9% ovulated and 94.1% does not ovulated. Since p-value is 0.000 difference is highly statistically significant as shown in table-3.

35 cases with normal AFC of which 74.5% ovulated after clomiphene & 15 cases with poor AFC of which no case ovulated. As the p-value is 0.000 the difference is highly statistically significant as shown in Table-4.

Study shows 20 cases with normal ovarian blood flow of which 100% ovulated after induction with clomiphene; 30 cases with decreased blood flow of which only 20% ovulated. p-value is 0.000 has the difference is highly statistically significant as shown in Table-5.

TABLE-1
OVARIAN RESPONSE TO STIMULATION AFTER CLOMIPHENE AND S.FSH

			OVULATION		TOTAL
			ABSENT	PRESENT	
S.FSH	NORMAL	COUNT	6	21	27
		% WITHIN S.FSH	22.2%	77.8%	100.0%
	POOR	COUNT	18	5	23
		% WITHIN S.FSH	78.3%	21.7%	100.0%
		COUNT	24	26	50
TOTAL		% WITHIN S.FSH	48.0%	52.0%	100.0%

CHI-SQUARE=15.626 DF=1 'P' VALUE= 0.000

TABLE-2
OVARIAN RESPONSE TO STIMULATION AFTER CLOMIPHENE AND S.AMH

			OVULATION		TOTAL
			ABSENT	PRESENT	
S.AMH	NORMAL	COUNT	9	25	34
		% WITHIN S.AMH	26.5%	73.5%	100.0%
	POOR	COUNT	15	1	16
		% WITHIN S.AMH	93.8%	6.3%	100.0%
		COUNT	24	26	50
TOTAL		% WITHIN S.AMH	48.0%	52.0%	100.0%

CHI-SQUARE=19.731 DF=1 'P' VALUE= 0.000

TABLE-3
-OVARIAN RESPONSE TO STIMULATION AFTER CLOMIPHENE AND OVARIAN VOLUME

			OVULATION		TOTAL
			ABSENT	PRESENT	
OVARIAN VOLUME	NORMAL	COUNT	8	25	33
		% WITHIN OVARIAN VOLUME	24.2%	75.8%	100.0%
	POOR	COUNT	16	1	17
		% WITHIN OVARIAN VOLUME	94.1%	5.9%	100.0%
TOTAL		COUNT	24	26	50
		% WITHIN OVARIAN VOLUME	48.0%	52.0%	100.0%

CHI-SQUARE=21.948 DF=1 'P' VALUE= 0.000

TABLE-4
OVARIAN RESPONSE TO STIMULATION AFTER CLOMIPHENE AND AFC

			OVULATION		TOTAL
			ABSENT	PRESENT	
AFC	NORMAL	COUNT	9	26	35
		% WITHIN AFC	25.7%	74.3%	100.0%
	POOR	COUNT	15	0	15
		% WITHIN AFC	100.0%	.0%	100.0%
		COUNT	24	26	50
TOTAL		% WITHIN AFC	48.0%	52.0%	100.0%

CHI-SQUARE=23.214 DF=1 'P' VALUE= 0.000

TABLE-5
OVARIAN RESPONSE TO STIMULATION AFTER CLOMIPHENE AND OVARIAN BLOOD FLOW

			OVULATION		TOTAL
			ABSENT	PRESENT	
OVARIAN BLOOD FLOW	NORMAL	COUNT	0	20	20
		% WITHIN OVARIAN BLOOD FLOW	.0%	100.0%	100.0%
	POOR	COUNT	24	6	30
		% WITHIN OVARIAN BLOOD FLOW	80.0%	20.0%	100.0%
		COUNT	24	26	50
TOTAL		% WITHIN OVARIAN BLOOD FLOW	48.0%	52.0%	100.0%

CHI-SQUARE=30.769 DF=1 'P' VALUE= 0.000

Discussion: Present study shows that cases with normal FSH have higher chances of ovulation after induction as compared to patients with abnormal FSH levels. This is in accordance to the study of El-Shawarby SA, Khalaf Y.² which showed that that age-specific FSH testing can serve as a good predictor of the oocyte yield in women with normal FSH concentrations undergoing IVF.

This study shows that cases with normal AMH have higher chances of ovulation after induction as compared to patients with low AMH. This is in concordance to the study of Mohamed S. Sweed et.al³ which showed that Anti-Müllerian hormone is a very useful predictor of poor responders to clomiphene citrate among women with polycystic ovary disease

This study shows that cases with normal AFC and ovarian volume have higher chances of ovulation after induction as compared to patients with low ovarian volume. This is in concordance to the study of Nozzhat Mousavifar, Leili Hafizi⁴ which showed that transvaginal ultrasound, measurement of ovarian volume and basal follicle numbers on day 3 of cycle prior to starting gonadotropins administration can help to predict the patient's response.

This study shows that cases with normal ovarian blood flow have higher chances of ovulation after induction as compared to patients with poor ovarian blood flow. This is in concordance to the study of Neena Malhotra et al⁵ which showed that ovarian blood flow has the potential to be used as a simple and non-invasive surrogate marker of capillary blood flow around recruitable follicles to predict response to ovarian stimulation and cycle outcome.

Conclusion: - Patients with normal FSH, AMH, ovarian volume, antral follicle count and ovarian blood flow have higher chances of ovulation after stimulation with clomiphene citrate. Of all the markers of ovarian reserve ovarian blood flow is the best predictor of ovulation after induction since 100 % cases with normal ovarian blood flow ovulated after induction.

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