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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.

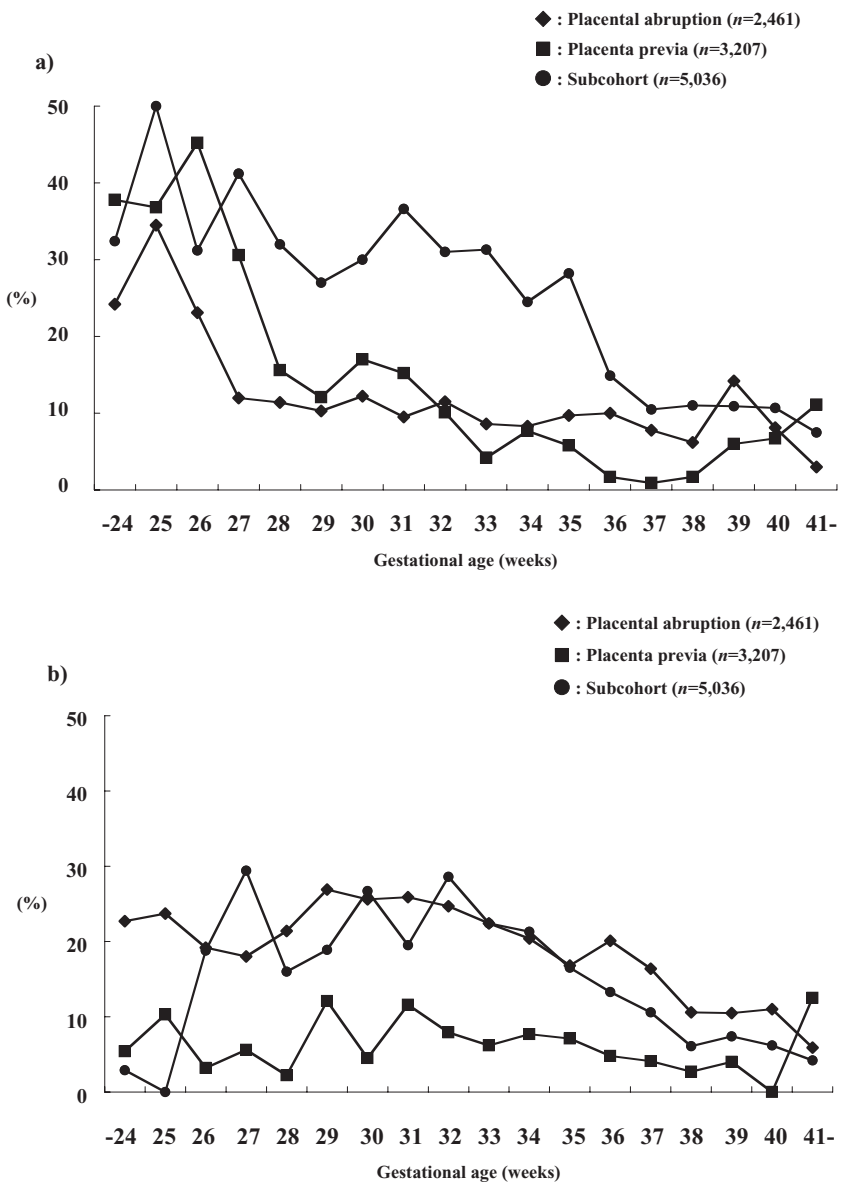

Figure 1 Rates (per 100 births) of acute-inflammation-associated conditions (a) and chronic clinical processes (b) among women with placental abruption (closed diamond), placenta previa (closed square), and subcohort (closed circle).

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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