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Original Research

Difference in pregnancy outcomes between primiparous and multiparous women older than 40 years

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Summary

Purpose of Investigation: This study aimed to compare pregnancy outcomes based on parity in women older than 40 years. *Materials and Methods:* This retrospective cohort study included women older than 40 years with singleton pregnancy, who delivered after 24 weeks of gestation. They were divided into two groups on the basis of parity, and maternal and perinatal outcomes were compared. *Results:* This study included 432 women, with primiparous women (n=111) comprising a quarter among them. The mean parity of multiparous women was 1.8, and the mean interval from the previous pregnancy was 9.5 years. On analyzing multivariable logistic regression-adjusted confounding factors, small for gestational age (SGA) neonates (OR, 2.525; 95% CI, 11.407–4.529) were associated with primiparous women. The occurrence of preterm birth before 37 weeks of gestation (OR, 1.783; 95% confidence CI, 1.080–2.942) was increased in multiparous women. *Conclusion:* There are different pregnancy outcomes between primiparous and multiparous women. Preterm birth is more frequent in multiparous women, with an extremely long interval to subsequent pregnancy. The incidence of SGA newborns was higher among primiparous women.

Key words: Maternal and perinatal outcomes; Parity; Small for gestational age (SGA).

Introduction

Advanced maternal age affects increased obstetric complications, including miscarriage, stillbirth, chromosomal abnormalities, congenital anomalies, gestational diabetes, preeclampsia, placenta previa, and cesarean delivery [1-3]. However, studies have also reported overall favorable pregnancy outcomes in women of very advanced maternal age [4, 5].

Previously, pregnancy at advanced maternal age was usually observed in multiparous women of a low socioeconomic status; most pregnancies were unintended, and the women did not undergo regular antenatal check-ups [6]. Multiparity, namely, grand parity, has been associated with adverse pregnancy outcomes [7, 8]. However, some studies have suggested that multiparous women tend to be older and have associated comorbidities and that multiparity might be associated with obstetric complications [9, 10].

Recently, there has been a trend toward births at an older maternal age with the increased population of women who married late because of wider educational and career opportunities, increased incidences of second marriages, evolving assisted reproductive technology, and better contraceptive options. Because of intensive family planning and deliberate delay of pregnancy, primiparous women often become pregnant at an advanced maternal age. Primiparous women are more likely to experience adverse pregnancy outcomes [11, 12]. These result from underlying primary or secondary infertility and increased proportion of pregnancies by assisted reproductive treatments [13, 14]. Other studies have reported the cumulative effect of both age and parity on adverse outcome [15].

In Korea, the number of live births from women older than 40 years increased by nearly three times between 2007 and 2017 despite the decrease in the total number of live births to 27.5% [16]. This trend usually reflects older primiparous women who delayed pregnancy by choice or due to underlying subfertility, and also includes continuing childbirth for multiparous women [17]. Parity will be of greater concern considering that women who became pregnant in the past decade were older [18]. Therefore, the relationship between obstetric complications and parity among women with advanced maternal age women need reinterpretation based on the changing reproductive trend. The authors aimed to investigate the tendency of women older than 40 years becoming pregnant and examine whether pregnancy outcome differs based on parity.

Material and Methods

Women older than 40 years who delivered at the Gil Medical Center between January 2006 and October 2016 were enrolled and analyzed retrospectively. The study was conducted in accordance with the ethical standards of the Helsinki Declaration, and the Gil Medical Center Institutional Review Board approved this study design.

Inclusion criteria were women with a singleton pregnancy, aged 40 years or older at the time of delivery, and who delivered after 24 weeks of gestation. Women with preterm deliveries before 24 weeks of gestation, multiple pregnancies, and with insufficient data were excluded.

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Table 1. — *Maternal clinical characteristics.*

	Total (n=432)	Primiparity (n=111)	Multiparas (N=321)	*p*-value
Maternal age	41.5±1.7	41.2±1.6	41.6±1.7	0.076
Parity			1.8±0.8	<0.001
Body mass index	23.4±4.2	23.0±3.7	23.6±4.4	0.164
Marriage status	415 (96.1%)	109 (98.2%)	306 (95.3%)	0.259
Smoking	6 (1.4%)	0	6 (1.9%)	0.345
Assisted conception	13 (3.0%)	7 (6.3%)	6 (1.9%)	0.046
Interdelivery interval			9.5±5.6	<0.001
Prenatal care	410 (94.9%)	108 (97.3%)	302 (94.1%)	0.184
Preterm birth history			31 (9.7%)	0.001

Table 2. — *Comparison of pregnancy outcomes.*

	Total (n=432)	Primiparity (n=111)	Multiparity (n=321)	*p*-value
Gestational age at delivery	36.6±3.2	37.3±2.6	36.4±3.4	0.003
Preterm birth <37 weeks of gestation	152 (35.2%)	28(25.2%)	124 (38.6%)	0.011
Major fetal anomaly	11 (2.5%)	3 (2.7%)	8 (2.5%)	1.000
Intrauterine fetal death	6 (1.4%)	2 (1.8%)	4 (1.2%)	0.650
No maternal disease	302 (69.9%)	80 (72.1%)	222 (69.2%)	0.564
Maternal disease	130 (30.1%)	31 (27.9%)	99 (30.8%)	
Preexisting hypertension	13 (3.0%)	5 (4.5%)	8 (2.5%)	0.333
Preeclampsia	59 (13.7%)	13 (11.7%)	46 (14.3%)	0.489
Pregestational diabetes mellitus	11 (2.5%)	3 (2.7%)	8 (2.5%)	1.000
Gestational diabetes mellitus	44 (10.2%)	14 (12.6%)	30 (9.3%)	0.327
Placenta previa	44 (10.2%)	11 (9.9%)	33 (10.3%)	0.911
Cesarean section	307 (71.1%)	84 (75.7%)	223 (69.5%)	0.214
Before labor	295 (96.1%)	79 (94.0%)	216 (96.9%)	0.320
In labor	12 (3.9%)	5 (6.0%)	7 (3.1%)	
Neonatal sex (M)	233 (54.2%)	59 (53.2%)	174 (54.4%)	0.824
Birth weight	2789.9±781.2	2810.2±721.4	2782.9±782.0	0.743
Small for gestational age	68 (15.8%)	26 (23.4%)	42 (13.1%)	0.010
Large for gestational age	14 (3.2%)	5 (4.5%)	9 (2.8%)	0.365
Apgar score <7 at 5 min	18 (4.2%)	3 (2.7%)	15 (4.7%)	0.581
No postpartum complication	393 (91.0%)	104 (93.7%)	289 (90.0%)	0.246
Postpartum complication	39 (9.0%)	7 (6.3%)	32 (10.0%)	
Transfusion	28 (6.5%)	6 (5.4%)	22 (6.9%)	0.593
Cardiovascular morbidity	5 (1.2%)	0	5 (1.6%)	0.334
Urogenital morbidity	3 (0.7%)	0	3 (0.9%)	0.573
Others	3 (0.7%)	1 (0.9%)	2 (0.6%)	1.000

Primiparous women were defined as those who had never completed a pregnancy after 20 weeks of gestation, whereas multiparous women were defined as women with at least one prior pregnancy who delivered after 20 weeks of gestation. Baseline clinical data on age, body mass index (BMI) before pregnancy, parity, social history (marital status, smoking), assisted conception, prenatal care, and history of previous preterm birth were collected. The interdelivery interval (IDI) was defined as the period between consecutive live births. Pregnancy outcomes included gestational age at delivery, preterm birth before 37 weeks of gestation, major fetal anomaly, fetal death in utero, and maternal disease. Maternal disease included underlying disease (preexisting diabetes mellitus, and hypertension) and obstetrical complication (preeclampsia, placenta previa, and gestational diabetes mellitus). The maternal state without underlying maternal disease and obstetrical complication was defined as "no maternal disease". Delivery by a cesarean section was categorized by the time of decision. A decision of cesarean section while in labor was made in cases of failed progression and fetal distress. A decision of cesarean section before labor was made in cases of malpresentation and those with a history of prior uterine surgery or placenta previa and upon maternal request. Neonatal outcomes included birth weight, Apgar score < 7 at five minutes, and neonate sex. Neonates were categorized on the basis of the Korean reference chart, wherein birth weight at the > 90^{th} and < 10^{th} percentiles was defined as large (LGA) and small for gestational age (SGA), respectively. Postpartum complications included transfusion, cardiovascular morbidity, and urogenital morbidity. Other complications included infection and wound dehiscence.

Categorical variables were reported as absolute numbers and percentages; continuous variables were reported as mean and standard deviation. Results were analyzed using the *t*-test and chi-squared test, with Fisher's exact test for comparison of each variable between the two groups. Multivariate logistic regression with stepwise selection of variables was used to determine which variables of pregnancy outcome showed an independent association with each pregnancy on the basis of parity. Statistical analysis was performed using SPSS ver. 21.0, and $p < 0.05$ was considered statistically significant.

Table 3. — *Multivariate logistic regression analysis of pregnancy outcomes in primiparous women compared with multiparous women.*

Pregnancy outcome	Primiparity	Multiparity
	aOR[1] (95% CI)	aOR[1] (95% CI)
Assisted conception	4.228 (1.285–13.906)	0.239 (0.073–0.787)
Small for gestational age	2.525 (1.407–4.529)	0.405 (0.226–0.726)
Fetal major anomaly	0.896 (0.2023–3.959)	1.125 (0.256–4.934)
No maternal disease	1.037 (0.613–1.757)	0.937 (0.554–1.584)
Intrauterine fetal death	3.851 (0.467–31.767)	0.272 (0.033–2.234)
Preterm birth <37 weeks of gestation	0.535 (0.322–0.887)	1.783 (1.080–2.942)
No postpartum complication	1.415 (0.562–3.565)	0.689 (0.274–1.732)

[1] *Variable adjusted include maternal age, body mass index, smoking state, married status, and history of preterm delivery.*

Results

Of 8,628 mothers who delivered in Gil Medical Center between January 2006 to October 2016, 540 mothers (6.3%) older than 40 years were selected as the study group. Of these, 34 cases of multiple pregnancies, 23 cases of previable births before 24 weeks of gestation, and 50 cases of insufficient data were excluded. Finally, 432 patients were enrolled, and they were divided into two groups on the basis of parity, and the clinical characteristics and pregnancy outcomes were analyzed. Of the enrolled women, approximately 25% were primiparous (n=111). Pregnancies conceived by assisted reproductive technology were significantly more frequent (6.3% *vs.* 1.9%, $p = 0.046$) in primiparous women. The mean parity was 1.8, mean IDI was 9.5 years, 6 women (1.9%) were smokers, and 31 (9.7%) had history of previous preterm birth in multiparous women (Table 1).

The mean gestation age at delivery was earlier (37.3 weeks *vs.* 36.4 weeks, $p = 0.003$) and preterm birth before 37 weeks of gestation was more frequent in multiparous women. Primiparous women had an increased incidence of SGA, whereas no differences were found in the mean birth weight, incidence of cases with Apgar score < 7 at five minutes, rate of fetal death in utero, and occurrence of major anomalies. The rate of cesarean section as the delivery mode was not significantly different, even upon classification by time of decision. The incidence of maternal disease and postpartum complications were not significantly different between the two groups (Table 2).

To determine independent association of parity on variable of pregnancy outcome, multivariable logistic regression performed after adjusting for confounding factors that could have influenced the identified pregnancy outcome. Pregnancy by assisted reproductive technology [odds ratio (OR); 4.228, 95% confidence interval (CI), 1.285–13.906], and SGA neonate (OR, 2.525; 95% CI, 1.407–4.529) showed independent associations with primiparous women. Preterm birth < 37 weeks of gestation (OR, 1.783; 95% CI, 1.080–2.942) revealed independent associations with multiparous women (Table 3).

Discussion

The mean maternal age at delivery has been increasing annually and was recently reported as 32.6 years in Korea [16]. Advanced maternal age is a well-known risk factor for adverse outcomes in pregnancy. Usually, advanced maternal age is defined as older than 35 years; however, because of recent medical advances, the range of fertility in women has become wider. However, further information is needed on the effects of advanced maternal age. In addition, as the population of women with advanced maternal age is increasing, their heterogeneity should be understood, and other risk factors related to adverse outcomes and older maternal age should be examined.

Primiparous mothers had more frequent complications at antenatal and intrapartum period than multiparous mothers 40 years and older, whereas the neonatal outcomes were comparable [19]. In systematic review, nulliparity especially compared with mothers with 2–4 parity correlated with unadjusted risk of low birth weight and small gestational age [20]. Uteroplacental perfusion by adaptation of the hemodynamic system to supply oxygen and nutrients to the fetus increased in subsequent pregnancies compared to that in the first pregnancy [21-23]. Exposure to the maternal immune system for the first time resulted in relatively restricted fetal growth compared to that in subsequent pregnancies [24]. Some changes of structure after childbirth, such as enlarged size and more collagen and elastin of the uterus, and these factors limit the uterine capacity in the first pregnancy [25, 26]. In addition, singleton pregnancies after assisted conception have a poor perinatal outcome, including SGA neonate compared with natural pregnancy [27]. Although the incidence of pregnancy by assisted conception was higher in the primiparity group, the present authors found that primiparity is related to the risk of delivering SGA neonates, after adjusting for maternal morbidity. This multiparity group had long interval, with a mean of 9.5 years, to subsequent pregnancy. Permanent modifications to fetal growth during the first pregnancy may remain, leading to more suitable condition in subsequent pregnancies [25, 28]. Because interpregnancy interval changes the relationship between birthweight and parity, birthweight increased in multiparous women with a long interval compared with that in those with a short interval [29]. Consequently, this study compared between long interval pregnancy and primiparity in women 40 years and older. The World Health Organization recommends that

insufficient birth spacing to subsequent pregnancy was associated with obstetric complications [30]. It showed a J-shaped association that optimal interval was 18–23 months to prevent adverse pregnancy outcomes, and interval of birth-to-pregnancy < 18 or > 59 months increased the risk of adverse pregnancy outcome [31]. There are several presumptions between long interval pregnancy and adverse outcomes. The longer the interval to the next pregnancy, the more physiological changes in previous pregnancy will regress. The circumstance for pregnancy after excessively long interval may be similar to nulliparity [32]. However, the present results showed different adverse outcomes between first birth and extremely long interval pregnancy. Another possibility, long interval pregnancy contain factors inducing secondary infertility and adverse perinatal outcomes; these increase the risk of adverse pregnancy outcome [31]. Particularly, secondary infertility is related to increasing prevalence of preterm birth [33, 34]. Not only earlier gestational age at delivery but also increasing preterm birth before 37 weeks of gestation was observed in the multiparous group. In Utah, which has a relatively homogenous population, women with pregnancy after extremely long intervals tend to be of advanced maternal age, unmarried, smokers, and with a low educational level. In addition, adverse pregnancy outcomes and delayed fertility were associated with anatomical or metabolic factors [32]. Data on the reason for long intervals, such as anatomical factors, a history of abortion, contraceptive choices, remarriage status, and sociodemographics, were inadequate, but the present population was composed of women older than 40 years, and maternal comorbidity conditions were comparable, excluding parity. In addition, preterm birth with SGA decreased in multiparous women. All reproductive aged women with interpregnancy interval of < 1 or > 3 years after live birth had an increased risk of preterm birth. Within mother analysis, for women with short interval also relate to increasing preterm birth, whereas not for long intervals [35]. This analysis used ancillary methods, but it is unlikely to analyze women 40 years and older.

Unplanned pregnancy comprises a considerable proportion in pregnancy with short or long intervals from previous births [36]. Women with underlying disease and infections in birth canal were more common to have an unplanned pregnancy [37]. Under stressful economics, social, or mental conditions in women, unplanned pregnancy is more frequent [38]. The reason for this long interval was uncertain, whether it is a planned or unplanned subsequent pregnancy, and factors associated for long interval pregnancy are yet to be elucidated. Factors associated with unplanned pregnancy may be similar to known risk factors for preterm birth.

Retrospective studies reported the performance of cesarean sections in women ≥ 40 years. Primary cesarean section was more frequent in Boston [39]; the cesarean section rate was 74.8% in Beijing [40], and risk of delivery-related perinatal death doubled in Scotland [41]. Usually, as parity increases, the necessity for a cesarean section reduces. However, because the rate of cesarean section increases with advanced maternal age, possible physiologic factors may be reduced oxytocin receptors and the contraction capacity of the aged myometrium. These findings reflect undeniable factors concerning risk and medicolegal issues that result in obstetrician preferences and maternal requests, such as cesarean section without trial of labor, becoming more common among older mothers [42]. No difference was found in the cesarean section rate between nulliparous and multiparous women as 44.5% of multiparous women already had a prior uterine surgery.

This study population was enrolled from a single tertiary medical center under the same criteria of diagnosis, antenatal care, and treatment. The selection bias may be inherent to that for studies performed at tertiary medical center. Statistical analysis was performed after adjusting for confounding factors; however, this study was a retrospective cohort study.

Improved accessibility of antenatal care service and enhanced public awareness and socioeconomic conditions contribute to the improvement in pregnancy outcomes in women of advanced maternal age compared with those reported in earlier studies. Furthermore, maternal behavior could be self-controlled, and the fetuses of mothers with advanced maternal age may be relatively healthier [42].

Conclusion

Further studies on supporting biological mechanisms for the present results, such as the higher incidence of SGA in primiparous women and preterm birth in multiparous women, targeted antenatal care, and counseling on complications related to parity will be helpful for women of advanced maternal age. Multiparous women with advanced maternal age tend to have a very long interval from the previous birth. Informed consultation regarding the increasing number of preterm births will be required for postpartum women with reversible long-acting contraception when planning a pregnancy. Nulliparous women with advanced maternal age need to consider antenatal care for an SGA fetus. The mean maternal age and proportion of older mothers are consistently increasing and predicted to continuously increase. Further studies focusing not only on older age but also on various aspects in women of advanced maternal age are needed.

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