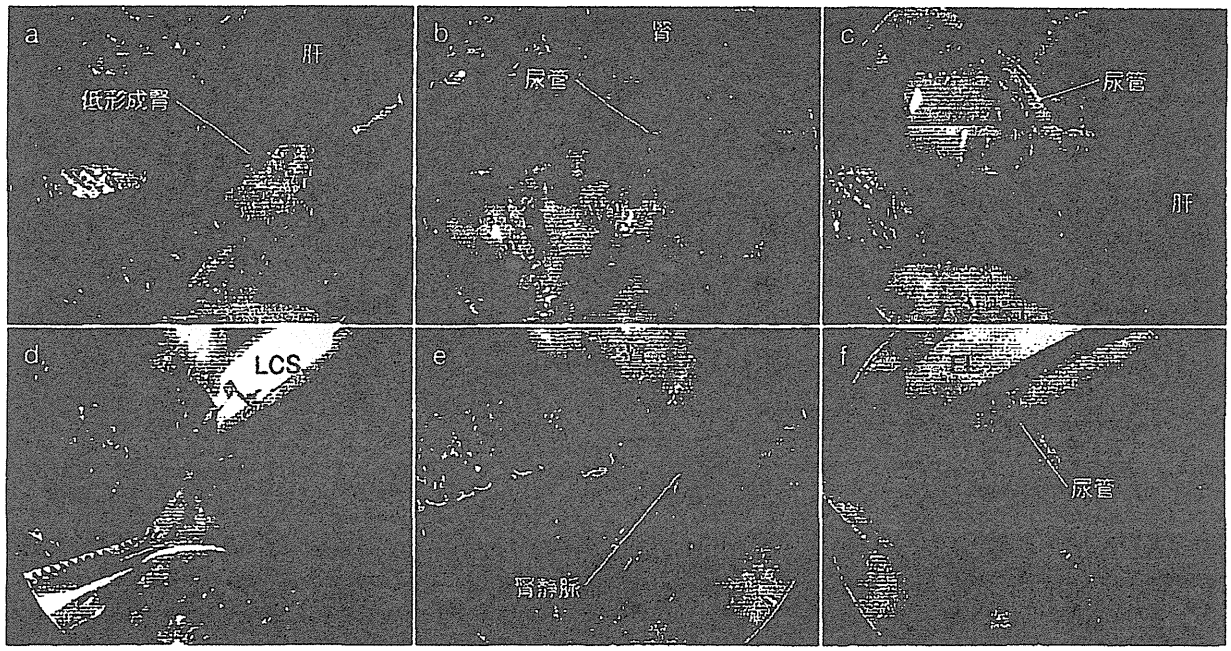

図 5　腹腔鏡下腎尿管摘除術（右腎）
a：結腸を授動後に Gerota 筋膜を切開して低形成腎を確認する。
b：低形成腎を確認しにくい場合には，腎の尾側の尿管から剝離する。この際，あらかじめ尿管カテーテルを留置してある尿管の硬度を鉗子で把持して確認すると，尿管の同定が容易である。
c：尿管の剝離を進めていき，尿管カテーテルを抜去する。
d：超音波凝固切開装置（LCS）などを用いて腎周囲を剝離する。
e：腎静脈および腎動脈に各々クリップを２本かけて切離するが，細いので LCS などでも切離は可能である。
f：尿管を尾側に可及的な範囲まで剝離していき，遠位側はエンドループ®にて結紮し切断する。

(1) 腹膜切開

Toldt の白線のやや内側をモノポーラまたは LCS で切開し，下行結腸を内側に授動する。さらに，横隔膜損傷に注意しながら腹膜切開を脾の外側へと延ばし，脾を脱転する。

5. 骨盤腎の場合（図 6）

(3)，(5)，(6) は「3. 右腎尿管摘除術」と同様。

(1) 腹膜切開

腸骨動静脈の近傍で腎を同定し，後腹膜に切開を置いて腎の周囲から剝離する方法もあるが，われわれは子宮の背側で尿管を同定し，後腹膜に切開を置いて尿管を頭側へ剝離していく方法を採用している。この際，挿入してある尿管カテーテルの硬度を確認すると尿管の同定が容易である。

(2) 尿管剝離

尿管の剝離を頭側へ進めるが尿管は切断せず，下腹部腹壁から刺入した絹糸でテーピングし尿管を腹壁側に吊り上げ牽引する。留置しておいた尿管カテーテルは抜去し，腎の剝離操作に移る。

(4) 腎動静脈処理

骨盤腎では内腸骨動静脈に腎茎部があることが多いが，血管径は細いので LCS または VSS で切離する。

4 手術成績（表 1）

当科で３年間に経験した単一尿管異所開口を伴う低形成腎に対する腹腔鏡下腎尿管摘除術の施行症例６例を検討した（表 1）。年齢は 2〜9 歳，全例が尿失禁を主訴とする女児で，患側は左１例，右５例であった。腎の位置は正常３例，骨盤内３例で，尿管開口部は全例が膣であった。手術時間は 78〜180 分であり，全例において術中・術後の合併症は認めず，尿失禁は完全に消失した。

5 おわりに

小児における腹腔鏡下腎尿管摘除術は低侵襲性で整容的に優れており入院期間も短いため，患児と家族の精神的な負担も軽減される[1〜3]。実際に

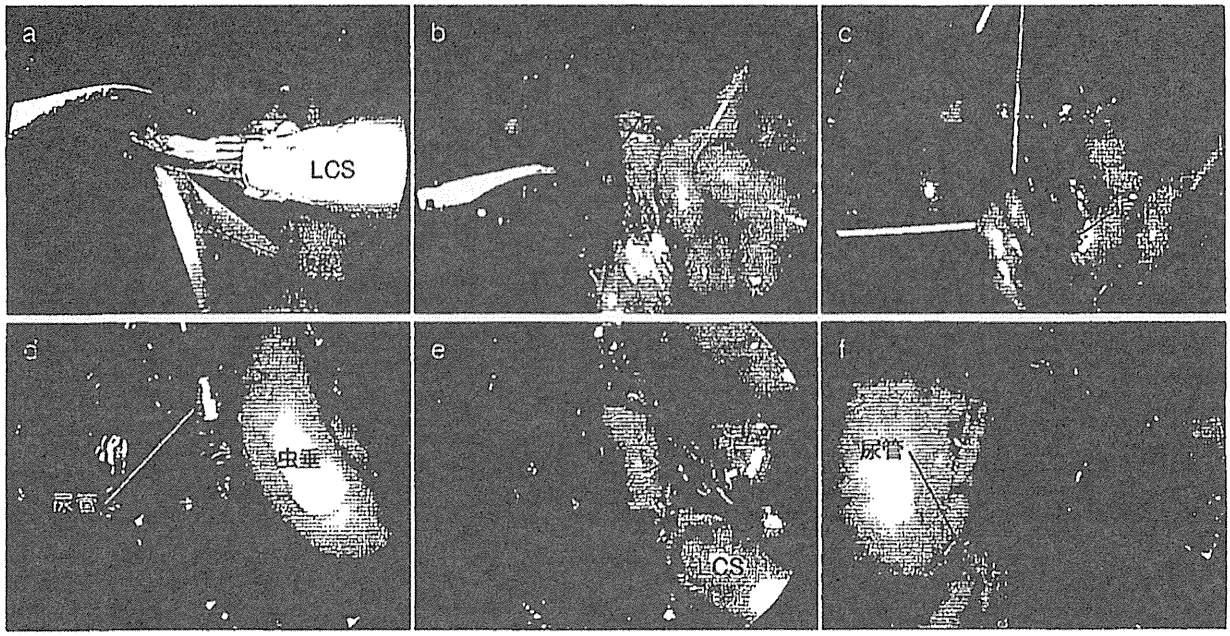

図 6　腹腔鏡下腎尿管摘除術（右骨盤腎）
a：子宮の背側で尿管を同定し，尿管を覆う後腹膜を切開する。
b：この際，挿入してある尿管カテーテルの硬度を確認すると尿管の同定が容易である。
c：剝離した尿管は切断せず，下腹部腹壁から刺入した絹糸でテーピングし尿管を腹壁側に吊り上げ牽引する。留置しておいた尿管カテーテルは抜去する。
d：鈍的・鋭的に尿管の剝離を頭側へ進め，腎周囲を剝離する。
e：骨盤腎では内腸骨動静脈に腎茎部があることが多いが，低形成腎の腎動静脈の血管径は細いので超音波凝固切開装置などでも切離は可能である。
f：尿管を尾側に可及的な範囲まで剝離していき，遠位側はエンドループ®にて結紮し切断する。

表 1　当科で 3 年間に経験した単一尿管異所開口を伴う低形成腎に対する腹腔鏡下腎尿管摘除術

症例	年齢	性	患側	低形成腎の位置	異所開口部	手術時間	合併症
1	4歳	女	左	正常	膣	135分	—
2	8歳	女	右	正常	膣	125分	—
3	7歳	女	右	骨盤内	膣	180分	—
4	9歳	女	右	正常	膣	94分	—
5	2歳	女	右	骨盤内	膣	78分	—
6	5歳	女	右	骨盤内	膣	139分	—

小児での腹腔鏡下腎尿管摘除術の適応となる症例数は決して多くはないが，特に尿失禁を主訴とする尿管異所開口を伴う低形成腎はよい適応である。最近では小児における単孔式腹腔鏡下腎尿管摘除術の報告も散見されるようになってきた[11,12]。

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BLOOD RESEARCH

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ORIGINAL ARTICLE

Can we predict neonatal thrombocytopenia in offspring of women with idiopathic thrombocytopenic purpura?

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Background
We aimed to investigate which factors in the clinical profile of mothers with idiopathic thrombocytopenic purpura (ITP) can predict neonatal risk of thrombocytopenia.

Methods
Data was retrospectively collected from all pregnant women with ITP who presented to our institution between 2001 and 2013. Neonatal offspring of these women were classified into 2 groups based on the presence or absence of neonatal thrombocytopenia (platelet count $<100\times10^9$/L). Several parameters were compared between the 2 groups, including maternal age, maternal platelet count, maternal treatment history, and thrombocytopenia in siblings. We further examined the correlation between maternal platelet count at the time of delivery and neonatal platelet count at birth; we also examined the correlation between the minimum platelet counts of other children born to multiparous women.

Results
Sixty-six neonates from 49 mothers were enrolled in the study. Thrombocytopenia was observed in 13 (19.7%) neonates. Maternal treatment for ITP such as splenectomy did not correlate with a risk of neonatal thrombocytopenia. Sibling thrombocytopenia was more frequently observed in neonates with thrombocytopenia than in those without (7/13 vs. 4/53, $P<0.01$). No association was observed between maternal and neonatal platelet counts. However, the nadir neonatal platelet counts of first- and second-born siblings were highly correlated (r=0.87).

Conclusion
Thrombocytopenia in neonates of women with ITP cannot be predicted by maternal treatment history or platelet count. However, the presence of an older sibling with neonatal thrombocytopenia is a reliable risk factor for neonatal thrombocytopenia in subsequent pregnancies.

Key Words Idiopathic thrombocytopenic purpura, Pregnancy, Neonatal thrombocytopenia

INTRODUCTION

Idiopathic thrombocytopenic purpura (ITP) is an immunohematological disorder characterized by acquired thrombocytopenia with no clinically apparent associated condition or other clear cause of thrombocytopenia. ITP is thought to be caused by autoantibodies against non-polymorphic platelet antigens, although antibodies cannot be detected in all women with ITP. A major problem associated with ITP in pregnancy is neonatal thrombocytopenia. Indeed, the pathogenic antiplatelet antibodies can cross the placenta and cause neonatal thrombocytopenia, which may increase the risk of cerebral hemorrhage in newborn infants [1, 2]. ITP is most prevalent in women of childbearing age; therefore, managing this disease is of great importance in clinical obstetrics. In this study, we investigated neonates with and without thrombocytopenia born to mothers with ITP and sought to identify factors that predict the risk of neonatal thrombocytopenia.

MATERIALS AND METHODS

Data was retrospectively collected from all pregnant women with ITP who presented to our institution between 2001 and 2013. The Kyushu University Hospital Ethical Review Board approved the study (approval number 26-134). The following information was extracted from the medical chart of each eligible patient: maternal age, prior splenectomy, medication during pregnancy, platelet count during early pregnancy and at delivery, treatments received to raise platelet count immediately before delivery (immunoglobulin infusion or platelet transfusion), gestational age at delivery, neonatal birth weight, Apgar scores, cord artery pH, and neonatal cord blood platelet count after delivery. Information collected for each infant included platelet count throughout the early neonatal period, bleeding complications, and medical/procedural treatments.

Neonates were classified into 2 groups based on the presence or absence of thrombocytopenia (defined as a minimum platelet count during the neonatal period of less than 100×10^9/L). The 2 groups were compared for differences in maternal age, parity, maternal platelet count, maternal treatment history, gestational age at birth, birth weight, and thrombocytopenia among an infant's siblings. We further examined the correlation between maternal platelet count at the time of delivery and neonatal platelet count at birth as well as correlations between the minimum platelet counts of other children born to multiparous women. In the latter analysis, if a woman had more than 3 pregnancies, only data from the first 2 pregnancies were used.

Maternal ITP had been previously diagnosed by hematology specialists at the Kyushu University Hospital. ITP is a diagnosis of exclusion, and criteria for its diagnosis were as follows: isolated thrombocytopenia for which other causes were excluded, normal or hypermegakaryocyte production in the bone marrow, and normal white and red blood cell counts. In the absence of a definite diagnosis of ITP before pregnancy, significant thrombocytopenia in the first trimester with a declining platelet count as gestation progressed was considered consistent with ITP. Meanwhile, mild thrombocytopenia during the second or third trimester and not associated with hypertension or proteinuria was considered gestational thrombocytopenia; these patients were not included in the study. Detection of maternal serum antiplatelet antibodies or platelet-associated immunoglobulin G was not systematically performed because these data were not required for diagnosis confirmation. Patients were treated with standard ITP treatment regimens, including corticosteroids and intravenous immunoglobulins (IVIG). Splenectomy was performed on patients who were either refractory to steroids or who were steroid-dependent and on those patients who failed to respond to IVIG therapy.

Institutional management policies for pregnant women with ITP were followed. In the second or third trimester, patients with an indication for treatment were administered standard-dose steroids as first-line treatment. If the platelet count was less than 50×10^9/L later in pregnancy, aggressive treatment with IVIG (0.4 g/kg/d for 5 days) was performed to prepare the patient for labor and delivery. If the maternal platelet count did not increase more than 50×10^9/L despite aggressive treatment, platelet transfusion was performed to increase maternal platelet counts to levels sufficient for vaginal delivery or cesarean section. After delivery, platelet counts were obtained from the neonatal cord blood of each infant and serial platelet counts were obtained during the first postpartum week until either the platelet count increased spontaneously or a stable platelet level was observed. All platelet counts were measured using a Coulter counter on blood samples collected in EDTA vacutainers.

Data are reported as median (range), discrete variables, or categories. Univariate analysis of the neonates with thrombocytopenia versus neonates without thrombocytopenia was performed by chi-squared or Mann-Whitney tests for categorical and continuous outcomes, respectively. Correlations were analyzed using Spearman's correlation. A P value less than 0.05 was considered statistically significant. Statistical analysis was performed using Statistical Package for the Social Sciences, version 21.0, for Windows (SPSS, Chicago, IL, USA).

RESULTS

During the study period, 74 neonates were born to 56 mothers with ITP. Because of incomplete data collection, 8 neonates from 7 mothers were excluded from the study. In total, 66 neonates from 49 mothers were enrolled in the study.

Table 1 shows the maternal profiles and neonatal outcomes of all 66 deliveries. The average gestational age at delivery was 38^{+3} weeks (31^{+2}–41^{+2}). Eleven patients who had previously undergone splenectomy delivered 12 infants. The median maternal platelet count was 90×10^9/L (range, $10\text{–}325\times10^9$/L) during early pregnancy and 112×10^9/L (range, $26\text{–}425\times10^9$/L) at delivery. Treatment with corticosteroids had been performed during pregnancy in 18 cases (27%). Before delivery, 12 pregnant women (18%) had received IVIG injections and 9 (14%) had received platelet transfusions (these agents were used to elevate platelet counts to prevent bleeding complications during the intrapartum period). As a result, bleeding amounts at the time of delivery were less than 1,000 mL in these mothers. In this series, no asphyxiated neonates (Apgar score at 5 min $\leq$6 or umbilical cord pH $<$7.0) were observed. The neonatal platelet count at birth was $19\text{–}450\times10^9$/L with a median platelet count of 202×10^9/L. Thrombocytopenia (platelet count $<100\times10^9$/L) was diagnosed in 13 (19.7%) infants. No neonates required platelet transfusion and no neonate suffered from intracranial hemorrhage.

Table 2 shows the clinical profiles of neonates with thrombocytopenia (platelet count at nadir $<100\times10^9$/L). Thirteen neonates born to 9 mothers were thrombocytopenic. Among these neonates, the maternal platelet count was less than

100×10^9/L in 6 mothers during early pregnancy and less than 100×10^9/L in 6 mothers at the time of delivery. Postnatal treatment of infants with severe thrombocytopenia consisted solely of IVIG administration (N=2).

Table 1. Maternal profiles and neonatal outcomes.

Characteristic	Median (range) or number (%)
Maternal age at delivery (yr)	31 (20-43)
Parity	0 (0-3)
Primiparous	35 (53%)
Multiparous	31 (47%)
Maternal platelet count	
In early pregnancy ($\times10^9$/L)	90 (10-325)
At delivery ($\times10^9$/L)	112 (26-425)
Bleeding tendency during pregnancy	0 (%)
Maternal treatment for ITP	
Splenectomy before pregnancy	12 (18%)
PSL during pregnancy	18 (27%)
IVIG before delivery	12 (18%)
Platelet transfusion before delivery	9 (14%)
Neonatal outcome	
Gestational age at birth (wks)	38^{+3} (31^{+2}-41^{+2})
Birth weight (g)	2,905 (1,030-3,768)
Apgar score at 1 min	8 (4-9)
Apgar score at 5 min	9 (7-10)
Cord artery pH	7.316 (7.042-7.420)
Neonatal platelet count at birth ($\times10^9$/L)	202 (19-450)
Neonatal platelet count at nadir ($\times10^9$/L)	186 (11-450)
Intracranial hemorrhage	0 (0%)
Treatment for neonatal thrombocytopenia	
IVIG	2 (3%)
Platelet transfusion	0 (0%)

Abbreviations: ITP, idiopathic thrombocytopenic purpura; IVIG, intravenous immunoglobulins; PSL, prednisolone.

Table 3 shows the predictive value of maternal treatment history, maternal platelet count, and other parameters for predicting neonatal thrombocytopenia. Maternal treatments such as splenectomy, betamethasone use during pregnancy, IVIG administration, and platelet transfusion before delivery did not correlate with the risk of neonatal thrombocytopenia. Thrombocytopenia in siblings was more frequently observed in infants with neonatal thrombocytopenia than in those without ($P<0.01$).

Fig. 1 shows the correlation between maternal platelet count at delivery (x axis) and neonatal platelet count at birth (y axis). No correlation was observed between these 2 parameters.

Fig. 2 shows the distribution of the maternal platelet count during early pregnancy and at delivery relative to neonatal thrombocytopenia (platelet count at nadir $<100\times10^9$/L). Neonatal thrombocytopenia occurred at similar rates in each group and a definite tendency was not found.

Among the 49 mothers included in the study, 14 were multiparous. Fig. 3 shows the correlation between the minimum platelet counts of the first and second children born to multiparous mothers. A strong positive correlation was observed between neonatal platelet counts among the first and second children, with a Spearman correlation coefficient of 0.87 ($P<0.0001$).

DISCUSSION

ITP is an autoimmune disorder caused by autoantibodies against several platelet membrane glycoproteins and results in platelet destruction within the reticular endothelial system. ITP predominantly affects young women of reproductive age; therefore, managing maternal ITP is of great importance in clinical obstetrics. Pregnancy can exacerbate ITP, and platelet counts have been shown to decrease

Table 2. Clinical profiles of neonates with thrombocytopenia.

Neonate	Mother	Platelet count at nadir ($\times10^9$/L)	Neonatal treatment	Gestational age at birth (wks)	Birth weight (grams)	Delivery route	Maternal platelet count during early pregnancy ($\times10^9$/L)	Maternal platelet count at delivery ($\times10^9$/L)
1	A	62	None	37^{+0}	1984	CS	80	83
2	B	21	None	40^{+4}	2974	VD	32	53
3	B	50	None	36^{+0}	1984	VD	15	50
4	C	11	IVIG	38^{+6}	2468	CS	173	202
5	C	17	IVIG	38^{+4}	3090	CS	123	169
6	C	64	None	38^{+3}	3115	CS	153	183
7	D	85	None	40^{+1}	3244	VD	200	242
8	D	21	None	37^{+5}	2662	CS	335	325
9	E	72	None	38^{+4}	3155	VD	218	265
10	F	85	None	32^{+0}	1030	CS	97	112
11	G	95	None	39^{+0}	3566	VD	65	94
12	H	85	None	37^{+2}	3045	VD	128	87
13	I	58	None	38^{+0}	2635	CS	57	81

Abbreviations: CS, cesarean section; IVIG, intravenous immunoglobulins; VD, vaginal delivery.

Table 3. Predictive parameters for neonatal thrombocytopenia.

Parameter	Neonates with thrombocytopenia (platelet count <100×10^9/L) (N=13)	Neonates without thrombocytopenia (N=53)	P
Maternal age at delivery (yr)	27 (20-34)	31 (21-43)	0.01
Maternal parity	1 (0-3)	0 (0-2)	0.07
Multiparous mothers	9 (69%)	22 (42%)	0.14
Maternal platelet count during early pregnancy (×10^9/L)	123 (15-335)	85 (10-320)	0.33
Maternal platelet count before delivery (×10^9/L)	103 (50-325)	116 (26-425)	0.29
Maternal history of splenectomy	2 (15%)	10 (19%)	1.0
Maternal PSL therapy during pregnancy	2 (15%)	16 (30%)	0.49
Maternal IVIG before delivery	1 (8%)	11 (21%)	0.43
Maternal platelet transfusion before delivery	1 (8%)	8 (15%)	0.81
Gestational age at birth (wks)	38^{+3} (32^{+0}-40^{+1})	38^{+4} (31^{+2}-41^{+2})	0.25
Birth weight (g)	2,974 (1,030-3,566)	2,905 (1,782-3,768)	0.50
Thrombocytopenia in siblings	7 (54%)	4 (8%)	<0.01

Abbreviations: IVIG, intravenous immunoglobulins; PSL, prednisolone.

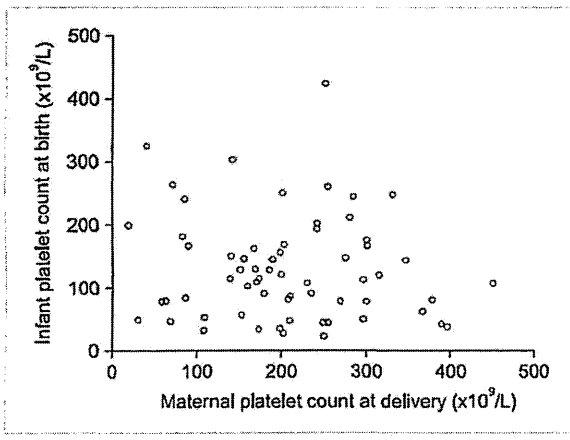

Fig. 1. Correlation between maternal platelet count at the time of delivery and neonatal platelet count at birth.

throughout gestation in 50% of pregnancies [3]. Although it is well known that pregnant women with ITP can deliver neonates with severe thrombocytopenia, the exact cause of the neonatal thrombocytopenia is unknown. Circulating antiplatelet antibodies can cross the placenta and may cause a passive neonatal immune thrombocytopenia, but antiplatelet antibodies are not always detectable in maternal serum.

Severe thrombocytopenia in the newborn can cause hemorrhagic manifestations, the most dangerous of which is intracranial hemorrhage. In our cohort, thrombocytopenia was observed in 19.7% of neonates, which is similar to rates previously described [4-8]. Although its incidence is relatively low, intracranial bleeding is a serious thrombocytopenia complication in neonates born to mothers with ITP [4, 5, 9, 10]. Further, a prenatally diagnosed case of fetal intracranial hemorrhage secondary to maternal ITP has recently been reported [11]. Fetal and neonatal hemorrhagic complications remain the most pressing issues in the obstetric management of women with ITP. Our study reviewed 66 deliveries in 49 women with ITP. No bleeding complications occurred in any neonate, despite platelet counts at birth being less than 100×10^9/L in 13 infants and less than 50×10^9/L in 4 infants.

Recent studies have attempted to determine which factors may predict thrombocytopenia in infants born to mothers with ITP. Several studies have found a poor correlation between maternal and neonatal platelet counts [12-15]. In agreement with these studies, we failed to find a definite correlation between these counts. Other investigators have found that maternal splenectomy before pregnancy is positively correlated with neonatal thrombocytopenia [2, 6, 13, 16-18], but we observed no such correlation. Hence, it may not be possible to predict neonatal thrombocytopenia based on maternal clinical profiles.

Given that many of the mothers in our study were multiparous, we compared platelet counts among first and second siblings. We found a strong positive correlation between neonatal thrombocytopenia among siblings. Thrombocytopenia in a sibling was more frequently observed in neonates with thrombocytopenia than in neonates without thrombocytopenia. Based on this result, we conclude that the presence of an older sibling with neonatal thrombocytopenia is a risk factor for neonatal thrombocytopenia in subsequent pregnancies. Previous studies have described similar findings [18-20]. The precise mechanisms underlying this phenomenon remain unclear. However, it is possible that the biological aggressiveness of the maternal antibodies and their avidity for platelets remain unchanged over time and over multiple pregnancies [20].

Our study has several limitations. The first is the retrospective study design. Our data collection was limited to information documented in the patient's medical chart and available in the laboratory database. For example, we were unable to include information on platelet-associated immunoglobulin G and serum antiplatelet antibody levels because these data were not collected for every patient.

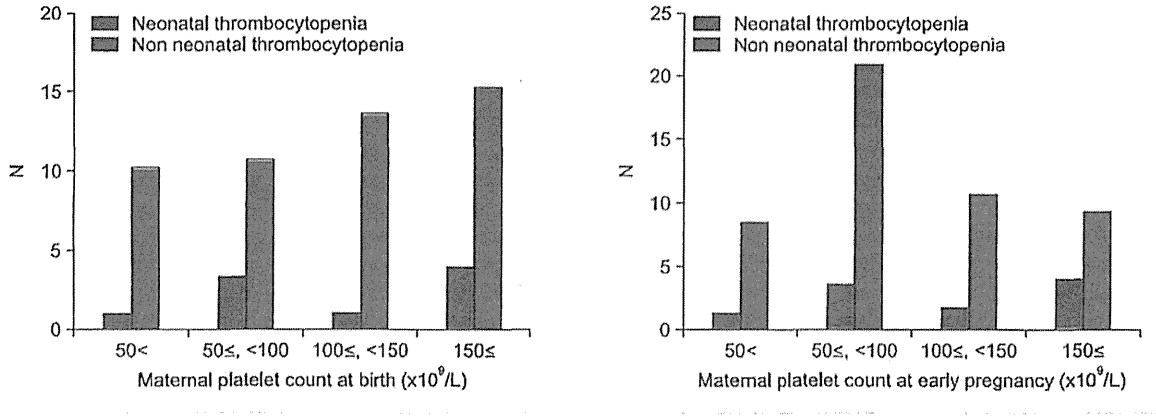

Fig. 2. Distribution of the maternal platelet count during early pregnancy and at delivery relative to neonatal thrombocytopenia.

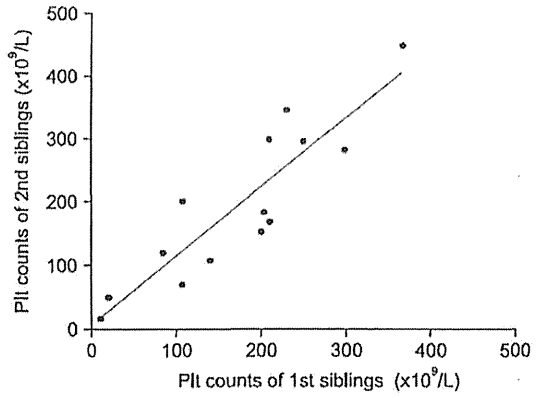

Fig. 3. Correlation between the minimum platelet (plt) counts of the first and second siblings born to multiparous mothers with idiopathic thrombocytopenic purpura.

Furthermore, the postnatal platelet count was not followed for every neonate with a normal platelet count at birth. For these neonates, the nadir platelet count was assumed to be identical to the platelet count at birth. The study is also limited by sample size. Although our sample size was relatively large compared with other single-center studies, a larger number of study participants is required for reliable multivariable analysis. Finally, our hospital is a major referral center for pregnancies complicated by severe maternal diseases; this referral bias may have led to the inclusion of patients with particularly severe diseases.

In conclusion, the incidence of poor neonatal outcomes for mothers with ITP is extremely low. We were unable to predict neonatal thrombocytopenia based on maternal factors such as treatment history or platelet count during pregnancy. The presence or absence of an infant's sibling with thrombocytopenia was the only parameter to predict the neonatal clinical course of a subsequent pregnancy.

Authors' Disclosures of Potential Conflicts of Interest

No potential conflicts of interest relevant to this article were reported.

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Increased risk of pregnancy-induced hypertension and operative delivery after conception induced by in vitro fertilization/intracytoplasmic sperm injection in women aged 40 years and older

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Objective: To clarify the association between preconception fertility status and obstetric outcomes in women aged 40 years and older.
Design: Retrospective study by reviewing medical records.
Setting: Tertiary perinatal center in a university hospital.
Patient(s): 330 women aged 40 years and older who delivered a singleton from 2006 to 2010, and 450 women aged 30 to 34 years who delivered at the same facility as controls.
Intervention(s): None.
Main Outcome Measure(s): Incidence of pregnancy-induced hypertension, gestational diabetes mellitus, preterm birth, low birth weight, and mode of delivery assessed based on the mode of conception; spontaneous conception (SC) and in vitro fertilization/intracytoplasmic sperm injection conception (IVF-ICSI).
Result(s): The incidence of pregnancy-induced hypertension was statistically significantly higher in IVF-ICSI group than the SC group. This gap was commonly observed in both the women aged 40 years and older and those in the 30 to 34 age group. No statistically significant difference was observed in the frequency of gestational diabetes mellitus, preterm birth, or low birth weight. As a characteristic of nulliparous women of advanced age, the rate of operative delivery, which includes emergency cesarean section and instrumental delivery, was statistically significantly higher in IVF-ICSI group than in the SC group. Detailed investigation into the medical indications for operative delivery revealed that the difference was attributable to the elevated incidence of labor protraction and arrest.
Conclusion(s): Preconception fertility status can be a predicting factor of the incidence of pregnancy-induced hypertension and labor outcome, especially for women aged 40 years and older. (Fertil Steril® 2014;102:1065–70. ©2014 by American Society for Reproductive Medicine.)
Key Words: Advanced maternal age, assisted reproduction technology, labor abnormality, preconception fertility status, pregnancy-induced hypertension

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In the last few decades, drastic changes in modern society and culture have affected women's lifestyle. In the area of reproduction, the mean age of women at first childbirth has been rising rapidly in many countries (1–3). The cause is probably multifaceted: longer time in school,

higher career goals, later age of marriage, and advances in assisted reproductive technology (ART). This trend is noticeable in Japan, especially in Tokyo, a representative city. According to the Tokyo metropolitan government's 2012 statistics, the percentage of women over age 35 giving birth has reached 33.2% (4). Further, at our facility located in central Tokyo, the proportion of women over age 35 exceeded 50% of all delivery cases in 2012. Although advanced maternal age has been defined as age 35 or over, the proportion of pregnancies that belong in that age category has been increasing in modern obstetrics.

It is generally acknowledged that women's reproductive capacity declines with age (5). With the emerging social tendency to delay childbirth, more and more women are benefiting from ART to overcome age-related infertility. Although a consensus is lacking, an increasing number of studies have suggested an adverse impact from in vitro fertilization with or without intracytoplasmic sperm injection (IVF-ICSI), on obstetric outcomes. These include preterm birth, low birth weight (LBW), hypertensive disorders, and congenital malformation (6, 7). The majority of these previous studies evaluated the data without categorizing the women into age groups. Reflecting the current increase of IVF-ICSI conceptions among advanced age women, it is important clinically to gain knowledge about obstetric outcomes in advanced age women who require IVF-ICSI.

Our study clarified the correlation of perinatal outcomes with the mode of conception, focusing on woman aged 40 and older (advanced age group). In addition, we conducted a comparison with a younger control group, aged 30 to 34 years, to confirm the age-specific influence.

MATERIALS AND METHODS

Under the approval of the institutional review board of the University of Tokyo, a retrospective analysis of pregnancies managed at the University of Tokyo Hospital (Tokyo, Japan) from January 2006 to December 2010 was performed. Clinical data were extracted by reviewing obstetric records. All the pregnant women aged 40 and older who delivered a singleton without fetal anomalies after 22 weeks of gestation during the study period (330 women) were classified into two categories based on the mode of conception: a group of spontaneous conception (SC) and a group of conception through IVF-ICSI procedures. All of the embryos transferred were autologous, as gamete donation is not approved in Japan. All the women aged 30 to 34 who delivered a singleton without fetal anomalies after 22 weeks of gestation at our facility from January 2009 to December 2010 (450 women) were set up as a control population to elucidate the age-associated impact.

In the analysis of obstetric complications, the incidence of pregnancy-induced hypertension (PIH), gestational diabetes mellitus (GDM), preterm birth (defined as delivery at <37 weeks of gestation), LBW (defined as birth weight <2,500 g), and umbilical artery pH were examined. We diagnosed PIH based on the clinical criteria set by the Japan Society for the Study of Hypertension in Pregnancy: systolic pressure >140 mm Hg or diastolic pressure >90 mm Hg after 20 weeks of gestation. We diagnosed GDM with a 75-g oral glucose tolerance test, which was interpreted as positive when the results met two of the following criteria: ≥100 mg/dL in fasting, ≥180 mg/dL at 1 hour after load, or ≥150 mg/dL at 2 hours.

In the analysis of delivery outcomes, the mode of delivery was evaluated by excluding women who received epidural analgesia because this can negatively affect the spontaneous vaginal delivery rate. In the assessment of delivery outcomes, total cases were separated into a group undergoing elective cesarean section and a group who tried vaginal delivery. The group who tried vaginal delivery was divided into women who completed a spontaneous vaginal delivery and those who received operative intervention by forceps/vacuum or emergency cesarean section. In all analyses, pregnancies with fetal major congenital abnormalities or chromosomal abnormalities were excluded because they affect obstetric management.

Statistical analysis was performed using JMP 9 software (SAS Institute). The incidences of obstetric complications and delivery outcomes were analyzed by chi-square test. $P<.05$ was considered statistically significant. Odds ratios (ORs) with 95% confidence intervals were calculated.

RESULTS

During the targeted study period, 330 women in the advanced age group and 450 women in the younger control group were found to meet the inclusion criteria described in *Materials and Methods*. Maternal characteristics in each age group are summarized separately based on the mode of conception in Table 1. In the advanced age group, 242 cases (73.3%) were conceived spontaneously and 88 cases (26.7%) by IVF-ICSI. In the younger control group, 422 cases (93.8%) were conceived spontaneously and 28 cases (6.2%) by IVF-ICSI. As expected, IVF-ICSI was more prevalent in the advanced age group than the younger control group. This reflects the generally-acknowledged impact age has on women's fertility. The mean age, prepregnancy body mass index (BMI), weight gain during pregnancy, and medical complications of women with SC and women with IVF-ICSI conception were comparable between both groups (see Table 1).

The incidences of the obstetric complications were analyzed, targeting total cases from each age group, as shown in Table 2 (analysis 1 in Supplemental Fig. 1, available online). A statistically significant increase in the incidence of PIH was confirmed in pregnancies conceived by IVF-ICSI in both groups ($P=.002$ advanced age group, and $P=.010$ younger control group). When the two groups were compared, PIH occurred more frequently in the advanced age group regardless of mode of conception, with statistical significance in the SC group ($P=.002$) (Fig. 1A). No statistically significant differences that depended on the mode of conception were observed in the incidence of GDM, preterm birth, or LBW (see Table 2).

The relevance of prepregnancy fertility status to mode of delivery was examined. There were 53 cases (23.9%) of elective cesarean sections in SC group and 28 cases (34.6%) in the IVF-ICSI group among the advanced age group. There were 76 cases (18.6%) and 5 cases (19.2%), respectively, in the younger

TABLE 1

Summary of basic characteristics.

	Age ≥40 (n = 330)			Age 30–34 (n = 450)		
Characteristic	**SC 73.3% (242)**	**IVF-ICSI 26.7% (88)**	***P* value**	**SC 93.8% (422)**	**IVF-ICSI 6.2% (28)**	***P* value**
Age at delivery (y)	41.2 ± 1.4	41.5 ± 1.5	.066	32.1 ± 1.4	32.5 ± 1.5	.140
Parity						
Nulliparous	45.9% (111)	79.5% (70)		59.7% (252)	89.3% (25)	
Multiparous	54.1% (131)	20.5% (18)		40.3% (170)	10.7% (3)	
Prepregnancy BMI	21.2 ± 2.9	21.5 ± 3.0	.289	20.5 ± 3.2	21.3 ± 3.7	.214
<25	90.5% (219)	88.6% (78)		92.9% (392)	82.1% (23)	
25–29.9	7.4% (18)	8.0% (7)		5.2% (22)	10.7% (3)	
≥30	2.1% (5)	3.4% (3)		1.9% (8)	7.1% (2)	
Weight gain during pregnancy (kg)	8.8 ± 3.7	8.5 ± 3.4	.564	9.6 ± 3.6	8.4 ± 2.8	.081
Maternal complications						
Hypertension	1.2% (3)	2.3% (2)	.515	0.2% (1)	0 (0)	.720
Diabetes mellitus	1.2% (3)	0% (0)	.171	0.7% (3)	0 (0)	.534
Uterine fibroids	15.7% (38)	10.2% (9)	.195	6.6% (28)	7.1% (2)	.918
Birth weight of neonate (g)	2,956 ± 433	2,925 ± 644	.615	2,931 ± 463	2,954 ± 401	.799
Umbilical artery pH	7.30 ± 0.07	7.29 ± 0.05	.519	7.30 ± 0.06	7.28 ± 0.05	.165

Note: Values are presented as mean ± standard deviation. Values in parentheses represent the number of women in each group. BMI = body mass index; IVF-ICSI = in vitro fertilization/intracytoplasmic sperm injection; SC = spontaneous conception.

Toshimitsu. IVF pregnancy outcomes in women over 40. Fertil Steril 2014.

control group. No statistically significant difference in the proportion of elective cesarean sections between SC group and IVF-ICSI group was detected in either group (P=.067 advanced age group, and P=.939 younger control group).

The success rate of vaginal deliveries was assessed after excluding cases of elective cesarean section from both the SC and IVF-ICSI groups. Additionally, as anesthesia can diminish labor power and negatively affect the success rate of spontaneous delivery, the cases of tried vaginal delivery under epidural anesthesia were also excluded in the analysis of delivery outcomes (analysis 2 in Supplemental Fig. 1). As shown in Figure 1B and in the upper part of Table 3, within the advanced age group, the IVF-ICSI group showed a statistically significantly lower success rate of spontaneous vaginal delivery than the SC group: 52.8% in IVF-ICSI group and 83.4% in SC group. It is interesting that this gap in the success rate of spontaneous vaginal delivery was not observed in the younger control group: 81.0% in IVF-ICSI group and 85.5% in SC group. The parameters related to neonatal outcome, including birth weight and umbilical artery pH, were comparable between the SC and IVF-ICSI groups in both age categories (see Table 1).

The diminished success rate of spontaneous vaginal delivery after IVF-ICSI conception in the advanced age group was more apparent in nulliparous women than multiparous women (upper part in Table 3). Therefore, further analysis targeting nulliparous women was conducted (analysis 3 in Supplemental Fig. 1). To elucidate the causative factors associated with the diminished chance of spontaneous vaginal delivery, we investigated the medical indications for operative delivery in the nulliparous women (lower part in Table 3). In the advanced age group, increased occurrence of failed delivery progress, including protracted and arrested labor (14.9% in SC group vs. 38.1% in IVF-ICSI group), rather than nonreassuring fetal status (10.3% vs. 7.1%) contributed to the elevated incidence of operative delivery in IVF-ICSI conception. In contrast, in the younger control group, no difference in operative delivery rate was found depending on mode of conception, regardless of parity.

DISCUSSION

With the growing tendency within advanced societies to delay childbirth, IVF-ICSI pregnancy is becoming more

TABLE 2

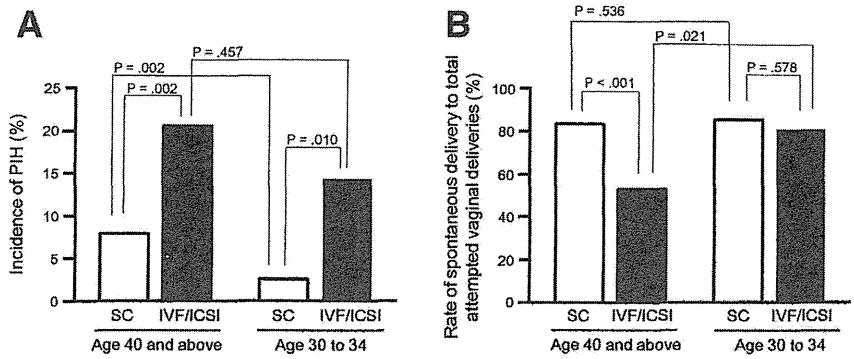
Incidence of obstetric complications.

	Age ≥40 (n = 330)				Age 30–34 (n = 450)			
Complication	**SC**	**IVF-ICSI**	***P* value**	**OR (95% CI)**	**SC**	**IVF-ICSI**	***P* value**	**OR (95% CI)**
PIH	7.9% (19)	20.5% (18)	.002	3.02 (1.49–6.09)	2.6% (11)	14.3% (4)	.010	6.23 (1.63–19.8)
GDM	2.1% (5)	1.1% (1)	.558	NA	0.5% (2)	0 (0)	.612	NA
Preterm birth	7% (17)	12.5% (11)	.128	NA	8.1% (34)	3.6% (1)	.344	NA
Frequency of LBW	7.9% (19)	2.3% (2)	.044	0.27 (0.04–0.97)	6.9% (29)	7.1% (2)	.957	NA

Note: Values in parentheses represents the number of women in each group. GDM = gestational diabetes mellitus; IVF-ICSI = in vitro fertilization/intracytoplasmic sperm injection; LBW = low birth weight; PIH = pregnancy-induced hypertension; SC = spontaneous conception.

Toshimitsu. IVF pregnancy outcomes in women over 40. Fertil Steril 2014.

FIGURE 1



The incidence of PIH and the rate of spontaneous delivery to total attempted vaginal deliveries. (A) The incidence of PIH in both age groups is indicated. (B) The rate of spontaneous delivery among the total cases trying vaginal delivery is indicated. In A and B, the data are shown separately based on the mode of conception. Spontaneous conception (SC), blank bars; IVF-ICSI conception, filled bars.

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common, even as the degree of age-dependent decline in fertility varies among women of advanced age. This study explored the impact of prepregnancy fertility status on pregnancy outcomes and its difference between two age groups.

One of our important findings is that PIH occurred more frequently in pregnancy after IVF-ICSI than SC. This difference was shared between two maternal age groups, and an age-dependent elevation in the prevalence was also indicated. Supporting our findings, maternal age and IVF pregnancy have been reported, respectively, as factors linked with increased risk for PIH (4, 6, 8). Indeed, aging is associated with systemic endothelial dysfunction even in normotensive women, which may then contribute to the age-related risk for PIH (9, 10). On the other hand, the exact etiology of high PIH incidence after IVF-ICSI is not understood. A possible explanation is that reduced reproductive capacity, manifested as infertility that requires artificial technology to achieve pregnancy, might be involved in the pathology of PIH. Supporting this idea, preconception maternal factors, rather than the type of ART procedure, are implied to be associated with adverse outcomes (11, 12). Another possibility is that hormonal pretreatment and/or the IVF-ICSI procedure directly affects the incidence of PIH (6, 13). In either case, the recognition of advanced-age pregnancy achieved by IVF-ICSI as the highest risk group for PIH could contribute to better risk assessment in obstetric practice.

Another significant finding in the present study was the reduced success rate of spontaneous vaginal delivery from

TABLE 3

Outcomes after trial of attempted vaginal delivery and indications for operative delivery.

	Age ≥40 (n = 222)				Age 30–34 (n = 353)			
Outcome	**SC**	**IVF-ICSI**	***P* value**	**OR (95% CI)**	**SC**	**IVF-ICSI**	***P* value**	**OR (95% CI)**
After trial of attempted vaginal delivery								
Total women	169	53			332	21		
Spontaneous	83.4% (141)	52.8% (28)			85.5% (284)	81.0% (17)		
Operative	16.6% (28)	47.2% (25)	<.001	4.50 (2.30–8.89)	14.5% (48)	19.0% (4)	.578	NA
Nulliparous women	87	42			209	19		
Spontaneous	73.6% (64)	47.6% (20)			79.9% (167)	78.9% (15)		
Operative	26.4% (23)	52.4% (22)	.004	3.06 (1.42–6.69)	20.1% (42)	21.1% (4)	.921	NA
Multiparous women	82	11			123	2		
Spontaneous	93.9% (77)	72.7% (8)			95.1% (117)	100% (2)		
Operative	6.1% (5)	27.3% (3)	.046	5.77 (1.04–28.5)	4.9% (6)	0 (0)	.656	NA
Indications for operative delivery in nulliparous women								
No complications	73.6% (64)	47.6% (20)			79.9% (167)	78.9% (15)		
Protracted and arrested labor	14.9% (13)	38.1% (16)	.004	3.50 (1.49–8.39)	12.0% (25)	21.1% (4)	.288	NA
NRFS	10.3% (9)	7.1% (3)	.549	NA	7.2% (15)	0 (0)	.100	NA
Other factors	1.1% (1)	7.1% (3)	.077	NA	1.0% (2)	0 (0)	.554	NA
Total	100% (87)	100% (42)			100% (209)	100% (19)		

Note: Values in parentheses represents the number of women in each group. CI = confidence interval; IVF-ICSI = in vitro fertilization/intracytoplasmic sperm injection; NRFS = nonreassuring fetal status; OR = odds ratio; SC = spontaneous conception.

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IVF-ICSI in the advanced age group. This observation is limited to the advanced age group. Detailed analysis of the indications for operative delivery revealed that nulliparous pregnancy after IVF-ICSI was at a higher risk for failed labor, consequently leading to forceps delivery and emergency cesarean section. As neonatal weight was not related to the mode of conception, functional impairment of uterine contractions and/or the birth canal might be involved in the confirmed reduction of successful spontaneous vaginal deliveries. Several past studies have proposed a correlation between advanced maternal age and dysfunctional labor (14) resulting in an increase in the cesarean delivery rate (15). Our data possibly give a novel insight into this simple understanding of the aging effect on labor progress. In cases of SC, a comparable success rate of spontaneous delivery was indicated between the advanced age group and the younger control group. This indicates that the negative aging effect hampering successful labor is negligible in women with a preserved capacity to conceive in spite of their age. Conversely, even in the same age population, women who need IVF-ICSI to achieve pregnancy have diminished potential to complete delivery without medical intervention. Aging-associated dysfunction of myometrial contractility and decrease in oxytocin responses were described in previous in vitro studies using human samples (16, 17). At present, however, a biophysiologic mechanism to explain why impairment of fertility and labor dysfunction concurrently occur in some women at an advanced age has yet to be answered. In the younger control group, we found no apparent difference in the success rate of vaginal delivery, marking a clear contrast with the advanced-age group. One possible explanation for the discrepancy between the two groups is that infertility factors in younger women may fundamentally differ from the age-dependent reduction in reproductive capacity in older women.

The present study has some limitations. Recent studies imply that infertility-causing factors and variation in IVF modality can alter the incidence of some obstetric outcomes (9, 18, 19). However, as a large number of women are referred to our facility after achieving conception at local IVF clinics, we could not obtain full clinical information, such as indications for IVF-ICSI treatment, mode of ovarian induction, use of cryopreserved embryo, and embryonic stage at transfer. Therefore, it remains unknown whether the adverse perinatal outcomes confirmed in IVF-ICSI pregnancy were attributable to some medical treatment conducted in ART or to prepregnancy physical conditions specific to infertile women.

Another limitation is the racial homogeneity of the target population. Because the majority of clinical data analyzed in this study are derived from Japanese women, it is necessary to be cautious about applying our results to other racial groups.

In addition, the influence of a confounding bias associated with socioeconomic status was not completely excluded in this study because the delivery records at our facility lacked detailed information on household income and education level. However, such a bias seems unlikely, as our study population was estimated to be relatively homogenous in income range and education status. Low-income woman were not included in this study population because welfare recipients were not admissible to our hospital during the research period. No obvious variation in insurance status exists in Japan because all people are covered under the same universal health insurance. The majority of pregnant women managed in our facility are highly educated, as women living in Tokyo show college/university attendance rates of more than 70% (20).

In conclusion, conception by IVF-ICSI is associated with an increased risk for PIH, independent from age on its incidence. In women aged 40 years and older, failed labor is more prevalent in pregnancies achieved by IVF-ICSI than SC. These observations suggest that giving consideration to preconception fertility status is important in risk assessment for obstetric outcomes, especially in cases of advanced-age women. This new concept of risk categorization based on prepregnancy infertility status could benefit modern perinatal medicine facing the issue of advancing maternal age.

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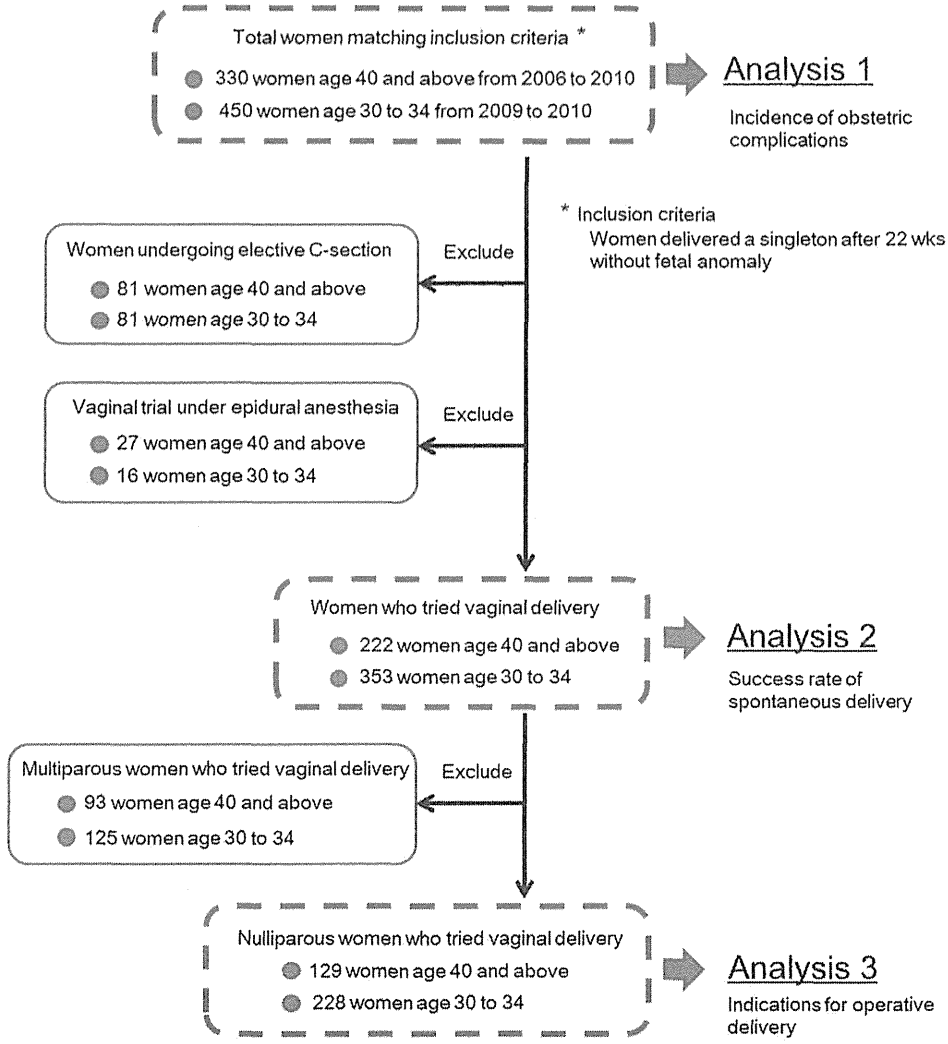
SUPPLEMENTAL FIGURE 1



Flow chart of study design. The number of women in each group is indicated, and the target populations of the three analyses are highlighted in dotted boxes.

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Factors that predict poor clinical course among patients hospitalized with pelvic inflammatory disease

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Abstract

Aim: The aim of this study was to identify factors that can predict clinical course among patients hospitalized with pelvic inflammatory disease (PID).

Methods: Ninety-three patients who needed hospitalization with a diagnosis of PID were retrospectively studied. Patients who were discharged within 7 days by conservative treatment were defined as favorable course cases ($n = 44$). Patients who needed more than 7 days of hospitalization and/or surgery were defined as poor course cases ($n = 49$). Twenty variables were evaluated by univariate and logistic regression analysis: age, history of pregnancy/delivery, gynecological open/laparoscopic surgery, PID, oral contraceptives/intrauterine device use and intrauterine operation before onset, body temperature, signs of peritoneal irritation, vomiting/diarrhea, abnormal vaginal discharge, endometriosis/fibroid/adenomyosis/any cystic lesion detected by ultrasonography, white blood cell counts/C-reactive protein (CRP) levels . The cut-off value was calculated by receiver–operator curve (ROC) analysis.

Results: Factors associated with poor clinical course were advanced age ($P < 0.01$), history of gynecological open surgery ($P < 0.05$), any cystic lesion detected by ultrasonography ($P < 0.05$) and high CRP levels ($P < 0.05$). High CRP levels and intrauterine operation before onset were independently associated with poor clinical course. The cut-off value for CRP was 4.4 mg/dL.

Conclusion: This study identified variables that can predict poor clinical course of PID. These results can assist gynecologists with identifying patients at risk and optimizing the choice of management.

Key words: C-reactive protein, pelvic inflammatory disease, risk factors, tubo-ovarian abscess, ultrasonography.

Introduction

Pelvic inflammatory disease (PID) occurs in approximately one in 10 women in their reproductive period.[1] Clinical diagnostic criteria for PID according to the Center for Disease Control and Prevention (CDC) include cervical motion tenderness, uterine tenderness, adnexal tenderness, oral temperature of more than 38.3C, abnormal cervical or vaginal mucopurulent discharge, elevated erythrocyte sedimentation rate, elevated C-reactive protein (CRP) level, histopathological evidence of endometritis, fluid-filled tubes with tubo-ovarian complex shown by transvaginal sonography or magnetic resonance imaging techniques, and laparoscopic abnormalities consistent with PID.[2] Once the clinical diagnosis of PID is made, however, the clinical course varies among cases, and no criteria exists to classify severity. Criteria proposed by CDC for

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PID that require hospitalization include: (i) surgical emergencies cannot be ruled out; (ii) the patient is pregnant; (iii) the patient does not respond to oral antimicrobial therapy; (iv) the patient is unable to follow or tolerate outpatient therapy; or (v) the patient has severe illness, nausea, vomiting or high fever. However, risk factors for a poor clinical course for patients who are hospitalized with PID are not well known.

One of the most frustrating aspects of managing PID is that it is difficult to predict clinical course on admission, where information such as microbiology results is limited. After admission, most patients are initially administrated i.v. antibiotics. However, some patients do not respond to antibiotics and therefore require an alternative antibiotic or surgery. The aim of this study was to identify risk factors for poor clinical course among patients hospitalized with PID, such as prolonged hospital stay and surgery, from patient information collected on admission. In this study, we chose 20 variables including epidemiological factors, clinical signs, ultrasonographic findings and laboratory data that can be obtained on admission, and evaluated their association with clinical course.

Methods

The medical records from 93 patients who were admitted to the University of Tokyo Hospital with a diagnosis of PID in the period January 2005 to April 2011 were studied retrospectively. Medical records from pregnant women were excluded from the study. Clinical data including medical history, results of physical examinations, laboratory and image analyses, and the clinical course of each patient were obtained from medical records. The diagnosis of PID and the decision of admission was made according to guidelines proposed by the CDC.[2] Of the total, 28 patients did not respond to oral antimicrobial therapy, 25 patients were unable to follow or tolerate outpatient therapy, and 40 patients had severe illness, nausea, vomiting or high fever. This study was approved by the institutional review board of the University of Tokyo.

According to the clinical course, patients were divided into two groups: those who were discharged within 7 days and given conservative treatment (favorable clinical course group, $n = 44$), and those who needed hospitalization for more than 7 days and/or surgical intervention (poor clinical course group, $n = 49$). Seven days was chosen because the median duration of hospitalization for all cases was 7 days and therefore cases were evenly distributed into two groups if they were divided by 7 days. After the admission, all patients were managed according to the guideline of the University of Tokyo Hospital's Infectious Disease Board. This guideline proposes that parenteral antibiotic therapy, principally the third generation of cephalosporin, is initially started, and second-line antibiotics and/or surgical interventions are considered if the first-line antibiotic therapy fails to control the inflammation.

Twenty variables that can be obtained on admission and before conducting invasive/time-consuming diagnostic tests (age, history of pregnancy/delivery, history of gynecological open/laparoscopic surgery, history of PID, history of oral contraceptives/intrauterine device [IUD] use, history of intrauterine operation before onset, body temperature on admission, signs of peritoneal irritation, vomiting and diarrhea, abnormal vaginal discharge, presence of endometriosis, fibroid, adenomyosis and any cystic lesion in the pelvis detected by ultrasonography, white blood cell [WBC] counts and C-reactive protein [CRP] level) were evaluated to assess their association with the clinical course of PID. Intrauterine operations include collection of endometrial cytology, intrauterine insemination, embryo transfer, induced abortion and removal of IUD. They were categorized into one group because they share common procedures: inserting instruments into the uterine cavity through the cervix. Factors such as microbiologic findings or magnetic resonance imaging (MRI)/laparoscopic findings are not included because these are not always available on admission.

Binary logistic regression univariate analysis of the possible risk factors for poor clinical course, followed by a forward stepwise variable selection and logistic regression analysis, were performed in order to eliminate confounding factors using StatView ver. 5.0 software. A P-value of less than 0.05 was considered statistically significant. The cut-off value for CRP level was calculated by receiver–operator curve (ROC) analysis.

Results

Patient characteristics are summarized in Table 1. Using univariate analysis, significant factors that were associated with poor clinical course were: advanced patient age (odds ratio [OR] = 1.07, 95% confidence interval [CI] = 1.02–1.13, $P < 0.01$), history of gynecological open surgery (OR = 3.68, 95% CI = 1.30–10.4, $P < 0.05$), presence of any cystic lesion in the pelvis detected by ultrasonography (OR = 5.11,

Table 1 Patients' characteristics, and univariate and logistic regression analysis of factors related to the clinical outcome PID

Factors	Favorable clinical course ($n = 44$)	Poor clinical course ($n = 49$)	Odds ratios	95% CI	*P*-values
Age (years)	34.2 ± 9.1	39.1 ± 7.9	1.071	1.017–1.129	<0.01
No. of pregnancies	0.48 ± 0.51	0.32 ± 0.48	0.582	0.253–1.340	NS
No. of deliveries	0.31 ± 0.47	0.29 ± 0.46	0.857	0.353–2.081	NS
History of gynecological open surgery	6 (13.6)	18 (36.7)	3.677	1.302–10.39	<0.05
History of gynecological laparoscopic surgery	5 (11.3)	11 (22.4)	2.258	0.717–7.155	NS
History of PID	7 (15.9)	13 (26.5)	1.909	0.683–5.331	NS
History of oral contraceptive use	3 (6.8)	4 (8.2)	1.21481	0.256–5.756	NS
History of IUD use	0 (0.0)	1 (2.0)	NA	NA	NA
History of intrauterine operation before onset	5 (11.4)	13 (26.5)	2.817	0.913–8.690	NS
Body temperature on admission	37.8 ± 0.8	37.7 ± 0.8	0.870	0.400–1.446	NS
Signs of peritoneal irritation	4 (9.1)	16 (32.7)	0.853	0.357–2.037	NS
Vomiting	2 (4.5)	8 (16.3)	4.098	0.820–20.46	NS
Diarrhea	2 (4.5)	3 (6.1)	1.370	0.218–8.603	NS
Abnormal vaginal discharge	0 (0.0)	2 (4.1)	NA	NA	NA
Endometriosis	27 (61.4)	38 (77.6)	2.175	0.880–5.376	NS
Fibroid	13 (29.5)	21 (42.9)	1.788	0.757–4.227	NS
Adenomyosis	7 (15.9)	14 (28.6)	2.144	0.764–5.853	NS
Any cystic lesion in the pelvis	33 (75.0)	46 (93.9)	5.111	1.321–19.77	<0.05
White blood cell counts on admission ($\times 10^3$)	13.7 ± 4.0	13.9 ± 4.8	1.000	1.000–1.000	NS
CRP levels on admission	6.67 ± 8.54	10.73 ± 8.49	1.060	1.006–1.120	<0.05

Values are give as mean ± standard deviation or number (percentage). CI, confidence interval; CRP, C-reactive protein; IUD, intrauterine device; NA, not applicable; NS, non-significant; PID, pelvic inflammatory disease.

Table 2 Multivariate analysis of factors related to the clinical course of PID

Factors	*P*-values	Odds ratios	95% CI
History of gynecological open surgery	NS	2.268	0.720–7.142
History of intrauterine operation before onset	$P < 0.05$	4.182	1.197–4.604
Vomiting	NS	3.922	0.693–22.20
Any cystic lesion in the pelvis	NS	2.268	0.897–18.08
CRP levels on admission	$P < 0.05$	1.07	1.006–1.130

Likelihood ratio $P < 0.0005$. CI, confidence interval; CRP, C-reactive protein; NS, non-significant; PID, pelvic inflammatory disease.

CI = 1.32–19.8, $P < 0.05$) and high CRP level (OR = 1.06, CI = 1.01–1.12, $P < 0.05$) (Table 1). According to a forward stepwise variable selection, five variables (history of gynecological open surgery, history of intrauterine operation before onset, vomiting, any cystic lesion in the pelvis detected by ultrasonography, CRP level) were selected for logistic regression analysis (likelihood ratio $P < 0.0005$). Significant factors that were independently associated with poor clinical outcome were history of intrauterine operation before onset (OR = 4.18, CI = 1.20–14.6, $P < 0.05$) and high CRP level (OR = 1.07, CI = 1.01–1.14, $P < 0.05$) (Table 2). The breakdown for gynecological open surgery was as follows (poor clinical course case/total case): oophorectomy/cystectomy due to ovarian tumor/abscess (11/14), Cesarean section (3/6), correction of uterine anomaly (2/2), salpingectomy due to abscess (1/1) and myomectomy (1/1). The breakdown for intrauterine operation was as follows (poor clinical course case/total case): collection of cytology (5/5), embryo transfer (4/5), intrauterine insemination (1/2), induced abortion (0/2), removal of IUD (1/1) and others (2/3).

As for CRP levels, ROC analysis showed that the area under the curve (AUC) was 0.67 and the cut-off level was 4.4 mg/dL, yielding a sensitivity of 76.2% and specificity of 58.4% (Fig. 1).

Discussion

This is the first study that has comprehensively analyzed the effect of multiple variables that are available

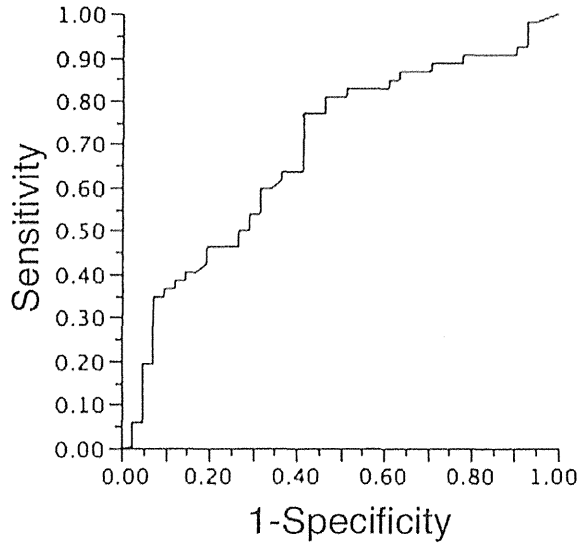

Figure 1 Cut-off value for C-reactive protein level was calculated by receiver–operator curve analysis. The area under the curve (AUC) was 0.67 and the cut-off level was 4.4 mg/dL, yielding a sensitivity of 76.2% and specificity of 58.4%.

on admission, on the clinical course of PID. In this study, five variables –advanced patient age, history of gynecological open surgery, presence of any cystic lesion in the pelvis detected by ultrasonography and high CRP levels on admission – were identified as factors associated with poor clinical course. These factors are potential predictors for poor prognosis, although they could be confounded. Using logistic regression analysis, a history of intrauterine operation before onset and high CRP levels on admission were found to be independently associated with poor clinical course. A history of pregnancy/delivery, history of oral contraceptives/IUD use, history of gynecological laparoscopic surgery, history of PID, body temperature on admission, signs of peritoneal irritation, vomiting and diarrhea, abnormal vaginal discharge, presence of endometriosis, fibroid, adenomyosis detected by ultrasonography and WBC counts were not associated with poor clinical course.

Our study findings were congruent with previous observations that indicated an association between advanced patient age and poor clinical course. Jamieson *et al.* demonstrated that older women (≥35 years) have an elevated risk of a complicated clinical course of PID, such as surgery and prolonged hospitalization (≥14 days).[3] Similarly, Viberga *et al.* found that advanced age (>35 years) was an independent factor strongly associated with an increased risk of surgery for PID.[4] This was also the case for tubo-ovarian abscess (TOA); that is, older age was identified as a risk for high failure rate of conservative treatment of TOA.[5,6] Possible explanations for poor clinical course in women of advanced age are inherent weakness or vulnerability, and a tendency to admit at an advanced stage of PID, due to a low index of suspicion among gynecologists, that results in delayed diagnosis. Careful management is needed for advanced aged PID patients.

In attempting to find risk factors that are available on admission, we analyzed the association of patients' histories of pregnancy, delivery, gynecological open/laparoscopic surgery and PID, oral contraceptives/IUD use, and clinical course of PID. Previous investigations have not evaluated the association between past operative histories and the severity of PID. In the current study, we have demonstrated that patients with a history of gynecological open surgery had a higher rate of poor prognosis. It is possible that women who have undergone open surgery may have intraperitoneal adhesion, which causes unfavorable effects on the peritoneal environment once PID has developed. Conditions that require open surgery such as severe endometriosis or congenital malformation per se may also have a negative impact on clinical course. History of PID, on the other hand, is not associated with clinical course, which is consistent with previous findings.[4]

This study concluded that specific clinical symptoms such as signs of peritoneal irritation, vomiting and diarrhea at admission and abnormal vaginal discharge were not predictors of clinical course. Similarly, the degree of cervical motion tenderness and adnexal tenderness was not associated with clinical course (data not shown). Instead, the presence of any cystic lesion in the pelvis detected by ultrasonography was a good predictor of poor clinical course. The effectiveness of transvaginal ultrasonography as a method for evaluating PID is well documented,[7,8] although enhanced computed tomography and MRI yield higher sensitivity and specificity.[9] According to the current study, we support the use of ultrasonography, which is usually equipped in gynecological examination units, as a routinely performed procedure for the initial assessment of PID.

Throughout this study, we did not distinguish TOA from PID, because the diagnosis of TOA is not always certain on admission. Alternatively, we defined a