

# The New England Journal of Medicine

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VOLUME 340

FEBRUARY 25, 1999

NUMBER 8



## EFFECT OF THE INTERVAL BETWEEN PREGNANCIES ON PERINATAL OUTCOMES

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### ABSTRACT

**Background** A short interval between pregnancies has been associated with adverse perinatal outcomes. Whether that association is due to confounding by other risk factors, such as maternal age, socioeconomic status, and reproductive history, is unknown.

**Methods** We evaluated the interpregnancy interval in relation to low birth weight, preterm birth, and small size for gestational age by analyzing data from the birth certificates of 173,205 singleton infants born alive to multiparous mothers in Utah from 1989 to 1996.

**Results** Infants conceived 18 to 23 months after a previous live birth had the lowest risks of adverse perinatal outcomes; shorter and longer interpregnancy intervals were associated with higher risks. These associations persisted when the data were stratified according to and controlled for 16 biologic, sociodemographic, and behavioral risk factors. As compared with infants conceived 18 to 23 months after a live birth, infants conceived less than 6 months after a live birth had odds ratios of 1.4 (95 percent confidence interval, 1.3 to 1.6) for low birth weight, 1.4 (95 percent confidence interval, 1.3 to 1.5) for preterm birth, and 1.3 (95 percent confidence interval, 1.2 to 1.4) for small size for gestational age; infants conceived 120 months or more after a live birth had odds ratios of 2.0 (95 percent confidence interval, 1.7 to 2.4), 1.5 (95 percent confidence interval, 1.3 to 1.7), and 1.8 (95 percent confidence interval, 1.6 to 2.0) for these three adverse outcomes, respectively, when we controlled for all 16 risk factors with logistic regression.

**Conclusions** The optimal interpregnancy interval for preventing adverse perinatal outcomes is 18 to 23 months. (N Engl J Med 1999;340:589-94.)

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A SHORT interval between pregnancies has been associated with adverse perinatal outcomes,<sup>1-7</sup> but whether it is an independent risk factor or whether the association is due merely to confounding by other factors (such as maternal age, socioeconomic status, and reproductive history) is unclear. Likewise, little is known about whether a long interpregnancy interval is associated with adverse perinatal outcomes. In the few studies that have been conducted of the relation between short and long interpregnancy intervals and adverse perinatal outcomes, no definitive conclusions could be drawn because of methodologic constraints or because the number of women studied was small.<sup>8-11</sup>

We addressed this question by studying vital-statistics data recorded in Utah. These data offer an excellent opportunity for evaluating the relation between interpregnancy intervals and birth outcomes because the average parity of mothers there is relatively high. Also, the association can be examined with less potential for confounding because other reproductive risk factors, notably tobacco and alcohol use, are less prevalent among mothers in Utah than among those in many other places.<sup>12</sup>

### METHODS

The data for this study were obtained from the birth certificates of singleton infants born alive between 1989 and 1996 to mothers who resided in Utah and who had previously delivered at least one live infant. We evaluated three adverse perinatal outcomes: low birth weight (less than 2500 g), preterm birth (birth at less than 37 weeks' gestation), and small size for gestational age (birth weight below the 10th percentile for the infant's gestational age and sex among singleton births in Utah from 1989 to

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1996). These outcomes are important determinants of infant mortality and morbidity,<sup>5,10,13-16</sup> and they are important risk factors for various health problems in children and adolescents.<sup>5,10,15-19</sup>

We estimated gestational age as the interval between the date of the first day of the mother's last normal menstrual period and the infant's birth date, as recommended by the National Center for Health Statistics.<sup>20</sup> If the information about the mother's last menstrual period was missing or implausible, gestational age was estimated clinically. This estimate, which was based on prenatal physical and neurologic assessments of the infant and on fetal ultrasonographic measurements, was abstracted from the medical record.<sup>16,20,21</sup> The interpregnancy interval was defined as the period between delivery and conception and was computed as the interval between two consecutive deliveries minus the gestational age of the second infant.<sup>20</sup> That interval was calculated in weeks and converted into months (13 weeks was assumed to equal 3 months).

We evaluated 16 maternal reproductive risk factors<sup>5,10,16</sup> as potential confounding factors: age at delivery, outcome of the most recent recognized pregnancy, number of previous live-born infants who were still alive, number of previous live-born infants who had died, number of previous spontaneous or induced abortions, height, prepregnancy weight, weight gain during pregnancy, trimester at which prenatal care was started, number of prenatal care visits, marital status, education, race or ethnic group, residence (rural or urban), tobacco use during pregnancy, and alcohol use during pregnancy. A mother's education was categorized as age-appropriate if she had completed high school or the appropriate number of grades for her age (for example, at least 11 years of education was considered age-appropriate for a 17-year-old mother). We also stratified the data according to years of education completed (0 to 11, 12, 13 to 15, and  $\geq 16$  years).

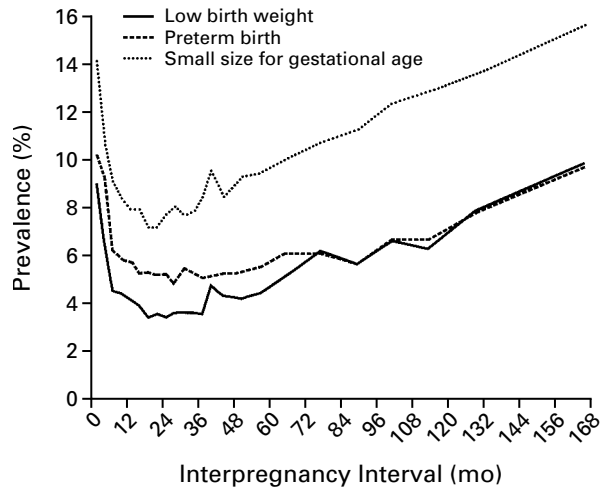
We performed stratified analyses according to the 16 maternal risk factors using scatter-plot and other graphic techniques. We simultaneously controlled for all 16 risk factors by using a separate logistic-regression model for each of the three adverse perinatal outcomes. Each model included the interpregnancy interval and the 16 risk factors as categorical variables.<sup>22</sup> The stratified analyses suggested no apparent interaction between the interpregnancy interval and the 16 risk factors; hence, we constructed the models with main effects only included.<sup>22</sup>

## RESULTS

Of the 309,583 births recorded in Utah between January 1, 1989, and December 31, 1996, we excluded 7366 multiple births and 108,164 births to primigravid mothers. For 20,848 (10.7 percent) of the remaining 194,053 infants, information on birth weight, sex, date of the mother's previous delivery of a live infant, or estimated gestational age was missing or implausible. The remaining 173,205 infants constituted the study population.

Of the 173,205 infants in the study population, 4.3 percent had a low birth weight, 5.7 percent were born prematurely, and 8.6 percent were small for their gestational age; 5.4 percent were conceived less than 6 months after the previous live birth, and 1.8 percent were conceived 120 months or longer after the previous live birth. The median interpregnancy interval was 23.8 months.

The risk of any of the three adverse perinatal outcomes was high if the interpregnancy interval was less than three months. The respective risks declined rapidly as the interpregnancy interval increased and were the lowest for women with interpregnancy intervals of 18 to 23 months. The risks increased linear-



**Figure 1.** Prevalence of Adverse Perinatal Outcomes According to Interpregnancy Interval among 173,205 Singleton Infants Born Alive in Utah from 1989 to 1996.

ly for women with interpregnancy intervals longer than 23 months (Fig. 1).

In analyses of the correlations between variables (Table 1), short interpregnancy intervals (i.e., shorter than six months) were associated with younger maternal age, death of a previous live-born child, inadequate frequency or timing of visits for prenatal care, less than age-appropriate education, Hispanic ethnicity or nonwhite race, being unmarried, and tobacco use during pregnancy. Long intervals (i.e., 120 months or longer) correlated with older maternal age, stillbirth or abortion as the outcome of the most recent pregnancy, being unmarried, and tobacco use or alcohol use during pregnancy. The interpregnancy interval was not correlated or was only slightly correlated with maternal height, weight before pregnancy, weight gain during pregnancy, number of previous stillbirths or abortions, total number of previous pregnancies, and area of residence (urban or rural) (data not shown).

When stratifying the data according to the risk factors that correlated with the interpregnancy interval, we found a persistent, J-shaped association between the interpregnancy interval and the risk of delivering a low-birth-weight infant (Table 2) in all subgroups. Infants conceived 18 to 23 months after a live birth had the lowest risk; both shorter and longer interpregnancy intervals were associated with higher risks. Similar associations were found for preterm birth and small size for gestational age (data not shown).

We also stratified the data according to 5-year increments in maternal age (14 to 19, 20 to 24, 25 to 29, 30 to 34, 35 to 39, and  $\geq 40$  years), the number

**TABLE 1.** DISTRIBUTION OF SELECTED MATERNAL REPRODUCTIVE RISK FACTORS ACCORDING TO INTERPREGNANCY INTERVAL AMONG THE MOTHERS OF 173,205 SINGLETON INFANTS BORN IN UTAH FROM 1989 TO 1996.\*

VARIABLE	INTERPREGNANCY INTERVAL						
	0–5 MO (N=9311)	6–11 MO (N=23,700)	12–17 MO (N=29,081)	18–23 MO (N=25,655)	24–59 MO (N=65,944)	60–119 MO (N=16,374)	≥120 MO (N=3140)
	percent						
Proportion of study births	5.4	13.7	16.8	14.8	38.1	9.5	1.8
Maternal age at delivery							
14–19 yr	12.8	6.5	4.1	2.5	1.0	0.0	0.0
20–29 yr	68.1	67.5	64.7	64.0	56.5	36.5	7.0
30–39 yr	18.3	25.1	29.9	32.2	40.8	59.3	76.6
40–50 yr	0.7	0.9	1.3	1.3	1.7	4.2	16.4
Outcome of most recent recognized pregnancy							
Live birth	99.1	97.2	94.2	90.7	84.4	77.2	73.5
Stillbirth or abortion	0.8	2.8	5.8	9.2	15.6	22.7	26.5
Death of a previous live-born child							
Yes	5.0	3.5	2.9	2.6	2.5	3.2	3.9
No	94.5	96.0	96.7	97.1	97.1	96.4	95.6
Trimester in which prenatal care started							
First	66.8	77.4	83.0	86.5	87.5	85.6	82.8
Second	23.5	17.3	13.2	10.8	9.8	11.0	12.8
Third or never	7.6	3.9	2.8	2.0	1.8	2.2	3.1
No. of prenatal care visits							
0–4	9.9	5.3	3.6	2.8	2.3	2.8	3.5
5–9	35.1	31.7	28.4	26.6	25.1	24.7	26.4
10–14	48.4	56.6	61.4	63.6	64.8	63.0	60.0
≥15	4.7	5.1	5.4	6.0	6.8	8.3	8.9
Race or ethnic group							
White	79.1	87.6	90.7	91.7	90.7	86.6	84.3
Hispanic	11.0	6.7	5.0	4.6	5.5	8.3	9.1
Other	9.8	5.5	4.0	3.5	3.7	4.9	6.3
Marital status							
Married	82.6	90.2	92.5	93.5	91.5	85.2	78.2
Not married	17.4	9.8	7.5	6.5	8.5	14.8	21.8
Education							
Appropriate for age	78.1	85.8	89.1	90.6	90.0	87.2	84.2
Less than appropriate for age	21.1	13.4	10.2	8.8	9.4	12.2	15.2
Tobacco use during pregnancy							
Yes	15.1	9.6	7.6	7.2	9.2	16.0	22.8
No	84.8	90.2	92.2	92.7	90.7	83.8	77.1
Alcohol use during pregnancy							
Yes	1.9	1.4	1.4	1.2	1.7	3.4	5.9
No	97.9	98.4	98.4	98.6	98.1	96.4	93.9

\*Because of missing data, not all percentages total 100.

of years of education (0 to 11, 12, 13 to 15, and ≥16 years), and weight before pregnancy, weight gain during pregnancy, height, total number of previous pregnancies, number of previous stillbirths or abortions, and rural or urban residence. The J-shaped association between interpregnancy interval and risk persisted in every case in which the data were sufficient for stratified analysis (data not shown).

When we simultaneously controlled for all 16 risk factors by logistic-regression analysis, both short and long interpregnancy intervals remained associated with the risks of all three adverse perinatal outcomes (Table 3). As compared with interpregnancy intervals of 18 to 23 months, the adjusted odds ratios for interpregnancy intervals shorter than 6 months were 1.4 for low birth weight, 1.4 for preterm birth, and 1.3 for small size for gestational age; the adjust-

ed odds ratios for interpregnancy intervals of 120 months or longer were 2.0 for low birth weight, 1.5 for preterm birth, and 1.8 for small size for gestational age.

We also evaluated the risks of the three adverse perinatal outcomes among infants born to primigravid mothers (who were otherwise excluded from the study). As compared with infants conceived 18 to 23 months after a live birth, infants born to primigravid mothers had relative risks of 1.8 (95 percent confidence interval, 1.7 to 1.9) for low birth weight, 1.3 (95 percent confidence interval, 1.2 to 1.4) for preterm birth, and 1.7 (95 percent confidence interval, 1.6 to 1.8) for small size for gestational age. This pattern persisted when the data were stratified according to other maternal risk factors (data not shown).

**TABLE 2.** FREQUENCY OF LOW BIRTH WEIGHT ACCORDING TO INTERPREGNANCY INTERVAL AND SELECTED MATERNAL RISK FACTORS AMONG 173,205 SINGLETON INFANTS BORN IN UTAH FROM 1989 TO 1996.\*

VARIABLE	INTERPREGNANCY INTERVAL						
	0-5 MO	6-11 MO	12-17 MO	18-23 MO	24-59 MO	60-119 MO	≥120 MO
	percent						
Frequency of low birth weight	7.0	4.4	4.0	3.4	3.8	5.7	8.7
Maternal age at delivery							
14-19 yr	12.2	8.4	8.6	7.3	7.3	—	—
20-29 yr	6.6	4.4	4.1	3.5	4.1	6.1	10.5
30-39 yr	5.0	3.4	3.1	3.0	3.2	5.3	8.4
40-50 yr	—	4.2	5.3	3.2	4.4	6.8	9.7
Outcome of most recent recognized pregnancy							
Live birth	7.0	4.4	3.9	3.3	3.6	5.3	9.1
Stillbirth or abortion	7.8	5.2	5.1	4.2	4.6	6.7	7.8
Death of a previous live-born child							
Yes	10.4	7.1	5.8	5.6	6.5	8.8	14.8
No	6.8	4.3	3.9	3.3	3.7	5.5	8.5
Trimester in which prenatal care started							
First	6.8	4.1	3.8	3.3	3.5	5.4	8.0
Second	6.4	4.7	4.1	3.4	4.8	6.2	8.7
Third or never	8.2	6.7	5.2	6.0	6.2	9.1	16.7
No. of prenatal care visits							
0-4	15.0	11.9	10.3	8.5	10.4	14.4	23.6
5-9	7.6	5.4	5.4	5.2	5.6	7.8	13.5
10-14	4.7	3.0	2.7	2.2	2.7	4.2	5.7
≥15	5.1	4.2	5.1	4.4	4.0	5.7	6.1
Race or ethnic group							
White	6.8	4.2	3.8	3.3	3.7	5.5	8.5
Hispanic	9.0	6.2	5.5	4.7	5.2	6.9	9.5
Other	6.4	4.8	5.5	4.0	5.2	5.8	10.6
Marital status							
Married	5.9	4.0	3.5	3.2	3.4	5.1	7.9
Not married	12.4	8.5	9.5	6.6	7.6	8.7	11.5
Education							
Appropriate for age	5.7	3.9	3.5	3.1	3.4	5.2	7.7
Less than appropriate for age	11.8	7.7	8.3	6.8	7.2	8.6	13.9
Tobacco use during pregnancy							
Yes	14.9	11.4	13.4	9.7	10.1	12.1	16.1
No	5.6	3.7	3.2	2.9	3.2	4.4	6.5
Alcohol use during pregnancy							
Yes	17.2	8.5	9.8	9.1	8.3	12.8	14.5
No	6.8	4.3	3.9	3.3	3.7	5.4	8.3

\*Dashes indicate that data were insufficient for analysis (i.e., the standard error was at least half of the estimated percentage).

## DISCUSSION

We found that infants conceived 18 to 23 months after a live birth had the lowest risks of low birth weight, preterm birth, and small size for gestational age; both shorter and longer interpregnancy intervals were associated with higher risks. This J-shaped association was not the result of confounding by common reproductive risk factors, and short and long interpregnancy intervals therefore appear to be independently associated with a higher risk of adverse perinatal outcomes.

Three limitations should be considered when the results of this study are interpreted. First, we were unable to assess directly a potentially important con-

foundings factor: the number of unrecognized losses of pregnancy. However, this limitation is unlikely to have caused the observed association, since the J-shaped pattern existed regardless of the number of recognized stillbirths or abortions. Second, our study and previous studies that have drawn data from records of vital statistics were limited by inaccuracies in the measurements of gestational age.<sup>21</sup> However, non-differential misclassification, which is a likely consequence of such inaccuracies, tends to bias an association toward a null result.<sup>23</sup> Thus, we would have found a more profound J-shaped pattern had there been no misclassification. In addition, in the analysis of low birth weight in relation to a short interpreg-

**TABLE 3.** RESULTS OF LOGISTIC-REGRESSION ANALYSES OF THE INTERPREGNANCY INTERVAL AS A RISK FACTOR FOR LOW BIRTH WEIGHT, PRETERM BIRTH, AND SMALL SIZE FOR GESTATIONAL AGE AMONG 173,205 SINGLETON INFANTS BORN IN UTAH FROM 1989 TO 1996.\*

INTERPREGNANCY INTERVAL (MO)	LOW BIRTH WEIGHT		PRETERM BIRTH		SMALL SIZE FOR GESTATIONAL AGE	
	ODDS RATIO	95% CI	ODDS RATIO	95% CI	ODDS RATIO	95% CI
0-5	1.4	1.3-1.6	1.4	1.3-1.5	1.3	1.2-1.4
6-11	1.1	1.0-1.2	1.0	0.9-1.1	1.1	1.0-1.2
12-17	1.1	1.0-1.2	1.0	0.9-1.1	1.1	1.0-1.1
18-23†	1.0		1.0		1.0	
24-59	1.1	1.0-1.1	1.0	0.9-1.1	1.1	1.1-1.2
60-119	1.5	1.3-1.6	1.1	1.0-1.2	1.4	1.3-1.5
≥120	2.0	1.7-2.4	1.5	1.3-1.7	1.8	1.6-2.0

\*Analyses were controlled for maternal age at delivery, outcome of most recent recognized pregnancy, number of previous live-born children who were still alive, number of previous live-born children who had died, number of previous spontaneous or induced abortions, height, weight before pregnancy, weight gain during pregnancy, trimester when prenatal care started, number of prenatal care visits, marital status, education, race or ethnic group, rural or urban residence, tobacco use during pregnancy, and alcohol use during pregnancy. CI denotes confidence interval.

†This was the reference group.

nancy interval, the results changed little after further analysis accounted for those inaccuracies.<sup>6</sup> Likewise, when we used the clinically estimated gestational age instead of that based on the mother's last menstrual period, the results were similar (data not shown). Third, the prevalence of reproductive risk factors was relatively low in our study population, and hence caution should be used in generalizing our results to other populations.

The relation between birth outcomes and both short and long interpregnancy intervals has been studied previously. In a study of the 7,151,631 live births and stillbirths in the United States from 1937 to 1941, both short and long interpregnancy intervals were associated with a higher risk of stillbirth,<sup>8</sup> but an optimal interpregnancy interval could not be identified, because the intervals were estimated indirectly. Similarly, in an analysis of data on 5301 births to multiparous British mothers from March 3 to 9, 1946, birth intervals of three to six years were associated with the lowest risk of birth weights less than or equal to 5.5 lb (2.5 kg).<sup>9</sup> The study, however, was based on birth interval, which overestimates the risk of adverse outcomes for short intervals between pregnancies.<sup>2,3</sup> Moreover, among white infants born in the United States during 1981, both short and long interpregnancy intervals correlated with an increased risk of low birth weight,<sup>10</sup> although that analysis did not consider maternal age. In a study of hospital data on 4467 mothers who had delivered

their previous live infants at full term, interpregnancy intervals of 0 to 3 months, as well as interpregnancy intervals of 49 months or longer, were associated with a higher risk of preterm labor than were intervals of 25 to 36 months. However, after adjustment for confounding factors, the latter association was not statistically significant.<sup>11</sup>

The relation between short interpregnancy intervals and adverse perinatal outcomes has been attributed to maternal nutritional depletion and postpartum stress.<sup>24,25</sup> However, it is unknown why a long interpregnancy interval is associated with adverse perinatal outcomes. We offer two hypotheses that might explain the association. One is that pregnancy may help mothers gain growth-supporting capacities (such as increased uterine blood flow and other physiologic and anatomical adaptations of the reproductive system).<sup>26</sup> After delivery, those capacities may gradually decline, and the mother's physiologic characteristics may become similar to those of primigravid women if another fetus is not conceived for a long time. This hypothesis is supported by our additional finding that births to primigravid women were associated with a higher risk of adverse outcomes than were those of infants conceived 18 to 23 months after a live birth. Another possibility is that metabolic or anatomical factors that we did not measure may cause both delayed fertility and adverse birth outcomes.

Our findings suggest several ways to improve perinatal outcomes. Providers of reproductive health care could counsel mothers on the association between adverse perinatal outcomes and short and long interpregnancy intervals, and on the benefits of optimizing that interval. Public health programs could identify women who become pregnant after short or long interpregnancy intervals, especially those who have other risk factors (such as tobacco or alcohol use or a young or advanced maternal age) for interventions to improve perinatal outcomes. Public health agencies could consider measures to improve family-planning<sup>7</sup> and fertility services.

Presented in part at the annual meeting of the Society for Epidemiologic Research, Chicago, June 25, 1998.

We are indebted to Dr. Gulzar Shah and Jeffrey Duncan for data management, to Dr. Andrew Pelletier (Epidemiology Program Office, Centers for Disease Control and Prevention, Atlanta) for his comments and assistance, and to Dr. Wu Xu and Dr. Jennifer Lloyd (Utah Department of Health, Salt Lake City) for their comments.

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