Original

Relationship between Advanced Maternal Age and Assisted Reproductive Technology: A Retrospective Single Center Study

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Objective: To elucidate the relationship between advanced maternal age and assisted reproductive technology (ART) with respect to perinatal outcomes. **Materials and Methods:** In this retrospective single center study, we have reviewed 831 consecutive pregnant women who gave birth at one tertiary care center between January 2013 and December 2013. Perinatal clinical findings were reviewed, and the perinatal outcome, such as delivery weeks, blood loss at parturition, Apgar scores, and umbilical arterial pH (UApH), was compared between three groups divided by age at delivery and/or ART. A p value less than 0.05 was considered to be significant. **Results:** In pregnant women with advanced maternal age, 1) blood loss at parturition, 2) significant increase in cesarean delivery rate, and 3) decreased UApH were seen. In elder primiparous pregnant women with ART, blood loss and cesarean delivery rate were significantly increased, and UApH was significantly decreased. **Conclusions:** In pregnant women with advanced maternal age with or without ART, blood loss at parturition or at cesarean section and cesarean rate were increased.

Key Words: advanced maternal age, assisted reproductive techniques, high-risk pregnancy

Introduction

Maternal age has been increasing with a declining birth rate and aging of the population in Japan in the last two decades. The population database published by Japan's Ministry of Health, Labour and Welfare shows that advanced maternal age (>34 years old) accounted for 26.9% (277,399/ 1,029,800) of all births in 2013[1]. The number of births by women over 39 years old was 47,663, which was 4.6% of all births. The same statistical indicators in 1985 were 101,970 (7.1%) and 8,469 (0.6%), respectively. Thus, there has been a three- to eight-fold increase in the last 28 years. This increase is the result of many factors, such as late marriage, advanced academic training, and widespread use of assisted reproductive technology (ART)[2].

Elder primipara has been defined as a nulliparous woman aged 35 and over who has been treated as a high-risk pregnancy in Japan[3]. These pregnant women are known to have many complications and consequently show high mortality and morbidity rates[4].

In this study, we have compared perinatal outcomes between elder primiparas with or without ART versus non-elder pregnant women and between elder primiparas with ART versus those without ART to elucidate the relationship between

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Table 1 Background of study subjects

	non-elder pregnancy n = 427	elder pregnancy n = 404	
		primipara n = 234	multipara n = 170
Age	30.2 ± 3.1	38.4 ± 2.5	38.0 ± 2.4
Primigravida	239 (56.0%)	161 (68.8%)	0 (0%)
Primipara	311 (72.8%)	234 (100%)	0 (0%)
Height [cm]	159.0 ± 5.2	159.0 ± 5.6	159.0 ± 6.2
Body weight before pregnancy [kg]	52.1 ± 8.0	52.8 ± 9.0	53.3 ± 8.5
BMI before pregnancy	20.6 ± 2.9	20.9 ± 3.4	21.1 ± 2.9
Body weight at parturition [kg]	62.0 ± 8.6	62.6 ± 9.1	62.9 ± 9.0
BMI at parturition	24.5 ± 3.1	24.8 ± 3.5	24.9 ± 3.2
ART	35 (8.2%)	90 (38.5%)*	20 (11.8%)
Ovulation induction	12 (2.8%)	3 (1.3%)	3 (1.8%)
IVF-ET	7 (1.6%)	39 (16.7%)*	12 (7.1%)
AIH	6 (1.4%)	10 (4.3%)	3 (1.8%)
ICSI	6 (1.4%)	31 (13.3%)*	0 (0%)
Others	4 (0.9%)	7 (3.0%)	2 (1.2%)

Values are shown as mean ± SD or the number with percentage. *: statistical significance by Chi-square test versus non-elder pregnancy. BMI: body mass index, ART: assisted reproductive technique, IVF-ET: *in vitro* fertilization and endometrial transfer, AIH: artificial insemination of husband, ICSI: intracytoplasmic sperm injection.

advanced maternal age and poor perinatal outcomes, and to shed light on the relationship between elder primiparas and ART.

Materials and Methods

We reviewed the computerized records of 831 consecutive patients who gave birth at our hospital between January 2013 and December 2013. In this study, more than 20 variables were assessed, including demographic data and perinatal events, such as maternal age at delivery, body weight, body height, weight gain during pregnancy, body mass index, parity, gravidity, birth weight, Apgar scores, blood loss at parturition, delivery route, umbilical arterial blood gas analysis, and placental weight. Study subjects were categorized into two groups: 404 women of advanced maternal age (≥35 years) and 427 pregnant women under 35 years old. The latter 427 women were regarded as normal control. The advanced maternal age group was comprised of 234 elder primiparous women and 170 multiparous women. In order to clarify the relationship between advanced maternal age and ART, we extracted 90 elder primiparous women who received ART. Each of the above three groups was compared to the normal control (non-elder pregnancy).

Data are shown as mean ± standard deviations or the number with percentage. Statistical analysis was performed by SPSS (IBM Japan, Tokyo, Japan) and/or StatFlex 6.0 (Artech Co., Ltd., Osaka, Japan. URL: http://www.statflex.net/). Means of the two groups were compared with the Mann-Whitney U test. Statistical analysis was carried out using the χ^2 test, Fisher's exact probability test. A p value less than 0.05 was considered to be significant. This study protocol was approved by our institutional review board (approval number: 3273R).

Results

There were no significant differences in background factors between the non-elder pregnancy and elder pregnancy groups except for maternal age, parity, and ART, as shown in Table 1. In elder primiparous pregnancy, the use of ART was significantly higher than the normal control, especially pregnancy by *in vitro* fertilization and endometrial transfer (IVF-ET) and intracytoplasmic sperm injection (ICSI).

Pregnancy and perinatal outcomes are shown in Table 2. Grade A emergent cesarean section, i.e., expecting the baby's delivery within 30 minutes from the decision, was performed at mainly 29 to 33 weeks of gestation; however, grade B emergent cesarean section, i.e., expecting the baby's delivery within 60 minutes from the decision, was mostly performed around 35 gestational weeks. The rate of

Table 2 Pregnancy and perinatal outcomes in study subjects

	non-elder pregnancy n = 427	elder pregnancy n = 404	
		primipara n = 234	multipara n = 170
Delivery weeks	37.3 ± 3.2	37.2 ± 3.1	37.3 ± 2.3
Cesarean delivery	36.0 ± 3.8	35.9 ± 3.7	36.3 ± 2.7
Emergency: grade A	33.2 ± 6.5	33.8 ± 4.9	29.3 ± 4.0
Emergency: grade B	35.4 ± 2.2	35.6 ± 4.2	35.4 ± 2.8
Planned	37.1 ± 1.9	37.1 ± 1.2	37.3 ± 1.5
Vacuum extraction	38.7 ± 1.2	38.1 ± 1.4	38.7 ± 0.8
Forceps delivery	38.2 ± 1.0	38.1 ± 0.6	not available
Normal delivery	37.2 ± 2.8	38.6 ± 1.9	38.0 ± 1.7
Delivery route			
Cesarean delivery	148 (34.7%)	115 (49.1%)	74 (43.5%)
Emergency: grade A	6 (1.4%)	5 (2.1%)	3 (1.8%)
	(4.1%)	(4.3%)	(4.1%)
Emergency: grade B	87 (20.4%)	76 (32.5%)	26 (15.3%)
	(58.8%)	(66.1%)	(60.8%)
Planned	55 (12.9%)	34 (14.5%)	45 (26.5%)
	(37.2%)	(29.6%)	(35.1%)
Vacuum extraction	11 (2.6%)	14 (6.0%)	7 (4.1%)
Forceps delivery	13 (3.0%)	8 (3.4%)	0 (0%)
Normal delivery	255 (59.7%)	97 (41.5%)	89 (52.4%)
Blood loss [g]	559.7 ± 416.5	719.6 ± 567.9 [†]	620.8 ± 498.4
Cesarean	879.8 ± 463.8	963.7 ± 670.4	872.2 ± 504.2
	n = 148	n = 115	n = 74
Non-cesarean	408.0 ± 242.8	430.4 ± 238.3 [†]	430.6 ± 238.4
	n = 279	n = 119	n = 96
Birth weight [g]	2,706 ± 670	2,672 ± 662	2,769 ± 562
Birth height [cm]	47.4 ± 4.0	47.4 ± 3.9	47.5 ± 4.6
Placental weight [g]	554 ± 155	578 ± 190	569 ± 139
Fetal/placental weight ratio	5.03 ± 1.20	4.87 ± 1.28	5.00 ± 0.95
Apgar score			
less than 7 at 1 min	40 (9.4%)	23 (9.8%)	12 (7.1%)
less than 7 at 5 min	17 (4.0%)	13 (5.6%)	5 (2.9%)
Umbilical artery pH	7.31 ± 0.06	7.30 ± 0.07	7.31 ± 0.08
less than 7.20	14 (3.3%)	14 (6.0%)	7 (4.1%)

Values are shown as mean ± SD or the number with percentage. [†]: statistical significance by Mann-Whitney U test versus non-elder pregnancy.

cesarean delivery in elder primiparous pregnancy (115/234; 49.1%) was higher than that in the normal control (148/427; 34.7%), but the difference was not significant. In this group, grade B cesarean section, the main indication for which was protracted labor, was performed in 76 cases (66.1%). Blood loss at parturition in elder primiparas was significant higher than that in the normal control (719.6 ± 567.9 vs 559.7 ± 416.5, p<0.05), especially in non-cesarean delivery (430.4 ± 238.3 vs 408.0 ± 242.8, p<0.05).

Table 3 shows the pregnancy and perinatal outcomes in elder primiparous pregnancy achieved with ART. The rate of cesarean delivery was 1.5 times higher than that in the normal control, with the rate of normal vaginal delivery consequently decreasing to 33.3% of all deliveries. Blood loss was higher than that in the normal control for both cesarean and non-cesarean delivery. Umbilical arterial blood pH, representing fetal stress at parturition, was significantly lower than that in the normal control.

Table 4 shows the pregnancy and perinatal outcomes in elder primiparous pregnancy achieved with or without ART. The rate of cesarean delivery in the group with ART was significantly higher than that in the group without ART, especially in planned cesarean delivery. Blood loss was significantly higher than that in the group without ART for cesarean delivery, but not significantly in non-cesarean delivery.

Table 3 Pregnancy and perinatal outcomes in elder primiparous pregnancy with ART

	non-elder pregnancy n = 427	elder primiparous pregnancy with ART n = 90
Delivery weeks	37.3 ± 3.2	37.2 ± 3.1
Delivery route		
Cesarean delivery	148 (34.7%)*	53 (58.9%)*
Emergency: grade A	6 (1.4%)	3 (3.3%)
	(4.1%)	(5.7%)
Emergency: grade B	87 (20.4%)*	29 (32.2%)*
	(58.8%)	(54.7%)
Planned	55 (12.9%)*	21 (23.3%)*
	(37.2%)	(39.6%)
Vacuum extraction	11 (2.6%)	3 (3.3%)
Forceps delivery	13 (3.0%)	4 (4.4%)
Normal delivery	255 (59.7%)*	30 (33.3%)*
Blood loss [g]	559.7 ± 416.5[†]	832.3 ± 635.1[†]
Cesarean	879.8 ± 463.8[†]	1,092.8 ± 699.7[†]
	n = 148	n = 53
Non-cesarean	408.0 ± 242.8[†]	459.1 ± 217.0[†]
	n = 279	n = 37
Birth weight [g]	2,706 ± 670	2,667 ± 651
Birth height [cm]	47.4 ± 4.0	47.3 ± 4.0
Placental weight [g]	554 ± 155	604 ± 241
Fetal/placental weight ratio	5.03 ± 1.20	4.82 ± 1.49
Apgar score		
less than 7 at 1 min	40 (9.4%)	9 (10.0%)
less than 7 at 5 min	17 (4.0%)	5 (5.6%)
Umbilical artery pH	7.31 ± 0.06[†]	7.21 ± 0.78[†]
less than 7.20	14 (3.3%)	4 (4.5%)

Values are shown as mean ± SD or the number with percentage. *: statistical significance by Chi-square test. [†]: statistical significance by Mann-Whitney U test.

Discussion

This study was conducted to elucidate the pregnancy and perinatal outcomes of aged pregnancy at a single tertiary center. The main finding from our study was higher blood loss associated with advanced maternal age, especially among pregnant women who achieved pregnancy with ART. It is well known that mean blood loss at parturition is increased with cesarean delivery. However, in cases of aged pregnancy with ART, blood loss was significantly increased with both cesarean delivery and non-cesarean delivery. Therefore, the increase of blood loss in aged pregnancy was not simply caused by a higher cesarean rate. Uterine atony is known to be the main reason for postpartum hemorrhage (PPH). Emergent cesarean delivery, advanced maternal age, and intrauterine infection are risk factors for uterine atony. Our results from this study support the above evidence. There was a very interesting report by Lutomski et al concerning the relationship between labor induction and PPH[5]. They retrospectively analyzed deliveries over a 10-year period, in which they found a 2.5-fold increase in PPH and a 3.4-fold increase in uterine atony. The main contributing factor for blood loss at parturition was cesarean delivery followed by labor induction in their study. We could not analyze labor induction in the present study, but cases with labor induction were included in grade B cesarean delivery. We assumed that grade B cesarean delivery followed by labor induction had the most influence on blood loss at parturition. However, Table 4 could negate this assumption. The rate of grade B cesarean delivery in elder primiparous women with ART was not different from that in those without ART, and the rate of planned cesarean in women with ART was significantly higher than that in those without ART. These results might suggest that some other factors, such

Table 4 Pregnancy and perinatal outcomes in elder primiparous pregnancy with or without ART

	without ART n = 144	with ART n = 90
Delivery weeks	37.3 ± 3.1	37.2 ± 3.1
Delivery route		
Cesarean delivery	62 (43.1%)*	53 (58.9%)*
Emergency: grade A	2 (1.4%)	3 (3.3%)
	(3.2%)	(5.7%)
Emergency: grade B	47 (32.6%)	29 (32.2%)
	(75.8%)	(54.7%)
Planned	13 (9.0%)*	21 (23.3%)*
	(21.0%)	(39.6%)
Vacuum extraction	11 (7.6%)	3 (3.3%)
Forceps delivery	4 (2.8%)	4 (4.4%)
Normal delivery	67 (46.5%)*	30 (33.3%)*
Blood loss [g]	649.2 ± 511.3†	832.3 ± 635.1†
Cesarean	853.4 ± 629.2†	1,092.8 ± 699.7†
	n = 62	n = 53
Non-cesarean	494.7 ± 327.7	459.1 ± 217.0
	n = 82	n = 37
Birth weight [g]	2,677 ± 671	2,667 ± 651
Birth height [cm]	47.4 ± 3.7	47.3 ± 4.0
Placental weight [g]	561 ± 147	604 ± 241
Fetal/placental weight ratio	4.91 ± 1.14	4.82 ± 1.49
Apgar score		
less than 7 at 1 min	14 (9.7%)	9 (10.0%)
less than 7 at 5 min	8 (5.6%)	5 (5.6%)
Umbilical artery pH	7.15 ± 1.05	7.21 ± 0.78
less than 7.20	6 (4.3%)	4 (4.5%)

Values are shown as mean ± SD or the number with percentage. *: statistical significance by Chi-square test. †: statistical significance by Mann-Whitney U test.

as uterine myoma or uterine adenomyosis, caused higher blood loss at parturition, but it is just a guess.

Mean umbilical arterial pH was significantly decreased in aged pregnancy achieved with ART, but it was not significant according to Chi-square tests performed on a contingency table. There were no significant differences in Apgar scores. That is why no differences in fetal stress during labor were seen. This showed that fetal stress had no relation to maternal age.

The findings in this study were derived from only one tertiary center and a short study period of only one year; therefore, the sample size was small and there was a possible bias in medical care. A future study with a larger sample size is needed.

Conclusion

In conclusion, in pregnant women with advanced maternal age with or without ART, blood loss at parturition or at cesarean section and cesarean rate were increased.

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本院における生殖補助医療と高齢妊娠との関係に関する後方視的検討

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〔目的〕本邦における出産年齢は経年的に上昇している．35 歳以上の初産婦は，周産期予後を悪化させるハイリスク妊娠である．本研究では周産期予後に対する高齢妊娠の影響を明らかにすること，および高齢妊娠初産に対する生殖補助医療（ART）の影響を明らかにすることを目的として遂行された．〔対象および研究方法〕2013 年 1 月 1 日から 12 月 31 日の期間に東京女子医科大学母子総合医療センターで妊娠および出産の管理が行われた 831 例を対象とした．対象例について患者背景（年齢，身長，体重，妊娠中の体重増加量，body mass index：BMI 値，妊娠中の BMI 増加量，経妊回数，経産回数など），妊娠経過情報（入院の有無，治療内容，治療期間など），および周産期予後（分娩週数，分娩方法，分娩経過時間，出生児体重，アプガー値，分娩時出血量，臍帯動脈血 pH，胎盤重量など）について，医療記録より抽出し後方視的な検討を行った．出産時の年齢により，35 歳未満の非高齢妊娠群（427 例）と 35 歳以上の高齢妊娠群（404 例）とに分けた．また高齢妊娠群では，経産回数の違いにより，高齢妊娠初産群（234 例）と高齢妊娠経産群（170 例）に分類した．ART により妊娠が成立した高齢妊娠初産群（90 例）を抽出し検討した．〔結果〕高齢妊娠，特に高齢妊娠初産において，①分娩時出血量が増加する，②帝王切開分娩が増加する，③臍帯動脈血 pH は低下する傾向にある，ことが示された．また ART により妊娠が成立した高齢妊娠初産では，①帝王切開分娩が増加する，②正常経腟分娩が減少する，③帝王切開における分娩時出血量が増加する，④経腟分娩における分娩時出血量が増加する，⑤臍帯動脈血 pH は有意に低下する，ことが示された．〔結論〕高齢妊娠初産においては，帝王切開比率および分娩時出血量が増加する．ART をともなう高齢妊娠初産群では，この傾向は顕著となり，臍帯動脈血 pH も低下する．

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