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Impact of interpregnancy interval on the subsequent risk of adverse perinatal outcomes

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Abstract

Aim: The aim of this study was to investigate the impact of interpregnancy interval as a risk factor on multiple adverse perinatal outcomes.

Material and Methods: Interpregnancy intervals and confounding factors were determined for healthy pregnancies (controls [$n = 357$]) and for pregnancies complicated by adverse perinatal outcomes. Interpregnancy interval was categorized as <6, 6–11, 12–17, 18–23, 24–35 and ≥36 months. Adverse outcomes included spontaneous labor leading to preterm birth ($n = 265$), preterm premature rupture of membranes ($n = 245$), pre-eclampsia ($n = 286$), gestational diabetes ($n = 302$), abnormal placentation ($n = 154$), anemia ($n = 314$), congenital anomalies ($n = 459$), post-partum hemorrhage ($n = 326$) and small for gestational age ($n = 168$). Multivariate logistic regression analysis was performed to assess the association of each outcome with the interpregnancy interval categories.

Results: Spontaneous labor leading to preterm birth (odds ratio [OR], 1.86; 95% confidence interval [CI], 1.13–1.97), preterm premature rupture of membranes (OR, 1.69; 95%CI, 1.28–2.39), congenital anomalies (OR, 1.38; 95%CI, 1.09–1.76) and small for gestational age (OR, 1.68; 95%CI, 1.14–2.34) were significantly associated with intervals of <6 months. Among congenital anomalies, short interpregnancy interval represents an increased risk for cardiac defects (OR, 1.55; 95%CI, 1.09–5.46), neural tube defects (OR, 2.06; 95%CI, 1.32–7.64) and central nervous system anomalies (OR, 1.45; 95%CI, 1.12–3.65).

Conclusion: Short interpregnancy interval is an independent risk factor for adverse perinatal outcomes.

Key words: congenital anomaly, interpregnancy interval, preterm premature rupture of membranes, small for gestational age, spontaneous preterm birth.

Introduction

Interpregnancy interval (IPI), which is defined as duration between previous birth and following conception, is an important consideration for mothers contemplating subsequent pregnancies. Some studies have recommended an interval of 18–23 months for optimal pregnancy spacing.[1,2] However, more than half of second or higher-order singleton pregnancies occur out of this range.[3] In addition, both short (<18 months) and long intervals (>23 months) have been shown to be associated with adverse perinatal outcomes compared with intermediate intervals of 18–23 months.[2] Studies have demonstrated that short IPI is a risk factor for preterm birth, preterm premature rupture of membranes (PPROM), anemia, third-trimester bleeding, puerperal endometritis and early neonatal death.[4,5] Long IPI are also associated with an increased risk of pre-eclampsia, preterm birth, labor dystocia and small for gestational age (SGA).[4,6,7]

Some authors proposed that IPI is not causal and that the relation between IPI and pregnancy outcomes may have been inadequately adjusted for maternal factors.[7] For example, history of preterm birth, which is the strongest risk factor for early delivery in the next pregnancy, was not taken into account in most of the studies.[7–9]

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Similarly, previous congenital anomaly was not controlled for a confounding variable in the evaluation of the effect of IPI on congenital anomalies.[5]

If short or long IPI are found to be independently associated with adverse perinatal outcomes, obstetric interventions that are not very complicated could be considered to prevent such adverse outcomes.[10] Therefore, the purpose of this study was to evaluate whether IPI is independently associated with increased risk of adverse perinatal outcomes.

Methods

This study was conducted with the database of Tepecik Training and Research Hospital, Izmir, Turkey between January 2008 and September 2014. Our study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and research protocol was approved by the ethics committee of our center. The records of 2758 consecutive patients with adverse perinatal outcomes, including spontaneous preterm birth, PPROM, pre-eclampsia, gestational diabetes, anemia, abnormal placentation, congenital anomalies, SGA and post-partum hemorrhage (PPH), were retrospectively evaluated. For comparison, the control group consisted of 379 patients randomly selected from the antenatal care unit.

In order to examine the IPI as a risk factor for adverse pregnancy outcomes in the subsequent pregnancy, women who delivered two or more singletons during the study period were included. In the case of mothers who delivered more than two infants, only the first two consecutive pregnancies were examined. Multiple deliveries and deliveries before 20 weeks of gestation were excluded. IPI was calculated as the time between the dates of first delivery and last menstrual period for the index pregnancy. Measures of crown–rump length by first trimester ultrasonography were used when data regarding menstruation were questionable or missing. IPI were categorized as follows: <6 months, 6–11 months, 12–17 months, 18–23 months, 24–35 months, and ≥36 months. Short IPI was defined as <6 months' duration.

Spontaneous labor leading to preterm birth was defined as delivery < 37 weeks of gestation after spontaneous onset of labor. PPROM was defined as rupture of membranes before 37 weeks of gestation. SGA was defined as birthweight < 10th centile for gestational age. Post-partum hemorrhage was defined as clinically estimated blood loss of ≥ 500 mL after vaginal delivery or ≥ 1000 mL after caesarean delivery or a peripartum change in hemoglobin level greater than 2 g/dL.[11] Anemia was defined as hemoglobin < 10.5 g/dL and <11 g/dL in the second and third trimesters, respectively.[12] Pre-eclampsia was defined as blood pressure ≥ 140/90 mm/Hg and proteinuria ≥ 300 mg/24 h. Gestational diabetes was diagnosed by using a two-step glucose tolerance test. Abnormal placentation included cases with placenta previa and placental invasion anomalies. Congenital anomalies, which included major structural and chromosomal anomalies other than soft markers, were classified as follows: cardiac, central nervous system (excluding neural tube defects), skeletal, genitourinary, gastrointestinal, facial, respiratory, chromosomal, neural tube defects and others.

To investigate the association between IPI and the risk of adverse perinatal outcomes at the index pregnancy, the following potentially confounding variables were collected from the database: maternal age at delivery of subsequent pregnancy (<20 years, 20–34 years or ≥35 years), parity (1, 2–3 or ≥4 births), body mass index before subsequent pregnancy (kg/m^2), type of conception (spontaneous vs *in vitro* fertilization), smoking habit, pregestational diabetes mellitus, fetal sex and outcome of previous pregnancy.

The data were analyzed using SPSS 20. Results were converted into categorical data and presented as number of patients. Categorical variables for cases and controls were compared by χ^2 or Fisher's exact test. Statistically significant confounding factors in univariate analyses were then adjusted for each of the adverse pregnancy outcomes by multivariate logistic regression models. The risks of perinatal outcomes in each of the IPI categories are expressed as odds ratios (OR) with 95% confidence intervals (CI). Associations were considered significant if $P < 0.05$.

Results

For this study, we considered 379 pregnancies as the control group and excluded 22 of these whose data were incomplete. Similarly, a total of 2758 pregnancies were identified as having an adverse outcome. Of these, 35 patients with spontaneous labor leading to preterm birth, 27 patients with PPROM, 33 patients with pre-eclampsia, 28 patients with gestational diabetes, 21 patients with abnormal placentation, 24 patients with anemia, 32 patients with congenital anomalies, 25 patients with PPH and 14 patients with SGA were excluded due to insufficient data.

Eventually, the study was conducted with 357 controls and with women experiencing spontaneous labor leading to preterm birth ($n = 265$), PPROM ($n = 245$), pre-eclampsia ($n = 286$), gestational diabetes ($n = 302$), abnormal placentation ($n = 154$), anemia ($n = 314$), congenital anomalies ($n = 459$), PPH ($n = 326$) and SGA ($n = 168$). IPI and selected maternal risk factors of controls and pregnancies with adverse perinatal outcomes are presented in Table 1. The rate of short IPI was higher in pregnancies with spontaneous labor leading to preterm birth (10.2%), PPROM (11%), anemia (9.2%), congenital anomalies (10%), PPH (6.7%) and SGA (11.3%) compared with controls (4.5%). Logistic regression models were constructed to assess further the association of adverse perinatal outcomes with the IPI categories.

Potentially confounding maternal risk factors for spontaneous labor leading to preterm birth were maternal age ≤ 20 years, parity ≥ 4 and preterm birth, PPROM, cesarean delivery, anemia, and abnormal placentation in the prior pregnancy. For PPROM, the risk factors were maternal age ≥ 35 years, BMI ≥ 30 kg/m^2 and preterm birth and PPROM in the prior pregnancy. For pre-eclampsia, the risk factors were maternal age ≥ 35 years, BMI ≥ 30 kg/m^2, parity ≥ 4, smoking, pregestational diabetes mellitus (DM) and stillbirth, pre-eclampsia and gestational DM in the prior pregnancy. For gestational DM, the risk factors were maternal age ≥ 35 years, parity ≥ 4, BMI ≥ 30 kg/m^2 and GDM in the prior pregnancy. For abnormal placentation, the risk factors were maternal age ≥ 35 years, parity ≥ 4, BMI ≥ 30 kg/m^2, smoking, and pre-eclampsia, abnormal placentation, anemia, cesarean delivery and SGA in the prior pregnancy. For anemia, the risk factors were maternal age ≥ 35 years, parity ≥ 4 and abnormal placentation, anemia and cesarean delivery in the prior pregnancy. For congenital anomalies, the risk factors were maternal age ≥ 35 years and congenital anomalies and SGA in the prior pregnancy. For PPH, the risk factors were maternal age ≤ 20 years, parity ≥ 4, BMI ≥ 30 kg/m^2, smoking, and pre-eclampsia, cesarean delivery, anemia and abnormal placentation in the prior pregnancy. For SGA, the risk factors were maternal age ≥ 35 years, parity ≥ 4, smoking, and preterm birth, pre-eclampsia, abnormal placentation, anemia, PPH, and SGA in the prior pregnancy.

After controlling for major confounding factors, pregnancies with spontaneous labor leading to preterm birth, PPROM, congenital anomaly and SGA compared with controls were significantly associated with intervals of <6 months (Table 2 and Fig. 1). The distribution of IPI of pregnancies with pre-eclampsia, gestational diabetes, abnormal placentation, anemia and PPH were not significantly different from those of controls. This short interval had an OR of 1.86 (95%CI, 1.13–2.97) for spontaneous labor leading to preterm birth, 1.69 (95% CI, 1.28–2.39) for PPROM, 1.38 (95%CI, 1.09–1.76) for congenital anomaly and 1.68 (95%CI, 1.14–2.34) for SGA.

In multivariate logistic regression analysis, among congenital anomalies, an interval of <6 months represents an increased risk for cardiac defects (OR, 1.55; 95%CI, 1.09–5.46), neural tube defects (OR, 2.06; 95% CI, 1.32–7.64) and central nervous system anomalies (OR, 1.45; 95%CI, 1.12–3.65) (Table 3). In addition, the adjusted OR (aOR) for cardiac defects and central nervous system anomalies associated with IPI of 6–11 months were statistically significant (OR, 1.35; 95%CI, 1.06–2.65; and OR, 1.27; 95%CI, 1.04–3.24, respectively) (Table 3).

Discussion

Our study evaluated the IPI as a risk factor for adverse perinatal outcomes after reproductive confounding variables were controlled by using logistic regression analysis. When compared with the IPI of controls, an interval of <6 months independently increases the risk of spontaneous labor leading to preterm birth, PPROM, congenital anomaly and SGA. However, no such association was found for long intervals.

In this study, the risk of spontaneous labor leading to preterm birth was increased 1.86-fold (95%CI, 1.13–2.97) with intervals of <6 months. A direct relation between short IPI and preterm birth has been demonstrated in most of the studies. An IPI of <6 months was found to be an independent risk factor for both extremely preterm birth (OR, 2.8; 95%CI, 1.3–5.9) and for moderately preterm birth (OR, 1.2; 95%CI, 1.2–2.4).[13] A meta-analysis showed a 40% increased risk of preterm birth in women with intervals <6 months compared with IPI of 18–23 months' birth spacing.[2] In the same study, the risk of preterm birth was increased 1.9% for each month that IPI was shortened from 18 months.[2] Additionally, DeFranco *et al*. observed an increased risk for preterm birth and preterm birth recurrence at the following pregnancy for women with an IPI of <6 months (aOR: 1.48 and 1.44, respectively) and for women with an IPI of 6–12 months (aOR: 1.14 and 1.24, respectively).[14] However, the aforementioned studies included both spontaneous and medically indicated preterm birth, which differs from our study. The relation between short IPI and preterm birth was also investigated by Rodrigues and Barros, who reported that women with

Table 1 Distribution of maternal risk factors in controls and cases with adverse perinatal outcomes

	Controls ($n = 357$)	Preterm birth ($n = 265$)	PPROM ($n = 245$)	Pre-eclampsia ($n = 286$)	Gestational DM ($n = 302$)	Abnormal placentation ($n = 154$)	Anemia ($n = 314$)	Congenital anomalies ($n = 459$)	Post-partum hemorrhage ($n = 326$)	SGA ($n = 168$)
Interpregnancy interval (months)										
<6	16 (4.5)	27 (10.2)	27 (11)	11 (3.9)	9 (3)	5 (3.3)	29 (9.2)	46 (10)	22 (6.7)	19 (11.3)
6–11	54 (15.1)	58 (21.9)	56 (22.9)	41 (14.3)	38 (12.6)	14 (9.1)	68 (21.6)	96 (20.9)	61 (18.7)	24 (14.3)
12–17	87 (24.4)	48 (18.1)	55 (22.4)	64 (22.4)	85 (28.1)	33 (21.4)	65 (20.7)	82 (17.9)	72 (22.1)	44 (26.2)
18–23	94 (26.3)	52 (19.6)	51 (20.8)	49 (17.1)	77 (25.5)	50 (32.5)	79 (25.2)	97 (21.1)	70 (21.5)	47 (28)
24–35	70 (19.6)	38 (14.3)	34 (13.9)	76 (26.6)	59 (19.5)	39 (25.3)	52 (16.6)	68 (14.8)	49 (15)	23 (13.7)
≥36	36 (10.1)	42 (15.9	22 (9)	45 (15.7)	34 (11.3)	13 (8.4)	21 (6.7)	70 (15.3)	52 (16)	11 (6.5)
Maternal age (years)										
<20	45 (12.6)	52 (19.6)	37 (15.1)	40 (14)	33 (10.9)	23 (14.9)	41 (13.1)	65 (14.2)	64 (19.6)	18 (10.7)
20–34	245 (68.6)	172 (64.9)	142 (58)	167 (58.4)	188 (62.3)	83 (53.9)	193 (61.4)	268 (58.4)	192 (58.9)	102 (60.7)
≥35	67 (18.8)	41 (15.5)	66 (26.9)	79 (27.6)	81 (26.8)	48 (31.2)	80 (25.5)	126 (27.4)	70 (21.5)	48 (28.6)
Parity										
1	221 (61.9)	182 (68.7)	131 (53.5)	180 (62.9)	175 (57.9)	73 (47.4)	188 (59.9)	251 (54.7)	176 (54)	93 (55.3)
2–3	105 (29.4)	45 (17)	88 (35.9)	64 (22.4)	79 (26.2)	52 (33.8)	82 (26.1)	163 (35.5)	101 (31)	47 (28)
≥4	31 (8.7)	38 (14.3)	26 (10.6)	42 (14.7)	48 (15.9)	29 (18.8)	44 (14)	45 (9.8)	49 (15)	28 (16.7)
BMI > 30 (kg/m^2)	15 (4.2)	13 (4.9)	18 (7.3)	25 (8.7)	29 (9.6)	12 (7.8)	16 (5.1)	24 (5.2)	27 (8.3)	10 (5.9)
Conception by IVF	9 (2.5)	7 (2.6)	4 (1.6)	6 (2.1)	6 (2)	3 (1.9)	5 (1.6)	6 (1.3)	4 (1.2)	3 (1.8)
Smoking	19 (5.3)	22 (8.3)	16 (6.5)	28 (9.8)	17 (5.6)	20 (13)	11 (3.5)	32(7)	33 (10.1)	20 (11.9)
Pregestational DM	—	5 (1.9)	6 (2.4)	8 (2.8)	—	4 (2.6)	5 (1.6)	11 (2.4)	6 (1.8)	4 (2.4)
Fetal sex (F/M)	1.02	1.14	1.09	1.05	0.96	1.11	0.91	0.94	0.94	1.12
Outcome of previous pregnancy										
Stillbirth	4 (1.1)	3 (1.1)	2 (0.8)	11 (3.8)	2 (0.6)	1 (0.6)	2 (0.6)	5 (1.1)	2 (0.6)	7 (4.2)
Preterm birth	24 (6.7)	42 (15.8)	29 (11.8)	18 (6.3)	35 (11.6)	15 (9.7)	18 (5.7)	32 (7)	16 (4.9)	25 (14.9)
PPROM	9 (2.5)	17 (6.4)	19 (7.7)	6 (2.1)	8 (2.6)	7 (4.5)	5 (1.6)	18 (3.9)	14 (4.3)	7 (4.2)
Pre-eclampsia	10 (2.8)	11 (4.1)	15 (6.1)	22 (7.7)	8 (2.6)	15 (9.7)	8 (2.5)	25 (5.4)	27 (8.3)	13 (7.7)
Gestational DM	5 (1.4)	6 (2.3)	10 (4.1)	12 (4.2)	17 (5.6)	5 (3.2)	7 (2.2)	7 (1.5)	8 (2.4)	6 (3.6)
Abnormal placentation	11 (3.1)	18 (6.8)	11 (4.5)	6 (2.1)	4 (1.3)	13 (8.4)	21 (6.7)	14 (3)	24 (7.4)	14 (8.3)
Anemia	19 (5.3)	29 (10.9)	13 (5.3)	17 (5.9)	30 (9.9)	16 (10.4)	34 (10.8)	24 (5.2)	28 (8.6)	24 (14.3)
Congenital anomalies	17 (4.8)	12 (4.5)	7 (2.9)	10 (3.5)	9 (3)	5 (3.2)	11 (3.5)	45 (9.8)	10 (3.1)	5 (3)
Cesarean delivery	86 (24.1)	91 (34.3)	71 (29)	72 (25.2)	65 (21.5)	60 (39)	103 (32.8)	112 (24.4)	115 (35.3)	58 (34.5)
PPH	15 (4.2)	11 (4.1)	12 (4.9)	9 (3.1)	12 (4)	9 (5.8)	13 (4.1)	14 (3)	29 (8.9)	16 (9.5)
SGA	9 (2.5)	8 (3)	10 (4.1)	13 (4.5)	11 (3.6)	14 (9.1)	7 (2.2)	30 (6.5)	15 (4.6)	17 (10.1)

Data are presented as *n* (%). BMI, body mass index; DM, diabetes mellitus; F, female; IVF, *in vitro* fertilization; M, male; PPH, post-partum hemorrhage; PPROM, preterm premature rupture of membranes; SGA, small for gestational age.

Table 2 OR, aOR† and 95%CI for adverse perinatal outcomes by interpregnancy intervals

		Interpregnancy interval (months)					
		<6	6–11	12–17	18–23	24–35	≥36
Preterm birth	OR (95%CI)	2.42 (1.27–4.59)*	1.57 (1.04–2.37)*	0.69 (0.46–1.02)	0.68 (0.46–1)	0.69 (0.45–1.06)	1.68 (1.04–2.70)*
	aOR (95%CI)	1.86 (1.13–2.97)*	1.13 (0.88–1.45)	0.68 (0.45–1.01)	0.67 (0.45–1)	0.68 (0.43–1.05)	1.45 (0.91–2.11)
PPROM	OR (95%CI)	2.64 (1.39–5.01)*	1.66 (1.10–2.52)*	0.90 (0.61–1.32)	0.73 (0.50–1.08)	0.66 (0.42–1.03)	0.88 (0.50–1.54)
	aOR (95%CI)	1.69 (1.28–2.39)*	1.35 (0.98–1.86)	0.87 (0.59–1.30)	0.71 (0.48–1.01)	0.65 (0.39–1.01)	0.86 (0.47–1.51)
Pre-eclampsia	OR (95%CI)	0.85 (0.39–1.87)	0.93 (0.6–1.46)	0.90 (0.62–1.29)	0.58 (0.39–0.85)	1.48 (1.02–2.15)*	1.66 (1.04–2.66)*
	aOR (95%CI)	0.82 (0.35–1.81)	0.87 (0.55–1.39)	0.92 (0.65–1.33)	0.61 (0.42–0.88)	1.22 (0.79–1.81)	1.26 (0.81–1.84)
Gestational DM	OR (95%CI)	0.65 (0.28–1.50)	0.81 (0.52–1.26)	1.22 (0.86–1.72)	0.96 (0.67–1.36)	0.95 (0.65–1.41)	1.13 (0.69–1.86)
	aOR (95%CI)	0.63 (0.25–1.46)	0.75 (0.44–1.09)	1.13 (0.75–1.69)	0.89 (0.42–1.39)	0.90 (0.54–1.42)	1.08 (0.55–1.76)
Abnormal placentation	OR (95%CI)	0.71 (0.26–1.99)	0.56 (0.30–1.04)	0.85 (0.54–1.33)	1.34 (0.89–2.03)	1.39 (0.89–2.17)	0.82 (0.42–1.60)
	aOR (95%CI)	0.68 (0.21–1.78)	0.54 (0.25–1.02)	0.80 (0.46–1.16)	1.21 (0.84–1.74)	1.25 (0.87–2.03)	0.77 (0.38–1.52)
Anemia	OR (95%CI)	2.17 (1.15–4.07)*	1.55 (1.04–2.30)*	0.81 (0.56–1.17)	0.94 (0.66–1.33)	0.81 (0.55–1.21)	0.64 (0.36–1.12)
	aOR (95%CI)	1.27 (0.96–1.62)	1.18 (0.85–1.64)	0.79 (0.45–1.21)	0.89 (0.62–1.25)	0.80 (0.53–1.20)	0.62 (0.32–1.11)
Congenital anomaly	OR (95%CI)	2.37 (1.32–4.27)*	1.48 (1.03–2.14)*	0.67 (0.48–0.95)*	0.75 (0.54–1.04)	0.71 (0.49–1.03)	1.60 (1.04–2.46)*
	aOR (95%CI)	1.38 (1.09–1.76)*	1.35 (0.97–1.94)	0.64 (0.45–1.05)	0.69 (0.46–1.02)	0.70 (0.45–1.01)	1.44 (0.94–1.96)
PPH	OR (95%CI)	1.54 (0.79–2.99)	1.29 (0.86–1.93)	0.88 (0.62–1.26)	0.76 (0.54–1.09)	0.72 (0.49–1.08)	1.69 (1.07–2.67)*
	aOR (95%CI)	1.48 (0.86–2.27)	1.12 (0.79–1.68)	0.85 (0.61–1.21)	0.75 (0.51–1.01)	0.70 (0.44–1.05)	1.42 (0.95–2.23)
SGA	OR (95%CI)	2.72 (1.36–5.43)*	0.93 (0.56–1.57)	1.10 (0.72–1.68)	1.09 (0.72–1.64)	0.65 (0.39–1.08)	0.62 (0.31–1.26)
	aOR (95%CI)	1.68 (1.14–2.34)*	0.78 (0.44–1.25)	1.05 (0.65–1.64)	1.04 (0.66–1.52)	0.64 (0.37–1.07)	0.54 (0.21–1.02)

*$P < 0.05$. †Adjusted for maternal age, parity, body mass index, smoking, pregestational DM, fetal sex and outcomes of previous pregnancy. aOR, adjusted odds ratio; CI, confidence interval; DM, diabetes mellitus; OR, odds ratio; PPH, post-partum hemorrhage; PPROM, preterm premature rupture of membranes; SGA, small for gestational age.

IPI of 6 months or less had significantly increased risk of preterm delivery secondary to spontaneous onset of labor before 34 weeks of gestation (OR, 3.9; 95%CI, 1.91–8.10).[15]

The finding of increased PPROM in women with short IPI corresponds with previous studies. A study by Getahun *et al*. examining the recurrence risk of PPROM showed that the risk of PPROM was substantially higher when the interval between births was <18 months.[16] Conde-Agudelo and Belizan observed a 70% increased risk of PPROM in pregnancies with intervals of <6 months compared with intervals of 18–23 months.[4] In contrast, Razzaque *et al*. did not find a statistically significant association between IPI and PPROM.[17] In that study, however, they found that IPI of <6 months and 6–14 months had the highest odds ratios for PPROM (1.94 and 2.86, respectively) compared with an IPI of 27–50 months.[17]

Our study demonstrated short IPI as a risk factor for SGA. This finding is consistent with studies by Zhu *et al*. and Shults *et al*. who reported that women with a short IPI were more likely to have an SGA newborn.[7,18] Additionally, Conde-Agudelo *et al*. demonstrated a 61% higher risk of SGA in infants conceived <6 months after a birth compared to those conceived 18–23 months after a previous birth.[4] Conversely, Auger *et al*. found no significant association between IPI <12 months and SGA.[19] However, they did not evaluate IPI <6 months because of sample size restrictions.[19] Therefore, inconsistent reports regarding SGA and short IPI may be attributed to the use of different reference groups.

Infants born following a shorter IPI had 38% increased risk of a birth defect. Consistent with this finding, Grisaru-Granovsky *et al*. and Kwon *et al*. identified increased risk (14% and 20%, respectively) for congenital malformations among infants born after an IPI of <6 months versus 12–23 months and 18–23 months, respectively.[5,20] A more recent population-based study from Canada revealed that the rate of congenital anomalies was highest (2.5%) in women with the shortest IPI (0–5 months).[21] It seems that our study is one of the few studies to document IPI as a new risk factor for congenital anomalies.

Several mechanisms are proposed to explain the association between a short interval between pregnancies and adverse perinatal outcomes. One explanation relies on the maternal nutritional depletion hypothesis, which states that a close succession of pregnancies and lactation do not allow the mother sufficient time to restore the nutritional reserves before she is subjected to the stresses of the subsequent pregnancy.[22] In particular, folate

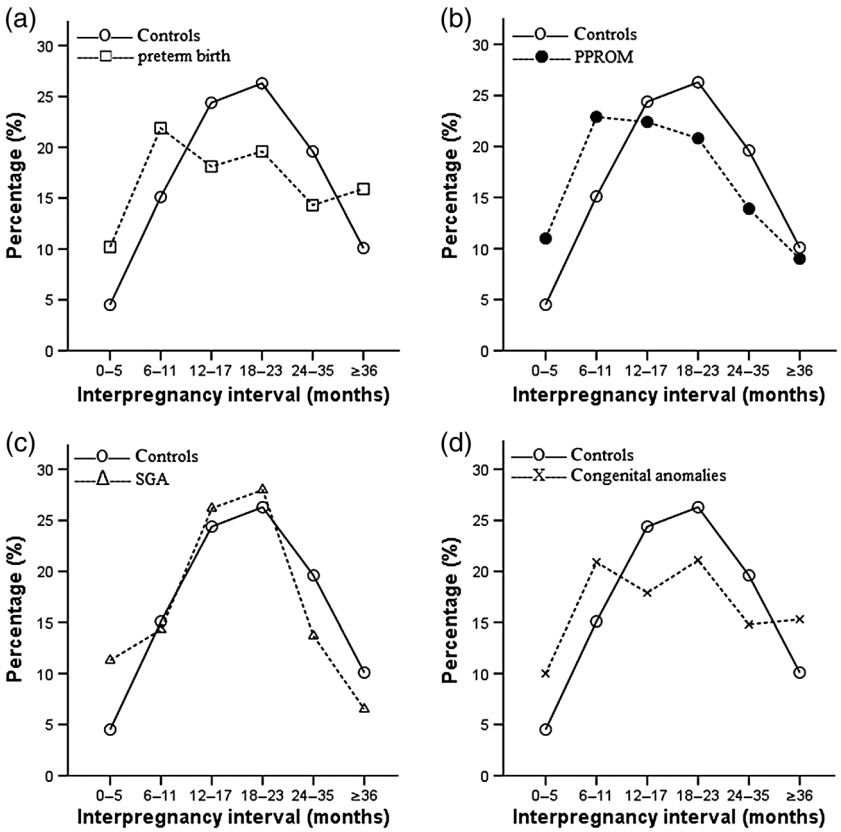

Figure 1 Frequency distribution of controls and cases with adverse. perinatal outcomes by interpregnancy interval categories. (a) Preterm birth. (b) Preterm premature rupture of membranes (PPROM). (c) Small for gestational age (SGA). (d) Congenital anomalies.

deficiency has been put forward as a contributing factor in the cause of pregnancy complications.[23] By 6 months after birth, 20% of mothers still had subnormal folate levels.[24] Mothers who become pregnant within this period after delivery are at greater risk of folate deficiency at the time of conception and during pregnancy. Consequently, their offspring have higher risks of growth restriction, preterm birth and birth defects. Based on folate-deficiency theory, one might think that types of congenital anomalies associated with short IPI were solely folate-dependent. However, not only folate-dependent anomalies (cardiac and neural tube defects) but also those with folate-independent (central nervous system) anomalies were found to be increased with short interval. This interesting finding of our study suggests that folate deficiency is not the only mechanism for the relation between IPI and congenital anomalies.

Another possible scenario for the association between short IPI and spontaneous preterm labor and PPROM is the persistent inflammatory processes of genital tract (especially endometritis) extending from previous birth to the next pregnancy.[25] Inadequate time after delivery may prevent uterine involution and healing of endometritis, leading to recurrence of inflammation in the following pregnancy.

As with short IPI, we did not demonstrate any adverse outcome associated with long IPI (>35 months). Contrary to our finding, the association of long intervals and pregnancy complications, such as pre-eclampsia, preterm birth and SGA, were also reported in some studies.[4,7] Conflicting results may be due to lack of standardized definitions used for IPI. Short IPI is most frequently defined as <6 months, whereas no uniform threshold is defined for long IPI.[1,7,17,19,21] Advanced maternal age is another reason for these poor perinatal outcomes in women with long IPI. Although studies of long IPI and adverse outcomes adjust for maternal age in their analyses, it is still possible that residual and unmeasured confounding is present.[26]

The major strength of this study is that IPI were stratified on and controlled for the strongest risk factors (outcomes of previous pregnancy, such as preterm birth, PPROM, pre-eclampsia and congenital anomalies) for adverse perinatal outcomes in the succeeding infant. The study is limited by incomplete data due to its retrospective design. We did not have information regarding

Table 3 Rates, OR, aOR† and 95%CI for congenital anomalies by interpregnancy intervals

Type of congenital anomaly		Interpregnancy interval (months)					
		<6	6–11	12–17	18–23	24–35	≥36
		(*n* = 46)	(*n* = 96)	(*n* = 82)	(*n* = 97)	(*n* = 68)	(*n* = 70)
Cardiac	*n* (%)	11 (11.7)	24 (25.5)	15 (16)	17 (18.1)	14 (14.9)	13 (13.8)
	OR (95%CI)	2.82 (1.26–6.31)*	1.92 (1.11–3.32)*	0.59 (0.32–1.08)	0.62 (0.35–1.10)	0.72 (0.38–1.34)	1.43 (0.72–2.82)
	aOR (95%CI)	1.55 (1.09–5.46)*	1.35 (1.06–2.65)*	0.54 (0.27–1.04)	0.57 (0.21–1.09)	0.58 (0.34–1.14)	1.05 (0.71–1.65)
NTD	*n* (%)	9 (18.4)	15 (30.6)	7 (14.3)	8 (16.3)	5 (10.2)	5 (10.2)
	OR (95%CI)	4.79 (1.99–11.56)*	2.47 (1.26–4.85)*	0.52 (0.22–1.19)	0.55 (0.25–1.21)	0.47 (0.18–1.22)	1.01 (0.38–2.72)
	aOR (95%CI)	2.06 (1.32–7.64)*	1.43 (0.98–3.65)	0.41 (0.21–1.16)	0.54 (0.24–1.21)	0.41 (0.14–1.10)	1.03 (0.45–2.82)
Genitourinary	*n* (%)	6 (14.3)	7 (16.7)	6 (14.3)	9 (21.4)	6 (14.3)	8 (19)
	OR (95%CI)	3.55 (1.31–9.65)*	1.12 (0.47–2.66)	0.52 (0.21–1.27)	0.76 (0.35–1.65)	0.68 (0.28–1.69)	2.1 (0.90–4.88)
	aOR (95%CI)	2.21 (0.98–8.24)	1.10 (0.45–2.29)	0.49 (0.18–1.13)	0.72 (0.30–1.20)	0.55 (0.21–1.41)	1.35 (0.68–3.38)
Skeletal	*n* (%)	1 (1.9)	5 (9.5)	12 (22.6)	13 (24.5)	10 (18.9)	12 (22.6)
	OR (95%CI)	0.41 (0.05–3.16)	0.58 (0.22–1.53)	0.91 (0.46–1.81)	0.91 (0.47–1.77)	0.95 (0.46–1.99)	2.61 (1.26–5.41)*
	aOR (95%CI)	0.27 (0.03–2.86)	0.48 (0.18–1.25)	0.79 (0.35–1.54)	0.76 (0.35–1.52)	0.42 (0.14–1.02)	1.87 (0.97–4.12)
Respiratory	*n* (%)	2 (7.4)	2 (7.4)	5 (18.5)	7 (26)	5 (18.5)	6 (22.2)
	OR (95%CI)	1.70 (0.37–7.83)	0.45 (0.1–1.95)	0.70 (0.26–1.92)	0.98 (0.40–2.39)	0.93 (0.34–2.55)	2.55 (0.96–6.72)
	aOR (95%CI)	1.32 (0.30–6.52)	0.35 (0.07–1.32)	0.68 (0.25–1.90)	0.87 (0.34–2.15)	0.78 (0.21–1.85)	1.63 (0.64–4.85)
CNS	*n* (%)	9 (11.4)	20 (25.3)	(17.7)	13 (16.5)	13 (16.5)	10 (12.6)
	OR (95%CI)	2.74 (1.16–6.45)*	1.90 (1.06–3.41)*	0.67 (0.36–1.25)	0.55 (0.29–1.04)	0.81 (0.42–1.55)	1.29 (0.61–2.73)
	aOR (95%CI)	1.45 (1.12–3.65)*	1.27 (1.04–3.24)*	0.57 (0.28–1.09)	0.51 (0.22–1.02)	0.69 (0.31–1.11)	1.17 (0.41–2.24)
Gastrointestinal	*n* (%)	1 (2.9)	4 (11.4)	8 (22.9)	12 (34.3)	6 (17.1)	4 (11.4)
	OR (95%CI)	0.63 (0.08–4.87)	0.72 (0.25–2.13)	0.92 (0.40–2.10)	1.46 (0.70–3.05)	0.85 (0.34–2.12)	1.15 (0.38–3.44)
	aOR (95%CI)	0.44 (0.06–4.13)	0.62 (0.23–1.76)	0.75 (0.29–1.75)	1.32 (0.65–3.03)	0.62 (0.21–1.54)	1.10 (0.28–2.54)
Face	*n* (%)	5 (16.1)	10 (32.3)	5 (16.1)	6 (19.4)	3 (9.7)	2 (6.4)
	OR (95%CI)	4.1 (1.39–12.07)*	2.67 (1.19–5.99)*	0.60 (0.22–1.60)	0.67 (0.27–1.69)	0.44 (0.13–1.49)	0.61 (0.14–2.68)
	aOR (95 % CI)	1.89 (0.87–10.65)	1.25 (0.78–4.62)	0.52 (0.14–1.47)	0.63 (0.24–1.56)	0.43 (0.12–1.48)	0.59 (0.11–2.23)
Chromosomal	*n* (%)	1 (4.3)	3 (13.1)	5 (21.7)	5 (21.7)	3 (13.1)	6 (26.1)
	OR (95%CI)	0.97 (0.12–7.64)	0.84 (0.24–2.93)	0.86 (0.31–2.39)	0.78 (0.28–2.15)	0.61 (0.18–2.13)	3.15 (1.17–8.49)*
	aOR (95%CI)	0.95 (0.11–7.52)	0.79 (0.22–2.56)	0.84 (0.28–2.34)	0.75 (0.24–2.01)	0.52 (0.11–1.96)	2.12 (0.97–7.52)
Others	*n* (%)	1 (3.9)	6 (23.1)	5 (19.2)	7 (26.9)	3 (11.5)	4 (15.4)
	OR (95%CI)	0.85 (0.11–6.69)	1.68 (0.65–4.38)	0.74 (0.27–2.02)	1.03 (0.42–2.53)	0.53 (0.16–1.83)	1.62 (0.53–4.97)
	aOR (95%CI)	0.80 (0.08–5.45)	1.25 (0.42–3.52)	0.70 (0.22–1.59)	1.02 (0.40–2.52)	0.48 (0.12–1.45)	1.29 (0.47–4.23)

*$P < 0.05$. †Adjusted for maternal age, parity, body mass index, smoking, pregestational diabetes mellitus, fetal sex and outcomes of previous pregnancy. aOR, adjusted odds ratio; CNS, central nervous system; CI, confidence interval; NTD, neural tube defect; OR, odds ratio.

maternal breast-feeding and folate use, which interact with the association between folate depletion and IPI. In addition, missing data regarding intrapartum events in the prior pregnancy could also contribute to confounding effects.

In conclusion, our findings suggest that a short IPI is a causal factor for spontaneous labor leading to preterm birth, PPROM, congenital anomalies and SGA and also demonstrated the importance of optimal birth spacing. Based on the results, we believe that women who conceive shortly after a birth need to be informed about elevated risk of adverse perinatal outcomes and monitored closely during antenatal care. Another important clinical practice implication is that the adverse effects of short IPI could be prevented by the use of folate supplements and effective family planning methods in the period between consecutive pregnancies.

Disclosure

The authors declare that there are no conflicts of interest.

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