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Effect of interpregnancy interval on adverse perinatal outcomes — a national study

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Abstract

Background: The interpregnancy interval (IPI) has been reported to influence the outcome of pregnancy and birth. We performed a national study in Israel to determine the impact of IPI on multiple adverse perinatal outcomes.
Study Design: This longitudinal cohort study used birth certificates of siblings born to the same biological mother, with at least one previous birth and a subsequent singleton pregnancy. Adverse pregnancy outcomes included preterm delivery, very preterm birth, small for gestational age (SGA), very SGA (VSGA), early neonatal death and major congenital malformations. Multivariate logistic regression was performed for each outcome.
Results: The study included 440,838 of a total of 846,845 reported live births in Israel over 5 years; excluded were primiparas (32%), multifetal births (4.9%) and those with incomplete data (10.9%). For IPIs shorter than 6 months, there were significantly increased risks for preterm birth (OR=1.23), SGA (OR=1.14), VSGA (OR=1.15), early neonatal death (OR=1.62) and congenital malformations (OR=1.14). Intervals of 60 months or longer had higher risks for preterm birth (OR=1.39) and VSGA (OR=1.16).
Conclusion: Optimal IPI recommendation of >11 months is an accessible and low-cost means to improve multiple adverse perinatal outcomes.

Keywords: Interpregnancy interval; Preterm delivery; Small for gestational age; Early neonatal death; Major congenital malformations

1. Introduction

The interpregnancy interval (IPI) has been reported to influence the outcome of pregnancy and birth: short interpregancy intervals have been linked to increased risk for preterm birth, low birth weight, small for gestational age (SGA), labor dystocia and maternal morbidity and mortality [1–3]. The increased risk of adverse pregnancy outcomes due to short IPI has been attributed to a number of mechanisms including maternal nutritional status and folate depletion [4], hormonal imbalance in the postpartum period and lactation stress [5,6]. The various putative mechanisms suggested to explain this association, the multifaceted nature of pregnancy outcomes [2,7] and racial and socioeconomic heterogenicity of sampled populations [8,9] have undoubtedly led to several as yet unproven hypotheses [10]. Therefore, we designed a population-based cohort study to investigate the impact of the IPI on adverse perinatal outcomes, in the hope of both ascertaining if indeed IPI impacts neonatal and maternal outcome and assessing possible mechanisms.

2. Materials and methods

Data for this study were prospectively obtained through longitudinal collection of birth certificate records for singletons born in Israel to the same biological mother in

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the years 2000–2005 and who had a previous live birth in Israel between the years 1993 and 2005. The IPI was computed as the interval between two consecutive deliveries minus the gestational age of the second infant, that is, between live births ending with the subsequent conception. All pairs of live birth intervals are included, for example, from first to second, second to third and so on. The IPIs were grouped as follows (months): 0–5, 6–11, 12–23, 24–59 and 60 and more.

Data are left censored at 1993, further left censored due to the high rate of immigration during the 1990s. IPI as calculated does not include previous spontaneous or induced abortions or stillbirths. Prenatal and antenatal care is provided for all citizens and permanent residents of Israel by virtue of the National Health Insurance Law (1995) without prejudice; prior to 1995, 95% of the population was insured by a health fund. Each maternity center, by law, files a birth certificate, which is the basis of updating the Israeli population registry and is referred to the Ministry of Internal Affairs and the Ministry of Health, which recruits the data on a monthly basis. The information obtained is under quality control of both ministries. Each center has a daily delivery room report that is transferred automatically from the hospital data and is checked by a doctor and a midwife and the clerk of the Ministry of Internal Affairs who is present in each center. Databases are validated by the Department of Health Information and Computer Services, Ministry of Health. In the present study, we did not include data that were not validated.

Data are based on birth certificates from all live births in Israel, as reported by the hospitals to the Ministry of Internal Affairs and the Ministry of Health. The overwhelming majority of deliveries were born in a hospital (99.5%).

Adverse birth outcomes were defined as follows: preterm delivery (<37 weeks' gestation), very preterm birth (<33 weeks' gestation), SGA (birth weight <10th centile for gestational age), very SGA (VSGA, <5th centile), large for gestational age (LGA; >10th centile for gestational age), early neonatal death (0–6 days after delivery) and major congenital malformations as reported to the Ministry of Health according to Ministry guidelines.

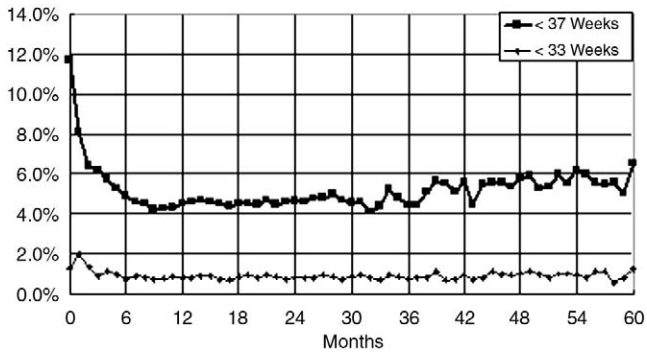

Fig. 1. The crude rates of newborns born before term: before 37 weeks of gestation (black cubes) and before 33 weeks of gestation (black diamonds) as a function of the IPI (months); note the significant increase of cases as the interval is shorter than 6 months.

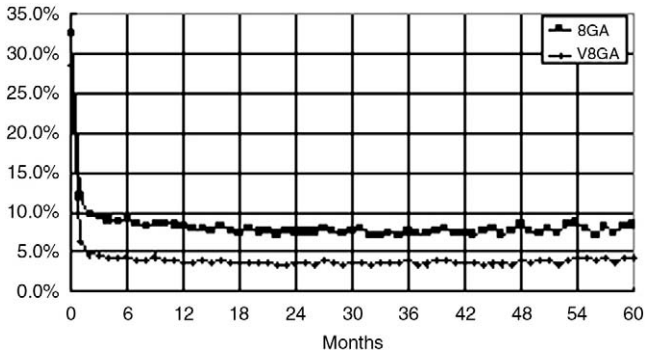

Fig. 2. The crude rates of newborns with a birth weight less than 10th (SGA) (black cubes) and less than 5th (VSGA) (black diamonds) for the gestational age as a function of the IPI (months); note the significant increase of cases as the interval is shorter than 6 months.

Demographic and other potentially confounding maternal reproductive risk factors included in the models were ethnicity (Jewish or Arab), maternal age at delivery (<20 years, 20–34 years or ≥35 years), parity (2–5 or ≥6 live births), previous small live births (<2500 g) and previous large live births (>3800 g).

Socioeconomic indicators on the birth certificate include maternal education defined as years of formal schooling (≤12, 12 or >12) and marital status (married, single or other). Because maternal schooling is not captured in certain regions of the country, a separate model analyzed the impact for these cohorts.

Separate multivariate logistic regression analyses were performed for each of the possible adverse pregnancy outcomes. Maternal age and parity confounders were measured for the subsequent reported birth. SAS version 9.1 was used to estimate the odds ratios (ORs) and 95% confidence intervals (CIs) for each outcome.

The Israeli Ministry of Health/Department of Health Information and Computer Services gave approval for use of the information that was used and not an institutional approval since it is a national study.

3. Results

During the years 2000–2005, there were 846,845 live births in Israel. We excluded 271,545 primiparous mothers, 41,974 multifetal pregnancies and 92,488 births with missing information. These resulted in a study population of 440,838 live births out of a potential cohort of 533,206 (83%).

Fig. 1 shows the percentage of preterm and very preterm births as a function of the IPI. There is a significant increase in the rates when the interval is less than 6 months. Fig. 2 shows the percentage of newborns that are SGA and VSGA as a function of the IPI. The crude rates shown are substantially higher when the interval is less than 6 months.

Table 1
Description of the study population, the pregnancy outcome and explanatory factors

	All		Preterm delivery		Very preterm delivery		SGA		VSGA		LGA		Early neonatal death		Major congenital malformation	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
All	440,838	100.0	22,135	5.0	4016	0.9	35,311	8.0	17,206	3.9	49,534	11.2	494	0.1	7966	1.8
IPI (months)																
0–5	36,020	8.2	2141	5.9	407	1.1	3364	9.3	1652	4.6	3177	8.8	71	0.2	726	2.0
6–11	77,899	17.7	3479	4.5	627	0.8	6641	8.5	3209	4.1	7947	10.2	103	0.1	1411	1.8
12–23	124,152	28.2	5660	4.6	1040	0.8	9659	7.8	4604	3.7	13,927	11.2	133	0.1	2164	1.7
24–59	158,636	36.0	7966	5.0	1394	0.9	11,988	7.6	5835	3.7	19,110	12.0	143	0.1	2833	1.8
60+	44,131	10.0	2889	6.5	548	1.2	3659	8.3	1906	4.3	5373	12.2	44	0.1	832	1.9
Maternal age (years)																
≤19	2812	0.6	237	8.4	62	2.2	288	10.2	157	5.6	176	6.3	4	0.1	53	1.9
20–34	352,359	79.9	16,847	4.8	3033	0.9	28,600	8.1	13,781	3.9	37,262	10.6	388	0.1	6074	1.7
35+	85,667	19.4	5051	5.9	921	1.1	6423	7.5	3268	3.8	12,096	14.1	102	0.1	1839	2.1
Ethnicity																
Jewish	321,859	73.0	15,794	4.9	2747	0.9	25,576	7.9	12,278	3.8	35,279	11.0	223	0.1	5083	1.6
Arab	118,979	27.0	6341	5.3	1269	1.1	9735	8.2	4928	4.1	14,255	12.0	271	0.2	2883	2.4
Previous small																
No	412,900	93.7	17,978	4.4	3196	0.8	29,310	7.1	13,784	3.3	48,515	11.7	425	0.1	7362	1.8
Yes	27,938	6.3	4157	14.9	820	2.9	6001	21.5	3422	12.2	1019	3.6	69	0.2	604	2.2
Previous large																
No	386,183	87.6	20,558	5.3	3696	1.0	34,519	8.9	16,782	4.3	30,816	8.0	451	0.1	6927	1.8
Yes	54,655	12.4	1577	2.9	320	0.6	792	1.4	424	0.8	18,718	34.2	43	0.1	1039	1.9
Parity																
2	168,616	38.2	8800	5.2	1571	0.9	14,590	8.7	6927	4.1	15,740	9.3	160	0.1	2693	1.6
3–5	215,941	49.0	10,588	4.9	1920	0.9	16,925	7.8	8311	3.8	25,100	11.6	237	0.1	3901	1.8
6+	56,281	12.8	2747	4.9	525	0.9	3796	6.7	1968	3.5	8694	15.4	97	0.2	1372	2.4
Maternal education (years of schooling)																
<12	53,559	12.1	3110	5.8	593	1.1	4879	9.1	2533	4.7	6313	11.8	124	0.2	1345	2.5
12	114,895	26.1	6245	5.4	1125	1.0	9577	8.3	4671	4.1	12,617	11.0	115	0.1	2093	1.8
>12	111,885	25.4	5491	4.9	988	0.9	7656	6.8	3510	3.1	13,398	12.0	73	0.1	1880	1.7
Unknown	160,499	36.4	7289	4.5	1310	0.8	13,199	8.2	6492	4.0	17,206	10.7	182	0.1	2648	1.6
Marital status																
Married	427,356	96.9	21,037	4.9	3771	0.9	33,961	7.9	16,470	3.9	48,134	11.3	459	0.1	7614	1.8
Single	5987	1.4	477	8.0	112	1.9	610	10.2	337	5.6	606	10.1	24	0.4	226	3.8
Divorced	6371	1.4	539	8.5	118	1.9	629	9.9	343	5.4	649	10.2	9	0.1	101	1.6

The percentage for each adverse outcome is calculated for the group of each explanatory factor.

Table 2
Logistic regression model results for each adverse pregnancy outcomes (separate models)

	IPI (months)					C statistic	Hosmer–Lemeshow
	0–5	6–11	12–23	24–59	60+		
Preterm delivery	1.23 (1.17–1.29)**	0.98 (0.93–1.02)	1.00	1.09 (1.05–1.13)**	1.39 (1.32–1.46)**	0.610	0.000
Very preterm delivery	1.22 (1.08–1.37)*	0.95 (0.86–1.05)	1.00	1.04 (0.96–1.13)	1.42 (1.27–1.58)**	0.614	0.908
SGA	1.14 (1.09–1.19)**	1.10 (1.07–1.14)**	1.00	0.96 (0.93–0.99)*	1.07 (1.03–1.12)*	0.617	0.040
VSGA	1.15 (1.08–1.22)**	1.11 (1.06–1.16)**	1.00	0.98 (0.94–1.02)	1.16 (1.10–1.23)**	0.626	0.007
LGA	0.83 (0.80–0.87)**	0.91 (0.88–0.93)**	1.00	1.10 (1.07–1.12)**	1.04 (1.00–1.08)*	0.680	0.002
Early neonatal death	1.64 (1.22–2.19)*	1.22 (0.94–1.58)	1.00	0.86 (0.68–1.10)	0.93 (0.65–1.33)	0.608	0.912
Major congenital malformation	1.14 (1.04–1.24)*	1.04 (0.97–1.11)	1.00	1.03 (0.98–1.10)	1.05(0.96–1.14)	0.565	0.000

* .0001≤p<.05.
** p<.0001.

Table 1 shows the characteristics of the study population, the pregnancy outcome and explanatory factors. The rates for preterm birth, SGA, early neonatal death and major congenital malformations were 5.02%, 8.01%, 0.11% and 1.81%, respectively. The mean IPI was 27.78 (95% CI=27.71–27.84) months.

Table 2 shows the ORs for the IPI for each of the adverse outcomes considered. A short IPI (0–5 months) represents a substantial increase in risk for all outcomes. This short interval had an OR of 1.23 (95% CI=1.17–1.30) for preterm births, 1.14 (95% CI=1.09–1.19) for SGA, 1.15 (95% CI=1.08–1.22) for VSGA, 1.64 (95% CI=1.22–2.19) for early neonatal death and 1.14 (95% CI=1.04–1.24) for major congenital malformation. An IPI of 60 or more months represents an increased risk for preterm birth (OR=1.39, 95% CI=1.32–1.46) and VSGA (OR=1.16, 95% CI=1.10–1.23). A model that specifically analyzes the possible interaction between ethnicity and IPI shows the impact of population of origin and IPI on the adverse pregnancy outcomes; the Arab population had an additional significant risk of 28.7% magnitude at an IPI of 0–5 months only for congenital malformation. For other pregnancy outcomes, no significance interactive effect was found between ethnicity and IPI.

Risk factors, including the model built for the socioeconomic confounders identified when building separate models based on parity, showed little difference; therefore, parity was considered as a confounding factor in the models. In particular, overall, we identified 3% of the population with an "unmarried" status (divorced, widow or single) while 97% of the population are referred to as married mothers. Inclusion of the marital status did not change the model results. Maternal education was reported in detail in 60% of the population. In a model that analyzed this fraction of population, education less than 12 years compared to 12 years and more raised the risk for SGA (OR=1.16, 95% CI=1.11–1.22) and VSGA (OR=1.19, 95% CI=1.11–1.26). A maternal education of more than 12 years of schooling was found to be protective for both SGA (OR=0.81, 95% CI=0.78–0.83) and preterm birth (OR=0.88, 95% CI=0.85–0.92). However, no change in the results was obtained for the pregnancy outcomes in relation to the model that included the entire population without the education confounder.

We further aimed to verify whether analysis of the population by using only the first two successive births as opposed to parity classes would change the impact of the IPI on adverse pregnancy outcomes (Table 3). This type of analysis further confirmed the ORs for each of the adverse outcomes reported by the main analysis model and widened the range of high-risk IPI to 11 months for the early neonatal death outcome in particular.

4. Discussion

This national study is the first attempt to determine the impact of IPI on several adverse perinatal outcomes. We found that very short IPI and prolonged IPI are related to increased risk of preterm birth, low birth weight, early

Table 3
The IPI and the first 2 births — logistic regression model results for each adverse pregnancy outcomes (separate models)

	IPI (months)					C statistic	Hosmer–Lemeshow
	0–5	6–11	12–23	24–59	60+		
Preterm delivery	1.28 (1.19–1.38)**	1.00 (0.93–1.06)	1.00	1.12 (1.06–1.19)**	1.57 (1.43–1.72)**	0.615	0.933
Very preterm delivery	1.35 (1.14–1.59)*	1.09 (0.94–1.27)	1.00	1.12 (0.98–1.27)	1.80 (1.46–2.20)**	0.616	0.385
SGA	1.11 (1.05–1.18)*	1.15 (1.09–1.20)**	1.00	0.98 (0.93–1.02)	1.11 (1.02–1.20)*	0.619	0.220
VSGA	1.15 (1.06–1.25)*	1.18 (1.10–1.26)**	1.00	1.03 (0.97–1.10)	1.30 (1.17–1.46)**	0.633	0.573
LGA	1.77 (1.09–2.89)*	1.62 (1.04–2.51)*	1.00	1.12 (0.72–1.74)	1.25 (0.55–2.84)	0.659	0.305
Early neonatal death	0.81 (0.76–0.87)**	0.88 (0.83–0.92)**	1.00	1.08 (1.03–1.12)*	1.07 (0.98–1.15)	0.601	0.981
Major congenital malformation	1.20 (1.05–1.36)*	1.01 (0.90–1.13)	1.00	1.00 (0.91–1.10)	1.31 (1.11–1.56)*	0.535	0.876

* .0001≤p<.05.
** p<.0001.

neonatal death and major congenital malformations. The linkage between short IPI and preterm delivery has been noted in cohorts of European, American and Asian populations [7–9,11–13]. The IPI per se was designated as an independent marker for SGA newborns and vice versa, that is, that women with shorter IPI were a priori at risk of having a small infant [14–16].

Published reports on the association between short IPI outcome and early neonatal death are conflicting, mainly because of selection bias [10,17,18]. Long IPIs have also been shown to be associated with an increased risk for stillbirth and early neonatal death [9,10]. This may be explained by a higher incidence of coexistent maternal complications of pregnancy such as infertility, hypertension and diabetes.

Little or no information as to the risk of major congenital malformations is given in the literature. A unique and novel finding of our study is the association of short IPI, that is, <12 months and especially <6 months, with major congenital malformation. Even more, additional analysis of interaction between ethnicity and IPI pointed that Arabs had an additional significant risk of 28.7% magnitude at an IPI of 0–5 months for congenital malformation. This may be explained by the high intra-family marriages in the Arab population and/or lower compliance with, and/or demand for, antenatal genetic screening. Interestingly, Arab women in Israel appear to fulfill the reproductive potential at a younger age. For example, data from the last four consecutive years show that only 0.6% of Jewish mothers are <20 years compared to 4.8–5.0% of Arab mothers; 24.5–28.9% of the Arab mothers are between 20 and 24 years, while 14.8–13.1% of Jewish mothers are between 20 and 24 years; thereafter, maternity age relative to rates are similar [19].

Other than the percentages, we were unable to analyze an interaction between age and IPI in the very youngest mothers in the two ethnic groups because of low numbers of very young Jewish mothers. We postulate that the teen age and very young maternal age in the Arab observant population, along with prearranged intra-familial marriages, may represent the missing link between some adverse pregnancy outcomes, especially the high congenital malformation rate in this population. These findings highlight the strong influence of IPI on specific pregnancy outcomes within subpopulations because of social and/or religious traditions.

We and others have also considered nutritional stress as a common denominator. Animal studies have demonstrated that severe malnutrition and vitamin B_{12} and folate depletion during gestation adversely affect morphologic development of the neocortex [20–23]. The extent to which these findings are relevant in humans is still uncertain with the exception of the studies on folate suboptimal intake and neural tube defect incidence [24–27]. We speculate that maternal ethnic origin and very young maternal age may predispose to various dietary deficiencies, and awareness for prenatal supplements may be critically valuable here.

Similar to other large-scale reports, longer IPIs here were also associated with a higher risk for adverse pregnancy outcomes [1,7,8]; in the current study, this relatively circumscribed subgroup did not reach significance for the rarer outcomes of early neonatal death and major congenital malformations.

Overall, the size of the study population enabled us to investigate a spectrum of adverse pregnancy outcomes and specifically rare events such as early neonatal death and congenital malformations. The population studied is uniformly covered for the birth and neonatal care by the National Social Security and for the antenatal and neonatal care by the National Health Insurance Law [19]. Under this program, all women are offered a second-trimester ultrasound examination and entitled to three ultrasound examinations during the pregnancy. Unfortunately, data on maternal formal education, as a marker of socioeconomic status, were reported in only 60% of the births, an inherent bias in the design and results for this specific question. Uniform and accessible medical care minimized population selection bias. Within the last 5 years, there has been a significant increase in the report of the maternal formal education (80%), but review of the data using the same model showed identical trends.

By definition, IPI includes births without information of previous spontaneous or induced abortions. This may cause misclassification of the IPI, spuriously prolonging the IPI. There was also 11% of births during this period for which data were incomplete; a similar percentage has been reported by others [10], but this is a relatively minor problem for comparisons and for internal validity of a study of this large size.

The risk for adverse pregnancy outcomes correlates with the previous reproductive maternal history and maternal age [28,29]. The models for the present study results are controlled for maternal age, ethnicity, parity and previous small or large births, thus isolating IPI. No information regarding possible causes of low or high birth weight of the previous birth was available. The definitions used in the present study do not overlap with SGA and preterm births [15], and the association of these two outcomes with short IPI remains. Extreme cases of these conditions were also analyzed. The present study indicates a positive association between short IPI and early neonatal death and is in agreement with some previous studies [17,30]. In contrast, a recent Swedish report found no correlation between short IPI and early neonatal death [10]. This latter study included only the first two deliveries and was for the study period that preceded the current study by nearly a decade [10]. Our results were comparable, with similar associations, whether we used parity in the model or the first two successive births. The strong impact of Arab ethnicity on major congenital malformations that are related to neonatal death is again underscored. Nevertheless, adverse pregnancy outcomes are strongly influenced by ethnicity, immigration and other environmental confounders that are difficult to assess in a

model. These factors, such as genetic polymorphic variation of genes and familial associations, may delineate the magnitude of the effect of IPI not evident in other populations. Thus, we suggest that pregnancy adverse outcome risk estimation should be related to specific populations and geographic area.

All studies, including our own, incur similar limitations as they may be biased by the "replacement phenomenon"; that is, a previous adverse outcome may prompt a shorter interval. In such cases, a tendency to adverse outcomes may confound the IPI and enhance the estimated effect. Moreover, the duration of the lactation (both the actual duration and the degree of nutritional depletion or supplementation) further biases the overall results in the direction of extending the IPI; unfortunately, data on breast-feeding practices in this study population were unavailable.

The novel findings in this large national study suggest that IPI is an independent determinant of the pregnancy outcome within a population with equal access to medical facilities, regarding the standard of medical care, and controlled for maternal characteristics and previous reproductive history in a population. The adverse pregnancy outcomes and mainly the preterm birth and SGA rates represent a major financial burden for any public health system. The association of the short IPI with this complex cluster of outcomes in an otherwise accessible universal national health program underscores the importance of this factor in the vulnerable groups of women. This study is not designed to assess the financial impact of IPI optimal spacing on the national financial resources. The cluster of adverse pregnancy outcomes discussed has little or no alternative for prevention or cure in large-scale unselected populations. As such, it is clear that recommending "optimal pregnancy spacing" as a public health intervention represents an easy, accessible and low-cost means to improve perinatal outcomes. Further prospective studies involving selected high-risk populations are required to measure the impact of this recommendation for these groups in particular.

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