Use of nonaspirin nonsteroidal anti-inflammatory drugs during pregnancy and the risk of spontaneous abortion

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Abstract

Background: The association between the use of nonaspirin nonsteroidal anti-inflammatory drugs (NSAIDs) during pregnancy and the risk of spontaneous abortion remains unclear because of inconsistent research results and the lack of evidence for an effect due to specific types or dosages of nonaspirin NSAIDs. We aimed to quantify the association between having a spontaneous abortion and types and dosages of nonaspirin NSAIDs in a cohort of pregnant women.

Methods: Using a nested case–control design, we obtained data from the Quebec Pregnancy Registry for 4705 women who had a spontaneous abortion. For each instance, we randomly selected 10 controls from the remaining women in the registry who were matched by index date (date of the spontaneous abortion) and gestational age. Use of nonaspirin NSAIDs (identified by filled prescriptions) and nonuse were compared. We also looked for associations between different types and dosages of nonaspirin NSAIDs and having a spontaneous abortion. Analyses of associations and adjustment for confounding were done using conditional logistic regression.

Results: We identified 4705 cases of spontaneous abortion (352 exposed [7.5%]); 47 050 controls (1213 exposed [2.6%]). Adjusting for potential confounders, the use of nonaspirin NSAIDs during pregnancy was significantly associated with the risk of spontaneous abortion (odds ratio [OR] 2.43, 95% confidence interval [CI] 2.12–2.79). Specifically, use of diclofenac (OR 3.09, 95% CI 1.96–4.87), naproxen (OR 2.64, 95% CI 2.13–3.28), celecoxib (OR 2.21, 95% CI 1.42–3.45), ibuprofen (OR 2.19, 95% CI 1.61–2.96) and rofecoxib (OR 1.83, 95% CI 1.24–2.70) alone, and combinations thereof (OR 2.64, 95% CI 1.59–4.39), were all associated with increased risk of spontaneous abortion. No dose–response effect was seen.

Interpretation: Gestational exposure to any type or dosage of nonaspirin NSAIDs may increase the risk of spontaneous abortion. These drugs should be used with caution during pregnancy

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Nonaspirin nonsteroidal anti-inflammatory drugs (NSAIDs) are one of the most commonly used medications during pregnancy (17%).[1] Nevertheless, gestational use of nonaspirin NSAIDs remains controversial, partly due to the inconsistency of results from studies on their potential risks, the potential for residual confounding by comorbidities and the lack of data on the risks associated with specific types and dosages.[1–5] The strongest association thus far was seen when nonaspirin NSAIDs had been used close to the time of conception, suggesting bias that could be partly explained by women using the drug to alleviate cramping, a precursor to spontaneous abortion.[4] No one has documented the risk of spontaneous abortion according to type and dosage of nonaspirin NSAIDs — both important elements to consider when determining causality.

We performed a nested case–control study to quantify the risk of spontaneous abortion associated with specific types and dosages of nonaspirin NSAIDs in a cohort of pregnant women, adjusting for potential confounders.

Methods

Study design

We used a nested case–control study design. We chose this design because it shows similar effect sizes to a prospective cohort approach with time-varying exposure to medication, but with greater computational efficiency.[6]

Data collection

We used data from the Quebec Pregnancy Registry, an ongoing registry of all pregnancies in Quebec since 1997. Records in the registry are

linked to those in three administrative databases: the Régie de l'assurance maladie du Québec (RAMQ) database, Med-Écho and the Institut de la statistique du Québec.

The RAMQ database contains prospectively collected information on medical services, filled prescriptions, physician-based diagnoses (according to the *International Classification of*

Table 1: Characteristics of cases and controls

Characteristic	No. (%)* Cases (*n = 4 705*)	Controls (*n = 47 050*)	*p* value†
Age on gestation day 1, yr, mean (SD)	28.7 (6.6)	27.4 (5.6)	< 0.0001
Gestational age at index date, w, mean (SD)	10.5 (4.2)	10.5 (5.6)	0.99
Urban residence	3 676 (78.1)	36 208 (77.0)	0.07
Receiving social assistance	1 618 (34.4)	14 044 (29.8)	< 0.0001
Use of medication from start of pregnancy to index date			
Use of NSAIDs	352 (7.5)	1 213 (2.6)	< 0.0001
Use of other medications			1.00
Antidepressant agents	227 (4.8)	1 159 (2.5)	< 0.0001
Systemic anti-infective agents	721 (15.3)	6 544 (13.9)	0.008
Oral corticosteroids	60 (1.3)	283 (0.6)	< 0.0001
Antiemetic agents	162 (3.4)	7 151 (15.2)	< 0.0001
Other	1 937 (41.2)	13 544 (28.8)	< 0.0001
Prenatal visits, no.			
0–2	4 231 (89.9)	28 587 (60.8)	1.00
≥ 3	474 (10.1)	18 463 (39.2)	< 0.001
Comorbidities during year before pregnancy			
Diabetes mellitus	77 (1.6)	459 (1.0)	< 0.0001
Cardiovascular disease	81 (1.7)	667 (1.4)	0.10
Asthma	932 (19.8)	8 099 (17.2)	< 0.0001
Untreated thyroid disease	23 (0.5)	165 (0.4)	0.13
Depression and/or anxiety	314 (6.7)	2 080 (4.4)	< 0.0001
Systemic lupus erthematosus	1 (0.0)	5 (0.0)	0.52
Rheumatoid arthritis	9 (0.2)	64 (0.1)	0.34
Visits to a physician during year before pregnancy, no.			
0–2	1 298 (27.6)	15 248 (32.4)	1.00
3–5	1 105 (23.5)	11 594 (24.6)	1.00
≥ 6	2 302 (48.9)	20 208 (43.0)	< 0.0001
Different prescribers, no.			
0–2	3 286 (69.8)	34 697 (73.7)	1.00
≥ 3	1 419 (30.2)	12 353 (26.3)	< 0.0001
Visited emergency department or admitted to hospital during year before pregnancy	727 (15.4)	6 807 (14.5)	0.07
Obstetric complications			
History of spontaneous abortion	73 (1.6)	706 (1.5)	0.78
History of planned abortion	179 (3.8)	1 441 (3.1)	0.005
Use of medications during year before pregnancy			
Nonaspirin NSAIDs	833 (17.7)	7 028 (14.9)	< 0.0001
Antidepressant agents	364 (7.7)	2 469 (5.2)	< 0.0001
Systemic anti-infective agents	1 878 (39.9)	17 184 (36.5)	< 0.0001
Systemic corticosteroids	108 (2.3)	982 (2.1)	0.34
Other	3 217 (68.4)	30 452 (64.7)	< 0.0001

Note: NSAID = nonsteroidal anti-inflammatory drug, SD = standard deviation.
*Unless otherwise indicated.
†Pearson χ^2 test.

Diseases, 9th revision), visits to physicians and emergency departments, medical procedures, admissions to hospital, characteristics of patients and providers of health care. The RAMQ covers the health care costs of all residents of Quebec, but it only covers a portion of the cost of medications. People covered by the drug portion of the plan include those aged 65 years and older, recipients of social assistance and workers and their families who do not have access to a private drug insurance program. These people account for about 43% of the overall population of Quebec and 36% of pregnant women in the province.[7]

Med-Écho is a provincial database that records data on admissions to acute care hospitals for all residents of Quebec. These data include the gestational ages (defined from the first day of the last menstrual period to the end of pregnancy, as confirmed by ultrasound) for planned and clinically detected spontaneous abortions and deliveries.

The Institut de la statistique du Québec database provides data on all births and deaths in Quebec, including birth weight and gestational age.

Women are followed in the Quebec Pregnancy Registry from the date of entry (the first day of the last menstrual period, as confirmed by ultrasound) until the end of pregnancy. Data recorded in these three databases have been validated previously.[8–10] Studies involving pregnant women insured by the RAMQ for their medications have been shown to generate valid risk estimates.[7] Our study was approved by the Centre hospitalier universitaire Ste-Justine Ethics Committee, and the linkage between databases was approved by the Commission d'accès à l'information du Québec.

Study population

We included all women who were 15–45 years old on the first day of gestation who were continuously insured by the RAMQ drug plan for at least 12 months before and during their pregnancies. Women who had a planned abortion, who had spontaneous abortions after 20 weeks' gestation or who had been exposed to misoprostol, NSAID suppositories or known teratogens before 20 weeks' gestation were exluded. For each individual woman, only her first pregnancy meeting our eligibility criteria was included.

Selection of cases and controls

Our case definition was a clinically detected spontaneous abortion occurring between the start of pregnancy and 20 weeks' gestation. Index date was defined as the calendar date of the clinically detected spontaneous abortions. Because

Table 2: Association between the use and the percent maximum daily doses of different nonaspirin NSAIDs and risk of having a spontaneous abortion

Variable	Controls *n = 47 050*	Cases *n = 4 705*	OR (95% CI) Crude	OR (95% CI) Adjusted*
Type of NSAID				
None	45 837 (97.4)	4 353 (92.5)	1.00	1.00
Naproxen	435 (0.9)	133 (2.8)	3.22 (2.65–3.92)	2.64 (2.13–3.28)
Ibuprofen	258 (0.6)	61 (1.3)	2.49 (1.88–3.30)	2.19 (1.61–2.96)
Rofecoxib	152 (0.3)	39 (0.8)	2.70 (1.90–3.85)	1.83 (1.24–2.70)
Diclofenac	82 (0.2)	31 (0.7)	3.99 (2.63–6.03)	3.09 (1.96–4.87)
Celocoxib	111 (0.2)	30 (0.6)	2.85 (1.90–4.27)	2.21 (1.42–3.45)
Other	57 (0.1)	32 (0.7)	2.86 (1.93–4.23)	2.65 (1.71–4.12)
Combination	118 (0.2)	26 (0.6)	4.80 (3.02–7.65)	2.64 (1.59–4.39)
Maximum daily dose, %				
None	45 837 (97.4)	4 353 (93.0)	1.00	1.00
1–50	228 (0.5)	59 (1.3)	2.73 (2.05–3.64)	2.61 (1.90–3.59)
51–65	259 (0.6)	56 (1.2)	2.28 (1.70–3.05)	1.90 (1.39–2.61)
66–80	365 (0.8)	120 (2.6)	3.47 (2.81–4.27)	2.55 (2.03–3.21)
≥ 81	304 (0.6)	91 (1.9)	3.16 (2.49–4.00)	2.55 (1.96–3.32)
Unknown	57 (0.1)	26 (0.6)		

Note: CI = confidence interval, NSAID = nonsteroidal anti-inflammatory drug, OR = odds ratio.
*Odds ratios were adjusted for confounders listed in Methods.

we wished to assess several types of nonaspirin NSAIDs simultaneously, 10 controls were randomly selected for each case. Controls were selected from among pregnant women who did not have a spontaneous abortion at the same gestational age of their matched case, but who were at risk of having one, resulting in similar probabilities of exposure to medication. Controls were matched to the index date and gestational age of the case, because the risk of pregnancies ending in a loss is highly dependent on the gestational age at which the pregnancy is recognized.

Exposure

We defined exposure to nonaspirin NSAIDs as either having filled at least one prescription for any type of nonaspirin NSAID between the start of pregnancy and the index date, or as having filled a prescription for a nonaspirin NSAID before pregnancy, the duration of which overlapped with the start of pregnancy. We only considered nonaspirin NSAIDs that were reimbursed by the RAMQ drug plan during the study period. Single exposure to nonaspirin NSAIDs was defined as having filled a prescription for at least one dose of only one type of nonaspirin NSAID between the start of pregnancy and the index date. Combination use of nonaspirin NSAIDs was defined as filling a prescription for at least one dose of two or more different nonaspirin NSAIDs from the same or different classes between the start of pregnancy and the index date. In all analyses, the reference category was defined as pregnant women not exposed to nonaspirin NSAIDs between the start of pregnancy and the index date.

In addition, we investigated the association between recent exposure to nonaspirin NSAIDs and the risk of spontaneous abortion using the two weeks immediately before the index date as our window for exposure. Finally, we examined the dose–response relationship by classifying

Table 3: Crude and adjusted odds ratios for the association between use of nonaspirin NSAIDs during pregnancy and having a spontaneous abortion (part 1 of 2)

Variable	OR (95% CI)	
	Crude	Adjusted*
No use of nonaspirin NSAIDs	1.00	1.00
Use of nonaspirin NSAIDs	3.06 (2.71–3.46)	2.43 (2.12–2.79)
Patient characteristics		
Age, yr	1.04 (1.03–1.04)	1.04 (1.03–1.04)
Urban residence	1.07 (1.00–1.15)	1.00 (0.92–1.08)
Receiving social assistance	1.23 (1.16–1.31)	1.06 (0.99–0.13)
Comorbidities during year before pregnancy		
None	1.00	1.00
Diabetes mellitus	1.69 (1.32–2.15)	1.25 (0.96–1.63)
Cardiovascular disease	1.22 (0.97–1.54)	0.83 (0.64–1.07)
Asthma	1.19 (1.10–1.28)	1.03 (0.94–0.13)
Untreated thyroid disease	1.40 (0.90–2.16)	1.15 (0.72–1.84)
Depression and/or anxiety	1.55 (1.37–1.75)	1.25 (1.08–1.45)
Systemic lupus erythematosus	2.00 (0.23–17.12)	0.54 (0.06–5.01)
Rheumatoid arthritis	1.41 (0.70–2.83)	1.12 (0.52–2.41)
Vsits to physicians during year before pregnancy, no.		
0–2	1.00	1.00
3–5	1.12 (1.03–1.22)	1.12 (1.03–1.23)
≥ 6	1.34 (1.25–1.44)	1.31 (1.20–1.44)
Different prescribers, no.		
0–2	1.00	1.00
≥ 3	1.21 (1.14–1.30)	0.93 (0.85–1.02)
Visited an emergency department or admitted to hospital during year before pregnancy		
No	1.00	1.00
Yes	1.08 (0.99–1.17)	0.88 (0.80–0.97)

women according to the overall percent maximum daily dose of nonaspirin NSAIDs they took between the start of pregnancy and the index date. These doses were subdivided into four clinically relevant categories: 1%–50%, 51%–65%, 66%–80% and 81% or more. Women who did not fill a prescription for a nonaspirin NSAID before their index date were considered not to have been exposed.

Confounding

We considered variables associated with both the exposure to nonaspirin NSAIDs and the risk of spontaneous abortion as potential confounders. To assess confounding by indication, we considered variables potentially associated with the use of nonaspirin NSAIDs or their different classes and types. These variables included sociodemographic characteristics on the first day of gestation, comorbidities in the year before pregnancy (diabetes mellitus, cardiovascular disease [hypertension, coronary atherosclerosis, generalized and unspecified atherosclerosis, primary cardiomyopathies and diffuse cardiac disease resulting from disorders of the connective tissue], asthma, untreated thyroid disease [defined as having a diagnosis of hyper- or hypothyroidism without having filled a prescription for a corresponding medication], depression and/or anxiety, systemic lupus erythematosus and rheumatoid arthritis), use of medications suspected of increasing the risk of spontaneous abortion as well as use of other medications in the year before pregnancy, use of nonaspirin NSAIDs before pregnancy, use of health services in the year before pregnancy and during the period between the first day of gestation and the index date, and history of planned or spontaneous abortion.

Statistical analyses

To describe the study population, we presented

Table 3: Crude and adjusted odds ratios for the association between use of nonaspirin NSAIDs during pregnancy and having a spontaneous abortion (part 2 of 2)

Variable	OR (95% CI)	
	Crude	Adjusted
Use of medications during year before pregnancy		
None	1.00	1.00
Nonaspirin NSAIDs	1.23 (1.13–1.33)	1.04 (0.95–1.13)
Antidepressant agents	1.51 (1.35–1.70)	0.98 (0.82–1.16)
Systemic anti-infective agents	1.16 (1.09–1.23)	1.07 (0.99–1.15)
Oral corticosteroids	1.10 (0.90–1.35)	0.85 (0.67–1.07)
Other	1.18 (1.11–1.26)	1.02 (0.94–1.11)
Obstetric complications		
None	1.00	1.00
Spontaneous abortions	1.04 (0.81–1.32)	0.90 (0.67–1.21)
Planned abortions	1.25 (1.07–1.47)	1.24 (1.03–1.51)
Prenatal visits before index date, no.		
0–2	1.00	1.00
≥ 3	0.13 (0.12–0.15)	0.13 (0.12–0.14)
Visits to an obstetrician before index date, no.		
No	1.00	1.00
Yes	1.02 (0.96–1.08)	1.19 (1.11–1.27)
Use of medications between conception and index dates		
None	1.00	1.00
Antidepressant agents	2.01 (1.74–2.32)	1.54 (1.25–1.88)
Systemic anti-infective agents	1.12 (1.03–1.22)	0.98 (0.90–1.08)
Oral corticosteroids	2.14 (1.61–2.83)	1.60 (1.16–2.19)
Antiemetic agents	0.20 (0.17–0.23)	0.22 (0.19–0.26)
Other	1.74 (1.63–1.85)	1.70 (1.59–1.83)

Note: CI = confidence interval, NSAID = nonsteroidal anti-inflammatory drug, OR = odds ratio.
*Odds ratios were adjusted for confounders listed in Methods.

means for continuous variables and proportions for dichotomous variables. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using conditional logistic regression and adjusted for the potential confounders described earlier. We conducted sensitivity analyses to evaluate whether our results were robust using a 60-day window of exposure to nonaspirin NSAIDs before the index date.

Results

A total of 67 160 pregnant women met our inclusion criteria. Of those women, 4705 had a spontaneous abortion, to whom 47 050 controls were matched according to index date and gestational age. Overall, 352 women with a spontaneous abortion (7.5%) had filled one or more prescriptions for nonaspirin NSAIDs during pregnancy, compared with 1213 (2.6%) women among those who did not have a spontaneous abortion ($p < 0.05$). Women who had a spontaneous abortion were slightly older, lived in an urban area, received social assistance and had more comorbidities in the 12 months before pregnancy than those who did not. In addition, women who had a spontaneous abortion used health care services more frequently in the year before pregnancy than those who did not (Table 1). Moreover, women who had a spontaneous abortion had fewer prenatal visits and were taking more antidepressant, systemic anti-infective or other medications during pregnancy compared with women who did not.

Naproxen was the most common nonaspirin NSAID used during pregnancy among women who had a spontaneous abortion (2.8%, 133/4 705) and among those who did not (0.9%, 435/47 050), followed by ibuprofen (1.3% [61/4 705] v. 0.6% [258/47 050]), rofecoxib (0.8% [39/4 705] v. 0.3% [152/47 050]), diclofenac (0.7% [31/4 705] v. 0.2% [82/47 050]) and celecoxib (0.6% [30/4 705] v. 0.2% [111/47 050]) (Table 2). Among our cases, 0.6% of women (26/4 705) used two or more nonaspirin NSAIDs during pregnancy compared with 0.2% (118/47 050 of women in the control group.

Adjusting for potential confounders, use of nonaspirin NSAIDs during pregnancy was significantly associated with a 2.4-fold increase in the risk of spontaneous abortion (OR 2.43, 95% CI 2.12–2.79; 4705 cases, of which 352 were exposed) compared with nonuse (Table 3). Analyzing exposure to nonaspirin NSAIDs in the two weeks immediately before the spontaneous abortion, we found that the risk was higher (OR 3.47, 95% CI 2.01–6.00; data not shown), although not significantly different from our previous overall estimate. All types of nonaspirin NSAIDs significantly increased the risk of spontaneous abortion (Table 2). The highest risk was seen among women who used diclofenac alone (OR 3.09, 95% CI 1.96–4.87), whereas the lowest risk was seen among women who used rofecoxib alone (OR 1.83, 95% CI 1.24–2.70). However, no dose–response relationship was seen based on the overall percent maximum daily dose of nonaspirin NSAIDs (Table 2).

Our sensitivity analysis based on a 60-day window of exposure resulted in the calculation of similar risk (data not shown).

Interpretation

Main findings

The use of nonaspirin NSAIDs during early pregnancy is associated with statistically significant risk (2.4-fold increase) of having a spontaneous abortion. We consistently saw that the risk of having a spontaneous abortion was associated with gestational use of diclofenac, naproxen, celecoxib, ibuprofen and rofecoxib alone or in combination, suggesting a class effect. We did not see a dose–response relationship.

Explanation and comparison with other studies

Our results agree with those of other studies involving human subjects.[3,4] Indeed, our study agrees with Li and colleagues, who reported a risk of spontaneous abortion when nonaspirin NSAIDs were taken around the time of conception (hazard ratio [HR] 5.6, 95% CI 2.3–13.7).[4] However, our study did not replicate their finding that the association was even higher when exposure occurred immediately before the spontaneous abortion.[4] This may be because the use of nonaspirin NSAIDs immediately before spontaneous abortion was to relieve cramping, which is a precursor to the loss of pregnancy. If this were the case, exposure would occur after the event. This was not the case in our study, given that both of our estimates (use of nonaspirin NSAIDs at any time during pregnancy or in the two weeks immediately before spontaneous abortion) did not significantly differ from one another.

Although much remains unclear regarding the mechanism of action, prostaglandins play a putative role. The concentrations of prostaglandins in the human decidua during early pregnancy are lower than those in the endometrium at any stage of the menstrual cycle, primarily due to a decrease in the synthesis of prostaglandins.[11,12] Data suggest that pregnancy is maintained by a mechanism that suppresses uterine synthesis of prostaglandins throughout gestation, and a defect in this inhibitory mechanism may be associated

with early loss of pregnancy.[12] Prostaglandins are probably involved not only in the initial vascular changes, but also throughout decidualization.[13,14]

Strengths and limitations

Our study's large sample size allowed us to evaluate several types of nonaspirin NSAID and various dosages. We used accurate information on filled medications rather than rely on patient recall. We also used physician-based diagnoses and records of procedures related to spontaneous abortion, which limited the potential for detection and misclassification biases on outcome status. Gestational age, validated by Vilain and coworkers,[9] was obtained from hospital charts on the index date, allowing us to calculate the exact timing of exposure to nonaspirin NSAIDs during pregnancy. We adjusted our results for indication for the use of nonaspirin NSAIDs by adjusting for variables such as history of rheumatoid arthritis and systemic lupus, and for the duration of exposure in the year before pregnancy; we further adjusted for history of planned and spontaneous abortions. It is therefore unlikely that residual confounding by indication, if present, would explain our results. Finally, the nested case–control design we used enabled us to select our controls from the same population as our cases, thereby limiting the potential for selection bias.

The potential limitations of our study include the lack of data on exposure to over-the-counter formulations of nonaspirin NSAIDs during pregnancy, in addition to the lack of information on the indications for which nonaspirin NSAIDs were used and on covariables such as smoking and body mass index (BMI).

The use of acetylsalicylic acid and over-the-counter nonaspirin NSAIDs were not accounted for, which could potentially lead to misclassification of exposure. However, the extent of this bias is likely minimal. The only nonaspirin NSAID available over-the-counter in Quebec is ibuprofen, and women covered by the RAMQ drug plan had the opportunity to receive a prescription for the over-the-counter medication. In addition, cases and controls would have been equally likely to purchase the over-the-counter medication. Hence, any such misclassification would have been nondifferential, resulting in an underestimation of risk.

To our knowledge, smoking and maternal BMI are not risk factors for spontaneous abortion,[15] and are thus not confounders in our study.

Exposure data based on filled prescriptions might not necessarily reflect actual intake of a medication. However, we believe that women who filled a prescription for nonaspirin NSAIDs took at least one dose, since the provincial drug plan requires that they make a copayment for their medications. Given the design of our study, this limitation is unlikely to invalidate our findings.

Only clinically detected spontaneous abortions were included. Spontaneous abortions that were never detected by the women themselves were excluded, as has been done in other similar studies done thus far.[3,4] If nonaspirin NSAIDs increase the risk of spontaneous abortions that are not clinically detected, our findings are conservative and are underestimations of the true risk. On the other hand, if nonaspirin NSAIDs are not associated with nonclinically detected spontaneous abortions, there is no reason to believe that misclassification would be different between cases and controls, resulting in nondifferential misclassification.

We cannot rule out the possibility of chance findings for 5.0% of our statistically significant associations due to the number of comparisons made in our study.

Finally, our study population covered only 36% of pregnant women in Quebec; although this will not affect the validity of our results, it might alter their ability to be generalized to the wider population.

Conclusion

Women who were exposed to any type and dosage of nonaspirin NSAID during early pregnancy were more likely to have a spontaneous abortion. Given that the use of nonaspirin NSAIDs during early pregnancy has been shown to increase the risk of major congenital malformations[1] and that our results suggest a class effect on the risk of clinically detected spontaneous abortion, nonaspirin NSAIDs should be used with caution during pregnancy. Future research should focus on determining exact mechanisms of action.

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Contributors: Hamid Reza Nakhai-Pour and Anick Bérard conceived of and designed the study and drafted the manuscript. Anick Bérard acquired the data and supervised the study; she had full access to all of the data and takes responsibility for the integrity of the data and the accuracy of the data analysis. Hamid Reza Nakhai-Pour, Perrine Broy, Odile Sheehy and Anick Bérard analyzed and interpreted the data. Odile Sheehy and Anick Bérard provided administrative, technical and material support. Hamid Reza Nakhai-Pour, Perrine Broy and Odile Sheehy performed the statistical analyses. All of the authors critically revised the manuscript for important intellectual content and approved the final version submitted for publication.

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