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Effects of Birth Spacing on Maternal, Perinatal, Infant, and Child Health: A Systematic Review of Causal Mechanisms

Agustín Conde-Agudelo, Anyeli Rosas-Bermudez, Fabio Castaño, and
Maureen H. Norton

This systematic review of 58 observational studies identified hypothetical causal mechanisms explaining the effects of short and long intervals between pregnancies on maternal, perinatal, infant, and child health, and critically examined the scientific evidence for each causal mechanism hypothesized. The following hypothetical causal mechanisms for explaining the association between short intervals and adverse outcomes were identified: maternal nutritional depletion, folate depletion, cervical insufficiency, vertical transmission of infections, suboptimal lactation related to breastfeeding–pregnancy overlap, sibling competition, transmission of infectious diseases among siblings, incomplete healing of uterine scar from previous cesarean delivery, and abnormal remodeling of endometrial blood vessels. Women’s physiological regression is the only hypothetical causal mechanism that has been proposed to explain the association between long intervals and adverse outcomes. We found growing evidence supporting most of these hypotheses. (STUDIES IN FAMILY PLANNING 2012; 43[2]: 93–114)

Evidence from systematic reviews and meta-analyses indicates that short and long intervals between pregnancies are independently associated with increased risk of adverse maternal, perinatal, infant, and child outcomes (Conde-Agudelo, Rosas-Bermudez, and Kafury-Goeta 2006, 2007; Rutstein 2008). Interpregnancy intervals shorter than 18 months and longer than 59 months are significantly associated with increased risk of adverse perinatal outcomes

such as preterm birth, low birth-weight, and small for gestational age (Conde-Agudelo, Rosas-Bermudez, and Kafury-Goeta 2006). Moreover, short intervals are associated with increased risk of premature membrane rupture (Conde-Agudelo, Rosas-Bermudez, and Kafury-Goeta 2007; Getahun et al. 2010), uteroplacental bleeding disorders such as abruptio placentae and placenta previa (Getahun et al. 2006; Conde-Agudelo, Rosas-Bermudez, and Kafury-Goeta 2007), and uterine rupture in women attempting a vaginal birth after previous cesarean delivery (Conde-Agudelo, Rosas-Bermudez, and Kafury-Goeta 2007; Stamilio et al. 2007; Bujold and Gauthier 2010); and long intervals (longer than 5 years) are associated with an increased risk of preeclampsia (Conde-Agudelo, Rosas-Bermudez, and Kafury-Goeta 2007). Preceding interpregnancy intervals shorter than 36 months are significantly associated with a greater risk of child and under-five-years mortality, and intervals shorter than 24 months significantly increase risk of early neonatal, neonatal, and infant mortality (Rutstein 2008).

The mechanisms by which short and long intervals between pregnancies may affect maternal, perinatal, infant, and child health have been the subject of much debate. Hypotheses generally adopt either biological or

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behavioral orientations, but no one framework or hypothesis has emerged as dominant (Erickson and Bjerkedal 1979; Winikoff 1983; Klebanoff 1999). In 2005, a WHO technical consultation on birth spacing recommended the development of a comprehensive theoretical framework to explain and analyze possible causal mechanisms of birth spacing (WHO 2006). Toward this end, the present study systematically collates, appraises, and synthesizes the literature on this topic.

We identified hypothetical causal mechanisms for explaining the effects of short and long intervals between pregnancies on maternal, perinatal, infant, and child health. Then, we critically examined the scientific support for each hypothesized causal mechanism proposed by using formal methods for systematic reviews of observational studies (Levine et al. 1994; Egger, Schneider, and Davey Smith 1998; Stroup et al. 2000) and recommended methods for assessing mechanisms of disease and causal association (Hill 1965; Weed and Hursting 1998; Mignini, Villar, and Khan 2006).

Methods

We used a prospective protocol prepared specifically for this purpose. The systematic review was conducted following this protocol and is reported using the checklist proposed by the MOOSE group for the reporting of systematic reviews of observational studies (Stroup et al. 2000).

Identification of Studies

The investigators conducted computerized searches in Medline, Embase, CINAHL, Popline, and LILACS (all from inception to 30 June 2011) using a combination of keywords and text words related to birth spacing and causal mechanisms. The search terms related to birth spacing included "birth interval," "birth-to-birth interval," "birth-to-conception interval," "birth spacing," "delivery-to-conception interval," "interbirth interval," "interdelivery interval," "intergenesic interval," "interpregnancy interval," "pregnancy interval," and "pregnancy spacing." Search terms related to causal mechanisms included "cause," "hypothesis," "mechanism," "model," "pathway," "postulate," and "theory." Index Medicus (1955–1966), proceedings of several international meetings on birth spacing, bibliographies of retrieved articles, and reviews were also searched by hand. To find unpublished studies, we contacted relevant researchers in the field. No language restrictions were employed.

During the initial search, we identified ten hypothetical causal mechanisms for explaining the association between short and long pregnancy intervals and adverse maternal, perinatal, infant, and child outcomes (Table 1). A secondary computerized search was conducted using key terms related to each hypothesized causal mechanism identified.

Inclusion Criteria

We included observational studies (cohort, cross-sectional, or case-control) examining causal mechanisms or hypotheses for explaining the association between birth spacing and adverse maternal, perinatal, infant, and child outcomes. The use of any interval as the measure of birth spacing was considered adequate. The three main definitions of interval used are: "interpregnancy interval" (the time elapsed between delivery of previous infant and conception of current pregnancy); "birth interval" (the time elapsed between the woman's last delivery and birth of index child); and "recuperative interval" (the amount of time the woman was neither lactating nor pregnant). We considered the most important confounding factors in the association between birth or interpregnancy or recuperative intervals and adverse health outcomes to be maternal age, parity, and socioeconomic status (measured indirectly by occupation and work status, educational level, income, housing, or other variables). Therefore, the studies had to have adjusted their results for at least maternal age or parity and socioeconomic status. We included observational studies that did not adjust their results for confounding factors, as well as randomized controlled trials on folate supplementation if data were available on maternal folate levels during the postpartum period. Also included were unadjusted observational studies that provided data for evaluating the incomplete healing of the uterine scar from the previous cesarean delivery hypothesis. Excluded from the systematic review were case series and reports, editorials, letters to the editor, reviews without original data, studies without data, studies that did not adjust for at least maternal age or parity and socioeconomic status, and studies that exclusively used univariate analysis. All potentially relevant studies were retrieved and reviewed independently by two authors to determine inclusion. Disagreements were resolved through consensus.

Assessment of Study Quality

Although conceptually similar, it is difficult to automatically apply the same strategy for clinical and basic biologic models (Parascandola and Weed 2001). The differences

Table 1 Hypothetical causal mechanisms identified in the literature

Causal mechanism	Associations that causal mechanism explains
Maternal nutritional depletion	Short intervals and adverse maternal, perinatal, infant, and child outcomes
Folate depletion	Short intervals and adverse perinatal outcomes
Cervical insufficiency	Short intervals and preterm birth
Vertical transmission of infections	Short intervals and adverse perinatal/neonatal outcomes
Suboptimal lactation related to breastfeeding–pregnancy overlap	Short intervals and adverse neonatal outcomes
Sibling competition	Short intervals and both infant and child death
Transmission of infectious diseases among siblings	Short intervals and both infant and child death
Incomplete healing of uterine scar from previous cesarean delivery	Short intervals and uterine rupture in women who attempt a vaginal birth after cesarean delivery
Abnormal process of remodeling of endometrial blood vessels	Short intervals and uteroplacental bleeding disorders
Women’s physiological regression	Long intervals and adverse perinatal and maternal outcomes (preeclampsia and dystocia)

between the probabilistic modeling used in epidemiology and the study of events at the molecular level described in basic science literature are well recognized (Stroup et al. 2000). Causal criteria, however, remain at the center of establishing disease mechanisms, the most common being strength, consistency, dose response, temporality, and biological plausibility of disease mechanisms (Hill 1965; Weed 1997; Weed and Hursting 1998).

Two of the authors independently assessed the methodological quality of the studies, and only those articles that both authors deemed to contain relevant and sufficient data for interpretation were included in the review. Methodological quality was defined as the confidence that the study design, conduct, and analysis had minimized biases in assessing the hypothetical causal mechanisms involved in the relationship between birth spacing and adverse health outcomes. The methodological quality of each study that was included was judged according to the following nine criteria: study design, measure of spacing used, selection of participants, assessment of exposure and outcome(s), blinding of investigators to both exposition and the outcome(s), loss to follow-up or exclusions and/or period of time for recruitment of participants, control for confounding factors, report of a dose–response gradient, and biologic/behavioral plausibility of hypothetical causal mechanisms. High-quality studies met seven or more of these methodological criteria; non-high-quality studies met six or fewer.

Data Extraction

Two of the authors independently extracted data from each article by means of a predesigned and piloted form. Discrepancies were resolved by consensus. We recorded from each article the title, first author’s name, year, geographic location of the study (country and region), study design, characteristics and source of study population, sample size, definition of adverse health outcomes, methodological quality, confounding factors controlled for by

matching or adjustment, strength of association, report of dose–response gradient (if applicable), unadjusted and/or adjusted relative risks (RRs) or odds ratios (ORs) with 95 percent confidence intervals (CIs), and mean serum, urinary, or erythrocyte levels of metabolites analyzed with corresponding standard error or deviation (if applicable) for each study group. When necessary, we contacted article authors to request additional information.

Data Analysis

When developing the protocol for the systematic review, we anticipated using several meta-analytical techniques to investigate the scientific evidence supporting the causal mechanisms hypothesized. Performing meta-analyses was not feasible, however, because of the differences in measures of birth spacing, categories of intervals, reference categories used, and outcome measures evaluated in the studies that met the minimal criteria for inclusion. We therefore prepared a narrative synthesis based on the overall results of the included studies, and produced an appendix table listing all of the 58 selected studies and their key characteristics and findings (see Appendix Table A1).

Results

The searches produced 3,279 citations, of which 198 were considered to be potentially relevant (163 were drawn from computer searching, 33 from references cited in articles, and 2 from meeting proceedings). One hundred forty studies were excluded, mainly because they lacked data on hypothetical causal mechanisms and lacked adjustment for confounding factors. Fifty-eight studies were included in the review: 41 (19 cohort and 22 cross-sectional) examined hypothetical causal mechanisms or hypotheses that explain the association between birth spacing and adverse maternal, perinatal, infant, and child

outcomes, and 17 (13 cohort and 4 randomized controlled trials) provided data on maternal folate levels during the postpartum period (see Appendix Table A1). Thirty-six studies (62 percent) were conducted in developing countries and the remaining 22 in developed countries. Of the 41 observational studies examining hypothetical causal mechanisms, 19 (46 percent) were considered to be of high methodological quality. The remaining 22 studies had three or more methodological flaws. The most common shortcomings were the use of birth interval instead of pregnancy interval, the inconsistent characterization of intervals categories, failure to adjust for confounding factors and to report losses to follow-up or exclusions, and lack of control for effects of pregnancy duration in studies evaluating neonatal mortality.

Fifteen studies provided data for assessing the maternal nutritional depletion hypothesis, 20 for assessing the folate deficiency hypothesis, 1 each for assessing the cervical insufficiency and vertical transmission of infections hypotheses, 17 for assessing the sibling competition hypothesis, 2 for assessing the hypothesis of transmission of infectious diseases among siblings, and 3 for assessing the hypothesis of incomplete healing of the uterine scar from a previous cesarean delivery (see Appendix Table A1). (Pathak and colleagues 2004 provided data for assessing both maternal depletion and folate depletion hypotheses and is counted twice here.) No studies provided data for evaluating the hypotheses concerning suboptimal lactation related to breastfeeding–pregnancy overlap, the abnormal process of remodeling of endometrial blood vessels, or women’s physiological regression.

Maternal Nutritional Depletion

An adequate supply of nutrients is required to maintain the balance between the needs of the mother and the fetus. An inadequate supply will cause a state of biological competition in which the well-being of both the mother and fetus is at risk. The original definition of maternal depletion referred to the cumulative effect of successive pregnancies and lactations but did not take into account the interval between pregnancies (Jelliffe and Maddocks 1964). The current maternal nutritional depletion hypothesis states that a close succession of pregnancies and of periods of lactation worsens the mother’s nutritional status because of inadequate time to recover from the physiological stresses of the preceding pregnancy before becoming subject to the stresses of the next pregnancy (Winkvist, Rasmussen, and Habicht 1992; King 2003). The mother’s nutritional status at conception might be compromised and her ability to support fetal growth could

be suboptimal, resulting in increased risk of adverse perinatal outcomes. The child born after a short interval could be disadvantaged as a result of fetal malnutrition and a compromised intrauterine environment, which would increase risk of death during childhood. The maternal nutritional depletion hypothesis has been theorized to operate through changes in protein and energy balance and in maternal weight (Winkvist, Rasmussen, and Habicht 1992). Macronutrients and micronutrients (such as trace minerals and vitamins) might be depleted during pregnancy and in the first few months postpartum, leading to deficiencies if a new pregnancy occurs (King 2003). Weight change is used here as an indicator of change in energy stores. Weight change, nevertheless, is a less accurate indicator for stores of other nutrients. The analytical framework proposed by Winkvist, Rasmussen, and Habicht (1992) is useful for studying the maternal nutritional depletion hypothesis. A reproductive cycle is defined as the time interval between two consecutive pregnancies and is made up of four phases: pregnancy, full lactation, partial lactation, and nonpregnancy / nonlactation. This analytical framework defines maternal depletion as a condition characterized by a negative change in maternal nutritional status during a single reproductive cycle, where the change is more negative the shorter the length of the potential repletion phase relative to the potential depletion phase. Maternal depletion is most likely to occur among women with marginally inadequate food intake and inability to make behavioral and thus energy expenditure adjustments to low intake.

Maternal nutritional depletion has been hypothesized as a mechanism that contributes to the detrimental effect of a short interpregnancy interval on maternal, perinatal, infant, and child health. We examined this hypothesis through studies that evaluated the effects of interpregnancy, birth-to-birth, or recuperative intervals on indexes of maternal anthropometric status, anemia, and micronutrient status. The characteristics and main findings of studies that provided data for assessing the maternal nutritional depletion hypothesis are shown in Appendix Table A1.

Nine studies examined the association between birth spacing and maternal anthropometric outcomes (Greene et al. 1988; Miller and Huss-Ashmore 1989; Merchant, Martorell, and Haas 1990a and 1990b; Farahati, Bozorgi, and Luke 1993; Pebley and DaVanzo 1993; Winkvist et al. 1994; Herman and Yu 1997; Khan, Chien, and Khan 1998). Three used interpregnancy interval, two used birth interval, three used recuperative interval, and one used both interpregnancy and recuperative interval as measures of birth spacing. Conflicting results were found for the association between birth spacing and maternal an-

thropometric outcomes. Four studies reported a positive association between birth spacing and maternal anthropometric outcomes. Greene and colleagues (1988) and Merchant, Martorell, and Haas (1990a) found that long interpregnancy or recuperative intervals were associated with greater weight gain between pregnancies or with greater maternal anthropometric measures. Merchant, Martorell, and Haas (1990b) and Khan, Chien, and Khan (1998) reported that short recuperative or birth intervals were significantly associated with reduced maternal fat stores or with a negative change in postpartum maternal weight and body mass index.

One study reported an increased risk of obesity associated with longer interpregnancy intervals (Herman and Yu 1997), whereas another (Farahati, Bozorgi, and Luke 1993) found that differences in interpregnancy interval were not associated with higher postpartum weight or subsequent pregravid weight. Miller and Huss-Ashmore (1989) found no significant association between birth interval and either body mass index or triceps skinfold. Contrary to expectations, mothers with birth intervals of 12–17 months had lower arm muscle area than mothers with birth intervals shorter than 12 months. Two other studies reported mixed results. Pebley and DaVanzo (1993) reported that short recuperative intervals were associated with lesser weight gain during pregnancy, although they were not associated with preconception weight for height. Short interpregnancy intervals were associated with greater preconception weight for height, contrary to expectations. Winkvist and colleagues (1994) found that in malnourished and marginally nourished women, periods of moderate reproductive stress (breast-feeding duration or overlap of breastfeeding and pregnancy) were associated with weight loss, but periods of high reproductive stress were associated with weight gain. In well-nourished women, slight weight gain was found across the reproductive cycle. These results suggest that maternal nutritional status at conception influences how nutrients are partitioned between the mother and the fetus. In severe deficiencies, maternal nutrition is given preference, whereas in a marginal state, the fetus is favored (King 2003).

Seven studies evaluated the relationship between interpregnancy or birth intervals and maternal anemia, hemoglobin concentration, or iron deficiency (Khan, Chien, and Khan 1998; Singh, Fong, and Arulkumaran 1998; Conde-Agudelo and Belizan 2000; Dairo and Lawoyin 2004; Pathak et al. 2004; Razzaque et al. 2005; Uche-Nwachi et al. 2010). One study controlled for prophylactic iron supplementation during pregnancy (Singh, Fong, and Arulkumaran 1998). The seven studies yielded

conflicting results. Two reported an association between interpregnancy intervals shorter than 6 months (Conde-Agudelo and Belizan 2000) and birth intervals shorter than 24 months (Dairo and Lawoyin 2004) and increased risk of anemia during pregnancy. Three studies found no significant association between interpregnancy or birth interval and anemia (Singh, Fong, and Arulkumaran 1998; Razzaque et al. 2005; Uche-Nwachi et al. 2010). The study by Razzaque and colleagues reported that anemia was diagnosed on a clinical basis but not by laboratory test. The sixth study (Pathak et al. 2004) reported no association between interpregnancy intervals shorter than 30 months and serum ferritin levels after 28 weeks of gestation. In the remaining study (Khan, Chien, and Khan 1998), birth interval was not associated with change in hemoglobin levels recorded at 48 hours after delivery over two consecutive pregnancies.

Only one study reported data on the association between serum concentrations of several micronutrients and interpregnancy intervals. Pathak and colleagues (2004) evaluated the risk of deficiency of several micronutrients (zinc, magnesium, copper, ferritin, and folate) according to interpregnancy interval in 283 pregnant women in a rural area of India. Univariate analysis revealed that women with intervals shorter than 30 months were 2.1 times more likely than primiparous women to develop folic acid deficiency (95 percent confidence interval [CI]: 1.1–4.1) and magnesium deficiency (CI: 1.2–3.7). Nevertheless, in the multivariate analysis, which took into account parity, socioeconomic status, education, and pregnancy duration as confounding factors, no relation was found between an interpregnancy interval shorter than 30 months and deficiency of either folate or magnesium. This study examined only two categories of interpregnancy intervals, thus precluding evaluation of the relationship between micronutrient deficiencies and shorter intervals such as less than 6, 6–11, 12–17, 18–23, or 24–29 months.

In summary, the studies that evaluated the effects of birth spacing on maternal anthropometric status, anemia, and micronutrient status did not provide clear evidence to support the maternal nutritional depletion hypothesis.

Folate Depletion

Smits and Essed (2001) hypothesized that the excess risk of adverse pregnancy outcomes after short intervals could be attributed to insufficient repletion of maternal folate resources. In pregnant women not taking folic acid supplements, maternal serum and erythrocyte concentrations of folate decrease from the fifth month of pregnancy

onward and remain low for several months after delivery. In breastfeeding women, the drain on maternal folate reserves continues after delivery. Folate concentration in breast milk increases as lactation progresses, at the expense of maternal tissue store (Butte, Calloway, and Van Duzen 1981). The effects of short interpregnancy intervals on pregnancy outcomes may therefore be greater among breastfeeding women, especially if they do not replenish folate resources during the interpregnancy interval or early pregnancy. According to this theory, if a new pregnancy starts before complete folate restoration, the woman will be at higher risk of maternal folate deficiency and subsequent adverse perinatal outcomes such as low birthweight, preterm birth, and small for gestational age.

To test the folate depletion hypothesis, the first step is to assess whether folate deficiency occurs during the postpartum period. Seventeen studies (13 cohort and 4 randomized controlled trials) examined maternal folate levels during the postpartum period, mainly in lactating women. Twelve studies were conducted in developed countries and five in developing countries. Fourteen studies (ten in developed countries and four in developing countries) reported low serum or erythrocyte folate levels during any stage of the postpartum period (4 weeks to 12 months). Three studies (two in developed countries and one in a developing country) did not find folate depletion during the postpartum period. Across the ten studies that evaluated folate concentrations up to three months postpartum, 9 percent to 27 percent of women supplemented with folate and 38 percent to 64 percent of unsupplemented women had low serum or erythrocyte folate levels. At four months postpartum, one study reported low serum folate levels in 73 percent of women; another did not find deficiency. One study reported that at six months postpartum, 45 percent of women had low serum folate levels. At seven months postpartum, one study reported that no women had low serum folate levels. At nine months postpartum, one small study reported that all 16 women with inadequate diets unsupplemented with folate had low serum folate levels. Two other studies did not find folate deficiency in any women at nine months postpartum. Another study reported that mean erythrocyte folate levels decreased 23 percent from the first four months postpartum to 12 months postpartum.

The second step for testing the folate depletion hypothesis is evaluating the association between birth spacing and maternal folate status. Two studies assessed serum maternal folate levels according to interpregnancy interval. Pathak and colleagues (2004) did not find an association between interpregnancy intervals shorter than

30 months and folic acid deficiency after 28 weeks of gestation. Megahed and Taher (2004) determined serum and erythrocyte folate levels as well as serum homocysteine and vitamin B₁₂ levels in 50 healthy pregnant women following a live birth (half with a previous interpregnancy interval of six months or less, and half with a previous interval of 18–24 months) and compared them with 25 healthy nonpregnant women. The mean erythrocyte and serum folate levels were significantly lower among women with short interpregnancy intervals (six months or less) than among women with interpregnancy intervals of 18–24 months ($p = 0.002$ for erythrocyte folate levels and $p < 0.00001$ for serum folate levels). No statistically significant differences in mean serum vitamin B₁₂ and homocysteine levels were found between women with short interpregnancy intervals and women with interpregnancy intervals of 18–24 months.

The third step for testing the hypothesis was performing a population-based study to assess whether use of folic acid supplements prior to conception mitigates the unfavorable effects of short interpregnancy intervals on birth weight and the risk of small for gestational age (van Eijsden et al. 2008). This study's population consisted of 3,153 pregnant Dutch women classified as either "early users" of folic acid (supplementation began before conception), "late users" (supplementation began after conception), or "nonusers" (no folic acid supplementation). Univariate and multivariate regression analyses were performed to estimate the association of interpregnancy interval as a categorical variable with term birth weight and small for gestational age. Models were adjusted for maternal physiologic, obstetric, lifestyle, and sociodemographic characteristics. To specifically test the folate depletion hypothesis, a multivariate regression analysis was performed to evaluate the mitigating influence of folic acid supplementation in the three strata described above. Overall, each one-month increase in the interpregnancy interval (from 1–24 months) was associated with an increase in birth weight of 63 ± 20 g and, correspondingly, a decrease in small for gestational age risk of approximately 40 percent (OR: 0.61; CI: 0.46–0.82). In line with the folate depletion hypothesis, the study found a dose-dependent mitigating effect of folic acid supplementation on the relationship of interpregnancy interval with birth weight and small for gestational age. Stratified analysis showed that, in both early and late supplement users, the association between interval and birth weight or small for gestational age no longer existed. The change in birth weight per one-month increase in interpregnancy interval was a decrease of 6 ± 34 g for early users ($p = 0.861$) and an increase of 34 ± 36 g for late users

($p = 0.347$). The corresponding OR for small for gestational age was 1.28 (CI: 0.58–2.84) for early users and 0.83 (CI: 0.48–1.44) for late users. In contrast, the study found a significant birth weight increase for nonusers of 165 ± 40 g ($p < 0.001$) per one-month increase in interpregnancy interval, with a corresponding decrease in small for gestational age risk of 62 percent (OR: 0.38; CI: 0.24–0.60). The authors concluded that folate depletion contributes to the excess risk of fetal growth restriction associated with short interpregnancy intervals. The results of this study could be explained by maternal characteristics associated with supplement use or by the concurrent intake of other micronutrients relevant to fetal growth, although study authors reported that 65 percent of women were single supplement users.

Strong evidence exists that folate depletion occurs in women during the first three to four months postpartum, and growing evidence supports the hypothesis that this depletion constitutes a hypothetical causal mechanism that explains the increased risk of adverse perinatal outcomes in women with short interpregnancy intervals.

Cervical Insufficiency

Based on meta-analysis of birth spacing and adverse perinatal outcomes (Conde-Agudelo, Rosas-Bermudez, and Kafury-Goeta 2006), evidence indicates that interpregnancy intervals shorter than 18 months are associated with increased risk of preterm birth. Haaga (1988) proposed that inadequate time to regain muscle tone in reproductive tissues after a pregnancy might lead to increased incidence of cervical insufficiency (formerly called cervical incompetence) toward the end of the next pregnancy, resulting in increased incidence of preterm birth. Cervical insufficiency is described as the inability of the uterine cervix to retain a pregnancy in the absence of contractions or labor. It is generally attributed to a structural weakness of the cervix (Ludmir and Sehdev 2000). Strong evidence suggests that cervical insufficiency is a cause of spontaneous preterm birth (Romero et al. 2006). We found no studies evaluating the risk of cervical insufficiency according to interpregnancy or birth intervals. Nonetheless, a study by Sundtoft, Sommer, and Uldbjerg (2010) evaluated the normalization of the cervical collagen after labor, taking into account that a prerequisite for vaginal delivery is a decrease in the cervical collagen concentration. Cervical biopsies were collected from 15 women at 3, 6, 9, 12, and 15 months after spontaneous delivery. Collagen concentration in cervical tissue increased until 12 months after delivery: $50.2 \mu\text{g}/\text{mg}$ dry weight at 3 months, $57.9 \mu\text{g}/\text{mg}$ at 6 months, $61.9 \mu\text{g}/\text{mg}$ at 9

months, and $65.2 \mu\text{g}/\text{mg}$ at 12 months. These differences in cervical collagen concentration were statistically significant. The investigators concluded that the human uterine cervix is not normalized until 12 months after spontaneous delivery, and suggested that the lower cervical collagen concentrations could explain the association between short interpregnancy interval and preterm birth.

A short cervical length (less than 2.5 cm in most studies) increases the risk of preterm birth, with increments proportional to decreasing length (Iams et al. 1996). The finding of a shortened cervix on transvaginal sonography is often considered equivalent to cervical insufficiency. This is particularly true if there is no vaginal bleeding or symptomatic contractions. Our search found no studies assessing the risk of short cervix according to interpregnancy or birth intervals.

Emerging evidence supports the hypothesis that cervical insufficiency could be one of the factors responsible for the association between short intervals and increased risk of preterm birth.

Vertical Transmission of Infections

Maternal infections are associated with increased risk of adverse perinatal outcomes such as preterm birth, fetal growth restriction, low birth-weight, neonatal morbidity, and fetal and neonatal death (Goldenberg, Culhane, and Johnson 2005). Adverse perinatal outcomes associated with maternal infections can occur because of direct infections of the fetus or neonate, or because of infections that cause early delivery without directly involving the fetus. For organisms that attack the fetus directly, transmission may occur within the uterus via transplacental or ascending infection, or in the intrapartum period secondary to fetal contact with infected genital secretions or maternal blood (vertical transmission).

Pregnant women who are colonized with a wide variety of bacterial, fungal, protozoan, or viral organisms may continue to carry the organism for several weeks to months after delivery. Thus, unrecognized or recognized preconceptional maternal infection could pose a persistent risk. Women infected months before pregnancy may harbor the organism at a site from which the newly conceived fetus can be infected. Theoretically, the risk to the fetus or newborn of transmission of persistent maternal infections would be increased among women with short intervals between pregnancies. Based on these concepts, we have hypothesized that vertical transmission of infections could be an additional causal mechanism by which short intervals are associated with adverse perinatal and neonatal outcomes. We found two studies (Fowler, Stag-

no, and Pass 2004; Cheng et al. 2008) that examined this hypothesis, although only one met minimal inclusion criteria (Cheng et al. 2008).

Fowler, Stagno, and Pass (2004) evaluated the effect of the interval between births on the risk of congenital cytomegalovirus (CMV) infection. Women in whom CMV seroconversion occurred within two years of pregnancy (as determined by analysis of cord serum samples obtained during two successive deliveries; $n = 142$) had a four-fold higher risk of delivering a congenitally infected baby than did mothers whose prior pregnancy occurred more than two years before the most recent pregnancy (RR: 3.8; CI: 1.6–9.0). Assuming that the risk of exposure to CMV was equally distributed over time, this suggests that infection during the two years before conception poses a risk for the fetus. Immune mothers who delivered less than 24 months apart also had a two-fold greater risk of delivering an infant with congenital CMV infection, compared with seropositive mothers who delivered more than 24 months apart (RR: 2.3; CI: 1.1–4.8). Unfortunately, this study did not adjust for major confounding factors in the association between short intervals and CMV infection such as maternal age, race, and socioeconomic status.

Cheng and colleagues (2008) assessed maternal risk factors for recurrence of group B streptococci (GBS) colonization in a subsequent pregnancy. This cohort study included 251 women who had documented vaginal or rectal GBS colonization during an index pregnancy and then had a subsequent pregnancy. Multivariate regression models showed that women with birth intervals shorter than 12 months were 60 percent more likely to have recurrent GBS colonization than women with intervals longer than 36 months (adjusted RR: 1.6; CI: 1.1–2.4). Although the authors of the study did not provide data on perinatal outcomes, the higher risk of recurrent GBS colonization associated with short intervals may lead to increased risk of early-onset neonatal infection.

In conclusion, emerging evidence supports the hypothesis that the association between short intervals and adverse perinatal outcomes could also be mediated by vertical transmission of infections.

Suboptimal Lactation Related to Breastfeeding–Pregnancy Overlap

Breastfeeding–pregnancy overlap is defined as the continuation of breastfeeding into the first, second, or even third trimester of pregnancy. Several studies have shown that this practice is widespread in many countries around the world (Cantrelle and Leridon 1971; Huffman et al. 1980; Bracher and Santow 1982; Merchant, Martorell, and

Haas 1990a; Boerma and Bicego 1992). Boerma and Bicego (1992) reported that, in most countries, overlap between pregnancy and breastfeeding was more common for short birth intervals than for intervals of 24–35 months and rare for intervals longer than 35 months. When births are closely spaced, overlap of breastfeeding with pregnancy is more prevalent, which could affect the breastfeeding of the newborn. Consequently, short intervals could indirectly increase the risk of adverse neonatal/infant outcomes through changes in breastfeeding patterns or the composition and/or quantity of breast milk secondary to breastfeeding–pregnancy overlap.

Two studies from Peru examined the effects of breastfeeding–pregnancy overlap on neonatal outcomes (Marquis et al. 2002 and 2003). In these studies, no maternal nutritional supplement was provided. One study reported that at one month postpartum the intakes per feeding tended to be lower among infants whose mothers breastfed during the last trimester of pregnancy (Marquis et al. 2002). After controlling for confounders, the authors found that breastfeeding during late pregnancy was also associated with a decrease in one-month weight gain. In fact, infants whose mothers breastfed during pregnancy gained 125 grams less (CI: 8–241) than infants whose mothers did not (about 15 percent of mean weight gain). The study noted that a sustained 15 percent decline in expected weight gain would move an infant born at the 50th percentile to below the 25th percentile of weight-for-age by six months of age.

The second Peruvian study examined the effects of breastfeeding–late pregnancy overlap on breast milk composition and neonatal morbidity (Marquis et al. 2003). Overall, breastfeeding–pregnancy overlap was associated with change in breast milk composition that affects immunity properties. On day two postpartum, the lysozyme concentration among nonbreastfeeding mothers during pregnancy was almost 30 percent greater than that of the overlap group. It was also reported that lactoferrin concentration was 23 percent lower in mothers who breastfed during the last trimester of pregnancy. Additionally, at one month postpartum, the Immunoglobulin A intake was 25 percent lower among infants whose mothers breastfed during pregnancy. This study found that breastfeeding–pregnancy overlap was not associated with an increased risk of diarrhea, but infants whose mothers breastfed during late pregnancy were five times as likely to have a cough for at least seven days, compared with infants whose mothers did not breastfeed during pregnancy (CI: 1.8–14.1). A recent study in Egypt (Ismail et al. 2009) also found changes in the breast milk composition of lactating pregnant women, compared with that of lactating nonpregnant

women. Total solids, fat, lactose, and ash contents were lower in the breast milk of lactating pregnant mothers, which meant the milk was more watery and had less nutrient content. The breast milk of lactating pregnant mothers had higher levels of sodium and lower levels of calcium and potassium.

Merchant, Martorell, and Haas (1990b) evaluated the association between breastfeeding–pregnancy overlap and birth weight in Guatemala. Pregnancies ($n = 504$) were divided into two groups based on time of weaning the previous child: “no overlap” ($n = 251$) if the previous child was weaned two weeks or less after the date of conception, and “overlap” ($n = 253$) if the previous child was weaned more than two weeks after the date of conception. The “no overlap” group was divided into two subgroups: “long recuperative interval” if the previous child was weaned more than six months before conception ($n = 110$), and “short recuperative interval” if the previous child was weaned within six months before conception ($n = 141$). The “overlap” group was divided into a “short overlap” subgroup (if the previous child was weaned during the first trimester of pregnancy ($n = 141$) and a “long overlap” subgroup (if the previous child was weaned during the second or third trimester of pregnancy [$n = 112$]). No statistically significant difference was found in mean birth weight between the “overlap” and “no overlap” groups. The mean birth weight decreased, however, across the four subgroups as the postulated energetic stress increased ($3,204 \pm 470$ g for the subgroup with a long recuperative interval, $3,120 \pm 466$ g for the subgroup with a short recuperative interval, $3,105 \pm 458$ g for the subgroup with a short overlap, and $3,089 \pm 457$ g for the subgroup with a long overlap). The study found this trend to be nearly statistically significant ($p = 0.10$). During the study, mothers received a nutritional supplement that was available freely and conveniently between meals each day of the eight-year study period. Primary health care was also free and available. This study did not evaluate neonatal outcomes.

Although we did not identify any studies that specifically evaluated suboptimal lactation related to the breastfeeding–pregnancy overlap hypothesis for explaining the association between short intervals and neonatal/infant health, some evidence presented above supports this hypothetical causal mechanism.

Sibling Competition

Some researchers have suggested that the relationship between short interpregnancy or birth intervals and infant and child mortality may be explained by sibling compe-

tition, which may interact with other proposed mechanisms such as the transmission of infectious diseases among closely spaced siblings. If two or more young children within a family are close in age, they may compete for resources and for parental care and attention.

We examined the sibling competition hypothesis through studies that evaluated the effects of short preceding or subsequent intervals on infant and child mortality according to survival of the preceding or index child. The survival status of the preceding sibling is a potential confounding factor that has a direct effect on length of interpregnancy interval. When the elder of a sibling pair dies in infancy, the interval to the next birth will tend to be shortened by involuntary cessation of breastfeeding leading to early resumption of ovulation and/or a desire to replace the deceased child. Hence, a spurious association may be found between short preceding birth intervals and survival of the younger of the sibling pair.

Seventeen cross-sectional studies evaluated the association between interpregnancy or birth interval and the risk of any mortality that occurred during the five years following the birth, according to survival of the previous sibling. Thirteen of the studies were conducted in developing countries and four in developed countries. Six studies provided data on neonatal mortality, eight on post-neonatal mortality, nine on infant mortality, three on child mortality, and one on mortality at less than five years of age. Eleven studies provided data on more than one outcome. Eight studies were considered high quality. Only three controlled for the effects of gestational age at delivery. The most common shortcomings were the inconsistent characterization of interval categories, the failure to report losses to follow-up or exclusions, and, among studies evaluating neonatal mortality, the nonuse of interpregnancy interval or the lack of control for the effects of pregnancy duration.

Among the six studies that provided data on the association between preceding short birth intervals and the increased risk of neonatal mortality, three reported that the association was stronger when the preceding sibling died than when she/he survived, one reported that the association was stronger when the preceding sibling survived than when she/he died, and two reported that preceding child survival status did not alter the effects of short intervals on neonatal mortality. With regard to studies that reported data on the association between short birth intervals and increased risk of post-neonatal death, four found that the association was stronger when the preceding sibling survived than when she/he died, one found the association was stronger when the preceding sibling died, and three found that preceding child survival status did not alter the effects of short intervals

on post-neonatal mortality. Among the studies providing data on the association between preceding short birth intervals and the increased risk of infant mortality, five reported that the association was stronger when the preceding sibling died than when she/he survived, two reported that the association was stronger when the preceding sibling survived, and two reported that preceding child survival status did not alter the effects of short intervals on infant mortality. With regard to studies providing data on the association between preceding short birth intervals and the increased risk of child and under-five-years mortality, two found that the association was stronger when the preceding sibling died than when she/he survived, one found that the association was stronger when the preceding sibling survived, and one found that preceding child survival status did not alter the effects of short intervals on neonatal mortality. Swenson (1978) reported that, irrespective of the survival of the younger sibling for at least one year, subsequent interpregnancy intervals shorter than 12 months were associated with increased risk of early childhood mortality in the older sibling.

In conclusion, although the results are conflicting, they suggest that the effects of preceding short birth intervals on neonatal and infant mortality seem to be stronger when the preceding sibling dies than when she/he survives. This finding suggests that neither competition nor transmission of infectious diseases among siblings is the main mechanism by which short birth intervals may affect neonatal and infant mortality. The effects of preceding short birth intervals on post-neonatal mortality seem to be stronger when the preceding sibling survives than when she/he dies, which is consistent with both the sibling competition hypothesis and the hypothesis of transmission of infectious diseases among siblings. Evidence regarding the effects of preceding short birth intervals on child and under-five-years mortality according to survival status of the preceding sibling is inconclusive.

Transmission of Infectious Diseases among Siblings

The association between short interpregnancy intervals and infant and child mortality could also be explained by an increased exposure to infectious diseases suffered by the younger child. Closely spaced children would thereby be more likely to transmit infectious disease to one another because the chances of exposure are greater if more than one child of susceptible age is present in the household (Swenson 1978). The older sibling of a short in-

terpregnancy interval reaches an age at which infectious diseases are particularly prevalent (around two years) just as the younger infant is particularly vulnerable (because immunity acquired from the mother has declined but the infant has not yet fully acquired his/her own). Additionally, secondary cases of disease have frequently been shown to be severe, and the younger child of the interval is usually the secondary case of infection.

We found evidence that short birth intervals are associated with increased risk of worm infestation, respiratory infection, and gastroenteritis (Kumar, Qureshi, and Mathur 1976; Ahmad et al. 1982; Böhler and Bergström 1995). Furthermore, the presence of several young siblings in the home (often evidence of short birth intervals) increases the exposure of infants to measles, gastrointestinal diseases, and herpes (Haaga 1988; Zerr et al. 2005) and increases the severity of infections when two or more siblings are sick simultaneously (Aaby et al. 1983). We found only two studies that evaluated the transmission of infections among siblings according to birth interval. In a longitudinal study of 2,082 children aged 3–35 months from a rural area of Zaire, Manun'ebo and colleagues (1994) reported that short birth intervals were associated with an increased risk of diarrhea. Goodman and Correa (2000) studied the transmission of *H. pylori* among 684 children aged 2–9 years in rural Colombia, adjusting for hygiene-related exposures, socioeconomic indicators, and number of children in the household. They found that, compared with children born ten or more years after the next-older sibling, those born within four years were 4.1 times more likely to be infected with *H. pylori* (CI: 2.0–8.6). The study reported that *H. pylori* infection was transmitted most frequently from older to younger siblings.

In summary, some evidence indicates that transmission of infectious diseases among siblings could explain the association between short intervals and the increased risk of infant and child mortality.

Incomplete Healing of the Uterine Scar from Previous Cesarean Delivery

Strong and consistent evidence shows that short intervals are associated with increased risk of uterine rupture in women who attempt a vaginal birth after cesarean delivery (Conde-Agudelo, Rosas-Bermudez, and Kafury-Goeta 2007; Stamilio et al. 2007; Bujold and Gauthier 2010; Landon 2010). The main hypothesis to explain this association is incomplete healing of the uterine scar from a previous cesarean delivery. One ultrasonographic study evaluated the healing of the uterine scar from a

previous cesarean section according to interpregnancy intervals. Ait-Allah, Abdelmonem, and Rasheed (2009) published the results of a cohort study that evaluated the impact of interpregnancy interval on ultrasonographic measurement of lower uterine segment at 36 weeks of gestation in 90 women with a singleton pregnancy and previous cesarean section. A thickness of less than 3 mm was considered abnormal. The sonographic measurement of the thickness of the lower uterine segment has been considered a reliable method for determining the strength of the scar from the previous cesarean delivery. A thickness less than 3 mm was found in 69 percent (9 of 13) of women with an interpregnancy interval shorter than 6 months, in 26 percent (7 of 27) of women with interpregnancy intervals of 6–12 months, and in 10 percent (5 of 50) of women with interpregnancy intervals longer than 12 months. The difference between interpregnancy intervals of less than 6 months and greater than 12 months was statistically significant ($p = 0.0011$). The study concluded that an interpregnancy interval greater than 6 months after a cesarean section can be considered safe for pregnancy and that safety increases with intervals greater than 12 months.

Dicle and colleagues (1997) examined the healing period of the incision scar in the myometrial wall after cesarean section by means of magnetic resonance imaging (MRI). Seventeen women were examined in the early postpartum period (the first five days) after their first delivery by cesarean section, and were examined three more times in three-month intervals. During follow-up examinations, incision scar tissues lost their signals within the first three months, and zonal anatomy of the uterus reappeared completely six months after the cesarean section. The study concluded that the maturation time of myometrial scar tissue in an uncomplicated cesarean section is approximately three months, whereas the complete restoration of uterine anatomy required at least six months and possibly nine. Mareeva, Levashova, and Mil'man (1989) assessed uterine scarring in 32 women one year after cesarean section by using hysteroscopy and found complete muscularization (normal uterine scarring) in 18 cases, partial replacement of muscular tissue by connective-tissue elements in 8 cases, and full replacement of muscularization (abnormal uterine scarring) in 6.

Radiographic and hysteroscopic evidence indicates that incomplete healing of the uterine scar from a previous cesarean delivery could explain the association between short intervals and the increased risk of uterine rupture in women who attempt a vaginal birth after cesarean delivery.

Abnormal Process of Remodeling of Endometrial Blood Vessels

Irrespective of the method of delivery in a preceding birth, emerging evidence indicates that short interpregnancy intervals are associated with an increased risk of placenta previa and abruption placenta (Conde-Agudelo, Rosas-Bermudez, and Kafury-Goeta 2007). Additionally, Wax and colleagues (2000) reported increased risk of abnormally adherent placentas (placenta accreta, increta, and percreta) among pregnancies with short cesarean-to-conception intervals. Conde-Agudelo and Belizan (2000) postulated that a short interval between pregnancies might interfere with the normal processes of remodeling of endometrial blood vessels after delivery with subsequent uteroplacental underperfusion, thereby increasing the likelihood for placental abruption and placenta previa. We did not find studies that assessed this hypothesis.

Women's Physiological Regression

Interpregnancy intervals longer than five years are associated with an increased risk of adverse perinatal outcomes, such as preterm birth, low birth-weight, small for gestational age (Conde-Agudelo, Rosas-Bermudez and Kafury-Goeta 2006), and preeclampsia (Conde-Agudelo, Rosas-Bermudez, and Kafury-Goeta 2007). A large cross-sectional study (Zhu et al. 2006) reported that risk of labor dystocia was associated with the interpregnancy interval in a dose-response fashion. The association between long interpregnancy interval and labor dystocia was stronger for functional dystocia than for mechanical.

Zhu and colleagues (1999) proposed the women's physiological regression hypothesis for explaining the relationship between long interpregnancy intervals and adverse perinatal outcomes. According to this hypothesis, the mother's physiological processes are primed for fetal growth during pregnancy and decline gradually after delivery. The benefit gained during pregnancy declines gradually postpartum if the mother does not become pregnant again. The physiological regression hypothesis is supported by the observation that perinatal outcomes for infants conceived after a long interpregnancy interval are similar to outcomes of infants born to primigravid women. These researchers also proposed the women's physiological regression hypothesis to explain the association between long interpregnancy interval and labor dystocia. Accordingly, the pregnancy may physiologically prepare and optimize the growth-supporting capacities of the mother. After delivery, the mother may gradually lose the childbearing capacities developed dur-

ing the preceding pregnancy and become physiologically similar to a primigravida woman if another pregnancy is not timely conceived.

The effect of long intervals on the risk of preeclampsia is independent of advanced maternal age and change of partner, variables that may confound or modify this association. A large study from Latin America (Conde-Agudelo and Belizan 2000) found the rate of preeclampsia among nulliparous women was similar to that of parous women who conceived five or more years after a previous birth (6.5 percent versus 6.6 percent, respectively). Parous women with long intervals are similar to nulliparous women with regard to risk of preeclampsia, suggesting that the protective effect for preeclampsia acquired by a woman through a previous birth is lost after a long interval. We did not find studies that evaluated the women's physiological regression hypothesis for explaining the association between long interpregnancy intervals and adverse perinatal outcomes, preeclampsia, and labor dystocia.

Discussion

The results of our review indicate that, overall, no clear evidence exists for explaining the mechanisms through which both short and long intervals between pregnancies are associated with increased risk of adverse maternal, perinatal, infant, and child outcomes. In summary, we found: growing evidence supporting the "folate depletion" and "incomplete healing of the uterine scar from the previous cesarean delivery" hypotheses; emerging evidence supporting the "vertical transmission of infections" and "cervical insufficiency" hypotheses; limited evidence supporting the "maternal nutritional depletion," "sub-optimal lactation related to breastfeeding-pregnancy overlap," and "transmission of infectious diseases among siblings" hypotheses; conflicting evidence supporting the "sibling competition" hypothesis (because it could be the main mechanism for explaining the negative effects of short birth intervals on postneonatal mortality but not on both neonatal and infant mortality); and no evidence supporting the "abnormal process of remodeling of endometrial blood vessels" and "women's physiological regression" hypotheses.

The maternal nutritional depletion hypothesis has been widely used to explain the association between short intervals and adverse maternal, perinatal, infant, and child outcomes. The study of these associations has provided only indirect evidence for the existence of maternal nutritional depletion, however, because in this

conceptualization maternal nutrition is simply assumed to be a mediating variable (Winkvist, Rasmussen, and Habicht 1992). We found a few studies that investigated the effect of birth spacing on maternal nutrition. Taken as a whole, the findings of our systematic review provide no clear evidence to support the validity of the maternal nutritional depletion hypothesis. Our results were similar to those reported by a systematic review of the effects of birth spacing on maternal nutritional status (Dewey and Cohen 2007). Recently, DaVanzo and colleagues (2008) provided indirect evidence to support the validity of the maternal nutritional depletion hypothesis. In fact, their large study conducted in Bangladesh found that very short inter-outcome intervals were generally more detrimental when following a live birth or stillbirth than when following a preceding miscarriage or induced abortion. Because of their longer gestation, live births and stillbirths should be more depleting than miscarriages or induced abortions. Moreover, the breastfeeding that follows a live birth would lead to further maternal depletion.

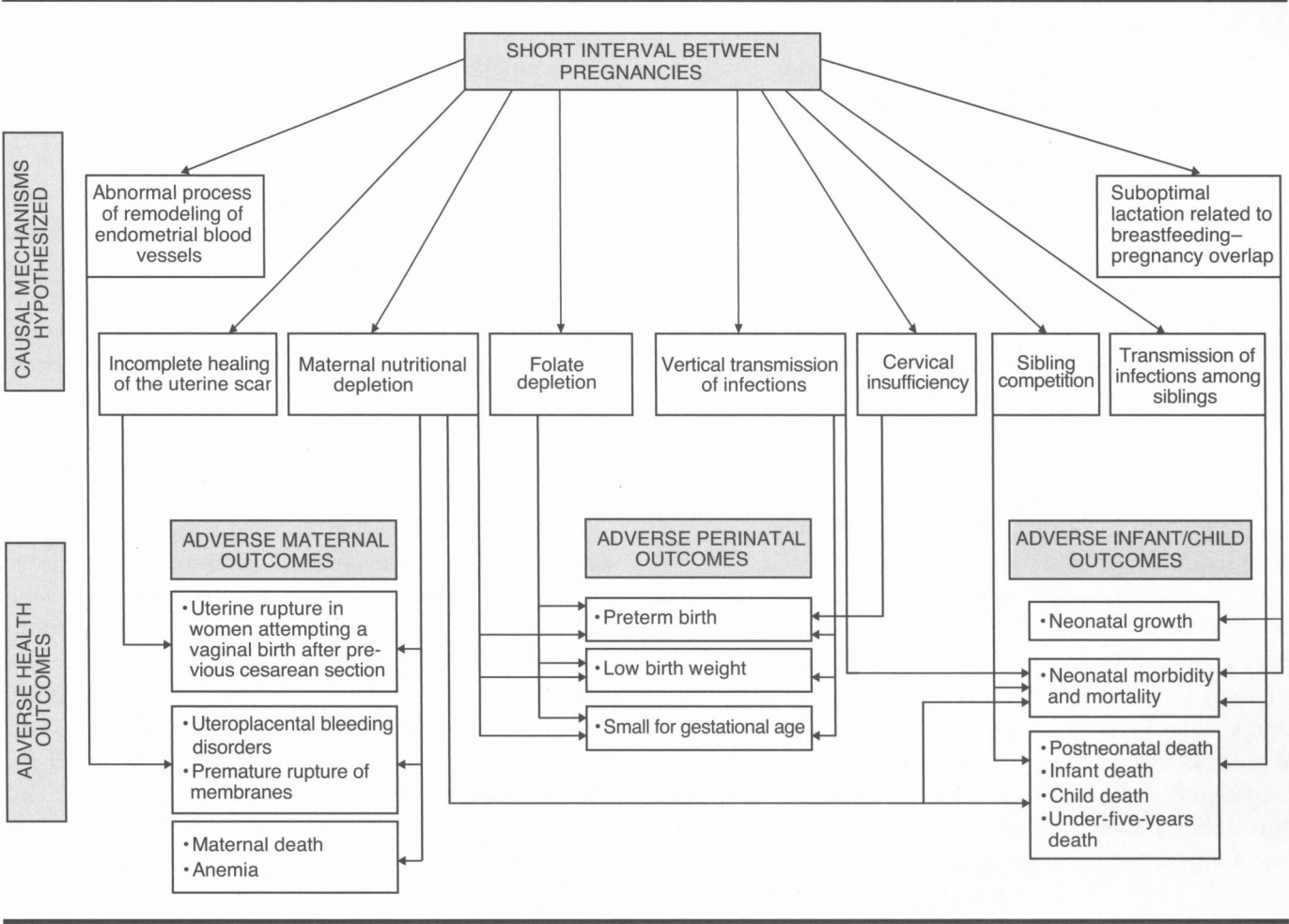
The maternal folate depletion hypothesis states that folate depletion is a major contributor to the excess risk of adverse pregnancy outcomes after short interpregnancy intervals. Some evidence indicates that low folate levels during the second and third trimesters are associated with an increased risk of preterm birth (Martí-Carvajal et al. 2004; Siega-Riz et al. 2004; Bodnar et al. 2010). Folate deficiency, through its contribution to the development of hyperhomocysteinemia, could also lead to weakening of the connective tissue by preventing collagen cross-linking. This weakening could cause preterm premature rupture of membranes and, thus, preterm delivery (Ferguson, Smith, and Walker 2001). Recently, van Eijsden and colleagues (2008) reported a dose-dependent mitigating effect of folic acid supplementation on the relationship between short interpregnancy intervals and birth weight and small for gestational age, supporting the idea that the link could be mediated by folate depletion. On the other hand, of the two studies that assessed serum maternal folate levels according to interpregnancy interval, one did not find an association between short intervals and folic acid deficiency (Pathak et al. 2004), whereas the other (Megahed and Taher 2004) found that mean erythrocyte and serum folate levels were significantly lower among women with short interpregnancy intervals than among women with interpregnancy intervals of 18–24 months.

The mechanisms by which short birth intervals may affect children's survival have been the subject of much speculation but little research. According to the present study, it appears that some factors are significantly asso-

ciated with mortality risk in the neonatal period, whereas others are important in the postneonatal period. This reflects changes in the relative importance of biological and behavioral factors in determining the mechanism by which short intervals are associated with increased risk of infant and child mortality. Our finding that the survival of the preceding sibling leads to increased effects of short intervals on postneonatal mortality suggests that competition and/or transmission of infectious diseases among siblings are the main mechanisms for explaining this association. In the postneonatal period, the death of the previous sibling reduces the impact of short intervals on the mortality risk for the index child, suggesting that the removal of competition for resources reduces the risk of competition and/or transmission of deadly diseases among siblings. On the other hand, the finding that the effects of preceding short birth intervals on neonatal mortality seem to be stronger when the preceding sibling dies

than when she/he survives could indicate that competition and/or transmission of infectious diseases among siblings are not significant pathways in this relationship, and suggests that part of the association between short intervals and neonatal mortality could result from increased intrafamilial mortality risks. Families that have a high probability of repeating neonatal deaths may have behavioral or social (child-care practices, health care, or mother's personal abilities) or biological (maternal propensity to low birth-weight and prematurity, or genetic) risk factors. The combination of the adverse effect of a short interval and the increased familial risk would increase the risk of neonatal mortality associated with these factors. Some authors (Cleland and Sathar 1984; Nault, Desjardins, and Légaré 1990; DaVanzo et al. 2008) have postulated that, regardless of the survival status of the preceding sibling, maternal nutritional depletion is the primary mechanism responsible for the adverse effects of

Figure 1 Hypothetical causal mechanisms proposed for the association between short interpregnancy or birth or recuperative intervals and the increased risk of adverse maternal, perinatal, infant, and child outcomes



short intervals on infant and child survival through the increased risk of low birth-weight, prematurity, and inadequate breast milk. Nevertheless, maternal nutritional depletion effects should be weaker if the preceding sibling dies, because the physiological demands of lactation cease after the infant's death. Rutstein (2008) reported that, compared with interpregnancy intervals of 36–47 months, interpregnancy intervals shorter than 36 months were significantly associated with an increased risk of both stunting and underweight. Rutstein postulated that stunting and underweight (chronic and overall undernutrition) could be an additional pathway by which short intervals increase the risk of child mortality.

Some investigators have attributed the increased risk of adverse maternal, perinatal, infant, and child outcomes among women with short intervals to several factors associated with both short intervals and poor health outcomes, such as socioeconomic status, lifestyle, stress, and adequacy of prenatal care (Erickson and Bjerkedal 1979; Klebanoff 1999). The evidence we examined suggests that adverse health outcomes associated with both short and long interpregnancy intervals are not explained by socio-demographic, behavioral, or reproductive risk factors. In fact, large studies from developing and developed countries have reported that the association between short interpregnancy intervals and adverse pregnancy and child outcomes persists after controlling for many potential confounders (Marquis et al. 2003; Conde-Agudelo et al. 2005; Stamilio et al. 2007; DaVanzo et al. 2008; Rutstein 2008).

Based on the findings of this systematic review, we have constructed a conceptual framework (see Figure 1), which, although insufficient for generating causal inferences, provides a starting point for generating and supporting hypotheses regarding the mechanisms through which short intervals between pregnancies affect maternal, perinatal, infant, and child health. Causal mechanisms explaining these associations could vary according to the outcome and setting. Multiple causal mechanisms might explain the effects of short intervals on adverse health outcomes.

Broadening our understanding of the mechanisms by which adequate birth spacing might improve health for mothers and children is essential for the development of effective counseling protocols, policies, programs, and evidence-based interventions to address the remediable determinants of poor maternal, perinatal, and infant health. Future research should assess the validity of the maternal nutritional depletion hypothesis using the conceptual framework suggested by Winkvist, Rasmus-

sen, and Habicht (1992). Assessing changes in maternal anthropometric and micronutrient status over two or more consecutive pregnancies using the interpregnancy interval as a measure of birth spacing is necessary, after adjusting for potential confounding factors. Each woman must be used as her own control in the analyses of data from consecutive pregnancies. Studies should be conducted in populations from developed and developing countries and should distinguish between the different levels of nutritional stress within a reproductive cycle, such as during the overlap of lactation with pregnancy and the nonpregnancy/nonlactation period. More studies are needed to understand the role that breastfeeding (and its intensity) plays in the relationship between birth spacing and infant and child mortality. For example, studies might examine the extent to which the breastfeeding of one child leads to maternal depletion that has detrimental effects on the next.

Emerging evidence shows that short intervals between pregnancies are associated with an increased risk of adverse neurodevelopmental and cognitive outcomes such as autism (Cheslack-Postava, Liu, and Bearman 2011), cerebral palsy (Pinto-Martin, Cnaan, and Zhao 1998), schizophrenia (Smits et al. 2004), impaired intellectual ability (Bella et al. 2005), and school unreadiness (Hayes et al. 2006). Researchers should be encouraged to examine these associations further, to advance knowledge about causal mechanisms.

Additional studies are needed to evaluate the role of folate depletion and/or folate supplementation in explaining the association between short interpregnancy intervals and adverse perinatal outcomes such as preterm birth, small for gestational age, and congenital malformations. Moreover, the association between maternal deficiencies of other micronutrients at conception and pregnancy outcomes should be assessed. The potential joint effects of short intervals and overlap of breastfeeding and pregnancy on neonatal, infant, and child health deserves further attention. Investigating specific pathways by which familial characteristics may influence the effects of short intervals on neonatal, postneonatal, infant, and child mortality is essential for directing health interventions toward high-risk families. Studies are needed to assess the role of cervical insufficiency as a causal mechanism for the association between short intervals and preterm birth and to determine underlying mechanisms that explain the association between long intervals and increased risk of adverse perinatal outcomes, preeclampsia, and labor dystocia.

Appendix

Table A1 Characteristics of 58 studies included in systematic review, by hypothesized causal mechanism

Author/year (country)	Design/ population	Outcome and confounding variables	Main findings
Maternal nutritional depletion			
Greene et al. 1988 (US)	Cohort 7,116 women who had two pregnancies within six years	Outcome: Interpregnancy weight change Confounders: Age, parity, race, socioeconomic status, prepregnancy weight, cigarette smoking, breastfeeding, marital status, complications of pregnancy	Longer interpregnancy intervals were significantly associated with greater weight gain between pregnancies.
Miller and Huss-Ashmore 1989 (Lesotho)	Cross-sectional 873 women attending a rural clinic	Outcomes: Body mass index (BMI), triceps skinfold, arm muscle area Confounders: Parity, age, pregnancy status, socioeconomic status	Mothers with birth intervals of 12–17 months had lower arm muscle area than mothers with birth intervals < 12 months. No significant association between birth interval and body-mass index and triceps skin-fold.
Merchant, Martorell, and Haas 1990a (Guatemala)	Cohort 504 women participating in a trial of nutritional supplementation	Outcome: Thigh fatfold thickness (at 3 month intervals during pregnancy and at 3 months postpartum) Confounders: Maternal age, parity, relative measurement date, study month (similar ethnicity and socioeconomic status)	For all three trimesters of pregnancy, the mean thigh fatfold thickness for women in which the previous child was weaned ≤ 2 weeks after the date of conception of the index child (no overlap) was slightly but consistently greater than that for women in which the previous child was weaned > 2 weeks after the date of conception of the index child (overlap). After birth, mean thigh fatfold thickness was similar in both groups. Short recuperative intervals (< 6 months) resulted in reduced maternal fat stores compared to recuperative intervals ≥ 6 months.
Merchant, Martorell, and Haas 1990b (Guatemala)	Cohort 102 women with two consecutive pregnancies in which overlap (lactating while pregnant) occurred in any or both	Outcome: Thigh fatfold thickness (at 3 month intervals during pregnancy and at 3 months postpartum) Confounders: Maternal age, parity, relative measurement date, study month (similar ethnicity and socioeconomic status)	Longer recuperative intervals were associated with greater thigh fatfold thickness during first and second trimester, but not during third trimester or 3 months postpartum.
Farahati, Bozorgi, and Luke 1993 (US)	Cohort 47 nonsmoking women with three consecutive pregnancies	Outcomes: Pregravid weight in subsequent pregnancy, postpartum weight Confounders: Maternal age, prepregnancy weight, gestational age (similar socioeconomic status)	Interpregnancy intervals were not associated with pregravid weight in subsequent pregnancy or postpartum weight.
Pebley and DaVanzo 1993 (Guatemala)	Cohort 489 women (interpregnancy interval used in 227 women and recuperative interval used in 262)	Outcomes: Preconception weight for height, pregnancy weight gain Confounders: Maternal age, parity, education, energy supplementation, breastfeeding duration	Short interpregnancy intervals were associated with greater preconception weight for height. Interpregnancy intervals were not associated with pregnancy weight gain. Short recuperative interval was associated with lesser weight gain during pregnancy. Recuperative interval was not associated with preconception weight for height
Winkvist et al. 1994 (Pakistan)	Cohort 76 nonsmoking women (well-nourished = 17; marginally nourished = 38; malnourished = 21)	Outcome: Change in postpartum maternal weight Confounders: Maternal age, parity, initial maternal weight, income	In malnourished and marginally nourished women, periods of moderate reproductive stress (breastfeeding duration or overlap of breastfeeding and pregnancy) were associated with weight loss but periods of high reproductive stress were associated with weight gain. In well-nourished women a slight weight increase existed across the reproductive cycle.
Herman and Yu 1997 (US)	Cohort 43,160 women who had their first pregnancy as teenagers	Outcome: Obesity (BMI > 29.0 kg/m ²) prior to subsequent pregnancy Confounders: Maternal age, race, education, marital status, body-mass index in the first pregnancy, interpregnancy weight gain, medical risk, smoking, food stamps, Medicaid status	Long interpregnancy intervals were significantly associated with an increased risk of obesity prior to subsequent pregnancy
Khan, Chien, and Khan 1998 (Pakistan)	Cohort 278 women with two consecutive pregnancies	Outcomes: Changes in maternal postpartum hemoglobin, weight, BMI Confounders: Maternal age, parity, postpartum maternal weight at first pregnancy (similar socioeconomic status)	Shorter birth intervals were significantly associated with a negative change in postpartum maternal weight and body-mass index. Birth interval was not associated with change in hemoglobin.
Singh, Fong, and Arulkumaran 1998 (Singapore)	Cross-sectional 3,728 women delivering at university hospital	Outcome: Anemia at delivery Confounders: Age, parity, socioeconomic status, history of anemia in previous pregnancy, prophylactic iron supplementation, prenatal care onset, race, hemoglobin level at booking	Although the prevalence of anemia decreased with increasing interval, the multivariate analyses showed no significant association between interval and anemia.
Conde-Agudelo and Belizan 2000 (18 Latin American countries)	Cross-sectional 456,889 women delivering singleton infants	Outcome: Anemia during pregnancy Confounders: Age, education, marital status, prepregnancy BMI, weight gain during pregnancy, prenatal care onset, number of prenatal care visits, previous abortions, smoking, outcome of previous pregnancy, geographic area, type of hospital, year of delivery, chronic hypertension	Women with interpregnancy intervals < 6 months had higher risk for anemia than women with interpregnancy intervals of 18 to 23 months.
Dairo and Lawoyin 2004 (Nigeria)	Cohort 597 low-risk pregnant women	Outcome: Anemia during pregnancy Confounders: Age, housing, antenatal care onset, parity	Birth intervals less than 24 months were associated with increased risk of anemia.
Razaque et al. 2005 (Bangladesh)	Cross-sectional 11,122 pregnant women during third trimester	Outcome: Clinical anemia during pregnancy Confounders: Age, gravidity, previous pregnancy losses, education, household space, religion	No significant association between interpregnancy interval and clinical anemia.

(continued)

Table A1 (continued)

Author/year (country)	Design/population	Outcome and confounding variables	Main findings
Uche-Nwachi et al. 2010 (Trinidad and Tobago)	Cross-sectional 2,287 pregnant women	Outcome: Anemia during pregnancy Confounders: Age, parity, race, socioeconomic status, chronic infections, chronic renal disease, dietary differences, bleeding or hemoglobin disorders, eating disorders, substance abuse, marital status, occupation, religion	No association between birth intervals less than 24 months and anemia.
Maternal nutritional depletion and folate depletion			
Pathak et al. 2004 (India)	Cross-sectional 283 pregnant women with gestational age > 28 weeks	Outcome: Serum levels of zinc, copper, magnesium, ferritin, and folate Confounders: Parity, education, socioeconomic status, and pregnancy duration	No association between interpregnancy intervals < 30 months and deficiency of micronutrients evaluated
Folate depletion			
Shapiro et al. 1965 (South Africa)	Randomized controlled trial 39 lactating Bantu women	Outcome: Maternal folate levels during postpartum period Confounder: Not applicable.	At 12 weeks postpartum, the prevalence of low serum folate levels was 9% and 38%, respectively, for women supplemented and unsupplemented.
Willoughby and Jewell 1968 (Scotland)	Randomized controlled trial 29 pregnant women	Outcome: Maternal folate levels during postpartum period Confounder: Not applicable.	At 6 weeks postpartum, the proportion of women with low serum folate levels was 64% for those receiving iron alone, compared with 13% for those receiving iron plus folate.
Butte, Calloway, and Van Duzen 1981 (US)	Cohort 23 Navajo women	Outcome: Maternal folate levels during postpartum period Confounder: None	Low serum and erythrocyte folacin levels were detected in 24% and 37% of women, respectively, at 1 month postpartum.
Ek 1983 (Norway)	Cohort 91 lactating women	Outcome: Maternal folate levels during postpartum period Confounder: None	Regardless of lactation duration, no folacin deficiency was noted in the mothers within 9 months postpartum. Plasma and erythrocyte folacin levels increased during most of the period.
Smith, Picciano, & Deering 1983 (US)	Cohort 24 lactating women	Outcome: Maternal folate levels during postpartum period Confounder: None	Erythrocyte folate concentrations declined from 6 to 12 weeks of lactation in mothers without folic acid supplementation; serum folate concentrations remained unchanged.
Bruinse, van der Berg, and Haspels 1985 (The Netherlands)	Cohort 70 pregnant women	Outcome: Maternal folate levels during postpartum period Confounder: None	At 6 months postpartum, 45% of women had serum folate levels in the marginal or deficient range. Twenty percent of this group had deficient or marginal erythrocyte folate levels as well. Serum folate concentrations were significantly lower in women who breastfed for more than 6 weeks, compared with those who did not.
Qvist et al. 1986 (Denmark)	Cohort 45 pregnant women	Outcome: Maternal folate levels during postpartum period Confounder: None	At two months postpartum, 50% of women had low serum folate levels.
Bates, Fuller, & Prentice 1986 (The Gambia)	Cohort 81 pregnant or lactating women	Outcome: Maternal folate levels during postpartum period Confounder: None	At 3 months postpartum, 56% of women who did not receive a food supplement during lactation had low erythrocyte folate levels.
Black et al. 1994 (Mexico)	Cohort 20 lactating women	Outcome: Maternal folate levels during postpartum period Confounder: None	At 7 months \pm 60 days postpartum, no women had low serum folate levels.
Keizer, Gibson, and O'Connor 1995 (Canada)	Randomized controlled trial 71 pregnant adolescents	Outcome: Maternal folate levels during postpartum period Confounder: Not applicable.	At 12 weeks postpartum, the prevalence of low serum folate levels was 13%, 40%, and 44% for supplemented lactating group, placebo lactating group, and formula feeding group, respectively.
Açkurt et al. 1995 (Turkey)	Cohort 95 postpartum women	Outcome: Maternal folate levels during postpartum period Confounder: None	At 4 months postpartum, 73% of women had deficient or low plasma folate levels.
Casterline, Allen, and Ruel 1997 (Guatemala)	Cohort 113 lactating women	Outcome: Maternal folate levels during postpartum period Confounder: None	At 3 months postpartum, 9% of women had deficient or low plasma folate levels.
O'Rourke, Redlinger, and Waller 2000 US	Cohort 188 postpartum Hispanic women	Outcome: Maternal folate levels during postpartum period Confounder: None	Mean erythrocyte folate levels decreased 23% from the first 4 months postpartum to 12 months postpartum. Use of postpartum vitamin supplements was significantly associated with higher folate levels.
Cikot et al. 2001 (The Netherlands)	Cohort 102 pregnant women	Outcome: Maternal folate levels during postpartum period Confounder: None	Serum folate concentrations remained decreased up to 6 weeks after delivery. Erythrocyte folate concentrations 6 weeks postpartum were similar to preconception concentrations.
Doyle et al. 2001 (England)	Randomized controlled trial 38 women who had given birth to a low birth-weight infant	Outcome: Maternal folate levels during postpartum period Confounder: Not applicable.	At 3 months postpartum, the prevalence of low serum folate levels was 27%, 64%, and 63% for groups with adequate diet, inadequate diet (supplemented), and inadequate diet (unsupplemented), respectively. At 9 months postpartum, the values were 18%, 9%, and 100%, respectively.
Ramlau-Hansen et al. 2006 (Denmark)	Cohort 91 postpartum women	Outcome: Maternal folate levels during postpartum period Confounder: None	At 4 and 9 months postpartum, no depletion of serum folate levels; folate-supplemented women had higher folate levels.

(continued)

Table A1 (continued)

Author/year (country)	Design/population	Outcome and confounding variables	Main findings
Milman et al. 2006 (Denmark)	<i>Cohort</i> 404 pregnant women	Outcome: Maternal folate levels during postpartum period Confounder: None	At 8 weeks postpartum, the prevalence of low serum and erythrocyte folate levels was 19% and 17%, respectively.
Megahed and Taher 2004 (Egypt)	<i>Case-control</i> 50 pregnant women	Outcome: Maternal folate levels at 36 weeks of gestation Confounders: Age, parity, race, socioeconomic status	Interpregnancy intervals ≤ 6 months were associated with significantly lower mean erythrocyte and serum folate levels.
van Eijsden et al. 2008 (The Netherlands)	<i>Cohort</i> 3,153 pregnant women	Outcomes: Birth weight, small for gestational age Confounders: Gestational age at birth, sex of infant, maternal age, height, parity, prepregnancy BMI, smoking, alcohol consumption, psychosocial stress, pregnancy intention, cohabitant status, education, ethnicity	Increasing interpregnancy interval was associated with increase in birth weight and decrease in risk of small for gestational age. There was a mitigating effect of folic acid supplementation on the relationship of interpregnancy interval with birth weight and small for gestational age.
Cervical insufficiency			
Sundtoft, Sommer, and Uldbjerg 2010 (Denmark)	<i>Cohort</i> 15 postpartum women	Outcome: Cervical collagen concentrations Confounders: Age, parity, socioeconomic status, marital status	Cervical collagen concentration increased until 12 months postpartum; significant differences among collagen concentrations at 3, 6, 9, and 12 months postpartum.
Vertical transmission of infections			
Cheng et al. 2008 (Taiwan)	<i>Cohort</i> 251 women with previous group B streptococcus (GBS) colonization in an initial pregnancy	Outcome: Recurrent GBS colonization Confounders: Maternal age, marital status, prepregnancy weight, weight gain during pregnancy, infant birth weight, breastfeeding, intensity of GBS colonization, ethnicity	Women with short birth intervals had a higher risk of recurrent GBS colonization than women with long intervals.
Sibling competition			
Swenson 1978 (Bangladesh)	<i>Cross-sectional</i> 17,066 infants	Outcome: Early childhood mortality Confounders: Survival of younger sibling for at least 1 year, maternal age, birth order (similar socioeconomic status)	Irrespective of survival of younger sibling for at least 1 year, subsequent interpregnancy intervals shorter than 12 months were associated with increased risk of early childhood mortality in older sibling.
Chowdhury 1981 (Bangladesh)	<i>Cross-sectional</i> 19,876 infants	Outcome: Early and late neonatal and postneonatal mortality Confounders: Survival of previous sibling for at least 1 year, birth order, sex of index child, maternal age (similar socioeconomic status)	Preceding birth intervals less than 27 months were only associated with an increased risk of post-neonatal mortality when the previous child survived at least 1 year.
Cleland and Sathar 1984 (Pakistan)	<i>Cross-sectional</i> 13,525 infants	Outcome: Neonatal, postneonatal, early childhood, and later childhood mortality Confounders: Survival of previous sibling for at least 2 years, maternal age, birth order, education, length of lactation, residence, sex of index child	Preceding birth intervals less than 3 years were significantly associated with increased risk of neonatal and post-neonatal mortality; intervals shorter than 2 years were significantly associated with increased risk of child mortality. Neonatal, post-neonatal, and early childhood mortality were much higher when the previous child died than when the previous child survived. The association was less clear for later childhood mortality.
Gubhaju 1985 (Nepal)	<i>Cross-sectional</i> 6,562 infants; 5,502 children	Outcomes: Infant and child mortality Confounders: Survival of previous sibling at time index child was born, maternal age, birth order, residence	Preceding birth intervals less than 36 months were associated with increased risk of infant and child mortality. The effects were stronger when the previous sibling survived than when she/he died.
Hobcraft, McDonald, and Rutstein 1985 (39 developing countries)	<i>Cross-sectional</i> Unreported	Outcome: Infant and early child mortality Confounders: Survival of previous sibling at time index child was born, maternal age, birth order, maternal education, sex of child	Preceding birth intervals less than 24 months were associated with increased risk of infant mortality. The effects were stronger when the previous sibling died than when she/he survived.
Nault, Desjardins, and Légaré 1990 (Canada)	<i>Cross-sectional</i> 17,010 infants	Outcome: Infant mortality Confounders: Survival of previous sibling during first year of life, maternal age, parity, birth order, and fate of siblings (similar socioeconomic status)	Irrespective of length of previous birth interval, mortality of the index child was higher when the previous sibling died than when she/he survived.
Pebley, Hermalin, and Knodel 1991 (Germany)	<i>Cross-sectional</i> 5,749 infants	Outcome: Infant mortality Confounders: Survival of previous sibling during first year of life, maternal age, father's education, region, breastfeeding, number of previous children who died in infancy	Preceding birth intervals less than 24 months were associated with increased risk of neonatal mortality. Short preceding birth intervals were only associated with an increased risk of infant mortality when the previous child survived during the first year of life.
Boerma and Bicego 1992 (17 developing countries)	<i>Cross-sectional</i> 58,162 infants	Outcome: Neonatal, 1–6 months, and 7–23 months mortality Confounders: Survival status of the preceding sibling at time of conception of the index birth for neonatal mortality and, at the time of the index child's birth for postneonatal mortality, maternal age, mother's education, residence, household, sex of child, multiple birth, birth order, breastfeeding duration, prenatal and delivery care	In more than half the countries, preceding birth intervals < 24 months were associated with increased risk of neonatal and postneonatal (age 1–6 months) mortality and, to a much lesser extent, mortality at 7–23 months of age. Overall, preceding child survival did not lead to an increase of the effects of short intervals on all mortalities evaluated.
Curtis, Diamond, and McDonald 1993 (Brazil)	<i>Cross-sectional</i> 4,752 infants	Outcome: Postneonatal mortality Confounders: Survival status of previous sibling at conception of index child, maternal age, birth order, sex of child, maternal education, region of residence	Preceding birth intervals < 18 months were associated with increased risk of postneonatal mortality irrespective of survival of the previous sibling. Intervals of 18–23 months were associated with increased risk of post-neonatal mortality when the previous sibling died.

(continued)

Table A1 (continued)

Author/year (country)	Design/ population	Outcome and confounding variables	Main findings
Zenger 1993 (Bangladesh)	Cross-sectional 7,304 infants	Outcome: Neonatal mortality Confounders: Survival of previous sibling at neonatal period, maternal age, birth order, religion, maternal education, sex of child, age, year of birth	Preceding birth intervals < 18 months were associated with increased risk of neonatal mortality. The effects were stronger when the preceding sibling survived the neonatal period than when did not.
Alam 1995 (Bangladesh)	Cross-sectional 4,184 infants	Outcome: Neonatal, postneonatal, and 12–35 months mortality Confounders: Survival status of older sibling, maternal age, number of older surviving siblings, sex of the index child, and household socioeconomic status	Preceding birth intervals < 15 months were associated with an increased risk of postneonatal and 12–35 months mortality. No association was found between birth interval and neonatal mortality. Preceding birth intervals < 15 months were only associated with an increased risk of postneonatal mortality when the previous child survived at least 1 year.
George et al. 2000 (Russia, US)	Cross-sectional 2,418 infants	Outcome: Neonatal, postneonatal, and child mortality Confounders: Survival of previous sibling at the time the index child was born, maternal age, parity, marital status, birth order, multiple birth	Preceding birth intervals < 24 months were associated with increased risk of all mortalities evaluated. Preceding child survival did not affect the association between short intervals and all mortalities evaluated.
Whitworth and Stephenson 2002 (India)	Cross-sectional Unreported	Outcome: Neonatal, 1–7 months, and 8–24 months mortality Confounders: Survival of previous sibling, maternal age, prematurity, birth weight, maternal education, standard of living index, household density, water supply, prenatal care, geographic area	Preceding birth intervals < 18 months were associated with an increased risk of all mortalities evaluated. The effects of short intervals on neonatal mortality were stronger when the preceding sibling died than when she/he survived. The effects of short intervals on mortality at ages 1–7 months were stronger when the preceding sibling survived than when she/he died.
Becher et al. 2004 (Burkina Faso)	Cross-sectional 10,122 infants	Outcome: Infant and child mortality Confounders: Survival of previous sibling during first year of life, maternal age, birth order, year of birth, sex of child, ethnic group, religion, season of birth, twin birth, vital status of mother	Preceding birth intervals < 18 months were associated with an increased risk of infant mortality. No association was found between short intervals and child mortality. The effect of short intervals on infant mortality was stronger when the preceding sibling died before age 1 or before the birth of the index child.
Rutstein 2008 (44 developing countries [2000–2005])	Cross-sectional 1,123,454 infants	Outcome: Early neonatal, neonatal, postneonatal, infant, child, and under-five years mortality Confounders: Survival status of previous sibling at conception of index child, maternal age, birth order, multiple birth, pregnancy duration, sex of child, breast-feeding, antenatal care, delivery care, prenatal tetanus toxoid vaccination, maternal education, residence, socioeconomic status, wantedness of pregnancy	Preceding interpregnancy intervals < 36 months were associated with increased risk of child and under-five-years mortality. Preceding interpregnancy intervals < 24 months were associated with increased risk of early neonatal, neonatal, and infant mortality. Overall, the effects of interpregnancy intervals < 36 months on under-five-years mortality were stronger when the preceding sibling died than when she/he survived.
DaVanzo et al. 2008 (Bangladesh [1982–2002])	Cross-sectional 125,720 infants	Outcome: Early neonatal, late neonatal, postneonatal, and child mortality Confounders: Survival status of previous sibling at conception of index child, gestational age, parity, maternal age, maternal education, father's education, father's presence, religion, household space size, month of birth, calendar year period, area of residence	Preceding birth intervals < 24 months were associated with an increased risk of all mortalities evaluated. Overall, the effects of birth intervals < 24 months on both early and late neonatal mortality were stronger when preceding sibling died than when she/he survived. The effects of birth intervals < 24 months on both postneonatal and child mortality were stronger when the preceding sibling survived than when she/he died.
Blanco Villegas and Fuster 2009 (Spain)	Cross-sectional 7,872 infants	Outcome: Infant mortality Confounders: Survival status of previous sibling, maternal age, sex of dead child, number of preceding deaths of siblings, socioeconomic status	Preceding birth intervals < 17 months were associated with increased risk of infant mortality. The effects of birth intervals < 17 months were stronger when the preceding sibling died than when she/he survived.
Transmission of infectious diseases among siblings			
Manun'ebo et al. 1994 (Zaire)	Cohort 2,082 children	Outcome: Diarrhea Confounders: Maternal age, parity, infant age, water quality and sanitation, parental education, household size, survival of previous sibling	Short birth intervals were associated with increased risk of diarrhea in siblings.
Goodman and Correa 2000 (Colombia)	Cohort 684 children	Outcome: H. pylori infection Confounders: Several hygiene-related exposures, socioeconomic indicators, number of children in household	Children born within 4 years after the previous sibling were more likely to be infected by H. pylori than children born 10 or more years after the previous sibling.
Incomplete healing of uterine scar from previous cesarean delivery			
Ait-Allah, Abdelmonem, and Rasheed 2009 (Egypt)	Cohort 90 pregnant women with a previous cesarean section	Outcome: Ultrasonographic measurement of uterine scar in third trimester of pregnancy Confounder: None	Short intervals were significantly associated with increased risk of ultrasonographic thin lower uterine segment (uterine scar).
Dicle et al. 1997 (Turkey)	Cohort 17 women after cesarean section	Outcome: Magnetic resonance imaging healing period of incision scar Confounder: None	Maturation time of myometrial scar tissue in uncomplicated cesarean section was approximately 3 months; complete involution and recovery of zonal anatomy required at least 6 months.
Mareeva, Levashova, and Mil'man 1989 (Russia)	Cohort 32 women after cesarean section	Outcome: Hysteroscopic assessment of uterine scar at 1 year post-cesarean Confounder: None	Complete muscularization, partial replacement of muscular tissue by connective-tissue elements, and full replacement observed in 56%, 25%, and 19% of cases, respectively.

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