CLOMIPHENE CITRATE A MAJOR RISK FACTOR OF MULTIPLE PREGNANCY IN PATIENTS ADMITTED AT KHYBER TEACHING HOSPITAL, PESHAWAR

Naila Bukhari[1], Gul Hassan[2], Umair Wadood[2], Suleman[3]

ABSTRACT

Objective: To find the role of clomiphene citrate as a major risk factor of multiple pregnancy.

Background: Clomiphene citrate is the main drug used to induce ovulation in our set up. Beside other side effects, the risk of multiple birth is significant with its use. This study was designed to asses the role of clomiphene citrate as a major etiological agent of multiple pregnancy in our patients.

Material and Methods: This was a descriptive, cross sectional study which continued from may 2013 to August 2014. All patient with multiple pregnancy reporting to Gynae Department of Khyber Teaching Hospital were assessed for different risk factors of multiple pregnancy. The diagnosis was made by clinical assessment and ultrasound findings. Patients were interviewed for clomiphenc citrate use i.e, dose, and duration especially.

Results: The patients ages ranged from 20-45 years. Most cases 48 (98%) were twin pregnancy while one patient (2%) was found with triplet pregnancy. Clomiptiene citrate was found as etiological agent in most cases 58% (29 patients). Most of the patients (88%) used low doses 50 mg daily, while 100 mg dose was needed in some cases (10%) for conception. Higher does i.e 150 mg daily, was needed rarely (1%).

Conclusion: Clomiphene citrate is a major etiological agent of multiple pregnancy. Its used should be monitored effectively by our gynecologist to decrease the risk of multiple pregnancy in our patients.

Key words: Clomiphene citrate, ovulation induction, twin pregnancy.

INTRODUCTION

Clomiphene citrate is a nonsteriodal estrogen antagonist that increases FSH and LH levels by blocking estrogen negative feed back at the hypothalamus[1]. It stimulates ovulation in women with oligomenorrhoea or amenorrhea and ovulatory dysfunction. Clomiphe-citrate is used in the treatment of disorders of ovulation in patients who wish to conceive[2]. Ovulation induction occurs in 80% of women, and pregnancy occurs only in about 40% of cases[3].

In our community the main drug used to induce ovulation is clomiphene citrate. It is cheap, easy to use and has few significant adverse effects[4]. The adverse effects are dose related and include ovarian enlargement, vasomotor flushes and visual disorders[5]. Multiple births occurred in 6% of women receiving clomiphene citrate[6] Ovarian hyperstimulation syndrome occurs in 1% of women taking clomiphene citrate[7] (0.9% in Pakistan[8]. Although this syndrone is rare but life threatening[9], and can be predicted by serum estradiol and ultrasound, findings[10].

Multiple pregnancy is a high risk pregnancy[11]. The risks include high rates of perinatal morbidity and mortality, preterm births, low birth weight, gestational hyperteasion and plancenta previa[12], which puts a significant burden on our limited health resources. This results in a hidden healthcare cost of infertility therapy and may lead to social and political concerns[13]. The rational of this study was to find out the role of clomiphene citrate in multiple pregnancy in our setup. The results of this study will help our gynaecologist and obstetricians to provide effective follow up to the patients using clomiphene citrate as infertility treatment.

MATERIAL AND METHODS

The study continued from may 2013 to August 2014. All patients with multiple pregnancy reporting to antenatal clinic or labour room of gynae department of Khyber Teaching Hospital Peshawar were included in the study. The study was reviewed by the Ethical Committee, and formal consent was obtained. 50 Such case were studied. The diagnosis of multiple pregnancy was made by the history, clinical assessment and ultrasound findings. The singleton pregnancy cases were excluded from the study. In case of induced conception, a detailed history of infertility treatment was obtained. The dose

[1] Department of Gynaecology, KTH Peshawar
[2] Department of Pharmacology, Gandhara University, Peshawar
[3] Department of Medicine, Gandhara University, Peshawar

Address for correspondence:
Dr. Naila Bukhari
Senior Registrar Gynae B Unit, KTH Peshawar
Cell: 0321-9071768
E-mail: gulhassan74@hotmail.com

and duration of treatment with clomiphene citrate were also recorded-All these information along with personal biodata (name, age, address etc) were entered into a proforma and was processed by computer program SPSS version 11.

RESULTS

The study continued from may 2013 to August 2014. Results of 50 patients were obtained and analyzed which are summarized as under.

The patients ages ranged from 20-45 years. Majority 30(60%) patients were aged 30 year and above while 20(40%) patients were aged 30 year and below. The mean age was 30.68±06.50. Only one patient was above 40 years.

The ethnic group (Asian) was present in all our patients. Almost all (98%) of our patients were having twin pregnancy while only one (2%) patient had triplet pregnancy No quadruplet pregnancy was found.

The mode of conception was ovulation indiction in most cases (58%). All of our patients used clomiphene citrate for conception. Different doses of clomophene citrate were found. Most patients 44(88%) conceived with low dose of clomiphene i.e 50mg daily. Higher doses of clomiphene were required in only few cases. i.e 10% of patients used 100 mg of clomphene citrate daily while only one patient (2%) needed 150mg daily dose for conception to achieve. Thus beside offer risk factors, clomiphene citrate was found to be a major risk for multiple pregnancy.

DISCUSSION

Clomiphene citrate is a nonsteroidal estrogen antagonist that increases FSH and LH levels by blocking estrogen negative feedback at the hypothalamus level[9,10]. Stimulation of ovarian follicular development is, at present the most widely used therapeutic modality for treatment of the infertile couple and ovulation induction has becomes one of the most successful areas for the practicing reproductive endocrinologists. This practice however increases the number of women exposed to the possibility of iatrogenic multiple pregnancies.

Table No. 1: Dosages of Clomiphene citrate in patients (n=50)

Brand and Dosage	No. of Cases	Percentage
Clomiphene 50mg	44	88%
Clomiphene 100mg	05	10%
Clomiphene 150mg	01	02%
TOTAL	50	100%

Table No 2: Number of Fetuses in patients (n=50)

Fetuses	No. of Cases	Percentage
Twin	49	98%
Triplet	01	02%
Total	50	100%

Clomiphene citrate does ranged from 50-150mg per day. Almost 75% patients with an ovulation are treated successfully with CC in doses of 50-150 mg[14]. Efficacy of doses above 100mg per day is questionable[15]. In our study 88% patient used 50mg/day which 10% needed 100mg clomiphene citrate. Only 2 % used 150mg/day (Table 1).

We found multiple pregnancy in younger age group i.e. 58% between 30 and 35 years while 21% between 36 and 40 years. The reason was the use of ovulation inducing drugs by the younger women.

In our patients, the only drug used to induce ovulation was clomiphene citrate. Other drugs like bromocriptine, metformin and injectable gonadotrophins were not used by any of our patients and so risk of multiple pregnancies with these drugs could not be studied. These drugs have non tolerable side effects for example the frequent side effect of bromocriptine in nausea and vomiting which results in non compliance of this drugs. Also injectable gonadotrophins like follicle stimulation hormone (FSH) is more expensive than clomiphene citrate. Intramuscular injections to induce ovulation is an expensive treatment in our setup. Similarly taking a clomiphene citrate once or twice daily is more convenient for our patients. All these factors can explain the wide use of clomiphene citrate by our patients with induced multiple pregnancies. In this study 58% of women had multiple gestation as the result of ovulation induction with clomiphene citrate. This risk is comparable to the to the risk found in other studies in our country, like Mazhar SB[16] found it to be 55.5% while in another local study it was found to be somehow higher i.e. 83.3%[17].

The risk of multiple pregnancy is higher in our setup than reported in Western studies. This can be attributed to several factors. First no recent detailed data of risk factors of multiple pregnancy with ovulation inducation especially clomiphene citrate is available in Western studies where mostly ARTs with IUI with or without controlled ovarian hyperstimulation is the treatment widely offered to infertile women. Secondly in developed countries several measures are also considered to reduce the risk of multiple pregnancies with ovulation induction. In our set up lack of these facilities with lack of patients follow up result in high risk of multiple gestations. Also in our community the treatment of infertility is started at a higher maternal age. The infertile couples seek non medical remedies for long. Also due to literacy and social factors the stigma of infertility is kept secret for long. All these factors result in higher risk of multiple pregnancies with ovulation induction especially with clomiphene citrate.

CONCLUSIONS

From the results of study it is concluded that Multiple pregnancy is common in our setup. Among the several risk factors of multiple pregnancy, the most common risk factor found in our study was ovulation induction with Clomiphene citrate.

REFERENCES

1. Janet E.H. The Female Reproduction System: infertility and conception in. Fauci, Braunward, Kasper, Hauser, Longo Jameson, Loscalzo. Harrison,s Principles of Internal Medicine 17th Editions McGraw Hill 2008; 2324-34.
2. George P, Chrousos MD. The Gonadal Hormones and Inhibitors In. Bertram G, Katzung, Susan B. Masters AJ. Trevor. Basic and Clinical Pharmacology. 12th Edt. 2012; 715- 41.
3. Adam B. Polycystic Ovary Syndrome and Secondary Amenorohoea In. Keith E. Dewhurt,s Text book of Obstetrics and Gynecology 8th Ed 2012; Weley Black well; 514 – 33.
4. Ovulatory disorders in Siladitya B, Mark H. Management of Infertility 3rd Edit; 2013: 31-44
5. Karen W. Estrogens and Androgens In. Richard A, Harvey. Lippincott,s Illustrated Reviews Pharmacology 6th Edit 2015; 251 – 63
6. D. E. Newby, N.R Grubb, A Bradbury. Endocrine diseases in. Brain R. Walker NR. Colledge SH. Raiston ID, Penman. Davidson,s Principles and practice of Medicine. 22th Edt 2014; 733 – 96.
7. The menstrual cycle, menstrual disorders, infertility and the menopauses In Bavry OR, Cecilia B, Janice R. Essentials of Obstetrics and Gynecology 2nd Edit 2012 saunders Elsevier: 19 – 51
8. Kennedy R. Aetiology, prevention and treatment of ovarian hyperstimulation syndrome. In: Bonnar J, editor. Recent advances in obstetrics and gynecology-21. Edinburgh: Churchill Livingstone, 2001. p.123-40.
9. Siddiq S, Zaman F, Khan RL. Four years review of incidence and management of ovarian hyperstimulation syndrome in a specialized centre for reproductive medicine in Pakistan. Ann King Edward Med Coll 2002;8:63-5.
10. The practice committee of the American Society for reproductive medicine. Ovarian hyperstimulation syndrome. Fertil Steril 2008;90:S188-93.
11. Ogunnowo T, Olumole O, Aimaku CO, Lesannmi AO, Omigbobun AO. Term quadruplet pregnancy: a case report. NJ Surg Res 2004; 6: 56-8.
12. Allen VM, Weilson RD, Cheung A, Halifax NS. Pregnancy outcome after reproduction technology. Obstet Gynecol Can 2006;28:220-50.
13. Ombelet W, De Sutter P, Vander Elst J, Martens G. Multiple gestation and infertility treatment. Hum report Update 2005;11:3-14.
14. Imani B, Eijkemans MJ, Te Velde ER. A nomogram to predict the probability of live birth after clomiphene citrate induction of ovulation in normogonadotropic oligomenorrheic infertility. Fertil Steril 2002; 77: 91-7.
15. Duckey RP. Taylor SN, Curole DN et al. Relationship of clomiphene dose and patient,s weight to successful treantment. Hum Reprod 1997; 12: 449-53
16. Mazhar SB, Peerzada A, Mahmud G. Maternal an perinatal complications in multiple versus singleton pregnancies: a prospective two years study. J Pak Med Assoc 200l;52:143-7. patient's weight to successful treatment. Hum Reprod 1997;12:499-53.
17. Fahim F, Nisa M. Contribution of preterm delivery to perinatal mortality. J Postgrad Med Inst 2004; 18: 275-79.