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A Descriptive clinical study on Placenta Praevia at a tertiary care hospital

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Abstract
Aetiology of placenta praevia is obscure. It is caused by low implantation of the blastocyst at a site low in uterine cavity. The cause of low implantation is unknown, but certain factors are known to predispose to development of placenta praevia. All patients who came with history of painless bleeding per vagina after 28 weeks of gestation were hospitalized. A thorough history of vaginal bleeding (warning haemorrhage) was taken .Cases with confirmed diagnosis of placenta praevia on ultrasonography were included in the study. Placental anomalies were present in 4 (4.76 percent) cases, out of which, 2 cases (2.38 percent) were of adherent placenta. Placenta was removed in piece meal and PPH was controlled by bimanual compression and injection prostodin and methergin.

Keywords: Placenta Praevia, Warning Haemorrhage, Painless Bleeding

Introduction
At full term, the placenta has a discoid shape, a diameter of 15-25 cm, is approximately 3cm thick, and has a weight of about 500-600gm. At birth, it is torn from the uterine wall and approximately 30 minutes after birth of the child, is expelled from the uterine cavity. When, after birth, the placenta is viewed from the maternal side, 15-20 slightly bulging areas, the cotyledons, covered by a thin layer of decidua basal is are clearly recognizable. Grooves between the cotyledon are formed by decidual septa. Much of the decidua remains temporarily in the uterus and is expelled with subsequent uterine bleeds [1, 2].

The fetal surface of the placenta is covered entirely by the chorionic plate. A number of large arteries and veins, the chorionic vessels, converge toward the umbilical cord. The chorion in turn, is covered by the amnion. Attachment of the umbilical cord is usually eccentric and occasionally even marginal. Rarely, however it does insert into the chorionic membranes outside the placenta [3, 4].

Aetiology of placenta praevia is obscure. It is caused by low implantation of the blastocyst at a site low in uterine cavity. The cause of low implantation is unknown, but certain factors are known to predispose to development of placenta praevia. Two forms of implantation have been described, (a) primary is thmial implantation (b) secondary is thmial implantation. Cases of cervical pregnancies were reported.

The fertilized ovum drops down and is implanted in LUS, Poor decidual reaction in UUS or a delayed implantation maybe the cause. Defective decidua and multiple pregnancy, with large placental surface predisposes to lower implantation. Incidence of recurrence is 12 fold according to Eastman [5, 6].

Methodology:
During this study period 8633 cases were delivered. Among these 84 cases were identified as having placenta praevia.

All patients who came with history of painless bleeding per vagina after 28 weeks of gestation were hospitalized. A thorough history of vaginal bleeding (warning haemorrhage) was taken. Cases with confirmed diagnosis of placenta praevia on ultrasonography were included in the study. If patients had come in emergency without USG, diagnosis of placenta praevia was confirmed by per vaginal examination or examination of the placenta after the delivery, were included in the study. Cases which presented below 28 weeks of gestation, with confirmed diagnosis of abruptio placenta or local lesions of vagina and cervix or patients in preterm labour

without confirmed placenta praevia were excluded from the study.

Those cases who came with history of painless bleeding per vagina or warning haemorrhage after 28 weeks of gestation were admitted in the hospital. USG was done, if found to be placenta praevia, with live premature fetus, haemodynamically stable, with no or minimal bleeding and not in established labour were managed expectantly with tocolytics, antibiotics, steroids and bed rest. Anaemia was defined as haemoglobin< 10gm% or haematocrit <30%. If found to be anaemic, depending on the degree of anaemia, correction was done with either blood transfusion or parenteral iron therapy. This expectant management was continued till term or maturity of fetus and later taken for elective C/S. If patient develops severe bout of bleeding then emergency C/S was done irrespective of the maturity. Occassionally if patient is in established labour, with minimal bleed, good general condition and minor degree of placenta praevia, vaginal delivery was allowed.

If the patient is admitted in emergency with severe painless bleeding per vaginum without any previous USG, and is in shock, resuscitative measures were carried out in the form of IV fluids, blood transfusion and antibiotics. Vaginal examination was done in a "double set up" condition, if turns out as placenta praevia, then emergency C/S was done. Placenta was examined to confirm the diagnosis whether delivered vaginally or by C/S.

Results

Table 1: Ultrasound in Placenta Praevia

USG	No. of cases	Percentage
Done	52	61.90
Not done	32	38.10
Total	84	100

The above table shows that, only in 52 (61.90 percent) cases USG was done before delivery and placenta praevia confirmed. In the remaining 32 (38.10 percent) placenta praevia was confirmed either by PV examination or during C/S or by retrospective inspection of placenta after delivery.

Table 2: Sensitivity and specificity of USG in Placenta Praevia

Ultrasound	No. of cases	Percentage
Done	52	61.90
False positive	0	--
False negative	2	3.85

The above table shows, out of 52 cases of USG done placenta praevia was not diagnosed in 2 cases giving false negative rate of 3.85 percent.

USG is a quick, safe and accurate mode of localizing placenta and also the fetal well-being. It has greatly influenced the management of placenta praevia and also the maternal and perinatal outcome [6].

Table 3: APGAR score in placenta praevia

Sl. No.	APGAR	No. of babies	Percentage
1	Good	35	41.67
2	Poor	20	23.81
3	Absent	29	34.52
Total		84	100

The above table shows that out of 84 babies, 35 (41.67 percent) babies were born with good APGAR score. 29 (34.52 percent) babies did not show any sign of life and the remaining 20 (23.81 percent) were born with poor APGAR, out of which 11 survived till 8th postoperative day and 9 died by 4th postnatal day.

Table 4: Placental Anomalies in Placenta praevia

Sl. No.	Placenta anomaly	Number of cases	Percentage
1.	Adherent placenta	2	2.38
2.	Placenta increate	1	1.19
3.	Succenturate lobe	1	1.19
Total		4	4.76

The above table shows that placental anomalies were present in 4 (4.76 percent) cases, out of which, 2 cases (2.38 percent) were of adherent placenta. Placenta was removed in piece meal and PPH was controlled by bimanual compression and injection prostodin and methergin.

In 1 case (1.19 percent), placenta was adherent to posterior wall of the bladder wall, subtotal hysterectomy was done. In 1 (1.19 percent) case succenturate lobe was found in the LUS. Placental pathologies are known to be associated and hence increase the incidence of placenta praevia**.**

Discussion

Placenta praevia has a classic presentation of painless vaginal bleeding. Pain may be a feature of the initial presentation and suggests the possibility of concurrent placental abruption or the onset of painful contraction. The degree of bleeding is variable from slight spotting of fresh blood to a torrential haemorrhage. However, the first warning bleed from placenta praevia is rarely severe and delivery may be safely delayed for a period of time in most cases.

The management of a women with bleeding from a placenta praevia will depend on 2 main factors. The degree of haemorrhage and the fetal maturity at the time of haemorrhage. Absolute indications for delivery include, bleeding of any type at fetal maturity, fetal distress at viable gestations and persistant haemorrhage causing maternal haemodynamic instability at any stage in pregnancy [7].

Initial management involves rapid assessment of maternal cardiovascular status and the rate of continuing blood loss, followed by fetal assessment. IV access with a 16 Guage cannula should be established in all women, regardless of the degree of bleeding or vital observations. Baseline investigations, including haemoglobin estimation, blood cross matching and in women with heavy bleeding, clotting studies are indicated. Fluid replacement with crystalloid is appropriate initially; this may be supplemented with a calcified in the presence of heavier blood loss. In women requiring delivery because of heavy bleeding, transfusion of cross matched blood should begin as soon as possible, because further severe haemorrhage at the time of C/S is likely [8].

Transfusion to maintain maternal haemoglobin levels is also essential in women with active bleeding in whom immediate delivery is not considered necessary, because of the risk of heavier bleeding, concerns regarding the transmission of human immuno deficiency virus (HIV) have resulted in more conservative transfusion policies in obstetrics. The risk of transmission has been estimated as 1 in 1,53,000 and is in this situation vastly outweighed by the risk of serious morbidity secondary to further bleeding.

Fetal hypoxia related to a bleeding episode of placenta praevia is less common than that associated with placental abruption. Fetal distress may occur as a result of placental separation, developing fetal anaemia or labour. Monitoring of FHR should be

commenced at viable gestations and delivery to be undertaken if evidence of suspected fetal compromise develops [9].

Bleeding from placenta praevia is usually associated with uterine activity. A vicious cycle occurs where small changes in cervical effacement and dilatation, which occurs as a physiological phenomenon in many women in the third trimester, precipitate placental bleeding. This in turn stimulates the release of Prostaglandins from the lower segment decidua and thereby the onset of at contraction, which will aggravate the amount of bleeding by exerting further shearing forces on the placenta at the level of the cervix. The initial uterine activity is usually not perceived by woman herself.

Scanning technique used is important. Placenta in the mid trimester scan can be diagnosed as early as 9th week of Intra uterine life has a relatively homogenous parenchymal structure. The combined scanning technique, increases the echoes and improves the quality of image. In a typical longitudinal plane sonogram, placenta appears as semilunar areas with multiple echoes bordered on the maternal side by uterus and fetal side by chorionic plate. The lower pelvic brim is a line joining the pubic symphysis and sacrum arbitrarily [10].

Conclusion

Placental anomalies were present in 4 (4.76 percent) cases, out of which, 2 cases (2.38 percent) were of adherent placenta.

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PREDICTORS OF PREGNANCY IN WOMEN WITH POLYCYSTIC OVARY SYNDROME

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ABSTRACT

BACKGROUND

The most common cause of anovulatory infertility is Polycystic Ovary Syndrome. It affects approximately 6.6% of women who are reproductive aged.

The aim of the study was to clinically predict the parameters which result in live births in pregnant women with polycystic ovary syndrome.

MATERIALS AND METHODS

This was a double blinded, randomised clinical study. 500 infertile women patients with PCOS were divided into three groups namely Group A: (n=167) Placebo plus Clomiphene citrate, Group B (n=166) Placebo plus metformin and Group C: (n=167) Combination of Clomiphene citrate and Metformin.

RESULTS

Among the three groups, there was no significant difference in the baseline characteristics. In all three groups, baseline free androgen index, proinsulin levels, treatment interaction with body mass index, duration of conception were predictors significantly. A modified hirsutism score of less than 8 was also predictive in conception, live births and pregnancy. Age was another predictive factor in ovulation, age less than 34 was predictive factor in pregnancy and live births.

CONCLUSION

To counsel and select treatments for infertile women with PCOS, body mass index, proinsulin levels, hirsutism, duration of conception can be used as predictive factors.

KEYWORDS

Clomiphene Citrate, Metformin, Polycystic Ovary Syndrome.

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BACKGROUND

The most common cause of anovulatory infertility is Polycystic Ovary Syndrome. It affects approximately 6.6% of women who are reproductive aged.[1] Diagnostic criteria are signs of hyperandrogenism or biochemical hyperandrogenemia, irregularities of menstruation and sonographic evidence of polycystic ovaries. Women with PCOS are phenotypically diverse, glucose tolerance impairment and obesity are other manifestations. Restoration of ovulation is the first step in treating infertility and this doesn't guarantee a live birth. The reproductive issues with PCOS are many starting with anovulatory cycles leading to subfertility. The women with PCOS are at increased risk for early pregnancy loss post conception. After the first trimester, the women with PCOS suffer with gestational diabetes mellitus, pregnancy induced hypertension, preeclampsia, preterm delivery, small for gestational age infant birth.[2,3,4] For treatment of infertility, there is lack of recommendations, leading to expert opinions of small and poorly designed trials. Metformin alone is inferior to clomiphene citrate at achieving live births, although selective oestrogen receptor modulator clomiphene citrate and insulin sensitizer metformin are used for induction of ovulation. In counselling patients and planning infertility treatment, determining which baseline characteristics are associated with achieving a successful pregnancy and live birth after ovulation induction would be beneficial.[5,6] More aggressive treatments such as laparoscopic ovarian diathermy, exogenous gonadotropins, invitro fertilization should be employed to patients who have a low chance of success. Before attempting first line therapy, pretreatment should focus on improving BMI or hirsutism.

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MATERIALS AND METHODS

It is a randomized controlled infertility trial of 500 women with PCOS performed at academic health centers. Women patients with PCOS were divided into three groups namely Group A: (n=167) Placebo plus Clomiphene citrate, Group B (n=166) Placebo plus metformin and Group C: (n=167) Combination of Clomiphene citrate and Metformin. This was a double blinded, randomised clinical study which was

conducted from October 2014 to November 2016 in multicenters. Informed consent was obtained from all the patients and this study was approved by Institutional review board.

Inclusion Criteria

The patients with PCOS were oligomenorrhoea who had history of not more than eight spontaneous menses per year, and hyperandrogenemia which is elevated testosterone levels. 90% who had morphology of polycystic ovary, mean volume of each ovary should be 10 cm3 or more and it should have the ultrasound features of PCOS.

Exclusion Criteria

Congenitally adrenal hyperplasia, hyperprolactinemia, thyroid disease, premature ovarian failure, Cushing's syndrome and androgen secreting neoplasm.

Modified Ferriman Gallway score was used to measure midline, androgen dependent hair growth and hirsutism was also assessed. Other investigations like laboratory testing was performed after an overnight fasting and all blood samples were analysed under calibrated assays in laboratories, Patients were treated upto six cycles or 30 week. Metformin (500 mg tablets) 1-3 daily and CC (50 mg tablets) 1-3 daily depending on response of ovulation was administered. Progesterone was given weekly and ovulation was assessed and documented based on level of progesterone elevation. If pregnancy test was positive, all medications was stopped and a follow up was taken until the foetal viability was detected on ultrasound examination.

RESULTS

Out of 500 patients, the number of subjects in group A was 167, group B was 166 and group C was 167. Among the three groups, there was no significant difference in the baseline characteristics in the three arms.

Parameter	Group A	Group B	Group C	P Value
Age	28.9 ± 5.0	28.5 ± 5.0	28.6 ± 5.0	0.659
Weight(kg)	96.6 ± 25.4	91.5 ± 24.4	94.9 ± 24.9	0.058
BMI (kg/m^2)	35.9 ± 8.6	36.6 ± 8.1	34.1 ± 9.0	0.129
Waist Circumference (cm)	100.9 ± 22.9	103.5 ± 22.5	102.9 ± 20.4	0.135
Waist/Hip ratio	0.894 ± 0.098	0.854 ± 0.087	0.827 ± 0.099	0.110
Hirsutism score	14.1 ± 8.1	14.8 ± 8.9	14.2 ± 8.6	0.505
Length of conception	40.6 ± 36.1	41.8 ± 39.0	41.1 ± 35.0	0.352

Table 1. Shows Clinical Parameters 1

There were no statistically significant differences in the baseline characteristics among the treatment arms.

Parameter	Group A	Group B	Group C	P Value
Prior Conception	55/167	45/166	47/167	0.105
Prior pregnancy loss	43/167	30/166	44/167	0.238
Prior parity	60/167	55/166	59/167	0.538

Table 2. Shows Clinical Parameters 2

Parameter	Group A	Group B	Group C	P Value
Total testosterone	60.6 ± 30.5	60.5 ± 25.0	64.5 ± 24.6	0.258
Glucose (mg/dl)	88.6 ± 15.9	89.3 ± 17.6	88.2 ± 16.8	0.369
Insulin (µU/ml)	22.9 ± 21.5	22.7 ± 22.3	22.6 ± 22.9	0.639
Proinsulin (pmol/liter)	25.9 ± 20.9	26.3 ± 27.9	23.6 ± 23.7	0.117
White Blood Cells (10^3/µl)	7.1 ± 3.0	7.8 ± 4.2	7.6 ± 3.6	0.490

Table 3. Shows Baseline Laboratory Parameters

Effect	Ovulation	Conception	Pregnancy	Live birth
Baseline BMI ≥35 (kg/m^2)				
Group-A	1	1	1	1
Group-B	3.2 (2.20, 4.6)	6.3 (2.7, 14.9)	5.9 (2.3, 15.4)	5.22 (2.0, 13.7)
Group-C	5.1 (3.55, 7.40)	11.7 (4.9, 27.5)	11.5 (4.47, 29.5)	8.83 (3.41, 22.82)
Baseline BMI 30–34 (kg/m^2)				
Group-A	1	1	1	1
Group-B	2.02 (1.27, 3.28)	2.32 (0.94, 5.80)	1.62 (0.58, 4.49)	2.02 (0.71, 5.80)
Group-C	1.95 (1.17, 3.26)	2.56 (1.06, 6.16)	1.60 (0.62, 4.19)	1.95 (0.72, 5.40)
Baseline BMI <30 (kg/m^2)				
Group-A	1	1	1	1
Group-B	2.23 (1.40, 3.56)	2.38 (1.15, 4.95)	4.01 (1.72, 9.34)	5.96 (2.34, 15.1)
Group-C	3.77 (2.43, 5.83)	2.85 (1.41, 5.75)	4.52 (2.00, 10.23)	5.77 (2.32, 14.3)

Age (yrs.)				
>34	1	1	1	1
≤34	0.62 (0.42, 0.93)	2.05 (0.94, 4.43)	5.85 (1.68, 20.2)	5.04 (1.45, 17.51)
History of prior loss	1.72 (1.35, 2.16)	1. 50(1.05, 2.19)	N.A.	N.A.
Baseline proinsulin (pmol/liter)				
≥23 (reference)	1	1	1	1
<23	1.42 (1.13, 1.79)	1.56 (1.04, 2.25)	1.72 (1.09, 2.70)	1.71 (1.07, 2.74)
Baseline FAI				
≥10	1	1	1	1
<10	1.36 (1.10, 1.67)	1.95 (1.32, 2.87)	1.71 (1.32, 2.84)	1.53 (1.42, 3.10)
Hirsutism score				
≥16		1	1	1
8–15		1.28 (0.87, 1.89)	1.44 (0.94, 2.22)	1.40 (0.89, 2.18)
<8		1.70 (1.07, 2.69)	2.44 (1.48, 4.05)	2.51 (1.50, 4.17)
Duration of attempting conception				
≥1.5 yrs.	1	1	1	1
<1.5 yrs.	1.43 (1.15, 1.77)	1.77 (1.25, 2.51)	1.95 (1.34, 2.85)	2.12 (1.44, 3.12)

Table 4. Baseline Measurements

120 of 500 women conceived. As in the model of ovulation, success in the conception model was predicted by history of prior loss, baseline proinsulin level, baseline FAI, and duration of attempting conception. Although hirsutism was not predictive of ovulation, it was predictive of conception when comparing women with a normal score (<8) *vs.* hirsute women with a score of at least 16. There was interaction effect of treatment and BMI where Group-B and Group-C treatment was predictive of a higher chance of conception over metformin monotherapy for a given BMI category, except for the comparison of Group-B *vs.* Group-A therapy in the intermediate BMI group (30–34 kg/m^2) which was not statistically significant. Although age greater than 34 was predictive of ovulation, in the model for conception, women age 34 or younger had a higher, but nonsignificant, odds of conception over the older group.

There were 120 pregnancies, of which 115 resulted in a live birth. The predictive models for both pregnancy and live birth included baseline proinsulin level, baseline FAI, duration of attempting conception, and hirsutism score for the less than 8 *vs.* at least 16 groups. Age of 34 yrs. or less was predictive of a successful pregnancy as well as live birth. Again, there was significant interaction effect of treatment with BMI, where Group-A and Group-C were significantly more predictive of pregnancy and live birth in both the lowest and highest BMI categories (<30 kg/m^2 and ≥35 kg/m^2, respectively), with a trend toward greater pregnancy success in the intermediate category (BMI, 30–34 kg/m^2).

DISCUSSION

This study was done to predict successful ovulation, conception, pregnancy, and most importantly live birth in women with PCOS undergoing ovulation induction, we used these clinical data to predict live birth success. The factors that were persistently significant in treatment were baseline BMI, FAI, proinsulin level, and duration of attempting conception. Conversely, age greater than 34 yrs. was predictive only of successful ovulation. History of a prior pregnancy loss predicted only ovulation and conception, but not clinical pregnancy or live birth. The presence of hirsutism was noted to have an adverse prognosis when comparing both the extremes of less than 8 (nonhirsute) and 16 or greater (severely hirsute) for conception, pregnancy, and live birth, but not ovulation. These analyses further underscore the importance of following PCOS subjects participating in ovulation induction clinical trials until a live birth is achieved and not relying solely on ovulation as the primary end-point for such studies.

However, BMI should be considered both according to severity and in the context of other predictive factors when counseling patients about the likelihood of pregnancy. The usual clinical (and expert panel) advice for obese women with PCOS is to "lose weight". This recommendation must be tempered by the now known adverse effects of age and duration of infertility. Because for most patients it would take an extended period of time to change their BMI by the 5 or more units necessary to significantly improve their prognosis based on this model, it is possible that the delay may actually be counterproductive to the goal of achieving a successful pregnancy. In fact, we noted that there were some cases where a low BMI did not improve the estimated chance of live birth, such as in the case of overall very poor prognosis (0–10% estimated chance of live birth) in the metformin group, and in the case where all the other prognostic factors were poor (age >34 yrs. duration of attempting conception ≥1.5 yrs. and higher hirsutism scores) in the combined group. In all other scenarios, however, women with a BMI below 30 kg/m^2 had a better chance of success than obese women with a BMI of at least 35 kg/m^2.

A low hirsutism score was not predictive of ovulation success, but was significant in the models of conception, pregnancy, and live birth. In a population-based cohort, women with oligomenorrhoea and/or hirsutism had a higher risk of infertility and lower fecundity than asymptomatic women. Therefore, hirsutism may be a measurable bioassay for the extent and duration of androgen excess, reflecting similar changes in other androgen-responsive tissues, such as the ovary and endometrium. The following evidence suggests that intraovarian androgen excess may perturb oocyte development: 1) intrafollicular androstenedione and testosterone concentrations have been shown to be elevated in PCOS women after undergoing gonadotropin-stimulated

cycles, which has been inversely correlated with oocyte maturation and developmental potential; and 2) a low follicular estradiol/testosterone ratio is associated with decreased pregnancy potential. In addition, factors other than androgens, including an excess of insulin and other growth factors, contribute to the recruitment and terminal maturation of hair follicles in women with PCOS and may also contribute to the decreased pregnancy rates in hirsute women.

In one study from Italy evaluating 80 infertile anovulatory PCOS patients treated with either metformin or CC monotherapy, it was found that BMI was the strongest predictor of both ovulation and pregnancy in the metformin group, and baseline FAI was the strongest predictor in the CC arm.[7] In another study from Spain, predictors of pregnancy in 76 PCOS patients treated with CC or recombinant FSH were duration of infertility and use of FSH with 25 resultant pregnancies.[8] The best previous study to predict the chance for live birth, based on 259 women with oligomenorrhoeic infertility (most with PCOS) is from The Netherlands and used a two-part clinical nomogram with factors to predict ovulation, and then if ovulation occurred, factors to predict live birth.[9] These factors included FAI, BMI, cycle history, and age. With the exception of proinsulin, our results are similar, but our clinical predictive chart has the advantage that it is more user-friendly and uses information from the history and physical, easily obtained at the initial consult.

Many studies have been reported regarding the predictors of pregnancy in women with polycystic ovarian syndrome. Mary E Rausch et al[10] conducted a study which aimed to develop a clinically useful predictive model of live birth with varying ovulation induction methods. This study built four prognostic models from a large multicenter randomized controlled infertility trial of 626 women with PCOS performed at academic health centers in the United States to predict success of ovulation, conception, pregnancy, and live birth, evaluating the influence of patients' baseline characteristics. Ovulation was induced with clomiphene, metformin, or the combination of both for up to six cycles or conception. The primary outcome of the trial was the rate of live births. Baseline free androgen index, baseline proinsulin level, interaction of treatment arm with body mass index, and duration of attempting conception were significant predictors in all four models. Age was a divergent predictor based on outcome; age greater than 34 predicted ovulation, whereas age less than 35 was a predictive factor for a successful pregnancy and live birth. Smoking history had no predictive value. A live birth prediction chart developed from basic clinical parameters (body mass index, age, hirsutism score, and duration of attempting conception) may help physicians counsel and select infertility treatments for women with PCOS.

Imani B et al[9] conducted a study to establish whether initial screening characteristics of normogonadotropic anovulatory infertile women can aid in predicting live birth after induction of ovulation with clomiphene citrate (CC). It was a prospective longitudinal single-center study which was conducted in a specialist academic fertility unit. Two hundred fifty-nine couples with a history of infertility, oligomenorrhoea, and normal follicle-stimulating hormone (FSH) concentrations who have not been previously treated with any ovulation-induction medication. 50, 100, or 150 mg of oral CC per day, for 5 subsequent days per cycle. The main outcome measure was conception leading to live birth after CC administration. After receiving CC, 98 (38%) women conceived, leading to live birth. The cumulative live birth rate within 12 months was 42% for the total study population and 56% for the ovulatory women who had received CC. Factors predicting the chances for live birth included free androgen index (testosterone/sex hormone-binding globulin ratio), body mass index, cycle history (oligomenorrhoea versus amenorrhea), and the woman's age. It is possible to predict the individual chances of live birth after CC administration using two distinct prediction models combined in a nomogram. Applying this nomogram in the clinic may be a step forward in optimizing the decision-making process in the treatment of normogonadotropic anovulatory infertility. Alternative first line of treatment options could be considered for some women who have limited chances for success.

Lopez E et al[8] study on 66 infertile patients with PCOS were randomized to receive clomiphene citrate (50-150 mg/day for 5 days) (clomiphene citrate group, n = 38) or recombinant human FSH (FSH group, n = 38) in a chronic, low-dose, step-up protocol (daily starting dose 75 IU) for up to three consecutive cycles. Ovarian response was monitored by transvaginal ultrasonography and human chorionic gonadotrophin (HCG) was given to trigger ovulation in all cycles with appropriate follicular development. The primary outcome measure was cumulative pregnancy after undergoing up to three treatment cycles. Secondary outcomes were cycle cancellation rate, ovulation rate per cycle, cumulative ovulation rate, pregnancy rate per cycle, incidence of OHSS, cumulative live birth rate, and multiple birth rate. One hundred and four clomiphene citrate cycles and 91 FSH cycles were evaluable. The relative risk and its 95% confidence interval were 1.17 (0.97-1.46) for HCG cycles with ovulation, 1.78 (0.92-3.54) for the pregnancy rate per woman, and 1.83 (0.79-4.40) for live births per woman in favour of FSH. The cumulative pregnancy rate after three treatment cycles was 43% with FSH and 24% with clomiphene citrate (P = 0.06). This randomized controlled trial suggests that low-dose recombinant FSH may be an effective alternative to clomiphene citrate in first-line treatment for anovulatory PCOS patients.

M. Maliqueo et al[11] conducted a study on proinsulin and C peptide were determined at 0 and 30 min and the fasting proinsulin/insulin ratio (PI/I) was calculated. Insulin sensitivity was estimated by insulin sensitivity index (ISI) composite, and β cell function was estimated by insulinogenic index. Insulin, proinsulin and C-peptide concentrations were higher in women with PCOS than in NC women (P < 0.05). PI/I and insulinogenic index were similar in both groups. Proinsulin concentrations increased with

body mass index (P <0.05) only in women with PCOS; therefore, proinsulin concentrations were higher in obese PCOS patients compared with obese control women (P<0.05). Moreover, a positive association between proinsulin concentrations and waist diameter adjusted for C-peptide (P<0.05) and a negative association between proinsulin concentrations and ISI composite values were observed in PCOS patients (P <0.05). Data suggest that in PCOS patients an elevated proinsulin concentration could reflect insulin resistance more than β-cell dysfunction. However, the elevated concentration of proinsulin in these patients could also result from impaired β-cell function resulting from intraabdominal obesity independently of insulin resistance.

Elting MW et al[12] study interviewed 346 patients of 30 years and older, and excluded 141 from analysis mainly because of the use of oral contraceptives. The remaining 205 patients showed a highly significant linear trend (P <0.001) for a shorter menstrual cycle length with increasing age. Logistic regression analysis for body mass index, weight loss, hirsutism, previous treatment with clomiphene citrate or gonadotrophins, previous pregnancy, ethnic origin and smoking showed no influence on the effect of age on the regularity of the menstrual cycle.

CONCLUSION

We conclude that to counsel and select treatment for infertile women with PCOS; basic clinical and biochemical parameters (body mass index, proinsulin levels, hirsutism, and duration of conception) can be used as predictive factors.

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Original Research Article

Comparison of different ovulation protocols in patients undergoing controlled ovulation hyperstimulation with intra uterine insemination

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ABSTRACT

Background: For many couples' advent of a baby is the most beautiful gift of life. Involuntary childlessness by itself does not threaten physical health but can have a strong impact on the psychological and social wellbeing of couples. The aim of the present investigation was comparison of different ovulation protocols in patients undergoing controlled ovulation hyperstimulation with Intra uterine insemination.
Methods: A Prospective observational study was conducted in the department of obstetrics and gynaecology. 200 couples who underwent 541 cycles with controlled ovarian hyperstimulation. Variables selected for analysis were female age, menstrual history, duration of infertility, number of cycles, number dominant follicle diameter, endometrial thickness.
Results: Maximum patients underwent ovulation induction with clomiphene citrate (202/541) and then with letrozole (202/541).
Conclusions: Nowadays when the costs of health care are limited, intrauterine insemination can hold its place as a low-cost method of infertility treatment. Conclusively with careful selection of subjects, appropriate controlled ovarian stimulation and intra uterine insemination, good pregnancy rates with low multiple pregnancy rates can be achieved.

Keywords: Controlled ovulation hyper stimulation, Intra uterine insemination, Ovulation protocols

INTRODUCTION

For many couples' advent of a baby is the most beautiful gift of life. Involuntary childlessness by itself does not threaten physical health but can have a strong impact on the psychological and social well-being of couples. Infertility is defined as failure of a couple to conceive after one year of unprotected intercourse. Approximately 85%-90% couple conceive within one year. Infertility therefore affects 10-15% couples.[1,2]

Though prevalence of infertility has been stable, the demand for infertility cure has increased significantly over the past decade. Intra uterine insemination (IUI) is the first step in the ladder of fertility management in couples with no evidence of tubal damage or severe male factor.[3,4]

IUI with husband's sperm has been widely used for treatment of infertility with variety of indications, such as moderate male infertility, unexplained infertility, cervical mucus hostility and ovulatory disturbances.[5] The overall success of intra uterine insemination varies, with pregnancy rates between 5 and 26% per cycle.[6] IUI with controlled ovarian hyperstimulation is more effective than intra uterine insemination alone or intra cervical

insemination.[7] Ovarian stimulation has been shown to significantly improve the outcome in IUI cycles by two mechanisms; by increasing the number of eggs available for fertilisation and by overcoming a subtle defect in ovulatory function in ovulatory function and luteal phase.[8]

IUI is widely used for treating infertility in couples because it is simple, inexpensive. Ejaculated semen is a mixture of spermatozoa and seminal plasma, seminal plasma is constituted by secretions of epididymis, seminal vesical and prostate, semen may also contain other components like microorganisms and leucocytes. The main objective of semen preparation techniques is to harvest the most functional sperms from this ejaculate with minimal damage. Pregnancy outcomes after IUI are determined by a number of factors, these factors include the use ovulation induction protocols, patient age, duration of infertility and the type of infertility.[9,10]

So, the aim of the study is to compare different ovulation protocols in patients undergoing controlled ovulation hyper stimulation with Intra uterine insemination.

METHODS

This prospective observational study was conducted at Department of Obstetrics and Gynaecology. The study was approved by Ethics Committee. This study included 200 couples who underwent 541 intra uterine insemination cycles, with controlled ovarian hyper stimulation and who fulfil the inclusion and exclusion criteria. The duration of infertility was defined by the time interval from beginning of unprotected intercourse until registration at the fertility centre.

Detailed history of the couple include age, duration of infertility, regularity of periods, duration of contraception, sexual history, previous treatments if taken, occupation, family history. After obtaining history general physical and systemic examination was carried out. Per speculum examination was performed & Pap smear taken if indicated. Per vaginal examination was done. Abnormal findings noted. Semen analysis done for male partner as per WHO criteria.[8]

Inclusion criteria

- women of age less than 40
- negative pregnancy test
- patent fallopian tubes
- normal uterine cavity
- history of Infertility >1 year
- Men age <50, history of Infertility >1 year
- normal semen analysis.

Exclusion criteria

- women with previous IVF
- previous H/O PID
- previous IVF
- Men with previous H/O of intrauterine insemination.

Couple were requested not to have inter course for 3-5 days before the day of semen collection. Semen samples were produced by masturbation and collected in sterile containers. After complete liquefaction for 30 min samples were assessed according to WHO criteria.

After analysis, standard swim up technique was employed using Hams F-10 medium. Briefly, sample was centrifuged at 500 rpm for 15 min. The supernatant discarded, and the pellet diluted in 2.5 ml of medium and recentrifuged. After removing the supernatant, the final pellet was gently covered with medium and incubated for 1 hr at 37^0 C in an incubator.

Different methods of ovulatory stimulation in our study. Administration of Clomiphene citrate 100 mg daily from third day of patient's cycle up to five days (d3 d4 d5 d6 d7). Administration of Letrozole 2.5 mg from third day patient's cycle up to five days. Administration of Inj recombinant FSH 75 IU intramuscular alternately on three days, starting from third day of patient's cycle (d3 d5 d7) Administration of Tab Clomiphene citrate and Inj. recombinant FSH 75IU, Tab. Clomiphene citrate 100mg was administered orally from day 3 to day 7 and Inj recombinant FSH 75IU intra muscular injection of 75 mg from day 3 to days 7 on alternate days. Administration of Letrozole and Inj recombinant FSH 75IU. Tab Letrozole 2.5 mg. orally from d3 to d7 daily for 5 days and Inj recombinant FSH 75IU IM on alternative days from day 3 to day 7.

All patients were followed using vaginal ultrasound with Siemens sonoline Siena Ultra sound imaging system using 7.5 MHz vaginal probe. Folliculate diameters were calculated as a mean of the largest diameter and its perpendicular value. When they had at least one dominant follicle (>18 mm) 5000 units of human chorionic gonadotropin was injected intramuscularly and after 36 hrs, intra uterine insemination was done. Intra uterine insemination procedure. Patient is given lithotomy position. Vagina is cleaned with saline and cervical mucus is removed. Cervix is exposed using bivalve speculum.

IUI was performed using intra uterine insemination catheter with 2 ml syringe. The catheter was gently passed through cervical canal and the sperm suspension expelled into the uterine cavity. Insemination volumes ranged from 0.5ml to 1ml injected slowly over 1-2 minutes. Avoid any trauma to cervix or endometrium. The women remained supine for 10-15 minutes. Clinical pregnancy was defined as transvaginal ultrasonographic visualisation of intrauterine gestational sacs.

Data from 200 patients who attended the infertility clinic were included in this study. Variables selected for analysis were female age, menstrual history, duration of

infertility, number of cycles, number dominant follicle diameter, endometrial thickness.

Statistical analysis

All the continuous variables were represented by mean with standard deviation and it was analyzed by independent sample t-test. Categorical variables were presented by frequency and percentages; it was analyzed by Chi-square and Fisher exact test. Logistic regression analysis was used for multiple variable comparisons to pregnancy rate. All the analysis was done by using SPSS 14.0 version. A p value less than 0.05 was considered as significant.

RESULTS

A total of 541 IUI cycles in 200 women resulted in 65 pregnancies. The number of treatment cycles varied from 1 to 8 with a mean of 2.06±1.49 per couple. The average clinical pregnancy rate was 12% per cycle and the pregnancy rate was higher in first treatment cycle (66.77%) and decreased from second cycle onwards. The overall pregnancy rate was 33% per patient. The age range varied from 19-38 years and the average age was 29.08±4.19 years. The pregnancy rate in the age group <30 years was 33.04% in comparison to 31.76 in the age group more than 30 years (p=0.849), therefore the pregnancy rate and age of women are not statistically significant.

The pregnancy rate was 9.5% when one follicle was produced, whereas with more than 1 follicle, the rate increased to 18.1%. The pregnancy rate increased with the number of mature follicles upto 3, being significantly higher if more than one mature follicle developed and its statistically significant (p=<0.001). The mean number of follicles was 1.42±0.64.

In present study the size of the follicle is not a significant variable. This might be because most of the follicles are above 1.5cm. Insemination between day 10 and 14 resulted in a pregnancy rate of 9.9% compared to 20.4% if insemination was carried out between day 16 and 25 and it is statistically significant (p=0.003).

Among the different ovulation induction protocols maximum number of patients underwent ovulation induction with clomiphene citrate, clomiphene citrate when combined with r FSH gives maximum pregnancy rate 38.5% and it is statistically significant as compared to other drugs (p= <0.001).

Multivariate analysis of the variable shows that number of follicles, endometrial thickness. Ovulation induction with clomiphene citrate and r FSH, number of cycles and insemination after 15th day are significant variables for better pregnancy rates.

Table 1: Number of cycles with respect to different ovulation induction protocols.

Drugs	No. of cycles	Percent
Clomiphene citrate	237	43.8
Letrozole	202	37.3
r FSH	38	7.0
Clomiphene citrate+ r FSH	13	2.4
Letrozole+ r FSH	51	9.4
Total	541	100

Maximum patients underwent ovulation induction with clomiphene citrate (202/541) and then with letrozole (202/541).

DISCUSSION

A total of 541 IUI cycles in 200 women resulted in 65 pregnancies. The number of treatment cycles varied from 1 to 8 with a mean of 2.06±1.49 per couple. The average clinical pregnancy rate was 12% per cycle and the pregnancy rate was higher in first treatment cycle (66.77%) and decreased from second cycle onwards. The overall pregnancy rate was 33% per patient. The age range varied from 19-38 years and the average age was 29.08±4.19 years. The pregnancy rate in the age group <30 years was 33.04% in comparison to 31.76 in the age group more than 30 years (p=0.849), therefore the pregnancy rate and age of women are not statistically significant.

Clomiphene citrate is considered as the drug of first choice in oligo and anovulatory patients.[11,12] Various studies obtained rates from 9 to 12 % Present study the rate is 8.4 %. Present study is in accordance with most of the studies and showed that Clomiphene citrate is the drug of first choice as well as it is cost effective.[13-15]

Letrozole is in accordance with most of the studies which has exceptionally very high pregnancy rates of 3 to 14% with Letrozole.[16-18] For Letrozole and recombinant FSH various studies gave pregnancy rate of between 17 to 19%. Present study showed a pregnancy rate of 18.2%.[19,20]

Clomiphene citrate and Recombinant FSH. This regimen shows a significantly higher results in accordance with other studies.[21-23] In present study ovulation induction drug is a significant prognostic variable with Clomiphene citrate and Recombinant FSH regimen showing the best results.

The average pregnancy rate was 12% per cycle and 33% per couple. Multiple pregnancy rate was 7.6% mostly associated with Clomiphene Citrate. Stimulation with sequential Clomiphene citrate and recombinant FSH resulted in best pregnancy rates with low multiple pregnancy rates. Nowadays when the costs of health care are limited, intrauterine insemination can hold its place as a low-cost method of infertility treatment.

CONCLUSION

Conclusively with careful selection of subjects, appropriate controlled ovarian stimulation and intra uterine insemination, good pregnancy rates with low multiple pregnancy rates can be achieved.

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Original Research Article

Evaluation of female prognostic factors influencing pregnancy rate after intrauterine insemination with controlled ovarian hyper stimulation in infertile couples in a tertiary care hospital

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ABSTRACT

Background: To study the influence of various female prognostic factors on the outcome of pregnancy.
Methods: A Prospective observational study was conducted in the department of obstetrics and gynaecology to study the effect of different female prognostic variables in a total of 200 couples who underwent 541 cycles with controlled ovarian hyperstimulation. Variables selected for analysis were female age, menstrual history, duration of infertility, number of cycles, number dominant follicle diameter, endometrial thickness.
Results: A total of 541 IUI cycles in 200 women resulted in 65 pregnancies. The average pregnancy rates were 12% per cycle and 33% per couple. Multiple pregnancy rates were 7.6%mostly with clomiphene citrate. Endometrial thickness of more than 1 mm, ovulation stimulation protocol with clomiphene citrate plus recombinant FSH, day of insemination after 16thday, duration of infertility of less than 5 years and treatment with less than 5 cycles has been proved as the significant prognostic variables for successful IUI. Stimulation with sequential clomiphene citrate and recombinant FSH resulted in best pregnancy rates with low multiple pregnancy rates.
Conclusions: Careful selection of subjects, appropriate controlled ovarian stimulation and intra uterine insemination lead to good pregnancy rates with low multiple pregnancy.

Keywords: Clomiphene, Endometrial thickness, Induction protocols, Recombinant FSH

INTRODUCTION

For many couples advent of a baby is the most beautiful gift of life. Infertility is defined as failure of a couple to conceive after one year of unprotected intercourse. Approximately 85%-90% couple conceive within one year. Infertility therefore affects 10-15% couples.[1] Intra uterine insemination (IUI) is the first step in the ladder of fertility management in couples with no evidence of tubal damage or severe male factor.[2] The overall success of intra uterine insemination varies, with pregnancy rates between 5 and 26% per cycle.[3] IUI with controlled ovarian hyperstimulation is more effective than intra uterine insemination alone or intra cervical insemination.[4] Ovarian stimulation has been shown to significantly improve the outcome in IUI cycles by two mechanisms; By increasing the number of eggs available for fertilisation and By overcoming a subtle defect in ovulatory function in ovulatory function and luteal phase.[4] Pregnancy outcomes after IUI are determined by a number of factors, these factors include the use ovulation induction protocols, patient age, duration of infertility and the type of infertility.[5] The need to establish how these factors can be manipulated to maximise the likelihood of pregnancy is, therefore, a reasonable question that needs a crystal clear answer. So

the purpose of the study to evaluate the female prognostic factors influencing pregnancy rate after intrauterine insemination with controlled ovarian hyperstimulation in infertile couples.

METHODS

This prospective observational study was conducted at Department of Obstetrics and Gynaecology, Apollo Hospital, and Chennai from April 2009 to Oct 2010. The study was approved by Ethics Committee. This study included 200 couples who underwent 541 intra uterine insemination cycles, with controlled ovarian hyper stimulation and who fulfil the inclusion and exclusion criteria. The duration of infertility was defined by the time interval from beginning of unprotected intercourse until registration at the fertility centre. Detailed history of the couple include age, duration of infertility, regularity of periods, duration of contraception, sexual history, previous treatments if taken, occupation, family history.

After obtaining history general physical and systemic examination was carried out. Per speculum examination was performed and Pap smear taken if indicated. Per vaginal examination was done. Abnormal findings noted. Semen analysis done for male partner as per WHO criteria

Inclusion criteria: Women of age less than 40,negative pregnancy test, Patent fallopian tubes, Normal uterine cavity, History of Infertility >1 year. Men of Age <50 History of infertility >1 year, Normal semen analysis.

Exclusion criteria: Women with Previous IVF, Previous H/O PID, Previous IVF, Men with Previous H/O of Intrauterine insemination. For statistical analysis variables selected for analysis were female age, menstrual history, duration of infertility, no. of cycles, number dominant follicle diameter, endometrial thickness. All the continuous variables were represented by mean with standard deviation and it was analysed by independent sample t-test. Categorical variables were presented by frequency and percentages; it was analysed by Chi-square and Fisher exact test. Logistic regression analysis was used for multiple variable comparisons to pregnancy rate. All the analysis was done by using SPSS 14.0 version. A p value less than 0.05 were considered as significant.

RESULTS

A total of 541 IUI cycles in 200 women resulted in 65 pregnancies (Table 1). The number of treatment cycles varied from 1 to 8 with a mean of 2.06 ± 1.49 per couple. The average clinical pregnancy rate was 12% per cycle (Table 1) and the pregnancy rate was higher in first treatment cycle (66.77%) and decreased from second cycle onwards.

The overall pregnancy rate was 33% per patient. The age range varied from 19-38 years and the average age was 29.08 ± 4.19 years. The pregnancy rate in the age group <30 years was 33.04% in comparison to 31.76 in the age group more than 30 years (p=0.849), therefore the pregnancy rate and age of women are not statistically significant.

Table 1: Clinical pregnancy per couple and per cycle.

Outcome	Frequency	Percentage
Negative	135	67.5
Positive	65	32.5
Outcomes	No. of cycles	Percent
Negative	476	88.0
Positive	65	12.0
Total	541	100.0

Table 2: Number of cycles.

No of cycles	No. of patients	Percentage
1	45	22.5
2	47	23.5
3	60	30.0
4	27	13.5
5	12	6.0
6	7	3.5
7	1	.5
8	1	.5
Total	**200**	**100.0**

Table 3: Number of cycles during pregnancy.

	Clinical pregnancy	N	Mean	Std. Deviation	P value
No. of cycles	Negative	135	3.04	1.242	<0.001
	positive	65	2.06	1.488	

The number of patients was 102 with a period of infertility less than 5 years accounting to 51 % whereas percentage of patients with a period of infertility was 34.5%. Duration of infertility is a highly significant factor with maximum positive outcome when the mean duration of infertility is 4.78yrs. Out of the 200 respondents 164 patients had regular cycles that are 82% whereas the percentage of those who had irregular cycles was 18%. The pregnancy rate was 9.5% when one follicle was produced, whereas with more than 1 follicle, the rate increased to 18.1%.

Most of the patients underwent less than 3 cycles (Table 2). Day of insemination is a significant factor with maximum pregnancy after 15th day of insemination.

Among the different ovulation induction protocols maximum patients underwent ovulation induction with clomiphene citrate (202/541). The pregnancy rate increased with the number of mature follicles up to 3,

being significantly higher if more than one mature follicle developed and is statistically significant (p=<0.001). The mean number of follicles was 1.42±0.64. In our study the size of the follicle is not a significant variable this might be because most of the follicles are above 1.5cm. Insemination between day 10 and 14 resulted in a pregnancy rate of 9.9% compared to 20.4% if insemination was carried out between day 16 and 25 and it is statistically significant (p=0.003) (Table 3).

Table 4: Size of follicles.

Size of follicles			
1- 1.5	**0**	**0**	
1.5- 2	**2/46**	**4.3**	**0.235**
2- 2.5	**55/438**	**12.6**	
>2.5	**8/57**	**14.0**	
Day of insemination			0.003*
10-15	43/433	9.9	
16-25	22/108	20.4	
Ovulation induction drug			
CC	20	8.4	<0.001**
Gonal	10	26.3	
CC and Gonal	5	38.5	
Endometrial thickness			
0.60	0	0	
0.70	6/91	6.6	
0.80	7/179	3.9	
0.90	34/176	19.3	
1.00	4/43	9.3	<0.001**
1.10	11/35	31.4	
1.20	2/3	66.7	

Among the different ovulation induction protocols maximum number of patients underwent ovulation induction with clomiphene citrate, clomiphene citrate when combined with r FSH gives maximum pregnancy rate 38.5% and it is statistically significant as compared to other drugs (p=<0.001). Multivariate analysis of the variable shows that number of follicles, endometrial thickness, ovulation induction with clomiphene citrate and rFSH, number of cycles and insemination after 15th day are significant variables for better pregnancy rates.

DISCUSSION

It took almost 80 years before the first pregnancy achieved by way of intrauterine insemination was reported by Sims in 1867.[6] Intrauterine insemination is defined as direct transfer of motile spermatozoa into the uterine cavity after semen preparation and concentration in a small volume of medium.[7] The pregnancy rate (PR) after intra uterine insemination has varied between 9 and 21% per cycle.[8-10] Insemination as a low cost and patient friendly method still has a definitive role in the field of infertility treatment. A recent metaanalysis evaluated the effectiveness of intrauterine insemination showed PR of 7% with Clomiphene citrate and 12% with FSH and MPR being 13% with intra uterine insemination [11]. In planning infertility treatment, the most effectiveness of the treatment and MPRs should be considered. Now days when IVF and ICSI are widely available, over treatment should be avoided and intra uterine insemination appears be a more cost effective option than immediate IVF.[12] It has been demonstrated that three cycles of intra uterine insemination result in the same cumulative pregnancy rate as IVF and intra uterine insemination is more cost effective as regards unexplained infertility & moderate male factor infertility.[13]

Endometriosis decreased the effectiveness of controlled ovarian hyper stimulation and intra uterine insemination by half in the treatment of persistent unexplained infertility.[14] Endometrial thickness of more than 1 mm, ovulation stimulation protocol with clomiphene citrate plus recombinant FSH, day of insemination after 16th day, duration of infertility of less than 5 years and treatment with less than 5 cycles has been proved as the significant prognostic variables for successful IUI. Farimani M et al 2007 shows a PR of 1.4 % when ET 10 mm. and 6.8% when <10 mm. [15]

Stimulation with sequential clomiphene citrate and recombinant FSH resulted in best pregnancy rates with low multiple pregnancy rates. In this protocol clomiphene citrate 100 mg – 150 mg administered from Day 3 to Day 7 inj FSH 75 IU is given on Day 3, 5, 7. Trans Vaginal scan done on day 2 (basal) and from Day 8 thereafter to monitor the follicles thereafter.

Jee BC et al compared the pregnancy rates between letrozole and clomiphene citrate+ FSH in intra uterine insemination. The study indicated that matured follicles were comparatively lower in letrozole group as compared to clomiphene citrate + FSH group (3.2 ± 1.7 Vs 5.6 ± 2.4).No significant difference in endometrial thickness and pregnancy rates(18.2 vs 25 %). There was no significant difference in both the groups.[16] Moreover letrozole is banned for this indication.

Zahrat et al showed no significant difference in the pregnancy rates of the different treatment group clomiphene citrate vs HMG Vs clomiphene citrate+ HMG (pr 17% Vs 7.1 % Vs 23%).[17] Farimani M et al, also did not shown significant differences in the pregnancy rates between FSH and clomiphene citrate+ FSH(PR 15.7 % vs 11.3%) Clomiphene citrate+ Gonadotropins has the advantages of being more cost effective as the dose of gonadotropins is reduced.[2] Nowadays when the costs of health care are limited, intrauterine insemination can hold its place as a low cost method of infertility treatment. Conclusively with careful selection of subjects, appropriate controlled ovarian stimulation and intra uterine insemination, good

pregnancy rates with low multiple pregnancy rates can be achieved.

So it was concluded that the primary goal of the clinician is to choose the most appropriate treatment with least invasive technology for an individual couple. In the present study average pregnancy rates was 12% per cycle and 33% per couple. Multiple pregnancy rates was 7.6% mostly associated with clomiphene citrate. Endometrial thickness of more than 1 mm, ovulation stimulation protocol with clomiphene citrate plus recombinant FSH, day of insemination after 16th day, duration of infertility of less than 5 years and treatment with less than 5 cycles has been proved as the significant prognostic variables for successful IUI. Female age, menstrual history were not significant prognostic indicators .Stimulation with sequential clomiphene citrate and recombinant FSH resulted in best pregnancy rates with low multiple pregnancy rates.

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