Short interbirth interval and adverse pregnancy outcomes: a Bayesian network approach

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BACKGROUND: Interbirth interval (IBI), the time between consecutive births, has been tied to perinatal outcomes.
OBJECTIVE: To analyze adverse perinatal events following short IBI in a large South American sample.
STUDY DESIGN: Observational, retrospective, hospital-based study including malformed and nonmalformed live- and stillbirths. Outcomes were preterm birth (PTB), low birth weight (LBW), and specific birth defects. Logistic regressions were used to evaluate the risk of selected variables for short IBI and for adverse outcomes after short IBI, adjusting by confounders. Bayesian networks exhibited relationships among short IBI, outcomes, and variables.
RESULTS: Short IBI rate was 2%−3%. Maternal age and a previous abortion were the main confounders. A significant high risk for short IBI was found in mothers ≤19 years while mothers ≥30 were at low risk, mediated by a previous abortion. The risk of short IBI, adjusted by confounders, was significant for LBW but not for PTB. An unadjusted risk of short IBI was observed for gastroschisis, which disappeared after adjusting for confounders. Maternal age ≤19 and previous abortion were directly related with gastroschisis; the relationship between gastroschisis and short IBI occurred through any of these two variables. A direct relationship between gastroschisis and maternal age ≥30 was observed.
CONCLUSIONS: Only young mothers were directly related with short IBI. In older mothers, a short IBI mainly occurred after a previous abortion. Short IBI was a risk factor only for LBW. The PTB and gastroschisis relationship with short IBI was indirect, mediated by young maternal age and/or a previous abortion.

Key words: gastroschisis, interbirth interval, low birth weight, maternal age, previous abortion

Introduction

Interbirth or interpregnancy spacing, the period between two deliveries or two pregnancies, has been tied to the resulting perinatal outcomes. Both short and long interpregnancy intervals have been associated with an increased risk of adverse perinatal outcomes such as low birth weight (LBW), preterm birth (PTB), and small for gestational age.[1,2] Some authors have shown that the risk is the highest for children born after the shortest interpregnancy interval, then it drops to a stable level at around 36 months, and gradually increases again after 60 months spacing, giving rise to a J-shaped curve.[1,3−5] Although the duration mentioned in the literature varies, most studies have considered <6 months for short interpregnancy interval while the definition of a long interpregnancy interval is more variable.[6,7] WHO recommends at least 24 months birth spacing after a live birth and at

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The authors report no conflict of interest.

This work analyzes the occurrence of adverse perinatal outcomes following a short interbirth interval in a large South American sample using Bayesian networks.

Patient consent statement: Written signed informed consents were obtained from all subjects before data collection.

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Why was this study conducted?

To analyze the occurrence of adverse pregnancy events following a short interbirth interval (IBI).

Key findings

A short IBI increases the risk of low birth weight without any mediator, while for the other adverse outcomes, maternal age and a previous abortion acted as mediators.

What does this study add to what is already known?

Overall short interbirth interval rate was 2%−3%. It was a risk factor for low birth weight but not for preterm birth. Gastroschisis and a short interbirth interval were indirectly related.

least six months after a miscarriage or pregnancy termination, before getting pregnant.[8] Some authors have examined the association between the interpregnancy interval and the risk of birth defects and found that a spacing of less than 12 months increased the risk of overall congenital anomalies.[5,9] Getz et al. (2012), investigating specific birth defects, reported an association of interpregnancy intervals shorter than one year with gastroschisis while Ekin et al. (2015) found such an association with neural tube defects, heart defects, and nervous system anomalies. Similarly, Liberman et al. (2022) reported an association of a short interval with gastroschisis and anencephaly in younger mothers, and both of short and long intervals, with Fallot tetralogy and oral clefts.[7,10,11] Todoroff and Shaw (2000) found an increased risk of a short interval for neural tube defects but only if the prior pregnancy had ended in a live birth.[12] These inconsistencies which are possibly due to differences in the study population, the methods of design or analysis, or of birth defects monitoring,[13,14] led us to analyze the occurrence of adverse perinatal events (LBW, PTB, and selected birth defects) following a short interbirth interval (IBI) in a large South American sample.

Material and methods

The present observational, retrospective, case-control, hospital-based study used database records of live and stillborn infants, delivered at 161 maternity hospitals of the ECLAMC network, from 10 South American countries, over a total of 3,332,833 births registered between 1995 and 2021. ECLAMC (Latin American Collaborative Study of Congenital Anomalies) is a program dedicated to the research of birth defects through a network of maternity hospitals where data on socioeconomic and demographic characteristics, previous birth outcomes, and prenatal factors are obtained from medical records and by interviewing the mothers of malformed infants and their nonmalformed controls (next infant of the same sex born in the same hospital) before discharge. A detailed description of ECLAMC has been previously published.[15]

Twelve birth defects were selected based on their conspicuity. Malformed infants were matched with nonmalformed controls (at least 4 per case) by hospital and year of birth. Infants with more than one defect were excluded, as well as primigravid mothers and multiple births.

In the present work, IBI, used as a proxy for interpregnancy interval, was defined as the period between the study birth and the immediately previous delivery (live birth, stillbirth, or abortion). IBI was considered as short and not short (≤12 and >12 months, respectively).

The following variables were compared between mothers with a short and a not short IBI: (1) Maternal age (≤19 and ≥30 years); (2) Socioeconomic status (low and high according to an *ad hoc* scale of maternal and paternal schooling and occupation);[16] (3) Multigravidity (≥3 pregnancies, with 2 as reference); (4) Previous abortion including spontaneous and induced; and (5) Difficulty to conceive (women having received any treatment, medical, surgical, or assisted reproductive technology for infertility).

The analyzed outcomes were PTB, LBW, and birth defects.

Nonmalformed newborns (*n*=47,226) were classified according to their birth weight (BW) and gestational age (GA) into the following categories: adequate (*n*=41,107), GA≥37 weeks and BW≥2500 g; LBW (*n*=2,725), BW<10th percentile, at any GA; and PTB (*n*=3,394), GA<37 weeks and BW≥10th percentile.

Analyses

A logistic regression was used to evaluate the risk of the selected variables for short IBI. Odds ratios and 95% CI were calculated.

To estimate the risk of an adverse outcome after a short IBI, a logistic regression was applied adjusting by the identified main confounders. Odds ratios and 95% CI were calculated.

In order to detect a minimum 2-fold risk for a 2%−3% frequency of short IBI, at least 300 cases of each adverse outcome were required. This sample size allowed an 80% power with 5% false positives.

We use Bayesian networks to visualize the relationships among a short IBI, adverse outcomes, and the included variables. Bayesian networks are graphical probabilistic models defined from a set of random variables. They consist of a directed acyclic graph where the nodes represent the variables and the edges the conditional dependencies between them. A contribution of Bayesian networks to epidemiology is to facilitate the visualization and interpretation of dependencies among variables.[17] Observational data related to IBI were analyzed without the need of a pre-existing causality hypothesis. This approach involves selecting variables and outcomes, using a scoring method to find the best network structure, and assessing the network's fit with statistical methods. The method calculates odds ratios and suggests key predictors of outcomes by analyzing variable relationships.

The study protocol was approved by the Ethics Committee "Centro de Educación Médica e Investigaciones Clínicas (CEMIC)" (DHHS-IRB #1745, IORG #1315). Written signed informed consents were obtained from all subjects participating in the ECLAMC program before data collection. All data were fully anonymized prior to their utilization.

Results

Database records of 47,226 nonmalformed live newborns (1,061 with a short and 46,165 with a not short interbirth interval [IBI]) and 11,816 records of malformed live- or stillborn infants (242 with a short and 11,574 with a not short IBI) were included in the study.

In our sample, the overall short IBI rate was 2%−3%. Demographic and reproductive characteristics of mothers with an immediately previous short and not short IBI are shown in Table 1. Two main confounders associated with a short IBI were identified: maternal age and abortion as the result of a previous pregnancy. A significant high risk (OR=4.50, CI=3.84−5.26, P<.001) for a short IBI was found in mothers ≤19 years while mothers ≥30 were at a significant low risk (OR=0.42, CI=0.36−0.49, P<.001). The risk of a short IBI for abortion was OR=2.74, CI=2.42−3.11, P<.001.

The relationship between the included variables and a short IBI is shown in Figure 1. A direct relationship of short IBI with a previous abortion and maternal age ≤19 years was observed, the latter related to low socioeconomic status, while previous abortion appeared as a mediator of the indirect relationships between short IBI and most of the other variables.

The risk of short IBI, adjusted by maternal age and previous abortion, was significant for LBW (OR=1.72, CI=1.39−2.12, P<.001) while no risk was observed for PTB (OR=1.18, CI=0.94−1.48, P=.155) (Table 2). Figure 2 shows the relations between adverse outcomes and a short IBI. A direct relationship between LBW and short IBI can be seen (Figure 2A), with previous abortion as a direct confounder, and low socio-economic status, mainly in young mothers, as an indirect one. PTB showed no direct relationship with short IBI (Figure 2B); however, indirect connections mediated by multigravidity and a previous abortion, and by low socioeconomic status and maternal age ≤19 years, were observed.

When comparing malformed infants with their nonmalformed controls, no significant association with a short IBI was observed except for gastroschisis whose unadjusted risk was significant (OR=1.69, CI=0.95−2.83, P=.041). However, this risk, as well as the observed low risk for Down syndrome (OR=0.72, CI=0.51−0.98, P=.036), disappeared after adjusting for maternal age and previous abortion (Table 3).

As shown in Figure 3, maternal age ≤19 as well as previous abortion were directly related with gastroschisis, while the relationship between gastroschisis and short IBI was an indirect one that occurred through any of these two variables. Furthermore, a direct relationship between gastroschisis and maternal age ≥30 was also observed.

Comment

Principal findings

Of the three analyzed adverse pregnancy outcomes, we observed a higher risk only for LBW after a short IBI when compared to women with an interval longer than one year, and this risk did not decrease after controlling for the two main confounders (maternal age and a previous abortion). We also observed a relationship between gastroschisis and a short IBI which was mediated by low maternal age and/or a previous abortion.

Results in the context of what is known

With the aid of Bayesian networks, we observed that of the three analyzed outcomes, only LBW showed a direct relationship with short IBI. A plausible

TABLE 1
Demographic and reproductive characteristics of mothers of nonmalformed newborns, with and without a short interbirth interval

	IBI≤12 months (N=1061)		IBI>12 months (N=46165)				
Characteristics	N	%	N	%	OR	95% CI	P
Maternal age ≤19	218	20.55	2507	5.43	4.50	3.84-5.26	<0.001
Maternal age ≥30	258	24.32	19943	43.2	0.42	0.36-0.49	<0.001
Low SES	229	21.58	10266	22.24	0.98	0.84-1.14	0.753
High SES	250	23.56	11110	24.07	0.99	0.85-1.14	0.861
Multigravidity	569	53.63	22357	48.43	1.11	0.98-1.26	0.083
Previous abortion	449	42.32	9695	21.00	2.74	2.42-3.11	<0.001
Difficulty to conceive	6	0.57	565	1.22	0.46	0.17-1.01	0.054

Abbreviations: IBI, interbirth interval; CI, confidence interval; SES, socioeconomic status.

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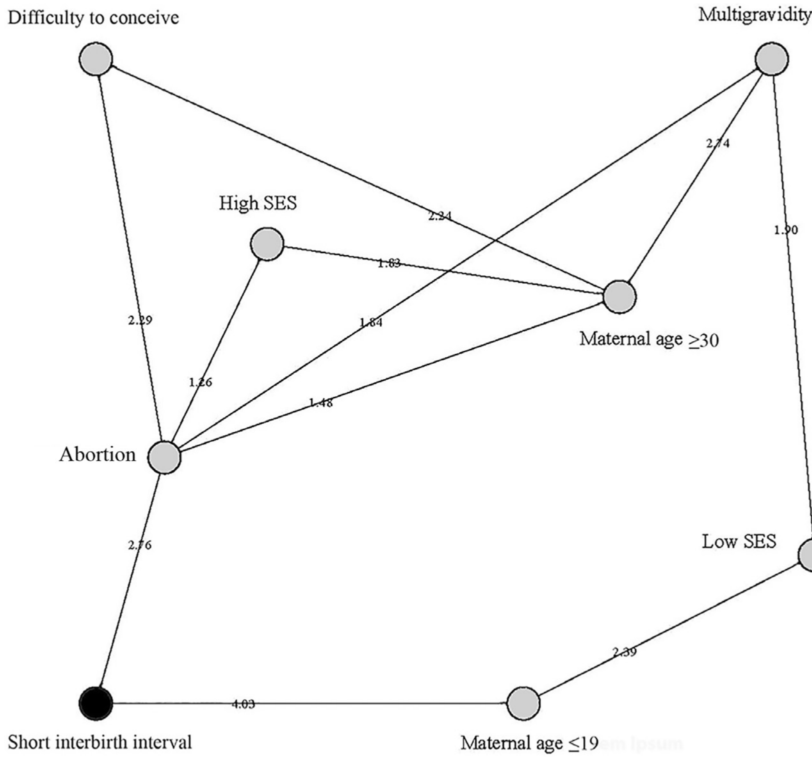
FIGURE 1
Relationships among a short interbirth interval and the included variables



The black node in the network represents the short interbirth interval, while the light gray nodes depict the variables included in the study.

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sequence could be that an abortion, which showed to be directly related with both short IBI and LBW, was the reason for a short interval before the next pregnancy, which in turn led to LBW, due to an insufficient time for nutritional recovery.[18]

Based on a systematic review including 67 studies conducted in different populations, with different study designs, interval definitions, and reference groups, Conde-Agudelo et al. (2006) concluded that interpregnancy intervals shorter than 18 months were significantly associated with LBW.[3] However, these authors included PTB in the LBW category, while we evaluated the risks individually.

A number of authors observed a relationship between short interpregnancy interval and PTB,[1,19–21] while Ball et al. (2014) found no association with PTB nor with any other adverse outcome, which led them to question the methods applied by other authors.[22] Similarly, we found no risk for PTB after a short IBI; as reinforcement, the Bayesian network showed that while PTB was directly related with multigravidity and low socioeconomic status, its connection with a short IBI occurred through an indirect path mediated by these two variables, plus a number of other ones. van Eijsden et al. (2008) found an association between short interpregnancy interval and LBW and mentioned the role of folic acid as possibly involved.[23] Smits and Essed (2001) hypothesized that a short interval and, as a result, folate deficiency could lead to LBW, PTB, and neural tube defects while Petersen et al. (2021) reported that short interpregnancy intervals and a related absence of folic acid supplementation, were associated with a trend of higher risks for several defects.[6,24]

Considering that our study sample belongs to a population where food fortification with folic acid began shortly after the start of the present study period,[25] and although the majority of South American countries' fortification policies do not include population blood folate measurements, an overall close to adequate folate intake can be assumed. Therefore, in our population, folate deficiency seems not to be related with the association between LBW and a short IBI.

Several authors have related the occurrence of birth defects with a short or both a short and a long interpregnancy interval.[5,9,12,26] Kangatharan et al. (2017) found an association between short interpregnancy interval, a

TABLE 2
Risk of low birth weight and preterm birth for nonmalformed liveborn infants, after the exposure to a short interbirth interval

	IBI≤12 months		IBI>12 months							
	N	%	*N*	%	ORu	95% CI	*P*	ORad	95% CI	*P*
Low birth weight	104	11.05	2621	6.23	1.87	1.51−2.31	<.001	1.72	1.39−2.12	<.001
Preterm birth	86	9.32	3308	7.73	1.23	0.97−1.54	.075	1.18	0.94−1.48	.155

Abbreviations: IBI, interbirth interval; ORu, unadjusted risk; ORad, risk adjusted by previous abortion and maternal age; CI, confidence interval.

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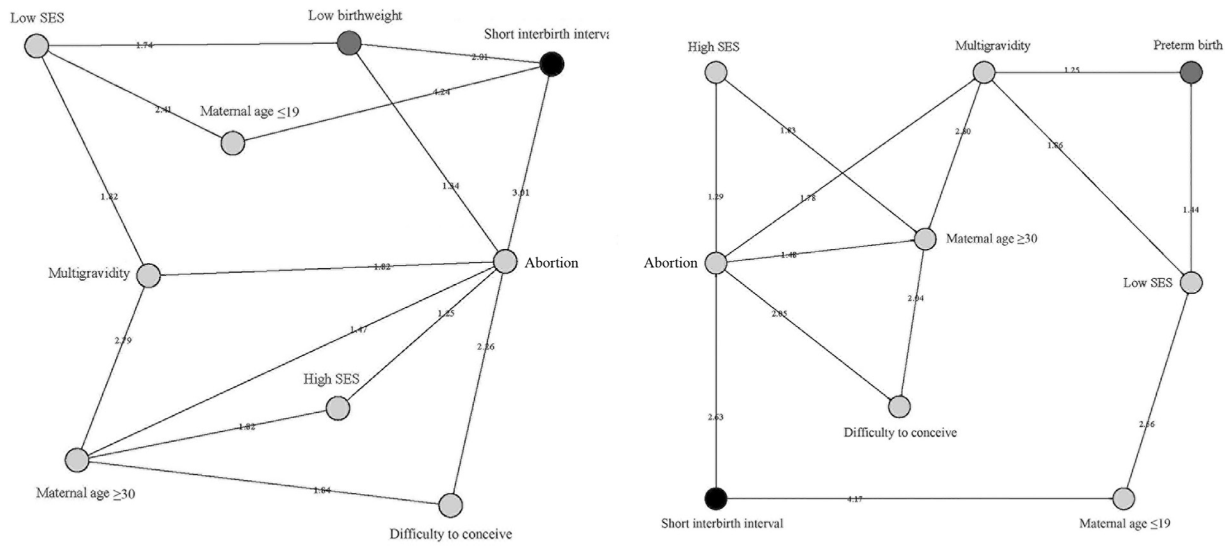
FIGURE 2

Relationships among a short interbirth interval, low birth weight (A), preterm birth (B), and the included variables



2a **2b**

The black node represents the short interbirth interval, the dark gray node the adverse outcome, and the light gray nodes the variables included in the study.

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previous abortion, and adverse outcomes,[27] and Getz et al. (2012) reported the association between a short interpregnancy interval and gastroschisis, especially in women who lived in northern regions (≥37°N latitude), had conceived during fall/winter, and whose previous pregnancy had ended in miscarriage or pregnancy termination, and they suggested vitamin D3 deficiency as a related factor.[10] Vitamin D3 has been noted for its important immunomodulatory functions while immune imbalances have been implicated as a risk factor for spontaneous abortions.[28,29]

TABLE 3

Risk for twelve selected birth defects after exposure to a short interbirth interval

	Infants IBI≤12 months									
	Malformed		Nonmalformed							
Birth defect	*N*	%	*N*	%	ORu	95% CI	*P*	ORad	95% CI	*P*
Down syndrome	42	1.57	823	2.17	0.72	0.51-0.98	.036	0.97	0.70−1.33	.831
Postaxial polydactyly	32	1.66	738	2.17	0.76	0.52-1.09	.132	0.75	0.52−1.07	.111
Cleft lip ± Cleft palate	34	2.38	711	2.24	1.06	0.73-1.51	.728	1.04	0.73−1.48	.832
Talipes equinovarus	24	2.01	633	2.19	0.92	0.58-1.39	.686	0.93	0.61−1.41	.729
Hypospadias	21	2.24	561	2.10	1.07	0.65-1.66	.761	1.20	0.77−1.87	.428
Hydrocephaly	23	2.60	599	2.34	1.11	0.70-1.70	.619	1.12	0.73−1.71	.613
Spina bifida	17	2.05	607	2.36	0.86	0.50-1.40	.550	0.88	0.54−1.44	.612
Anencephaly	14	2.24	446	2.09	1.07	0.58-1.83	.797	1.07	0.63−1.85	.795
Gastroschisis	16	4.56	376	2.74	1.69	0.95-2.83	.041	1.16	0.69−1.95	.583
Preaxial polydactyly	8	2.38	303	2.07	1.15	0.49-2.33	.694	1.16	0.57−2.37	.688
Diaphragmatic hernia	8	2.52	343	2.36	1.07	0.46-2.17	.845	1.12	0.55−2.30	.749
Cleft palate	3	0.98	318	2.25	0.43	0.09-1.29	.139	0.46	0.15−1.45	.185

Abbreviations: IBI, interbirth interval; ORu, unadjusted risk; ORad, risk adjusted by previous abortion and maternal age; CI, confidence interval.

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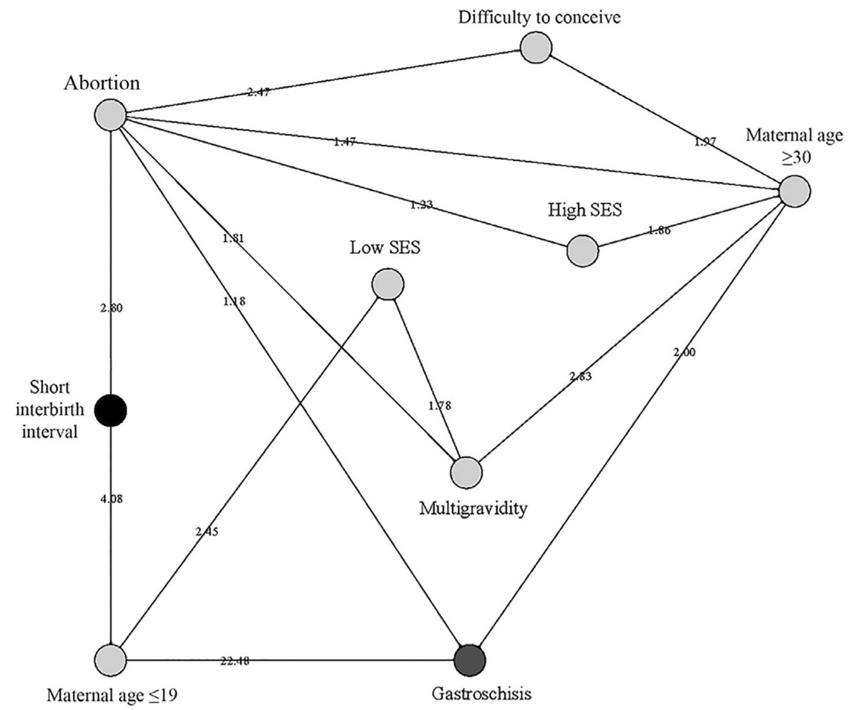
FIGURE 3
Relationships among a short interbirth interval, gastroschisis, and the included variables



The black node represents the short interbirth interval, the dark gray node the outcome (gastroschisis), and the light gray nodes the variables included in the study.

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Getz et al. (2012) also proposed that vitamin D3 depletion at the time of conception could on the one hand depend on the residential region and the season of conception, and on the other, result from excessive inflammatory responses to uterine trauma after elective terminations.[10] The findings of these authors indicating that the risk for gastroschisis after a short interpregnancy interval was higher in women more susceptible to vitamin D3 deficiency and, among those, whose previous pregnancy had ended as spontaneous abortion or termination, are consistent with results from other studies suggesting that immune or inflammatory mechanisms could potentially be involved in the etiology of gastroschisis.[30−32]

Our results were similar to those of Getz et al. (2012),[10] since in our study the frequency of gastroschisis after a short IBI was twice as high when the previous pregnancy had ended in an abortion (data not shown). However, while in the study of Getz et al. (2012) the association between a short interpregnancy interval and gastroschisis maintained its significance even after adjusting for maternal age among other confounders,[10] we showed that the relationship between gastroschisis and a short IBI was mediated by low maternal age and/or a previous abortion, variables that have already been identified as risk factors for gastroschisis.[33,34] Perhaps different young maternal age thresholds and/or population characteristics are responsible for these discordances.

The observed relationship between gastroschisis and older maternal age (≥30) was unexpected although it could depend on the mediating effect of a previous abortion, which on the one hand, as mentioned before, is a risk factor for gastroschisis, and on the other, has already been associated with advanced maternal age.[35] Nevertheless, the observed relationship might deserve further research.

Our observations of the role of young maternal age and a previous abortion as the main confounders or mediators of the analyzed associations between outcomes and a short IBI could perhaps depend on a low socioeconomic status, as a common factor, and which has already been related with young-aged motherhood.[36] A possible interpretation is that girls living in an unfavorable environment lack access to sexual education, which leads to unplanned and closely following pregnancies which, being unwanted, are subsequently terminated. On the other hand, with limited access to reproductive health services, perhaps undernutrition, or an underlying and/or undiagnosed health problem could lead to a miscarriage and then, in an attempt to achieve a normal pregnancy, to a short spacing between the lost one and the next.

Clinical and research implications

Our findings and the current recommendations are in agreement with the clinical importance of an adequate spacing between pregnancies to reduce the risk of adverse perinatal outcomes. However, more research is needed to clarify the relationships among the involved variables, in order to provide mothers with the best possible information.

Limitations and strengths

The main strengths of this work were a large enough sample size to detect a risk at least twice as high for an infrequent exposure and the availability of a standardized and complete case and control reproductive history which was registered, as well as the birth defects diagnoses, by trained pediatricians who followed strict operational rules.

Furthermore, the Bayesian networks methodological approach allowed to more clearly observe the relationships among variables.

A limitation of this work was the lack of adequate information on a number of factors potentially involved in the studied outcomes such as nutrition or exposure to risky habits, such as alcohol intake and tobacco smoking.

The results could have been biased due to lack of memory, under-reporting or -registration, which are recognized limitations when obtaining retrospective information through interviews. For instance, early miscarriages could have passed unnoticed, pregnancy terminations could have been reported as spontaneous abortions, and birth defects, mainly in stillbirths, could have not been diagnosed.

Having used interbirth instead of interpregnancy interval could have overestimated the risk in case of very short pregnancies.

Conclusion

Approximately 2% of all mothers delivered after a short IBI, regardless of their socioeconomic status. Only young mothers of a low socioeconomic status were directly related with a short IBI, while in older mothers, a short IBI mainly occurred after a previous abortion. For the here analyzed adverse outcomes, a short IBI between the present and the previous pregnancy was a risk factor only for LBW; this was the only outcome directly related to a short IBI, without any mediating variables. For PTB and gastroschisis, the relationship with a short IBI was an indirect one, mediated by young maternal age and/or a previous abortion. Among the selected birth defects, gastroschisis was the only one at risk by a short IBI. However, the risk disappeared after adjusting for previous abortions and maternal age. ■

CRediT authorship contribution statement

Silvina L. Heisecke: Writing – review & editing, Writing – original draft, Software, Conceptualization. **Hebe Campaña:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Conceptualization. **María R. Santos:** Writing – review & editing, Writing – original draft, Formal analysis, Data curation, Conceptualization. **Jorge S. López Camelo:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Mónica Rittler:** Writing – review & editing, Writing – original draft, Supervision, Investigation, Formal analysis, Conceptualization. ■

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