Birth Spacing and Risk of Adverse Perinatal Outcomes

A Meta-analysis

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Context Both short and long interpregnancy intervals have been associated with an increased risk of adverse perinatal outcomes. However, whether this possible association is confounded by maternal characteristics or socioeconomic status is uncertain.

Objective To examine the association between birth spacing and relative risk of adverse perinatal outcomes.

Data Sources Studies published in any language were retrieved by searching MEDLINE (1966 through January 2006), EMBASE, ECLA, POPLINE, CINAHL, and LILACS, proceedings of meetings on birth spacing, and bibliographies of retrieved articles, and by contact with relevant researchers in the field.

Study Selection Included studies were cohort, cross-sectional, and case-control studies with results adjusted for at least maternal age and socioeconomic status, reporting risk estimates and 95% confidence intervals (or data to calculate them) of birth spacing and perinatal outcomes. Of 130 articles identified in the search, 67 (52%) were included.

Data Extraction Information on study design, participant characteristics, measure of birth spacing used, measures of outcome, control for potential confounding factors, and risk estimates was abstracted independently by 2 investigators using a standardized protocol.

Data Synthesis A random-effects model and meta-regression analyses were used to pool data from individual studies. Compared with interpregnancy intervals of 18 to 23 months, interpregnancy intervals shorter than 6 months were associated with increased risks of preterm birth, low birth weight, and small for gestational age (pooled adjusted odds ratios [95% confidence intervals]: 1.40 [1.24-1.58], 1.61 [1.39-1.86], and 1.26 [1.18-1.33], respectively). Intervals of 6 to 17 months and longer than 59 months were also associated with a significantly greater risk for the 3 adverse perinatal outcomes.

Conclusions Interpregnancy intervals shorter than 18 months and longer than 59 months are significantly associated with increased risk of adverse perinatal outcomes. These data suggest that spacing pregnancies appropriately could help prevent such adverse perinatal outcomes.

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BOTH SHORT AND LONG INTERvals between pregnancies have been associated with increased risk of several adverse perinatal outcomes, such as preterm birth, low birth weight (LBW), small for gestational age (SGA), and perinatal death.[1-3] However, there has been disagreement on whether the relationship is due to confounding by other risk factors. For example, some researchers have argued that short intervals between pregnancies merely designate women already at higher reproductive risk, either because of underlying disorders, socioeconomic status, or lifestyle factors.[4,5] Furthermore, previous research in this area has several methodological limitations, such as small sample size, lack of control for potential confounding factors, dichotomization of the measure of birth spacing on the basis of an arbitrarily defined cut point, and use of birth interval (time elapsed between the woman's last delivery and the birth of the index child) instead of interpregnancy interval (time elapsed between the woman's last delivery and the conception of the next pregnancy) as the measure of birth spacing. The use of birth intervals overestimates the risk of adverse perinatal outcomes for very short intervals between pregnancies.

For editorial comment see p 1837.

This issue is relevant to public health and clinical practice because if short and/or long interpregnancy intervals are found to be independently associated with increased risk of adverse perinatal outcomes, birth spacing might then be considered an intervention to prevent such adverse outcomes, mainly in the developing world. Therefore, we performed a systematic review, including meta-analysis, of the relationship between birth spacing and the risk of adverse perinatal outcomes that provided an overall summary of the effect

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measure and determined both the riskiest and the optimal interpregnancy intervals. In addition, we determined whether estimates of the effect measure depend on dimensions of study quality of the primary studies and whether the relationship differs in subgroups defined by the characteristics of women, and we highlight deficits that need to be addressed in future studies.

METHODS

We used a prospective protocol prepared specifically for this purpose. The systematic review was conducted following this protocol and reported using the checklist proposed by the Meta-analysis of Observational Studies in Epidemiology (MOOSE) group for reporting of systematic reviews of observational studies.[6]

Identification of Studies

A search was conducted by the investigators in MEDLINE (1966 through January 2006), EMBASE (1980 through January 2006), ECLA (1980 through January 2006), POPLINE (1980 through January 2006), CINAHL (1982 through January 2006), and LILACS (1982 through January 2006), using a combination of Medical Subject Headings or key word terms for birth spacing and adverse perinatal outcomes. Terms for birth spacing included *interpregnancy interval*, *birth interval*, *interbirth interval*, *pregnancy spacing*, *pregnancy interval*, *birth spacing*, *intergenesic interval*, *birth to birth interval*, *birth to conception interval*, *delivery to conception interval*, and *interdelivery interval*. Terms for adverse perinatal outcomes included *perinatal outcomes*, *infant outcomes*, *pregnancy outcomes*, *adverse outcomes*, *low birth weight*, *preterm delivery*, *preterm birth*, *small for gestational age*, *intrauterine growth retardation*, *intrauterine growth restriction*, *Apgar scores*, *neonatal depression*, *neonatal intensive care unit*, *fetal death*, *stillbirth*, *perinatal death*, *fetal mortality*, *perinatal mortality*, *perinatal morbidity*, *perinatal outcomes*, *neonatal death*, *neonatal mortality*, and *neonatal outcomes*. Proceedings of several international meetings on birth spacing and bibliographies of the retrieved articles were also searched by hand. No language restrictions were imposed. In the case of studies discussing more than 1 outcome, each outcome was considered independently. To find unpublished studies, we contacted relevant researchers in the field. Twelve authors were contacted as well, in an attempt to obtain additional data.

Inclusion Criteria

Studies were included if (1) they were cohort, cross-sectional, or case-control studies that evaluated the relationship between birth or interpregnancy interval and any adverse perinatal outcome; (2) the definition of interpregnancy interval corresponded to the period between delivery of the previous infant and conception of the current pregnancy. Although the use of birth-to-birth interval overestimates the risks of adverse perinatal outcomes for very short intervals, studies using birth interval were included and analyzed separately; and (3) the authors of the studies adjusted their results for at least maternal age and socioeconomic status (measured indirectly by occupation and work status, educational level, income, housing, or other variables), because we considered these variables to be the most important confounding factors in the association between birth spacing and adverse perinatal outcomes. Studies were excluded from the systematic review if they were case series or reports, editorials, letters to the editor, or reviews without original data; if they exclusively used univariate analysis; if they did not adjust for at least maternal age and socioeconomic status; or if they did not provide data. Studies included in the systematic review were also included in the meta-analyses if they met the following additional criteria: (1) used interpregnancy interval as measure of birth spacing; (2) provided data for 4 or more interpregnancy interval strata; and (3) reported odds ratio (OR) or relative risk estimates and 95% confidence intervals (CIs) or data to calculate them. Studies of different designs and different measures of birth spacing that are included in the systematic review were analyzed separately because of different threats to their internal validity.

All published studies deemed suitable were retrieved and reviewed independently by 2 authors (A.C.-A., A.R.-B.) to determine inclusion. Disagreements were resolved through consensus. The degree of agreement was expressed as percentage agreement and κ statistics.

Study Quality Assessment

Study methodological quality was judged by the following 6 validated criteria believed to be important for the quality of observational studies evaluating the relationship between birth spacing and adverse perinatal outcomes[7,8]: (1) pregnancy interval used (adequate if the study used interpregnancy interval; inadequate if the study used birth interval); (2) categorization of exposure (adequate if the study examined $\geq$4 categories of pregnancy intervals; inadequate if the study examined $<$4); (3) birth spacing measurement and inquiry of outcomes (adequate if birth spacing measurement and ascertainment of outcomes were made by medical records or direct measurement; inadequate if not); (4) blinding of both birth spacing status and ascertainment of outcomes (adequate if assessment of both birth spacing status and outcomes was blinded; inadequate if not blinded or unreported); (5) loss to follow-up or exclusions (only for cohort and cross-sectional studies) (adequate if loss to follow-up or nonvalid exclusions [eg, improper elimination of records] was $<$10%; inadequate if $\geq$10% or unreported); and (6) control for confounding factors (adequate if the study additionally controlled for $\geq$2 of 5 confounding factors [parity, outcome of the most recent recognized pregnancy, access to prenatal care, breastfeeding, and maternal nutritional status]; inadequate if additionally controlled for $<$2).

Assessment of methodological quality of each study was carried out by 2 of the authors (A.C.-A., A.R.-B.) work-

ing independently. Differences of opinion were resolved through discussion.

Data Abstraction

Data were extracted independently from each article by 2 investigators (A.C.-A., A.C.K.-G.) by means of a standardized and pilot-tested data collection form. The following information was sought from each article: title, first author's name, year, geographic location of the study (country and region), study design, characteristics and source of the study population, sample size, measures of outcome, measure of birth spacing used, categorization of intervals, method of data collection, exposure measurement and ascertainment of outcome(s), blinding of birth spacing status and ascertainment of outcome(s), loss to follow-up or invalid exclusions, confounding factors controlled for by matching or adjustment, and unadjusted and adjusted relative risks or ORs and their 95% CIs for individual adverse perinatal outcomes associated with all pregnancy intervals.

Statistical Analysis

The studies included in our meta-analyses differed in the units used for measurement of the interpregnancy interval (days, weeks, months, or years). Therefore, we converted these different units of interpregnancy interval to months. We used 3 different meta-analytical techniques to investigate whether a relationship exists between interpregnancy interval and the risk of adverse perinatal outcomes.

Meta-regression Analysis. We first examined the shape of the dose-response relation between interpregnancy interval and risk of adverse perinatal outcomes. For this purpose, we used the method proposed by Greenland and Longnecker[9] and Berlin et al[10] for meta-analysis of epidemiologic dose-response data. The dose-specific confounder-adjusted natural logarithms of the ORs from all studies were pooled, and a curve using weighted quadratic spline meta-regression with no intercept term was fitted. This method was chosen because several studies have reported finding a nonlinear, J-shaped relationship between interpregnancy interval and the risk of adverse perinatal outcomes such as preterm birth, LBW, and SGA. The main fields in the data set were the value x of exposures (expressed in months) assigned as the midpoints for the ranges of the reported categories of interpregnancy intervals and as 1.2 times for the lower bound of the open-ended upper categories as suggested by Berlin et al,[10] and the y-axis estimates of natural logarithm of the adjusted OR for each exposure level.

Pooled ORs. Depending on data availability in the original studies, we categorized interpregnancy interval into 6 groups: shorter than 6 months, 6 to 11, 12 to 17, 18 to 23, 24 to 59, and 60 months or longer. Odds ratios were used as the measure of the relation between interpregnancy interval and adverse perinatal outcomes. The interval of 18 to 23 months was used as the referent category, because this was the interval with the lowest risk for preterm birth, LBW, and SGA. Data abstracted from each study were arranged in 2×2 tables. Then, ORs with their 95% CIs for each adverse perinatal outcome considered were calculated separately for 5 predefined categories of interpregnancy interval. Separate analyses of the associations in 2×2 tables were combined to produce pooled unadjusted ORs and corresponding 95% CIs. We also calculated pooled adjusted ORs within each category using the estimated adjusted effect and its estimated standard error (often obtained indirectly from the CI) reported in each study.

Dose-Response Regression Slopes. Under the assumption of independence of the dose-specific OR, we estimated the dose-response regression slopes of each study using the OR, 95% CIs, and the midpoint of the exposure interval.[9] For open-ended intervals, a point 20% higher than the low end of the interval was used. Pooled dose-response slopes and estimates of risks were then obtained from random-effects models applied to the study-specific slopes. The exponentiation of the slope gave the OR for a unit increase or decrease of the interpregnancy interval (1 month). To overcome the problem of assuming independence of dose-specific ORs (which is incorrect, as they have a common reference group), we adjusted the standard error of the within-study slopes estimating the covariance.

Heterogeneity of the results between the studies was formally tested with the quantity I^2, which describes the percentage of total variation across studies that is due to heterogeneity rather than chance. The I^2 can be calculated from basic results obtained from a typical meta-analysis as

$$I^2 = 100\% \times (Q - df)/Q$$

where Q is the Cochran heterogeneity statistic.[11] We pooled results from individual studies using DerSimonian and Laird random-effects models[12] because moderate to high heterogeneity ($I^2 \geq 50\%$) was present in the majority of results.

To further explore the origin of heterogeneity, we restricted the analyses to subgroups of studies defined by study characteristics such as study quality, date of publication, and sample size. Moreover, we calculated separate estimates according to race/ethnicity and study setting (developed vs developing countries). Since a number of the largest studies were multinational, we could not analyze by country. Subgroup and sensitivity analyses were performed pooling adjusted ORs provided by the studies.

To detect publication and location biases, we explored asymmetry in funnel plots. This was examined visually, and the degree of asymmetry was measured using the Egger unweighted regression asymmetry test, with $P < .10$ indicating significant asymmetry.[13] All statistical analyses were performed using STATA version 8.0 (StataCorp, College Station, Tex).

RESULTS

One hundred thirty studies were considered relevant, and the complete manuscripts were obtained. Of the 130 studies, 122 were published in En-

glish, 4 in Spanish, 3 in French, and 1 in Portuguese. Sixty-three studies were excluded, the main reasons being lack of adjustment for confounding factors at statistical analysis (46%) and lack of data on the relationship between birth spacing and adverse outcomes considered (35%). (The list of excluded studies is available from the corresponding author on request.) A total of 67 studies (52 cohort or cross-sectional studies[14-65] and 15 case-control studies[66-80]), including 11 091 659 pregnancies, met the inclusion criteria. The computerized search located 64 of the studies, 2 were found in proceedings of meetings on birth spacing, and the remaining 1 was found through contact with a relevant researcher in the field.

Twenty studies (30%) were conducted in the United States. The remaining 47 were conducted in 61 countries from Latin America (22 countries), Asia (20 countries), Africa (11 countries), Europe (7 countries), and Australia. Overall agreement on the inclusion of studies was 97% ($\kappa = 0.84$).

The characteristics and main findings of the cohort and cross-sectional studies included in the systematic review are presented in **TABLE 1** (developed countries) and **TABLE 2** (developing countries); those of the case-control studies are presented in **TABLE 3**. The sample size in the cohort or cross-sectional studies ranged from 201[44] to 4 841 418.[43] The number of case participants enrolled in case-control studies ranged from 36[71] to 416,[69] and the corresponding number of controls ranged from 50[71,79] to 1710.[67] Thirty studies provided data on preterm birth, 26 on LBW, 24 on SGA, 10 on fetal death, 4 on early neonatal death, 6 on perinatal death, and 2 on low Apgar scores. Twenty-four studies (36%) reported more than 1 adverse perinatal outcome. Among the 52 cohort or cross-sectional studies, 37 (71%) used birth-to-conception interval, 14 (27%) used birth-to-birth interval, and the remaining 1 used both intervals. Of the 15 case-control studies, 9 (60%) used birth-to-conception interval and 6 (40%) birth-to-birth interval as measures of birth spacing. The studies varied in methodological quality, with 21 cohort or cross-sectional studies (40%) meeting 5 or more criteria and only 3 case-control studies (20%) meeting 4 or more criteria. The most common shortcomings were failure to blind investigators to both exposure status and ascertainment of outcome, the report of loss to follow-up or exclusions, and the categorization of pregnancy intervals.

Overall, among the studies that provided data on preterm birth, 21 (18 cohort or cross-sectional and 3 case-control) reported an association with short intervals, 6 (5 cohort or cross-sectional and 1 case-control) an association with long intervals, and 9 (8 cohort or cross-sectional and 1 case-control) found no association. With regard to studies that reported data on LBW, 20 (18 cohort or cross-sectional and 2 case-control) found an association with short intervals, 7 (6 cohort or cross-sectional and 1 case-control) an association with long intervals, and 6 (all cohort or cross-sectional) found no association. Among the studies that provided data on SGA, 14 (13 cohort or cross-sectional and 1 case-control) reported an association with short intervals, 6 cohort or cross-sectional studies reported an association with long intervals, and 10 (6 cohort or cross-sectional and 4 case-control) found no association. Two studies did not find an association between birth spacing and low Apgar scores. With regard to perinatal mortality (fetal death, early neonatal death, and perinatal death), 10 studies reported an association with short intervals, 8 with long intervals, and 7 found no association.

It was not possible to perform a meta-analysis of the case-control studies because only 3 met the minimal inclusion criteria. Moreover, different categories of intervals and reference categories were used in the few studies. Twenty-six cohort and cross-sectional studies provided data for meta-analyses. Sixteen studies provided data for preterm birth,* 10 for LBW,† 13 for SGA,‡ 7 for fetal death,[14,27,34,55,57,63,64] and 4 for early neonatal death.[34,57,63,64]

The dose-response association between interpregnancy interval and the natural logarithm of the OR of the 5 adverse perinatal outcomes in cohort and cross-sectional studies was J-shaped (**FIGURE**). For preterm birth, LBW, and SGA, the highest risk was for intervals shorter than 20 months and longer than 60 months. For both fetal and early neonatal death, the highest risk was for intervals shorter than 6 months and longer than 50 months.

Infants born to women with interpregnancy intervals shorter than 6 months had pooled unadjusted ORs (95% CIs) of 1.77 (1.54-2.04), 2.12 (1.98-2.26), and 1.39 (1.20-1.61) for preterm birth, LBW, and SGA, respectively, compared with infants born to women with intervals of 18 to 23 months (**TABLE 4**). Likewise, women with intervals of 6 to 17 months were 8% to 23% more likely to give birth to infants with these adverse outcomes. Infants conceived 60 months or more after a birth had ORs (95% CIs) of 1.27 (1.17-1.39) for preterm birth, 1.49 (1.17-1.89) for LBW, and 1.36 (1.20-1.54) for SGA. The minimal increase in the risk for adverse perinatal outcomes associated with intervals of 24 to 59 months (3%-7%) was not statistically significant. It was not possible to estimate pooled ORs for the relation between interpregnancy interval and both fetal and early neonatal death, because the categories of intervals used and the reference categories did not coincide in all studies.

The estimates of pooled adjusted ORs were lower than estimates of pooled unadjusted ORs (Table 4). Nevertheless, the associations between intervals of shorter than 6, 6 to 11, 12 to 17, and longer than 59 months and preterm birth, LBW, and SGA remained statistically significant. Compared with infants of mothers with interpregnancy intervals of 18 to

*References 25, 27, 29, 33, 36, 39, 40, 45-47, 49, 50, 52, 55, 61, 64.

†References 16, 21, 27, 33, 36, 40, 47, 49, 56, 64.

‡References 21, 22, 24, 29, 33, 35, 36, 39, 45, 49, 52, 55, 64.

Table 1. Characteristics of Cross-sectional and Cohort Studies Included in the Systematic Review of Birth Spacing and Adverse Perinatal Outcomes—Developed Countries

				Methodological Quality*					
Source	Country (Region)	Outcome	Sample Size	Interval Used	Interval Categories, mo†	Blinding	Lost to Follow-up/ Nonvalid Exclusions, %	Confounders‡	Main Findings
Fedrick and Adelstein,[14] 1973	England, Scotland, Wales	Late fetal death (≥28 wk)	8356	IPI	≤6; 7-12§; 13-24; 25-36; 37-72; 73-108; >108	Not reported	Not reported	1, 2, 6, 7	No relationship between interval and late fetal death
Eisner et al,[16] 1979	United States (nation-based [1974])	LBW	1 118 963	IPI	<6; 6-11; 12-23; ≥24 [>6]§	Adequate	54.8	1-8	Intervals <6 mo associated with increased risk of LBW for both white and black women
Spratley and Taffel,[17] 1981	US (nation-based)	LBW	Not reported	BI	<12; 12-17; 18-23; 24-35; 36-47; 48-59; ≥60‖	Adequate	Not reported	1, 3, 5-7, 15	Intervals <24 mo and >59 mo associated with increased risk of LBW
Brody and Bracken,[20] 1987	US (New Haven, Conn)	LBW	1683	IPI	<5; 5-8; ≥9§	Not reported	5.6	1-7, 12	Intervals <9 mo associated with increased risk of LBW
Klebanoff,[21] 1988	US (multicenter)	LBW, IUGR	5938	IPI	<3§; 3-5.9; 6-8.9; 9-11.9; 12-14.9; 15-17.9; 18-20.9; 21-23.9; ≥24	Not reported	Not reported	1, 3, 5-7, 10, 12	No relationship between interval and LBW or IUGR
Lieberman et al,[22] 1989	US (Boston, Mass)	SGA	4489	IPI	≤3; 3-6; 6-12; 12-18; 18-24; 24-36§; 36-48; 48-60; 60-72; 72-96; >96	Not reported	Not reported	1-3, 5, 6, 9, 10, 12, 13	Intervals <18 mo and >72 mo associated with increased risk of SGA
Miller,[24] 1989	Sweden	IUGR	54 725	IPI	<12; 12-17; 18-23; 24-35; 36-47; 48-59; ≥60; [18-59]§	Adequate	Not reported	1, 2, 6, 7, 15	Intervals <12 mo associated with increased risk of IUGR
Lang et al,[25] 1990	US (Boston, Mass)	Preterm birth	4467	IPI	≤3; 4-6; 7-12; 13-18; 19-24; 25-36§; 37-48; ≥49	Not reported	Not reported	1, 3-6, 8-10, 12	No relationship between interval and preterm birth
Miller,[27] 1991	Hungary, Sweden, US	LBW, preterm birth, late fetal death (>6 mo gestation)	Hungary (77 256) Sweden (51 096) US (4290)	For Hungary and Sweden BI, and for the USA IPI	<12; 12-17; 18-23; 24-35§; 36-47; 48-59; ≥60;	Adequate	Not reported	1, 3-8, 10	Birth intervals <12 mo associated with increased risk of LBW and preterm birth. No relationship between interval and late fetal death
Kallan,[29] 1992	US	Preterm-LBW, IUGR-LBW, fetal loss (miscarriage and stillbirths)	2104	IPI	<7; 7-12; 13-24; 25-48; ≥49§	Not reported	Not reported	1-3, 5-7, 12	Intervals <12 mo and >48 mo associated with increased risk of IUGR-LBW and fetal loss but not with preterm-LBW

(continued)

Table 1. Characteristics of Cross-sectional and Cohort Studies Included in the Systematic Review of Birth Spacing and Adverse Perinatal Outcomes—Developed Countries (cont)

				Methodological Quality*					
Source	Country (Region)	Outcome	Sample Size	Interval Used	Interval Categories, mo†	Blinding	Lost to Follow-up/ Nonvalid Exclusions, %	Confounders‡	Main Findings
Rawlings et al,[36] 1995	US	LBW, preterm birth, IUGR	1922	IPI	<3; 3-5.9; 6-8.9§; ≥9	Not reported	9.1	1, 4, 6-8, 12	Intervals <3 mo and <9 mo associated with an increased risk of LBW and preterm birth among white and black women, respectively. No relationship between interval and IUGR
Ochoa Sangrador et al,[38] 1996	Spain	LBW, preterm birth	279	IPI	<3§; 3-5; 6-8; 9-11; ≥12	Not reported	Not reported	1, 4, 6, 7, 12	No relationship between interval and LBW and preterm birth
Kallan,[39] 1997	US (nation-based [1981])	Preterm birth, IUGR	1 045 393	IPI	<7; 7-12; 13-18; 19-24; 25-36§; 37-48; 49-60; >60	Adequate	Not reported	1-4, 6-10, 12	Intervals <7 mo and >60 mo associated with increased risk of preterm birth and IUGR for both black and white women
Adams et al,[40] 1997	US (Georgia)	LBW, preterm birth	28 273	IPI	<3; 3-5; 6-8; 9-11; 12-17; 18-23; 24-35§; 36-47; ≥48	Adequate	Not reported	1, 3, 6, 8	For white women, intervals <3 mo and >47 mo associated with increased risk of LBW, whereas intervals <6 mo and >47 mo associated with increased risk of preterm birth. For black women, intervals <6 mo and >47 mo associated with increased risk of LBW, whereas intervals <6 mo were associated with increased risk of preterm birth
Bakewell et al,[41] 1997	US (Missouri)	LBW	182 285	IPI	<9; ≥9§	Adequate	10.0	1, 3-8, 10, 12	For both women with prior LBW and women with prior normal birth weight, intervals <9 mo associated with increased risk of LBW
Khoshnood et al,[43] 1998	US (nation-based [1989-1991])	LBW, preterm birth	4 841 418	IPI	<6; 6-12; >12§	Adequate	0.0	1-3, 6-8, 12	Intervals <6 mo and <12 mo associated with increased risk of LBW and preterm birth, respectively
Klerman et al,[45] 1998	US (Alabama)	Preterm birth, IUGR	4400	IPI	<3; 3-5; 6-11; 12-23; ≥24 [≥6]§	Adequate	Not reported	1, 2, 5-8, 10, 12, 19	Interval <6 mo associated with increased risk of preterm birth. No association between interval and IUGR
Ekwo and Moawad,[46] 1998	US (Chicago)	Preterm birth	761	IPI	≤3; 4-6; 7-9§; 10-24; ≥25	Adequate	Not reported	1, 5-8, 12, 14	Intervals ≤6 mo not significantly associated with increased risk of preterm birth
Basso et al,[47] 1998	Denmark	LBW, preterm birth	10 187	IPI	≤4; 4.01-8; 8.01-12; 12.01-24; 24.01-36§; >36	Adequate	6.2	1, 2, 6	Intervals <8.01 mo associated with an increased risk of preterm birth. No association between interval and LBW
Shults et al,[48] 1999	US (North Carolina)	Preterm birth, SGA	Preterm birth (34 569) SGA (27 651)	IPI	<4; 4-12; 13-24§	Adequate	Not reported	1-8, 12	Women with intervals <4 mo had higher risks for preterm birth and SGA

(continued)

Table 1. Characteristics of Cross-sectional and Cohort Studies Included in the Systematic Review of Birth Spacing and Adverse Perinatal Outcomes—Developed Countries (cont)

				Methodological Quality*					
Source	Country (Region)	Outcome	Sample Size	Interval Used	Interval Categories, mo†	Blinding	Lost to Follow-up/ Nonvalid Exclusions, %	Confounders‡	Main Findings
Zhu et al,[49] 1999	US (Utah)	LBW, SGA, preterm birth	173 205	IPI	<6; 6-11; 12-17; 18-23§; 24-59; 60-119; ≥120	Adequate	10.7	1-8, 10, 12, 13	The risk for LBW, preterm birth, and SGA increased with intervals <6 mo. Intervals >59 mo associated with increased risks for LBW and SGA
Fuentes-Afflick and Hessol,[50] 2000	US (California)	Preterm birth	289 842	IPI	<6; 6-11; 12-17; 18-23§; 24-59; >59	Adequate	Not reported	1-3, 5-8, 11, 19	Intervals <18 mo and >59 mo associated with increased risk of preterm birth
Zhu et al,[52] 2001	US (Michigan)	Preterm birth, SGA	435 327	IPI	<6; 6-11; 12-17; 18-23§; 24-59; 60-119; ≥120	Adequate	5.1	1-8, 12, 13	Among white women, the risk for preterm birth increased with intervals <12 mo and >59 mo, whereas the risk for SGA increased with intervals <12 mo and >23 mo. Among black women, the risk for preterm birth increased with intervals <12 mo and >119 mo, while the risk for SGA increased with intervals <6 mo and >119 mo
Rousham and Gracey,[53] 2002	Australia (Kimberley)	Birth weight, birth length	782	BI	<24; ≥24§	Not reported	1.8	1, 5, 6, 10, 11	Birth interval not significantly associated with birth weight or birth length
Dafopoulos et al,[54] 2002	Greece	Preterm birth	1 230	IPI	<6; ≥6§	Not reported	Not reported	1, 5, 6, 8, 12	Intervals of <6 mo associated with greater risk of preterm birth
Smith et al,[55] 2003	Scotland	Preterm birth, IUGR, fetal death (≥24 wk gestation)	89 143	IPI	<6; 6-11; 12-17; 18-23; 24-59	Adequate	13.8	1, 4, 6, 7, 10, 12	Interval <6 mo an independent risk factor for preterm birth. No relationship between intervals <6 mo and IUGR or fetal death
Zhu and Le,[56] 2003	US (Michigan)	LBW	565 816	IPI	<6; 6-11; 12-17; 18-23§; 24-59; 60-95; 96-136	Adequate	21.7	1-3, 5-8, 12, 13	Intervals <6 mo and >59 mo associated with an increased risk of LBW
Stephansson et al,[57] 2003	Sweden	Late fetal death (≥28 wk gestation), early neonatal death (≤7 d of life)	410 021	IPI	<4; 4-7; 8-11; 12-35§; 36-71; ≥72	Adequate	12.0	1, 3, 4, 6, 7, 9, 11, 12, 17	Intervals ≥72 mo associated with an increased risk of late fetal death. Intervals <12 mo not associated with an increased risk of late fetal death or early neonatal death

Abbreviations: BI, birth interval; IPI, interpregnancy interval; IUGR, intrauterine growth restriction; LBW, low birth weight; SGA, small for gestational age.
*See "Methods" section for definitions of methodological quality criteria. Interval and outcomes inquiries were determined to be "adequate" for all studies.
†Intervals in square brackets indicate the reference group in the studies that did not use as a reference one of the intervals originally categorized.
‡For multivariate adjustments, 1 indicates maternal age; 2, parity; 3, education; 4, marital status; 5, ethnic group or race; 6, factors related to socioeconomic status; 7, previous pregnancy outcome; 8, factors relating to prenatal care; 9, medical risk factors; 10, maternal nutritional status; 11, region; 12, smoking; 13, alcohol use; 14, illicit drug use; 15, gestational age or birth weight; 16, type of hospital; 17, year of delivery; 18, religion; 19, sex of the child.
§Reference group.
‖Reference group not specified.

23 months, those born to women with intervals shorter than 6 months had a 40% increased risk of preterm birth, a 60% increased risk of LBW, and an approximately 25% increased risk of SGA. Intervals of 6 to 17 months were associated with a significantly greater risk for the 3 adverse perinatal outcomes (adjusted ORs, 1.05-1.14). On the other hand, infants born to mothers with intervals longer than 59 months faced a 20% to 43% increase

Table 2. Characteristics of Cross-sectional and Cohort Studies Included in the Systematic Review of Birth Spacing and Adverse Perinatal Outcomes—Developing Countries

				Methodological Quality*					
Source	Country (Region)	Outcome	Sample Size	Interval Used	Interval Categories, mo†	Blinding	Lost to Follow-up/ Nonvalid Exclusions, %	Confounders‡	Main Findings
Swenson and Harper,[15] 1978	Bangladesh	Late fetal death (≥28 wk)	9295	IPI	<12; 12-24; >24§	Not reported	Not reported	1, 2, 6, 7	No relationship between interval and late fetal death
Fortney and Higgins,[18] 1984	Iran	LBW, early neonatal death	12 995	BI	≤12; 13-24; 25-36§; 37-48; 49-60; 61-72; ≥73	Not reported	Not reported	1, 2, 6, 7	Intervals <12 mo associated with increased risk of LBW and early neonatal death
DaVanzo et al,[19] 1984	Malaysia	Birth weight	2171	BI	<15; 15-23; 24-35; 36-47; 48-59; 60-71; 72-83; ≥84	Adequate	Not reported	1, 2, 5, 6, 11, 17	Intervals <15 mo significantly associated with reduced birth weight
Casterline,[23] 1989	Ivory Coast, Tunisia, Syria, Korea, Philippines, Costa Rica, Mexico, Guyana	Fetal losses (miscarriages plus stillbirths)	74 916	IPI	<9; 9-15; 16-23; 24-35§; ≥36	Adequate	Not reported	1-3, 6	Intervals <9 mo and >35 mo associated with increased risk of fetal death
Neel and Alvarez,[26] 1991	Guatemala	IUGR	306	BI	<18; 18-35; 36-47§; 48-59; ≥60	Not reported	Not reported	1, 6	Intervals <18 mo associated with increased risk of IUGR
Huttly et al,[28] 1992	Brazil (Pelotas)	LBW, perinatal death	3587	BI	<18; 18-23; 24-35; 36-47; 48-71; >71	Adequate	2.0	1-3, 6, 10, 12	Intervals <24 mo associated with increased risk of LBW. Intervals longer than 71 mo associated with increased risk of LBW and perinatal death
Barros et al,[30] 1992	Brazil (Pelotas)	Preterm birth, IUGR	4747	BI	<24§; 24-35; 36-48; >48	Adequate	0.9	1-3, 6, 10, 12	Intervals <24 mo associated with increased risk of IUGR. No relationship between interval and preterm birth
Leong et al,[31] 1993	Singapore	Preterm birth	11 085	BI	<20; 20-39; ≥40	Not reported	Not reported	1-3, 5-8	No relationship between interval and preterm birth
Gribble,[32] 1993	Mexico	LBW	2234	BI	≤12; 13-21; 22-30; 31-39; 40-48; 49-57; ≥58 [22-58]§	Not reported	Not reported	1-3, 6, 7, 10	Intervals <22 mo associated with increased risk of LBW
Miller,[33] 1994	Philippines	LBW, preterm birth, SGA	1155	IPI	<6; 6-11; 12-17; 18-23; 24-47; ≥48	Not reported	Not reported	1, 3, 6-8, 10, 12	Intervals <6 mo associated with increased risk of LBW, preterm birth, and SGA in fifth or higher birth order infants. No excess risk among lower-order infants
Greenwood et al,[34] 1994	Jamaica	Perinatal death	7512	IPI	<12; 12-23; 24-59; ≥60	Not reported	15.0	1-3, 6, 7, 9	No relationship between interval and perinatal death
Fikree and Berendes,[35] 1994	Pakistan	IUGR	624	IPI	<13; 13-24§; 25-36; ≥37	Not reported	Not reported	1-3, 6, 7, 10, 18	Intervals <13 mo associated with increased risk of IUGR
Fourn et al,[37] 1996	Benin	IUGR, preterm birth	2862	BI	<12; 12-23; 24-35; >35§	Not reported	Not reported	1-4, 6, 7, 10	No relationship between interval and preterm birth or IUGR

(continued)

Table 2. Characteristics of Cross-sectional and Cohort Studies Included in the Systematic Review of Birth Spacing and Adverse Perinatal Outcomes—Developing Countries (cont)

				Methodological Quality*					
Source	Country (Region)	Outcome	Sample Size	Interval Used	Interval Categories, mo†	Blinding	Lost to Follow-up/ Nonvalid Exclusions, %	Confounders‡	Main Findings
Şener et al,[42] 1997	Turkey	SGA	420	IPI	<12;13-24; 25-48§; >48	Not reported	2.1	1-3, 6-8, 10, 12	Intervals <12 mo associated with increased risk of SGA
Deshmukh et al,[44] 1998	India	LBW	201	BI	Not reported	Not reported	1.0	1, 2, 6, 10, 12	"Short interval" associated with increased risk of LBW
Sachar and Soni,[51] 2000	India (Punjab)	Perinatal death (deaths from the 28th week gestation through first week of life)	2424	IPI	<23; ≥24§	Not reported	Not reported	1-3, 6-8, 10, 11	Intervals <23 mo associated with an increased risk of perinatal death
van Eijk et al,[58] 2004	Kenya	LBW, preterm birth, SGA	2218	IPI	<6; 6-23; ≥24	Not reported	6.5	1-3, 6, 19	No association between interval and LBW, preterm birth, and SGA
Arafa et al,[59] 2004	Egypt	Preterm birth	1202	IPI	<12; 12-36; 37-48; 49-60; >60§	Not reported	0.0	1, 2, 6, 8-10	No relationship between intervals <12 mo and preterm birth
Pedroso et al,[60] 2004	Brazil (Campinas)	LBW, preterm birth	15 314	BI	<25; 25-36; ≥37§	Not reported	Not reported	1-8, 10, 12, 13	Intervals <24 mo associated with increased risk of LBW and preterm birth
Hsieh et al,[61] 2005	Taiwan	Preterm birth	4072	IPI	<6; 6-11; 12-18; 18-48§ ; >48	Adequate	Not reported	1-4, 6, 7, 12	Intervals <12 mo associated with increased risk of preterm birth
DaVanzo et al,[62] 2005	Bangladesh (Matlab)	Early neonatal death (≤7 d)	125 720	BI	<15; 15-17; 18-23; 24-35; 36-59§; 60-83; ≥84	Adequate	Not reported	1, 2, 6, 7, 11, 17, 18	Intervals <24 mo and ≥84 mo associated with increased risk of early neonatal death
Rutstein,[63] 2005	9 Asian countries, 7 Latin American countries, and 4 African countries	Perinatal death (deaths from the 28th week of pregnancy through first week of life)	267 261	IPI	<6; 6-11; 12-17; 18-23; 24-29§; 30-35; 36-41; 42-47; 48-53; 54-59	Adequate	Not reported	1-3, 6, 7, 11	Intervals <18 mo and ≥42 mo significantly associated with increased risk of perinatal death
Conde-Agudelo et al,[64] 2005	18 Latin American countries	LBW, preterm birth, SGA, fetal death, early neonatal death, low Apgar scores at 5 min	1 080 650	IPI	<6; 6-11; 12-17; 18-23§; 24-35; 36-47; 48-59; ≥60	Adequate	10.7	1-4, 6-12, 15-17	Intervals <12 mo and >59 mo significantly associated with increased risks of LBW, preterm birth, SGA, fetal death, and early neonatal death
Hosain et al,[65] 2005	Bangladesh	LBW	227	BI	<24; ≥24§	Not reported	16.4	1-3, 6, 8, 10, 12	No relationship between intervals <24 mo and LBW

Abbreviations: BI, birth interval; IPI, interpregnancy interval; IUGR, intrauterine growth restriction; LBW, low birth weight; SGA, small for gestational age.
*See "Methods" section for definitions of methodological quality criteria. Interval and outcomes inquiries were determined to be "adequate" for all studies except Swenson and Harper (not reported).
†Intervals in square brackets indicate the reference group in the studies that did not use as a reference one of the intervals originally categorized.
‡For multivariate adjustments, 1 indicates maternal age; 2, parity; 3, education; 4, marital status; 5, ethnic group or race; 6, factors related to socioeconomic status; 7, previous pregnancy outcome; 8, factors relating to prenatal care; 9, medical risk factors; 10, maternal nutritional status; 11, region; 12, smoking; 13, alcohol use; 14, illicit drug use; 15, gestational age or birth weight; 16, type of hospital; 17, year of delivery; 18, religion; 19, sex of the child.
§Reference group.

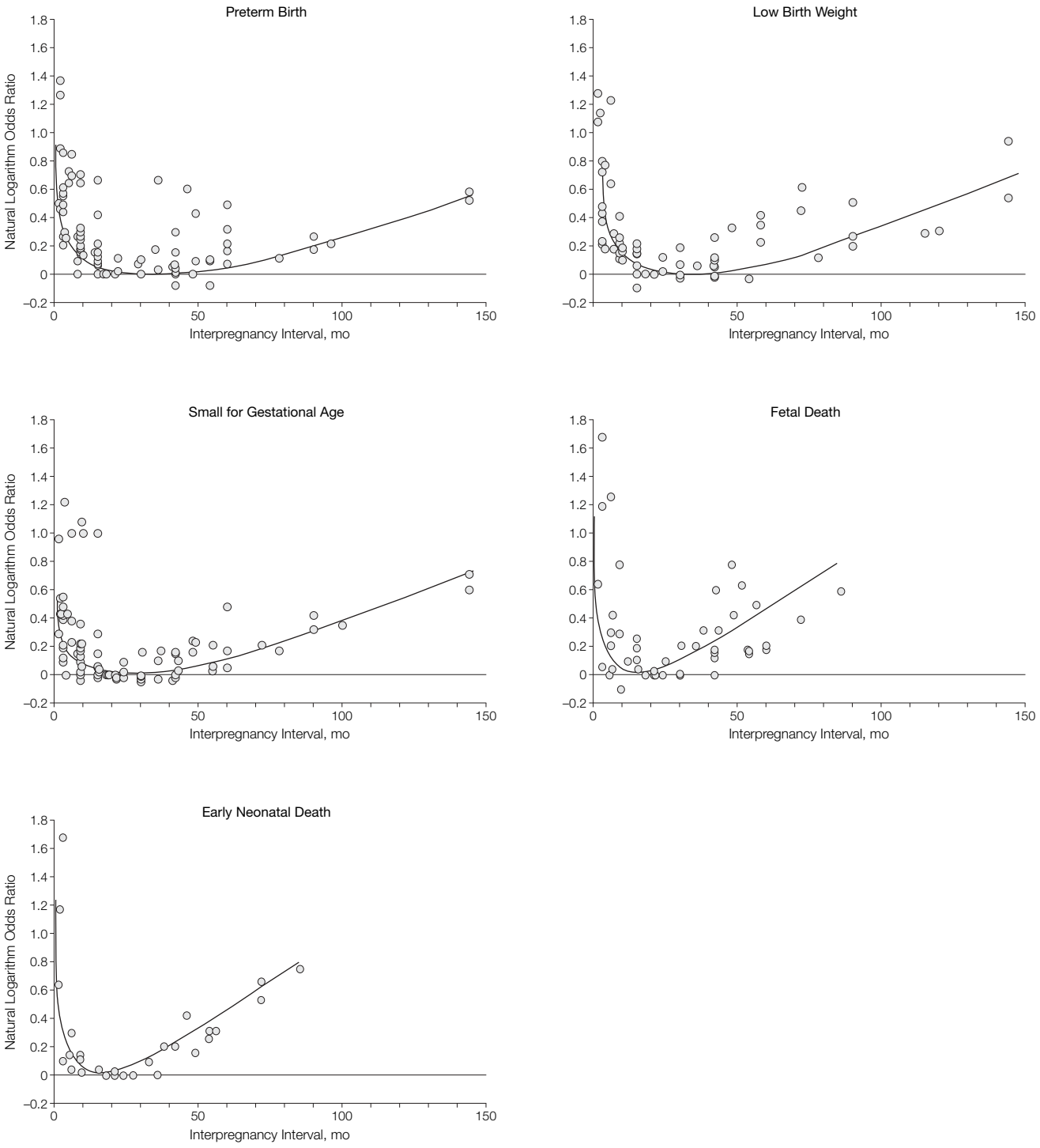
in risk of the 3 adverse perinatal outcomes. There were no differences in the risk of adverse perinatal outcomes between women with intervals of 24 to 59 months and those with intervals of 18 to 23 months. All funnel plots showed no asymmetry, either visually (funnel plots available from the corresponding author on request) or in

Table 3. Characteristics of Case-Control Studies Included in the Systematic Review of Birth Spacing and Adverse Perinatal Outcomes

				Methodological Quality*				
Source	Country (Region)	No. of Cases, Source	No. of Controls, Source	Interval Used	Intervals Categories, mo	Blinding	Confounders†	Main Findings
Ruelas-Orozco et al,[66] 1985	Mexico	104 perinatal deaths (from the 27th week of pregnancy through first week of life), community	208 live births, community	IPI	<7; 7-46‡; >46	Not reported	1-4, 6, 7, 9, 10, 12, 13	Intervals <7 mo and >46 mo significantly associated with increased risk of perinatal death
Ferraz et al,[67] 1988	Brazil (Natal)	303 infants with birth weight <10th percentile for gestational age, 282 preterm infants, hospital	1710 term infants with birth weight ≥2500 g and appropriate for gestational age, hospital	IPI	≤6; 7-12; ≥13‡	Not reported	1-3, 6, 7, 10, 12	Intervals ≤6 mo associated with increased risk of IUGR. No relationship between interval and preterm birth
Bartlett and Paz de Bocaletti,[68] 1991	Guatemala	42 Mayan Indian infants who died during birth or in the first month of life, community	54 Mayan Indian infants who survived the first month of life, community	BI	<14; ≥14‡	Not reported	1-4, 6, 8, 11	Interval <14 mo associated with increased risk of intrapartum and neonatal deaths
Mavalankar and Gray,[69] 1991	India	416 preterm-LBW infants, hospital	926 normal birth weight infants, hospital	IPI	≤6; 7-12; 13-24; 25-48‡; ≥49	Not reported	1-4, 6-12, 15, 18, 19	Intervals <13 mo and >48 mo significantly associated with increased risk of preterm LBW
Dechering and Perera,[70] 1991	Sri Lanka	245 LBW infants	399 with birth weight ≥2500 g	BI	<12; 12-48‡; >48	Not reported	1-3, 6-8, 10, 19	Intervals <12 mo and >48 mo significantly associated with increased risk of LBW
Kumar and Singhi,[71] 1992	India	36 late fetal deaths, community	50 live birth infants, community	BI	<24; ≥24‡	Not reported	1-3, 6	Intervals <24 mo not associated with increased risk of late fetal death
Mavalankar et al,[72] 1992	India	343 term-LBW (IUGR) infants	926 normal birth weight infants, hospital	IPI	≤6; 7-12; 13-48‡; ≥49	Not reported	1-4, 6-12, 15, 18, 19	No relationship between interval and IUGR
Arif et al,[73] 1998	Pakistan	236 LBW-SGA infants, hospital	293 infants with birth weight ≥2500 g, hospital	BI	<24; ≥24‡	Not reported	1, 3, 6, 10	Intervals <24 mo not associated with risk of LBW-SGA birth
Grau et al,[74] 1999	Cuba	202 preterm infants, hospital	319 term infants, hospital	IPI	<24; ≥24‡	Not reported	1, 3, 4, 6-8, 10, 12	Intervals <24 mo associated with increased risk of preterm birth
Wang and Lin,[75] 1999	Taiwan	208 perinatal deaths (from the 22nd week of pregnancy through first week of life), hospital	619 live births, hospital	BI	<12; 12-24; >24‡	Not reported	1-3, 6, 8-10, 14	Intervals <24 mo associated with increased risk of perinatal death
Mafina-Mienandi et al,[76] 2002	Congo	247 infants with birth weight <10th percentile for gestational age, hospital	293 infants with birth weight appropriate for gestational age, hospital	IPI	<12; 12-24; >24‡	Not reported	1-4, 6, 10	No relationship between interval and IUGR
Al-Jasmi et al,[77] 2002	United Arab Emirates	128 preterm infants, hospital	128 term infants, hospital	IPI	2.8-8.9; 9.0-15.9; 16.0-22.9‡; 23.0-82.7	Not reported	1, 2, 6-8, 10	Intervals <16 mo associated with increased risk of preterm birth
Khan and Jamal,[78] 2003	Pakistan	190 LBW infants, hospital	760 normal birth weight infants, hospital	IPI	<5; 5-10; >10‡	Not reported	1-3, 6, 8, 10	Risk for LBW increased with intervals <5 mo
Orji et al,[79] 2004	Nigeria	50 women with intervals ≥72 months, hospital	50 women with intervals 24 to 60 months, hospital	BI	24-60‡; ≥72	Not reported	1, 2, 6	No difference in Apgar scores between the study groups
Kleijer et al,[80] 2005	Australia (Adelaide)	233 infants with birth weight <10th percentile for gestational age, hospital	241 infants with birth weight between the 25th and 75th percentile	IPI	<48; ≥48‡	Not reported	1, 2, 4-7, 10, 12, 14	No relationship between interval <48 mo and IUGR

Abbreviations: BI, birth interval; IPI, interpregnancy interval; IUGR, intrauterine growth restriction; LBW, low birth weight; SGA, small for gestational age.
*See "Methods" section for definitions of methodological quality criteria. Interval and outcomes inquiries were determined to be "adequate" for all studies except Bartlett and Paz de Bocaletti (inadequate).
†For multivariate adjustments, 1 indicates maternal age; 2, parity; 3, education; 4, marital status; 5, ethnic group or race; 6, factors related to socioeconomic status; 7, previous pregnancy outcome; 8, factors relating to prenatal care; 9, medical risk factors; 10, maternal nutritional status; 11, region; 12, smoking; 13, alcohol use; 14, illicit drug use; 15, gestational age or birth weight; 16, type of hospital; 17, year of delivery; 18, religion; 19, sex of the child.
‡Reference group.

Figure. Scatterplot of Natural Logarithm Odds Ratio and Meta-regression Curves of Adverse Perinatal Outcomes According to Interpregnancy Interval in Cohort and Cross-sectional Studies



The dose-response curve line represents estimates from a smoothed spline regression. The horizontal line at y=0 represents no effect. Most studies provided ≥1 odds ratio estimate for several categories of interpregnancy intervals.

terms of statistical significance ($P>.10$ for all, by Egger test).

Important statistical heterogeneity among studies was present, as confirmed by I^2 values greater than 50% in half of meta-analyses, and this remained in the prespecified subgroups. An examination for sources of heterogeneity among studies found that a significant portion of the heterogeneity in studies evaluating the relation between intervals shorter than 6 months and both preterm birth and LBW was explained by the study by our group[64] since the estimates of pooled adjusted ORs were significantly lowered when this study was excluded (1.30; 95% CI, 1.23-1.38; and 1.48; 95% CI, 1.40-1.57, respectively). Study quality, date of publication, sample size, and study setting provided no explanation for heterogeneity in studies evaluating the relationship between intervals of 6 to 11, 12 to 17, and 24 to 59 months and both preterm birth and LBW, because the CIs in the subgroups overlapped (data available from corresponding author on request). Compared with the overall results, the summary ORs calculated from sensitivity and subgroup analyses were almost identical. Pooled adjusted ORs calculated from subgroups evaluating intervals of 60 months or longer and preterm birth were similar to the overall adjusted OR calculated from all studies. With regard to studies evaluating the association between intervals longer than 59 months and LBW, studies from developed countries were significantly associated with higher pooled adjusted ORs. There were no significant differences in pooled adjusted ORs obtained from subgroups of studies and the overall estimates obtained from all studies assessing the association between interpregnancy interval and SGA. In general, there were no significant differences in estimates of summary adjusted ORs between white and black women in subgroups that evaluated the effects of interpregnancy interval on adverse perinatal outcomes according to race/ethnicity.[39,40,52]

For each month that interpregnancy interval was shortened from 18 months, the risk increase for preterm birth, LBW, and SGA was 1.9%, 3.3%, and 1.5%, respectively (**TABLE 5**). On the other hand, the risk for the 3 adverse perinatal outcomes increased by 0.6%, 0.9%, and 0.8%, respectively, for each month that interpregnancy interval was lengthened from 59 months.

Table 4. Odds Ratios for the Association Between Interpregnancy Interval and Adverse Perinatal Outcomes in Cohort and Cross-sectional Studies

Interpregnancy Interval, mo	Preterm Birth	Low Birth Weight	Small for Gestational Age
Pooled Unadjusted Results			
<6			
No. of Studies	8[25,33,40,49,50,52,55,64]	6[21,33,40,49,56,64]	7[21,22,33,49,52,55,64]
OR (95% CI)	1.77 (1.54-2.04)	2.12 (1.98-2.26)	1.39 (1.20-1.61)
I^2 , %*	95	63	93
6-11			
No. of studies	9[25,27,33,40,49,50,52,55,64]	6[21,33,40,49,56,64]	8[21,22,24,33,49,52,55,64]
OR (95% CI)	1.23 (1.16-1.31)	1.23 (1.15-1.32)	1.18 (1.14-1.23)
I^2, %*	85	73	39
12-17			
No. of studies	9[25,27,33,40,49,50,52,55,64]	7[21,27,33,40,49,56,64]	8[21,22,24,33,49,52,55,64]
OR (95% CI)	1.11 (1.03-1.20)	1.08 (1.02-1.14)	1.08 (1.06-1.11)
I^2, %*	56	51	14
18-23†			
No. of studies	9[25,27,33,40,49,50,52,55,64]	7[21,27,33,40,49,56,64]	8[21,22,24,33,49,52,55,64]
OR	1.00	1.00	1.00
24-59			
No. of studies	6[27,49,50,52,55,64]	6[27,33,40,49,56,64]	7[22,24,33,49,52,55,64]
OR (95% CI)	1.03 (1.00-1.07)	1.07 (0.99-1.15)	1.07 (0.98-1.18)
I^2, %*	28	78	93
≥60			
No. of studies	5[27,49,50,52,64]	4[27,49,56,64]	5[22,24,49,52,64]
OR (95% CI)	1.27 (1.17-1.39)	1.49 (1.17-1.89)	1.36 (1.20-1.54)
I^2, %*	93	98	96
Pooled Adjusted Results			
<6			
No. of studies	8[25,39,40,49,50,52,55,64]	4[40,49,52,64]	6[22,39,49,52,55,64]
OR (95% CI)	1.40 (1.24-1.58)	1.61 (1.39-1.86)	1.26 (1.18-1.33)
I^2, %*	69	87	89
6-11			
No. of studies	8[25,39,40,49,50,52,55,64]	4[40,49,52,64]	7[22,24,39,49,52,55,64]
OR (95% CI)	1.14 (1.10-1.17)	1.14 (1.10-1.18)	1.11 (1.04-1.19)
I^2, %*	87	91	32
12-17			
No. of studies	8[25,39,40,49,50,52,55,64]	4[40,49,52,64]	7[22,24,39,49,52,55,64]
OR (95% CI)	1.07 (1.03-1.11)	1.05 (1.01-1.09)	1.06 (1.01-1.10)
I^2, %*	26	34	0
18-23†			
No. of studies	8[25,39,40,49,50,52,55,64]	4[40,49,52,64]	7[22,24,39,49,52,55,64]
OR	1.00	1.00	1.00
24-59			
No. of studies	8[25,39,40,49,50,52,55,64]	4[40,49,52,64]	7[22,24,39,49,52,55,64]
OR (95% CI)	0.99 (0.97-1.02)	1.01 (0.98-1.03)	1.02 (0.99-1.05)
I^2, %*	0	0	0
≥60			
No. of studies	7[25,39,40,49,50,52,64]	4[40,49,52,64]	6[22,24,39,49,52,64]
OR (95% CI)	1.20 (1.17-1.24)	1.43 (1.27-1.62)	1.29 (1.20-1.39)
I^2, %*	95	84	88

Abbreviations: CI, confidence interval; OR, odds ratio.
*Heterogeneity test (see "Methods" section).
†Reference category.

COMMENT

Using 3 different meta-analytical techniques, we show that birth to conception intervals shorter than 18 months and longer than 59 months are significantly associated with increased risk of several adverse perinatal outcomes, such as preterm birth, LBW, and SGA. Infants can have LBW either because they are born early (preterm birth) or are born SGA. Thus, the association between interpregnancy interval and LBW could be due to the independent effect of interval on both preterm birth and SGA. Less clear is the association between birth spacing and the risk of fetal and early neonatal death, although results from meta-regression curves suggest that interpregnancy intervals shorter than 6 months and longer than 50 months are associated with increased risk of these adverse perinatal outcomes. The strength of our inferences is based on compliance with stringent criteria for performing a rigorous systematic review. These included the use of a prospective protocol designed to address a research question; the methods used in the identification of relevant studies; no language restrictions; the exclusion of studies that did not adjust for at least maternal age and socioeconomic status; the strict assessment of methodological quality of included studies; the use of several techniques of meta-analysis (both unadjusted and adjusted analyses); the exploration of sources of heterogeneity; the quantitative summarization of the evidence; and the inclusion of a large number of women from different populations throughout the world.

The reasons for the association between a short interval between pregnancies and adverse perinatal outcomes are unclear. A plausible explanation is the maternal nutritional depletion hypothesis,[27,81] which states that a close succession of pregnancies and periods of lactation worsen the mother's nutritional status because there is not adequate time for the mother to recover from the physiological stresses of the preceding pregnancy before she is subjected to the stresses of the next. This results in depletion of maternal nutrient stores, with the subsequent increased risk of adverse perinatal outcomes.[81] The folate depletion hypothesis claims that maternal serum and erythrocyte concentrations of folate decrease from the fifth month of pregnancy onward and remain low for a fairly long time after delivery. Women who become pregnant before folate restoration is complete have an increased risk of folate insufficiency at the time of conception and during pregnancy. As a consequence, their offspring have higher risks of neural tube defects, intrauterine growth restriction, preterm birth, and LBW.[82] Some investigators have attributed the higher risk of poor pregnancy outcomes to several factors associated with having short intervals, such as socioeconomic status, unstable lifestyles, failure to use health care services or inadequate use of such services, unplanned pregnancies, and other behavioral or psychological determinants.[4,5] However, the fact that the birth spacing effects are not strongly attenuated when socioeconomic and maternal characteristics are controlled for suggests that the effects are not caused by these confounding factors.

Table 5. Meta-analysis of Dose-Response Regression Slopes and Prediction of the Risk of Adverse Perinatal Outcomes for Interpregnancy Intervals <18 Months and >59 Months

Risk Increase	Increase, % (95% CI)		
	Preterm Birth (12 Studies)	LBW (7 Studies)	SGA (12 Studies)
Per month for intervals <18 mo*	1.92 (1.80-3.04)	3.25 (3.09-3.41)	1.52 (1.40-1.64)
Per month for intervals >59 mo†	0.55 (0.49-0.61)	0.91 (0.83-0.99)	0.76 (0.71-0.81)
Predicted by the model			
Interpregnancy interval, mo			
3	28.8 (27.0-30.6)	48.8 (46.4-51.2)	22.8 (21.0-24.6)
6	23.0 (21.6-24.5)	39.0 (37.1-40.9)	18.2 (16.8-19.7)
9	17.3 (16.2-18.4)	29.3 (27.8-30.7)	13.7 (12.6-14.8)
12	11.5 (10.8-12.2)	19.5 (18.5-20.5)	9.1 (8.4-9.8)
15	5.8 (5.4-6.1)	9.8 (9.3-10.2)	4.6 (4.2-4.9)
18-59‡	1.00	1.00	1.00
72	6.6 (5.9-7.3)	10.9 (10.0-11.9)	9.1 (8.5-9.7)
96	19.8 (17.6-22.0)	32.8 (29.9-35.6)	27.4 (25.6-29.2)
120	33.0 (29.4-36.6)	54.6 (49.8-59.4)	45.6 (42.6-48.6)
144	46.2 (41.2-51.2)	76.4 (69.7-83.2)	63.8 (59.6-68.0)

Abbreviations: CI, confidence interval; LBW, low birth weight; SGA, small for gestational age.
*Risk increase per each month that interpregnancy interval is shortened from 18 months.
†Risk increase per each month that interpregnancy interval is lengthened from 59 months.
‡Reference category.

Some hypotheses have also been proposed to explain the relationship between long intervals and adverse perinatal outcomes. Zhu et al[49] have hypothesized that, after delivery, a woman's physiologic reproductive capacities gradually decline, becoming similar to those of primigravid women (ie, "the physiological regression hypothesis"). This hypothesis is supported by the observation that perinatal outcomes for infants conceived after an excessively long interpregnancy interval are similar to outcomes of infants born to primigravid women. Another possibility is that unmeasured factors, such as sexually transmitted infections or maternal illnesses, may cause both adverse fertility and pregnancy outcomes.[5,49] These factors could differ for women in developed and developing countries. Finally, residual confounding may still be an explanation for at least part of the reported associations.

Several potential limitations of our review must also be considered. First, like any systematic review, it is limited by the quality of original data. The great majority of studies calculated the interpregnancy interval using mother's recall of her previous child's date of birth and her last menstrual period,

instead of birth dates recorded on the birth records and gestational age estimated from ultrasonography. In most studies the intervals were calculated as the time elapsed between 2 consecutive live births, ignoring induced or spontaneous abortions or fetal deaths between them, which can produce even longer intervals between live births. Nevertheless, this problem would not affect the findings for short intervals. In addition, several studies did not properly address the potential confounding effects of factors other than maternal age and socioeconomic status. Second, because there was considerable statistical heterogeneity in most of the meta-analyses performed, our findings should be interpreted with caution. Nevertheless, in the great majority of comparisons the estimates showed the same direction of effect, which could suggest the absence of clinical heterogeneity among the studies. Investigation of possible sources of heterogeneity provided no plausible explanations. In addition, it is possible that the I^2 heterogeneity test could have excessive power when there are studies with large sample size, as was the case with some of the ones included in our meta-analyses. Third, the number of studies available for analysis on the relationship between birth spacing and some adverse perinatal outcomes is still too small to provide conclusive evidence.

The effects of birth spacing on perinatal health found in our study, as well as the effects of both short and long intervals on infant, child, and maternal health,[1,2] should furnish a strong motivating force for health personnel to provide family planning. The health sector should supply such care not only to those wishing to limit their fertility for personal, social, or economic reasons, but should also provide the needed services to those practicing family planning for health reasons. The results of our systematic review could be used by reproductive clinicians around the world to advise women on the benefits of delaying a subsequent pregnancy for approximately 2 to 5 years to improve the health of both mother and the next infant.

Despite the advances during the last 2 decades in understanding the relationship between birth spacing and adverse pregnancy outcomes, little information is available to explain the mechanisms by which birth spacing might improve the health of mothers and their children. Also, more studies are needed on whether the effects of birth spacing on perinatal health differ in developed vs developing nations. Finally, it is imperative to understand the causes for both short and long intervals in any population to interpret the data on health risks. The consequence of this may be that family planning policies and messages may need to be tailored to different populations.

Author Contributions: Dr Conde-Agudelo had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
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