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Determination of outcomes of pregnancy (in terms of miscarriages and multiple pregnancies) in primigravidas with successful ovulation induction

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ABSTRACT

Introduction: Regular ovulation is associated with regular menstruation. Women with irregular periods, occasional periods or no periods will often have an ovulation disorder. When a woman with an ovulation disorder is trying to conceive, she will usually require medication to induce normal follicle development and regular ovulation. For some women who already have regular menstrual cycles, e.g. in unexplained or poorly explained fertility, her fertility specialist may recommend ovulation induction medication in an attempt to increase the chance of pregnancy.

Objective: Objective of my study was to determine outcomes of pregnancy (in terms of miscarriages and multiple pregnancies) in primigravidas with successful ovulation induction

Study Design: Descriptive case study

Setting: This study was carried out in department of obstetrics and gynaecology of Nisthar Hospital Multan.

Duration of Study: This study was conducted from 1st September 2015 to 1st February 2016.

Subjects and methods: A total of 135 infertile women with successful ovulation induction at gestational age of 9 weeks were included in the study. Women conceiving after IUI or IVF, previous history of Diabetes in medical record, Medical history of Hypertension, heart diseases and malignancies were excluded. These studies cases were checked for any abortion and multiple pregnancies by ultrasound at gestational age of 9 weeks. These study cases was followed for four months for final outcome evaluation. All information was recorded.

Results: Age range in this study was from 25 to 35 years with mean age of 31.296±2.83 years and gestational age of 18.400±4.05. Multiple pregnancies was seen in 10(7.4%) patients. Spontaneous miscarriage was seen in 51(37.8%) patients.

Conclusion: It is concluded that patients taking ovulation induction has association with high multiple births miscarriages. Assisted reproduction techniques can largely benefit couples with

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infertility, but doctors must be aware of the possible consequences and medical risks of these procedures and consequently inform their patients properly. They should be cautious in prescribing drugs that induce ovulation, in spite of the heavy pressure exerted on them by the public.

Keywords:
Ovulation induction, Multiple pregnancies, Spontaneous miscarriage

INTRODUCTION

Regular ovulation is associated with regular menstruation. Women with irregular periods, occasional periods or no periods will often have an ovulation disorder [1, 2]. When a woman with an ovulation disorder is trying to conceive, she will usually require medication to induce normal follicle development and regular ovulation. For some women who already have regular menstrual cycles, e.g. in unexplained or poorly explained fertility, her fertility specialist may recommend ovulation induction medication in an attempt to increase the chance of pregnancy [3, 4].

Ovulation induction is the most natural and least invasive method. The administration of drugs that induce ovulation to treat infertile couples has become more frequent in the last decade. Medications used for final maturation and/or release of oocytes include hCG, GnRH agonist ,FSH injections [5, 6] . These work directly on the ovaries to develop a follicle(s). Rarely, an additional medication called luteinizing hormone (LH) is used to aid follicle development. After the follicle has developed the fertility specialist may use another injection of synthetic human chorionic gonadotrophin (hCG) to trigger the release of the egg from the follicle. The fertile time is for 36 hours from the time of trigger. Clomiphene or FSH may be used in conjunction with timed intercourse or intrauterine insemination (IUI) (which ensures that the sperm is introduced into the uterus at the right time) [7, 8].

Approximately 25% of infertile women have problems with ovulation. These include the inability to produce fully matured eggs or failure to “ovulate” (release) an egg. The inability to produce and/or release eggs is called anovulation. Fertility specialists use a group of medications, often called “fertility drugs,” to temporarily correct ovulatory problems and increase a woman’s chance for pregnancy. Fertility drugs may be used to correct other fertility problems such as improving the lining of the uterus (endometrium) in addition to inducing ovulation. In certain circumstances, these medications also may be used to stimulate the development of multiple eggs, such as in an in vitro fertilization (IVF) cycle. This booklet explains the basics of normal ovulation and the diagnosis and treatment of ovulatory problems. The specific uses for several types of ovulation drugs are presented, along with the intended results and possible side effects of each drug.

Ovulation can be detected and confirmed in several ways. A woman who menstruates consistently each month probably is also ovulating each month, with ovulation occurring about 14 days before the first day of each menstrual period. However, it is important to remember that a woman can have uterine bleeding even though she never ovulates. There are several ways to detect ovulation, including commercially available ovulation prediction kits that measure LH and basal body temperature (BBT) charts. Other diagnostic tests used to detect ovulation include measuring luteal

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phase serum progesterone levels, monitoring ovarian follicles with serial transvaginal ultrasounds, and endometrial biopsies.

Medications for inducing ovulation are used to treat women who ovulate irregularly. Women with irregular menstrual cycles (oligo-ovulatory) or absence of menstruation (amenorrhea) are likely to have ovulatory dysfunction. Prior to the administration of fertility drugs to induce ovulation, a diagnostic evaluation should be performed to try to determine the cause of ovulatory dysfunction. Women might not ovulate because of polycystic ovary syndrome (PCOS), insufficient production of LH and FSH by the pituitary, ovaries that do not respond well to normal levels of LH and FSH, thyroid disease, prolactin excess, obesity, eating disorders, or extreme weight loss or exercise. Sometimes the cause of anovulation cannot be identified confidently. Women with ovulatory dysfunction are the subgroup of infertile patients that is most likely to benefit from ovulation induction with fertility drugs. Clomiphene citrate is the most frequently used oral medication to stimulate ovulation in these patients with ovulatory dysfunction. Ovulation induction with fertility drugs is also commonly used in patients without ovulatory dysfunction to stimulate the ovaries to produce more than one mature follicle per cycle, leading to the release of multiple eggs. This controlled ovarian stimulation (COS), or superovulation, may be accomplished with either oral or injectable fertility medications. Superovulation, combined with either intercourse or intrauterine insemination (IUI), is an empiric strategy for the treatment of several forms of infertility. The intent is to develop several mature eggs in hopes that at least one egg will be fertilized and result in pregnancy. Controlled ovarian stimulation is also an important component of IVF treatment. Prior to ovulation induction with fertility drugs, it is recommended that a patient's fallopian tube patency be confirmed by hysterosalpingogram (injection of a dye into the fallopian tubes) or laparoscopy. Patients with blocked fallopian tubes will not become pregnant with fertility drugs and should not undergo ovulation induction unless the purpose of the ovulation induction is to stimulate the ovaries in preparation for IVF. Also the male partner should have a semen analysis to help guide whether ovulation induction should be combined with intercourse, IUI, or IVF. For more information on IVF, consult the ASRM patient information booklet titled, Assisted Reproductive Technologies.

The most commonly prescribed ovulation drug is clomiphene citrate (for brevity, this booklet will refer to clomiphene citrate as "CC" or "clomiphene"). This drug is most often used to stimulate ovulation in women who have infrequent or absent ovulation. It is also used in combination with IUI as an empiric treatment for unexplained infertility, and sometimes in those who are unable to pursue more aggressive therapies involving greater costs, risk, or logistical demands.

The standard dosage is 50 -100 milligrams (mg) of clomiphene per day for five consecutive days. Treatment begins early in the cycle, usually on the third to fifth day after menstruation begins. If a woman does not have periods, a period can be induced by administering oral progestin for 10 days.

Clomiphene works by causing the pituitary gland to secrete more FSH. The higher level of FSH stimulates the development of ovarian follicles that contain eggs. As the follicles grow, they secrete estrogen into the bloodstream. If treatment is successful, about a week after the last tablet of CC is taken, the pituitary is hypersensitive to GnRH and releases an LH surge. The LH surge causes the egg to be released from the mature follicle during ovulation. It is important to determine whether a given dosage of clomiphene results in ovulation. Most doctors rely on the menstrual pattern, ovulation prediction kits, measurement of serum progesterone levels or the basal body temperature chart to monitor a patient's response to the standard dose of clomiphene.

A basal body temperature chart is a chart in which the patient's temperature is taken upon awakening using a special thermometer, and this temperature is plotted every morning before she gets up. The

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readings help identify ovulation, which is indicated by a persistent temperature rise of one-half degree or more. If there is doubt, however, measuring the progesterone level about 14 to 18 days after the start of clomiphene, or examining the ovaries with ultrasound, can help to determine if and when ovulation occurred.

If ovulation does not occur at the 50-mg dosage, CC may be increased by 50-mg increments in subsequent cycles until ovulation is achieved. Exceeding a dosage of 200 mg each day for five days is rarely of any benefit, and patients who fail to ovulate on a clomiphene dosage of 200 mg are likely to benefit from a different ovulation induction regimen such as injections of gonadotropins. Your physician will determine the appropriate dose for you. Occasionally, the physician may choose to add other medications to clomiphene if the drug is not successful in inducing ovulation. The cervical mucus acts as a barrier to sperm. The properties of the cervical mucus may be altered in patients taking clomiphene citrate. Intrauterine insemination frequently is used in conjunction with clomiphene ovulation induction by CC. Clomiphene sometimes can alter endometrial thickness, making it thin and unreceptive to implantation. The lowest dose of clomiphene sufficient to induce ovulation in anovulatory women is usually prescribed for at least three cycles to provide an adequate trial for most patients. Clomiphene will induce ovulation in about 80% of properly selected patients. Most authorities suggest that clomiphene be given for no more than six cycles, because the chance of pregnancy is very low after six cycles. After that, alternatives may be considered.

Women who have irregular/absent ovulation due to hypothalamic disorders or very low estrogen levels generally do not respond well to clomiphene. Women who are obese may have better success after weight loss. Clomiphene is generally tolerated well. Side effects are relatively common, but generally mild. Hot flashes occur in about 10% of women taking clomiphene, and typically disappear soon after treatment ends. Mood swings, breast tenderness, and nausea are also common. Severe headaches or visual problems, such as blurred or double vision, are uncommon, and virtually always reversible. If these side effects occur, it is prudent to stop treatment immediately and call the physician. Women who conceive with clomiphene have approximately a 10% chance of having twins. Triplet and higher order pregnancies are rare (<1%), but may occur. Ovarian cysts, which can cause pelvic discomfort, may form as a result of ovarian overstimulation. A pelvic exam or ultrasound may be performed to look for ovarian cysts before beginning another clomiphene treatment cycle. Side effects are more frequent with higher doses.

Ovulation induction increases the risk of multiple births and it was found to be 9.7 % versus 69.8 % [9]. Miscarriage rate after ovulation induction was 27.5% whereas miscarriage rate after spontaneous conception was 13% according to a research published in 2014 by Adam H balen in Infertility and practice, fourth edition [10]. A study conducted by Chohan et al[11] reported 54.76 % ovulation induction, of which 35 % conceived and. Miscarriage rate was reported in 62.5 % of these study cases. [11-15]

This proposed study is planned to be conducted to document pregnancy outcomes in patients having assisted conception and natural conception. Chohan et al[16-19] conducted a study with ovulation induction with only 46 cases, sample size was small to generalize on our large population. This study is being carried out with larger sample size and hence results of this study will be more acceptable. The results of this study will generate useful baseline database of our local population which will be compared with the already available data from other parts of the world. This study will provide better statistics regarding pregnancy outcomes with ovulation induction in terms of miscarriages and multiple pregnancies which will help clinicians to pre-empt these outcomes and

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will lead to proper management. The results will form the basis for more studies in this area, once baseline data is available from our population.

MATERIALS AND METHODS:
Settings: Gynae unit 3, Nishtar hospital Multan
Study design: Descriptive Case Series

Sample size:
A sample size of 135 primigravidas calculated on following basis p=9.7%(multiple pregnancy)[9]
95% confidence interval
Margin of error 5%
Duration of study: This study was conducted from 1st September 2015 to 1st February 2016.
Sampling technique: non-probability consecutive sampling.
Inclusion criteria:

- Infertile women of age group of 25-35 years with successful ovulation induction at gestational age of 9 weeks.

Exclusion criteria:

- Women conceiving after IUI or IVF.
- Those with previous history of Diabetes in medical record.
- Medical history of Hypertension, heart diseases and malignancies.
- Those who do not give consent of participation.

DATA COLLECTION PROCEDURE:
Patients conceiving spontaneously and those conceiving after ovulation induction fulfilling the criteria was selected from outpatient department of gynae unit 3, nishtar hospital Multan. Proper permission was taken from institutional ethical committee to conduct this study. Informed consent was taken from each patient/attendant, describing them objectives of this study, ensuring them confidentiality of the information provided and fact that there is no risk involved to the patient while taking part in this study. These studies case was checked for any abortion and multiple

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pregnancies by ultrasound at gestational age of 9 weeks. These study cases was followed for four months for final outcome evaluation. All information was recorded in specially designed Proforma (attached).

DATA ANALYSIS PROCEDURE:

Data was entered and analyzed using computer program SPSS-I8. Descriptive statistics was applied to calculate mean and standard deviation for the age of patients and gestational age. Frequencies and percentages was calculated for miscarriages and multiple pregnancies. Effect modifiers like age, gestational age, compliance with medication, dosage of medicine, short inter-pregnancy intervals, previous history of miscarriages and family history of twins was controlled by stratification. Post-stratification chi-square test was applied to see their effect on outcome. P value equal to or less than 0.05 was considered as significant.

RESULTS

Age range in this study was from 25 to 35 years with mean age of 31.296±2.83 years and gestational age of 18.400±4.05 as shown in Table I. Multiple pregnancies was seen in 10(7.4%) patients as shown in Table-II. Spontaneous miscarriage was seen in 51(37.8%) patients as shown in Table-III.

Table-I: Mean ± SD of Demographics
n=135

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Demographics		Mean ± SD
	Age	31.296±2.83
	Gestational Age	18.400±4.05

Table- II: %age of Multiple pregnancies in Patients

Multiple pregnancies		No. of Patients	%age
	Yes	10	7.4%
	No	125	92.6%
	Total	135	100%

Table-III : %age of Spontaneous miscarriage in Patients

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Spontaneous miscarriage		No. of Patients	%age
	Yes	51	37.8%
	No	84	62.2%
	Total	135	100%

Stratification of multiple pregnancy and spontaneous miscarriage with respect to age, gestational age, compliance with medication, dosage of medicine, short inter-pregnancy intervals, previous history of miscarriages and family history of twins are shown in Table-IV, V, VI, VII, VIII, IX, X, XI, XII, XIII, XIV, XV, XVI and XVII respectively.

Table- IV: Stratification of Multiple pregnancies with respect to age groups

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	Multiple pregnancies		
Age Groups(years)	Yes	No	P value
25-30	6(10.9%)	49(89.1%)	0.198
31-35	4(5%)	76(95%)	
Total	10(7.4%)	125(92.6%)	

Table- V: Stratification of Multiple pregnancies with respect to Gestational age groups

	Multiple pregnancies		
Gestational Age Groups(weeks)	Yes	No	P value
9-20	6(6.3%)	89(93.7%)	0.455
>20	4(10%)	36(90%)	
Total	10(7.4%)	125(92.6%)	

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Table- VI: Stratification of Multiple pregnancies with respect to Compliance with Medicine

	Multiple pregnancies		
Compliance with Medicine	Yes	No	P value
Yes	6(5.4%)	105(94.6%)	0.056
No	4(16.7%)	20(83.3%)	
Total	10(7.4%)	125(92.6%)	

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Table- VII: Stratification of Multiple pregnancies with respect to Dosage of Medicine

	Multiple pregnancies		
Dosage of Medicine	Yes	No	P value
50	0(0%)	6(100%)	0.000
100	0(0%)	87(100%)	
150	10(23.8%)	32(76.2%)	
Total	10(7.4%)	125(92.6%)	

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Table- VIII: Stratification of Multiple pregnancies with respect to Short Interpregnancy interval

	Multiple pregnancies		
Short Interpregnancy interval	Yes	No	P value
Yes	3(6.7%)	42(93.3%)	0.816
No	7(7.8%)	83(92.2%)	
Total	10(7.4%)	125(92.6%)	

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Table- IX: Stratification of Multiple pregnancies with respect to History of Miscarriage

		Multiple pregnancies		
History of Miscarriage		Yes	No	P value
	Yes	4(8.3%)	44(91.7%)	0.760
	No	6(6.9%)	81(93.1%)	
Total		10(7.4%)	125(92.6%)	

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Table- X: Stratification of Multiple pregnancies with respect to Family History of Twins

	Multiple pregnancies		
Family History of Twins	Yes	No	P value
Yes	5(15.2%)	28(84.8%)	0.051
No	5(4.9%)	97(95.1%)	
Total	10(7.4%)	125(92.6%)	

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Table- XI: Stratification of spontaneous miscarriage with respect to age groups

	Spontaneous miscarriage		
Age Groups(years)	Yes	No	P value
25-30	21(38.2%)	34(61.8%)	0.936
31-35	30(37.5%)	50(62.5%)	
Total	51(37.8%)	84(62.2%)	

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Table- XII: Stratification of spontaneous miscarriage with respect to Gestational age groups

	Spontaneous miscarriage		
Gestational Age Groups(weeks)	Yes	No	P value
9-20	51(52%)	47(48%)	0.000
>20	0(0%)	50(62.5%)	
Total	51(37.8%)	84(62.2%)	

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Table- XIII: Stratification of spontaneous miscarriage with respect to Compliance with Medicine

	Spontaneous miscarriage		
Compliance with Medicine	Yes	No	P value
Yes	40(36%)	71(64%)	0.369
No	11(45.8%)	13(54.2%)	
Total	51(37.8%)	84(62.2%)	

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Table- XIV: Stratification of spontaneous miscarriage with respect to Dosage of Medicine

	Spontaneous miscarriage		
Dosage of Medicine	Yes	No	P value
50	2(33.3%)	4(66.7%)	0.731
100	35(40.2%)	52(59.8%)	
150	14(33.3%)	28(66.7%)	
Total	51(37.8%)	84(62.2%)	

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Table- XV: Stratification of spontaneous miscarriage with respect to Short Interpregnancy Interval

	Spontaneous miscarriage		
Short Interpregnancy Interval	Yes	No	P value
Yes	19(42.2%)	26(57.8%)	0.451
No	32(35.6%)	58(64.4%)	
Total	51(37.8%)	84(62.2%)	

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Table- XVI: Stratification of spontaneous miscarriage with respect to History of Miscarriage

	Spontaneous miscarriage		
History of Miscarriage	Yes	No	P value
Yes	33(68.8%)	15(31.2%)	0.000
No	18(20.7%)	69(79.3%)	
Total	51(37.8%)	84(62.2%)	

Table- XVII: Stratification of spontaneous miscarriage with respect to Family History of Twins

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		Spontaneous miscarriage		
Family History of Twins		Yes	No	P value
	Yes	14(42.4%)	19(57.6%)	0.526
	No	37(36.3%)	65(63.7%)	
Total		51(37.8%)	84(62.2%)	

Discussion:

This study confirms that the risk of multiple births increases when drugs that induce ovulation are administered to the mother. This is the first report presenting such results in our general population and can be regarded as a picture of the present situation in that country. Other papers have also reported an association between the use of ovulation induction and an increased risk of multiple pregnancies (mainly dizygotic and polyzygotic); the more and more frequent use of ovulation induction therapies in the last decade has been considered responsible for the sharp increase in the rate of twin or higher order births observed in some countries. Although an increased prevalence of congenital malformations associated with the use of assisted conception has been suggested in some reports,[21] neither an increased incidence of aneuploidy in oocytes after the administration of drugs that induce ovulation nor an increased prevalence of major birth defects after assisted reproduction in large-scale studies has been demonstrated so far.

Data about zygosity were not directly available in our study, but we could separately analyze the unlike-sexed multiple births. The estimate of the relative risk obtained in such a way applies to all dizygotic and polyzygotic births, owing to the case-control design employed.[22] The effect of ovulation induction was not separately assessed in the like-sexed multiple births because these included both monozygotic and dizygotic births, whose biology, epidemiology, and risk factors differ in many respects[23.] Therefore, in no way could the results be applied to monozygotic multiple

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births only.The odds ratios for unlike-sexed twin births appeared to be higher than those found for all twin births. The overall proportion of twin births attributable to the use of drugs for ovulation induction, alone or in conjunction with assisted reproduction. These values can be considered too small to have produced a visible increase in the rate of twin births over time, but they might have balanced a small natural decrease during the 1980s [24]. The increase in the rate of multiple pregnancies is of great concern from a public health perspective because if the trend continues, the rate of very-low birth weight infants in the population will doubtless rise. These infants are at high risk of mortality, morbidity, and adverse long-term outcome"[182] and represent a heavy burden, both emotional-psychological and financial, for their families and society [25].

CONCLUSION

It is concluded that patients taking ovulation induction has association with high multiple births miscarriages. Assisted reproduction techniques can largely benefit couples with infertility, but doctors must be aware of the possible consequences and medical risks of these procedures and consequently inform their patients properly. They should be cautious in prescribing drugs that induce ovulation, in spite of the heavy pressure exerted on them by the public.

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