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ROLE OF CLOMIPHENE CITRATE IN UNEXPLAINED INFERTILITY AT CMC LARKANA

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ABSTRACT

PURPOSE: *To assess the results of clomiphene citrate in unexplained infertility*
MATERIAL AND METHODS:
STUDY DESIGN: *Cross-sectional observational study.*
PLACE AND DURATION: *This study was conducted at Shaikh Zaid Women Hospital Gynae & Obs: unit -II, CMC, Larkana from August 2008 to July 2009.*
The entire patients were received in out patient department. Total numbers of patients received were 60 in number. All the patients were investigated for U/S and Hormonal assay such as, FSH, LH, S. prolactin level, serum fasting insulin level, S.Testosterone level in some selective cases.
RESULTS: *Out of 60 patients, 28 (46.66%) patients were non-cooperated in follow up and were discontinued. The entire 60 patient received induction of ovulation with clomiphene citrate. Seven (11.66%) women were not conceived and 25 (41.66%) were conceived. Dose was started from 50 mg from 2nd day of menstrual cycle up to 6th day. 12(48%) patients were conceived with 1st: course, 8 (32%) conceived with 2nd course, 2 patients (8%) conceived with 4th course, and 03 (12%) patients conceived with 6th course of clomiphene citrate.*
All the patients received injection of IVF-C10000 at 11th – 14th day of the menstrual cycle.
CONCLUSION: *Clomiphene citrate is a first line drug in women with ovulatory disorder and it is a primary treatment option in unexplained infertility. In the absence of specific diagnosis any form of treatment for unexplained infertility is speculative.*
As clomiphene citrate is inexpensive so its use is more preferred as compared to other expensive treatment.

KEY WORDS: Clomiphene Citrate, Unexplained, Infertility.

INTRODUCTION:

Infertility is defined as the inability to conceive after 1 year of regular unprotected intercourse[1]. Unexplained infertility means when all standard clinical investigations including semen analysis, assessment of ovulation and tubal potency yield normal results[2].Chance of conception is most closely related to age, duration of fertility of female partner and whether infertility is primary or secondary[3]. There are certain limitation to our ability to evaluate human fertility for example ovulation as assessed by history (regular periods) temperature charting, urine LH testing or even serial ultrasound and progesterone level provide only indirect evidence of egg release and very little information about egg quality but do not confirm that ovum pickup will occur, hysterosalpingography asses the fallopian tubes but do not confirm that patient ovum pickup will occur[4]. Therefore treatment of unexplained infertility is empiric because it does not address a specific defect or functional impairment[2]. The principle treatment for unexplained infertility, expectant observation with timed intercourse and life style changes. Clomiphene citrate and intrauterine insemination (IUI) Controlled ovarian hyperstimulation (Coh) with intrauterine insemination and IVF. With expectant management female partner should be counceled to achieve a normal BMI, reduce caffeine intake to no more than 250mg daily (2 cups of coffee) and reduce alcohol intake to no more than 4 standardized drinks per week[5]. Age of female partner influenced the pregnancy rate associated with expectant management[6].

Role of Induction of Ovulation:

Clomiphene citrate: A selective estrogen receptor modulator leads to high ovulation rates

by inhibiting the recycling of estrogen receptor and over secretion of FSH from the pituitary gland[7, 8].

The rational for giving clomiphene citrate to women with unexplained infertility is to over come subtle but as yet unknown defect or to increase the number of follicles available per cycle to augment the chance of conception[9]. CC exhibited High ovulatory rate (86%) and pregnancy rate (49%) [10].

Controlled ovarian hyperstimulation (Coh) and Intrauterine Insemination (IUI): Use of clomiphene citrate with timed intercourse in patient with unexplained infertility has been shown to have a small effect on pregnancy rates. Combined analysis of available evidence revealed that 40 cycles with empiric Clomiphene citrate (cc) therapy even necessary to achieve additional pregnancy[11]. Gonadotrophin therapy is superior to CC therapy and both are most effective when combined with IUI. A meta-analysis of 27 studies involving 2939 cycles revealed that the pregnancy rate cycle was 8% with gonadotrophin treatment alone and 18% will gonadotrophin treatment combined with IUI[12].

Intrauterine insemination (IUI): A recent Cochrane review that IUI with ovulation induction increase the live birth rate compared with IUI alone[13].

In Vitro Fertilization (IVF) and Intracytoplasmic Sperm Injection (ICSI): The most complex and expensive empiric therapy for unexplained infertility are IVF pregnancy rates of 14-32% per cycle have been reported in couples with unexplained infertility[14].

MATERIAL AND METHODS

The study was conducted at Shaikh Zaid Women Hospital, Gynae & Obs: Unit-II CMCH Larkana. The latter being a tertiary care center, received patients from all over the Sindh and Balouchistan.

All the staff participating in the study was specially instructed regarding detail of research study and about a specially designed Proforma.

Once the patient came with history of failure to conceive, management included History, general physical, abdominal and pelvic examination followed by base line and special investigations.

The investigations required to make a diagnosis of unexplained infertility include ultrasound, ovulation confirmation, Hysterosalpingography for females and semen analysis for males.

All the patients were investigated for hormonal assay such as FSH, LH, S.Prolactin level, S. fasting insulin level, S.Testosterene level in some selective cases.

Points elaborated during history were, age, duration of infertility and any associated complained, regularity of menstrual cycle, husband occupation, and family history of infertility or late conception, history of trauma, surgery, cigarette smoking and alcohol habitual. Physical examination included systemic review, abdominal, local pelvic examination and vaginal examination to know the position of uterus and other pelvic pathology, vaginal discharge and tenderness in fornices.

All the women of unexplained infertility received clomiphene citrate from 2nd to 6th day, with starting dose 50 mg increase up to 200mg. U/S was advised from day 12-14 depend upon the length of menstrual cycle. Once leading follicle reached a diameter of 18mm the ovulation was induced with injection of HCG 10,000 international units.

TABLE NO. 1 AGE OF PATIENTS

NO: PATIENTS	AGE OF PATIENTS
10	22 Years
5	28 Years
7	25 Years
3	20 Years

TABLE NO. 2 DURATION OF INFERTILITY

NO: Patients	DURATION
12	15 Years
3	3-10 Years
4	3 Years
4	8 Years
2	12 Years

TABLE NO. 3 TOTAL NUMBER OF PATIENTS (n=60)

No: OF Patients	Results
28 (46.66%)	None Cooperation Defaulter (withdraw treatment)
25 (41.66%)	Conceived
7 (11.66%)	Not conceived

TABLE NO. 4 CONCEPTION RATE

NO: OF PATIENTS	COURSE OF CC
12 (48%)	1ST: Course
8 (32%)	2nd Course
2 (8%)	4th Course
3 (12%)	6th Course

Inclusion Criteria

1: Normal Semen analysis in male partner
2: Normal ovulation assessment.
3: Normal Hysterosalpingography in female partner.

Exclusion Criteria

1: Tubal diseases in females
2: Semen abnormalities in males.
3: Ovulation disorders in females.

RESULTS:

From August 2008 to July 2009, one year study at SZWH Gynae & Obs: Unit-II CMCH Larkana. During this time 150 cases of infertility were found. Of these 60 (40%) were with unexplained infertility.

Among 60 patients of unexplained infertility, 28 (46.66%) were not Co-operative. 7(11.66%) were not conceived and 25 (41.66%) were conceived. Of these patients 12 (48%) conceived with 1st: course of clomiphene citrate (cc), 08 (32%) conceived with 2nd course, 02 (8%) conceived with

4th course and 03 (12%) conceived with 6th course. In our study, most common age group is between 22-25 years. The duration of infertility in patients were as follows, 12 patients have 15 years, followed by 3-8 years duration. The results of clomiphene citrate (CC), was pronounced with first dose conception rate was 12 (48%), followed by with 2nd dose of CC ,conception rate was 8(32%) and with 4th dose & 6th dose ,conception rate was 2(8%) ,3(12%) respectively.

DISCUSSION:

At the present time it is estimated that one in 10 couples are infertile and unexplained infertility constitutes approximately 15% in these cases.

At our clinic we carry out ovarian hyperstimulation with clomiphene citrate or gonadotrophin to induce ovulation. We are referring the cases to specific infertility clinics when women had not conceived after controlled ovarian stimulation when necessary.

At our areas no other facilities available such as IUI, IVF & ICSI.

Patients with unexplained infertility, clomiphene citrate used as initial therapy for ovarian stimulation because of relative economic price, safety and easy of administration.

Maximum number of the patients in this study was found between 20-25 years of age. Treatment of unexplained infertility as empiric. CC was used alone from day 2-6 with starting dose 50 mg to 200mg for 6 cycles. In our study 25 (41.66%) women concieved with induction of ovulation.

A systemic review and meta- analysis for randomized controlled trial comparing the aromatase inhibitors versus clomiphene citrate to estimate live pregnancy rates in women with unexplained infertility. No difference was observed for live pregnancy (pooled or 0.87, 95% C, 0.46-1.65, P-0.666) for aromatase inhibitors versus clomiphene citrate[15].

A systemic review and Meta- analysis for randomized controlled trials concluded that, there does not appear to be clinical benefit to the use of clomiphene citrate for unexplained infertility, although the lack of homogeneity among the studies should be noted when making this treatment choice. Potential side effects should be discussed e.g. multiple pregnancies, minor symptoms and the use for more than 12 cycles has been associated with an increase risk of ovarian cancer[16].

The empiric use of Clomiphene citrate (CC) has been evaluated in various studies. These studies involved comparison of clomiphene citrate use with placebo. A consistent doubling of pregnancy rates is seen in patients with unexplained infertility when cc and HMG is used.

In a randomized trial comparing superovulated cycle and IUI with timed intercourse in women with unexplained infertility has determined that the pregnancy rates is higher with superovulated cycle and IUI 20% verses 11.4%[17].

In a meta- analysis of method use to treat unexplained infertility pregnancy rate with IUI alone was 3.8 %, clomiphene citrate and IUI 8.3% and gonadotrophin IUI (17.1 %) [18, 19].

The evidence of the effectiveness of clomiphene citrate, a meta- analysis by hughes *et al* (2000) has demonstrated clinically and statistically a significant benefit with clomiphene in comparison with placebo in couples with unexplained infertility. The combined odd ratio for clinical pregnancy per patient was shown to be 2.37 (95% CL 1.22- 4.62). Current NICE guidelines (NCCWCH 2004) suggest that women with unexplained infertility should be informed that clomiphene increases the chance of pregnancy but that it needs to be balanced by the possible risks of treatment especially multiple pregnancies, ovarian hyperstimulation, hot flushes and there is a putative link with ovarian cancer.

CONCLUSION:

Clomiphene citrate (CC) is a first line drug in women with ovulatory disorders and it is a primary treatment option in unexplained infertility. In the absence of specific diagnosis, any form of treatment for unexplained infertility is speculative .As clomiphene citrate is inexpensive so its use is more preferred as compared to other expensive treatment.

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