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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