Risk of Preterm Delivery in Non-Diabetic Women with Polycystic Ovarian Syndrome

Miya Yamamoto, MD[1], **Seth L. Feigenbaum, MD MPH**[2,3], **Yvonne Crites, MD**[3,4], **Gabriel J. Escobar, MD**[3,5,6], **Jingrong Yang, MA**[6], **Assiamira Ferrara, MD PhD**[6], and **Joan C. Lo, MD**[3,6]

[1]Department of Obstetrics and Gynecology, Kaiser Permanente Oakland Medical Center

[2]Department of Obstetrics and Gynecology, Kaiser Permanente San Francisco Medical Center

[3]The Permanente Medical Group

[4]Department of Obstetrics and Gynecology, Kaiser Permanente Santa Clara Medical Center

[5]Department of Inpatient Pediatrics, Kaiser Permanente Walnut Creek Medical Center

[6]Division of Research, Kaiser Permanente Northern California

Abstract

Objective—To examine the risk and etiology of preterm delivery in women with polycystic ovary syndrome (PCOS).

Design—Retrospective cohort study comparing preterm delivery rate among non-diabetic PCOS and non-PCOS women with singleton pregnancy. Multivariable logistic regression was used to identify predictors of preterm delivery among PCOS women.

Results—Among 908 PCOS women with singleton pregnancy, 12.9% delivered preterm compared to 7.4% among non-PCOS women (p<0.01). Causes of preterm delivery among PCOS women included preterm labor (41%), cervical insufficiency (11%), hypertensive complications (20%), preterm premature rupture of membranes (15%), fetal-placental concerns (9%) and intrauterine fetal demise (5%). Maternal age, race/ethnicity and nulliparity were significant predictors of preterm delivery in PCOS, while body mass index and fertility medications were not.

Conclusions—A higher proportion of PCOS women delivered preterm (12.9%) compared to non-PCOS women, with the majority of cases due to spontaneous preterm birth. Future studies should explore etiologies and strategies to improve pregnancy outcomes in PCOS.

Keywords

Polycystic ovary syndrome; pregnancy; preterm delivery

ADDRESS CORRESPONDENCE TO: Joan C. Lo MD, Division of Research, Kaiser Permanente Northern California, 2000 Broadway, Oakland, CA 94612, 510-627-2986 office, 510-627-2573 fax, Joan.C.Lo@kp.org.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is a common endocrinopathy in women, affecting approximately 4–7% of reproductive age women.[1–4] This complex reproductive metabolic disorder is associated with insulin resistance, hypertension, obesity and weight-related disorders, infertility and a chronic low-grade inflammatory state. [5–6] Numerous studies suggest that maternal PCOS is associated with an increased rate of adverse pregnancy outcomes, including early pregnancy loss,[7–8] gestational diabetes,[8–14] hypertensive disorders,[8, 11–19 20] small-for-gestational age infants,[8, 21] and preterm birth.[8, 10, 20]

There are multiple known risk factors which predispose women to preterm delivery including a history of preterm delivery, Black race, extremes of maternal age, smoking and low maternal weight[22–23] and multiple gestation.[23–24] Preterm births may be categorized as either spontaneous preterm delivery secondary to preterm labor and preterm premature rupture of membranes, or indicated preterm delivery for maternal and/or fetal indications.[25] While the former is characterized broadly by pathways associated with infection or systemic inflammation, as well as specific maternal and biologic risk factors,[25] the latter is typically due to pregnancy disorders such as preeclampsia or placental abruption, or related to compromised maternal or fetal status. Relevant to women with PCOS, underlying maternal comorbidities such as older age, obesity, prediabetes, chronic hypertension and fertility treatment may also contribute to risk of preterm birth. However, there are few population-based studies examining pregnancy outcomes in women with PCOS, and our current understanding of preterm delivery risk within this specific patient subset remains limited.

In this study, we examined the frequency and etiology of preterm delivery in a large cohort of PCOS women with sustained pregnancy and compared these findings to a control group of non-PCOS women delivering within the same time period and hospital facilities. We focused primarily on singleton gestation pregnancy, given the known association of multiple gestation pregnancy and premature delivery, and also compared these findings to background rates within our source population of pregnant women receiving care in Kaiser Permanente Northern California.

METHODS

Kaiser Permanente Northern California (KPNC) is a large integrated health care delivery system in the San Francisco Bay area encompassing 14 delivery hospitals with more than 30,000 total births per year.[9] During 2002–2005, approximately 6.8% of KPNC singleton births were preterm < 37 weeks gestation, 2.5% were preterm < 35 weeks gestation and 1.0% were preterm < 32 weeks gestation, based on regional perinatal outcome data.

We utilized KPNC databases and conducted retrospective chart review to identify a large sample of non-diabetic women with confirmed PCOS who delivered beyond 20 weeks gestation between January 1, 2002 and December 31, 2005. Demographic and clinical features, parity, pregnancy history, conception method (including metformin therapy and use of assisted reproductive technology) and gestational outcomes were obtained by detailed review of preconception, antenatal and delivery records. All obstetric outcomes were

adjudicated by physicians involved in the research study. Polycystic ovary syndrome was defined using 2003 ESHRE/ASRM Rotterdam criteria which require at least 2 of the following: oligo- or amenorrhea, evidence of androgen excess and polycystic ovaries by ultrasound.[26] Gestational age was based on prenatal assignment of estimated date of confinement and confirmed or adjusted by first and/or second trimester ultrasound. A non-PCOS cohort of 1023 pregnant women matched by hospital facility and delivery year to the PCOS women was used to estimate the rate of preterm delivery among non-PCOS pregnant women. The study was approved by the Kaiser Permanente Northern California Institutional Review Board and the requirement for informed consent was waived.

Preterm delivery was defined as delivery before 37 completed weeks of gestation.[27] For singleton pregnancies, we further classified the cause of preterm delivery. These included spontaneous preterm delivery due to cervical insufficiency, preterm premature rupture of membranes, and preterm labor. Separately classified were iatrogenic or inevitable delivery for hypertensive complications (pre-ecclampsia, worsening gestational or chronic hypertension), fetal or placental indications (e.g. placental abruption or abnormal fetal heart rate pattern), intrauterine fetal demise, and delivery for maternal indication (e.g. worsening of systemic lupus erythematosus). The American College of Obstetrics and Gynecology (ACOG) definitions for pre-eclampsia and hypertensive disorders were used for diagnosis of these complications,[28–29] and for preterm labor (regular contractions occurring before 37 weeks gestation associated with cervical change), preterm premature rupture of membranes (membrane rupture before 37 weeks gestation and prior to onset of labor) and cervical insufficiency (painless cervical dilation in the absence of other precipitating factors) for outcome assessment. [30–31 32]

Gestational diabetes mellitus was determined by standard glucose tolerance test criteria as previously described.[9] Maternal age, race/ethnicity, parity, pre-pregnancy body mass index, method of conception, preconception metformin treatment (during the three months prior), and use of fertility medications (clomiphene citrate, gonadotropins) including assisted reproductive technology were ascertained by pharmacy records and detailed chart review.

Statistical Methods

Differences between groups were compared using the chi-squared test or Student's t test. The proportion of preterm births was reported as point estimate with 95% confidence intervals (95% CI). Multivariable logistic regression was used to examine independent predictors of singleton preterm delivery. All analyses were conducted using STATA version 8.2 (StataCorp LP, College Station TX). A two-sided P value <0.05 was considered statistically significant.

RESULTS

Our initial study population consisted of 1023 non-diabetic PCOS women with pregnancy delivery, of whom 1019 delivered after 20 weeks gestation. All had confirmed PCOS although radiographic images were not available for 5% to verify reproductive endocrine chart notation of polycystic-appearing ovaries. The overall racial/ethnic distribution among PCOS women was 41.2% White, 25.7% Hispanic, 25.3% Asian, 4.2% Black and 3.5%

other. There were 111 multiple gestation pregnancies, accounting for 10.9% of the PCOS cohort, resulting in a final cohort of 908 PCOS women with singleton pregnancy. Among the comparison group of 1023 non-diabetic non-PCOS women (40.9% White, 7.1% Black, 24.0% Hispanic, 24.6% Asian and 3.5% other), only 31 (3%) had multiple gestation pregnancies, resulting in a final cohort of 992 non-PCOS women with singleton pregnancy.

For the 908 PCOS women with singleton pregnancy, the mean gestational age at delivery was 38.7 weeks and preterm delivery occurred in 12.9% (95% CI 10.7–15.1%) of pregnancies. As shown in Figure 1, the singleton preterm delivery rate in PCOS women was substantially higher than that seen among the non-PCOS women (7.4%, 95% CI 5.8–9.2). The proportion of preterm deliveries among PCOS compared to non-PCOS women was more than 2-fold higher using criteria of less than 32 or 35 weeks gestation (Figure 1). One fifth of preterm births in PCOS women occurred extremely preterm, between 20–27 weeks gestation. Having PCOS was associated with a greater odds of having a singleton preterm delivery (unadjusted odds ratio OR 1.86, 95% confidence interval CI 1.37 – 2.53). This remained significant after adjusting for maternal age, race/ethnicity, parity, body mass index, chronic hypertension and infertility treatment (adjusted OR 1.69, 95% CI 1.14 – 2.49). PCOS status was associated with an even higher odds of early singleton preterm delivery (adjusted OR 2.26, 95% CI 1.10–4.64) prior to 32 weeks gestation.

Preterm singleton delivery rates also differed by race/ethnicity among PCOS women, with the highest proportion among Black (31.6%) and Asian (16.5%) women compared to White women (8.7%, p<0.01, Figure 2). In contrast, differences by race/ethnicity were not statistically significant within the non-PCOS group, although Black, Hispanic and Asian non-PCOS women had significantly lower percentages of singleton preterm delivery (14.3%, 7.6% and 5.4%) compared to PCOS women of the same race/ethnicity (p<0.05, Figure 2). The proportion of preterm deliveries was similar among white women with and without PCOS (7.4% vs 8.7%, respectively, p=0.51).

The underlying etiologies for preterm birth in PCOS women included preterm labor (41.0%), preterm premature rupture of membranes (14.5%) and cervical insufficiency (11.1%) for spontaneous preterm deliveries, and hypertensive disorders (19.7%), fetal-placental complications (8.6%), and intra-uterine fetal demise (5.1%) for indicated deliveries. When preterm births among PCOS women were classified by gestational age category (Figure 3), those occurring beyond 32 weeks were largely due to preterm labor, premature rupture of membranes, fetal/placental indications or hypertensive disorders. Most cases of cervical insufficiency and intrauterine fetal demise resulting in preterm birth occurred prior to 32 weeks gestation. Among the non-PCOS cohort, the underlying etiologies for singleton preterm delivery at less than 37 weeks included preterm labor (35.6%), preterm premature rupture of membranes (20.6%) and cervical incompetence (2.7%) for spontaneous preterm deliveries, and hypertensive disorders (27.4%), fetal-placental or maternal complications (9.6%), and intra-uterine fetal demise (4.1%) for indicated deliveries. Differences in the proportion of spontaneous preterm birth among PCOS and non PCOS women (67.7% and 58.9%, respectively) were not statistically significant (p= 0.28).

The clinical characteristics of the PCOS women by preterm delivery status are shown in Table 1. Nulliparous PCOS women had a significantly higher rate of preterm delivery compared with multiparous women (14.7% vs. 9.8%, p = 0.03). Women with preterm delivery also tended to be older, but did not differ by pre-pregnancy body mass index or treatment with fertility drugs, including *in vitro* fertilization. Only 46 PCOS women with singleton pregnancy underwent *in vitro* fertilization, with a trend towards greater proportion of preterm births among those conceiving by *in vitro* fertilization compared to those who did not 8.6% vs 4.6%, p=0.07). Preterm birth rates did not differ between the specific subset of PCOS women receiving preconception metformin alone (defined as within 3 months prior to conception) compared to those conceiving spontaneously (15.5% vs 11.4%, p= 0.34). Furthermore, the presence of gestational diabetes mellitus in the ascertained pregnancy was not associated with an increased risk of preterm birth (Table 1).

Using multivariable logistic regression, maternal age, race/ethnicity and nulliparity were significant predictors of singleton preterm delivery among PCOS women while body mass index and fertility treatment were not (Table 2). The adjusted odds of preterm delivery was five-fold higher among PCOS women of black race and approximately two-fold higher among women of Asian and Hispanic race/ethnicity compared to White women.

DISCUSSION

In a large, diverse cohort of PCOS women with singleton pregnancy, the frequency of preterm delivery was 12.9%, substantially higher than non-PCOS women and the background rates for Kaiser Permanente Northern California. These findings, reported from a real world clinical population of women with PCOS, support and extend prior studies examining adverse obstetric outcomes among women with PCOS. While an increase in preterm deliveries among PCOS compared to non-PCOS women has also been reported in smaller series,[10, 13, 15, 20] this is one of the first studies examining premature birth within a large cohort of PCOS women with singleton pregnancy.

Preterm births account for 35% of U.S. Health care spending for infants and 10% of spending for children.[33] In addition to a general trend towards earlier mean delivery among spontaneous births in the United States,[34] the frequency of preterm deliveries has steadily risen in the past two decades.[35–36] Two factors that may contribute to the national rise in preterm birth rates include the rise in "late" preterm births between 34–36 weeks gestation[34, 36] (potentially due to a greater number of indicated deliveries), and the increasing rate of multiple gestation pregnancies.[36] Data from the CDC National Vital Statistics report an increase in the overall rate of PTD from 10.6% in 1990, to 12.7% in 2005.[35–36] For singleton gestation, the rate increased from 9.7% to 11% in 2005.[35–36] In comparison, the rate of preterm delivery within KPNC is substantially lower, in the range of 7% for singleton pregnancies, based on regionwide perinatal outcome data and supported by the preterm delivery rate in our non-PCOS cohort. The higher rate of singleton preterm delivery among PCOS women observed in this study does not appear to be explained by an increase in late preterm births.

Within the general U.S. population, the proportion with preterm delivery is highest among Non-Hispanic Blacks (approximately two-fold higher compared to white women)[37] and similar for Hispanics and non-Hispanic Whites.[23] More recent data have shown increased rates of preterm delivery among various Asian subgroups, particularly Asian-Indians and Pacific Islanders.[38–40] In our PCOS population, Black women also had the highest preterm delivery rate and comprised a relatively small subset of 43 (4.2%) within our cohort. We similarly noted an increased risk of preterm birth among Asian compared to White women with PCOS. Our Asian subgroup consisted of 56% East Asian or Pacific Islander and 44% South Asian women, although our numbers are too small to effectively examine specific Asian subgroups. We also observed a significantly higher proportion of nonwhite PCOS women experiencing singleton preterm delivery compared to non-PCOS women. These race/ethnic disparities, in conjunction with maternal PCOS status, remain an important area for future investigation.

PCOS has been characterized by a similar state of chronic low-grade inflammation, with complex associations to insulin resistance, visceral adiposity, hyperandrogenism, and resultant increased production of specific cytokines and chemokines including TNF-alpha, IL-6 and IL-1,[5] adhesion molecules implicated in endothelial dysfunction,[41] follistatin and c-reactive protein.[42] Molecular and biochemical findings support the theory that in some situations labor may be viewed as part of an inflammatory cascade model, including pathways involving specific leukocyte subsets and pro-inflammatory mediators.[43] Chemokines and cytokines implicated in term deliveries may also play a role in preterm deliveries associated with and without intra-uterine infection,[43] with several studies reporting higher levels of inflammatory cytokines in amniotic fluid of women in premature labor. [44–45] An elevation in specific amniotic fluid biomarkers obtained during routine second trimester amniocentesis has been associated with preterm delivery,[46–48] including biomarkers differentially associated with preterm labor versus preterm premature rupture of membranes.[49–50] As such, underlying inflammatory mediators associated with PCOS may also contribute to predisposition for preterm delivery. One of the limitations of this study is that we do not have data pertaining to other known risk factors for preterm delivery, including history of prior preterm delivery, prior pregnancy interval, smoking, drug and alcohol use, cervical cone biopsy and cervical length.

Women with infertility are thought to be at higher risk for preterm delivery than spontaneously conceived non-infertility pregnancies.[51] Several studies also suggest a potential relationship with infertility treatment intervention, even after adjustment for multiple gestation pregnancy.[52–53] Among singleton pregnancies, assisted reproductive technology has been associated with increased rates of preterm delivery and low birth weight,[51, 53–58] although these complications have not been associated with other fertility medications (e.g. clomiphene citrate).[59] About half of the women in our study received fertility treatment, including *in vitro* fertilization in a small subset of 5%. While we did not see specific differences by treatment exposure, our cohort was not large enough to examine preterm delivery rates among specific infertility treatment subsets. Furthermore, subfertility has also been associated with an increase in adverse perinatal outcomes in the absence of assisted reproduction, including very preterm delivery.[60] Hormonal differences among

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PCOS subsets (e.g. oligo-amenorrhea versus hyperandrogenism) may also be associated with differential adverse outcomes,[8] and remain an area of active investigation.

In summary, this large, community-based pregnancy study demonstrates a relatively high rate of singleton preterm births among PCOS women, especially among Black and Asian PCOS women. These data confirm and extend prior findings of increased adverse pregnancy outcomes in PCOS women and raise the possibility that increased antenatal surveillance and facilitated access to higher levels of perinatal and neonatal services should be considerations for pregnant women with PCOS. Future research should more fully investigate the relationship of PCOS and preterm delivery and the role of specific maternal factors, including, race/ethnicity, age, underlying gestational condition, specific PCOS phenotypes, and target inflammatory mediators and chemokines. Our preliminary findings also suggest that potential areas of intervention to reduce adverse gestational outcomes in this growing population of affected women should be explored.

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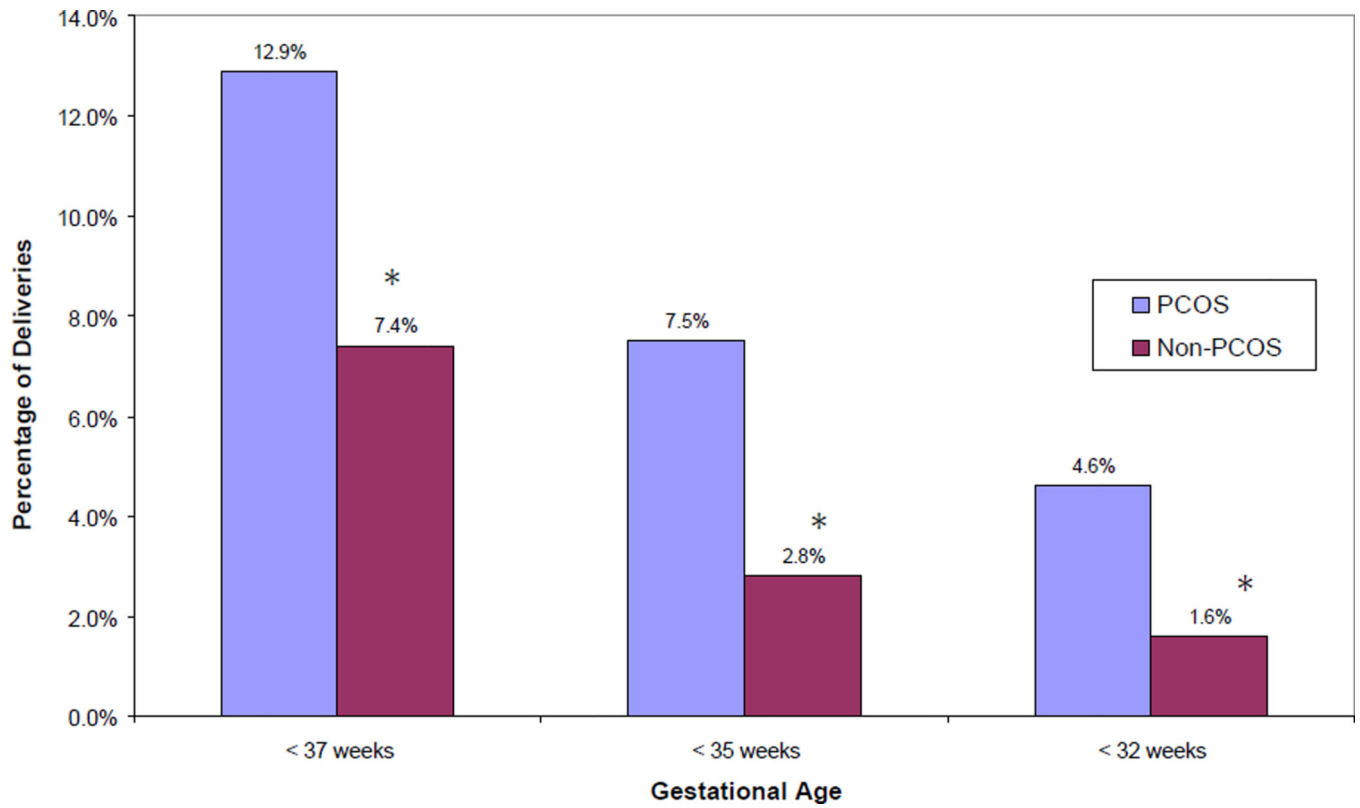
Figure 1.
The Percentage of Preterm Deliveries among Non-diabetic PCOS and Non-PCOS Women
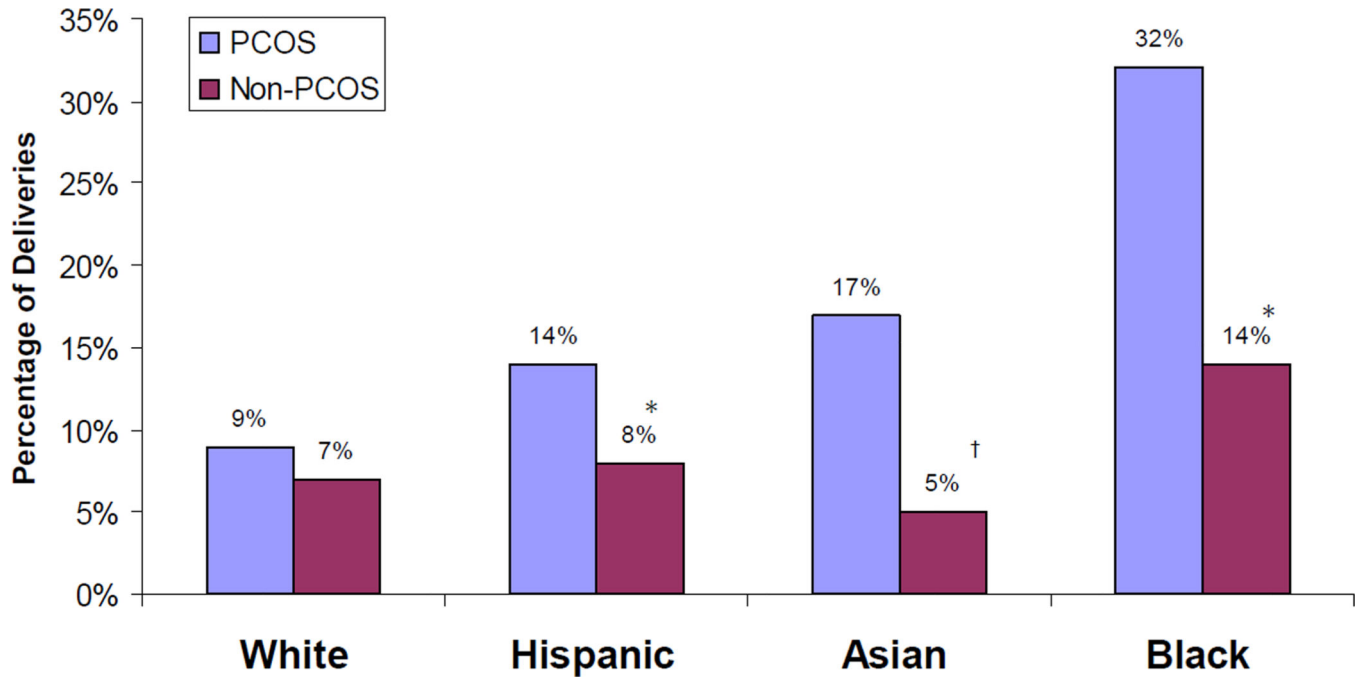with Singleton Pregnancy.
* p< 0.01 comparing PCOS to non-PCOS women

Figure 2.
Proportion of Singleton Preterm Delivery by Race/Ethnicity in PCOS and non-PCOS
Women

* p <0.05 compared to White women for PCOS and non-PCOS subsets.

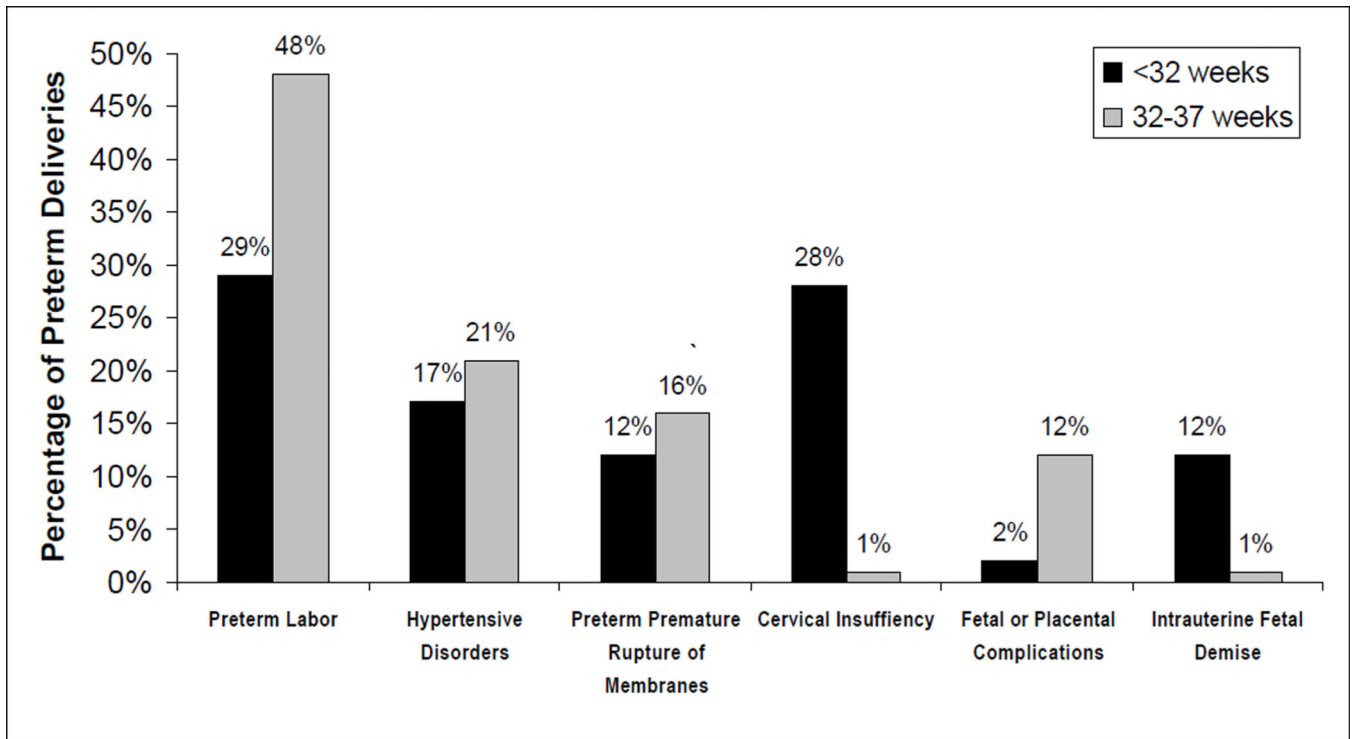† p < 0.01 comparing PCOS to non-PCOS women

Figure 3.
Singleton Preterm Delivery Etiology and Gestational Age Category among Pregnant
Women with Polycystic Ovary Syndrome

Table 1

Clinical Characteristics of Pregnant Women with Polycystic Ovary Syndrome by Preterm Delivery Status (< 37 weeks gestation)

	<37 weeks gestation N = 117	37 weeks gestation N = 791	P value
Nulliparity	72.7%	62.6%	0.03
Maternal age (years)	32.0 ± 4.9	31.2 ± 4.4	0.07
Maternal age 35 years	27.4%	19.9%	0.06
Pre-pregnancy Body Mass Index			0.37
<25 kg/m^2	22.2%	28.1%	
25–30 kg/m^2	33.3%	29.0%	
30 kg/m^2	44.4%	43.0%	
Fertility Medications[*]	53.9%	53.4%	0.92
Gestational Diabetes Mellitus	20.0%	18.0%	0.61

[*]Clomiphene citrate, gonadotropins and *in vitro* fertilization.

Table 2

Multivariable Predictors of Singleton Preterm Delivery in Polycystic Ovary Syndrome

Variable	Odds Ratio	95% Confidence Interval
Maternal age (per year)*	1.06	1.01–1.11
Race/Ethnicity: White	reference	
Black*	5.38	2.45–11.83
Asian*	2.11	1.20–3.49
Hispanic*	1.81	1.07–3.07
Nulliparity*	1.92	1.19–3.07
Body Mass Index (kg/m^2)	1.01	0.98–1.04
Fertility Medication†	0.83	0.54–1.26

*Significant predictors

†Clomiphene citrate, gonadotropins and *in vitro* fertilization.