で 32.7%であった。

## E. 考察

平成 20 年度に行った周産期疫学研究における研究デザインの検討では，ケース・コホート研究が本研究課題には最も適した研究デザインと判断された。コホート内ケース・コントロール研究に比べ，ケース・コホート研究の認知度は小さく，その応用事例は少ないものの，コントロール抽出におけるバイアス混入の少なさ，条件設定の容易さなど，計画段階における研究デザインの特徴は，本研究班の課題である周産期の重大イベントにおけるリスク因子の把握では，大きな利点になると考えられた。特に，指定した部分コホートを共通のコントロール群として，多くの疾患発生に利用できることは，本研究課題に適したものと言える。また，海外での母子保健領域でのケース・コホート研究の事例の検討からも，わが国の周産期における重大イベントのリスク因子を探索するために，ケース・コホート研究を応用することは十分に実施可能と考えられた。

そこで，平成 21 年度には，日本産科婦人科学会周産期登録データベースを利用して，妊娠中喫煙の影響をケース・コホート研究で検討した。その結果，妊娠高血圧症候群，前期破水，切迫早産，頚管無力症，絨毛膜羊膜炎，胎盤早期剥離の 6 つの疾患で，妊娠中喫煙によって統計学的に有意な発生増加がみられた。相対過剰発生割合、相対集団過剰発生割合においては，前期破水，絨毛膜羊膜炎，頚管無力症が特に影響の大きな疾患であった。これらの多くは，海外の先行研究結果と符合する知見であるが，大規模データベースを用いたわが国で初めての系統的な疫学エビデンスといえる。また，妊娠高血圧症候群や頚管無力症では海外研究結果との差異もみられ，海外情報を無批判に一般化するのではなく，本邦女性のデータベースからリスク因子評価することの重要性が認識された。

平成 22 年度には，周産期情報を成人期での疫学研究に活用することの実施可能性を検討した。近年，米国では周産期情情報を含む登録データは，州単位で電子媒体してデータベース化されており（Electronic Birth Registration System），このデータベースを利用した疫学研究や，他の情報ベースとリンクした疫学研究に利用されつつあった。また，登録されている周産期情報も豊富で，本研究班の疫学研究で利用された日本産科婦人科学会の周産期登録データ [6]にも匹敵する情報量となっている。

わが国の出生証明書も人口動態統計調査・出生票として電子媒体化されているが，出生時体重，出生時身長，単胎・多胎，妊娠週数，児の出産順位と周産期情報は限られている。また，他情報と連結するような疫学研究での利用は困難である。そのため，わが国では，出生証明書以外に，疫学研究に利用にきる周産期情報源が必要と考えられた。そのもっとも有用と考えられる情報源が，母子健康手帳と考えられた。母子健康手帳に記載されている情報は，米国の出生証明書 long form の情報をはるかにしのぎ，また出生時点以降の情報も追加されてゆくといった大きな利点をもつ。その有効な活用を考えるとき，母子健康手帳の情報は，統一された情報記録方法によって，後年になっても容易に電子媒体として利用できる管理保管法が必要であると考えられた。

## F. 結論

周産期情報データベースを利用する疫学研究において，ケース・コホート研究が最適な研究デザインと考えられた。日本産科婦人科学会周産期委員会の周産期登録データベースを利用し，妊娠中喫煙の妊娠合併症に与える影響をケース・コホート研究によって検討した結果，妊娠高血圧症候群，前期破水，切迫早産，頚管無力症，絨毛膜羊膜炎，胎盤早期剥離の 6 疾患で，妊娠中喫煙者に有意な発症増加がみられた。周産期情報の疫学研

究への利用可能性を検討した結果，母子健康手帳がその有効なデータ源になると考えられた。

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## G. 健康危険情報

なし

## H. 研究発表

1．林邦彦：基礎資料の収集にあたって－ケース・コホート研究の重要性．ワークショップ「新たな妊婦健診体制の構築に向けて母子手帳を考える－必要な母体・胎児情報は何か」第 45 回日本周産期・新生児医学会学術集会（名古屋），2009 年 7 月 12－13 日．

2．Hayashi K, Matsuda Y, Kawamichi Y, Shiozaki A, Saito S: Smoking during pregnancy increases risks of obstetric complications: A case-cohort study of the Japan Perinatal Registry Database. Journal of Epidemiology 21(1): 61-6, 2011.

## I. 知的財産権の出願・登録状況

なし

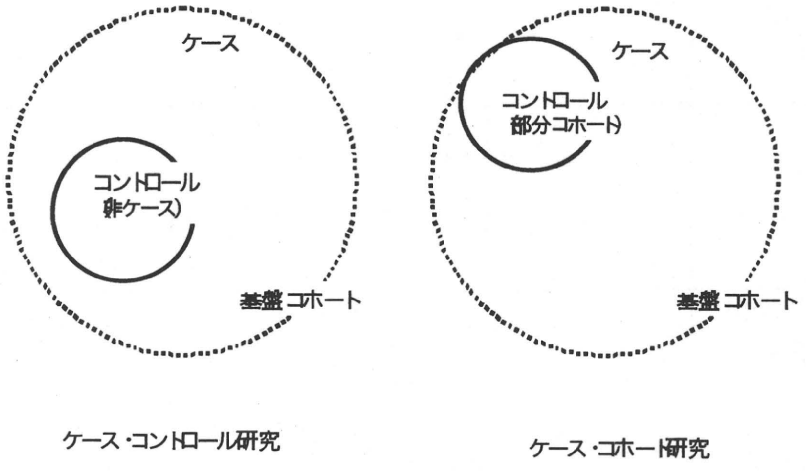


図 1. コホート内ケース・コントロール研究とケース・コホート研究における
コントロール抽出の違い

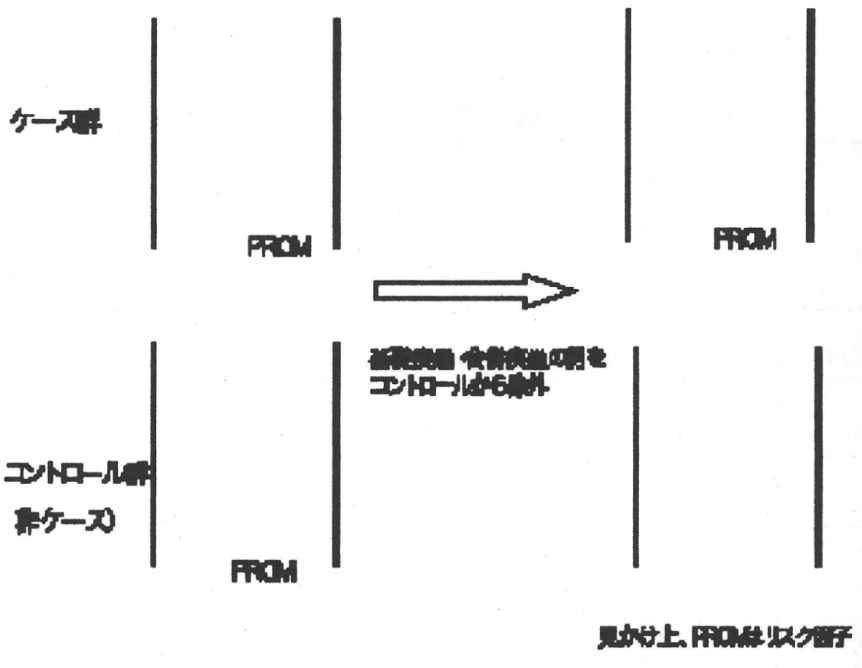


図 2. 完全な非ケースをコントロールにすることの危険

**表１．コホート内ケース・コントロール研究とケース・コホート研究の比較**

| 特徴 | コホート内<br>ケース・コントロール研究 | ケース・コホート研究 |
|---|---|---|
| 認知度 | 広く応用されている | 応用例は少ない |
| サンプル・サイズ<br>計算 | 基盤コホートの大きさに<br>依存しない | 基盤コホートの観察が<br>確定しないと，計算困難 |
| コントロール抽出<br>での条件設定 | 非ケースの条件設定は困難 | 特に条件設定はいらない |
| コントロール抽出<br>での容易さ | ケースが発生するたびに，<br>非ケースの抽出が必要 | コントロールの抽出は，<br>ケース発生とは独立<br>しているため容易 |
| 多数の疾病事象 | 疾病事象ごとに非ケースを<br>抽出しなくてはならない | 共通のコントロール群と<br>して部分コホートを利用 |
| リスクの解析方法 | オッズ比で近似 | リスクおよびリスク比<br>を直接推定可能 |
| 他集団との<br>外的比較 | リスク推定ができず，<br>外的比較は困難 | 発生割合などでの<br>比較が可能 |

**表２．各種妊娠合併症における喫煙の影響**

| 妊娠合併症 | 年間全国<br>推定発生<br>件数(件) | 相対過剰<br>発生割合<br>REI（%） | 全国集団<br>過剰発生数<br>PEI（件） | 相対集団過剰<br>発生割合<br>RPEI（%） |
|---|---|---|---|---|
| 妊娠高血圧症候群 | 44,605 | 16.7 | 508 | 1.1 |
| 前期破水 | 41,767 | 40.1 | 1,552 | 3.7 |
| 切迫早産 | 34,378 | 27.5 | 736 | 2.1 |
| 頚管無力症 | 17,809 | 38.7 | 624 | 3.5 |
| 絨毛膜羊膜炎 | 15,177 | 39.4 | 548 | 3.6 |
| 胎盤早期剥離 | 10,711 | 27.0 | 224 | 2.1 |

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Original Article

# Smoking During Pregnancy Increases Risks of Various Obstetric Complications: A Case-Cohort Study of the Japan Perinatal Registry Network Database

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## ABSTRACT

**Background:** The adverse effects of maternal smoking on the health of pregnant women have been examined mostly on a disease-by-disease basis. The aims of this study were to evaluate simultaneously the effects of smoking during pregnancy on various obstetric complications, using data from a large medical database, and to investigate the expediency of using a case-cohort design for such an analysis.

**Methods:** A case-cohort study was conducted within the Japan Perinatal Registry Network database. Perinatal information on infant deliveries was entered into the database at 125 medical centers in Japan. The base population of the study was 180 855 pregnant women registered in the database from 2001 through 2005. The outcome measures were the incidences of 11 different obstetric complications. Logistic regression models were used to estimate age-adjusted risk ratios (aRRs) and relative excess incidence proportions (REIs).

**Results:** The overall prevalence of smoking during pregnancy was 5.8% in the base cohort, and the prevalence was higher among younger women. A comparison of the cases and control cohort showed that smokers during pregnancy had statistically significant higher risks for preterm rupture of the membrane (aRR: 1.67, 95% confidence interval [CI]: 1.43–1.96; REI: 40.2%, 95% CI: 29.9%–49.1%), chorioamnionitis (1.65, 1.36–2.00; 39.4%, 26.4%–50.0%), incompetent cervix (1.63, 1.35–1.96; 38.5%, 25.8%–49.1%), threatened premature delivery (1.38, 1.17–1.64; 27.7%, 14.5%–38.9%), placental abruption (1.37, 1.10–1.72; 27.1%, 8.8%–41.7%), and pregnancy-induced hypertension (1.20, 1.01–1.41; 16.4%, 1.2%–29.3%).

**Conclusions:** Maternal smoking was associated with a number of obstetric complications. This highlights the importance of smoking cessation during pregnancy. In addition, case-cohort analysis proved useful in estimating RRs for multiple outcomes in a large database.

***Key words:*** smoking during pregnancy; obstetric complications; perinatal epidemiology; case-cohort study; registry database

## INTRODUCTION

According to the Organisation for Economic Co-operation and Development (OECD), the prevalence of current smoking in adult women is 13% in Japan, 14% in the United States, 19% in Germany, and 20% in the United Kingdom.[1] Although many pregnant women try to quit smoking, and some tobacco control programs have successfully reduced the proportion of smoking mothers,[2] the prevalence of smoking during pregnancy is approximately 6.5% in Japan,[3,4] 12% in the United States,[5] 12% in Germany,[6] and 15% in the United Kingdom.[7]

The adverse effects of maternal smoking during pregnancy on the health of a fetus are well known and include still births, fetal growth restriction, decreased infant birth weight, and neonatal death. In addition, pregnant women who smoke may themselves experience complications such as premature rupture of the amniotic membrane. However, there are no comprehensive evaluations of the adverse effects of smoking on the health of pregnant women, because many different obstetric complications are possible and most studies examine these complications individually.

A case-cohort study—which is identical to a case-base design in which the base cohort is closed and the measure of

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interest is an incidence proportion rather than an incidence rate—is a variation of the case-control design in which the controls are drawn from the entire base population, regardless of their disease status.[8–10] These conditions for the base cohort in a case-cohort design are common in perinatal epidemiologic studies.[9,10] We evaluated the adverse effects of smoking during pregnancy on 11 different obstetric complications, using a population-based database, and examined the expediency of using a case-cohort design for such a comprehensive evaluation.

## METHODS

### Study design and data source

We conducted a case-cohort study using the Japan Perinatal Registry Network database, which was started in 1974 and is managed by the Japan Society of Obstetrics and Gynecology. This database was converted to its present database structure in 2001. It includes all live and stillbirths at 125 medical centers in Japan, including 76 university hospitals, 14 national hospitals, 10 Japanese Red Cross hospitals, and 25 other hospitals, and covered 5.2% (56 671 registered births) of the total 1 094 434 live and stillbirths in Japan in 2005.

A detailed description of the database has been published elsewhere.[11] In brief, a self-administered questionnaire, interview, and medical records were used to collect information on maternal age, parity, cigarette smoking during pregnancy, alcohol intake during pregnancy, medical history, history of treatment for infertility, major obstetric complications during pregnancy, mode of delivery, and neonatal outcomes. Data entry was routinely performed by attendants at the time of delivery. The data conform to uniform coding specifications and diagnostic criteria for complications and were subject to rigorous quality checking. Smoking during pregnancy and the incidence of each obstetric complication were coded as "yes" or "no" in the database. The dataset for the study was provided by the Japan Society of Obstetrics and Gynecology. The study protocol was reviewed and approved by the ethics committee of Tokyo Women's Medical University.

The base cohort of the study consisted of 180 855 pregnant women carrying a singleton fetus who were registered in the database from 2001 through 2005. Complete information on obstetric complications and smoking status during pregnancy was present for all women included in the base cohort.

### Case identification and control selection

From the base cohort, the cases were independently identified for 11 obstetric complications: threatened premature delivery before 37 completed weeks of pregnancy, incompetent cervix, pregnancy-induced hypertension, eclampsia, pulmonary edema, placental abruption, placenta previa, preterm premature rupture of the membrane (PROM) before 37 completed weeks of pregnancy, chorioamnionitis, placenta accreta, and disseminated intravascular coagulation syndrome.

The procedures for control selection in a conventional nested case-control study and a case-cohort study are illustrated schematically in Figure 1. To perform a comprehensive evaluation of multiple outcomes using a large database, a case-cohort study is preferable to a conventional nested case-control study, which is the most common study design.[10] An advantage of the case-cohort design is that it allows the use of the same controls (ie, a subcohort selected from the base cohort) for several different outcome diseases. The control cohort in the current case-cohort study was selected randomly from the entire base cohort and included both cases and non-cases. We selected 3749 women for the control cohort, which represented at least 2% of all registered pregnant women in each hospital. The same control cohort was used in the analysis of each obstetric complication.

### Statistical analysis

Unconditional logistic regression models were used to estimate ratios of incidence proportions (risk ratios, RRs) and 95% confidence intervals (CIs) for the association of smoking during pregnancy with the incidence of each obstetric complication. The RR is estimated from the ratio of pseudo-risks by sampling controls from subjects at risk in a case-cohort design, and the incidence odds ratio (OR) is estimated by sampling from non-cases in a cumulative case-control study.[9] We conducted a case-cohort comparison; therefore, logistic regression analysis provided an exact estimate of the RR without any arguments on a rare-disease assumption for outcome events. It is often assumed that the outcome disease under study is rare when the incidence OR approximates the RR. In general, this assumption is not needed, however, even in a case-control study. However, the incidence OR in a case-control study is not expected to be a good approximation of the RR, unless the incidence proportion is less than approximately 0.1.[9]

Smoking is one of the most preventable risk factors. For that reason, relative excess incidence proportions (REIs), which are identical to attributable fractions in the exposed population, and 95% CIs were calculated using the exact estimate of RRs:

$$\mathrm{REI}\ (\%) = \frac{\mathrm{RR} - 1}{\mathrm{RR}} \times 100$$

The REI is the fraction of the obstetric complication burden among smokers during pregnancy that would not have occurred if the smokers had the same incidence of complications as nonsmokers during pregnancy.[12]

Wald's $\chi^2$ test was performed in the logistic regression analysis, and $P < 0.05$ was considered statistically significant. All statistical data analyses were carried out using SAS ver. 9.1 (SAS Institute Inc., Cary, NC, USA).

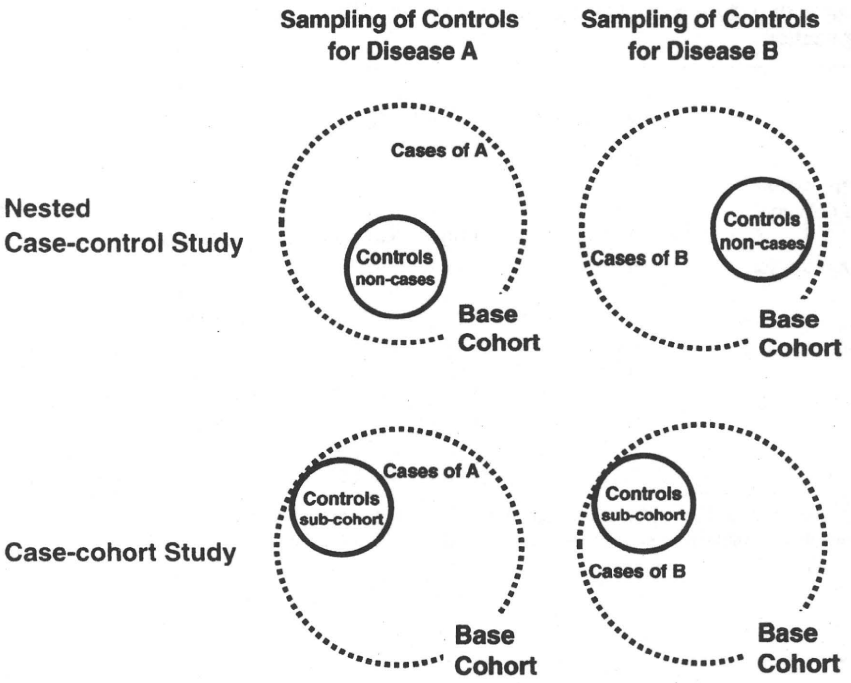


Figure 1. Control selection in nested case-control and case-cohort studies

## RESULTS

### Smoking during pregnancy in base cohort

The base cohort included 180 855 women. At the time of delivery, 2834 (1.6%) of the women were younger than 20 years, 17 867 (9.9%) were 20 to 24 years of age, 54 057 (29.9%) were 25 to 29 years of age, 67 886 (37.5%) were 30 to 34 years of age, 32 173 (17.8%) were 35 to 39 years of age, and 6038 (3.3%) were 40 years or older.

A total of 10 527 women (5.8%) in the base cohort smoked during pregnancy. The prevalence of smoking during pregnancy tended to gradually increase as maternal age decreased. In particular, the prevalence of smoking during pregnancy was high in women younger than 20 years (15.7%) and in women aged 20 to 24 years (10.7%), as shown in Table 1.

**Table 1. Prevalence of smoking during pregnancy in base cohort**

| | Prevalence | No. of smokers | | No. of women |
|---|---|---|---|---|
| All women | 5.8% | 10527 | / | 180855 |
| Maternal age at delivery, years | | | | |
| ≤19 | 15.7% | 444 | / | 2834 |
| 20–24 | 10.7% | 1910 | / | 17867 |
| 25–29 | 5.8% | 3136 | / | 54057 |
| 30–34 | 4.7% | 3166 | / | 67886 |
| 35–39 | 4.8% | 1545 | / | 32173 |
| ≥40 | 5.4% | 326 | / | 6038 |

### Cases of obstetric complications identified in base cohort

In the base cohort, we identified 5681 cases (incidence proportion 3.14%) of threatened premature delivery before 37 completed weeks of pregnancy, 2943 cases (1.63%) of incompetent cervix, 7371 cases (4.08%) of pregnancy-induced hypertension, 143 cases (0.08%) of eclampsia, 76 cases (0.04%) of pulmonary edema, 1770 cases (0.98%) of placental abruption, 2369 cases (1.31%) of placenta previa, 6902 cases (3.82%) of preterm PROM before 37 completed weeks of pregnancy, 2508 cases (1.39%) of chorioamnionitis, 202 cases (0.11%) of placenta accreta, and 343 cases (0.19%) of disseminated intravascular coagulation syndrome.

### Effect of maternal smoking on obstetric complications

A total of 216 women (5.8%) in the control cohort smoked during pregnancy. The prevalence of smoking during pregnancy in the identified cases is shown in Table 2. The crude ratios of incidence proportions (crude RRs) of smoking were statistically significant for threatened premature delivery before 37 completed weeks of pregnancy, incompetent cervix, placental abruption, preterm PROM before 37 completed weeks of pregnancy, and chorioamnionitis. The estimates of ratios of incidence proportions adjusted by maternal age at delivery (age-adjusted RR) are also shown in Table 2. Maternal smoking during pregnancy was significantly associated with threatened premature delivery before 37 completed weeks of pregnancy (age-adjusted RR 1.38), incompetent cervix (1.63), pregnancy-induced hypertension (1.20), placental abruption

**Table 2. Prevalence of smoking during pregnancy, and risk ratios (RRs) and relative excess incidence proportions (REIs) for obstetric complications**

| | Smoking prevalence | Crude RR (95% CI) | Age-adjusted RR (95% CI) | Age-adjusted REI[a] (95% CI) |
|---|---|---|---|---|
| **Control cohort** | 5.8% | | | |
| **Cases of obstetric complications** | | | | |
| Threatened premature delivery[b] | 8.0% | 1.42 (1.20–1.68) | 1.38 (1.17–1.64) | 27.7% (14.5%–38.9%) |
| Incompetent cervix | 8.8% | 1.58 (1.31–1.90) | 1.63 (1.35–1.96) | 38.5% (25.8%–49.1%) |
| Pregnancy-induced hypertension | 6.5% | 1.14 (0.97–1.35) | 1.20 (1.01–1.41) | 16.4% (1.2%–29.3%) |
| Eclampsia | 4.9% | 0.84 (0.39–1.82) | 0.82 (0.38–1.78) | |
| Pulmonary edema | 6.6% | 1.15 (0.46–2.88) | 1.22 (0.49–3.06) | |
| Placental abruption | 7.6% | 1.34 (1.07–1.67) | 1.37 (1.10–1.72) | 27.1% (8.8%–41.7%) |
| Placenta previa | 5.6% | 0.97 (0.77–1.21) | 1.07 (0.85–1.34) | |
| Preterm PROM[b] | 9.3% | 1.68 (1.43–1.97) | 1.67 (1.43–1.96) | 40.2% (29.9%–49.1%) |
| Chorioamnionitis | 9.3% | 1.68 (1.38–2.03) | 1.65 (1.36–2.00) | 39.4% (26.4%–50.0%) |
| Placenta accreta | 7.9% | 1.41 (0.83–2.39) | 1.52 (0.89–2.59) | |
| DIC syndrome | 7.3% | 1.29 (0.84–1.98) | 1.35 (0.88–2.08) | |

CI: confidence interval; DIC: disseminated intravascular coagulation; PROM: premature rupture of the membranes.
[a]REI was calculated for obstetric complications significantly associated with maternal smoking during pregnancy.
[b]Before 37 weeks of pregnancy.

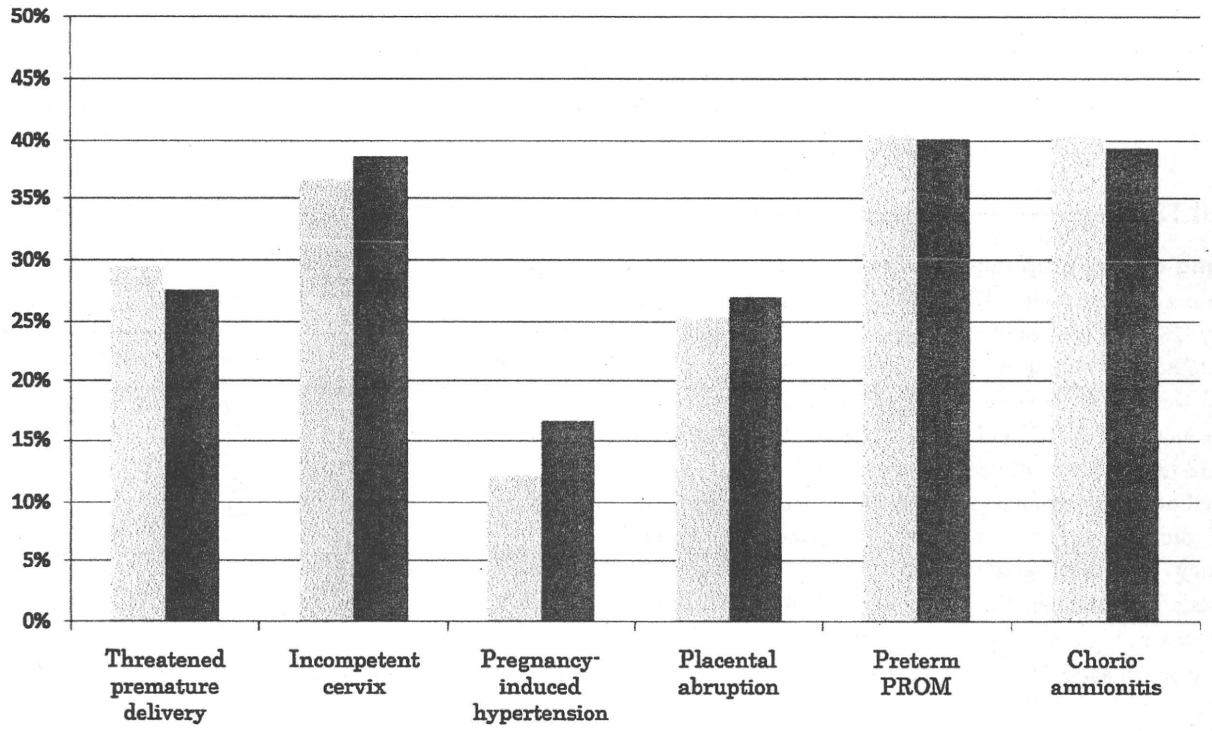


Figure 2. Relative excess incidence proportion (REI) of obstetric complications associated with smoking during pregnancy (left bars: crude REI, right bars: age-adjusted REI)

(1.37), preterm PROM before 37 completed weeks of pregnancy (1.67), and chorioamnionitis (1.65).

As for obstetric complications significantly associated with maternal smoking during pregnancy, crude and age-adjusted REIs are shown in Figure 2. The figure includes both crude and age-adjusted REI for pregnancy-induced hypertension, although the crude association was not statistically significant. Among smoking women, the age-adjusted REIs for threatened premature delivery before 37 completed weeks of pregnancy, incompetent cervix, pregnancy-induced hypertension, placental abruption, preterm PROM before 37 completed weeks of pregnancy, and chorioamnionitis were 27.7%, 38.5%, 16.4%, 27.1%, 40.2%, and 39.4%, respectively (Figure 2, Table 2).

## DISCUSSION

### Effects of maternal smoking on pregnancy-related complications

We found a statistically significant association between

maternal smoking and the incidence of 6 of 11 obstetric complications. Obstetric complications may share many risk factors, of which maternal smoking appears to be one of the most relevant. Previous studies have reported similar adverse effects of maternal smoking on preterm PROM (OR 1.25 to 2.5),[13–15] chorioamnionitis (bacterial vaginosis; OR 1.72),[16] threatened premature delivery (OR 1.34 and 1.3),[13,17] and placental abruption (OR 1.62 to 2.05).[15,18–20] However, to the best of our knowledge, no other epidemiologic study has shown an association between maternal smoking and incompetent cervix, which was the fourth most common obstetric complication in the base cohort of the current study. This newly discovered association with maternal smoking deserves greater attention.

There is controversy regarding the effect of smoking on pregnancy-induced hypertension. Some studies have reported a large reduction in the risk of pregnancy-induced hypertension with maternal smoking (ORs of 0.6 and 0.80 for primiparous women[21] and 0.81 for multiparous women)[22]; other studies have reported a statistically nonsignificant change (OR 1.1)[23] or a strong positive association.[24] We observed a slight increase in the risk of pregnancy-induced hypertension in smokers: the aRR was 1.20, which lies between the values noted in other studies. It is possible that the effect size in different studies varies according to other risk factors, such as chronic hypertension.

Eclampsia was the only obstetric event for which the risk was lower among women who smoked (aRR 0.82), although this decrease was not statistically significant. Other studies have also shown that smoking decreases the incidence of eclampsia (ORs of 0.7,[25] and 0.74 for primiparous women and 0.75 for multiparous women).[22]

### Expediency of case-cohort design

The present case-cohort design was useful for comprehensively evaluating the risk of multiple outcomes associated with maternal smoking. Only 1 control subcohort was required for the analyses of 11 different obstetric complications. In contrast, if we had applied a nested case-control design, 11 different control groups would have been needed. Although we could have selected this 1 control group from subjects who were completely free from all 11 obstetric complications in a case-control study, this would have led to significant selection bias, as there are many common risk factors for the complications we studied. The subjects exposed to these common risk factors would have been systematically excluded if we had included only subjects free of complications. Such bias does not occur in a case-cohort design.

The case-cohort design was also advantageous in estimating REIs in the present study. The estimated RRs were relatively small: the largest aRR was 1.67 for preterm rupture of the membrane. REI is by definition more sensitive to a change in the estimated RR when the RR is closer to 1. In such a situation, the fact that case-cohort analyses provide an exact estimate of the RR, without the need for an approximation, made it possible for us to estimate accurate REIs.

### Methodological strengths and limitations of the study

Many studies have shown an effect of maternal smoking on a single obstetric complication. Such a disease-by-disease approach cannot distinguish between disease-specific variations and study-specific variations. However, the current case-cohort study revealed the adverse effects of maternal smoking on multiple complications.

This study does have some limitations. First, we could not examine the effect of smoking after adjusting for potential socioeconomic confounders because information on socioeconomic status was not available in the database. Second, smoking status during pregnancy was self-reported on questionnaires and in interviews. This type of information gathering likely underestimates the prevalence of pregnant smokers, because not all women will report their smoking[26] and because smokers who quit during pregnancy tend to describe themselves as nonsmokers. This underestimation of smokers leads to potential underestimation of the effect size of smoking. Third, the database has no information on the number of cigarettes smoked daily. Therefore we could not examine any dose-response relationship between smoking and the incidences of obstetric complications.

### Conclusions

Maternal smoking was associated with a number of obstetric complications in a case-cohort analysis of a large perinatal registry database. The study highlighted the importance of smoking cessation during pregnancy. In addition, the case-cohort design proved useful in estimating relative risks for multiple outcomes in a large medical database.

## ACKNOWLEDGMENTS

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Conflicts of interest: None declared.

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# Comparison of risk factors for placental abruption and placenta previa: Case-cohort study

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## Abstract

***Aim:*** A case-cohort study was performed to clarify and compare the risk factors for placental abruption and placenta previa.

***Material & Methods:*** This study reviewed 242 715 births at 125 centers of the perinatal network in Japan from 2001 through to 2005 as a base-cohort. Women with singleton pregnancies delivered after 22 weeks of gestation were included. The evaluation determined the risk factors for placental abruption and placenta previa. Five thousand and thirty-six births (2.1%) were determined as the subcohort by random selection. Acute-inflammation-associated clinical conditions (premature rupture of membranes and clinical chorioamnionitis) and chronic processes associated with vascular dysfunction or chronic inflammation (chronic and pregnancy-induced hypertension, pre-existing or gestational diabetes and maternal smoking) was examined between the two groups.

***Results:*** Placental abruption and placenta previa were recorded in 10.1 per 1000 and 13.9 per 1000 singleton births. Risk factors for abruption and previa, respectively, included maternal age over 35 years (adjusted risk ratios [RRs] = 1.20 and 1.78), IVF-ET (RRs = 1.38 and 2.94), preterm labor (RRs = 1.63 and 3.09). Smoking (RRs = 1.37), hypertension (RRs = 2.48), and pregnancy-induced hypertension (RR = 4.45) were risk factors for abruption but not for previa. On the other hand, multiparity (RR = 1.18) was a risk factor for previa but not for abruption. The rates of acute-inflammation-associated conditions and chronic processes were higher among women with abruption than with previa. (RR 2.0 and 4.08, respectively).

***Conclusion:*** The case-cohort study technique elucidated the difference in the risk factors for placental abruption and placenta previa.

**Key words:** case-cohort study, placental abruption, placenta previa, risk factors.

## Introduction

Placental abruption, defined as premature separation of the placenta from the uterine wall prior to delivery, is an uncommon but serious obstetric complication.[1] Placenta previa, defined as a placenta located at the internal os, is also a serious complication.[2] These two clinical conditions are responsible for up to one fourth of all perinatal deaths because they may cause third trimester bleeding.[3,4] This is due, at least in part, to the excessively high rates of prematurity, fetal growth restriction, and stillbirth that accompany placental

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abruption or placenta previa.[5,6] Therefore, it is essential to know these risk factors, with regard to differences of ethnicity, socio-economical background, or medical systems in order to manage high-risk pregnancies with placental abruption and placenta previa effectively.

The etiologies of placental abruption and placenta previa are speculative and perhaps multifactorial, but a number of risk factors have been identified. These include advanced maternal age, multiparity, cigarette smoking, drug abuse, rapid uterine decompression, a short umbilical cord, prolonged premature rupture of membranes (PROM), chorioamnionitis, folate deficiency, chronic hypertension, preeclampsia, and prior history of placental abruption or placenta previa.[7–10]

However, the mechanism associated with these risk factors is still unclear. A case-cohort study, identical to a case-base study where the base cohort is closed, is a variation of the case control design in which the controls are drawn from the entire base population, regardless of their disease status. A case-cohort study is superior to a conventional case-control study for elucidating the risk factors of diseases in many aspects; however, the former design is not familiar to clinical practitioners.[11]

Therefore, this study examined risk factors for abruption and previa among singleton births in Japan's perinatal registry database from 2001 to 2005 and compared the risk factor profiles with subcohort of the database over the same period.

## Methods

### Study design

A case-cohort design was applied to clarify the risk factors for placental abruption and placenta previa. A case-cohort study has various advantages with respect to the planning stage of a study, such as a low risk of bias in control selection, ease of establishing conditions for selecting the controls, and common utilization of the same control group for a large number of diseases.[11,12] Moreover, the case-cohort study is considered to be advantageous with respect to the analytical stage. In a conventional case-control study, we have to assume that the outcome disease under study is rare in order to estimate relevant relative risk. Conversely, in the case-cohort study, the 'rare-disease assumption' in not required; the risks and risk ratio (RR) can be estimated directly.

Perinatal epidemiological studies are a suitable setting to apply the case-cohort design,[13–15] because cumulative incidences are generally preferred to incidence rates as outcome measures and we can assume that there is no loss-to-follow-up during pregnancy and the base cohort is closed.

### Patient selection

The Tokyo Women's Medical University Ethics Committee approved this study. Informed consent was obtained from all of the subjects in the present study.

Gestational age was determined based on the menstrual history, prenatal examination and ultrasound findings during early pregnancy (gestational sac diameter, crown rump length and biparietal diameter).

There were 285 123 singleton births that resulted in live birth or fetal death at 125 centers of perinatal research network in Japan from 2001 to 2005. These data were assembled by the perinatal committee in the Japan Society of Obstetrics and Gynecology under a cooperative agreement with these hospitals in Japan.[16] The linked data included information on maternal characteristics: maternal age (coded in 6 classes: less than 20, 20–24, 25–29, 30–34, 35–39, and 40 or more years and examined as a continuous variable), parity (parity 0, 1 or more), cigarette smoking (smoker or non smoker), and alcohol use during pregnancy, history of treatment for infertility (ovulation induction, artificial insemination from husband, and *in vitro* fertilization-embryo transfer [IVF-ET]), medical complications, complications of pregnancy. And fetal and infant outcomes were routinely recorded by attendants at the time of delivery. These data conform to uniform coding specifications and have passed rigorous quality checks. The data have been edited and reviewed, and the current study limited the analysis to women who delivered a singleton live birth or stillbirth at 22 or more weeks, excluding missing data. These exclusions left 242 715 singleton births for analysis.

The diagnosis of placental abruption was based on clinical symptoms such as abdominal pain and vaginal bleeding, usually confirmed by ultrasonographic findings[1] and a histopathological examination of the placenta. Placenta previa was classified according to the results of ultrasound examinations into total, partial and marginal previa.[2,3] In summary, total previa is the internal cervical os covered completely by placenta, partial previa is the internal os partially covered by placenta, and marginal previa is the edge of the placenta at the margin of the internal os. The diagnosis of abruption and previa, as well as medical complications, was recorded on a database using a check-box format.

### Statistical analysis

Statistical analyses were performed using the SAS 9.1 statistical software package (SAS Institute, Cary, NC). The differences between placental abruption, placenta previa, and subcohort were compared by multiple comparisons with Bonferroni's correction. $P < 0.05$ was considered statistically significant.

The odds ratio is not a good estimator of the cumulative incidence ratio (ie, RR) when the incidence of the outcome is not rare in a nested case-control study. A case-cohort design was applied to this study; therefore, the design provides an exact estimate of the cumulative incidence ratio (RR) no matter how much the cumulative incidence of the outcome is.[12]

A subcohort of 5039 singleton pregnant females (2.1%) was selected in a random fashion from the entire base cohort including cases. The choice of risk factors for inclusion in the regression model was based on the results of a univariate analysis. RR with 95% confidence intervals (CI) was derived from these models to quantify the association between the causative determinant and abruption and previa. An unconditional logistic regression analysis was used for the multivariate analysis. All models included age at delivery, multipara, smoking, infertility, medical complications (respiratory, cardiovascular, hypertension, thyroid, gastrointestinal, renal, gynecologic, diabetes), and obstetric complication (cervical incompetence, pregnancy-induced hypertension, preterm labor, hydramnios, oligohydramnion, PROM, chorioamnionitis). The incidence of these examined risk factors for abruption and previa in a subcohort was almost as same as that of the perinatal registry database (base-cohort).

The rates of acute-inflammation-associated conditions (PROM and clinical chorioamnionitis) and chronic clinical processes associated with vascular dysfunction or chronic inflammation were estimated between placental abruption and placenta previa mainly based on the report of Ananth *et al.*[17] PROM was defined as all pregnancies in which membranes had been ruptured for over 1 h before the onset of labor. Clinical chorioamnionitis was defined as a maternal temperature more than 38°C and at least one of the following four criteria: maternal tachycardia more than 100 bpm/min, uterine tenderness, white blood cell count more than 15 000 and foul smelling vaginal discharge. If no temperature elevation was present, all four of the other criteria had to be present to diagnose clinical chorioamnionitis.[18] Acute-inflammation-associated conditions included PROM with or without clinical chorioamnionitis and clinical chorioamnionitis in the absence of PROM. Chronic clinical processes included chronic hypertension (blood pressure at least 140/90 mmHg before pregnancy or within the first 20 weeks of gestation), pregnancy-induced hypertension (PIH); hypertension (systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg) that occurred after 20 weeks of gestation), diabetes (types I and II, or gestational diabetes), and smoking during pregnancy (yes or no).

## Results

### Perinatal outcome

There were 2104 cases (0.87%) and 1556 cases (0.64%) of intrauterine fetal death (IUFD) and neonatal death, respectively, in a total of 242 715 cases. Abruption and previa were recorded in 1.01 % and 1.32 %. The raw numbers of IUFD and neonatal deaths in abruption and previa were 409 and 20 for IUFD, and 52 and 20 for neonatal deaths, respectively.

The mean gestational age of delivery in placental abruption and placenta previa was 34.2 +/- 4.1 and 35.1 +/− 3.2 weeks, respectively. Table 1 shows the comparison of perinatal death per 1000 births between the three groups. Perinatal mortality was significantly higher in abruption than in previa and the subcohort. The risk difference of abruption versus previa and of abruption versus subcohort for IUFD was 160 (95% CI 141–179) and 158 (95% CI 140–177), respectively. There was no risk difference between previa versus

**Table 1** Comparison of perinatal death between three groups

| | Placental abruption A ($n = 2461$) | Placenta previa B ($n = 3207$) | Subcohort C ($n = 5036$) | Risk difference A vs B | A vs C | B vs C |
|---|---|---|---|---|---|---|
| IUFD | 166 | 6 | 8 | 160 (141–179) | 158 (140–177) | 2 (–3–6) |
| Neonatal death | 21 | 6 | 5 | 15 (7–23) | 16 (9–24) | 1 (–3–6) |
| Total | 187 | 12 | 13 | 175 (155–195) | 174 (155–194) | 1 (–6–6) |

Results refer to deaths per 1000 births. ( ): 95% CI. IUFD, intrauterine fetal death.

subcohort (2 [95% CI −3–6]). The risk difference of abruption versus previa and of abruption versus subcohort for neonatal death was 15 (95% CI 7–23) and 16 (95% CI 9–24), respectively. There was no risk difference between previa versus subcohort (1 [95% CI −3–6]).

### Comparison of risk factors between abruption and previa

Table 2 shows the comparison of the adjusted RRs for the causative determinants between placental abruption and placenta previa. Factors for placental abruption and placenta previa, respectively, included maternal age over 35 years ($RR_s$ = 1.20 and 1.78), IVF-ET ($RR_s$ = 1.38 and 2.94), and preterm labor ($RR_s$ = 1.63 and 3.09). Smoking ($RR_s$ = 1.37), hypertension ($RR_s$ = 2.48), and pregnancy-induced hypertension (RR = 4.45) were risk factors for abruption but not for previa. On the other hand, multiparity ($RR_s$ = 1.18) was a risk factor for previa but not for abruption.

### Rates of acute-inflammation-associated conditions and chronic clinical processes among women with placental abruption and placenta previa

Figure 1 shows the gestational age-specific incidence rates (per 100 births) of acute- inflammation-associated conditions, and chronic clinical processes among women with placental abruption, with placenta previa, and in the subcohort. The rate of acute-inflammation-associated conditions showed a steady decline with advancing gestation among the abruption and previa births (Fig. 1a). Before 32 weeks of gestation, the rate of conditions was higher in previa than in abruption, and this rate has been reversed after 33 weeks of gestation. In total, the cumulative incidence of acute-inflammation-associated conditions was higher among women with abruption than with previa (10.6% in comparison to 5.6%; RR 2.0, 95% CI 1.64–2.44).

The rate of chronic clinical processes was almost constant throughout gestation among abruption and previa births (Fig. 1b). In total, the cumulative incidence of chronic processes was also higher among women with abruption than with previa (18.6% and 5.3%; RR 4.08, 95% CI 3.39–4.90).

## Discussion

The current study attempted to find an appropriate and efficient epidemiological study design for the identification of risk factors for major perinatal diseases in Japan, using the perinatal registry database established by the Perinatal Committee of the Japan Society of Obstetrics and Gynecology. The results demonstrated that despite low levels of awareness and application, a case-cohort study has various advantages with respect to both the planning stage and the analytical stage of a study. The current study revealed that a case-cohort study was entirely feasible for examining the risk factors for perinatal diseases in Japan and should provide appropriate and efficient analytical results.

Placental abruption and placenta previa occurred in 10.1 per 1000 and 13.9 per 1000 singleton births. The incidence of abruption among singleton pregnancies is usually reported to range from 0.7 percent to 1.0 percent.[19,20] Perinatal mortality was significantly higher in abruption than in previa and the subcohort, which reflected the maternal severity.[5]

The main strength of the current study is that it incorporated a large number of cases that were collected prospectively, with appropriate subcohort. Advanced maternal age and IVF-ET were common risk factors related closely to both placental abruption and placenta previa.

Ananth *et al.* compared the effect of maternal age and concluded that increased maternal age is associated independently with the risk of placenta previa as well as of placental abruption.[21]

The current series showed an increased incidence of abnormal placentation with IVF use, including a 1.4-fold increased risk of placental abruption and a 2.9-fold increased risk of placenta previa in comparison to the control subcohort. This association has also been noted by other authors, including Shevell *et al.* in 2005,[22] Kallen *et al.* in 2005,[23] Romundstad *et al.* in 2006,[24] and Allen *et al.* in 2008.[25] Although the underlying mechanism for this effect is unclear, when pregnancy and the formation of the chorion are initiated *in vitro*, an inherent difference in the nature of the placenta itself may predispose the patient to develop these conditions during gestation. Assisted Reproductive Technology places the embryos in the uterine cavity by the transcervical route using a catheter. This procedure may induce uterine contraction, possibly due to the release of prostaglandins after mechanical stimulation of the internal cervical os.[26]

Smoking, hypertension and pregnancy-induced hypertension were risk factors for abruption but not for previa. Cigarette smoking is protective against preeclampsia and pregnancy-induced hypertension because of nicotine's effects on prostaglandin synthesis[27] or because of the potentially hypotensive effect of

**Table 2** Risk ratio (RR) for the causative determinants of placental abruption and placenta previa

| | Placental abruption ($n = 2461$) (%) | Subcohort ($n = 5036$) (%) | RR | 95% CI | Placenta previa ($n = 3207$) (%) | Subcohort ($n = 5036$) (%) | RR | 95% CI |
|---|---|---|---|---|---|---|---|---|
| Underlying causes | | | | | | | | |
| Background | | | | | | | | |
| Age at delivery (years) | | | | | | | | |
| Less than 20 | 1.10 | 1.50 | 0.71 | 0.46–1.11 | 0.50 | 1.50 | 0.47 | 0.31–0.73 |
| More than 35 | 24.20 | 20.70 | 1.20 | 1.09–1.38 | 28.40 | 20.70 | 1.78 | 1.58–2.00 |
| Multipara | 50.10 | 48.60 | 1.10 | 0.99–1.22 | 57.40 | 48.60 | 1.18 | 1.02–1.35 |
| Smoking | 8.60 | 5.60 | 1.37 | 1.26–2.00 | 6.10 | 5.60 | 1.09 | 0.85–1.39 |
| Infertility | | | | | | | | |
| Ovulation induction | 2.20 | 2.20 | 0.99 | 0.71–1.39 | 2.60 | 2.20 | 1.14 | 0.84–1.57 |
| AIH | 1.10 | 1.30 | 0.87 | 0.56–1.35 | 1.70 | 1.30 | 1.31 | 0.88–1.93 |
| IVF-ET | 1.90 | 1.60 | 1.38 | 1.01–1.90 | 5.20 | 1.60 | 2.94 | 2.23–3.89 |
| Medical complications | | | | | | | | |
| Respiratory | 2.70 | 2.90 | 0.91 | 0.68–1.22 | 2.60 | 2.90 | 0.86 | 0.64–1.14 |
| Cardiovascular | 1.40 | 1.20 | 1.16 | 0.76–1.77 | 1.50 | 1.20 | 0.84 | 0.56–1.25 |
| Hypertension | 1.50 | 0.60 | 2.48 | 1.53–4.03 | 0.20 | 0.60 | 0.44 | 0.22–0.91 |
| Thyroid | 1.80 | 1.50 | 1.25 | 0.86–1.81 | 1.60 | 1.50 | 1.17 | 0.79–1.72 |
| Gastrointestinal | 0.90 | 1.10 | 0.79 | 0.48–1.29 | 0.90 | 1.10 | 0.82 | 0.51–1.29 |
| Renal | 1.30 | 1.10 | 1.19 | 0.77–1.85 | 0.70 | 1.10 | 0.64 | 0.39–1.04 |
| Gynecologic; uterus | 3.90 | 5.40 | 0.72 | 0.57–0.91 | 6.70 | 5.40 | 1.03 | 0.84–1.26 |
| Ovary | 1.00 | 2.00 | 0.49 | 0.31–0.77 | 1.80 | 2.00 | 0.90 | 0.64–1.27 |
| Diabetes | 1.30 | 2.10 | 0.59 | 0.40–0.89 | 1.40 | 2.10 | 0.67 | 0.47–0.95 |
| Obstetric complications | | | | | | | | |
| Cervical incompetence | 1.80 | 1.70 | 1.07 | 0.75–1.54 | 0.90 | 1.70 | 0.29 | 0.19–0.44 |
| PIH | 13.80 | 3.50 | 4.45 | 3.68–5.38 | 1.30 | 3.50 | 0.40 | 0.30–0.54 |
| Preterm labor | 23.00 | 15.50 | 1.63 | 1.44–1.84 | 32.30 | 15.50 | 3.09 | 2.75–3.47 |
| Hydramnios | 1.00 | 0.70 | 1.39 | 0.83–2.31 | 0.60 | 0.70 | 0.62 | 0.35–1.09 |
| Oligohydramnion | 2.50 | 2.20 | 1.13 | 0.83–1.56 | 1.50 | 2.20 | 0.79 | 0.56–1.12 |
| PROM | 9.40 | 11.80 | 0.78 | 0.66–0.91 | 5.40 | 11.80 | 0.43 | 0.36–0.51 |
| Chorioamnionitis | 2.00 | 1.70 | 1.11 | 0.78–1.59 | 1.20 | 1.70 | 0.75 | 0.51–1.11 |

AIH, artificial insemination from husband; IVF-ET, *in vitro* fertilization-embryo transfer; PIH, pregnancy-induced hypertension; PROM, premature rupture of membranes.

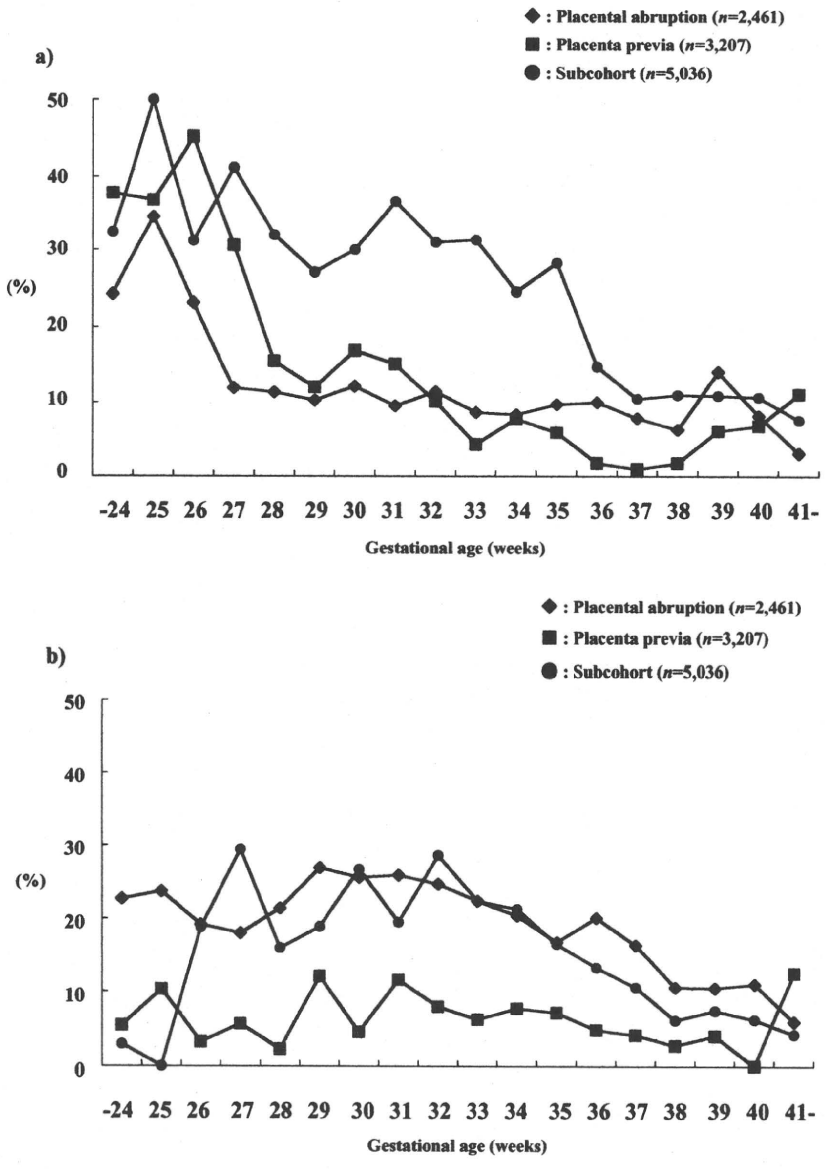


**Figure 1** Rates (per 100 births) of acute-inflammation-associated conditions (a) and chronic clinical processes (b) among women with placental abruption (closed diamond), placenta previa (closed square), and subcohort (closed circle).

thiocyanate contained in tobacco smoke.[28] However, both smoking and hypertensive disorders are established risk factors for placental abruption. A meta-analysis based on over 1.3 million singleton pregnancies concluded that smoking was associated with a 1.9-fold (95% CI, 1.8–2.0) increased risk for abruption. Furthermore, in the presence of smoking, the risk of abruption was dramatically increased with coexistent chronic hypertension or preeclampsia. The current results are considered to be consistent with those of a previous meta-analysis.[29] On the other hand, although maternal smoking during pregnancy might affect placental previa, the magnitude is substantially smaller than previously reported. This association may be attributable to other factors, such as a detection bias.[30]

Ananth *et al.* reported that the risk of pregnancy-induced hypertension was reduced by half among those with placenta previa (RR 0.5, 95% CI 0.3–0.7) and speculated that the pathophysiological mechanisms for this finding may be due to altered placental perfusion seen among women diagnosed with placenta previa.[31] In the case of previa, preterm delivery might occur before the onset of pregnancy-induced hypertension.

**Table 3** Comparison of risk ratio (or odds ratio) [95% CI] between ethnicity for placental abruption

| | Caucasian[29] | Caucasian[2] | Taiwanese[35] | Japanese (current study) |
|---|---|---|---|---|
| Underlying causes: background | | | | |
| Age at delivery: more than 35 years | 1.3–1.5 | 1.1–1.3 | 1.1–2.0 | 1.09–1.38 |
| Multipara | NA | 1.1–1.6 | NA | 0.99–1.38 |
| Prior abortion | 10.0–25.0 | 8.0–12.0 | NA | NA |
| Low BMI before pregnancy | NA | NA | 1.0–1.6 | NA |
| Smoking | 1.4–1.9 | 1.4–2.5 | 3.0–23.9 | 1.26–2.0 |
| Cocaine use | NA | 5.0–10.0 | NA | NA |
| Infertility(IVF-ET) | NA | NA | NA | 1.01–2.0 |
| Medical complications | | | | |
| Thrombophilia | 3.0––0.7 | NA | NA | NA |
| Hypertension | 1.8–3.0 | 1.8–5.1 | NA | 1.53–4.03 |
| Obstetric complications | | | | |
| PIH | 2.1–4.0 | NA | NA | 3.68–5.38 |
| Hydramnios | 2.00 | 2.0–3.0 | 1.7–7.7 | 0.83–2.31 |
| Oligohydramnion | NA | NA | 2.7–6.7 | 0.83–1.56 |
| Chorioamnionitis | NA | 2.0–2.5 | NA | 0.66–0.91 |

BMI, body mass index; CI, confidence interval; IVF-ET, *in vitro* fertilization-embryo transfer; PIH, pregnancy-induced hypertension; NA, no data available.

**Table 4** Comparison of risk ratio (or odds ratio) [95% CI] between ethnicity for placenta previa

| Underlying causes: background | Caucasian[36] | Taiwanese[37] | Japanese (current study) |
|---|---|---|---|
| Age at delivery: more than 35 years | 3.3–12.5 | 1.5–2.6 | 1.58–2.0 |
| Multigravida | 2.5–6.6 | NA | NA |
| Multipara | NA | NA | 1.02–1.35 |
| Prior preterm birth | NA | 4.1–10.6 | NA |
| Prior induced abortion | 2.04–3.83 | 1.4–2.9 | NA |
| History of cesarean section | 1.17–3.44 | NA | NA |
| Smoking | 1.4–1.9 | 1.2–9.1 | 0.85–1.39 |
| Infertility (IVF-ET) | NA | 4.1–10.6 | 2.23–3.89 |

CI, confidence interval; IVF-ET, *in vitro* fertilization-embryo transfer.

Multiparity was a risk factor for previa but not for abruption. Ananth *et al.* compared the effect of maternal age and parity on the risk of uteroplacental bleeding disorders in pregnancy and concluded that multiparity is associated with the risk of placenta previa, and, to a lesser extent, placental abruption, and increased maternal age is associated independently with the risk of placenta previa. From these observations, they speculated that these uteroplacental bleeding disorders do not share a common etiology in relation to maternal age and parity, and that placental previa is linked to aging of the uterus.[21] Dafallah and Babikir showed in a large population based data set that parity and maternal age were not associated with an increased incidence of placental abruption.[32]

The current study used the concept of acute-inflammation-associated conditions and chronic processes mainly based on the report of Ananth *et al.*[17] in order to clarify the difference between these two clinical entities. The present study showed that the rates of both acute-inflammation-associated conditions and chronic processes were higher among women with abruption than with previa. Although the rate of acute-inflammation-associated conditions showed a steady decline with advancing gestation among abruption and previa, the rate of these conditions was higher in previa than in abruption before 32 weeks of gestation, and this rate was reversed after 33 weeks of gestation. It might be apparent that acute-inflammation-associated conditions in abruption are more prevalent than in previa

when gestation advances.[8] On the other hand, the rate of chronic clinical processes was almost constant throughout gestation among abruption and previa births, and in total, the rates of chronic processes were also higher among women with abruption than with previa. This observation suggests that the relationship of chronic vascular conditions is more frequent in placental abruption.[33]

Faiz *et al.* conducted a systematic literature review concerning the risk factors of placenta previa and identified 58 studies published between 1966 and 2000. The review revealed strong heterogeneity in the associations between risk factors and placenta previa by study design, accuracy in the diagnosis of placenta previa and population-based versus hospital-based studies. They concluded that future etiological studies on placenta previa must, at the very least, adjust for potentially confounding effects of maternal age, parity, prior cesarean delivery and abortions.[34]

Despite the fact that this analysis was based on a large number of pregnancies subcohorts, some limitations of this study merit attention. First, the processes could not be investigated simultaneously in the current study. Second, the current study did not take into account at least three important risk factors for abruption: parity, chorioamnionitis and cocaine use, because such information on these factors is currently not available in the statistics data. After having considered such limitations, we determined the characteristic risk factors in Japanese pregnant women and compared with other Asian and Caucasian people, as shown in Table 3 and Table 4.[2,29,35–37] There is an increased risk of adverse events in a subgroup of these patients, and the information provided here should prove useful when counseling prospective patients.

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