Aspirin Use and Miscarriage Risk

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Background: Recent research has found nonsteroidal antiinflammatory drugs, including aspirin, to increase the risk of miscarriage. The objective of the present study was to evaluate the association between aspirin use and miscarriage.

Methods: We conducted a case–control study using data from the Collaborative Perinatal Project. This prospective cohort study recruited approximately 54,000 pregnant women at 12 sites in the United States from 1959 to 1965. Women who had miscarriages (n = 542) were matched by clinic and time in pregnancy when they came under observation to 2587 women who had live births. Participants were interviewed at each prenatal visit. Data on aspirin use were collected prospectively by in-person interviews and medical record review. Aspirin use among controls was considered only for the duration of pregnancy when the matched cases remained pregnant. The outcome of interest was miscarriage, defined as spontaneous pregnancy loss at less than 140 days from the last menstrual period.

Results: Twenty-nine percent of cases and 34% of controls used aspirin during pregnancy. Aspirin use was not associated with an increased risk of miscarriage. Adjusted odds ratios ranged from 0.64 to 0.92 (95% confidence intervals = 0.48–1.38) for individual lunar months and combinations of lunar months.

Conclusions: Use of aspirin during pregnancy is not associated with an increased risk of miscarriage.

METHODS

Twelve centers in the United States participated in the Collaborative Perinatal Project, a prospective cohort study of approximately 54,000 women and their offspring from 1959 to 1965. A previous publication has described the study’s methods.9 Women enrolled at their first prenatal visit with follow up through the remainder of the pregnancy. This case–control study of previously collected data was determined to be exempt from Institutional Review Board review by the National Institutes of Health Office of Human Subjects Research.

Methods to ascertain drug use in the Collaborative Perinatal Project have been described.10 At the first study clinic visit, study staff asked women about current use of medications, as well as illness, since the month before the last menstrual period (LMP). At each subsequent clinic visit, staff asked women about use or illness since the last visit. Staff also obtained and reviewed all medical records and recorded any data on medication use. Dates of drug use were noted and converted to lunar (28-day) months of pregnancy. Products containing aspirin alone, as well as products containing aspirin along with other drugs (eg, cold remedies), were included, but other NSAIDs were not included in the analysis because they were not commonly available during the time of the study.

Of the 830 women who experienced early fetal losses (less than 140 days after the first day of the LMP), 704 were included in a previous study of caffeine metabolites and miscarriage, which also provided matched controls.11 The 704 women were risk set-matched by study site and day of gestation when a study visit (usually the first) was done to 2816 women who gave birth to a live-born infant of at least 28 weeks’ gestation.11 Further review of original study records revealed that 46 cases were actually ectopic pregnancies, maternal deaths, iatrogenic terminations, or induced abortions. Information on medication based on prescription registry data for NSAID use 7 to 9 weeks before miscarriage (odds ratio [OR] = 2.69; 95% CI = 1.81–4.00) to 1 week before miscarriage (6.99; 2.75–17.74).2

Pain relievers such as acetaminophen, ibuprofen, and naproxen have increasingly displaced aspirin as over-the-counter drugs of choice in recent decades; however, aspirin is still frequently used.3 Aspirin use during pregnancy has been evaluated for a range of outcomes, including IQ of the child, preeclampsia, preterm birth, fetal growth, and stillbirth with little evidence for an adverse effect and some evidence of benefit.4–8 The present study evaluated the association between aspirin use, assessed at multiple time periods in early pregnancy, and miscarriage using prospective data from a large U.S. study. Our objective was to assess whether aspirin use is associated with an increased risk of miscarriage.
use was unavailable for 6 control and 62 case women (many of
the latter miscarried before they could be interviewed), and 61
women (7 controls, 54 cases) were first interviewed after deliv-
ery or the end of pregnancy, leaving 542 cases and 2803 controls
with prospective information on medication use. Exclusion of
matched controls for the 162 excluded cases reduced the number
of controls to 2587. Matching was updated for this study to
assure identical time periods at risk for aspirin exposure (see
subsequently) for cases and controls by randomly assigning at
least 4 controls to single cases with identical gestational age for
the assessment visit.

Time intervals of interest included the lunar month before
the LMP and the first through fourth lunar months; we
assessed association with miscarriage by lunar month of
pregnancy and combinations of lunar months. We derived
stratum-adjusted odds ratios from a conditional logistic re-
gression model containing only a term for aspirin use as well
as adjusted odds ratios from a conditional logistic regression
model containing terms for maternal age, smoking, education,
and race (defined as listed in Table 2). We made the
decision to adjust for these factors a priori based on previous
literature.

Aspirin use during the lunar month of pregnancy when
miscarriage occurred was not included in the analysis for 2
reasons: 1) women might have taken it in response to symp-
toms of miscarriage, and 2) the pregnancy may not have
lasted the entire month, thereby shortening the time during
which aspirin might have been taken. To avoid bias due to the
individually matched controls being pregnant longer than the
matched case and potentially taking aspirin during those
months, we set aspirin use to “missing” for the controls for
the months beyond the lunar month before miscarriage of the
matched case.

To assess the degree of variability of aspirin exposure
across months of pregnancy, we calculated kappa statistics as
well as overall time window (OTW) ratios. These ratios of
overall exposure prevalence to time window-specific expo-
sure prevalence, as suggested by Hertz-Picciotto et al,12 in
which $p_i = e_i/(n - d_{i\infty} - \tilde{n})$. For the time interval of interest
$i$, $e_i$ is the number reporting exposure, $n$ is the number of
respondents, $d_{i\infty}$ is the number who did not survive to the
beginning of the interval, and $\tilde{n}$ is the number exposed but
without information as to timing. In this study, $\tilde{n} = 0$
because we did not include women who received aspirin at an
unknown time. According to Hertz-Picciotto et al12 a series
of low OTW ratios (close to 1.0) across time intervals
suggests that the same participants tend to take aspirin across
multiple intervals.

RESULTS

Table 1 shows characteristics of the cases and controls.
Cases were more likely than controls to be older, to be
smokers, and to have fewer years of education but were
distributed similarly across categories of race or ethnicity.
Length of gestation at the time that the pregnancy ended
averaged 100 days (14 completed weeks) for cases and 275
days (39 completed weeks) for controls. There were 4 mis-
carriages in the second lunar month, 130 in the third, 224 in
the fourth, and 184 in the fifth. Black women were more
likely than white women to be aspirin users (Table 2). Aspirin
users and nonusers did not differ by age, smoking, education,

| TABLE 1. Characteristics of Women Who Experienced Miscarriage (Cases) and Those Who Delivered Live-Born Infants (Controls), and Characteristics of Aspirin Users and Nonusers, Collaborative Perinatal Project, 1959–1965 |
|-----------------------------------------------|----------------|----------------|----------------|
| Characteristic                          | Cases (n = 542) | Controls (n = 2587) | Aspirin Users (n = 1035) | Nonusers (n = 2094) |
|-----------------------------------------------|----------------|----------------|----------------|
| Age (years); mean ± SD                       | 26.9 ± 6.5      | 25.2 ± 5.7      | 25.6 ± 5.9      | 25.4 ± 5.9        |
| Race or ethnic group; %                     |                |                |                |                |
| White                                       | 62             | 66             | 61             | 67             |
| Black                                       | 32             | 28             | 36             | 25             |
| Other or unknown*                          | 6              | 6              | 3              | 7              |
| Smoking; %                                  | 48             | 40             | 41             | 41             |
| Education; %                                |                |                |                |                |
| <12 yr                                      | 51             | 39             | 43             | 40             |
| 12 yr                                       | 30             | 37             | 34             | 37             |
| >12 yr                                      | 19             | 24             | 23             | 23             |
| Length of gestation at time of miscarriage or delivery (days) |            |                |                |                |
| Mean                                        | 100            | 275            |                |                |
| Median                                      | 99             | 278            |                |                |
| Gestation at registration (days); mean ± SD |                | 75.1 ± 19.0    | 75.4 ± 19.8    |

*Within this category, 88% of cases and 85% of controls were Puerto Rican, 12% of cases and 11% of controls were Asian, and 5% of controls were unknown. Eighty-two percent of aspirin users and 86% of nonusers were Puerto Rican, 9% of users and 12% of nonusers were Asian, and 9% of users and 3% of nonusers were unknown.

SD indicates standard deviation.
or point in time during gestation when they came under observation.

Twenty-nine percent of cases and 34% of controls (159 cases and 876 controls) reported aspirin use at least once from the first lunar month of pregnancy to the lunar month before the month of miscarriage or equivalent for controls (Table 2). Aspirin use during the time period was reported by 1035 women, and 2094 women reported no aspirin use. Aspirin use by month for cases and controls is shown in Table 2. Among cases, 15% reported using aspirin in each of the first 4 lunar months, whereas 19% of controls reported similar use. Use was most common for cases and controls during the third and fourth lunar months (25% and 31% of eligible cases and 29% and 33% of controls in months 3 and 4, respectively).

Aspirin use had a moderate-to-high concordance across months of pregnancy. Kappa values across the first 4 months ranged from 0.38 to 0.77. The OTW ratios were 1.9, 1.7, 1.5, and 2.9 for months 1 to 4, respectively. These relatively constant and low ratios, particularly during the first 3 months, also suggest a high concordance of use. We constructed conditional logistic regression models for each lunar month of interest and various combinations of lunar months to examine the timing of aspirin exposure relative to risk of miscarriage (Table 2). All months and combinations of months showed odds ratios less than unity, with most 95% CIs excluding the null value. Use of aspirin at any time during pregnancy through the month before miscarriage or equivalent for controls showed an inverse association with miscarriage. Other combinations of months virtually always yielded similar ORs (data not shown), although the high concordance of use across months resulted in imprecise estimates. Use including the lunar month before the LMP showed similar results (OR = 0.72; 95% CI = 0.49–1.05). Fewer than 1% of women reported taking aspirin in the lunar month before LMP but no aspirin during pregnancy. A regression model examining aspirin use in only the lunar month before miscarriage produced results dissimilar to the results seen for the lunar months of pregnancy (1.43; 0.58–3.59). Adjustment for age, smoking, education, and race had little impact on any of the ORs.

Aspirin use was not associated with miscarriage occurring in lunar months 2 and 3 (OR = 0.94; 95% CI = 0.54–1.77), although it was associated with reduced odds of miscarriage occurring in lunar months 4 and 5 (0.76; 0.58–0.997). However, these ORs did not differ significantly from each other (P value for interaction = 0.54). The association between any aspirin use and miscarriage was similar among women with no history of prior miscarriage (0.75; 0.54–1.04) and among women with such a history (0.65; 0.37–1.14; P value for interaction = 0.74). The association in nonsmokers (0.76; 0.53–1.10) and smokers (0.65; 0.42–1.01; P value for interaction = 0.11) did not differ substantially.

### TABLE 2. Association of Aspirin Use by Lunar Month* With Miscarriage

<table>
<thead>
<tr>
<th>Stratum-Adjusted OR (95% CI)</th>
<th>Adjusted OR† (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anytime during pregnancy‡</td>
<td>0.75 (0.61–0.93)</td>
</tr>
<tr>
<td>No aspirin</td>
<td>383 (71)</td>
</tr>
<tr>
<td>Aspirin</td>
<td>159 (29)</td>
</tr>
<tr>
<td>First month</td>
<td>0.74 (0.57–0.97)</td>
</tr>
<tr>
<td>No aspirin</td>
<td>462 (85)</td>
</tr>
<tr>
<td>Aspirin</td>
<td>80 (15)</td>
</tr>
<tr>
<td>Second month</td>
<td>0.75 (0.58–0.97)</td>
</tr>
<tr>
<td>No aspirin</td>
<td>447 (83)</td>
</tr>
<tr>
<td>Aspirin</td>
<td>91 (17)</td>
</tr>
<tr>
<td>Third month</td>
<td>0.75 (0.58–0.97)</td>
</tr>
<tr>
<td>No aspirin</td>
<td>308 (75)</td>
</tr>
<tr>
<td>Aspirin</td>
<td>100 (25)</td>
</tr>
<tr>
<td>Fourth month</td>
<td>0.70 (0.49–0.98)</td>
</tr>
<tr>
<td>No aspirin</td>
<td>127 (69)</td>
</tr>
<tr>
<td>Aspirin</td>
<td>57 (31)</td>
</tr>
<tr>
<td>First, second, and third month</td>
<td>0.91 (0.64–1.29)</td>
</tr>
<tr>
<td>No aspirin</td>
<td>293 (85)</td>
</tr>
<tr>
<td>Aspirin</td>
<td>51 (15)</td>
</tr>
<tr>
<td>First, second, third, and fourth month</td>
<td>0.73 (0.42–1.27)</td>
</tr>
<tr>
<td>No aspirin</td>
<td>116 (85)</td>
</tr>
<tr>
<td>Aspirin</td>
<td>21 (15)</td>
</tr>
</tbody>
</table>

*Because of concordance of aspirin use across lunar months, the same women may have been exposed in multiple lunar months.
†Adjusted for age, smoking, education, and race.
‡Up to the month before miscarriage for cases and equivalent month for matched controls.
Information on aspirin use was missing for 97 of the 784 cases of miscarriage (excluding the 46 cases found not to be miscarriages). No substantial differences were observed between those who had data present and those with missing data for any of the following characteristics: maternal age, ethnicity or race, smoking, education, and history of miscarriage. Primiparity was more common among cases with missing data (31% for those with data present, 41% for those with missing data). Women with missing data tended to miscarry slightly earlier in gestation. Presence of aspirin data did not differ between study sites (data not shown). In addition, 145 cases had data present on aspirin but were excluded because they were first interviewed after the miscarriage or because they were not part of the original case-control study (the latter exclusion was necessary due to lack of resources to review the original records and confirm the diagnosis). Aspirin was used by 15.2%, 13.7%, 18.2%, and 14.8% of excluded case women in months 1 to 4, respectively. This fraction is similar to use by included case women to month 2 but is somewhat less in months 3 and 4 (Table 2).

DISCUSSION

Our results do not support the conclusion that aspirin use is associated with increased risk of miscarriage; this finding is consistent across all time intervals of interest. There is no obvious reason why the ORs less than one could be due to bias. Both cases and controls enrolled at a comparable time in pregnancy and were followed prospectively. Data about aspirin use were collected prospectively each month, but we excluded the month of miscarriage to avoid the possibility that women took aspirin in response to symptoms of miscarriage; there is no evidence of differential measurement error or bias due to recall. We cannot uncover any reason why women who are less likely to miscarry for another reason would be more likely to take or to report taking aspirin. Although it is possible that aspirin use may have been underreported, there is no reason to suspect differential underreporting between cases and controls with these prospectively collected data.

Our findings differ from the 2 previously mentioned reports examining NSAID use and miscarriage. The results from the Danish study reflecting increasing ORs with decreasing time between prescription and miscarriage could be accounted for by women taking NSAIDs close to the time of miscarriage in response to symptoms like cramping. That study was based on filled prescriptions, thereby confounding exposure with the need to visit a doctor. In the study by Li et al, aspirin use was assessed once shortly after pregnancy confirmation, and many women were interviewed after the miscarriage occurred, making it difficult to draw conclusions about use throughout pregnancy and raising questions of biased recall.

A considerable fraction of the potential cases were excluded from our analysis because the diagnosis could not be verified, they were interviewed after the miscarriage had occurred, or data on aspirin were missing. Compared with included case women, excluded cases with relevant data present were similar regarding aspirin use in early pregnancy but were less likely to use aspirin in months 3 and 4. Therefore, had these cases been included, several of the ORs for aspirin use would likely have been even further from the null than those observed here, and excluding these cases is unlikely to account for the observed lack of increased risk of miscarriage with aspirin use. Similarly, case women with missing data on aspirin did not differ substantially from case women with data present in a variety of characteristics related to miscarriage; missing data on aspirin is therefore unlikely to account for our results.

Information about the amount of aspirin taken in a given month is not available in this study. The only dose information collected was the number of days of use during each lunar month as a categorical variable, which we considered too crude to use to construct a dose–response analysis. If more data were available, a clearer dose–response relationship might be constructed; previous publications on this topic were also unable to assess a dose–response relationship.

In many circumstances, assessment of exposure during pregnancy when controls have gestation lengths much longer than cases can produce bias. We attempted to avoid this bias by individually matching controls to cases and setting exposure data for the controls to “missing” for the time intervals beginning with the matched case lunar month of miscarriage, thereby avoiding differential misclassification bias. Due to high intertime interval concordance in the exposure data and little indication of which lunar month(s) might be most important for aspirin to exert its effect on pregnancy, we calculated OTW ratios to check for the possibility of misclassification. We found relatively low ratios for each lunar month of interest, so our month-by-month exposure data seem to suggest that many of the same women are being exposed month after month and misclassification bias is unlikely. However, this pattern makes it difficult to pinpoint whether there is a critical time window for aspirin exposure. Nevertheless, the results observed for the few women who took aspirin only in the month before LMP were inconsistent with the results observed for women who took aspirin during pregnancy, supporting the conclusion that aspirin may exert an effect during pregnancy.

Women in this study might have taken aspirin for fever or other symptoms of infection; however, we did not control for fever or viral infection during pregnancy. Fever has been associated with miscarriage in previous studies, although this remains controversial. If fever is a risk factor for miscarriage, failure to control for it would increase the apparent risk of taking aspirin. Therefore, failure to control for fever or infection does not account for our results. Previous studies have also pointed to sources of hyperthermia, like hot tub use; the Collaborative Perinatal Project did not collect data on such sources of hyperthermia.

Compared with more modern cohorts, women in this study registered for care relatively late and so we have a small number of very early pregnancy losses relative to the total number of pregnancies registered. However, for late registration per se to bias the study results, women destined to miscarry and who used aspirin would need to be at different risk of registering for care than similar women who did not. Because we excluded from analysis women who were first...
interviewed at the time of the miscarriage, and because aspirin users and nonusers came under observation at nearly identical times in gestation, this seems unlikely. It is conceivable that aspirin could have caused very early pregnancy losses undetected in this study, making aspirin appear protective for miscarriage in this analysis. Recruiting women before conception and assessing aspirin use and pregnancy status prospectively could address this issue; however, no literature currently indicates that aspirin use increases the risk of very early losses.

First-trimester losses are more likely than second-trimester ones to be caused by anembryonic gestation, chromosomal or other developmental abnormalities. Such pregnancies are likely to abort spontaneously regardless of any environmental perturbations. Second-trimester losses are usually chromosomally normal, and their etiology is more likely to reflect vascular thrombosis, immunologic abnormalities, and other causes of inflammation. Aspirin exhibits both antithrombotic and anti-inflammatory effects. We found some evidence that aspirin use was not associated with first-trimester miscarriage, but a suggestion that the risk of second-trimester loss was reduced among women who took aspirin, which is consistent with these mechanisms. Aspirin is often used therapeutically in women with a history of miscarriage, but we found no evidence that the association between aspirin and miscarriage differed in women with such a history compared with other women.

Although the Collaborative Perinatal Project is an old cohort, aspirin use was very common during the time of the study, and physicians did not caution women to avoid aspirin or similar drugs during pregnancy. Women at that time were less concerned about drug exposure during pregnancy in general, and so bias in reporting drug use seems less likely than it might be in contemporary studies. These are advantages of this old cohort. Aspirin exposure is more difficult to evaluate today because fewer women overall take aspirin, and it can be easily confused with a large range of other over-the-counter painkillers and NSAIDs when reporting use. Also complicating the picture is the contemporary use of aspirin in some patient populations before conception and early in pregnancy to try to improve conception rates and perhaps to reduce miscarriage rates during the pregnancies resulting from assisted reproduction. Given the mix of findings from our study and others, future research on the effect of aspirin use before and at different times during pregnancy is needed to assure that its deliberate use in assisted reproductive technologies is not deleterious to pregnancy and to assess ongoing risk from incidental use unrelated to pregnancy.

REFERENCES