

# Incidence of Adverse Pregnancy Outcomes Based on the Degree of Short Interpregnancy Interval in Urban Milwaukee Population

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## ABSTRACT

**Introduction:** Short interpregnancy interval is defined as conception occurring within 18 months of a previous live birth. Studies show increased risks of preterm birth, low birth weight, and small for gestational age with short interpregnancy intervals; however, it is unclear if these risks are higher for all short interpregnancy intervals or only for those less than 6 months. The objective of this study was to evaluate prevalence of adverse pregnancy outcomes among people with short interpregnancy intervals, stratified by degree: less than 6 months, 6 to 11 months, and 12 to 17 months.

**Methods:** We conducted a retrospective cohort study of people with 2 singleton pregnancies between 2015 and 2018 at a single academic center. The following outcomes were compared between patients with interpregnancy intervals of less than 6 months, 6 to 11 months, 12 to 17 months, and 18 months or more; hypertensive disorders of pregnancy (gestational hypertension and preeclampsia), preterm birth at less than 37 weeks, low birth weight (<2500 g), congenital anomalies, and gestational diabetes. Bivariate and multivariate analyses were done to examine the independent role of the degree of short interpregnancy interval and each outcome.

**Results:** A total of 1,462 patients were included in the analysis, with 80 pregnancies occurring at interpregnancy intervals less than 6 months, 181 at 6 to 11 months, 223 at 12 to 17 months, and 978 at 18 months or more. In unadjusted analysis, patients with interpregnancy intervals less than 6 months had the highest rate of preterm birth at 15.0%. In addition, patients with interpregnancy intervals less than 6 months and 12 to 17 months had higher rates of congenital anomalies versus those with interpregnancy intervals of 18 months or more. In multivariate analysis, controlling for sociodemographic and clinical confounding factors, interpregnancy intervals less than 6 months were associated with 2.3 higher odds of preterm birth (95% CI, 1.13-4.68), and those 12 to 17 months were associated with 2.52 higher odds of congenital anomalies (95% CI, 1.22-5.20). The odds of gestational diabetes were lower with interpregnancy intervals of 6 to 11 months compared to those 18 months or more (aOR 0.26; 95% CI, 0.08-0.85).

**Conclusions:** In this single-site cohort, people with interpregnancy intervals less than 6 months had higher odds of preterm birth, while those with interpregnancy intervals 12 to 17 months had higher odds of congenital anomalies, compared with the control group with interpregnancy intervals greater than or equal to 18 months. Future research should focus on identifying modifiable risk factors for short interpregnancy intervals and interventions to reduce them.

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## INTRODUCTION

Short interpregnancy interval is defined as conception occurring within 18 months of a previous live birth.<sup>1</sup> Pregnancies occurring within short interpregnancy intervals increase the risk of adverse pregnancy outcomes, such as preterm birth.<sup>2</sup> About 1 in 3 pregnancies in the US are complicated by short interpregnancy intervals, with 12-17 months being the most common category.<sup>3,4</sup> The same statistics apply to Milwaukee,<sup>5</sup> Wisconsin—a city that has high infant mortality—with 49.2% of infant mortality being due to complications of prematurity.<sup>6</sup> Therefore, preventing short interpregnancy intervals, specifically in Wisconsin, could lead to substantial improvement in birth outcomes and reduction in infant mortality.

Current recommendations by the American College of Obstetricians and Gynecologists (ACOG) suggest avoiding interpregnancy intervals shorter than 6 months, and they urge clinicians to counsel patients about the risks of closely spaced pregnancies.<sup>7</sup> These risks include preterm birth, defined as birth before 37 weeks of gestation; low birth weight, defined as <2500 g; and small for gestational age, defined as birthweight at less than 10% for the gestational age.<sup>2,7-13</sup> The mechanistic link between short interpregnancy intervals and these adverse perinatal outcomes is not clearly understood; however, it could be related to nutritional store depletion.<sup>14,15</sup>

While association with neonatal outcomes is well documented, the association between short interpregnancy intervals and adverse maternal outcomes, such as hypertensive disorders of pregnancy or gestational diabetes, is less clear. More recent studies, including a systematic review of studies from high-resource settings, reported conflicting results regarding the association of short interpregnancy intervals and adverse maternal outcomes.<sup>16-19</sup> It is important to identify confounding factors for short interpregnancy intervals and adverse outcomes and determine the true independent role of short interpregnancy intervals in the association with adverse pregnancy outcomes, as short interpregnancy interval is one of a few modifiable risk factors for these complications. Therefore, the objective of this study was to examine the intersection of sociodemographic factors and the incidence of adverse maternal and neonatal outcomes based on the degree of short interpregnancy intervals in a cohort of an urban population in Milwaukee, Wisconsin, where short interpregnancy intervals complicate 30% of pregnancies.<sup>5</sup>

## METHODS

### Study Population and Design

This was a retrospective cohort study of individuals with a singleton pregnancy between 2015 and 2018 receiving prenatal care at Froedtert and the Medical College of Wisconsin (MCW) in Milwaukee, Wisconsin. Institutional review board approval was obtained at MCW prior to any study procedures. Individuals were included in the study if they were 18 years or older and delivered at least 2 singleton pregnancies at a gestational age of 20 to 42 weeks. Individuals were excluded if they had a multifetal gestation, a previous preterm birth, had no delivery information, or did not have enough information about the index pregnancy and prior pregnancy in electronic health records (EHR). The interpregnancy interval was calculated using the last menstrual period of the index pregnancy subtracted from delivery date of previous pregnancy. It was considered short if less than 540 days. If the date of the last menstrual period was not known, first trimester ultrasound dating was used to calculate the date of conception.

**Table 1.** Maternal Characteristics Stratified by Short Interpregnancy Intervals (IPI)

Maternal Characteristic	Control IPI ≥18 months (N = 978)	Short IPI <6 months (N = 80)	Short IPI 6-11 months (N = 181)	Short IPI 12-17 months (N = 223)	P value <sup>b</sup>
Maternal age at delivery (years) <sup>a</sup>	31.8 (27.8-34.7)	25.7 (22.6-30.8)	30.4 (25.2-33.5)	31.4 (28.3-34.1)	<0.001
Maternal race/ethnicity					<0.001
Non-Hispanic White	557 (57.0%)	27 (33.8%)	99 (54.7%)	165 (74.0%)	
Non-Hispanic Black	245 (25.1%)	42 (52.5%)	52 (28.7%)	35 (15.7%)	
Hispanic	93 (9.5%)	3 (3.8%)	11 (6.1%)	9 (4.0%)	
Other	83 (8.5%)	8 (10.0%)	19 (10.5%)	14 (6.3%)	
Prepregnancy body mass index (kg/m <sup>2</sup> ) <sup>a</sup>	26.9 (23.4-32.3)	29.7 (23.9-35.3)	26.0 (22.1-31.1)	24.3 (21.6-28.4)	<0.001
Marital status					<0.001
Married	593 (60.8%)	25 (31.3%)	107 (59.1%)	169 (75.8%)	
Single	354 (36.3%)	55 (68.8%)	70 (38.7%)	51 (22.9%)	
Divorced/widowed	29 (3.0%)	0 (0.0%)	4 (2.2%)	3 (1.4%)	
Insurance					<0.001
Private	567 (58.1%)	24 (30.0%)	98 (54.1%)	168 (75.3%)	
Public	405 (41.5%)	56 (70.0%)	82 (45.3%)	54 (24.2%)	
None	4 (0.4%)	0 (0.0%)	1 (0.6%)	1 (0.5%)	
Chronic hypertension	34 (3.5%)	2 (2.5%)	5 (2.8%)	4 (1.8%)	0.677
Smoking in pregnancy	88 (9.0%)	11 (13.8%)	12 (6.6%)	10 (4.5%)	0.033

<sup>a</sup>Data are presented as median and interquartile range.

<sup>b</sup>P value represents comparison of all 4 groups.

**Table 2.** Multivariable Adjusted Regression Model for Maternal Factors Associated With Short Interpregnancy Intervals (IPI)

	Short IPI < 6 months Adjusted OR (95% CI)	Short IPI 6 – 11 months Adjusted OR (95% CI)	Short IPI 12 – 17 months Adjusted OR (95% CI)
<b>Maternal age at delivery</b>	<b>0.86 (0.81 – 0.91)</b>	<b>0.92 (0.88 – 0.95)</b>	<b>0.92 (0.89 – 0.96)</b>
Maternal race/ethnicity			
Non-Hispanic White	Referent	Referent	Referent
Non-Hispanic Black	1.34 (0.71 – 2.50)	0.90 (0.56 – 1.44)	0.63 (0.38 – 1.04)
Hispanic	0.37 (0.10 – 1.30)	0.57 (0.28 – 1.16)	0.37 (0.17 – 0.82)
Other	1.71 (0.72 – 4.07)	1.23 (0.70 – 2.17)	0.62 (0.34 – 1.14)
Prepregnancy body mass index	1.03 (0.99 – 1.06)	0.96 (0.93 – 1.01)	0.96 (0.93 – 0.98)
Marital Status			
Married	Referent	Referent	Referent
Single	1.25 (0.63 – 2.47)	0.80 (0.50 – 1.30)	0.72 (0.44 – 1.18)
Divorced/widowed	—	0.84 (0.28 – 2.58)	0.63 (0.18 – 2.18)
Insurance			
Private	Referent	Referent	Referent
Public	1.26 (0.65 – 2.44)	1.08 (0.68 – 1.71)	0.62 (0.39 – 0.99)
None	—	2.22 (0.23 – 21.20)	1.65 (0.17 – 16.21)
Chronic hypertension	0.54 (0.12 – 2.58)	1.08 (0.40 – 2.91)	0.81 (0.27 – 2.39)
Smoking in pregnancy	0.99 (0.47 – 2.09)	0.67 (0.34 – 1.31)	0.62 (0.30 – 1.27)

### Assessment of Exposure and Outcome Variables

The primary outcome was incidence of preterm birth, defined as giving birth prior to 37 weeks. Secondary outcomes included hypertensive disorders of pregnancy, defined as gestational hypertension or preeclampsia using ACOG criteria;<sup>20</sup> low birth weight (<2500 g); gestational diabetes; and presence of congenital anomaly. These outcomes were compared by 4 groups of interpregnancy intervals: less than 6 months, 6 to 11 months, 12 to 17 months,

**Table 3.** Pregnancy Outcomes Stratified by Short Interpregnancy Intervals (IPI)

≥ 18 months Pregnancy Outcome	Controls	Short IPI	Short IPI	Short IPI	P value (N=223)
	<6 months (N=978)	6–11 months (N=80)	12–17 months (N=181)		
Cesarean delivery	43 (4.4%)	3 (3.8%)	8 (4.4%)	13 (5.8%)	0.799
Hypertensive disorders of pregnancy	60 (6.1%)	6 (7.5%)	6 (3.3%)	8 (3.6%)	0.201
Preterm birth (37 weeks)	61 (6.2%)	12 (15.0%)	8 (4.4%)	13 (5.8%)	0.011
Low birth weight (<2500 g)	53 (5.4%)	6 (7.5%)	6 (3.3%)	7 (3.1%)	0.244
Congenital anomalies	22 (2.3%)	4 (5.0%)	8 (4.4%)	13 (5.8%)	0.024
Gestational diabetes	62 (6.3%)	3 (3.8%)	3 (1.7%)	9 (4.0%)	0.041

**Table 3.** Unadjusted and Adjusted Analyses for Pregnancy Outcomes Stratified by the Length of Interpregnancy Interval

Pregnancy Outcome	Unadjusted OR (95% CI)	Adjusted OR <sup>a</sup> (95% CI)
Preterm birth (<37 weeks)		
Control (≥18 months)	Referent	Referent
Short interpregnancy interval <6 months	2.65 (1.36 – 5.16)	2.30 (1.13 – 4.68)
Short interpregnancy interval 6–11 months	0.70 (0.33 – 1.48)	0.72 (0.34 – 1.55)
Short interpregnancy interval 12–18 months	0.93 (0.50 – 1.73)	1.06 (0.56 – 1.20)
Congenital anomalies		
Control (≥ 18 months)	Referent	Referent
Short interpregnancy interval <6 months	2.28 (0.77 – 6.79)	2.39 (0.75 – 7.62)
Short interpregnancy interval 6–11 months	2.01 (0.88 – 4.58)	1.88 (0.80 – 4.38)
Short interpregnancy interval 12–18 months	2.69 (1.33 – 5.42)	2.52 (1.22 – 5.20)
Gestational diabetes		
Control (≥ 18 months)	Referent	Referent
Short interpregnancy interval <6 months	0.58 (0.18 – 1.88)	0.71 (0.21 – 2.41)
Short interpregnancy interval 6–11 months	0.25 (0.08 – 0.80)	0.26 (0.08 – 0.85)
Short interpregnancy interval 12–18 months	0.62 (0.30 – 1.27)	0.63 (0.30 – 1.30)

<sup>a</sup>Adjusted for maternal age, race and ethnicity, private insurance status, marital status, and smoking

and greater than or equal to 18 months. In addition, maternal demographic and clinical characteristics associated with short interpregnancy intervals were abstracted from the EHR and compared between the study groups. These included maternal age at delivery, maternal race and ethnicity, marital status, and insurance. Clinical factors abstracted included prepregnancy body mass index (BMI) (kg/m<sup>2</sup>), history of chronic hypertension, and cigarette smoking during pregnancy.

**Statistical Analysis**

Data were presented as n (%) or median and interquartile range. Chi-square or Fisher exact test was used to compare categorical variables, while Mann-Whitney-Wilcoxon or Kruskal-Wallis test was used to compare continuous variables. Multinomial logistic regression analysis was performed to examine how maternal factors were associated with interpregnancy intervals. The effect of length of interpregnancy intervals on pregnancy outcomes was tested by logistic regression. Maternal age, race and ethnicity, insurance status, marital status, smoking, and history of preterm birth were included as potential confounding factors. Odds ratio

(OR) or adjusted OR (aOR) with 95% confidence intervals were reported. All tests were 2-tailed and P value <0.05 was used to indicate statistical significance. All statistical analysis was done using SAS.

**RESULTS**

During the study period, a total of 1,462 patients met eligibility criteria and were included in the analysis. Of these, 484 (33.1%) had short interpregnancy intervals. Eighty pregnancies (5.5%) occurred at less than 6 months, 181 pregnancies (12.4%) at 6 to 11 months, 223 pregnancies (15.3%) at 12 to 17 months, and 978 pregnancies (66.9%) at 18 months or more.

Table 1 describes patient characteristics stratified by pregnancy interval. Individuals with interpregnancy intervals of less than 6 months were more likely to be non-Hispanic Black (P<0.001), have higher prepregnancy BMI (P<0.001), be single (P<0.001), have public insurance (P<0.001), and report smoking during pregnancy (P=0.033) compared to all other groups. Table 2 describes multivariate logistic regression, identifying sociodemographic characteristics independently associated with short interpregnancy intervals (IPI). Older maternal age (aOR 0.86, 95% CI, 0.81-0.91 for IPI <6 months; aOR 0.91, 95% CI, 0.88-0.95 for IPI 6-11 months; aOR 0.92, 95% CI, 0.89-0.96 for IPI 12-17 months), higher prepregnancy BMI (aOR 0.96; 95% CI, 0.93 – 0.98 for IPI 12-17 months), and Hispanic ethnicity (aOR 0.50; 95% CI, 0.31 – 0.79 for IPI 12-17 months) were associated with lower odds of short interpregnancy intervals.

Pregnancy outcomes stratified by short interpregnancy interval subgroups are depicted in Table 3. In univariate analysis, patients with interpregnancy intervals less than 6 months had the highest rate of preterm births at 15.0%, compared to a 6.2% preterm birth rate for the control group (IPI≥18 months). In addition, the rate of congenital anomalies was higher in the group with interpregnancy intervals less than 6 months and 12 to 17 months, compared to the control group (5.0% vs 5.8% vs 2.3%, respectively; P=0.024). In this cohort, there were 10 pregnancies with congenital anomalies: 6 with congenital cardiac anomalies, 2 with musculoskeletal anomalies, 1 with genitourinary anomaly, and 1 with neurologic anomaly. The rate of gestational diabetes was lower in the group with interpregnancy

intervals less than 6 months and 6 to 11 months compared to the control group (IPI  $\geq 18$  months) ( $P=0.041$ ).

Table 4 describes the multivariate analysis, controlling for sociodemographic and clinical confounding factors for the association between short interpregnancy intervals and adverse pregnancy outcomes. After controlling for potential confounding factors, interpregnancy intervals less than 6 months were associated with higher odds of preterm birth (aOR 2.30; 95% CI, 1.13 – 4.68). In addition, interpregnancy intervals of 12 to 17 months were associated with higher odds of congenital anomalies (aOR 2.52; 95% CI, 1.22 – 5.20). The 6- to 11-month group was associated with lower odds of gestational diabetes (aOR 0.26; 95% CI, 0.08 – 0.85).

## DISCUSSION

### Principal Findings

In this analysis, we found that older maternal age, Hispanic ethnicity, and higher prepregnancy BMI were associated with lower odds of short interpregnancy intervals. We also found that interpregnancy intervals less than 6 months were associated with higher odds of preterm birth, and interpregnancy intervals of 12 to 17 months were associated with higher odds of congenital anomalies. People with interpregnancy intervals of 6 to 11 months had lower risks of gestational diabetes.

### Results in the Context of What is Known

As comparable to other studies, our study found the strongest association between preterm births and interpregnancy intervals less than 6 months.<sup>21-22</sup> Although our study did not confirm the higher risk of preterm birth with short interpregnancy intervals of 6 to 17 months, this may be due to smaller sample size and a weaker association with preterm birth in these specific subgroups.<sup>10,23</sup>

Based on our findings, we demonstrate a novel association between short interpregnancy intervals of 12 to 17 months and congenital anomalies. Several studies demonstrate increased odds of specific birth defects associated with an interval of less than 5 months and less than 6 months, and one study found an increased risk of certain defects (specifically cardiac defects and central nervous system anomalies) associated with interpregnancy intervals of 6 to 11 months, but none have directly correlated a statistically significant interval such as ours.<sup>11,12,23,24,25</sup> The lack of standardized categorization of short interpregnancy interval subgroups makes comparing our results to previous studies less clear. Nevertheless, our findings reinforce that an association is plausible, as it may be related to maternal depletion of important micronutrients to fetal health, such as folic acid. Since at least 30% of pregnancies are complicated by short interpregnancy intervals and approximately 50% of pregnancies in the US are unplanned, one strategy to reduce the risk of congenital anomalies could be to recommend the continuation of prenatal vitamins 1 to 2 years after pregnancy, especially in lactating patients.<sup>1,4,26</sup>

The association between interpregnancy intervals of 6 to 11 months and lower rates of gestational diabetes was an unexpected finding. A previous study by Hanley et al found an opposite association between short interpregnancy intervals less than 6 months and higher rates of gestational diabetes.<sup>19</sup> This association was supported by the hypothesis that there is less time to lose weight that was gained during the previous pregnancy, which ultimately leads to an increased risk of gestational diabetes. It would be important to investigate if a confounding factor was lack of time to complete screening for gestational diabetes, given association between inadequate prenatal care/late prenatal care and short interpregnancy intervals.<sup>27</sup>

### Strengths and Limitations

A strength of the study is data verification through EHR abstraction, done by authors of this paper (EP, SA, MM, and BM). This allowed for high accuracy compared to most studies on this subject, which use administered data sets or birth certificate records.<sup>3</sup> Using verified medical record abstraction avoids the possibility of underreporting and/or data inaccuracy associated with administered and birth certificate records. Another strength is the characteristics of the study cohort. The cohort consisted of urban pregnant individuals of Milwaukee, Wisconsin—an area with high rates of preterm birth—where preventing short interpregnancy intervals could have a substantial impact on perinatal health. In addition, we excluded patients with prior preterm birth—the highest risk factor for preterm birth.

Despite these strengths, our study has a few limitations. First, the data collection regarding sociodemographic factors was based on EHR abstraction. Data on maternal education, housing instability, food insecurity, income, and many other important social risk factors, such as access to contraception, were missing. Second, we were unable to control for pregnancy intention. Knowing that unintended pregnancies previously have been linked to adverse obstetrical outcomes, this may have been a potential confounding factor.<sup>28</sup> Moreover, we did not have data on the degree of knowledge among reproductive-age individuals in our cohort regarding recommended pregnancy interval and risks associated with short interpregnancy intervals. One important future research direction could be assessing individual and community awareness of the definition of short interpregnancy intervals and associated pregnancy risks. Lastly, due to our desire to verify our data rather than use administered data, we had an overall small sample size.

## CONCLUSIONS

We found that an interpregnancy interval of less than 6 months was the only group of short interpregnancy intervals associated with higher odds of preterm birth and that the interpregnancy interval of 12 to 17 months was associated with higher odds of congenital anomalies. Future research should focus on assessing

community awareness of short interpregnancy intervals and the associated risks, identifying modifiable risk factors, and designing interventions to reduce short interpregnancy intervals.

**Funding/Support:** None declared.

**Financial Disclosures:** None declared.

**Acknowledgements:** Findings of this study were presented at the 42nd virtual annual meeting of the Society for Maternal-Fetal Medicine, Orlando, Florida, February 1-6, 2022.

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