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Q/ Time to conception after miscarriage: How long to wait?

EVIDENCE-BASED ANSWER

A/ AN INTERPREGNANCY INTERVAL (IPI) of < 6 months following miscarriage is associated with an increased live birth rate in subsequent pregnancy, lower risks of preterm birth and subsequent miscarriage, and no difference in rates of stillbirth, pre-eclampsia, and low birth weight infants (strength of recommendation [SOR]: A, well-done meta-analysis). (IPI is defined as the time between the end of one pregnancy and the last menstrual period of a subsequent one.)

A very short IPI (< 3 months), when

compared with an IPI of 6 to 18 months, is associated with the lowest rate of subsequent miscarriage (SOR: B, cohort study). However, for women who experience a pregnancy loss at 14 to 19 weeks' gestation, an IPI < 3 months is associated with an increased risk of miscarriage or birth before 24 weeks' gestation (SOR: B, cohort study).

Women with a short IPI following miscarriage may be at increased risk for anxiety and depression in the first trimester of the subsequent pregnancy (SOR: B, cohort study).

Evidence summary

To evaluate the longstanding belief that a short IPI after miscarriage is associated with adverse outcomes in subsequent pregnancies, a 2017 systematic review and meta-analysis of 16 studies (3 randomized controlled trials [RCTs] and 13 retrospective cohort studies) with a total of more than 1 million patients compared IPIs shorter and longer than 6 months (miscarriage was defined as any pregnancy loss before 24 weeks).¹ The meta-analysis included 10 of the studies (2 RCTs and 8 cohort studies), with a total of 977,972 women and excluded 6 studies because of insufficient data. The outcomes investigated were recurrent miscarriage, preterm birth, stillbirth, pre-eclampsia, and low birthweight in the pregnancy following miscarriage.

Only 1 study reported the specific gestational age of the index miscarriage at 8.6 ± 2.8 weeks.² All studies adjusted data for age, and some considered other confounders, such as race, smoking status, and body mass index (BMI).

Women included in the meta-analysis were from Asia, Europe, South America, and the United States and had a history of at least 1 miscarriage.¹ A study of 257,908 subjects (Conde-Agudelo) also included women with a history of induced abortion from Latin American countries, where abortion is illegal, and made no distinction between spontaneous and induced abortions in those data sets.³ Women with a history of illegal abortion could be at greater risk of subsequent miscarriage than women who underwent a legally performed abortion.

IPI shorter than 6 months carries fewer risks

Excluding the Conde-Agudelo study, women with an IPI < 6 months, compared with > 6 months, had lower risks of subsequent miscarriage (7 studies, 46,313 women; risk ratio [RR] = 0.82; 95% confidence interval [CI], 0.78-0.86) and preterm delivery (7 studies, 60,772 women; RR = 0.79; 95% CI, 0.75-0.83); a higher rate of live births (4 studies, 44,586 women; RR = 1.06; 95% CI, 1.01-1.11); and no

increase in stillbirths (4 studies, 44,586 women; RR = 0.88; 95% CI, 0.76-1.02), low birth-weight (4 studies, 284,222 women; RR = 1.05; 95% CI, 0.48-2.29) or pre-eclampsia (5 studies, 284,899 women; RR = 0.95; 95% CI, 0.88-1.02) in the subsequent pregnancy.

Including the Conde-Agudelo study, the risk of preterm delivery was the same in women with an IPI < 6 months and >6 months (8 studies, 318,880 women; RR=0.93; 95% CI, 0.58-1.48).¹ Four of the 10 studies evaluated the risk of miscarriage with an IPI < 3 months compared with > 3 months and found either no difference or a lower risk of subsequent miscarriage.^{2,4-6}

IPI shorter than 3 months has lowest risk of all

A 2017 prospective cohort study examined the association between IPI length and risk of recurrent miscarriage in 514 women who had experienced recent miscarriage (defined as spontaneous pregnancy loss before 20 weeks of gestation).⁷ Average gestational age at the time of initial miscarriage wasn't reported. Study participants were 30 years of age on average and predominantly white (76.8%); 12.3% were black.

The authors compared IPIs of < 3 months, 3 to 6 months, and > 18 months with IPIs of 6 to 18 months, which correlates with the IPIs recommended by the World Health Organization (WHO).⁸ They adjusted for maternal age, race, parity, BMI, and education. An IPI < 3 months was associated with the lowest risk of subsequent miscarriage (7.3% compared with 22.1%; adjusted hazard ratio = 0.33; 95% CI, 0.16-0.71). Women with IPIs of 3 to 6 months and > 18 months didn't experience statistically significant differences in subsequent miscarriage rates compared with IPIs of 6 to 18 months.⁷

But a short IPI after second-trimester loss increases risk of miscarriage

By including all miscarriages, the meta-analysis effectively examined IPI after first-trimester loss because first-trimester loss occurs far more frequently than does second-trimester loss.¹ A retrospective cohort study of Australian women, not included in the meta-analysis, assessed 4290 patients with

a second-trimester pregnancy loss to specifically examine the association between IPI and risk of recurrent pregnancy loss.⁹

After a pregnancy loss at 14 to 19 weeks, women with an IPI < 3 months, compared with an IPI of 9 to 12 months, had an increased risk of recurrent pregnancy loss (21.9 vs 11.3%; $P < .001$). Women with an IPI > 9 to 12 months had rates of pregnancy loss similar to an IPI of 3 to 6 months (RR = 1.24; 95% CI, 0.89-1.7) and 6 to 9 months (RR = 1.02; 95% CI, 0.7-1.5). Women who experienced an initial loss at 20 to 23 weeks, for unclear reasons, showed no evidence that the IPI affected the risk of subsequent loss.

Short IPI may be linked to anxiety in first trimester of next pregnancy

A large cohort study of 20,308 pregnant Chinese women, including 1495 with a previous miscarriage, explored the mental health impact of IPI after miscarriage compared with no miscarriage.¹⁰ Investigators used the Self-Rating Anxiety Scale to evaluate anxiety and the Center for Epidemiologic Studies Depression Scale to evaluate depression.

Women with an IPI of < 7 months after miscarriage were more likely to experience anxiety symptoms in the subsequent pregnancy than were women with no previous miscarriage (adjusted odds ratio [AOR] = 2.76; 95% CI, 1.4-5.5), whereas women with a history of miscarriage and IPI > 6 months weren't. Women with IPIs < 7 months and 7 to 12 months, compared with women who had no miscarriage, had an increased risk of depression (AOR = 2.5; 95% CI, 1.4-4.5, and AOR = 2.6; 95% CI, 1.3-5.2, respectively). Women with an IPI > 12 months had no increased risk of depression compared with women with no history of miscarriage.

The odds ratios were adjusted for age, education, BMI, income, and place of residence. The higher rates of depression and anxiety didn't persist beyond the first trimester of the subsequent pregnancy.

Recommendations

The American College of Obstetricians and Gynecologists' Practice Bulletin on Early Pregnancy Loss states that no quality data



An interpregnancy interval of < 6 months after miscarriage is associated with a higher live birth rate in the subsequent pregnancy than a longer IPI.

exist to support delaying conception after early pregnancy loss (defined as loss of an intrauterine pregnancy in the first trimester) to prevent subsequent pregnancy loss or other pregnancy complications.¹¹

WHO recommends a minimum IPI of at least 6 months after a spontaneous or elective abortion. This recommendation is based on a single multi-center cohort study in Latin America that included women with both spontaneous and induced abortions.⁸

Editor's takeaway

High-quality evidence now shows that shorter IPIs after first-trimester miscarriages result in safe subsequent pregnancies. However, some concern remains about *second*-trimester miscarriages and maternal mental health following a shorter IPI, based on lower-quality evidence. **JFP**

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