

## **Interpregnancy Interval and Neonatal Outcomes**

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## Abstract

Objectives: Interpregnancy interval (IPI), the time period between the end of one pregnancy and the conception of the next, can have a significant impact on maternal and infant outcomes. This study examines the relationship between interpregnancy interval and neonatal outcomes of low birth weight, preterm birth, and specific neonatal morbidities.

Study Design: Retrospective cohort study comparing neonatal outcomes across 6 categories of IPI using data on 202,600 cases identified from Arizona birth certificates and the Newborn Intensive Care Program data. Comparisons between groups were made using odds ratios and 95% confidence intervals, and multivariable logistic regression analysis.

Results: Interpregnancy intervals of < 12 months and  $\geq$  60 months were associated with low birth weight, preterm birth, and small for gestational age births. The shortest and longest IPI categories were also associated with specific neonatal morbidities, including periventricular leukomalacia, bronchopulmonary dysplasia, intraventricular hemorrhage, apnea bradycardia, respiratory distress syndrome, transient tachypnea of the newborn, and suspected sepsis. Relationships between interpregnancy interval and specific neonatal morbidities did not remain significant when adjusted for birth weight and gestational age.

Conclusions: Significant differences in neonatal outcomes (preterm birth, low birth weight, and small for gestational age) were observed between IPI categories. Consistent with previous research, interpregnancy intervals < 12 months and  $\geq$  60 months appear to be associated with increased risk of poor neonatal outcomes. Any difference in specific neonatal morbidities between IPI groups appears to be mediated through increased risk of low birth weight and preterm birth by IPI.

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Figure 2. Odds ratios and 95% confidence intervals for preterm birth, low birth weight, and small for gestational age (SGA) by IPI category.

Footnote: \*  $p < 0.05$  from the reference group; † reference group

Table 1. Demographic characteristics by length of IPI.

Footnote: Abbreviations: IPI, interpregnancy interval

\* The Kotelchuk index, or Adequacy of Prenatal Care Utilization index, is a classification based on when prenatal care was initiated and number of prenatal care visits (19.)

Table 2. Neonatal morbidities by IPI category, unadjusted.

Footnote: Abbreviations: CI, confidence interval; IPI, interpregnancy interval; OR, odds ratio

\*  $p < 0.05$  from the reference group; † reference group

## Introduction

Interpregnancy interval (IPI) is defined as the time period between the end of one pregnancy and the conception of a subsequent pregnancy.(1) It has been well demonstrated that suboptimal interpregnancy intervals are associated with poor birth outcomes. According to a meta-analysis by Conde-Agudelo et al., intervals of < 18 months and > 59 months have been associated with preterm birth, low birth weight, and small size for gestational age.(2) Even intervals just over 23 months have been associated with poor birth outcomes.(3) Interpregnancy intervals of < 6 months have been associated with higher rates of preterm birth(4) and neonatal death.(5) Increased risk of infant mortality has also been associated with IPI of < 18 months.(6) Risk of stillbirth and spontaneous abortion may also be increased with very short and very long interpregnancy intervals.(7)

Lowest risk of poor birth outcomes seems to be achieved with an IPI of one to two years. Zhu et al. found that IPI of 18-23 months had the lowest risk of low birth weight, preterm birth, and small for gestational age(8) while Conde-Agudelo et al. found that IPI of 12-23 months was associated with the lowest risk of poor birth outcomes.(9) Shachar & Lyell suggest 18 months or greater as the optimal IPI, with an IPI of 12 months possibly being appropriate for women of advanced maternal age.(10) The current WHO recommendation for ideal interpregnancy interval is 24 months after a live birth or 6 months after an abortion (spontaneous or therapeutic) to reduce the risk of adverse maternal and infant outcomes.(11)

Specific neonatal morbidities may be associated with shorter or longer interpregnancy intervals, independent of prematurity and low birth weight. IPI of < 12 months has been associated with higher risk of gastroschisis for some infants.(12) Interpregnancy interval of  $\leq 6$  months increased the risk of neural tube defects (13) and intervals of < 36 months was associated with increased risk of autism.(14) IPI of < 6 months or  $\geq 60$  months has been associated with increased risk of cardiovascular defects.(15) Longer IPI has also been associated with CNS defects and chromosomal abnormalities,(15) while shorter and longer IPI may increase risk of congenital abnormalities.(16)

Poor maternal outcomes may also be associated with interpregnancy intervals that are too short or too long. In a cross-sectional study, women with interpregnancy intervals of less

than 5 months had significantly higher rates of maternal death, hemorrhage, premature rupture of membranes, puerperal endometriosis, and anemia.(9) Women with interpregnancy intervals of more than 59 months were found to have higher rates of pre-eclampsia, eclampsia, and gestational diabetes mellitus. A systematic review of the literature found that long interpregnancy interval may be an independent risk factor for pre-eclampsia and is also associated with increased risk of labor dystocia.(2) That study also found that for women having a vaginal birth after a previous Caesarean section or uteroplacental bleeding disorder, a short interpregnancy interval was associated with increased risk of uterine rupture.

This project aims to add to the body of literature by looking at specific neonatal morbidities associated with IPI. Categories of morbidities to be considered include: neurologic (such as intraventricular hemorrhage, neonatal seizures), respiratory (respiratory distress syndrome, transient tachypnea of the newborn), infectious (suspected and proven sepsis), congenital anomalies, and other (necrotizing fasciitis). In addition, this project will add to prior research on association between interpregnancy interval and neonatal characteristics.

#### Specific Aims

1) Determine the relationship between interpregnancy interval and neonatal characteristics. Are there significant differences in the general characteristics of neonates, such as birth weight, gestational age, and APGAR scores, resulting from pregnancies with different interpregnancy intervals?

Hypothesis: It is expected that neonates born of pregnancies with interpregnancy intervals of less than 18 months or greater than 59 months will have lower birth weights, poorer APGAR scores, and be small for gestational age compared to neonates born of pregnancies with interpregnancy intervals between 18 and 59 months.

2) Determine the relationship between interpregnancy interval and neonatal morbidity. Are there significant differences in morbidity for neonates resulting from pregnancies with different interpregnancy intervals? Categories of morbidity will include: neurologic, respiratory, infectious, anomalies, and other.

Hypothesis: Interpregnancy intervals of less than 18 months and greater than 59 months will be associated with a higher rate of neonatal morbidities than interpregnancy intervals between 18 and 59 months.



## Research Materials and Methods

Approval for this project was obtained from the Maricopa Integrated Health System Institutional Review Board, to conduct a retrospective cohort study using de-identified data from a previously created linked dataset. The dataset used for this project contains data from the Newborn Intensive Care Program linked with Arizona birth certificate data from 1994 to 1998. The Newborn Intensive Care Program (NICP), provided by the Arizona Department of Health Services, assures care for very sick infants. Enrollment is not based on income, but on indicators for morbidity. Approximately 5.2% of all births in Arizona from 1994-1998 are represented in the NICP data. Of the 19,890 infants enrolled in the NICP during that time frame, 98% were matched to Arizona birth certificates. NICP data for an infant and data from the birth certificate to which the infant was matched were combined into a single case in the dataset used for this project. Cases were excluded from analysis if IPI was unknown or multiple gestation (Fig. 1). A resulting total of 202,600 cases were involved in the analysis.

For this study, IPI was defined as the time between the end of one pregnancy and the conception of a subsequent pregnancy. This was calculated as the time from the end of one pregnancy to the end of the next pregnancy, minus the gestational age at delivery of the case neonate. Individual IPIs were subdivided into six groups: < 6 months, 6-11 months, 12-17 months, 18-23 months, 24-59 months, and  $\geq$  60 months.(3,6,9,17,18)

Neonatal outcomes involved in the analysis included preterm birth, low birth weight, and small for gestational age; as well as several specific diagnoses assigned to the neonate by a clinician while enrolled in the Program. Preterm birth was defined as < 37 weeks gestation. Low birth weight was defined as birth weight of < 2500 grams. Small for gestational age was defined as birth weight in < the 10<sup>th</sup> percentile for gestational age. The specific diagnoses included in the analysis were neurological (periventricular leukomalacia, intraventricular hemorrhage, neonatal seizures), respiratory (bronchopulmonary dysplasia, respiratory distress syndrome, transient tachypnea of the newborn, apnea bradycardia), and other (suspected and proven sepsis, and necrotizing enterocolitis.)

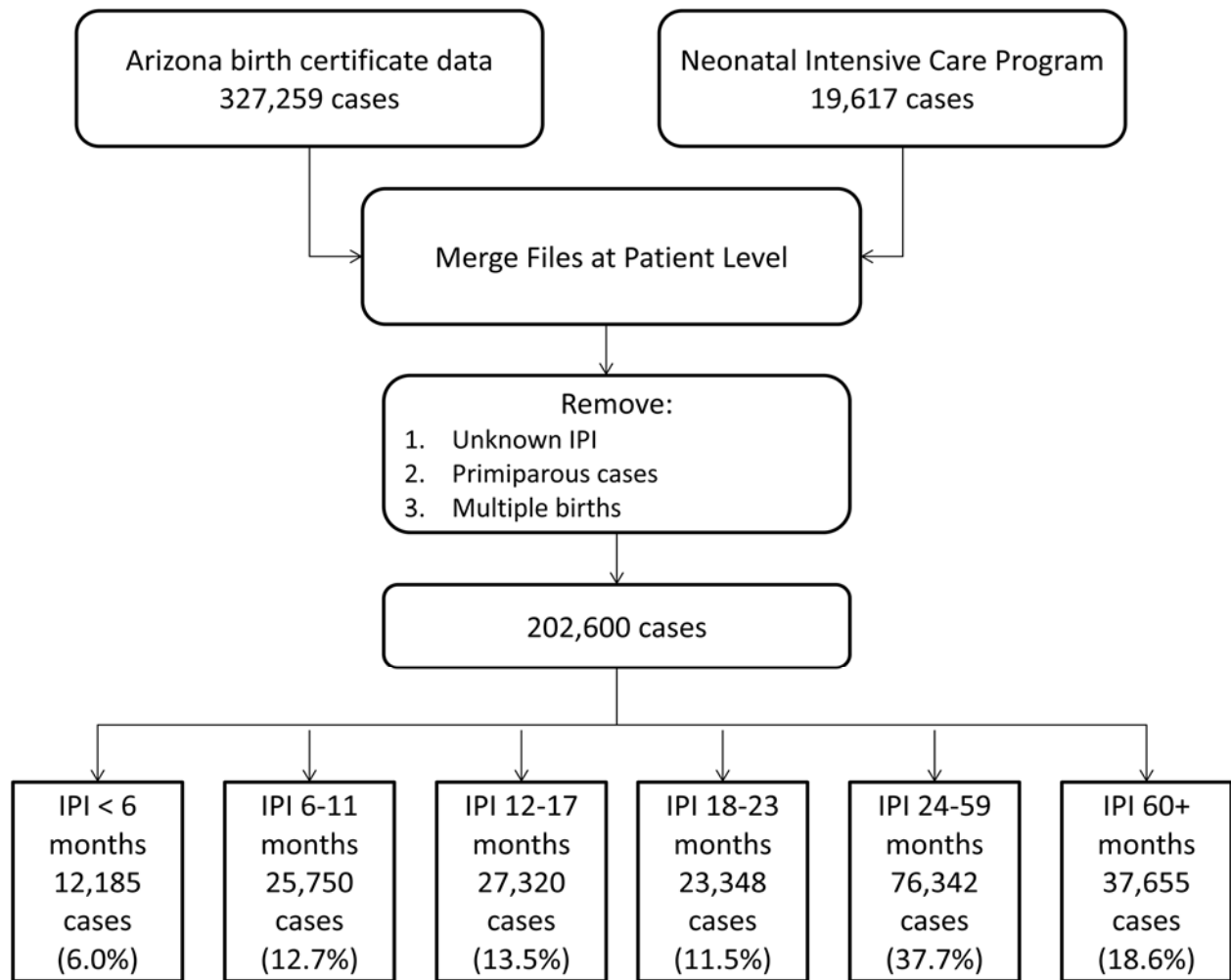


Figure 1. Diagram representation of the creation of a linked data set merging Arizona birth certificates and Neonatal Intensive Care Program data. Cases were excluded if IPI could not be determined from the information available, if a case represented a mother's first birth, and in cases with multiple births. A resultant 202,600 cases were included in the analysis and sorted by interpregnancy interval.

Several potential confounding variables were identified and included in the analysis; parity, maternal age, race/ethnicity, level of prenatal care, mother's education level, marital status, type of payor, birth weight, and gestational age. Since primiparity was a reason for exclusion from the study, for the analysis parity was categorized as "2 live births" or "> 2 live births." Maternal age was identified as mother's age at the birth of the case neonate, with 25-29 used as the reference group. Race/ethnicity was based on the mother's self-reported race, and was categorized as Caucasian (reference group), Black, US born Hispanic, foreign born Hispanic, Native American, or Asian. Level of prenatal care was based on the Kotelchuk index and was classified as inadequate, intermediate, adequate (reference group), and adequate plus (19). Education level was categorized as < 12 years, 12 years, and > 12 years (reference group.) Marital status was dichotomous based on self report. Type of payor was classified as private insurance (reference group), self-pay, and Arizona Health Care Cost Containment System (AHCCCS -- Arizona's Medicaid program). Birth weight was categorized as "< 750 grams", "750-1000g," "1001-1500g," "1501-2500g", and ">2500g," which was the reference group. Gestational age was the clinician's estimate of gestational age of the infant at time of delivery, and grouped as "extremely short" (20-27 weeks,) "moderately short" (28-31 weeks,) "mild short" (32-36 weeks,) and "normal" (37 weeks or greater; the reference group.)

IBM SPSS statistics version 19.0 was used to assist in the analysis. In the first analysis model, the relationship between IPI, birth weight, estimated gestational age, small for gestational age, and individual neonatal morbidities were calculated. Comparisons between groups were made using odds ratios and 95% confidence intervals. For the second step of the analysis, individual sociodemographic and biologic factors were tested for relationship with IPI using a Nagelkerke R-squared test. After identifying which variables had a significant relationship with IPI, separate multivariate logistic regression analysis was performed to evaluate whether or not the relationship with IPI persisted after controlling for demographic factors, birth weight, and gestational age.

## Results

Of the available 207,439 cases that met criteria, 4,839 had missing data and were excluded, with 202,600 cases included in the analysis (Fig. 1). By IPI category, 6.0% had IPI < 6 months, 12.7% had IPI of 6-11 months, 13.5% had IPI of 12-17 months, 11.5% had IPI of 18-23 months, 37.7% cases had IPI of 24-59 months, and 18.6% had an IPI of  $\geq$  60 months.

### Demographics (Table 1)

The percentage of women under the age of 18 was highest in the <6 months IPI group, and decreased with increasing length of IPI. The average age of the women in each IPI category increased with increasing length of IPI. Caucasian women comprised the highest percentage of every IPI category. Asian women were also evenly represented in all categories; while Native Americans, Blacks, and US-born Hispanics were overrepresented in the IPI of < 6 months category.

Women with IPI of < 6 months were more likely to be unmarried, have < 12 years of education, have AHCCCS as their payor, and have inadequate prenatal care. Women with IPI of  $\geq$  60 months were more likely to have chronic hypertension and diabetes. Smoking was more common among women with IPI of < 6 months or  $\geq$  60 months.

Table 1. Demographic characteristics by length of IPI.

	< 6 mos		6 - 11 mos		12 - 17 mos		18 - 23 mos		24 - 59 mos		≥ 60 mos	
	N	%	N	%	N	%	N	%	N	%	N	%
<b>Race / Ethnicity</b>												
Asian	455	3.75	943	3.68	1011	3.72	846	3.64	2808	3.69	1453	3.88
African American	591	4.87	964	3.76	853	3.13	668	2.87	2298	3.02	1343	3.58
White non-Hispanic	4823	39.73	12574	49.04	14437	53.05	12763	54.88	37480	49.28	17656	47.09
Hispanic US-born	2449	20.17	4133	16.12	3939	14.48	3266	14.04	11331	14.90	5603	14.94
Hispanic Mexico-born	2502	20.61	4762	18.57	4619	16.97	3860	16.60	16468	21.65	8342	22.25
Native American	1319	10.87	2262	8.82	2353	8.65	1853	7.97	5675	7.46	3096	8.26
<b>Age (years)</b>												
< 18	459	3.77	600	2.33	321	1.17	166	0.71	101	0.13	1	0.00
18 – 24	6110	50.14	10711	41.60	10203	37.35	7950	34.05	20996	27.50	1977	5.25
25-29	3078	25.26	7219	28.03	7828	28.65	7029	30.11	25745	33.72	10692	28.40
30 – 34	1822	14.95	4935	19.17	6034	22.09	5613	24.04	19515	25.56	13412	35.62
35+	716	5.88	2285	8.87	2934	10.74	2590	11.09	9984	13.08	11572	30.73
<b>Education (years)</b>												
<12	5166	42.40	8378	32.54	7719	28.25	6045	25.89	20955	27.45	9774	25.96
12	3772	30.96	7917	30.75	8108	29.68	6999	29.98	25145	32.94	13716	36.43
>12	3247	26.65	9455	36.72	11493	42.07	10304	44.13	30242	39.61	14165	37.62
<b>Marital Status</b>												
Unmarried	5617	46.11	8996	34.95	8104	29.67	6471	27.72	22417	29.37	12603	33.47
Married	6564	53.89	16747	65.05	19212	70.33	16873	72.28	53903	70.63	25046	66.53
<b>Insurance</b>												
Medicaid	7114	61.19	12441	50.31	11554	44.01	9295	41.31	32084	43.45	15018	41.33
Private	3616	31.10	10547	42.65	12908	49.17	11729	52.12	36798	49.84	18575	51.12
Self/Unknown	896	7.71	1739	7.03	1789	6.81	1479	6.57	4956	6.71	2746	7.56
<b>Parity</b>												
1	5544	45.52	12849	49.93	14129	51.73	12324	52.80	39323	51.52	17370	46.15
2+	6635	54.48	12887	50.07	13185	48.27	11016	47.20	37003	48.48	20267	53.85
<b>Kotelchuk Index*</b>												
Inadequate	4433	37.24	6902	27.20	5728	21.24	4187	18.13	12693	16.80	6110	16.39
Intermediate	1382	11.61	3303	13.02	3637	13.48	3064	13.27	10180	13.47	4918	13.19
Adequate	3549	29.81	9330	36.77	10986	40.73	9861	42.70	32351	42.82	15460	41.47
Adequate Plus	2541	21.34	5838	23.01	6622	24.55	5980	25.90	20326	26.90	10796	28.96
<b>Chronic Hypertension</b>												
No	12151	99.72	25679	99.72	27238	99.70	23273	99.68	76005	99.56	37372	99.25
Yes	34	0.28	71	0.28	82	0.30	75	0.32	336	0.44	283	0.75
<b>Smoker</b>												
No	10513	86.91	22812	89.14	24620	90.63	21028	90.55	68031	89.63	32075	85.70
Yes	1583	13.09	2779	10.86	2546	9.37	2195	9.45	7869	10.37	5353	14.30
<b>Diabetes</b>												
No	11936	97.96	25232	97.99	26729	97.84	22805	97.67	74127	97.10	35966	95.51
Yes	249	2.04	518	2.01	591	2.16	543	2.33	2214	2.90	1689	4.49

Abbreviations: IPI, interpregnancy interval

\* The Kotelchuk index, or Adequacy of Prenatal Care Utilization Index, is a classification based on when prenatal care was initiated and the number of prenatal visits.(19)

### Low birth weight, preterm birth, small for gestational age (Fig. 2)

Low birth weight was identified in 5.48% of total cases. A U-shaped relationship between IPI category and low birth weight was demonstrated, with IPI of < 6 months, 6-11 months, and  $\geq 60$  months all showing a significant relationship with low birth weight. Preterm birth was identified in 8.3% of cases. Similarly, a U-shaped relationship was also found for preterm birth. An IPI of < 6 months, 6-11 months, and  $\geq 60$  months were all associated with increased risk of preterm birth. Small for gestational age births comprised 11.44% of cases. IPI of < 6 months, 6-11 months, 24-59 months, and  $\geq 60$  months were all associated with a increased risk of small for gestational age births. When adjusted for demographics, these U-shaped relationships persisted.

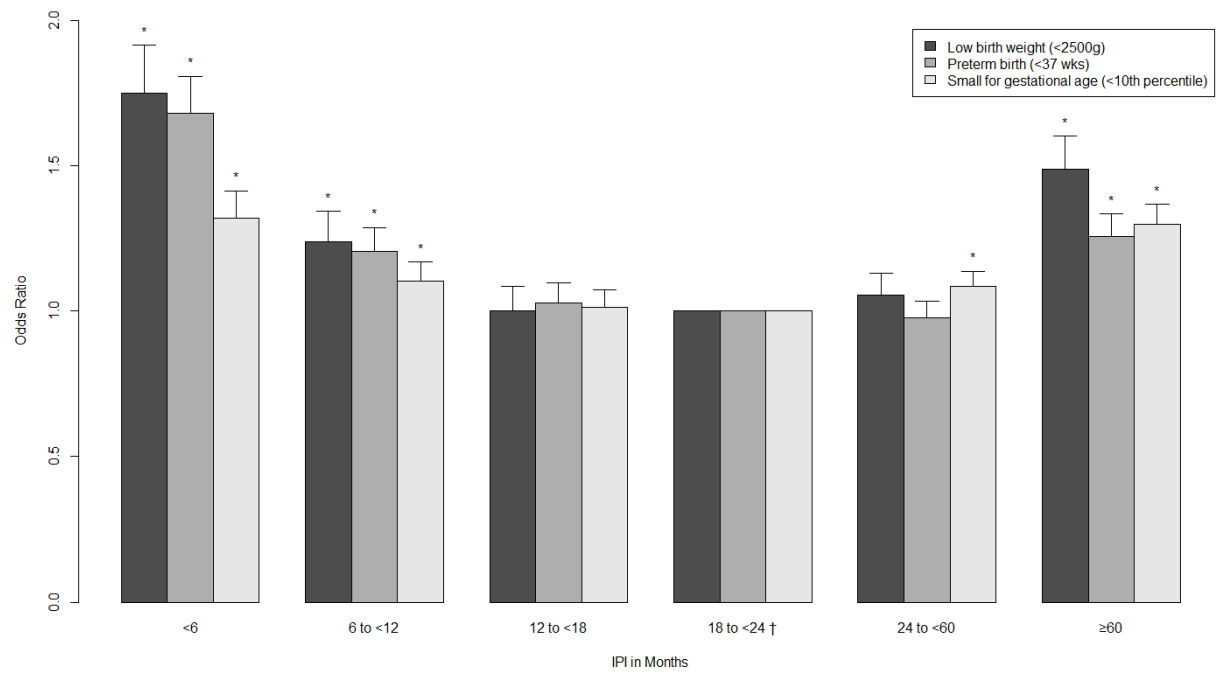


Figure 2. Odds ratios and 95% confidence intervals for preterm birth, low birth weight, and small for gestational age (SGA) by IPI category.

Footnote: \*  $p < 0.05$  from the reference group; † reference group

### Neonatal morbidities

Significant unadjusted relationships between the shortest and longest IPI categories and specific neonatal morbidities were identified (Table 2.) IPI of < 6 months was associated with periventricular leukomalacia and bronchopulmonary dysplasia. IPI of  $\geq 60$  months was associated with intraventricular hemorrhage. IPI of both < 6 months and  $\geq 60$  months were associated with increased risk of apnea bradycardia, respiratory distress syndrome, and suspected sepsis. These relationships did not persist after adjusting for demographics, birth weight, and gestational age. No relationship was found between IPI and Grade III or IV IVH, proven sepsis, transient tachypnea of the newborn, meconium aspiration, necrotizing enterocolitis, or seizures.



Table 2. Neonatal morbidities by IPI (unadjusted.)

Neonatal morbidities	< 6 months		6-11 months		12-17 months		18-23 months †		24-59 months		≥ 60 months	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Low birth weight	1.750	1.600 - 1.915*	1.239	1.143 - 1.343*	1.000	.921 - 1.087	1.000		1.056	.986 - 1.132	1.490	1.385 - 1.602*
Preterm birth	1.681	1.563 - 1.808*	1.207	1.132 - 1.288*	1.013	0.956 - 1.072	1.000		0.978	.925 - 1.034	1.257	1.184 - 1.334*
Small for Gestational Age	1.321	1.235 - 1.414*	1.104	1.042 - 1.169*	1.013	0.956 - 1.072	1.000		1.084	1.033 - 1.137*	1.298	1.233 - 1.367*
Interventricular hemorrhage	1.917	.831 - 4.423	1.072	.480 - 2.392	0.855	.370 - 1.971	1.000		1.148	.739 - 2.721	2.143	1.095 - 4.193*
Apnea bradycardia	1.576	1.102 - 2.252*	1.341	.983 - 1.830	0.854	.609 - 1.199	1.000		1.087	.828 - 1.426	1.399	1.049 - 1.866*
Bronchopulmonary dysplasia	3.152	1.621 - 6.127*	1.749	.917 - 3.337	0.977	.477 - 2.001	1.000		1.049	.578 - 1.902	1.506	.808 - 2.807
Periventricular leukomalacia	4.473	1.156 - 17.300*	2.116	.547 - 8.184	1.140	.255 - 5.092	1.000		1.223	.345 - 4.336	1.860	.504 - 6.872
Respiratory Distress Syndrome	1.674	1.423 - 1.969*	1.147	.989 - 1.330	0.993	.855 - 1.155	1.000		1.004	.885 - 1.138	1.312	1.147 - 1.500*
Suspected Sepsis	1.480	1.295 - 1.690*	1.091	.970 - 1.228	0.953	.845 - 1.074	1.000		1.026	.929 - 1.133	1.251	1.124 - 1.392*
Transient Tachypnea of the Newborn	1.351	0.992 - 1.840	1.046	.797 - 1.371	0.775	.582 - 1.034	1.000		0.983	.783 - 1.234	1.229	.963 - 1.567

Abbreviations: CI, confidence intervals; IPI, interpregnancy interval; OR, odds ratio

\* p < .05

† Reference Group

## Discussion

The relationship between interpregnancy interval and risk of preterm birth, low birth weight, and small for gestational age is well established. This study aimed to expand on this known relationship by also investigating specific neonatal morbidities diagnosed in a neonatal intensive care unit. Consistent with prior studies, our analysis showed that IPI of < 12 months or  $\geq 60$  months showed increased risk of low birth weight, preterm birth, and small for gestational age. That these relationships persisted when adjusted for other predictors confirms that IPI remains an independent risk factor for these neonatal outcomes. IPI categories between 12-59 months demonstrated comparably lower risk of poor neonatal outcomes. This represents a wider range of IPI with reduced risk of poor outcomes than what has been previously reported. Zhu et al.,(9) for example, found a lowest risk of adverse outcome associated with an IPI of 18-23 months while Conde-Agudelo et al. (10) reported similar results with an interval of 12-23 months.

With regard to specific neonatal morbidities, intervals at both ends of the IPI spectrum were associated with the highest risk. Risk of apnea bradycardia, respiratory distress syndrome, and suspected sepsis increased with IPI < 6 months or  $\geq 60$  months; risk of periventricular leukomalacia and bronchopulmonary dysplasia increased with short IPI (< 6 months); and risk of intraventricular hemorrhage increased with longer IPI ( $\geq 60$  months.) None of the relationships between IPI and specific neonatal morbidities remained significant once adjusted for other predictors such as birth weight, gestational age, and demographics. The contribution of IPI to these specific neonatal morbidities appears to be mediated through its affect on birth weight and gestational age.

Studies that have found independent associations between interpregnancy interval and other specific neonatal morbidities have been those less “gestational age dependent”. For example IPI of < 6 months or  $\geq 60$  months has been associated with increased risk of congenital malformations.(15,16) IPI of < 6 months has been associated with increased risk of neural tube defects (13) and IPI of < 12 months has been associated with increased risk of gastroschisis.(12) It is unclear whether these relationships exist independently of the association between IPI and

prematurity and low birth weight, as few studies have reported results after adjusting for these variables. One exception is autism risk, which has been associated with shorter IPI intervals even when adjusted for gestational age and birth weight.(14) Increased risk of schizophrenia has also been associated with shorter IPI intervals, independent of gestational age.(20)

One limitation to our study is that by using birth certificate data, we are unable to capture a true interpregnancy interval for women who have had therapeutic abortions or first trimester miscarriages, as these pregnancy outcomes would not generate a birth certificate. This limitation is consistent with other studies using birth certificate data to calculate IPI.(15,16) Using birth certificate data also limits our ability to adjust for confounding, as only variables listed on the birth certificate are available to us for analysis. Our study was also limited to the population of Arizona, which is demographically different from the United States as a whole, and thusly the results may not be representative of the general population.

## Future Directions

Since low birth weight and prematurity increase the risk of neonatal morbidity and mortality, and suboptimal IPI can increase the risk of low birth weight and prematurity, IPI remains a modifiable variable that could be an important target of intervention. Our study found the lowest incidence of preterm birth for IPI ranges of 18 – 59 months (7.4% compared to 8.3% overall.) This means 9 fewer preterm births per 1000 births for women with an IPI of 18-59 months. The estimated cost to society for one preterm birth is \$51,600, which adds up to \$464,400 for 9 preterm births.(21) The cost to prevent pregnancy for one year in these same 1,000 women would be between \$100,000- 200,000 depending on the contraceptive method used,(22) suggesting that improving access to contraception for an ideal IPI might be a cost effective strategy to reduce the societal burden of prematurity.

In addition to contraceptive access, education about birth spacing is needed to reduce the number of pregnancies with very short interpregnancy intervals. Very little data exists on interventions to help women achieve optimal birth spacing. Future research should examine models of preconception and interconception care to identify successful interventions.

## **Conclusions**

Premature birth and low birth weight are significant public health problems that can lead to poor outcomes for infants and substantial costs to the health care system. Many neonatal morbidities may be prevented by preventing prematurity and low birth weight. Suboptimal interpregnancy interval is an established risk factor for prematurity and low birth weight. Reducing the number of pregnancies that occur after a suboptimal interpregnancy interval could reduce the incidence of prematurity and low birth weight, thereby decreasing the number of babies born with significant health problems and decreasing health care costs.

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