OBSTETRICS

Second-trimester loss and subsequent pregnancy outcomes: What is the real risk?

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OBJECTIVE: This study was performed to determine whether second-trimester pregnancy loss was associated with an increased risk for spontaneous preterm birth or recurrent second-trimester loss in a subsequent pregnancy.

STUDY DESIGN: A retrospective cohort study was conducted. Patients with a second-trimester pregnancy loss (n = 38), a spontaneous preterm birth (n = 76), and a full term delivery (n = 76) were identified from 2002 to 2005 (index pregnancy). Computerized medical records were used to obtain demographic and obstetrical histories.

RESULTS: Frequencies of subsequent second-trimester loss were 27%, 3%, and 1% in the second-trimester loss, spontaneous preterm birth, and full-term delivery cohorts, respectively. Frequencies of subsequent spontaneous preterm birth were 33%, 39.5%, and 9% in the same 3 cohorts. Patients with a prior second-trimester loss were 10.8 times more likely to have recurrent second-trimester loss or spontaneous preterm birth, compared with those with prior full-term delivery (confidence interval 3.6 to 32.1, $P < .0001$).

CONCLUSION: Patients with a prior second-trimester loss are at significantly increased risk for spontaneous preterm birth and recurrent second-trimester loss in their next pregnancy.

Key words: pregnancy outcome, second-trimester pregnancy loss, spontaneous preterm birth, subsequent pregnancy

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Second-trimester pregnancy loss is defined as pregnancy loss after the 14th week of gestation and before the 24th week of gestation. It is estimated to complicate 1-2% of recognized pregnancies and as many as 50 pregnancies per year at the Hospital of the University of Pennsylvania.[1,2] Second-trimester loss has been associated with infection, cervical insufficiency, uterine malformations, gene polymorphisms, fetal and placental anomalies, and genetic and acquired thrombophilias.[3-14] Whereas multiple studies have examined possible etiologic factors in second-trimester loss and preterm birth before 28 weeks of gestation, there is a paucity of data regarding subsequent pregnancy outcomes in patients with a prior spontaneous second-trimester loss.[15] A limited number of studies have examined subsequent pregnancy outcomes in women with a spontaneous loss. However, most of these studies have been confounded by the inclusion of patients with first-trimester losses, patients with preterm delivery (24 to $36^{6/7}$ weeks), or patients with an intrauterine fetal demise (IUFD), failing to specifically address subsequent pregnancy outcomes in patients who have a spontaneous loss in the second trimester (14 to $23^{6/7}$ weeks).[16-20]

Although patients with a prior preterm birth are known to have an increased risk of recurrent preterm birth, and patients with a prior term delivery (37 weeks or longer) are thought to be relatively protected from preterm birth with a preterm delivery rate less than the national average,[21,22] subsequent pregnancy outcomes have not been well delineated in patients with a prior second-trimester loss. Because there is limited information about subsequent pregnancy outcomes in patients with prior second-trimester loss, counseling these patients about future pregnancy outcomes remains difficult.

The primary objective of this study was to investigate whether a history of a spontaneous second-trimester pregnancy loss was associated with an increased risk for second-trimester loss (14 to $23^{6/7}$ weeks) or spontaneous preterm birth (PTB) (24 to $36^{6/7}$ weeks) in a subsequent pregnancy. Our secondary aim was to characterize the risk of subsequent spontaneous PTB in patients with a prior second-trimester loss, compared with patients with a prior spontaneous PTB and patients with a prior full-term delivery.

Materials and Methods

A retrospective cohort study was performed with approval by the Institutional Review Board of the Hospital of the University of Pennsylvania. To investigate subsequent pregnancy outcomes in patients with a history of second-tri-

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mester pregnancy loss, we compared the subsequent pregnancy outcomes of 3 patient cohorts: (1) patients with a second-trimester loss, (2) patients with a history of spontaneous PTB, and (3) patients with a history of a full-term birth.

The second-trimester loss cohort was comprised of a subset of spontaneous second-trimester loss patients who were prospectively identified as part of an earlier study.[3] The original second-trimester loss cohort included all women with singleton pregnancy who had a spontaneous pregnancy loss between a gestation of 14 weeks, 0 days and 23 weeks, 6 days and presented to the labor and delivery unit at the Hospital of the University of Pennsylvania (HUP) between June 1, 2002, and Jan. 31, 2005 (n = 97), as previously reported.[3] Spontaneous pregnancy loss was defined as preterm premature rupture of membranes (PPROM), premature labor or cervical insufficiency, with a fetus that was alive at the time of rupture of membranes, labor, or cervical dilation. Cervical insufficiency was defined as presentation with painless cervical dilation in the second trimester.

Women with intrauterine fetal demise and/or multifetal pregnancies that were resolved with dilation and evacuation were excluded because these losses may be due to different mechanisms than spontaneous miscarriage. Estimated gestational age at the time of the index second-trimester loss was based on previous documented ultrasound or ultrasound at the time of presentation. The labor and delivery database at the University of Pennsylvania was then queried from September 2002 through August 2006 to determine which of the 97 women in the original second-trimester loss cohort had a subsequent pregnancy (n = 38) beyond 14 weeks' gestation (n = 34) that was delivered at our institution (n = 30) for a final cohort (n = 30).

Two control groups were utilized: (1) patients with a prior full-term delivery and documented subsequent pregnancy outcome and (2) patients with a prior spontaneous PTB and subsequent pregnancy outcome. Controls were matched 2:1 to the month of delivery for each patient with a second-trimester loss based on the original 38 women identified. Inclusion criteria for both spontaneous PTB and full-term delivery controls were the following: singleton pregnancy, documented subsequent pregnancy gestation of 14 weeks or longer before Aug. 31, 2006, and delivery at HUP. Women with multifetal pregnancy or preterm birth secondary to maternal or fetal medical indications in the index pregnancy were excluded. The estimated gestational age at the time of delivery for both control groups was established by the best obstetrical estimate (using earliest ultrasound documenting EDD or second-trimester ultrasound).

Controls were selected in the following manner: the medical record database was queried for all births at either gestational age of "less than 37 weeks" or ""37 weeks or longer" within 1 month of the delivery date of each index second-trimester loss. The results generated by the query were arranged alphabetically, and each patient was investigated to ascertain whether she met inclusion/exclusion criteria until the desired sample size was achieved.

Computerized medical records were utilized to collect data about the index and subsequent pregnancies for all 3 study groups. Similar information was collected for each subject including maternal demographic, medical, and obstetric data as well as delivery and fetal/neonatal information. Short interpregnancy interval was defined as 6 months or less from delivery date of index pregnancy to last menstrual period of subsequent pregnancy, based on recent studies that have suggested this interval is associated with adverse pregnancy outcomes.[23-27] Poor obstetric outcome was defined as second-trimester pregnancy loss (14 to $23^{6/7}$ weeks) or spontaneous PTB (24 to $36^{6/7}$ weeks) in a subsequent pregnancy.

Associations of interest were initially evaluated by Pearson χ^2 and Fisher exact tests. One-way analysis of variance was used to compare the means of continuous variables including birthweight, maternal age, interpregnancy interval, and gestational age at delivery. Significant associations were adjusted for potential confounders, including maternal age, race, prenatal care, obstetric history, interpregnancy interval 6 months or less, and tobacco use, using multivariable logistic regression (STATA, version 9.0, Stata Corp, College Station, TX).

Initial associations between interpregnancy interval and subsequent pregnancy outcome were evaluated using Pearson χ^2 test. Tests for effect modification or interaction between interpregnancy interval and index pregnancy group were performed. The final logistic regression model adjusted for potential confounders (race, age, and prenatal care) and included an interaction term between index pregnancy group and interpregnancy interval 6 months or less.

We assumed a spontaneous PTB rate of 35% in women with a prior PTB, 5% in women with a prior full-term delivery, and 20% in women with a prior second-trimester loss.[28,29] Assuming a power of 0.80, a type I (alpha) error of 0.05, and a 2:1 ratio of unexposed (full-term delivery) to exposed (second-trimester loss) patients, 30 second-trimester loss and 60 full-term delivery patients were needed to detect a 6-fold difference in spontaneous PTB.

RESULTS

Of the 97 women with a second-trimester loss prospectively collected between June 1, 2002, and Jan. 31, 2005, 38 had a subsequent pregnancy between December 2003 and May 2006. Of these 38, 4 were excluded because their subsequent pregnancy resulted in a first-trimester spontaneous abortion, and 4 additional patients were excluded based on incomplete medical records, for a final cohort (n = 30). The control populations were comprised of 76 women with a spontaneous PTB (June 2002 to February 2005) and subsequent pregnancy gestation of 14 weeks or longer delivered at HUP (May 2003 to May 2006) and 76 women with a full-term delivery (June 2002 to February 2005) and subsequent pregnancy gestation of 14 weeks or longer delivered at HUP (October 2003 to July 2006). The median gestational age at index pregnancy delivery for the spontaneous PTB cohort was 247 days (35 weeks, 2 days) ± 22.4 days (range 171 days [24

TABLE 1
Demographics

	Cohorts by index pregnancy			
	Second-trimester pregnancy loss (n = 30)	Spontaneous PTB (n = 76)	Full-term delivery (n = 76)	*P* value
Mean maternal age at index pregnancy, y	25.1 ± 6.1	24.2 ± 5.6	25.0 ± 5.6	.4
Mean maternal age at subsequent pregnancy, y	26.5 ± 6.1	25.8 ± 5.6	26.9 ± 5.7	.5
Smokers (subsequent pregnancy), % (n)	22.2 (6)	20 (15)	15.8 (12)	.7
African American race, % (n)	90 (27)	89.5 (68)	71 (54)	.006
Mean interpregnancy interval (d)	351.4 ± 220.5	344.9 ± 228.6	395.4 ± 207.8	.6
No prenatal care (index pregnancy), % (n)	10 (3)	14.4 (11)	2.6 (2)	.03
No prenatal care (subsequent pregnancy), % (n)	16.7 (5)	11.8 (9)	2.6 (2)	.03
Mean gestational age at delivery (subsequent pregnancy)	29.4 ± 9.3	35.8 ± 4.2	38.1 ± 3.3	.001

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weeks, 3 days] to 257 days [36 weeks, 5 days]). The median gestational age at index pregnancy delivery for women in the second trimester loss cohort was 143 (20 wks, 3 days) ± 17.0 days (range, 108 days [15 wks, 3 days] to 164 days [23 wks, 3 days]).

The 3 study groups did not differ significantly with respect to tobacco use, mean interpregnancy interval, or maternal age at index or subsequent pregnancy (Table 1). African American women comprised a significantly greater percentage of the second-trimester loss and spontaneous PTB groups, compared with the full-term delivery cohort. Women in the second-trimester loss and spontaneous PTB groups were more likely to have received no prenatal care than patients in the full-term delivery group (Table 1).

Table 2 describes obstetric history at the time of index pregnancy. Women in the spontaneous PTB cohort were less likely to be primiparous, compared with patients with a full-term delivery ($P = .03$). Of patients who were multiparous at time of index pregnancy, patients in the second-trimester loss cohort and spontaneous PTB cohort were significantly more likely to have had a history of spontaneous PTB, compared with patients in the full-term delivery cohort ($P < .0001$). Patients in the second-trimester loss cohort were the least likely to have had a prior full-term delivery and were significantly more likely to have had a second-trimester loss prior to the index pregnancy ($P < .0001$), compared with the other cohorts.

No patients in the index second-trimester loss cohort had a cerclage at the time of the index loss. There were 6 patients in the second-trimester loss cohort who had cerclage in their subsequent pregnancy. Of these 6, 4 had PPROM. Three of the 6 patients with cerclage had preterm birth, 2 at 34-37 weeks and 1 at less than 28 weeks. Two of the 6 patients with cerclage had recurrent second-trimester pregnancy loss.

The Figure depicts subsequent pregnancy outcomes in the 3 cohorts. Patients in the second-trimester loss cohort had a significantly higher frequency of recurrent second-trimester loss (27%) than women in the spontaneous PTB (3%) and full-term delivery (1%) control groups ($P < .0001$). The frequency of spontaneous PTB in the subsequent pregnancy was 33% for the second-trimester loss cohort, compared with 39.5% in the spontaneous PTB cohort and 9.2% in the full-term delivery cohort. Table 3 depicts frequencies of preterm delivery (at less than 34, less than 32, and <28 weeks' gestation) by index pregnancy cohort.

TABLE 2
Obstetric history by index pregnancy cohort

Index pregnancy	Primiparous at time of index pregnancy, %	≥1 SPTB before index pregnancy, %	≥1 FTD before index pregnancy, %	≥1 STPL before index pregnancy, %
STPL cohort (n = 30)	30	38.1	36.7	38.1
SPTB cohort (n = 76)	13.2	40.9	69.7	4.5
FTD cohort (n = 76)	30.3	5.7	67.9	1.9
P value	.03	< .0001	.33	< .0001

FTD, full-term delivery; *SPTB*, spontaneous PTB; *STPL*, second-trimester pregnancy loss.

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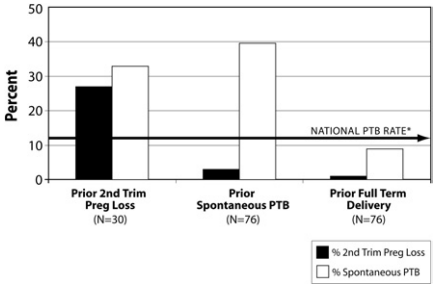
FIGURE
Subsequent pregnancy outcome by index pregnancy cohort



2nd Trim Preg Loss, second trimester pregnancy loss; *Spontaneous PTB,* spontaneous preterm birth.

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Patients with a prior second-trimester loss were nearly 11 times more likely to have a recurrent second-trimester loss or PTB, compared with those with a prior full-term delivery (odds ratio [OR] 10.8, confidence interval [CI] 3.6 to 32.1, $P < .0001$) after adjusting for maternal age, race, prenatal care, tobacco use, and interpregnancy interval of 6 months or less. Patients with a prior spontaneous PTB were 5.4 times as likely to have a poor obstetric outcome, compared with those with a prior full-term delivery, after adjusting for the same confounders (CI, 2.2 to 13.1, $P < .0001$). Patients with prior second-trimester loss were significantly more likely to have a second-trimester loss in their subsequent pregnancy, compared with those with prior PTB (OR 15.2, CI, 2.9 to 80.2, $P = .001$) or a full-term delivery (OR 24.4, CI, 2.8 to 210.3, $P = .004$).

In a subanalysis, we examined rates of second-trimester loss and spontaneous PTB in those patients for whom the index pregnancy (second-trimester loss, spontaneous PTB, or full-term delivery) was their first pregnancy. For patients who were primiparous at their index pregnancy, women with a second-trimester loss were 13.3 times more likely to have either a recurrent second-trimester loss or PTB in their subsequent pregnancy, compared with patients with a full-term delivery (CI, 1.05 to 169.56, $P = .046$).

We also examined frequencies of second-trimester loss and spontaneous PTB in subsequent pregnancy by gestational age at the index second-trimester pregnancy loss. In women with an index loss at 18 weeks or less, 43% had a recurrent second-trimester loss and 29% had spontaneous PTB. In women with their index second-trimester loss at longer than 18 weeks, 30% had a recurrent second-trimester loss, and 35% had a subsequent spontaneous PTB. Thus, the frequency of poor obstetric outcome in women with index loss at 18 weeks or less was 72% vs 65% in those with index loss at longer than 18 weeks ($P = .76$).

There was a significant interaction between interpregnancy interval and index pregnancy cohort (interaction P value = .04). For patients with an index spontaneous PTB or an index second-trimester loss, interpregnancy interval of 6 months or less had no significant effect on the risk of subsequent second-trimester loss (adjusted OR [AOR] 0.83, CI, 0.27 to 2.52, $P = .74$) or PTB (AOR 1.32, CI, 0.204 to 8.6, $P = .77$). However, for patients with an index full-term delivery, interpregnancy interval of 6 months or less resulted in 10.1 times greater odds of a second-trimester loss or spontaneous PTB in their subsequent pregnancy (CI, 1.9 to 52.9, $P = .006$), compared with women with an interval greater than 6 months.

TABLE 3
Frequency of spontaneous PTB by index pregnancy cohort

	Percent of women with spontaneous PTB		
Index pregnancy	SPTB less than 34 wks	SPTB less than 32 wks	SPTB less than 28 wks
STPL cohort (n = 30)	16.7	13.3	10.0
SPTB cohort (n = 76)	15.8	7.9	1.3
FTD cohort (n = 76)	4	2.6	1.3

FTD, full-term delivery; *SPTB*, spontaneous PTB; *STPL*, second-trimester pregnancy loss.

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Comment

This study examines subsequent pregnancy outcomes in women with second-trimester pregnancy loss, an understudied, but important, obstetric population. Our study suggests that: (1) patients with second-trimester loss are significantly more likely to have a recurrent second-trimester loss in a subsequent pregnancy, compared with preterm and full-term birth controls; (2) patients with a second-trimester loss are significantly more likely to have spontaneous PTB in a subsequent pregnancy, compared with full-term delivery controls; (3) the frequency of subsequent spontaneous PTB among women with a prior second-trimester loss approaches the frequency of recurrent PTB among women with a prior PTB; and (4) a short interpregnancy interval appears to pose an increased risk of poor obstetric outcome in patients with prior full-term delivery but not in those with prior second-trimester loss or PTB, most likely because the a priori risk of poor obstetric outcome in the latter 2 groups is already significant. Of great clinical concern is that women with prior second-trimester pregnancy loss have a high frequency of very early preterm birth (less than 28 weeks). Because our observed frequency of spontaneous PTB in the second-trimester loss cohort was much greater than the initial estimate, we had adequate power (80%) to detect a 4-fold difference between groups with 30 second-trimester loss and 76 full-term delivery patients, confirming the validity of these findings.

Other strengths of this study include: (1) the prospective collection of the initial second-trimester loss cohort, allowing for physician-verified second-trimester loss, rather than retrospective identification of patients by *International Classification of Diseases*, ninth revision codes or patient report; (2) a focus

exclusively on the second trimester (14 to $23^{6/7}$ weeks) for the index loss, providing clear outcomes data for this understudied group; (3) the inclusion of patients with only spontaneous, rather than indicated, second-trimester loss and PTB in the index cohorts; and (4) the random collection of 2 control groups from a similar time period and the same source population.

Although there are many strengths, there are also some notable limitations, including: (1) the retrospective collection of controls; (2) the generalizability of our findings, considering our predominantly inner-city, urban patient population; (3) the relatively small number of patients in the second-trimester loss cohort; (4) the inability to fully delineate the complex interplay of obstetrical history and its effect on subsequent pregnancy outcomes, given that the index groups are not comprised of exclusively primiparous women; (5) the use of best obstetrical estimate to determine the gestational age at time of delivery for the spontaneous preterm birth and full-term delivery cohorts imparts a degree of imprecision to outcome variables that are dependent on gestational age; and (6) it is possible that more than 38 women of the original 97 may have had subsequent pregnancies. These may have been spontaneous miscarriages occurring early in pregnancy prior to receiving care, or pregnancies for which the women sought care at another institution. If some of these women had uncomplicated term deliveries, our results may be biased toward overestimating the frequency of poor obstetric outcome in this cohort.

Our study adds significantly to the existing literature. Whereas several studies have examined subsequent pregnancy outcomes in women with prior spontaneous pregnancy loss, these studies have not focused exclusively on an index spontaneous second trimester loss. Some have defined the index pregnancy to include first-trimester losses,[16-20] patients with PTB (24 to 36.6 weeks),[17,19,20] patients induced for IUFD,[15,19,20] and patients with indicated preterm delivery secondary to maternal or fetal medical indications,[19] all of which may involve different mechanisms from a spontaneous second-trimester loss. In fact, only 1 study has examined subsequent pregnancy outcomes in women with a prior spontaneous second trimester loss. This study by Goldenberg et al[15] concluded that women with a second-trimester loss have significantly higher rates of preterm delivery than controls with a history of term delivery, finding a 39% rate of preterm delivery (20-37 weeks) after index second-trimester loss, and a 62% preterm delivery rate in subsequent pregnancy if the index loss occurred between 19 and 22 weeks.

Mercer et al[19] also found an increased risk of spontaneous PTB, citing a nearly 7% recurrence rate of periviable birth (20-26 weeks) in subsequent pregnancy and a nearly 36% rate of subsequent preterm delivery (30-36 weeks) following periviable birth. The results of our study are consistent with those of Goldenberg et al[15] and Mercer et al,[19] in that patients in our second-trimester loss cohort had high frequencies of PTB and recurrent loss in a subsequent pregnancy.

Our study differs from the 2 previously cited studies in the following ways: (1) collection of patients with second-trimester loss was prospective in our study; (2) our study excluded women with IUFD, which may have a different mechanism from spontaneous second-trimester pregnancy loss; and (3) unlike the Mercer study, which included patients from 20 to 26 weeks of gestation, our study delineated patients with second-trimester loss (less than 24 weeks) from those with early preterm birth (24-26 weeks). The prospective collection of patients with spontaneous STPL, and strict inclusion criteria of spontaneous loss of a gestation between 14 weeks, 0 days and 23 weeks, 6 days is unique to our study and adds strength to our findings.

In summary, pregnancy loss occurring at 14-24 weeks' gestation is significantly associated with recurrent second-trimester loss and spontaneous preterm birth. The frequency of spontaneous preterm birth in patients with a prior second-trimester loss approaches that of patients with a prior preterm birth. These data, and our prior work demonstrating a high rate of chorioamnionitis in patients with a spontaneous second-trimester pregnancy loss,[3] suggest that second-trimester loss and spontaneous preterm birth may have similar mechanisms.

Regardless of whether women had an early index loss (18 weeks or less) or a later index loss (longer than 18 weeks), the frequency of poor obstetric outcome in a subsequent pregnancy was high, 72% and 65% in each group, respectively. Although a higher percentage of women whose index loss occurred at 18 weeks or less had recurrent second-trimester loss, compared with women whose index loss was longer than 18 weeks, we had limited power to draw definitive conclusions regarding the impact of gestational age at index loss on subsequent outcome. What our study does demonstrate is that regardless of the gestational age at index second-trimester loss, this clinical outcome is strongly associated with an increased risk of preterm birth in a subsequent pregnancy, especially early preterm birth. This suggests that the mechanism for all second-trimester losses may be similar to that of spontaneous preterm birth. If, in fact, second-trimester loss and early preterm birth occur by similar biological mechanisms, women with second-trimester loss would be candidates for therapy that reduces subsequent preterm birth such as 17-hydroxyprogesterone and not for cervical cerclage.

In the absence of clarity regarding pathophysiology, these results demonstrate that women with a history of second-trimester pregnancy loss are at significant risk for recurrent second-trimester loss and spontaneous preterm birth in a subsequent pregnancy and should be counseled regarding this increased risk. This is especially true for patients whose only other pregnancy is a second-trimester loss. Research is warranted to understand the mechanisms leading to recurrent pregnancy loss as well as to explore the efficacy of potential therapies in preventing preterm birth in this cohort of women to improve subsequent obstetrical outcomes. Basic and translational research that targets cervical ripening as a primary event in both second-trimester loss and early pre-

term birth may hold promise for future therapies. ■

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