

- 10 Taylor PJ. Occupational and regional associations of death, disablement, and sickness absence among post office staff 1972-75. *Br J Ind Med* 1976;33:230-5.
- 11 Idler EL, Benyamini Y. Self-rated health and mortality: a review of twenty-seven community studies. *J Health Soc Behav* 1997;38:21-37.
- 12 Mansson N-O, Rastam L. Self-rated health as a predictor of disability pension and death—a prospective study of middle-aged men. *Scand J Public Health* 2001;29:151-8.
- 13 Stamler J, Stamler R, Neaton JD, Wentworth D, Daviglius ML, Garside D, et al. Low risk-factor profile and long-term cardiovascular and noncardiovascular mortality and life expectancy: findings for 5 large cohorts of young adult and middle-aged men and women. *JAMA* 1999;282:2012-8.
- 14 Miller TQ, Smith TW, Turner CW, Guizarro ML, Hallett AJ. A meta-analytic review of research on hostility and physical health. *Psychol Bull* 1996;119:322-48.
- 15 Kivimäki M, Leino-Arjas P, Luukkainen R, Riihimäki H, Vahtera J, Kirjonen J. Work stress and risk of cardiovascular mortality: prospective cohort study of industrial employees. *BMJ* 2002;325:357-61.
- 16 Kivimäki M, Vahtera J, Koskenvuo M, Uutela A, Pentti J. Response of hostile individuals to stressful change in their working lives: test of a psychosocial vulnerability model. *Psychol Med* 1998;28:903-13.
- 17 Heinrich J, Liese AD, Lowel H, Keil U. Self-rated health and its relation to all-cause and cardiovascular mortality in southern Germany: results from the MONICA Augsburg cohort study 1984-1995. *Ann Epidemiol* 2002;12:338-45.
- 18 Heistaro S, Jousilahti P, Lahti E, Vartiainen E, Puska P. Self-rated health and mortality: a long term prospective study in eastern Finland. *J Epidemiol Community Health* 2001;55:227-32.

(Accepted 2 July 2003)



This is an abridged version; the full version is on [bmj.com](http://bmj.com)

## Exposure to non-steroidal anti-inflammatory drugs during pregnancy and risk of miscarriage: population based cohort study

De-Kun Li, Liyan Liu, Roxana Odouli

Division of Research, Kaiser Foundation Research Institute, Kaiser Permanente, 2000 Broadway, Oakland, California 94612, USA

De-Kun Li  
*epidemiologist*  
Liyan Liu  
*programmer analyst*  
Roxana Odouli  
*research associate*

Correspondence to: D-K Li  
[dki@dor.kaiser.org](mailto:dki@dor.kaiser.org)

*BMJ* 2003;327:368-71

### Abstract

**Objective** To evaluate whether prenatal use of non-steroidal anti-inflammatory drugs (NSAIDs) is associated with increased risk of miscarriage.

**Design** Population based cohort study. Prenatal use of NSAIDs, aspirin, and paracetamol (acetaminophen) ascertained by in-person interview.

**Setting** Kaiser Permanente Medical Care Program, a healthcare delivery system, in the San Francisco area of the United States.

**Participants** 1055 pregnant women recruited and interviewed immediately after their positive pregnancy test. Median gestational age at entry to the study was 40 days.

**Main outcome measures** Pregnancy outcomes up to 20 weeks of gestation.

**Results** 53 women (5%) reported prenatal NSAID use around conception or during pregnancy. After adjustment for potential confounders, prenatal NSAID use was associated with an 80% increased risk of miscarriage (adjusted hazard ratio 1.8 (95% confidence interval 1.0 to 3.2)). The association was stronger if the initial NSAID use was around the time of conception or if NSAID use lasted more than a week. Prenatal aspirin use was similarly associated with an increased risk of miscarriage. However, prenatal use of paracetamol, pharmacologically different from NSAIDs and aspirin, was not associated with increased risk of miscarriage regardless of timing and duration of use.

**Conclusion** Prenatal use of NSAIDs and aspirin increased the risk of miscarriage. These findings need confirmation in studies designed specifically to examine the apparent association.

### Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most widely used drugs in the developed world<sup>1-3</sup> and are often used by pregnant women.<sup>4-6</sup> Because of their widespread use, any unintended effect

could have serious adverse public health consequences. Gastrointestinal and renal effects are among the most widely studied and recognised adverse effects of NSAIDs, but reproductive risk, especially from NSAID use in early pregnancy, has not been systematically evaluated.<sup>7, 8</sup>

A recent case-control study reported an association between use of prescribed NSAIDs and miscarriage, with odds ratios that ranged from 1.3 (95% confidence interval 0.9 to 1.9) for NSAID use 10-12 weeks before miscarriage to 7.0 (2.8 to 17.7) for NSAID use one week before miscarriage.<sup>9</sup>

We sought to examine the effect of NSAIDs on the risk of miscarriage by analysing existing data from our recently completed, population based, cohort study of risk factors for miscarriage.

### Participants and methods

We conducted a prospective cohort study of the risk factors for miscarriage among members of the Kaiser Permanente Medical Care Program in northern California. Members of the care programme are representative of the underlying population in the service areas. The primary interest of the study was prenatal exposure to magnetic fields.<sup>10</sup> Because paracetamol (acetaminophen) shares many of the indications for use with NSAIDs but has a different underlying pharmacological effect, we conducted a similar analysis for paracetamol use to control potential confounding by indication for use.

### Participants

From 1996 through 1998, any women members of the Kaiser Permanente care programme were eligible for the study if they met the following criteria: resided in the San Francisco or south San Francisco area, had a positive pregnancy test, spoke English, and intended to carry the pregnancy to term at the time of recruitment. Among 2729 eligible women, 1063 participated and completed the interview.



An extra table on [bmj.com](http://bmj.com) lists all the indications for prenatal use of the drugs studied.

## Data collection

We obtained information on use of NSAIDs, aspirin, and paracetamol during pregnancy in an interview conducted soon after each woman's pregnancy was confirmed. We asked the women about their drug use since their last menstruation (since they became pregnant). In the interviews we also asked the women about their reproductive history, known or potential risk factors for miscarriage, and sociodemographic characteristics. We ascertained pregnancy outcomes for all participants (see [bmj.com](http://bmj.com)).

## Statistical analysis

We used the Cox proportional hazard regression to take into account possible differing gestational ages at entry between the women who used NSAIDs or aspirin and those who did not.<sup>11–13</sup> The entry time in our study was the gestational age at the positive pregnancy test, and the median gestational age at study entry was 40 days. The variables included in the model for adjustment were potential confounders and known risk factors for miscarriage as well as common socioeconomic and demographic variables.

To avoid the possibility that the condition for which NSAID or aspirin was taken might cause miscarriage, rather than the drugs themselves, we excluded seven women who reported cramping as the reason for taking NSAID or aspirin, because cramping could be an early sign of miscarriage. After excluding one further woman with missing data on drug use, we included 1055 women in the final analysis.

## Results

The background characteristics of NSAID or aspirin users and non-users in our study population are shown on [bmj.com](http://bmj.com). In general, NSAID users had a slightly higher socioeconomic status than non-users and were more likely to be older, white, to have had a college or higher education, and to have had two or more prior miscarriages and more prior pregnancies. Since their last menstruation, they were more likely to have drunk coffee and alcohol, smoked, used a hot tub or Jacuzzi, and taken multivitamins. There was little difference between users and non-users in the frequency of illicit drug use and the occurrence of fever  $\geq 37.8^{\circ}\text{C}$ . None of the NSAID or aspirin users reported having diabetes, and they were less likely than non-users to report having hypertension.

### NSAIDs and risk of miscarriage

After adjustment for confounders (see table 1), we found that the use of NSAIDs during pregnancy increased the risk of miscarriage by 80%. The risk of miscarriage was much higher when NSAIDs were taken around conception or were used for longer than a week (table 1). Further adjustment for other variables, including drinking alcohol or coffee in the prenatal period, did not change the results.

### Aspirin and risk of miscarriage

The association of prenatal aspirin use with risk of miscarriage was similar to that observed for prenatal NSAID use, although the association was generally weaker and the estimates unstable because of the small number of aspirin users (table 2).

**Table 1** Prenatal use of NSAIDs by pregnant women and risk of miscarriage. Values are numbers (percentages) unless stated otherwise

NSAID use	Miscarriage		Hazard ratio (95% CI)*
	Yes (n=162)	No (n=871)	
Non-users (n=980)†	149 (15)	831 (85)	1.0
Users (n=53):	13 (25)	40 (75)	1.8 (1.0 to 3.2)
Gestational age at first use:			
At conception (n=12)‡	6 (50)	6 (50)	5.6 (2.3 to 13.7)
After conception (n=40)	7 (18)	33 (83)	1.2 (0.5 to 2.6)
Duration of use:			
≤1 week (n=47)	9 (19)	38 (81)	1.3 (0.7 to 2.6)
>1 week (n=6)	4 (67)	2 (33)	8.1 (2.8 to 23.4)

\*Adjusted for previous miscarriage, education, maternal age, gravidity, race, use of Jacuzzi or hot tub, multivitamin use, and smoked since last menstruation. Further adjustment for other variables did not change the results.

†Used neither NSAIDs nor aspirin.

‡At conception: within the first week of gestational age.

### Paracetamol and risk of miscarriage

Use of paracetamol during pregnancy was not associated with risk of miscarriage regardless of the timing or duration of use (table 3).

## Discussion

Our analysis of data from a population based prospective cohort study revealed a significantly increased risk of miscarriage associated with prenatal use of NSAIDs or aspirin. The associated risk was particularly high when NSAIDs were used around the time of conception or were used for longer than a week.

**Table 2** Prenatal use of aspirin by pregnant women and risk of miscarriage. Values are numbers (percentages) unless stated otherwise

Aspirin use	Miscarriage		Hazard ratio (95% CI)*
	Yes (n=154)	No (n=848)	
Non-users (n=980)†	149 (15)	831 (85)	1.0
Users (n=22):	5 (23)	17 (77)	1.6 (0.6 to 4.1)
Gestational age at first use:			
At conception (n=6)‡	3 (50)	3 (50)	4.3 (1.3 to 14.2)
After conception (n=14)	2 (14)	12 (86)	1.1 (0.3 to 4.5)
Duration of use:			
≤1 week (n=16)	3 (19)	13 (81)	1.4 (0.4 to 4.5)
>1 week (n=5)	2 (40)	3 (60)	3.0 (0.7 to 12.9)

\*Adjusted for previous miscarriage, education, maternal age, gravidity, race, use of Jacuzzi or hot tub, multivitamin use, and smoked since last menstruation. Further adjustment for other variables did not change the results.

†Used neither NSAIDs nor aspirin.

‡Within the first week of gestational age.

**Table 3** Prenatal use of paracetamol by pregnant women and risk of miscarriage. Values are numbers (percentages) unless stated otherwise

Paracetamol use*	Miscarriage		Hazard ratio (95% CI)†
	Yes (n=141)	No (n=793)	
Non-users (n=762)	117 (15)	645 (85)	1.0
Users (n=172):	24 (14)	148 (86)	1.2 (0.8 to 1.8)
Gestational age at first use:			
At conception (n=19)‡	2 (11)	17 (89)	0.8 (0.2 to 3.3)
After conception (n=147)	21 (14)	126 (86)	1.2 (0.8 to 2.0)
Duration of use:			
≤1 week (n=147)	22 (15)	125 (85)	1.3 (0.8 to 2.1)
>1 week (n=23)	2 (9)	21 (91)	0.7 (0.2 to 2.9)

\*NSAID or aspirin users were excluded from this analysis.

†Adjusted for previous miscarriage, education, maternal age, gravidity, race, use of Jacuzzi or hot tub, multivitamin use, and smoked since last menstruation. Further adjustment for other variables did not change the results.

‡Within the first week of gestational age.

### Strengths and limitations of study

Our study is a substantial improvement on the study that first reported an association between NSAID use and miscarriage.<sup>9</sup> Our ascertainment of NSAID and aspirin exposure was more complete and based on actual use rather than prescription, and our ascertainment of miscarriage was complete among all participants. We also identified indications for use of the drugs, controlled for confounding factors, evaluated the effect of timing and duration of use, and had an internal comparison group of paracetamol users.

However, because examination of the association of NSAID use with miscarriage was not the main aim of the original study, this study has potential limitations. Despite direct questioning of all participants, our ascertainment of NSAID and aspirin use during pregnancy was still probably incomplete. Because our study was a prospective cohort study, most of the participants were still pregnant when they were interviewed. Therefore, some of the participants who reported no use could have used the drugs after the interview and while still pregnant. However, this misclassification of some users into the non-user group would, if anything, have attenuated the observed association of NSAID and aspirin use with miscarriage. In addition, the reported frequency of NSAID use in our study (5%) was much higher than that reported in the previous study (1%),<sup>9</sup> indicating a more complete ascertainment of NSAID use. Finally, the risk of miscarriage was mainly associated with NSAID use around conception, which we should have completely ascertained for all participants.

### Probable mechanism of effect

The association between NSAID use and miscarriage is unlikely to be due to the underlying indications for use of NSAIDs or aspirin. Paracetamol, which shares many of the indications for use with NSAIDs (see table A on [bmj.com](http://bmj.com)) but has a different underlying pharmacological effect, had no effect on risk of miscarriage. NSAIDs and aspirin are considered to inhibit prostaglandin biosynthesis in most organ systems, whereas paracetamol inhibits prostaglandin biosynthesis only in the central nervous system.

Animal studies have shown that prostaglandins are needed for successful implantation of an embryo into the uterus wall.<sup>8</sup> Prostaglandins have also been reported to play an important part in human ovulation and implantation through their own effect and interaction with platelet activating factors and cytokines, both in the uterus and in the embryo.<sup>14-16</sup> Suppression of prostaglandin biosynthesis by NSAIDs in peripheral tissues, including those of the reproductive system, could therefore lead to abnormal implantation that predisposes an embryo to miscarriage. In fact, the newer selective NSAIDs (cyclo-oxygenase 2 inhibitors) are classified as pregnancy category C because of increased peri-implantation and post-implantation losses and reduced fetal survival in rats and rabbits. However, such an effect with non-selective NSAIDs has not been as well examined.

In addition, it has been suggested that a delicate balance of the concentration of various types of prostanoids is essential for maintaining normal blood pressure during pregnancy.<sup>8</sup> NSAID use that suppresses the production of prostaglandins may have an

### What is already known on this topic

A recent study reported an increased risk of miscarriage with NSAID use during pregnancy, but the study was limited, relying solely on linkage of data from registers

### What this study adds

This population based cohort study provides stronger evidence of an association between NSAID and aspirin use and miscarriage

The risk of miscarriage was highest with NSAID use around the time of conception increases and with NSAID use for longer than a week

Paracetamol, which shares many of the indications for use with NSAIDs but has a different underlying pharmacological effect, had no effect on risk of miscarriage

adverse effect on placental perfusion and circulation. Without a healthy placenta, the risk of fetal demise can increase greatly.

We found that the highest risk of miscarriage was with NSAID use around the time of conception. This supports the mechanism of normal implantation being altered by NSAID use.

### Conclusions

If NSAID use during pregnancy, especially around conception, is associated with miscarriage it will have wide clinical implications because many women are likely to be prescribed NSAIDs during the periconceptional period. Our findings will need confirmation in studies that are designed specifically to examine the association between NSAID use and the risk of miscarriage. Meanwhile, however, it may be prudent for physicians and women who are planning to be pregnant to be aware of this potential risk and avoid using NSAIDs around conception.

Contributors: see [bmj.com](http://bmj.com)

Funding: The study was supported in part by funds from the California Public Health Foundation and the National Institute of Child Health and Human Development (NICHD).

Competing interests: None declared.

Ethical approval: The Institutional Review Board of Kaiser Permanente approved the protocol and conduct of the study.

- 1 Setter SM, Corbett C, Gates BJ, Terriff C, Johns CA, Sclar DA, et al. Non-steroidal anti-inflammatory drugs: The need for assessment and education. *Home Care Provid* 2001;6:100-5.
- 2 Brooks P. Use and benefits of nonsteroidal anti-inflammatory drugs. *Am J Med* 1998;104:9-13S.
- 3 Hernandez-Diaz S, Garcia-Rodriguez LA. Epidemiologic assessment of the safety of conventional nonsteroidal anti-inflammatory drugs. *Am J Med* 2001;110(suppl 3A):20S-7S.
- 4 Hertz-Picciotto I, Hopenhayn-Rich C, Golub M, Hooper K. The risks and benefits of taking aspirin during pregnancy. *Epidemiol Rev* 1990;12:108-48.
- 5 Werler MM, Mitchell AA, Shapiro S. The relation of aspirin use during the first trimester of pregnancy to congenital cardiac defects. *N Engl J Med* 1989;321:1639-42.
- 6 Streissguth AP, Treder RP, Barr HM, Shepard TH, Bleyer WA, Sampson PD, et al. Aspirin and acetaminophen use by pregnant women and subsequent child IQ and attention decrements. *Teratology* 1987;35:211-9.
- 7 Janssen NM, Genta MS. The effects of immunosuppressive and anti-inflammatory medications on fertility, pregnancy, and lactation. *Arch Intern Med* 2000;160:610-9.
- 8 Dawood MY. Nonsteroidal antiinflammatory drugs and reproduction. *Am J Obstet Gynecol* 1993;169:1255-65.
- 9 Nielsen GL, Sorensen HT, Larsen H, Pedersen L. Risk of adverse birth outcome and miscarriage in pregnant users of non-steroidal anti-

- inflammatory drugs: population based observational study and case-control study. *BMJ* 2001;322:266-70.
- 10 Li DK, Odouli R, Wi S, Janevic T, Golditch I, Bracken TD, et al. A population-based prospective cohort study of personal exposure to magnetic fields during pregnancy and the risk of miscarriage. *Epidemiology* 2002;13:9-20.
- 11 Anderson PK, Gill RD. Cox's regression model for counting processes: a large sample study. *Ann Stat* 1982;10:1100-20.
- 12 Therneau TM, Grambsch PM. *Modeling survival data: extending the Cox model*. New York: Springer-Verlag, 2000.
- 13 Howards PP, Hertz-Picciotto L. Spontaneous abortion and left truncation [abstract] *Am J Epidemiol* 2002;155(11):S35.
- 14 Van der Weiden RM, Helmerhorst FM, Keirse MJ. Prostanoid excretion in incipient singleton and twin pregnancies. *Am J Obstet Gynecol* 1996;174:1614-7.
- 15 Van der Weiden RM, Helmerhorst FM, Keirse MJ. Influence of prostaglandins and platelet activating factor on implantation. *Hum Reprod* 1991;6:436-42.
- 16 Van der Weiden RM, Wouters JM. Infertility may sometimes be associated with non-steroidal anti-inflammatory drug consumption. *Br J Rheumatol* 1997;36:605.

(Accepted 2 June 2003)

## Doctors' knowledge of radiation exposure: questionnaire study

S Shiralkar, A Rennie, M Snow, R B Galland, M H Lewis, K Gower-Thomas

### Introduction

Despite the small but definite risk to patients' health, investigations involving radiation are an accepted and fundamental part of medical practice. In the United Kingdom an estimated 100-250 deaths occur each year from cancers directly related to medical exposure to radiation.<sup>1</sup> In March 2000, the UK secretary of state issued new regulations that emphasised the importance and dangers of radiation.<sup>2,3</sup>

We investigated the level of knowledge doctors have concerning radiation doses received by patients when they undergo commonly requested radiological investigations.

### Participants, methods, and results

We compiled a questionnaire listing the most commonly requested radiological investigations. Participants were asked to identify the average dose of radiation received when a person underwent a standard chest x ray. This was then used to represent a single dose of radiation, and doctors were asked to estimate the equivalent doses of radiation for various radiological investigations (table).

We asked a convenience sample of 130 doctors at all different grades from two separate hospitals (South Wales and Oxford) to take part in the study and interviewed each doctor on a one to one basis. All doctors agreed to complete the questionnaire. There was no negative marking. We accepted a deviation of 20% above and below the correct value (wider variations were allowed for those procedures for which the radiation dose can vary enormously). Correct answers to the questions were derived from information available on the internet<sup>4</sup> and counter checked with the Royal College of Radiologists.<sup>5</sup>

We interviewed 40 senior house officers, 40 specialist registrars, 40 consultants, and 10 consultant radiologists. None of them knew the approximate dose of radiation received by a patient during a chest x ray or even the measurement in units of radiation (0.02 mSv). The minimum score was 0% and the maximum score was 59%. Five doctors (4%) gave no correct answers. The estimated doses of radiation were much lower than the correct doses. For example, a patient

undergoing an arteriogram of the leg would receive 400 times the radiation of a chest x ray, but the average mean answer was 26 times—that is, doctors were submitting their patients to a radiation dose that was 16 times larger than they thought it was. The average mean dose of irradiation was six times the quantity estimated by the doctor.

Overall, 97% of the answers were underestimates of the actual dose; six (5%) doctors did not realise that ultrasound does not use ionising radiation; and 11 (8%) did not realise that magnetic resonance imaging does not use ionising radiation.

### Comment

In a convenience sample of doctors few had any knowledge about the level of radiation that their patients were exposed to during radiological investigations. Most patients entering hospital will have at least one x ray investigation and usually many more subsequent x rays. It is well known to both the lay public and to medical professionals that although radiological investigations are valuable, they represent a small but definite potential risk to health through exposure to ionising radiation.

Equivalent number of doses of radiation for most commonly requested investigations. Dose for chest x ray used as single unit dose of radiation. Figures are numbers (percentage) of doctors with correct answer for each investigation

Radiological investigation	Equivalent No of chest x rays	No of correct answers (n=130)
Abdominal x ray	75	2 (1.5)
Lumbar spine x ray	120	3 (2)
Thoracic spine x ray	50	4 (3)
Barium swallow	100	6 (5)
Peroperative cholangiogram	65	3 (2)
Fixation of fractured neck of femur	45	10 (8)
Ultrasound of abdomen	0	124 (95)
CT of abdomen	400	8 (6)
Spiral CT of abdomen	300	9 (7)
MRI of abdomen	0	119 (92)
MRI of knee	0	119 (92)
MRI of spine	0	119 (92)
Leg arteriogram	400	0
Renal arteriogram	80	1 (1)
Thyroid isotope scan	50	8 (6)
White cell scan	150	2 (1.5)

CT=computed tomography; MRI=magnetic resonance imaging.

Russells Hall Hospital, Dudley, West Midlands DY1 2HQ  
S Shiralkar  
consultant surgeon

Royal Berkshire Hospital, Reading RG1 5AN

A Rennie  
senior house officer in general surgery  
R B Galland  
consultant surgeon

continued over

*BMJ* 2003;327:371-2