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Interpregnancy Interval after Miscarriage: Less than Six Months vs. Greater than Six Months

Katherine Volk
Pacific University

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Interpregnancy Interval after Miscarriage: Less than Six Months vs. Greater than Six Months

Abstract

Background: After a woman experiences a pregnancy loss she often asks her clinician for recommendations on when to try conceiving again. Current recommendations to wait 6 or more months may not coincide with the woman's reproductive desires. Several studies have looked at interpregnancy intervals following a live birth, but few have ventured to answer the clinical question of how long a woman should wait to conceive after a miscarriage.

Methods: An exhaustive literature search using three databases was conducted with search terms: "interpregnancy interval," "spontaneous abortion," and "miscarriage." In addition bibliographies from several relevant background articles were used. Included were studies conducted on women with history of a spontaneous abortion at < 20 weeks of gestation who later became pregnant and evaluated interpregnancy intervals (IPI) with emphasis of IPI's 6 months. Studies needed to be based on humans and published in the English language. Exclusions were made for women whose preceding pregnancy resulted in live birth or if the study required recurrent spontaneous abortions (SABs).

Results: Three studies met inclusion and exclusion criteria and were included in this systematic review. One secondary review of a RCT assessed a population of 677 women who had a SAB then subsequently became pregnant found that live birth and complication outcomes were best in the 0-3 month IPI in comparison to longer IPI. A prospective cohort study that evaluated 4619 women who were nulliparous, had a SAB, and subsequently became pregnant found that women who conceived within 6 months after miscarriage had higher live birth outcomes with fewer complications. Another study with retrospective cohort design and a population of 30 937 Scottish women who had a SAB and subsequently became pregnant found that women with IPIrate.

Conclusion: Decreasing interpregnancy interval to less than 6 months after spontaneous abortion is shown to be associated with a higher live birth rate and fewer complications. More research is needed to evaluate interpregnancy intervals less than 3 months in order to determine the benefit or risk of recommending a 0-3 month interpregnancy interval after miscarriage.

Keywords: *Interpregnancy interval, spontaneous abortion, miscarriage.*

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Interpregnancy interval, spontaneous abortion, miscarriage

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Interpregnancy Interval after Miscarriage: Less than Six Months vs. Greater than Six Months

Katherine Volk



*A Clinical Graduate Project Submitted to the Faculty of the
School of Physician Assistant Studies
Pacific University
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*Faculty Advisor: Jennifer Van Atta
Clinical Graduate Project Coordinator: Annjanette Sommers, PA-C, MS*

Biography

Katherine Volk is a west coast native of California and Oregon. She earned a Bachelor of Science in Liberal Studies with a Print Media minor at Oregon State University in 2005. After completion of her undergraduate degree she moved to Portland and worked in the banking industry for five years. Deciding to pursue a career in medicine, she continued her science coursework at Portland Community College while working as a medical assistant and phlebotomist. Prior to graduate school she maintained a strong connection to her community, volunteering with the Leukemia & Lymphoma Society's Team in Training and SOS—a learn to ski/snowboard program for underprivileged urban youth, which she plans to resume once she graduates. She is married and has a four-year-old daughter.

Abstract

Background: After a woman experiences a pregnancy loss she often asks her clinician for recommendations on when to try conceiving again. Current recommendations to wait 6 or more months may not coincide with the woman's reproductive desires. Several studies have looked at interpregnancy intervals following a live birth, but few have ventured to answer the clinical question of how long a woman should wait to conceive after a miscarriage.

Methods: An exhaustive literature search using three databases was conducted with search terms: "interpregnancy interval," "spontaneous abortion," and "miscarriage." In addition bibliographies from several relevant background articles were used. Included were studies conducted on women with history of a spontaneous abortion at < 20 weeks of gestation who later became pregnant and evaluated interpregnancy intervals (IPI) with emphasis of IPI's <6 months in comparison to IPI > 6 months. Studies needed to be based on humans and published in the English language. Exclusions were made for women whose preceding pregnancy resulted in live birth or if the study required recurrent spontaneous abortions (SABs).

Results: Three studies met inclusion and exclusion criteria and were included in this systematic review. One secondary review of a RCT assessed a population of 677 women who had a SAB then subsequently became pregnant found that live birth and complication outcomes were best in the 0-3 month IPI in comparison to longer IPI. A prospective cohort study that evaluated 4619 women who were nulliparous, had a SAB, and subsequently became pregnant found that women who conceived within 6 months after miscarriage had higher live birth outcomes with fewer complications. Another study with retrospective cohort design and a population of 30 937 Scottish women who had a SAB and subsequently became pregnant found that women with IPI <6 months had the highest live birth rate and lowest pregnancy complication rate.

Conclusion: Decreasing interpregnancy interval to less than 6 months after spontaneous abortion is shown to be associated with a higher live birth rate and fewer complications. More research is needed to evaluate interpregnancy intervals less than 3 months in order to determine the benefit or risk of recommending a 0-3 month interpregnancy interval after miscarriage.

Keywords: *Interpregnancy interval, spontaneous abortion, miscarriage.*

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Table I: Characteristics of Reviewed Studies and GRADE profile

List of Abbreviations

SAB.....Spontaneous Abortion

IPI.....Interpregnancy Interval

D&C.....Dilate and Curettage

US.....Ultra Sound

CS.....Cesarean Section

WHO.....World Health Organization

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BACKGROUND

Miscarriage or spontaneous abortion is the most common complication of pregnancy, creating anxiety and emotional distress for women hoping for a child.¹ Often times after a miscarriage occurs, when pregnancy is desired by the woman, she will look to her medical provider for guidance on when to start trying to conceive again. This poses the clinical question, how long should a woman wait after a miscarriage before again trying to conceive?

Currently the World Health Organization (WHO)² recommends that at least 6 months should lapse before a woman conceives after a previous miscarriage. Their recommendation is based on the results of a systematic review³ which links abortion rates to a short interpregnancy interval. This systematic review referred to a specific study⁴ which evaluated causes for pregnancy complications relating to the interpregnancy interval. However, this study didn't isolate spontaneous abortions (SABs) from live births as the preceding pregnancy. This is important as longer gestation results in greater maternal nutritional demands and, therefore, longer recuperation times.

Very little research has been completed evaluating pregnancy outcomes at different time intervals between pregnancies when the first pregnancy resulted in abortion prior to 20 weeks gestation. With the current WHO² recommendations suggesting an interpregnancy interval (IPI) of at least 6 months this poses a source of discordance for women who are hoping to have less time elapse before a new conception after their SAB due to personal family planning goals, advancing maternal age, spouse availability, work or school commitments, emotional recovery, and etc. Moreover, some research¹ suggests that having a SAB puts the woman at a greater risk

for complications, including additional pregnancy loss in her subsequent pregnancy and therefore careful prenatal care is mandatory.

In this systematic review of current research, the goal is to address the question of how long a woman should wait after a pregnancy loss (less than 20 weeks gestation) before conceiving again if she so chooses. The hope is that the current research will help clinicians have a recommendation based on the most up to date research on the subject.

METHODS

An exhaustive literature search using MEDLINE-Ovid, Web of Science, and CINAHL was conducted. The following search terms were used: “interpregnancy interval,” “spontaneous abortion,” and “miscarriage.” The bibliographies from several relevant background articles were used and eligibility criteria were applied. Included were studies conducted on women with history of a spontaneous abortion at < 20 weeks of gestation who later became pregnant and evaluated interpregnancy intervals (IPI) with emphasis of IPI’s <6 months in comparison to IPI > 6 months. Other inclusion criteria required human studies and studies published in the English language. Studies were excluded if researchers included women whose preceding pregnancy resulted in live birth or if the study required recurrent spontaneous abortions. Additionally, editorials, conferences or poster reports that did not report study details were excluded. Applicable articles were assessed for quality using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE).⁸

RESULTS

The initial search yielded 64 articles for review. After eliminating duplicates and screening these results for relevant articles using eligibility criteria, three articles remained.

These articles were one secondary analysis of a randomized control trial,⁵ one prospective cohort study,⁶ and one retrospective cohort study.⁷ (See Table 1.)

Wong et al

This was a secondary data analysis of women enrolled in the randomized control trial⁵ Effects of Aspirin in Gestation and Reproduction (EAGeR), published in 2015, and was the only study to evaluate interpregnancy intervals at 3-month increments. The trial was a block randomized, multicenter, double-blinded, placebo controlled trial of preconception low-dose aspirin or placebo. The authors wanted to look at the effect of short IPI after a pregnancy loss and the rate of live births for the subsequent pregnancy. The primary outcome was live birth and the secondary outcomes included pregnancy loss and pregnancy complications in the subsequent pregnancy.⁵

The study included women whose last reproductive outcome was a pregnancy loss, defined as a loss between 10 0/7-19 6/7 weeks of gestation and who subsequently became pregnant. Exclusion criteria included women with documented history of infertility, women < 18 years of age, or >40 years of age. After meeting criteria 677 women became pregnant after a pregnancy loss and the outcome of the subsequent pregnancy was evaluated. The study divided IPI into 3 month time periods which included 0-3 month (mo), 3-6 mo, 6-9 mo, 9-12 mo, and >12 mo.⁵

Of the women included in the study 33.2% became pregnant in the first 3 months, 32.5% became pregnant in the 3-6 mo interval, 17.4% became pregnant in the 6-9 mo interval, 5.5% in the 9-12 mo interval, 11.4% in the >12 mo interval and the median IPI was 4.3 months. The median gestational age of loss for the previous pregnancy was 8.6 +/- 2.8 weeks. The overall live birth rate in the cohort was 76.5% with the highest live birth rate 80.4% in the IPI ≤ 3 mo

interval, IPI 3-6 mo birth rate 76.4%, IPI 6-9 mo birth rate 77.1%, 9-12 mo birth rate 75.7, and the lowest live birth rate 64.9% in the >12 mo interval.⁵

Secondary outcomes of pregnancy complications including preterm birth (8.1%), preeclampsia (9.0%), and gestational diabetes (3.1%) was evaluated in the same 3 month intervals and was shown to not differ for $IPI \leq 3$ mo or $IPI \geq 3$ mo. The overall rate of D&C performed on prior pregnancy loss (34%) was also similar across all intervals.⁵

The authors concluded that ≤ 3 mo IPI after a miscarriage resulted in similar live birth rates and obstetric complications to those who conceived ≥ 3 mo which challenges the WHO current guidelines recommending a minimum IPI of 6 months after SAB. Strengths of this study included evaluation of a IPI with shorter intervals, the cohort was actively trying to conceive and therefore had close follow-up, there was no loss to follow-up in the chosen cohort because it was a secondary analysis of a therapeutic trial. To date this is the only study that evaluates IPI in 3-month intervals. The secondary analysis is a limitation to this study because the initial trial was not set up to measure these primary outcomes which could result in some inaccuracies of data recording, namely date of initial loss. Also, participants in the original study were women who were actively trying to conceive which could mean that those who conceived > 6 months from previous loss could have subclinical fertility problems. The authors acknowledged the need for future studies with primary study design to evaluate short IPI after pregnancy loss.⁵

El Behery et al

This was a prospective cohort study,⁶ published in 2013, which looked to see if the interpregnancy interval after the first spontaneous abortion impacted the reproductive performance of the subsequent pregnancy. The study divided participants into two groups. Group A conceived with an $IPI < 6$ months and outcomes were compared to the reference group B who

had IPI > 12 months.⁶ All participants gave written consent to participate in the study and patients were invited to participate in the study if they received antenatal care for SAB at two selected hospitals between March 2009 and December 2012.⁶

The inclusion criteria for participants consisted of nulliparous women with history of one previous SAB between 5-14 weeks of gestation, documented history of a previous pregnancy by either a positive serum or urine hCG test, bedside US confirming gestational age before the SAB event, cases with nonviable or missed abortion and all patients to have antenatal care follow-up visits in outpatient clinics of either of the two hospitals chosen for the trial. Patients were excluded if the gestational age in the first pregnancy resulted in SAB was < 5 weeks or > 14 weeks or they had an undocumented history of a previous pregnancy, had calculated IPI was < 4 weeks, had twin or multiple pregnancies, lacked antenatal follow-up visits, or had delivery outside of either chosen hospital.⁶

The primary outcome was the reproductive result of the second pregnancy including: spontaneous and induced abortion, ectopic pregnancy, termination, stillbirth, and live birth. The confounding factors they identified were maternal age at delivery, body mass index, type of abortion, mode of termination, and whether intervals between pregnancies were voluntary or not. Of the women enrolled in the study 4619 met their inclusion criteria. Group A had 52% of the participants (n= 2,422) and group B had 47.6% of the participants (n=2197). The participants in group A were slightly older when compared to group B (28.7 years \pm 5.4 vs. 26.2 years \pm 4.2). Group A had the highest live birth rate at 79.31% and group B live birth rate was lowest at 71.6% (p < 0.01). All other primary outcomes were lowest in group A with threatened abortion 2.1% vs. group B 3.6%, induced abortion group A 2.6% vs. group B 3.1%, spontaneous abortion

group A 4.08% vs. 5.32%, ectopic pregnancy group A 0.07% vs. group B 1.7%, termination of pregnancy group A 13% vs. group B 16.2%.⁶

Secondary outcomes for this study included pregnancy complications such as preeclampsia, placenta previa, placental abruption, post-partum hemorrhage, manual removal of placenta, instrument assisted delivery, and preterm delivery (< 37 weeks). The authors found no association between IPI and incidence of preeclampsia, placenta previa, or placental abruption. They did find that reference group B had higher adverse outcomes including higher rates of induction of labor, elective cesarean section, preterm delivery, and infants with low birth weight.⁶

The authors concluded that women who had an IPI of less than 6 months after their first spontaneous abortion have a better reproductive outcome and the lowest complication rates in their subsequent pregnancy than those who conceive after 12 months. The only independent risk factor they identified between the two groups, which was not adjusted for, was whether or not the patient's interpregnancy interval was voluntary or not, which could lead to some inclusion of participants with subclinical infertility in reference group B. The strengths identified with this study were the large sample size, prospective study design, regular antenatal follow up and adjustments for confounding factors. Limitations the authors identified were the evaluated IPI at only < 6 months and > 12 months and the SAB information was retrospectively obtained which could lead to inaccuracies in reporting and dating.⁶

Love et al

This was a retrospective cohort study,⁷ published in 2010, which evaluated Scottish hospital data on women and the effect of interpregnancy interval on the outcomes of their subsequent pregnancy after a miscarriage. The authors divided the IPI into intervals of < 6 mo, 6-

12 mo, 12-18 mo, 18-24 mo, and > 24 mo and used the 6-12 month interval as the reference group. The patients were pulled from the Information Services Division of the National Health Service, Scotland database SMR01 and SMR02, which anonymized patients and is subject to regular quality assurance checks.⁷

Inclusion criteria included women who had a miscarriage recorded for a first pregnancy between 1981-2000 in Scotland and went on to have a subsequent pregnancy. Women were excluded if they had twins or multiple pregnancies, had hospital admission dates < 4 weeks apart, had IPI < 4 weeks, or had gestational age of the second delivery missing. After applying the inclusion and exclusion criteria 30 937 women were included in this study.⁷

The primary outcome was reproductive results of the second pregnancy including: miscarriage, ectopic pregnancy, termination, stillbirth, and live birth. Confounding factors identified were maternal age at delivery and socioeconomic status. The authors noticed that older women and higher socioeconomic status tended to have shorter IPI. Live birth rates were highest at a rate of 85.2% for the < 6 month IPI, declining for the longer intervals to 79% for IPI 6-12 mo, 77.8% for IPI 12-18 mo, 76.7% for IPI 18-24 mo and lowest at 73.3% for IPI >24 months ($p < 0.01$). The study results found IPI < 6 months to be less likely than the reference group of 6-12 months to experience miscarriage, termination, or ectopic pregnancy and the highest risk of adverse outcomes was in women with an IPI of more than 24 months.⁷

Secondary outcomes of maternal and perinatal complications including c-section (CS), preterm delivery (< 36 weeks), low birth weight (<2500 g), induced labor, preeclampsia, placenta previa, and placental abruption were analyzed as well. The authors found that women with IPI < 6 months were less likely to have CS, preterm delivery, or low birth weight infants however they were more likely to have induced labors. Women with IPI > 24 months were most

likely to have preterm delivery and were more likely to have a CS or infant with low birth weight.⁷

The authors concluded that in the Scottish population women who conceived within 6 months of an initial miscarriage have the best outcomes and the lowest complication rates in the subsequent pregnancy. Strengths identified with this study included the large population size and the utilization of a database containing routinely collected information. Limitations are the retrospective nature which lends itself to documentation errors, inaccuracy in dating, and documentation that is not uniformly collected for this study's purpose. The study spanned a long period of time which could impact results because of obstetric practice changes in that timeframe. The inclusion of only a Scottish population and miscarriages that required hospital contact make the data not generalizable to all populations.⁷

DISCUSSION

The three studies⁵⁻⁷ that matched inclusion and exclusion criteria for evaluating the effect of the interpregnancy interval after a miscarriage all showed benefit with reduced complication and increased live birth rates when women had an IPI less than 6 months after a miscarriage. The Wong et al⁵ study shortened the interval further, suggesting that IPI less than 3 months still had the reduced risk. While each study had its limitations in study design, there were three different study designs represented and all maintained the risk reduction and improved outcome in the subsequent pregnancy with < 6 month IPI intervals. Each study evaluated similar primary and secondary outcomes, which allowed for strong comparison of the data and improved confidence in the outcomes.

Because current WHO guidelines² for interval following a miscarriage is to wait at least 6 months before the next conception, these studies⁵⁻⁷ and their results are potentially practice

changing. The significance to the patients who are looking to their clinicians for guidance in their next pregnancy timing is quite large when paired with additional factors including advancing maternal age, individual family planning goals, emotional recovery, and other individual needs.

In appraising the current evidence, limitations and variability between the studies were apparent. The quality of evidence using GRADE criteria was low across the board for all primary outcomes, except for live births which is a moderate. Limitations arose when appraising the collective evidence presented, most notable was that only one study⁵ evaluated IPI in 3 month intervals making further research on that timetable necessary before a recommendation for an IPI of less than 3 months be made by clinicians. Each study used a different reference interval with Wong et al⁵ using a reference of 3-6 months, El Behery et al⁶ using a reference of > 12 months, and Love et al⁷ using a reference of 6-12 months which demonstrates that a standard reference for IPI after miscarriage is lacking at this time. Despite the difference in reference intervals the three studies were unified in their conclusions that IPI of less than 6 months had higher live birth rates and lower complication rates.

The Wong et al⁵ study limitations included its design as a secondary analysis because the initial trial was not set up specifically for IPI after SAB which could result in inaccuracies of data recording, namely date of initial loss. Additionally participants in the original study were women who were actively trying to conceive which could mean that those who conceived > 6 months from previous loss could have subclinical fertility problems, a confounding factor that was not addressed in the study design. The El Behery et al⁶ study limitations included analyzed IPI at only < 6 months and > 12 months. In addition the SAB information was retrospectively obtained which could lead to inaccuracies in reporting and dating. The Love et al⁷ study limitations included the retrospective design with potential for documentation errors, inaccuracy

in dating, and documentation that is not uniformly collected for this study's purpose. In addition the Love et al⁷ had a long time span which could have included obstetric practice changes that would alter outcomes and the inclusion of only a Scottish population and miscarriages that required hospital contact. All three studies had sizable populations to analyze with similar demographics between interval groups Wong et al⁵ n=677, El Beherey et al⁶ n= 4619 and Love et al⁷ n= 30 937. The large sample sizes comprising each study, strengthens confidence in the results obtained especially with all three studies finding similar outcomes.

Clinicians can present the most recent research findings to their patients who are looking for conception after miscarriage guidance and let them make the choice that works best for their individual family planning goals. Previous studies¹ have shown that having a SAB is a risk factor for future pregnancy complications which makes individual recommendations all the more valuable. The benefit of this body of research is that there does not appear to be contraindications for most individuals that are hoping to conceive shortly after miscarriage even though current practice guidelines² suggest that there are. Due to the sensitive nature of the subject studied, conceiving after a miscarriage, and the variables that go into conception including: ovulation time, intercourse frequency, intercourse during ovulatory periods, maternal health, paternal health, and etc. A randomized control trial (RCT) specifically designed to look at IPI after miscarriage is unlikely. The inability to create an RCT for this clinical question creates the need for multiple good quality cohort studies and further research into optimal IPI after miscarriage, specifically evaluating IPI in short intervals starting at the first ovulation after miscarriage.

CONCLUSION

A shortened interpregnancy interval after miscarriage can be considered for patients who are interested in pursuing another pregnancy after a preceding spontaneous abortion, if they are

emotionally ready and they are without medical contraindications. Allowing for a recommended interval less than 6 months may benefit a wide variety of patients who do not feel they have time to spare be it due to advancing maternal age, professional or school obligations, military leave, or other personal reasons for wanting to pursue rapid re-conception. Without other confounding risk factors clinicians can support their patients in their desire to conceive again and can give their patients confidence that a shorter IPI may increase the likelihood of having a live birth with their next pregnancy.

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Table 1: Quality Assessment of Reviewed Articles

Outcome	Number of studies	Study Designs	Downgrade Criteria					Upgrade Criteria	Quality
			Limitations	Indirectness	Inconsistency	Imprecision	Publication bias		
Live Birth	3	Secondary analysis, Cohort	Not Serious ^a	Not Serious	Not Serious	Not Serious	Unlikely	Exposure-response gradient ^b	Moderate
Miscarriage	2	Cohort	Not Serious	Not Serious	Not Serious	Not Serious	Unlikely	N/A	Low
Termination	2	Cohort	Not serious	Not Serious	Not Serious	Not serious	Unlikely	N/A	Low
Stillborn	2	Cohort	Not Serious	Not Serious	Not Serious	Not Serious	Unlikely	N/A	Low
Ectopic Pregnancy	2	Cohort	Not Serious	Not Serious	Not Serious	Not Serious	Unlikely	N/A	Low

^a Use of tertiary treatment center (eg, use of hospital data patients whose miscarriages led to hospitalization) in the Love et al⁷ study.
^b All three studies demonstrated improved live birth rates with shorter interpregnancy intervals.