Pregnancy outcome in infertile patients with polycystic ovary syndrome who were treated with metformin

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Objective: To analyze pregnancy complications and outcome in patients with polycystic ovary syndrome (PCOS) treated with metformin.
Design: Single center retrospective case analysis.
Setting: Private regional nonurban referral subspecialty practice.
Patient(s): After 7 months of average metformin use, 188 patients with PCOS (average infertility: 27 months) achieved 237 pregnancies.
Intervention(s): Of pregnancies established, metformin alone was used before conception in 124/237 (52%), oral fertility agents (CC or letrozole) in 81 (34%), gonadotropin therapy in 7 (3.0%), assisted reproduction in 17 (7.2%), and other fertility-promoting regimens in 8 (3.4%).
Main Outcome Measure(s): Analysis of prepregnancy health parameters (weight, blood pressure, glucose tolerance, fasting and stimulated insulin levels) and pregnancy outcomes (miscarriage, pregnancy length, hypertension, gestational diabetes, weight gain, birth weight, sex ratio, congenital malformations, and breastfeeding success).
Result(s): Metformin appears to decrease the rate of spontaneous abortion. The co-morbidities of PCOS including obesity, insulin resistance, and glucose sensitivity served as indicators of increased risk for pregnancy complications, especially gestational diabetes. No increase in pregnancy-induced hypertension was evident. Prematurity was increased. Neither PCOS nor metformin use appears to increase the rate of congenital anomaly. PCOS did not affect lactation.
Conclusion(s): PCOS or its co-morbidities are associated with poorer pregnancy outcome. Implications and interventions are discussed. (Fertil Steril® 2006;85:1002–9. ©2006 by American Society for Reproductive Medicine.)

Key Words: Polycystic ovary syndrome (PCOS), insulin resistance, metformin, gestational diabetes, pregnancy loss, pregnancy-induced hypertension, obesity, breastfeeding

Polycystic ovary syndrome (PCOS) and its associated ovulatory defects are a common cause of infertility (1). Indicated for treatment of type 2 diabetes mellitus, a potential co-morbidity of PCOS (2), metformin has become widely used to improve insulin resistance, a recognized precursor of type 2 diabetes mellitus and common finding in patients with PCOS (3, 4). Although there are now numerous reports on the improvement in metabolic, endocrine, and ovulatory parameters, with increased fertility rates in the patients with PCOS treated with metformin (3), much less is known about the impact of this drug on pregnancy outcome in these women who appear to be at increased risk for early pregnancy loss (5), gestational diabetes (GDM) (6–9), and pregnancy-induced hypertension (PIH) (7).

Preliminary reports indicate that metformin may reduce pregnancy loss and improve pregnancy outcome (10–12). We have used metformin since 1997 as an adjuvant in PCOS therapy and present pregnancy outcome data on our center's patients.

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MATERIALS AND METHODS

Criteria for Screening and Diagnosis of PCOS

Because of the broad spectrum of findings and associations present in PCOS, we established relatively liberal criteria for PCOS screening that include menstrual interval ≥32 days or disordered ovulation, previous pregnancy loss, previous pregnancy with infant >4,500 g or gestational diabetes, >110% of ideal weight, clinical hyperandrogenism (hirsutism, adult acne), or family history of type 2 diabetes.

We have used the following anatomical, biochemical, and clinical criteria to establish the diagnosis of PCOS. At least one component in two of three major criteria must be met (anatomical and biochemical, biochemical and clinical, anatomical and clinical, or anatomical, biochemical, and clinical).

Anatomical

- On ultrasound ≥10 follicle cysts ≤10 mm in size or ovarian volume ≥10 mL (three planes) on either or both ovaries

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- Sclerocystic changes and ovarian enlargement at laparoscopy
- Surgical pathology

Biochemical

- Fasting morning blood sampling occurs on cycle days 2–5; day 1 is the first day of spotting with natural or progestin-induced menses
- Elevated total T, free androgen index (total T/sex hormone binding globulin [SHBG]), or DHEAS
- Reverse in LH/FSH (LH/FSH ratio >1)
- Abnormal fasting glucose (≥100 mg/dL) or abnormal glucose tolerance test (GTT) after 75-g load (≥155 mg/dL at 1 or 2 hours) *or* elevated fasting insulin ≥16 μIU/mL fasting or ≥100 μIU/mL at 1 or 2 hours

Clinical

- Ovulatory dysfunction (cycle >32 days or cycles <32 days in presence of other diagnostic criteria of ovulatory defect, i.e., temperature tracking, ovulation predictor kit, midluteal P)
- Body weight ≥110% of ideal
- Clinical hyperandrogenism (i.e., adult cystic acne, hirsutism, or alopecia)

The diagnosis of PCOS was not made when the only findings were obesity and disordered glucose/insulin levels, although patients with these characteristics were considered candidates for metformin. Diagnosis of PCOS requires evidence of ovulatory/ovarian dysfunction, polycystic ovaries on ultrasound, or clinical/biochemical hyperandrogenism.

Patients with hyperprolactinemia or hypothyroidism were not excluded from diagnosis of PCOS, if when treated, hormone levels normalized and the diagnosis of PCOS was made by criteria other than anovulation. Evaluation of our center's patients has shown the incidence of 21-hydroxylase deficiency to be very low and measurement of 17α- hydroxyprogesterone (17-OHP) is not usually performed in absence of other factors that indicate higher risk.

Patient Selection

All patients included in our PCOS database (December 1997–January 2005) who desired pregnancy were started on metformin and upon a documented positive β-hCG were included in the analyses. Most patients had more than 12 months of unprotected intercourse, but the formal diagnosis of infertility was not necessary in patients with oligomenorrhea or proven anovulation.

As a part of their initial evaluation, all patients underwent a lifestyle assessment and received counseling from a registered dietician. Each received 500–2,000 mg of metformin in either standard or extended release formulations based on their weight, medication tolerance, and insulin levels.

All gave informed consent for "off label" use of metformin. Detailed informed consent concerning the purpose of the study and how the information was to be used for inclusion into the study was obtained when the data were collected by patient recall either at a postpartum visit or by telephone interview. Institutional review board approval was not obtained because it was a retrospective chart review with patient anonymity in the analysis without risk or direct benefit to the participants. There was no conflict of interest.

Laboratory Analysis

Plasma samples were collected in the early morning after an 8- to 12-hour fast during the early follicular phase on days 2–5 with day 1 as the first day of bleeding/spotting. Insulin testing was performed using the DPC Immulite (Diagnostic Products Corporation, Los Angeles, CA) and their commercial immunoradiometric insulin assay performed on a weekly basis. The sensitivity of the insulin assay was 2 μIU/mL with intra-assay coefficient of variation (CV) of 5.2%–6.4% and interassay CV of 5.9%–8.0%. In addition, the DPC Immunlite was used in testing for LH, FSH, DHEAS, T, and SHBG levels. The intra-assay CV and interassay CV for LH were 4.8%–6.5% and 7.2%–26.0%, for FSH were 2.3%–3.7% and 5.4%–6.7%, for DHEAS were 6.8%–9.5% and 8.1%–15%, for T were 7.1%–13.0% and 7.7%–16.4%, and for SHBG were 4.1%–7.7% and 5.8%–13%, respectively. There was no change in assay during the study period. Glucose testing was performed daily in our own laboratory or less commonly by outside reference laboratories.

Ultrasound

Transvaginal ultrasound was performed by the patient's physician using either a GE 3600 equipped with a 5-MHz probe or GE logic 500 with a 7.5-MHz probe (Rancho Cordova, CA).

Study Limitations

An obvious weakness is that the study is a retrospective single center analysis subject to recall bias. Populations of patients with PCOS may vary considerably. Controls for patients with PCOS can be very difficult to establish because of the heterogeneity of the PCOS phenotype. In a clinical practice, it is difficult to withhold metformin therapy from this group that would seem to benefit from its use.

Within the PCOS population, it may be appropriate to choose one specific factor, such as obesity, and compare the obese patients with PCOS to the nonobese patients of the same population. We were attempting to identify trends within this PCOS population and compare their pregnancy outcomes.

It is impossible to state the true risks of pregnancy in PCOS due to possible positive alterations with either metformin or lifestyle intervention that all patients received. The study's strength is a relatively large number of patients, who were prospectively identified by comprehensive standardized screening.

Statistical Analysis

When comparing the mean of two groups such as systolic blood pressure, diastolic blood pressure, and prepregnancy weight with PIH, the data were analyzed by Student's *t*-test (two-tailed). The Mann-Whitney U test was used to determine significance for GDM compared with total weight gain, fasting insulin, 1-hour insulin, and fasting glucose, and for birth outcome, macrosomia, and PIH compared with fasting insulin and fasting glucose. The ANOVA test was used for analysis of GDM in relation to age and prepregnancy weight as well as for prepregnancy weight compared with birth outcome and macrosomia. The χ^2 test for independence was used when evaluating body mass index (BMI) with incidence of live birth, development of GDM, and occurrence of PIH. Binomial distribution tests were used for sex ratio, for comparing miscarriages with and without metformin, and for comparison of preterm delivery. For all statistical tests, $P<.05$ was the level considered for significance. The Statistical Package for the Social Sciences (SPSS, Chicago, IL.) was used for statistical analysis.

RESULTS

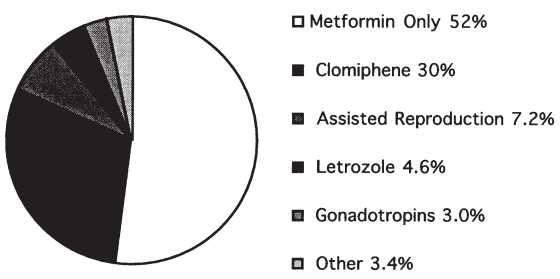
Pregnancy Demographics

From the study period, 250 pregnant patients were identified and 188 were available for continued analysis. This 188-patient study group with average length of infertility of 27.5 months established 237 pregnancies with 254 fetuses (217 single, 17 twin, and 1 triplet gestation). The average age of patients at the onset of pregnancy was 29 years (range, 18–38 years). The average length of metformin use before pregnancy was 7 months.

About half of the patients received metformin alone and the remainder required additional interventions to establish a pregnancy (Fig. 1). Although metformin was often our first-line of therapy, many patients had received clomiphene citrate (CC) before their referral. It has been our policy to stop metformin by the end of the first trimester. Only two patients were known to have used metformin for the entire pregnancy; 139 stopped metformin at 8–12 weeks, 5 at more than 12 weeks, and 35 stopped either with a positive pregnancy test or before 8 weeks. Among those patients on metformin at the time pregnancy was achieved, 57% (107/188) were nulliparous, 29% (54/188) had at least one previous miscarriage, and 14% (27/188) had at least one prior pregnancy that resulted in a delivery.

FIGURE 1

Therapeutic interventions.



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Of the 237 pregnancies, 72% (171/237) resulted in live births with 78% term deliveries (>37 weeks gestation) and 22% preterm deliveries. The 171 delivered pregnancies produced 184 live births, 102 female and 82 male. The difference in sex ratio did not reach statistical significance ($P=.16$).

Congenital Abnormalities

Four of 184 (2.2%) infants were born with a congenital abnormality. Of the four infants, two survived; one male had congenital salt losing 21-hydroxylase deficiency (congenital adrenal hyperplasia) diagnosed 3 days after birth. Neither parent had a family history of congenital adrenal hyperplasia and a successful unaffected pregnancy had been previously achieved on CC. Laboratory studies had shown typical PCOS pattern with insulin resistance, mild increase in T, and normal DHEAS levels. Maternal screening for congenital adrenal hyperplasia had not been performed.

One otherwise healthy neonate had cleft palate. One of the neonates died of Potter's syndrome; the other died of multiple abnormalities attributed to severe prematurity. The only other significant abnormality identified was a presently well infant of a triplet pregnancy delivered prematurely who had necrotizing enterocolitis resulting in a colostomy.

Pregnancy Loss

After intervention, 61 patients had 62 first trimester losses including one ectopic (28% of pregnancies established). There were no second trimester losses and four patients had third trimester fetal demises. One demise was after placental abruption, the second with intrapartum loss with fetal distress, third with Potter's syndrome, and causes are unknown for the fourth. Within the 66 pregnancies resulting in losses, 25 (38%) occurred in women who were nulliparous, 32 (49%) in women with a history of at least one previous miscarriage, and 9 (14%) in patients with prior pregnancies and no losses.

Among the 61 first trimester losses, 11 patients stopped metformin use at the onset of pregnancy, 2 patients stopped at 4 weeks, 2 patients stopped at 7 weeks, 1 patient stopped at 9 weeks, and 1 stopped at 10 weeks gestation. Forty-four patients were still taking metformin at the time of miscarriage.

Average fasting insulin (15.6 μIU/mL) and fasting glucose (94 mg/dL) in patients with miscarriages/demises did not differ ($P=.98$ and $P=.79$) when compared with averages from live births (18.3 μIU/mL and 94.3 mg/dL, respec-

tively). The average prepregnancy weight among patients with pregnancy loss was higher (199.7 pounds vs. 191.0 pounds) than for patients with live births, but did not reach statistical significance ($P=.17$).

Of 81 women with pregnancies before metformin use, 67% (54 patients) had miscarriages. Within this same group of women, 36% (29/81 patients) had pregnancies that resulted in miscarriage while taking metformin. This loss rate was equally divided between those who received metformin alone and those who received metformin and fertility-promoting agents. With therapy, pregnancy loss was significantly less likely ($P<.001$).

Recurrent pregnancy loss, as defined by loss of two or more pregnancies, was reported among 29.6% (24/81) of patients. With therapy, 16/24 (67%) had a successful delivery, but 3/16 had an additional loss with therapy before a successful outcome. Eight of 24 had at least one additional loss and no successful pregnancies while on metformin.

Prematurity

Among the 22% (38/171) preterm deliveries, 30 occurred in singleton pregnancies and 8 occurred in pregnancies with multiple gestations. Of singleton births, 19% (30/158) were preterm compared with 67% (8/12) multiple gestation deliveries. The rate of singleton preterm deliveries is significantly higher ($P<.01$) than the suggested rate of 11% in the general population (13). No specific risk factor was identified for prematurity, but the pregnancies were more likely to have known complications, including eight patients with GDM, nine with PIH, two with premature rupture of membranes, two with incompetent cervix, and one with placental abruption.

Birth Weight

Of the 184 infants born, 4 (2.2%) were small for gestational age according to established guidelines (14). Two of four small for gestational age infants were delivered at term, whereas one of two preterm small for gestational age births was nonviable. Of the 51 (28%) patients who delivered macrosomic babies (>4,000 g), 12 (24%) had GDM. When evaluating total weight gain of the mothers of macrosomic neonates in relation to the Centers for Disease Control guidelines (15), 22% (11/51) of patients gained within 5 pounds of the recommended amount, 3.9% (2/51) of patients gained 5 pounds or less, 63% (32/51) of patients gained within double the suggested amount, and 31% (16/51) of patients gained more than double the recommended amount. Neither fasting insulin nor fasting glucose had a significant relationship with macrosomia ($P=.79$ and $P=.66$, respectively). Average prepregnancy weight for patients with macrosomic infants was not significant ($P=.45$).

Body Mass Index

Comparing fasting insulin, 1-hour glucose, and 2-hour glucose levels with BMI by regression analysis trends were identified toward a direct relationship that did not reach statistical significance. No correlation was noted between 1-hour insulin and fasting glucose and BMI. A significant relationship ($P=.03$) was found between BMI and miscarriage/demise, with more obese patients more likely to miscarry. In addition to pregnancy loss, BMI was compared with the occurrence of GDM (Table 1). The relationship between BMI and GDM, although not statistically significant, is suggestive of an association between the two factors.

TABLE 1

PCOS and pregnancy: influence of BMI.

BMI	SAB n = 66	GDM deliveries	GDM n = 41
18–25	13 (19.7%)	2/28 (7.1%)	2 (4.9%)
26–30	11 (16.7%)	7/40 (17.5%)	7 (17.1%)
31–35	11 (16.7%)	12/43 (27.9%)	12 (29.3%)
36–40	26 (39.4%)	10/35 (28.6%)	10 (24.4%)
Over 40	5 (7.6%)	10/25 (40%)	10 (24.4%)

Note: BMI = body mass index (weight [kg]/height [m^2]); SAB = spontaneous abortion; GDM = gestational diabetes mellitus.

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Gestational Diabetes

Among the 171 patients with live births, 41 (24%) met the criteria for GDM by an abnormal 3-hour GTT. Most patients had received dietary advice after pregnancy was established and were following a modified diet for GDM prevention. Of the 41 cases of GDM, 19 were under age 30 years and 22 were more than 30 years old, with no age relationship evident (Table 2). The 41 pregnancies were distributed among 39 patients with 38 singleton gestations, 2 twin gestations, and 1 triplet gestation. Of the 39 patients, 3 had GDM in a previous pregnancy and 2 developed GDM in two separate pregnancies achieved while using metformin. Of those patients with GDM, 39% required insulin therapy.

Using established screening values during pregnancy of a fasting glucose ≥100 mg/dL and 2-hour glucose ≥140 mg/dL (16) on prepregnancy laboratory intake values to predict GDM, we identified 16/188 at-risk patients. Of those, gestational diabetes occurred in 56.3% (9/16) and among the remaining 7 pregnancies, 6 proceeded without GDM and 1 was unknown. If the prognostic parameters were expanded to include fasting glucose ≥95 mg/dL and 2-hour glucose ≥130 mg/dL (16), 40 pregnancies were judged at risk. Of these 40 pregnancies, 15 developed GDM, 24 did not develop GDM, and 1 was unknown. By expanding the parameters, the number of patients predicted more than doubled, whereas the occurrence of false negatives increased from 37.5% to 60%. Thirty-eight percent (15/40) of those predicted pregnancies developed GDM and of the 41 pregnan-

TABLE 2

PCOS and pregnancy: GDM vs. non-GDM.

	GDM	Non-GDM	*P*
Age (y)[a]	29.61	28.67	NS
Fasting insulin (μIU/mL)[b]	24.2	14.99	<.001
Insulin 1-hour (μIU/mL)[b]	199.89	98.51	<.001
Glucose fasting (mg/dL)[b]	101.7	91.95	.013
Prepregnancy wt (lbs)[a]	205.51	190.79	.014

Note: Data are given as means; GDM = gestational diabetes mellitus; NS = not significant.
[a] Statistical test: ANOVA test.
[b] Statistical test: Mann-Whitney U test.

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cies with GDM, 15 (37%) were predicted by the expanded parameters.

Pregnancies complicated by GDM had preconception elevated average fasting insulin, 1-hour insulin, and fasting glucose, as well as higher prepregnancy weights when compared with other live births. We set the upper limits of fasting and 1-hour insulin levels at 14 μIU/mL and 100 μIU/mL, respectively. Of those with GDM, 46% (19/41) of pregnancies had at least one of the two insulin levels with elevated values and 29.3% (12/41) had both values elevated (Table 2).

Pregnancy-Induced Hypertension

Pregnancy-induced hypertension was reported in 14% (24/171) of the pregnancies resulting in live birth. Of the 24 pregnancies with PIH, 11 (1 twin gestation) delivered at term and 13 (4 twin gestations) delivered preterm (≤37 weeks). No significant alteration in average prepregnancy systolic blood pressure was evident, but prepregnancy diastolic pressures showed a significant correlation with PIH risk (Table 3). Fasting insulin and prepregnancy weight also were found to have a significant association with PIH, whereas fasting glucose did not.

Breastfeeding

Of the 164 patients for whom information about breastfeeding was available, 97 (59%) succeeded at breastfeeding, 27 (17%) failed attempts, and 40 (24%) reported making no attempt. Breastfeeding was attempted in 76% (124/164), which is higher than the previously reported 60% of United States women in 1995 (17). Of those that attempted to breastfeed, 78% (97/124) succeeded and 22% (27/124) failed. Four of those who failed attributed the failure to poor milk production. Other reasons given included the demands of multiple births, prematurity, cleft palate, and mastitis.

DISCUSSION

Women with PCOS have disordered ovarian function often leading to defects in ovulation and infertility. The spectrum of PCOS also includes other health issues, specifically obesity and insulin resistance, which alone or in association, make the patients with PCOS at higher risk for pregnancy loss and health-compromising complications of pregnancy. The present study adds to a relatively small number of reports that have addressed outcome of pregnancy in patients with PCOS and confirms an increased risk for adverse outcome. An obvious caveat to this study is that the outcome of PCOS pregnancy without the possible protective effect of metformin was not studied, nor is it possible to determine what change there may have been in complication rate had metformin been continued for the entire gestation or if concurrent lifestyle improvement measures were not taken.

In agreement with several other studies (12, 18, 19), our data are reassuring that use of metformin before and at least during the first trimester of pregnancy does not compromise the health of either mother or fetus. No evidence that the PCOS pregnancy is at higher risk for congenital anomaly was found in the present study or in review of the relatively sparse literature on the subject. Although there were four infants with congenital abnormalities, none of the defects could be attributed to metformin or fertility agents used during the beginning of pregnancy.

It is increasingly apparent that patients with PCOS have a higher rate of pregnancy loss and that risk is decreased with metformin use (10–12). When miscarriage rate was compared in the same group of women with PCOS before and after metformin, Jakubowicz et al. (10) reported a reduction

TABLE 3

PCOS and pregnancy: PIH vs. non-PIH.

	PIH	Non-PIH	*P*
Systolic (mm Hg)[a]	121	117	NS
Diastolic (mm Hg)[a]	84	78	.006
Fasting insulin (μIU/mL)[b]	22	16	.02
Fasting glucose (mg/dL)[b]	95	95	NS
Prepregnancy wt (lbs)[a]	220	190.3	<.001

Note: Data are given as means; PIH = pregnancy-induced hypertension; NS = not significant.
[a] Statistical test: Student's *t*-test (two-tailed).
[b] Statistical test: Mann-Whitney U test.

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in miscarriage from 71% to 8.8%, whereas Glueck et al. (11) reported reduction from 73% to 10% in their pilot study, and later a decreased loss rate of 62% to 26% (12). In the present study, active intervention very significantly reduced the risk of early pregnancy loss to about half of this population's collective past obstetric history (67% vs. 36%). An equal number of losses occurred in the metformin alone group and the group receiving both metformin and additional fertility therapy, suggesting a direct positive effect of metformin.

The lower rate of pregnancy loss was still considerably higher than the projected 10%–15% rate in the general population (20, 21). Glueck et al. (11, 12) hypothesized that the reduction in loss was due to a favorable alteration in plasminogen activator inhibitor affecting improved implantation, whereas Jakubowicz et al. (22) suggested that metformin increased blood flow to the uterus. It is our hypothesis that the reduction in loss is mostly due to improvement in egg quality, possibly after a more timely ovulation. Substantiation for this is that the loss rate did not differ among those who immediately stopped metformin with pregnancy and those that continued through the first trimester.

Neither prepregnancy fasting insulin nor glucose levels are significant indicators of pregnancy loss. To the contrary, patients with prior pregnancy loss tended to be somewhat more metabolically fit when judged by their prepregnancy laboratory values than those who carried a pregnancy to term. Because insulin and glucose levels were not analyzed after metformin therapy was initiated, it is possible that a significant improvement by metformin may have been obscured. In agreement with an earlier study, BMI appears to be directly related to risk of pregnancy loss (23); however, the prepregnancy weight of patients with deliveries compared to patients with losses was not statistically significant.

Women with PCOS are at a higher risk of developing GDM (6–9) and this was confirmed in the present study where nearly one-fourth developed GDM compared to a general population rate of 2%–5% pregnancies in the United States (16). Among the patients in our study, 39% of those with GDM required insulin. This figure 1 is remarkably similar to the findings reported in the study performed by Langer et al. (24) in unselected patients with GDM.

An attempt was made to determine whether there were prepregnancy risk factors that might predict the risk of GDM. The American Diabetes Association recommends that women with known risks for GDM should be tested as soon as possible after establishment of a pregnancy (25) rather than waiting until early in the third trimester. Paradisi et al. (26) suggested that determining the risks for GDM at earlier times results in healthier pregnancies and better pregnancy outcomes. We suggest that all women with PCOS undergo a GTT as a part of preconception counseling.

If the traditional glucose levels of ≥100 mg/dL fasting and ≥140 mg/dL at 2 hours postchallenge were used as a diagnosis of GDM, 9 of 41 (22%) patients who developed GDM would have met the diagnostic criteria of GDM before the pregnancy was initiated. If, as suggested, the parameters were expanded to fasting glucose ≥95 mg/dL and 2-hour glucose ≥130 mg/dL (16), the diagnosis of prepregnancy GDM would have increased to 37% (15 of 41 patients with GDM). If an individual has an abnormal GTT before pregnancy then it seems likely that her glucose tolerance will worsen with the known increase in insulin resistance accompanying normal pregnancy (27).

We typically start our patients on a modified 1,500–2,000 kcal American Diabetes Association diet before pregnancy and reinforce its use during pregnancy. This intervention and possibly metformin use is thought to have reduced the incidence of GDM and potentially its complications in our study population.

Adding insulin levels to the GTT adds additional sensitivity to the prediction of GDM. For example, one patient who subsequently developed GDM had normal fasting glucose levels of 93 mg/dL and 122 mg/dL at 2 hours, but was quite insulin resistant with insulin levels of 41.2 μIU/mL fasting and 400 μIU/ml at 1 hour. The prepregnancy laboratory averages in GDM patients for fasting glucose, fasting insulin, and 1-hour insulin were significantly higher than those found in non-GDM women. If both insulin and glucose levels were considered when predicting GDM in our patients, 66% (27/41) of those with GDM would have been predicted with laboratory values of fasting insulin ≥14 μIU/mL, fasting glucose ≥95 mg/dL, and 2-hour glucose ≥130 mg/dL.

Both prepregnancy and total weight gain appear to be key determinants of GDM, with independent and statistically significant relationships established in previous studies (9, 28–31) as well as in our study. In addition, total weight gain influences the development of macrosomia (32). Of the 184 infants, 52 (28%) were born weighing more than 4,000 g, a number higher than the reported 10% rate of macrosomia (33). Applying normative data for appropriate weight gain during pregnancy (15) to our patients, it was determined that 75% of the patients with macrosomic infants gained more than the suggested amount.

Several studies have suggested that women with PCOS have an increased risk of developing hypertension and preeclampsia during pregnancy (6, 7). Clearly, insulin resistance and obesity, both common in PCOS, increase the risk of PIH (9, 32, 34). In the present study PIH occurred in 14% (24/171) of pregnancies that resulted in live births; a rate that is well within the approximated 12%–22% rate of occurrence among normal pregnancies (35). These findings agree with those of Mikola et al. (9) that failed to indicate that PCOS alone increased PIH occurrence. Prepregnancy weight was the best predictor of PIH risk followed by diastolic pressure and fasting insulin.

Studies assessing success with breastfeeding in the PCOS population are scarce. Clearly, there may be individual in-

stances in both the PCOS and general population where an endocrine basis for lactation failure can exist. However, we found no evidence to suggest that women with PCOS are any different from other mothers attempting to breastfeed. The percentage of women who initiated breastfeeding in our study is above the general population rate (17) and is possibly related to the high motivation of this group. Of those who attempted to breastfeed, 78% (97/124 patients) had successful outcomes. It remains possible that milk production is reduced in PCOS, but only four patients reported low milk production as a reason for stopping attempts to breastfeed.

In summary, active intervention that universally included metformin in the months before pregnancy resulted in fewer spontaneous abortions. Co-morbidities of PCOS, including obesity, insulin resistance, and glucose tolerance, served as reliable indicators for potential pregnancy complications, especially gestational diabetes. The increasingly apparent divergence in PCOS phenotype may explain the lack of agreement in previous studies. Quite possibly, our semirural population may have a higher BMI and higher instance of metabolic abnormalities than other PCOS populations with infertility.

In studying PCOS in pregnancy, care should be taken to separate PCOS from its associated co-morbidities, specifically obesity. Insulin resistance, although not a part of the recognized diagnostic criteria for PCOS (36), has such a strong association that we have added it into the diagnostic spectrum when it coexists with other diagnostic criteria. To better delineate the PCOS metabolic phenotype, PCOS should be added to the criteria for a GTT. Glucose tolerance testing significantly increases the sensitivity of screening for GDM, which is further improved by addition of insulin levels.

Metformin is clearly a useful adjuvant in treatment of PCOS. Metformin is also an attractive intervention for prevention or treatment of gestational diabetes and increasingly is being used during pregnancy on an empiric basis. When we compared immediate discontinuation of metformin with continued use in the first trimester there was no difference in spontaneous loss, or any other variable where there was sufficient power to test the association. However, insufficient patient numbers and variations in gestational age at which metformin was discontinued may have obscured a significant effect.

Metformin is classified as category B for use in pregnancy and to date there have been no adverse fetal or neonatal effects associated with its use. Data on maternal–fetal transport of metformin is limited. The manufacturer's package insert states that there is only a partial placental block to fetal transfer in animal experiments. No difference in placental glucose uptake or transport was found in a human placental model (37). Additional studies are needed to evaluate whether its use throughout pregnancy will lower pregnancy complication rates.

Lowering BMI should lead to improved pregnancy outcomes. By encouraging healthier diets and increased physical activity before and during pregnancy, risks of pregnancy complications should be reduced. Preconception counseling and identification of specific risk factors for women with PCOS is imperative.

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