—Report on Experiments and Clinical Cases—

The Influence of Assisted Reproductive Technology on Women with Pregnancy-induced Hypertension: A Retrospective Study at a Japanese Regional Perinatal Center

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Abstract

Objective: To evaluate clinical features of assisted reproductive technology (ART) patients with pregnancy-induced hypertension (PIH) compared to spontaneously conceived PIH patients.

Methods: We retrospectively compared PIH incidence, maternal outcomes, and neonatal outcomes among these patients.

Results: Preeclampsia, cesarean rate, and massive maternal bleeding were significantly more common in the ART group. Neonatal outcomes showed no significant difference between the groups. Multiple regression analysis revealed ART as an independent risk factor for preeclampsia. However, higher cesarean rate and massive bleeding were mainly associated with multiple pregnancy.

Conclusion: ART patients with PIH had an increased incidence of preeclampsia, cesarean delivery, and massive maternal hemorrhage.

(J Nippon Med Sch 2010; 77: 312–317)

Key words: assisted reproductive technology, maternal outcome, perinatal outcome, pregnancy-induced hypertension

Introduction

Hypertension is the one of the most common pregnancy-related medical disorders. Although the outcome for most women with pregnancy-induced hypertension (PIH) and their infants is good, PIH remains a major cause of morbidity and mortality[1]. PIH encompasses a wide spectrum of pregnancy-related hypertension, ranging from mild gestational hypertension to severe hypertension with multiple organ dysfunction, including severe gestational hypertension, preeclampsia, and eclampsia.

Assisted reproductive technology (ART) is a well-established and accepted method for treating female and male infertility. Recent studies have revealed that ART is associated with increased preeclampsia, gestational hypertension, preterm birth, placental

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abruption, placenta previa, and cesarean delivery in both singleton and twin pregnancies[2–6]. Although previous studies focused on PIH incidence in ART patients, the influence of ART on PIH is poorly understood. We compared the clinical features in ART patients with PIH to those in spontaneously conceived women.

Materials and Methods

The study protocol was approved by the Ethics Committee of Japanese Red Cross Katsushika Maternity Hospital. Informed consent concerning analysis from a retrospective database was obtained from all subjects. PIH patients who delivered at Japanese Red Cross Katsushika Maternity Hospital from January 2005 through December 2007 were retrospectively studied. Data were obtained from birth registries and medical charts. The database included antenatal data, PIH subclassifications, gestational age at delivery, delivery mode, birth weight, fetal demise, Apgar score at 1 and 5 minutes, umbilical arterial pH, HELLP (hemolysis, elevated liver enzymes, and low platelet count) syndrome, and placental abruption.

In this study, we defined ART as in vitro fertilization-embryo transfer (IVF-ET) or intracytoplasmic sperm injection-embryo transfer (ICSI-ET). We excluded patients undergoing only ovulation induction, and patients with chronic hypertensive and/or renal disease diagnosed before pregnancy. In controls, gestational age was established by ultrasonographic examination of the fetal crown-rump length at 8–11 gestational weeks.

We used Japanese Society of Obstetrics and Gynecology (JSOG) criteria—gestational hypertension, preeclampsia, superimposed preeclampsia, or eclampsia—to define PIH. PIH subclassifications included PIH clinical onset time and severity. Gestational hypertension was defined as a systolic blood pressure of ≥140 mm Hg and/or diastolic blood pressure of ≥90 mm Hg at rest after the 20th week of pregnancy in women known to be normotensive before pregnancy, and before the 20 gestational weeks. Severe gestational hypertension was defined as sustained elevation of systolic blood pressure of ≥160 mm Hg and/or diastolic blood pressure of ≥110 mm Hg. Preeclampsia was defined as PIH with proteinuria. Proteinuria was defined as ≥300 mg/day protein in a 24-h urine specimen. Superimposed preeclampsia was defined as one of the following conditions: (1) chronic hypertensive patients developing new-onset proteinuria after 20 weeks of pregnancy; (2) chronic hypertensive proteinuria patients with increasing hypertension and/or proteinuria after 20 weeks of pregnancy; and (3) proteinuria patients who developed new-onset hypertension after 20 weeks of pregnancy. Preeclampsia was considered severe when severe gestational hypertension was associated with abnormal proteinuria or when hypertension was associated with severe proteinuria (at least 2 g/24 h). Additionally, eclampsia patients were considered to have severe PIH. PIH with an earlier onset (<32 weeks gestation) was defined as early onset (EO), and that at >32 weeks gestation was defined as late onset (LO).

The HELLP syndrome required the presence of the following laboratory findings: (1) hemolysis, defined by elevated lactate dehydrogenase (>220 U/L) and/or elevated serum bilirubin (≥1.2 mg/dL); (2) elevated liver enzymes, defined as increased aspartate aminotransferase (>70 U/L); and (3) low platelets, defined as platelet counts <100,000 mm^3. Placental abruption was defined as complete or partial separation of a normally implanted placenta occurring before delivery, confirmed by evidence of retroplacental bleeding at delivery and placental pathological findings.

Infants with light-for-date or heavy-for-date birth weights were defined as those with sex- and age-adjusted birth weights below the 10th or above the 90th percentiles, respectively, according to the fetal growth curve for Japanese (Japanese Society of Perinatal and Neonatal Medicine, 1998).

For statistical analysis, the chi-square test or Fisher's exact test was used to compare maternal characteristics and perinatal outcomes. Student's *t*-test was used to compare mean values of the groups. Multiple logistic regression analysis was performed to evaluate the relationships between maternal factors and adverse outcomes. $P<0.05$ was

Table 1 Maternal characteristics of study groups

N	ART 20	Control 230	P value
Maternal Age (years)	34.1 ± 3.6	32.2 ± 5.1	0.11
≥35	9 (45.0%)	84 (36.5%)	0.48
Nulliparity	17 (85.0%)	146 (63.5%)	<0.01
Gestational age at delivery (weeks)	37.0 ± 2.7	37.3 ± 3.1	0.67
≤36	9 (45.0%)	82 (35.7%)	0.41
≤32	2 (10.0%)	28 (12.2%)	1
≤28	0 (0%)	3 (0.9%)	1
Twin pregnancy	8 (40.0%)	18 (7.8%)	<0.01

Note:
Data are presented as n (%)
Values are given as mean ± SD
ART, assisted reproductive technology

considered statistically significant. The statistical software package JMP 7.0.2 (SAS Institute Japan, Tokyo, Japan) was used for all data analyses.

Results

There were a total of 5,939 deliveries during the study period, 200 of which were the result of ART. Two hundred fifty women who met the inclusion criteria were included in the analysis. Of the 250 women with PIH, 230 had conceived spontaneously and 20 were ART patients. The 20 ART patients with PIH included 17 IVF patients and 3 ICSI patients. **Table 1** summarizes the maternal characteristics. The ART group had significantly higher numbers of nulliparous women and twin pregnancies than the controls.

Table 2 presents the correlations between ART and maternal outcomes in women with PIH. In the ART group, the incidence of preeclampsia was significantly higher than that in the natural conception group. Thus, the incidence of gestational hypertension was significantly low in the ART group. There were no differences in the other PIH subclassifications (superimposed preeclampsia, eclampsia, severity of PIH, or onset of PIH) and obstetric complications (HELLP syndrome and placental abruption) between the groups. Cesarean rates and estimated blood loss were significantly higher in the ART group. Neonatal outcomes are summarized in **Table 3**. There were no significant differences between the two groups.

Using multiple logistic regression analysis, we evaluated 4 maternal factors (ART, maternal age, nulliparity, and twin pregnancy) that influenced adverse outcomes, including preeclampsia incidence, gestational hypertension, and cesarean rate (**Table 4**). Preeclampsia incidence was significantly higher with ART (Odds ratio 3.34, P=0.02). On the other hand, gestational hypertension was significantly lower with ART (Odds ratio 0.29, P=0.02). Only twin pregnancy correlated with the cesarean rate (Odds ratio 3.31, P=0.02). We also evaluated 5 maternal factors (ART, maternal age, nulliparity, twin pregnancy, and cesarean section) that influenced massive maternal hemorrhage (≥1,000 mL) (**Table 5**). Maternal massive bleeding was influenced by twin pregnancy (Odds ratio 23.27, P<0.0001) and cesarean section (Odds ratio 7.11, P=0.002).

Discussion

In this study, ART patients with PIH had an increased incidence of preeclampsia, cesarean delivery, and massive maternal hemorrhage. Neonatal outcomes did not show any significant differences between the ART patients with PIH and those who conceived spontaneously. There are many potential confounders in evaluations of pathophysiologic correlations between PIH and ART. ART patients generally have a higher socioeconomic status, smoke less, and have a lower

Table 2 Assisted reproductive technology and maternal outcomes in women with pregnancy-induced hypertension

N	ART 20	Control 230	P value	Odds ratio (95% CI)
Preeclampsia	15 (75.0%)	111 (48.3%)	0.03	3.22 (1.13−9.14)
Gestational hypertension	5 (25.0%)	111 (49.8%)	0.04	0.36 (0.13−1.02)
Superimposed preeclampsia	0 (0%)	7 (3.0%)	1	NA
Eclampsia	0 (0%)	4 (1.8%)	1	NA
Early onset (≤32 weeks)	2 (10.0%)	52 (22.6%)	0.26	2.62 (0.59−11.70)
Severe type of PIH	13 (65.0%)	146 (63.5%)	0.89	1.07 (0.41−2.78)
HELLP syndrome	1 (5.0%)	2 (0.9%)	0.22	6.00 (0.52−69.23)
Placental abruption	0 (0%)	4 (1.8%)	1	NA
Cesarean delivery	15 (75.0%)	116 (52.0%)	0.04	2.94 (1.04−8.38)
Maternal bleeding	829 ± 480.2	507.4 ± 338.4	<0.01	
≥1,000mL	5 (25.0%)	15 (6.5%)	0.01	4.73 (1.61−14.79)

Note:
Data are presented as n (%)
Values are given as mean ± SD
NA means not applicable
ART, assisted reproductive technology
HELLP, hemolysis, elevated liver enzyme, and low platelet

Table 3 Assisted reproductive technology and neonatal outcomes in women with pregnancy-induced hypertension

N	ART 28	Control 248	P value	Odds ratio (95% CI)
Birth weight	2,404.6 ± 695.6	2,432 ± 709.6	0.84	
Light for date	7 (25.0%)	59 (24.5%)	0.95	1.02 (0.42−2.54)
Fetal demise	0 (0%)	2 (0.8%)	1	NA
Apgar score ≤7 at 1 minutes	5 (17.9%)	24 (9.7%)	0.19	2.02 (0.71−5.83)
Apgar score ≤7 at 5 minutes	1 (3.6%)	10 (4.0%)	1	0.89 (0.11−7.21)
Umbilical arterial pH	7.260 ± 0.069	7.274 ± 0.063	0.29	
<7.1	1 (3.6%)	3 (1.2%)	0.35	3.02 (0.30−30.10)
Admission to NICU	15 (53.6%)	102 (41.1%)	0.21	1.65 (0.75−3.62)

Note:
Data are presented as n (%)
Values are given as mean ± SD
NA means not applicable
ART, assisted reproductive technology
NICU, neonatal care unit

Table 4 Multiple logistic regression analysis for adverse outcomes in women with pregnancy-induced hypertension

	Preeclampsia		Gestational hypertension		Cesarean section	
	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value
Maternal age ≥35	0.71 (0.41−1.22)	0.21	1.54 (0.89−2.68)	0.12	0.81 (0.47−1.40)	0.45
Nulliparity	1.06 (0.61−1.84)	0.82	0.91 (0.53−1.58)	0.75	1.22 (0.70−2.13)	0.47
Conception by ART	3.34 (1.18−11.03)	0.02	0.29 (0.09−0.83)	0.02	1.96 (0.68−6.50)	0.22
Twin pregnancy	1.01 (0.41−2.47)	0.98	0.89 (0.37−2.18)	0.80	3.31 (1.24−10.44)	0.02

Note:
ART, assisted reproductive technology
CI, confidence interval

Table 5 Multiple logstic regression analysis for maternal bleeding in women with pregnancy-induced hypertension

	Maternal bleeding ≥1,000mL	
	Odds ratio (95% CI)	P value
Maternal age ≥35	0.47 (0.11−1.59)	0.23
Nulliparity	1.12 (0.35−4.06)	0.85
Conception by ART	2.93 (0.62−11.76)	0.17
Cesarean section	7.11 (1.98−35.95)	0.002
Twin pregnancy	23.27 (6.04−116.80)	<0.0001

Note:
ART, assisted reproductive technology
CI, confidence interval

incidence of monozygous twins than controls[2]. Additionally, a history of infertility has been associated with increased obstetric risks[3]. Although preeclampsia's etiology is unknown, potential causes include abnormal trophoblast invasion of uterine blood vessels, immunological intolerance, maladaptation to cardiovascular changes or inflammatory changes of pregnancy, dietary deficiencies, and genetic abnormalities[7].

Our results showed that PIH classification in ART women was associated with preeclampsia rather than gestational hypertension. Shevell et al.[4] showed that patients using IVF were 2.7 times likelier to develop preeclampsia and 1.6 times likelier to have a gestational hypertension in singleton pregnancy. Some women with gestational hypertension will subsequently progress to preeclampsia, and the rate of progression depends on gestational age at time of diagnosis; the rate reaches 50% when gestational hypertension develops before 30 weeks of gestation[8]. Mukhopadhaya and Arulkumaran[9] suggested that the process of IVF itself contributes to abnormal placentation resulting from an inherent difference in the initiation of the chorion formation while the embryo is in vitro. Our study supports the hypothesis that ART procedures might contribute to the development of preeclampsia. However, in PIH subclassifications and neonatal outcomes, the ART group did not differ from the controls. Our study cohort was too small and heterogeneous, and further large-scale study is indicated to clarify ART's effects on the PIH spectrum.

Our multiple logistic regression analysis revealed that massive maternal hemorrhage correlated with twin pregnancy and the cesarean rate. Because the cesarean rate was associated only with twin pregnancy, we agree with the generally accepted view that twin pregnancy is the most important risk factor for massive hemorrhage[10]. Even in ART twin pregnancy, PIH rates, uterine bleeding, premature contractions, intrauterine growth retardation, fetal death, discordance, and cesarean section are significantly higher than in spontaneous twin pregnancy[5]. Poikkeus and Tiitinen[11] suggested that the transfer of just one good-quality embryo reduces all previously identified risks of obstetric complications and preterm birth in ART singleton pregnancy. In contrast, we previously reported that the risk for transfusion was higher in ART patients having vaginal singleton delivery[12]. Even if single-embryo transfer becomes widely adopted, we would still carefully monitor for maternal bleeding in ART patients with PIH.

In conclusion, ART patients with PIH had an increased incidence of preeclampsia, cesarean delivery, and massive maternal hemorrhage. Adverse maternal outcome was mainly associated with twin pregnancy. We hope that single-embryo transfer will reduce the incidence of maternal complications in ART patients with PIH.

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(Received, June 1, 2010)
(Accepted, July 6, 2010)