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Interpregnancy Intervals and the Risk for Infant Mortality: A Case Control Study of Arizona Infants 2003–2007

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Abstract There is well-documented evidence on how interpregnancy interval (IPI) is associated with adverse perinatal outcomes and how short and long IPIs are associated with increased risk for preterm birth, low birth weight, and intra-uterine growth restriction. However, the extremes of IPI on infant mortality are less well documented. The current study builds on the existing evidence on IPI to examine if extremes of IPI are associated with infant mortality, and also examines if IPI is associated with both neonatal and post-neonatal mortality after adjusting for several known confounders. Matched birth and death certificate data for Arizona resident infants was drawn for 2003–2007 cohorts. The analysis was restricted to singleton births among resident mothers with a previous live birth (n = 1,466) and a randomly selected cohort of surviving infants during the same time-frame was used as a comparison group (n = 2,000). Logistic regression models were utilized to assess the odds for infant mortality at monthly interpregnancy intervals (<6, 6–11, 12–17, 18–23, 24–59, ≥60), while adjusting for established predictors of infant mortality (i.e., preterm birth, low birth weight, and small for gestational age), and other potential confounders. Unadjusted analysis showed greater clustering at extreme IPIs of <6 months and ≥60 months for infants that died (32 %) compared to infants that survived (24.7 %). Shorter IPI (i.e., <6 months, 6–11 months, and 12–17 months) compared to 'ideal' IPI (i.e., 18–23 months), were associated with infant mortality even after adjusting for confounders. Short intervals were significantly associated with neonatal, but not post-neonatal deaths. IPI above 23 months were not associated with infant mortality in our analyses. Shorter IPIs (18 months or less) significantly increases the risk for neonatal infant mortality even after controlling for known confounders, and our study adds to the existing evidence on adverse perinatal outcomes. Counseling women of reproductive age on the benefits of spacing pregnancies to at least 18 months addresses one preventable risk for early infant mortality.

Keywords Interpregnancy intervals · Short IPI · Infant mortality · Neonatal mortality · Preterm birth · Low birth weight · Preconception health

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Background

The infant mortality rate in Arizona remained persistent from 1999 to 2008 [1]. Although leading causal factors for neonatal infant mortality, such as preterm birth and low birth weight, are well documented, little progress has been made in reducing these outcomes during the past decade [2, 3]. There is well-documented evidence to link short

(<6 months) and long (greater than 59 months) interpregnancy intervals (IPI) and adverse perinatal outcomes [4–18]. In particular, short IPI is associated with maternal mortality [4] and is associated with negative birth outcome such as preterm birth [4–12], low birth weight [4, 5, 8, 18], and small for gestational age [4, 5, 8]. While the general causal mechanisms of short IPI and adverse perinatal outcomes are unclear [5, 19, 20], short IPI increases the risk of adverse outcomes through premature rupture of membranes, third trimester bleeding, and placental abruption [6, 18]. One of the causal explanations offered in the literature on adverse maternal and fetal outcomes is the nutrition depletion hypothesis [4] that links short interpregnancy intervals and negative birth outcomes [8]. According to this thesis, closely spaced pregnancies result in limited recovery from physiological stress of pregnancy and post-partum breastfeeding, thus 'depleting' the maternal nutrient store and increasing risk for negative birth outcomes. A related hypothesis links short interpregnancy intervals to folate depletion and the concomitant risks of neural tube defects, preterm birth, and low birth weight [9].

Addressing interpregnancy interval offers a key point of intervention for infant health [4]. Few studies have examined the effect of interpregnancy interval on infant survival [2]. Studies that have looked at infant mortality, have used different interpregnancy intervals [5], have looked at maternal populations outside the US [10, 21], have failed to control for important maternal characteristics [5] that may confound the relationship, and most importantly have been limited in making generalizations due to small sample sizes [5]. And thus have underestimated the true risk of short or long intervals on infant mortality.

The present study examines the independent effects of short and long interpregnancy intervals on infant mortality. The study controls for relevant predictors of infant mortality based on literature and research available to date for the Arizona population utilizing linked Arizona Birth and Death Certificate data.

Methods

Data and Sample

For this study the authors obtained data from the Arizona Death Certificates for infants (i.e., <365 days of age) that occurred between 1 of January 2003 and 31 of December 2007 (n = 3,204). This infant mortality cohort was matched to Arizona Birth Certificates by unique birth certificate numbers that are available on each death certificate.

Figure 1 shows the development of the sample. Multiple gestation pregnancies assume greater risk for neonatal death and have been excluded from previous studies on the effects of interpregnancy intervals due to potential confounding [22]. Therefore, singleton deliveries to resident mothers with a previous live birth were selected for this analysis (n = 1,466). A random sample of singleton infants that survived beyond age one and whose mothers had a previous live birth was drawn from the birth certificate database (n = 2,000).

Measures

The Arizona Birth Certificate is based on the 1989 U.S. Standard Birth Certificate and the data includes infant and mother's medical conditions, mother's demographic information and behaviors during pregnancy, and infant delivery status. These data have been used to predict the odds of infant mortality in cohort studies [23, 24]. Interpregnancy intervals are defined as the time between last live birth and the date of conception for the current live birth [12]. Interpregnancy intervals were calculated by subtracting the date of previous live birth from the calculated date of conception of current live birth. The date of conception for the current live birth was determined by the difference between the date of delivery and the physician's estimate of gestational age and/or clinical estimate.

Three conditions of the infant commonly associated with infant mortality were included in this analysis. First, gestational age was measured in weeks and dichotomized into preterm (<37 weeks), or term (37 or more weeks). Previous history of having a preterm delivery was also included in the analysis. Second, birth weight was measured in grams and was also dichotomized into low birth weight (<2,500 g), or normal birth weight (2,500 g or more). Finally, small for gestational age is a measure of fetal growth restriction and a marker for increased fetal and infant mortality [25]. Small for gestational age was defined as infants at or below the 10th percentile in birth weight compared to infants of the same gender and gestational age.

Table 1 gives an overview of the known causal and risk factors associated with infant mortality by infant status. As expected preterm birth, low birth weight and small for gestational age were more common among the infant mortality cohort than among the comparison group of infant survivors (see Table 1).

Other behavioral, medical, and demographic variables were included in the analysis (see Table 1). Tobacco use at anytime during pregnancy is a significant predictor of negative birth outcomes [26] and was included as a self-reported behavior for this study. The Arizona Birth Certificate does not contain detailed information about frequency or timing of tobacco use. Alcohol use was not included in the analysis because it is subject to excessive reporting bias [27].

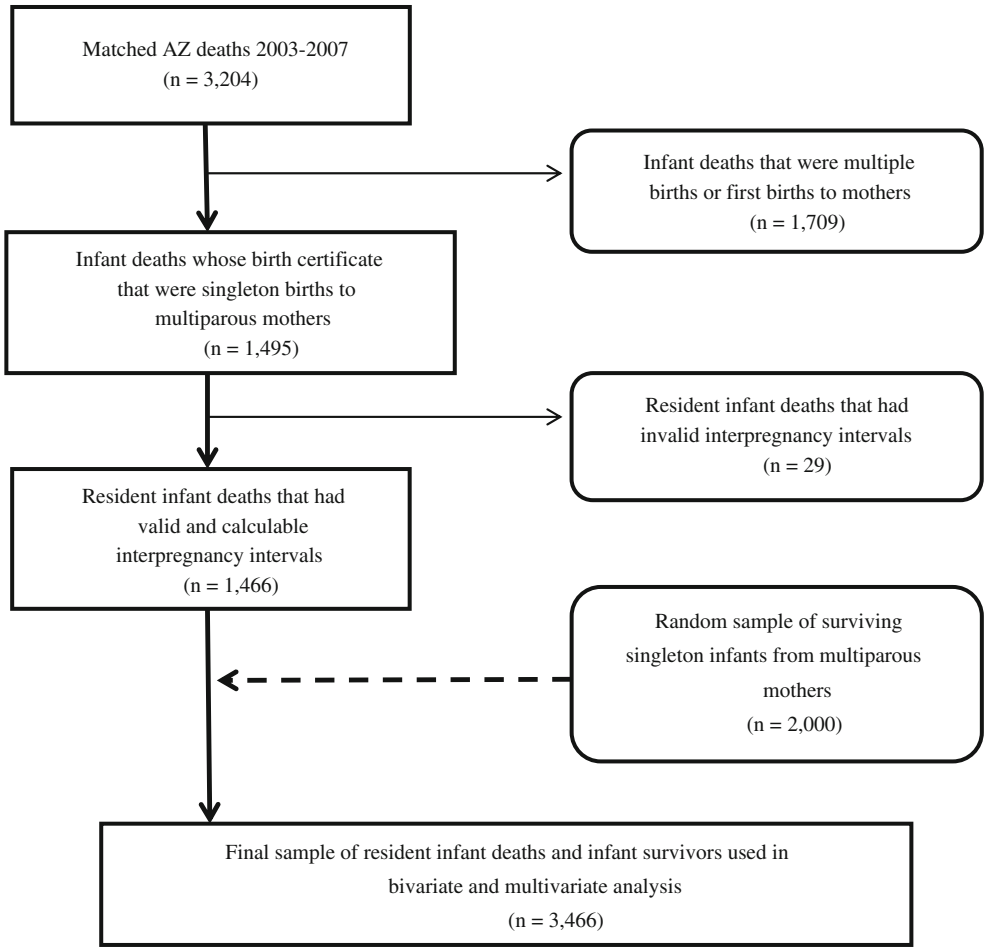

Fig. 1 Sample of infant deaths and survivors infants in Arizona residents 2003–2007

Medical risk factors such as anemia (hct. < 30/hgb. < 10), cardiac disease, acute or chronic lung disease, diabetes, genital herpes, hydramnios and/or oligohydramnios, hemoglobinopathy, hypertension, chronic hypertension, pregnancy-associated eclampsia, etcetera are available in the mother's medical record in the birth certificate data [27]. This variable was dichotomized to indicate whether a mother had one or more risks, or no medical risk factors prior to delivery. Recorded as a continuous variable in the birth certificates, mother's weight gain during pregnancy was transformed into an ordinal variable of <15, 15–30, and 31 or more lbs. The Arizona Birth Certificate does not collect data necessary to calculate body mass index at pregnancy. Young and older women assume greater risks for negative birth outcomes [28, 29], thus the continuous age variable was transformed into an ordinal variable of <18 years old, 18–34 years old, and 35 years and older.

Lack of prenatal care, public insurance coverage, and single mother are proxy indicators of socio-economic status. These indicators have been shown to be associated with negative infant health outcomes [30–32] and are, therefore, controlled in this analysis. Race and ethnicity are also strongly associated with infant health. Hispanic or Latina women delivered 45 % of all live births in both the infant mortality and infant survival cohorts from 2003 to 2007. White non-Hispanics comprise the next most common group in both cohorts. As is true across the US, Black or African American women and Native American women assume the greatest risk for infant mortality in Arizona [33]. Mother's level of education and residence are more distal factors in infant health that may influence the odds of infant survival.

Analytic Procedures

Bivariate and multivariate methods were utilized to compare the risks for infant mortality. Mantel–Haenszel Chi-Square tests and logistic regression analyses were conducted using SAS v9.2 (SAS Institute, Inc., Cary, NC,USA). The authors evaluated three major research questions. First, what

Table 1 Distribution of risk variables by infant status in Arizona with valid interpregnancy intervals during 2003–2007

Variables	Infant survivors (N = 2,000)	Infant deaths (N = 1,466)
1. Low birth weight	90 (4.5 %)	823 (57.0 %)
2. Preterm birth	175 (8.8 %)	834 (59.1 %)
3. Small for gestational age	145 (7.3 %)	316 (23.1 %)
4. One or more maternal medical risks	205 (10.3 %)	201 (13.7 %)
5. Male infant	1,020 (51 %)	833 (56.9 %)
6. Tobacco use during pregnancy	130 (6.5 %)	157 (10.8 %)
7. Previous history of preterm birth	16 (0.8 %)	18 (1.2 %)
8. Number of living children	$M = 1.9$ (1.2)	$M = 2.0$ (1.5)
9. Hispanic	908 (45.4 %)	671 (45.8 %)
10. Non-Hispanic White	813 (40.7 %)	487 (33.2 %)
11. Native American	117 (5.9 %)	137 (9.4 %)
12. Black or African American	60 (3.0 %)	97 (6.6 %)
14. Other race/ethnicity	92 (4.6 %)	68 (4.6 %)
15. <15 lbs weight gain	283 (14.8 %)	466 (35.5 %)
16. 15–30 lbs weight gain	910 (47.6 %)	561 (42.8 %)
17. 31 lbs and more weight gain	717 (37.5 %)	285 (21.7 %)
18. No prenatal care	60 (3.0 %)	125 (8.5 %)
19. Married	1229 (61.5 %)	693 (47.3 %)
20. Mother <18 years of age	83 (4.2 %)	98 (6.7 %)
21. Mother 18–34 years of age	1,612 (80.6 %)	1,130 (77.1 %)
22. Mother ≥35 years of age	305 (15.25 %)	238 (16.2 %)
23. Mother <high school ed.	611 (31.0 %)	521 (33.2 %)
24. Medicaid (AHCCCS)	1,093 (55.2 %)	948 (65.2 %)
25. Indian Health Service (IHS)	25 (1.3 %)	26 (1.8 %)
26. Private insurance	811 (41.0 %)	418 (28.8 %)
27. Rural residence	273 (13.7 %)	226 (15.3 %)

interpregnancy intervals are significantly associated with infant mortality? Second, do these same intervals remain associated with infant mortality after controlling for other predictors of infant mortality? Third, are these intervals more significantly associated with neonatal compared to post-neonatal death? Appropriate dummy variables for interpregnancy intervals were included in the logistic regression analyses.

Results

Table 2 shows differences in the distribution of interpregnancy intervals by infant status. Mothers in the infant mortality group were significantly more likely to have either short (i.e., <6 months) or long (i.e., 60 months or greater) intervals compared to mothers of the infant survival group. The 18–23 month interval and 24–59 month interval was significantly more common among mothers with surviving infants.

Table 3 presents interpregnancy intervals as the hypothesized predictor for infant mortality after adjusting for available confounders. Model I shows the unadjusted odd ratios that examines the association between interpregnancy interval and infant mortality. As expected shorter interpregnancy intervals (<11 months) and longer intervals (>60 months) are associated with higher infant mortality. When compared to the optimal interval (18–23 months), infant mortality is twice higher for IPI <6 months and 48 % higher for IPI between 6 and 11 months. Further, infant mortality is 49 % higher for longer IPIs (60 months or greater).

Model II assessed the independent effect of interpregnancy intervals after adjusting for maternal medical risks, gender of the infant, tobacco use during pregnancy, previous history of preterm birth, number of living children, race and ethnicity, weight gained during pregnancy, prenatal care, marital status, maternal age, mother's education, insurance status, and geographic area of mother's residence. It is evident from model II that short interpregnancy intervals are significant predictors of infant mortality. When compared to the optimal interval (18–23 months), infant mortality is 76 % higher for IPI <6 months and 38 % higher for IPI 12–17 months.

Model III assessed the independent effect of the causal factors such as preterm birth, low birth weight, and small for gestational age on infant mortality status after adjusting for available confounders without the inclusion of interpregnancy intervals. As anticipated preterm births increased the odds of infant mortality by four times; low birth weight increased the odds of infant mortality by seven times; and small for gestational age increased the odds of

Table 2 Distribution of interpregnancy intervals by infant status in Arizona during 2003–2007

Group	Number[a]	Interpregnancy intervals					
		<6 months***	6–11 months	12–17 months	18–23 months**	24–59 months***	≥60 months**
Infant deaths	1,466	168 (11.5 %)	221 (15.1 %)	201 (13.7 %)	132 (9.0 %)	443 (30.2 %)	301 (20.5 %)
Infant survivors	2,000	139 (7.0 %)	263 (13.2 %)	270 (13.5 %)	232 (11.6 %)	742 (37.1 %)	354 (17.7 %)

*** $p < 0.01$; ** $p < 0.05$; * $p < 0.10$

[a] Cases with valid data for interpregnancy intervals

Table 3 Interpregnancy intervals as predictors of infant mortality in Arizona during 2003–2007

Variables	Infant mortality			
	Model I[a]	Model II[b]	Model III[c]	Model IV[d]
1. <6 months	2.12*** (1.56–2.9)	1.76*** (1.24–2.51)		1.68** (1.09–2.59)
2. 6–11 months	1.48*** (1.12–1.95)	1.36 (1–1.86)		1.67*** (1.15–2.44)
3. 12–17 months	1.31 (0.99–1.73)	1.38** (1.01–1.88)		1.48** (1.01–2.17)
4. 18–23 months	Reference	Reference		Reference
5. 24–59 months	1.05 (0.82–1.34)	1.0 (0.76–1.31)		1.05 (0.75–1.47)
6. 60 months or more	1.49*** (1.15–1.94)	1.32 (0.98–1.78)		1.21 (0.83–1.76)
7. Preterm birth			4.50*** (3.40–5.95)	4.44*** (3.35–5.89)
8. Low birth weight			7.54*** (5.35–10.62)	7.71*** (5.46–10.87)
9. Small for gestation			1.94*** (1.44–2.62)	1.96*** (1.45–2.66)
−2LL	4,682.05	3,880.65	2,846.48	2,829.27

All models are adjusted (unless otherwise noted) for maternal medical risks, gender of the infant, tobacco use during pregnancy, previous history of preterm birth, number of living children, race and ethnicity, weight gained during pregnancy, prenatal care, marital status, maternal age, mother's education, insurance status, and geographic area of mother's residence

[a] Model I is an unadjusted model with interpregnancy intervals as predictors of infant mortality

[b] Model II adjusts for other confounding variables other than preterm birth, low birth weight, and small for gestation with interpregnancy intervals as predictors of infant mortality

[c] Model III is an adjusted without interpregnancy intervals as predictors of infant mortality

[d] Model IV is a full model with interpregnancy intervals as predictor of infant mortality after adjusting for all covariates

*** $p < 0.01$; ** $p < 0.05$

infant mortality by two times after adjusting for the confounders.

Model IV is the full model and includes interpregnancy intervals as the hypothesized predictor of infant mortality after adjusting for known causal factors such as preterm birth, low birth weight, and small for gestational age and other confounders (see Table 3). It is evident that in the full model shorter interpregnancy intervals consistently predict higher infant mortality. In particular, compared to the optimal interval (18–23 months) short interpregnancy intervals (<6 months) increased the risk of infant mortality by 68 %; increased the risk of infant mortality by 67 % (6–11 months); and increased the risk of infant mortality by 48 % (12–17 months) respectively. Although very long IPI (60 months or greater) predicted infant mortality in the unadjusted model, very long IPI (>60 months) was not a predictor of infant mortality after adjusting for known causal factors and other confounders.

Irrespective of adjustment, shortest IPI (<6 months) consistently predicted higher infant mortality and IPI (24–59 months) did not predict infant mortality. However, other interpregnancy intervals 6–11 months, 12–17 months, and 60 months or greater (see model I and model II) did not consistently predict infant mortality. These variables attained statistical significance either through inclusion and/or exclusion of known causal factors and/or other confounding variables. While longer IPI (60 months or greater) and shorter IPI (6–11 months) predicted higher infant mortality in the unadjusted model, the same intervals did not predict infant mortality when controlled for confounding variables such as maternal medical risks, gender of the infant, tobacco use during pregnancy, previous history of preterm birth, number of living children, race and ethnicity, weight gained during pregnancy, prenatal care, marital status, maternal age, mother's education, insurance status, and geographic area of mother's residence. Similarly, in the unadjusted model IPI (12–17 months) did not predict infant mortality (see Table 3 model 1); however, the same interpregnancy interval achieved statistical significance when we controlled for confounding variables. While there are no changes in the hypothesized direction of the effects for interpregnancy intervals, absence and/or the presence of a statistically significant effect (see model I and model II) suggests plausible 'cooperative suppression effect' [34] in the absence of a statistical interaction (effect modification). Alternatively, interpregnancy intervals may be interacting with other confounding variables. Overall model IV fits the data better as model I, model II, and model III are nested within the full model (see model IV) and comparison of log-likelihood ratio suggests that model IV has a significantly better fit compared to other models. Exploring interaction and cooperative suppression effect is beyond the scope of this paper.

Model V and model VI (see Table 4) examines the risk of neonatal mortality (i.e., <28 days of age) and post-neonatal mortality. The results of model V and model VI

Table 4 Interpregnancy intervals as predictors of neonatal and post-neonatal mortality in Arizona during 2003–2007

Variables	Neonatal mortality Model V	Post-neonatal mortality Model VI
1. <6 months	1.62** (1.04–2.52)	1.87 (0.68–5.12)
2. 6–11 months	1.64** (1.12–2.41)	1.99 (0.78–5.05)
3. 12–17 months	1.49** (1.01–2.2)	2.08 (0.82–5.29)
4. 18–23 months	Reference	Reference
5. 24–59 months	1.0 (0.71–1.41)	1.76 (0.79–3.93)
6. 60 months or more	1.14 (0.78–1.68)	2.09 (0.89–4.95)
7. Preterm birth	3.9*** (2.91–5.22)	8.96*** (4.94–16.24)
8. Low birth weight	5.04*** (3.53–7.2)	26.37*** (14.65–47.48)
9. Small for gestation	1.99*** (1.45–2.71)	2.49*** (1.38–4.48)
−2LL	2,644.84	673.29

Adjusted for maternal medical risks, gender of the infant, tobacco use during pregnancy, previous history of preterm birth, number of living children, race and ethnicity, weight gained during pregnancy, prenatal care, marital status, maternal age, mother's education, insurance status, and geographic area of mother's residence

*** $p < 0.01$; ** $p < 0.05$

confirmed that the association between interpregnancy interval and infant mortality is confined to the neonatal period. The odds of neonatal infant mortality were 62 % greater for intervals of <6 months, 64 % greater for intervals of 6–11 months, and 49 % greater for intervals of 12–17 months compared to the reference interval. Considering that the majority of infant mortality in this study occurred during the neonatal period (n = 983) and multiple other studies have demonstrated an association between short intervals and neonatal mortality [5], the results of model IV were expected. While model V demonstrated no significant association existed between short interpregnancy intervals and post-neonatal mortality, the sheer magnitude of the effects of preterm birth (8.96), low birth weight (26.37), and small for gestational age (2.47) suggests that post-neonatal mortality is perhaps mostly related to complications following preterm birth, low birth weight, and small for gestational age.

Discussion

The results of this study demonstrate that compared to intervals of 18–23 months, shorter interpregnancy intervals (<6 months, 7–11 months, and 12–17 months) significantly increase the odds for infant mortality, particularly, neonatal infant mortality even after adjusting for known causal factors such as preterm birth, low birth weight, and small for gestation and other available confounders in the birth certificate data. In particular, interpregnancy interval of <6 months consistently predicted higher neonatal infant mortality irrespective of adjustment for confounding variables. Other interpregnancy intervals attained statistical significance and/or lost statistical significance based on inclusion and/or exclusion of variables. As noted earlier, these could potentially relate to the suppression effect in the absence of a statistical interaction (effect modification) and/or these interpregnancy intervals (i.e., 6–11 months, 12–17 months, and >60 months) could be interacting with specific combinations of confounders. Nonetheless, evidence obtained suggests that short interpregnancy intervals have an independent effect on neonatal mortality. One plausible explanation is in line with the nutrition depletion hypothesis that suggests that short intervals result in decrease in nutrient storage and subsequently depletion in folate and increase the risks of neural tube defects, preterm birth, and low birth weight [9]. Increased risk of neural tube defects, preterm births, and low birth weight then increases the risk of neonatal infant mortality.

The study also confirmed well established associations between negative birth outcomes, such as low birth weight and preterm birth, and infant mortality. Post hoc analyses utilizing gestational age and birth weight as continuous variables did not change the hypothesized relationships of short interpregnancy intervals and the risk of neonatal mortality. This suggested that there was no residual confounding due to dichotomization of gestational age and low birth weight, and this result further confirmed the association that short interpregnancy intervals contribute to neonatal mortality. While short interpregnancy intervals were associated with an increase in neonatal mortality their effects were still lower (i.e., odds-ratio <2) compared to known causal factors such as low birth weight, and gestational age.

A major strength of this study included a large cohort of infant mortality and surviving infants, adjusted for socio-demographic, behavioral and medical variables missing in other studies [5]. The size of the cohort increased the power of the study to find differences across multiple pregnancy intervals. Access to birth and death certificate data allowed for a complete sample frame of infant mortality and surviving infants from 2003 to 2007, thus reducing the influence of selection bias on the results.

Women's BMI has been associated with negative pregnancy outcomes in other studies [35, 36], and the current Arizona Birth Certificate does not collect baseline height or weight and, therefore, BMI was not controlled for in this analysis. Also, at least one study of a large cohort of births in Sweden found that the effect of short interpregnancy intervals on fetal and neonatal infant mortality was confounded by mother's previous reproductive history [17]. While our study included mother's history of preterm birth, it did not control for history of spontaneous or induced termination. However, the Swedish study used different referent pregnancy intervals (12–35 months) and different categories of other intervals compared to this study. The breakdown of

intervals often differs across studies, therefore making comparisons of results difficult [5].

Short interpregnancy intervals are amenable to public health intervention and provide a vehicle for reducing infant mortality rates and other negative birth outcomes. International public health efforts promote adequate 'birth spacing' as a low cost intervention to limit adverse pregnancy outcomes [37] in low income nations. Interpregnancy intervals have also been recommended as an important preconception health indicator that can be reliably measured [38]. Reduced access to health care and the economic bifurcation of U.S. society challenge public health officials to consider low cost intervention strategies that empower women throughout their reproductive life-course. Birth spacing and healthy timing of subsequent pregnancies are important discussions providers should have around third trimester and postpartum. Such discussions offer a realistic intervention strategy to help reduce infant mortality in the U.S.

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