A 5-Year Retrospective Review of Pregnancy Loss Among Women with Polycystic Ovarian Morphology

Marianne O. Dela Rosa, MD and Marian C. Dichoso, MD, FPOGS, FPRSM
Department of Obstetrics and Gynecology, De La Salle University Medical Center

Background: Polycystic ovarian morphology is the most common ultrasound abnormality among women with recurrent pregnancy loss and as such, its presence has been postulated to have a relationship with a high rate of miscarriage among women conceiving spontaneously.
Objective: The study aimed to determine the prevalence of pregnancy loss among women who have polycystic ovaries on ultrasound, at a tertiary hospital from January 2010 to December 2015.
Materials and Methods: A cross-sectional investigation involving a retrospective review of hospital records of 377 women who were diagnosed with polycystic ovaries on transvaginal ultrasound was performed. Their pregnancy outcomes were followed up by retrieving their medical charts at the outpatient department, consultants' clinics and the medical records section. Approval from the Independent Ethics Committee and Center for Clinical Epidemiology and Biostatistics was obtained.
Results: Of the 377 women with polycystic ovarian morphology, 280 (74.27%) met the 2003 Rotterdam criteria for polycystic ovary syndrome. The prevalence of pregnancy loss was 40.23%, while the live birth rate was 59.77% among the 377 women with polycystic ovaries on ultrasound. The majority of pregnancy loss occurred in the first trimester of pregnancy with a mean age of gestation of 8.9 ± 4.8 weeks
Conclusion: The prevelance of pregnancy loss among women with polycystic ovarian morphology was 40.23%

Key words: polycystic ovaries, polycystic ovary syndrome, pregnancy loss

Introduction

Pregnancy loss, a traumatic experience for a couple, is also one of the most difficult areas in reproductive medicine. Currently there are two types of pregnancy loss: sporadic and recurrent. Thirty percent to 50% of all conceptions and 15% of clinically recognized pregnancies fail to result in a live birth. This may be due to random fetal chromosomal abnormality in 50%-60% of cases.[1] On the other hand, recurrent pregnancy loss is defined as two or more clinically failed pregnancies recognized by ultrasound or histopathological examination.[2] Accurate prevalence is not available but it has been estimated that 2%-5% of women will experience recurrent pregnancy loss and majority will occur before the 10th week age of gestation. Indeed, the disorder is a challenge to the clinician as the work-up will involve genetic, anatomic, immunologic, iatrogenic and endocrinologic causes.

The development and maintenance of pregnancy are dependent on numerous endocrinological events that lead to the successful growth and development of the fetus. Although the majority of pregnant women have no pre-

existing endocrine abnormalities, a small percentage of women may develop endocrine alterations that can lead to sporadic or recurrent miscarriage. Some examples of endocrine disorders affecting pregnancy are the following: thyroid disorders, hyperprolactinemia, diabetes mellitus and polycystic ovary syndrome.

Among the various causes, polycystic ovaries are the most commonly identified ultrasound abnormality among women with recurrent pregnancy loss[3]. Its incidence ranges from 40 to 56% of women with recurrent pregnancy loss. Conversely, rate of early pregnancy loss is reported to be 30 to 50% in women with polycystic ovaries, which is three-fold higher than the rate of 10 to 15% in women with normal ovaries.[4]

Women with polycystic ovaries frequently present with reproductive dysfunction. When these women do finally achieve pregnancy, they are faced with a substantially high risk of miscarriage in the first trimester. The study of Sagle,[5] et al. was the first to forward the possible association of polycystic ovarian morphology on ultrasound with recurrent pregnancy loss. The results of their study showed a high miscarriage rate of 82%.

Closely related to polycystic ovaries and another cited cause of recurrent miscarriage is polycystic ovary syndrome (PCOS). It is the most common endocrine abnormality in reproductive-aged women and has been noted to be associated with increased frequency of pregnancy loss. The most commonly used criteria used to diagnose PCOS is the 2003 Rotterdam criteria which includes oligo- or anovulation, hyperandrogenism and morphologic evidence of polycystic ovaries on ultrasound. Satisfying 2 out of the 3 defined criteria will give a diagnosis of PCOS.

Women with polycystic ovary syndrome form a heterogeneous group. At one end of the spectrum are those with chronic anovulation and hyperandrogenism and at the other end are the much larger number who have polycystic ovarian morphology on ultrasound but no menstrual or biochemical abnormality. Previous studies have reported that women who either hypersecrete luteinizing hormone (LH) or who are hyperandrogenemic, two classical endocrinopathies associated with polycystic ovary syndrome, are at increased risk of miscarriage.[8] However, a prospective randomized placebo-controlled study[9] have showed that suppression of LH does not significantly improve the live birth rates of women with PCOS who hypersecrete LH. Rai and colleagues[8] have also failed to show that elevated testosterone is associated with elevated miscarriage rate.

Therefore the search for a specific endocrine abnormality that can divide women with PCO into those with a good and those with a poor prognosis for a future successful pregnancy continues.

The study aimed to determine the prevalence of pregnancy loss among women who have polycystic ovarian morphology on ultrasound at a tertiary hospital from January 2011 to December 2015.

Materials and Methods

Study Design

This is a cross-sectional study involving a retrospective review of hospital records, whose subjects were all women diagnosed with polycystic ovaries on transvaginal ultrasound seen at the Ultrasound Section of the Department of Obstetrics-Gynecology of the De La Salle University Medical Center from January 2010 to December 2010. Their pregnancy outcomes from January 2011 until December 2015 were followed up by retrieving their medical charts at the outpatient department, consultants' clinics and medical records.

Setting

The study was conducted at De La Salle University Medical Center, a tertiary hospital in Dasmarinas, Cavite from September 2015 to January 2016.

Definition of Terms

Polycystic ovaries. The ultrasound diagnosis of polycystic ovary was defined as the presence of 12

or more follicles measuring 2-9mm in diameter and/or increased ovarian volume (>10cm^3) in one or both ovaries.[10]

Polycystic ovary syndrome (PCOS). PCOS was classically characterized by the findings of irregular (anovulatory) cycles, symptoms or signs of androgen excess and polycystic ovaries on ultrasound[10]. The study employs the Rotterdam criteria in the diagnosis of PCOS (Appendix B).

Pregnancy loss. The spontaneous loss of a pregnancy before the fetus has reached viability at 24 weeks and this includes all pregnancy losses from the time of conception until 23 completed weeks of gestation[11]. In this study, the term will include spontaneous abortion, embryonic/fetal demise, delivery of a non-viable fetus (<24 weeks) or fetal death in utero.

Sporadic pregnancy loss. One pregnancy loss of less than 24 weeks.

Recurrent pregnancy loss. Defined by 2 or more failed clinical pregnancies, and up to 50% of cases of recurrent pregnancy loss will not have a clearly defined etiology[10].

Participants

Inclusion Criteria

All women diagnosed with polycystic ovaries by transvaginal ultrasound and who had history of pregnancy, whether pregnancy loss or livebirth as outcome.

Exclusion Criteria

Medical charts of women with the following conditions were excluded:

1. Other causes of pregnancy loss such as ectopic gestation, induced abortion and those due to trauma

2. Ultrasonography-documented uterine anatomical anomalies

3. Pregnancies complicated by medical conditions such as hypothyroidism, diabetes mellitus, hypertension

4. Confirmed cases of immunoreproductive disorder

5. Patients who received metformin, progesterone or any tocolytics during pregnancy

6. Pregnancies achieved through fertility workup

The following independent variables were recorded:

1. Age (years)

2. Body mass index (BMI, kg/m^2)

3. Gestational age during delivery (weeks)

4. Gravidity and parity

The following dependent variables were recorded:

1. Number of pregnancy loss

2. Number of women with first, second and third trimester pregnancy loss

3. Number of women with a live birth

Data Collection

Patients with polycystic ovarian morphology on ultrasound were determined in 6556 women scanned at the Ultrasound Section of the Department of OBGYN between January 2010 and December 2010. Out-patient and in patient medical records of women presenting with PCO were screened for inclusion in the study. A patient's data sheet (Appendix) was the primary mode of data gathering.

Sample Size

A minimum sample size of 371 charts was required assuming a prevalence of pregnancy loss

in women with polycystic ovarian morphology at 40.7%[5], 95% confidence interval with 10% error.

Legend:
n = minimum sample
P = Prevalence of pregnancy loss among women with polycystic ovarian morphology = 40.7%
e = marginal error = 0.10
zα = 1.96

Sample size formula:[12]

$$n \geq \frac{Z^2{}_{1-\alpha/2} \times 4 \times P \times (1-P)}{e^2}$$

$$n \geq \frac{1.96^2 \times 4 \times 0.407 \times (1-0.407)}{0.10^2}$$

$$n \geq 370.87 \approx 371$$

Statistical Method

Demographic and clinical characteristics were summarized using descriptive statistics, such as frequency, percentage, mean and standard deviation. To calculate the prevalence of pregnancy loss among women with polycystic ovary, the number of pregnancy losses among these women was divided by the total number of pregnancies among the same group. Missing variables were neither replaced nor estimated. STATA 12 was used for data analysis.

Consent

A letter addressed to the custodian of the Records Section of the De La Salle – University Medical Center, as well as the Medical Director, for access to medical records was submitted. This is with the assurance that confidentiality in the perusal of records of patients was maintained throughout the conduct of the study.

Ethical Considerations

The study was conducted in accordance to the ethical principles based on the Declaration of Helsinki and the National Guidelines for Biomedical Research of the National Ethics Committee (NEC) of the Philippines. The research protocol underwent approval from the Center for Clinical Epidemiology and Biostatistics (CCEB) of De La Salle University Medical Center prior to its conduct. The results and patient information was kept strictly confidential by the primary investigator. A unique alphanumeric code was assigned to each research subject and the subjects' names did not appear on any of the data collection tools. Only the primary investigator had access to the patients' names and other pertinent information, to ensure patient confidentiality at all times. The data was stored in the primary investigator's database, password-protected, and the projected duration of storage is at least 10 years.

Results

A total of 377 women with polycystic ovaries were analyzed and their clinical characteristics are shown in Table 1. On average, the patients' group was aged 31.17 ± 5.15 years and the mean body mass index was 24.31 ± 4.09 kg/m^2. Fifty four percent were primigravida and 46% were multigravida. Fifty-eight percent were primiparous, 18% were nulliparous and 24% were multiparous. Seventy-eight (20.69%) women had pregnancy losses, 16 (4.24%) of which had recurrent pregnancy loss. Of the 377 women with polycystic ovarian morphology, 280 (74.27%) met the 2003 Rotterdam criteria for polycystic ovary syndrome.

Table 2 provides the total number of live births and pregnancy loss among patients with polycystic ovaries from 2011 to 2015.

Out of 377 women with polycystic ovaries, the prevalence of pregnancy loss was 40.23% while the live birth rate among these women was 59.77%. Table 3 specifies the gestational ages at delivery and at pregnancy loss among 377 patients with polycystic ovaries.

The mean age of gestation at delivery in this group of women was 38.71+2.44 weeks. The majority of pregnancy loss occurred in the first trimester of pregnancy with a mean age of gestation at 9.44 + 5.60 weeks.

Table 1. Demographic and clinical characteristics of women with polycystic ovaries (n= 377).

	Frequency (%); Mean ± SD
Age (years)	31.17 ± 5.15
Body mass index (kg/m^2)	24.31 ± 4.09
Gravida	
Primigravida	204 (54.11)
Multigravida	173 (45.89)
Parity	
Nulliparous	68 (18.04)
Primiparous	217 (57.56)
Multiparous	92 (24.40)
Women with pregnancy loss	78 (20.69)
Number of pregnancy loss	
1	62 (16.45)
2	12 (3.18)
3 or more	4 (0.27)
Confirmed to have polycystic ovary syndrome	280 (74.27)

Table 3. Outcomes of pregnancies from January 2011 until December 2015 among women with polycystic ovaries (n= 377).

	Frequency (%); Mean ± SD
Live births	
1st pregnancy (n=221)	139 (62.89)
2nd pregnancy (n=32)	17 (50)
3rd pregnancy (n=9)	2 (22.22)
4th pregnancy (n=3)	1 (33.33)
Gestational age upon delivery (weeks)	
1st pregnancy (n=139)	36.73 ± 7.64
2nd pregnancy (n=17)	34.90 ± 10.90
3rd pregnancy (n=2)	23.50 ± 21.92
4th pregnancy (n=1)	37.00 ± 0.00
Gestational age during pregnancy loss (weeks)	
1st pregnancy (n=82)	9.79 ± 6.20
2nd pregnancy (n=16)	7.75 ± 3.71
3rd pregnancy (n=7)	10.29 ± 8.34
4th pregnancy (n=2)	9 ± 4.24
Pregnancy loss	
1st pregnancy (n=82)	
1st trimester	73 (89.02)
2nd trimester	5 (6.10)
3rd trimester	4 (4.88)
2nd pregnancy (n=16)	
1st trimester	15 (93.75)
2nd trimester	1 (6.25)
3rd pregnancy (n=7)	
1st trimester	6 (85.71)
3rd trimester	1 (14.29)
4th pregnancy (n=2)	
1st trimester	2 (100)

On the other hand, women diagnosed with polycystic ovary syndrome deliver at a mean age of gestation of 38.51 ± 2.36 weeks. The majority of pregnancy loss also occurred in the first trimester of pregnancy with a mean age of gestation at 8.90 ± 4.8 weeks (Table 4).

Discussion

In this study, the mean age of the women studied was 31 years. Most definitions of recurrent pregnancy loss will not include the age of the

Table 2. Total number and proportion of live births and pregnancy loss among women with polycystic ovaries, 2011-2015.

Pregnancy	Live Birth	Pregnancy Loss	Total Number of Pregnancies
		Frequency (%)	
1st	139	82	221
2nd	17	16	33
3rd	2	7	9
4th	1	2	3
TOTAL	159 (59.77)	107 (40.23)	266 (100)

Table 4. Gestational ages at delivery and on pregnancy loss among 377 patients with polycystic ovaries and polycystic ovary syndrome.

	PCOS	PCO
Mean AOG at delivery	38.51 ± 2.36	38.71 ± 2.44
Mean AOG at miscarriage	8.90 ± 4.80	9.44 ± 5.60

woman. However, maternal age seems to be the single most important determinant of the condition through oocyte depletion and fetal aneuploidy. A study[13] showed increasing estimates of sporadic miscarriages with increasing maternal age. As such, the theoretical incidence of recurrent pregnancy loss according to maternal age for this set of women is 1 in 45 or 2.2%.

The mean body mass index of the women studied was 24.71 kg/m^2, which is considered overweight in South Asian countries. Obesity has often been associated with pregnancy loss and infertility. A study[6] conducted on 2349 women aimed to examine the relationship between body mass index (BMI) and spontaneous abortions has shown increasing miscarriage rates as BMI increases.

In this study, the prevalence of pregnancy loss among women with polycystic ovarian morphology is 40.23%. This is in agreement with data published by Rai, et al. (2000), revealing a 40.7% prevalence rate of polycystic ovarian morphology among women with recurrent miscarriages. The original description of polycystic ovaries as a risk factor for recurrent miscarriages and infertility is found in the study of Sagle, et al.[5] in 1988 where a miscarriage rate of 82% was established. They further pointed out that the study group had normal hormonal indices. This was further supported by a study done by Tulppala[14] who showed that androgen levels among women with anatomically polycystic ovaries did not differ significantly from the control group. This study also showed a 50% miscarriage rate among women with polycystic ovaries. Thus, through the years, it has been postulated that the finding of anatomically polycystic ovaries on ultrasound dictates a risk for pregnancy loss.

However, several authors had subsequently proven otherwise. Two studies[8,15] were performed to determine the pregnancy outcome of women who had habitual abortions. They had two study groups: those with polycystic ovaries and those without. They found out no significant difference in terms of the recurrent miscarriages between the two groups. Furthermore, the study[15] found a 36% miscarriage rate in women with polycystic ovaries but also noted that 82% of these women also had subsequent live births, similar to the live birth rate of 81% found in normal women.

The conclusion that can be drawn from these studies was that the finding of polycystic ovaries among women with pregnancy loss is overrepresented, implying an increased risk when in fact the finding of polycystic ovaries on ultrasound is not predictive of subsequent pregnancy outcome.

Of the 377 women with ultrasonographic polycystic ovaries, 280 were subsequently diagnosed with polycystic ovary syndrome. Among these women with PCOS, the incidence of pregnancy loss is 32.9% (92/280). This is in agreement with the findings of Glueck[6,] et al. where 40% or pregnant patients with PCOS result in abortion.

PCOS is a disorder more common among women with recurrent abortion.[16] However, establishing an association between PCOS and recurrent pregnancy loss is difficult due to the variability in disease etiologies and diagnostic criteria.

The multiple metabolic and endocrine abnormalities commonly observed in patients with PCOS are insulin resistance, hyperinsulinemia and hyperandrogenemia. It is presumed that these are the factors responsible for the increased abortion risk in pregnant patients with PCOS.[17] Hyperinsulinemia and insulin resistance are cited as independently related with recurrent miscarriages, but literature associating these with early pregnancy loss does not adequately differentiate the two. Elevated androgen levels and elevated insulin levels have detrimental effects on endometrial development.[18] Elevated androgen levels decrease oocyte quality and embryo viability.[19] There is a positive correlation between

increased body mass index in patients with PCOS and recurrent abortions[20]. This may be due to insulin resistance, hyperinsulinemia and hyperandrogenemia present in obese women. This demonstrates that the metabolic abnormalities seen in PCOS and the incidence of recurrent abortion may be interrelated.

Conclusion

In this study, the prevalence of pregnancy loss among women with polycystic ovarian morphology is 40.23%. Of the 377 women included in the study, 280 (79.3%) fulfilled the Rotterdam criteria for polycystic ovary syndrome.

References

1. Pluchino N, Drakopoulos P, Wenger JM, Petignat P, et al. Hormonal causes of recurrent pregnancy loss. Hormones 2014;13(3):314-22.
2. Practice Committee of the American Society for Reproductive Medicine, Evaluation and treatment of recurrent pregnancy loss: a committee opinion. Fertility and Sterility 2012;98: 1103-11.
3. Gallardo-Lozano E, Ayon P, Neuspiller F. A study of two different routes of administration of micronized progesterone in assisted reproduction. Ginecolía y Obstetricia de MPxico 2004;72: 407-10.
4. Shah D and Patel S. Polycystic ovarian syndrome as a cause of recurrent pregnancy loss. The Journal of Obstetrics and Gynecology of India 2007; 57(5):391-7.
5. Sagle M, Bishop K, Ridley N, et al. Recurrent early miscarriage and polycystic ovaries. British Medical Journal 1988; 297: 1027-8.
6. Rai R, Backos M, Rushworth F and Regan S. Polycystic ovaries and recurrent miscarriage – a reappraisal. Human Reproduction 2000; 15(3): 612-5.
7. Clifford K, Rai R, Watson H, et al. Does suppressing luteinising hormone secretion reduce the miscarriage rate? Results of a randomized controlled trial. British Medical Journal 1996; 312: 1508-11.
8. Philippine Society of Reproductive Endocrinology and Infertility Consensus Statements on Polycystic Ovary Syndrome. Philippine Obstetrical and Gynecological Society, Inc. 2009.
9. Royal College of Obstetricians and Gynecologists. The investigation and treatment of couples with recurrent first trimester and second trimester miscarriage. Green-top Guideline No. 17. London:RCOG;2009 [http://www.rcog.org.uk/en/guidelines-research-services/guidelines/gtg17.
10. Naing L, Winn T, Rusli B. Practical issues in calculating the sample size for prevalence studies. Medical Statistics 2006; 1(1): .http://www.dental.usm.my/aos/docs/Vol_1/09_14_ayub.pdf (accessed 24 September 2015).
11. Saravelos SH, Regan L. Unexplained recurrent pregnancy loss. Obstet Gynecol Clin N Am 2014; 41: 157-66.
12. Tulppala M, Stenman UH, Cacciatore B et al. Polycystic ovaries and levels of gonadotropins and androgens in recurrent miscarriage: prospective study in 50 women. Br J Obstet Gynecol 1993; 100: 348-52.
13. Liddell HS, Sowden K, Farquhar CM. Recurrent miscarriage: screening for polycystic ovaries and subsequent pregnancy outcome. ANZ J Obstet Gynecol 1997; 37: 402-6.
14. Clinical Practice Guidelines on Recurrent Pregnancy Loss. Philippine Obstetrical and Gynecological Society, Inc. 2014.
15. Cocksedge KA, Li C, Saravelos SH, Metwally M. A reappraisal of the role of polycystic ovary syndrome in recurrent miscarriage. Reproductive Biomedicine Online 2008;17(1):151-60.
16. Craig LB, Ke RW, Kutteh WH. Increased prevalence of insulin resistance in women with a history of recurrent pregnancy loss. Fertility and Sterility 2002; 78(3): 487-90.
17. van Wely M, Bayram N, van der Veen F, Bossuyt PM. Predicting ongoing pregnancy following ovulation induction with recombinant FSH in women with polycystic ovary syndrome. Hum Reprod 2005; 20(7): 1827-32.
18. Al-Azemi M, Omu FE, Omu AE. The effect of obesity on the outcome of infertility management in women with polycystic ovary syndrome. Arch Gynecol Obstet 2004; 270(4): 205-10.
19. Uyking-Naranjo M, Paulo Consencino E, Mirasol R, et al. The effect of metformin on pregnancy outcome among Filipino women with polycystic ovary syndrome. Journal of the ASEAN Federation of Endocrine Societies 2014;28(1),45. doi:http://dx.doi.org/10.15605/jafes.028.01.09.