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The effect of male fetal gender on the cesarean section rate in Greek women with induced labor

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ΑΡΧΕΙΑ ΕΛΛΗΝΙΚΗΣ ΙΑΤΡΙΚΗΣ 2019, 36(5):643–649

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OBJECTIVE **To explore the effect of fetal gender on the mode of delivery in women with induced labor.** METHOD **We collected data retrospectively on women who underwent induction of labor in a tertiary Greek hospital over a one-year period. The maternal demographic characteristics, details of labor and delivery, and neonatal data were retrieved from the medical records. Multiple logistic regression analysis was used to identify whether or not the fetal gender was an independent risk factor for cesarean section (CS).** RESULTS **The sample consisted of 359 women with a mean age of 30±5.4 years. Maternal characteristics were similar in women who delivered male and female babies. The birth weight was significantly greater in male than female babies. A significantly higher CS rate was recorded in women with male babies than in those with female babies (39.4% vs 25.5%). Multiple regression analysis showed that the male fetal gender increased almost two-fold the risk of CS, even after adjusting for birth weight (OR=2.04, 95% CI: 1.11-3.76; p=0.022).** CONCLUSIONS **We showed in this study that the male fetal gender is a factor that might affect the mode of delivery in women with induced labor. This gender relationship persisted after adjusting for birth weight, indicating that factors other than birth weight could explain this effect.**

Η επίδραση του άρρενος φύλου του εμβρύου στο ποσοστό καισαρικής τομής σε Ελληνίδες που υποβλήθηκαν σε πρόκληση τοκετού

Περίληψη στο τέλος του άρθρου

Key words

Birth weight
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A 1982 study reported a 17% increase in the rate of cesarean section (CS) delivery in women bearing male fetuses compared with those bearing female fetuses.[1] This was one of the first reports of the male fetal gender effect on the mode of delivery; the study was conducted in a population of women in Scotland with either spontaneous onset of labor or labor induced for various indications. The hypotheses to explain this phenomenon were, firstly, that male fetuses were bigger, which could explain the higher rates of cephalopelvic disproportion leading to CS delivery. In addition, the male fetal hormonal contribution to the progress of labor may be less effective than the female, resulting in maternal uterine dysfunction, and male babies might show signs of fetal distress in labor more often, or more severely, than female babies.

Since 2002, reports have been published of several large population-based studies and smaller cohort studies in different countries on the occurrence and magnitude of the male fetal gender effect on CS delivery.[2–10] These studies documented a male fetal gender effect on the CS rate in women of different ethnic background, both primiparous and multiparous, and with either spontaneous onset or induced labor. Because of the varying study design and features of the women giving birth, the reported magnitude of the male fetal gender effect on CS delivery varies across these studies.[11]

The primary objective of our study was to investigate the possible male fetal gender effect on the CS delivery rate in a cohort of women in Greece who had undergone induction of labor, and comparison with studies from other

countries. Review of the literature revealed no such study to date in the Greek population.

MATERIAL AND METHOD

A retrospective cohort study was conducted of women who underwent induction of labor for various indications at a tertiary maternity hospital in Athens over the 12-month period January to December 2012. Women with a singleton cephalic presentation were included, in whom labor was induced for one of the following reasons: Post-dates pregnancy, i.e., gestational age (GA) >41 weeks, reduced fetal movements, fetal growth restriction, pregnancy-induced hypertension (preeclampsia/eclampsia), diabetes mellitus (DM), gestational or preexisting, term (>37 weeks), pre-labor rupture of membranes for >24 hours, intrahepatic cholestasis of pregnancy, maternal age >40 years, and maternal request because of social or mental health issues. Women were excluded in the case of breech presentation, stillbirth, fetal congenital abnormalities, multiple pregnancy and elective CS delivery. The maternal, labor/delivery and neonatal data were collected manually through review of the medical charts and hospital records and anonymized for analysis.

The maternal data included maternal age, ethnicity (Greek, Albanian, Russian, other), educational status (university or higher, secondary, primary), parity, smoking status, body mass index (BMI) at booking and at the birth (underweight: <18.5 kg/m^2, normal: 18.5–24.9 kg/m^2, overweight: 25.0–29.9 kg/m^2, obese: ≥30.0 kg/m^2), and weight gain during pregnancy. Birth data included GA at delivery, including post-dates pregnancy, type of delivery (vaginal/instrumental/CS), use of epidural analgesia, amniotic fluid appearance (normal, meconium stained), and duration of first and second stages of labor, when applicable. Neonatal data included fetal gender (male, female), birth weight, Apgar score (at 1 and 5 minutes), and admission to the neonatal intensive care unit (NICU).

Statistical analysis

Quantitative variables were expressed as mean±standard deviation (SD) or as median±interquartile range (IQR). Qualitative variables were expressed as absolute and relative frequencies. For the comparison of proportions, Chi-square and Fisher's exact tests were used. Student's t-test was applied when the distribution was normal and the Mann-Whitney test when the distribution was not normal. Multiple logistic regression analysis was used to identify factors independently associated with the likelihood of CS. Crude and adjusted odds ratios (ORs) with 95% confidence intervals (CIs) were computed. All p values reported were two-tailed and statistical significance was set at 0.05. Statistical analysis was conducted using the Statistical Package for Social Sciences (SPSS), version 19.0.

Although formal statistical power analysis was not computed, in regression analysis, more than 100 cases are considered an acceptable number for detection of significant differences, 100–200 medium, and more than 200 cases large;[12] our study of more than 300 women thus had the capacity to generate statistically significant results.

This study was approved by the institutional ethics committee of the maternity hospital where the research took place.

RESULTS

A total of 359 women, mean age 30±5.4 years, met the inclusion criteria over the study period. These women gave birth to 194 (53.9%) male and 165 (46.1%) female neonates (tab. 1). Between the two subgroups of women according to fetal gender, there was no difference in their demographic data in terms of maternal age, ethnicity, BMI at booking and at birth, and smoking. In the total sample, the CS and instrumental delivery rates were 33.1% and 8.9%, respectively.

The characteristics labor, mode of delivery and neonatal outcome according to the fetal gender are presented in table 2. A significantly higher rate of CS was observed in women with male neonates than in those with female neonates (39.4% vs 25.5%; p=0.006). The birth weight of male babies was significantly greater than that of female babies.

Table 3 shows the results from the univariate and multiple logistic regression analysis with CS as the dependent variable. The maternal age at delivery, the Greek ethnic background, the educational level of the mother, the smoking status, the BMI at delivery, and post-dates pregnancy were not associated with CS delivery in either univariate and multiple analysis. After adjusting for confounding factors in the multiple analysis, multiparity and the use of epidural analgesia were associated with lower odds for a CS delivery, while higher birth weight, increased weight gain in pregnancy and male fetal gender were independently associated with greater odds for a CS delivery. Women who delivered male babies had an almost two-fold increased risk of CS delivery (OR=2.04, 95% CI: 1.11–3.76; p=0.022).

DISCUSSION

Small cohort studies have documented the magnitude of the male fetal gender effect on CS rate in women with spontaneous onset and induced labor. In primiparous women with spontaneous onset labor, the risk of CS delivery in male neonates in comparison to females was reported to be increased by 25–47% (OR=1.25–1.47),[9,13] whereas for induced labor in primiparous women it was found increased by 48–88% (OR=1.48–1.88).[2,7] This increase in CS rate in women with induced labor is in accordance with the finding that women who undergo induction of labor

Table 1. Maternal characteristics of women undergoing induction of labor (n=359) according to the fetal gender.

	Male neonates (n=194) n (%)	Female neonates (n=165) n (%)	p
Mother's age at delivery (years), mean (SD)	30 (5.3)	29.9 (5.6)	0.905*
Mother's age at delivery (years)			
≤24	24 (14.5)	29 (14.9)	0.578**
25–29	44 (26.7)	59 (30.4)	
30–34	65 (39.4)	63 (32.5)	
≥35	32 (19.4)	43 (22.2)	
Ethnicity			
Greek	142 (73.2)	109 (66.1)	0.483**
Albanian	19 (9.8)	23 (13.9)	
Russian	11 (5.7)	12 (7.3)	
Other	22 (11.3)	21 (12.7)	
Education			
University or higher	62 (32.0)	55 (33.3)	0.845**
Secondary	120 (61.9)	98 (59.4)	
Primary	12 (6.2)	12 (7.3)	
Parity			
Nulliparous	137 (70.6)	116 (70.3)	0.948**
Multiparous	57 (29.4)	49 (29.7)	
Smoking			
Current smokers	23 (11.9)	13 (7.9)	0.211**
Non-smokers	171 (88.1)	152 (92.1)	
Pre-pregnancy BMI, mean (SD)	22.8 (2.5)	22.3 (2.4)	0.113*
Underweight	1 (0.5)	4 (2.4)	0.178***
Normal	164 (84.5)	146 (88.5)	
Overweight	25 (12.9)	13 (7.9)	
Obese	4 (2.1)	2 (1.2)	
Weight gained, mean (SD)	14.9 (3.4)	14.2 (3.2)	0.054*
BMI at delivery, mean (SD)	28.1 (3)	27.6 (2.5)	0.063*
Normal	16 (8.2)	23 (13.9)	0.082**
Overweight	128 (66)	112 (67.9)	
Obese	50 (25.8)	30 (18.2)	

*Student's t-test, **Pearson's Chi-square test, ***Fisher's exact test
BMI: Body mass index, SD: Standard deviation

Table 2. Labor characteristics, mode of delivery, and neonatal outcome according to the fetal gender for women undergoing induction of labor (n=359).

	Male neonates (n=194) n (%)	Female neonates (n=165) n (%)	p
Gestation in days, median (IQR)	282 (275–288)	283 (276–288)	0.525*
Post-date pregnancy			
No	174 (89.7)	141 (85.5)	0.223**
Yes	20 (10.3)	24 (14.5)	
Type of delivery			
Cesarean section delivery	76 (39.4)	42 (25.5)	*0.013***
Operative vaginal delivery	18 (9.3)	14 (8.5)	
Normal vaginal delivery	99 (51.3)	109 (66.1)	
Cesarean section delivery			
No	118 (60.8)	123 (74.5)	*0.006***
Yes	76 (39.2)	42 (25.5)	
Duration of 1st stage (min), median (IQR)	300 (0–420)	360 (240–420)	0.096*
Duration of 2nd stage (min), median (IQR)	15 (0–30)	20 (5–35)	*0.023**
Amniotic fluid appearance			
Normal	162 (95.3)	141 (91.0)	0.121**
Meconium stained	8 (4.7)	14 (9.0)	
Epidural analgesia use			
No	128 (66.0)	109 (66.1)	0.987**
Yes	66 (34.0)	56 (33.9)	
Birth weight of baby (g), median (IQR)	3,470 (3,175–3,760)	3,290 (3,058–3,540)	*<0.001**
Birth weight of baby			
<2,500 g	4 (2.1)	3 (1.8)	*0.033****
2,500–4,000 g	171 (88.1)	157 (95.2)	
>4,000g	19 (9.8)	5 (3.0)	
Apgar score at 1 minute, median (IQR)	8.2 (0.7)	8.2 (0.8)	0.452*
Apgar score at 5 minutes, median (IQR)	9.9 (0.5)	9.8 (0.6)	0.462*
Admitted to NICU			
No	164 (84.5)	145 (87.9)	0.362**
Yes	30 (15.5)	20 (12.1)	

*Mann-Whitney test, **Pearson's Chi-square test, ***Fisher's exact test
IQR: Interquartile range, NICU: Neonatal intensive care unit

Table 3. Odds ratios (OR) and 95% confidence intervals (95% CI) derived from univariate and multivariate logistic regression analysis of risk factors for cesarean section delivery.

	OR (95% CI) Crude	p	OR (95% CI) Adjusted	p
Maternal age at delivery (years)				
≤24	1.00*			
25–29	1.04 (0.52–2.10)	0.902	2.34 (0.87–6.29)	0.093
30–34	0.84 (0.43–1.67)	0.622	2.12 (0.77–5.80)	0.144
≥35	1.03 (0.49–2.16)	0.934	1.07 (0.50–2.29)	0.863
Ethnicity				
Greek	1.00*			
Other	1.02 (0.63–1.64)	0.942	0.54 (0.26–1.14)	0.105
Education				
University	1.00*			
Secondary	1.10 (0.68–1.78)	0.691	1.03 (0.52–2.04)	0.939
Primary	1.31 (0.53–3.27)	0.558	2.49 (0.65–9.57)	0.184
Parity				
Nulliparous	1.00*			
Multiparous	0.22 (0.12–0.40)	<0.001	0.12 (0.05–0.27)	<0.001
Smoking				
Current smokers	1.00*			
No smokers	0.51 (0.26–1.03)	0.060	0.55 (0.23–1.36)	0.196
Weight gained	1.11 (1.03–1.18)	0.003	1.10 (1.00–1.21)	0.047
BMI at delivery				
Normal	1.00*			
Overweight	0.94 (0.46–1.93)	0.864	0.76 (0.27–2.13)	0.599
Obese	1.14 (0.51–2.55)	0.755	0.44 (0.12–1.57)	0.205
Post-date pregnancy				
No	1.00*			
Yes	1.18 (0.61–2.28)	0.619	1.7 (0.65–4.47)	0.280
Liquor appearance				
Normal	1.00*			
Meconium stained	2.41 (1.01–5.81)	0.049	1.89 (0.65–5.48)	0.242
Epidural use				
No	1.00*			
Yes	0.16 (0.09–0.30)	<0.001	0.13 (0.06–0.27)	<0.001
Fetal gender				
Females	1.00*			
Males	1.87 (1.20–2.97)	0.006	2.04 (1.11–3.76)	0.022
Baby's birth weight (g)				
<4,000	1.00*			
>4,000	2.56 (1.12–5.91)	0.027	2.59 (1.07–6.25)	0.035

* Reference category

BMI: Body mass index

are twice as likely to have a CS delivery than women with spontaneous onset of labor.[14] In cohorts of mixed primiparous and multiparous women, in those with induced labor the risk of CS delivery for male neonates was increased by 83–251% (OR=1.83–2.51).[8,15] Our study of a cohort of mixed primiparous and multiparous women with induced labor, has showed a 204% increased risk of a CS delivery for males (OR=2.04). This finding is in accordance with the literature evidence and the observed variation in rate can be attributed to the different characteristics of our Greek study population.

Our study identified the birth weight (OR=2.59) as the strongest risk factor for a CS delivery, but with male neonates weighing larger than females and also having a higher rate of macrosomia (>4 kg). After adjusting for the effect of birth weight, it was demonstrated that the male gender effect on the CS rates persisted and was the second strongest risk factor for CS (OR=2.04). This male fetal gender effect after adjusting for birth weight has also been demonstrated in several large population-based studies conducted since 2002 in several different countries, which documented an increase in the risk of CS for male neonates of 8–48% (OR=1.08–1.48).[3–6] The differences in the magnitude of risk for CS can be explained by the fact that the population-based studies had a different study design and involved women who were both primiparous and multiparous, and with both spontaneous onset and induced labor.

As early as 1982 certain assumptions were made as to why male fetuses have higher CS rates than females,[1] which were later corroborated by other studies. Firstly, it has been repeatedly shown that male neonates are larger and weigh more than females,[5,10] which could explain the higher rates of cephalopelvic disproportion and the higher subsequent CS delivery rates, as initially suggested.[1] Secondly, both the findings of the present study and the results from the large population-based studies lend support to the theory that factors other than birth weight could explain in part the male fetal gender-related phenomenon. Different steroidal pathways have been reported with regards to the onset of induced labor between female and male fetuses,[7] and also different fetoplacental responses to the induction of labor process,[15] which could explain the higher failure rates observed during induced labor for male fetuses.

Another proposed explanation is that male fetuses demonstrate fetal distress in labor more often than females, which could explain the gender related higher CS rates.[1] It has been suggested that male fetuses grow faster *in utero* and have smaller placentas than female fetuses relative to their birth weight.[16,17] As a result, when male fetuses are subjected to the stress of labor they have lower placental reserve to utilise under sub-optimal conditions.[18] In addition, intrinsic gender-related differences in the fetal response to hypoxia have been reported.[19–21] When a hypoxic event occurs during labor it has been demonstrated that the release of catecholamines from the fetus improves its ability to cope with the effects of hypoxia.[19,20] Lower levels of catecholamines have been reported in male than in female fetuses after a hypoxic event, which may explain their relative disability to cope with labor stress and therefore increased rates of CS.[21] In the present study, no difference was recorded in the neonatal outcome between males and females, although there are reports that males have higher rates of abnormal fetal blood sampling and lower Apgar scores.[2,8]

Our study identified risk factors other than the male fetal gender that might increase the CS rate. In our cohort, women with increased weight gain in pregnancy had a higher likelihood of CS (OR=1.10), in line with a multicenter study across many countries published in 2013 which reported that nulliparous women with an increased weight gain had a higher risk for CS (OR=1.46).[22] The possible explanation is that the adipose tissue, being hormonally active, may predispose to a reduced response to the induction of labor process which could result in a higher rate of CS in these women.[7,23]

Our study further identified that multiparity might reduce the risk of CS after induction of labor (OR=0.12). Primiparity has been identified as a risk factor for failed induced labor,[24,25] and it has been estimated that the risk of CS is 75% higher in nulliparous women than in multiparous women with the same cervical length.[26]

Our study also showed that the use of epidural analgesia might reduce the risk of CS (OR=0.13). A Cochrane systematic review in 2011 failed to show any significant differences in the risk of a CS delivery overall in women with epidural analgesia in labor compared to those without,[27] although other studies suggest that epidural analgesia may increase the CS rate,[25] or that factors other than epidural analgesia might contribute to a CS delivery, such as high birth weight.[28] Moreover, significantly higher cord pH has been found in neonates born to women with epidural analgesia,[28,29] indicating less fetal distress, which could explain the lower rates of CS. An immunohistochemical study[30] documented that pain-reducing anesthesia reduced oxidative stress in the human term placenta, which could also account for lower CS rates.

There are certain limitations to be considered in this study. First, it was conducted retrospectively, with the data

being manually extracted from the hospital-held maternity notes. This means that the accuracy of the final data was dependent on the practitioner entering the information in the patient's notes following delivery, and also on the researcher manually recording the data. Second, we were unable to retrieve detailed data about the induction of labor process. The cervical status, according to the Bishop score is important to the success of induced labor[31] and this information was not available for our calculations. Third, as umbilical cord gases were not routinely collected, we were unable to establish whether there was any fetal gender-related effect on the acid-base status and possible related fetal compromise. It is reassuring, however, that there were no differences in the Apgar scores between male and female neonates. The main strength of our study was that it included a sufficiently large sample of women to generate statistically significant results that are comparable to those reported for other countries.

In conclusion, we showed that in our cohort of women from a Greek population who underwent induction of labor that the male fetuses have a higher CS delivery rate than the females. We showed that this fetal gender-related phenomenon persists even after adjusting for the birth weight, and that the magnitude of effect is comparable to that reported for induced labor in cohort-type studies of mixed primiparous/multiparous women. Further research is required with larger cohorts and with the inclusion of risk assessment according to the indication for induction of labor, and the inclusion of other variables, such as the cervical Bishop score.

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ΠΕΡΙΛΗΨΗ

Η επίδραση του άρρενος φύλου του εμβρύου στο ποσοστό καισαρικής τομής σε Ελληνίδες που υποβλήθηκαν σε πρόκληση τοκετού

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ΣΚΟΠΟΣ Η διερεύνηση της επίδρασης του φύλου του εμβρύου στον τρόπο τοκετού σε γυναίκες που υποβλήθηκαν σε πρόκληση τοκετού. **ΥΛΙΚΟ-ΜΕΘΟΔΟΣ** Έλαβε χώρα συλλογή δεδομένων με αναδρομικό τρόπο για γυναίκες με πρόκληση τοκετού κατά τη χρονική περίοδο ενός έτους. Καταγράφηκαν τα δημογραφικά χαρακτηριστικά, τα δεδομένα του τοκετού και τα χαρακτηριστικά των νεογνών. Πραγματοποιήθηκε πολλαπλή λογιστική ανάλυση παλινδρόμησης, με σκοπό να καθοριστεί κατά πόσο το φύλο του εμβρύου αποτελεί ανεξάρτητο παράγοντα κινδύνου για καισαρική τομή μετά από προσαρμογή για συγχυτικούς παράγοντες. **ΑΠΟΤΕΛΕΣΜΑΤΑ** Το δείγμα αποτελούνταν από 359 γυναίκες με μέση ηλικία 30,0±5,4 έτη. Τα δημογραφικά χαρακτηριστικά ήταν ίδια μεταξύ γυναικών που γέννησαν άρρενα και θήλεα νεογνά. Το βάρος γέννησης ήταν σημαντικά μεγαλύτερο σε άρρενα νεογνά σε σύγκριση με θήλεα νεογνά. Το ποσοστό καισαρικής τομής ήταν σημαντικά υψηλότερο σε γυναίκες με άρρενα νεογνά σε σύγκριση με γυναίκες με θήλεα νεογνά (39,4% έναντι 25,5%). Η πολλαπλή ανάλυση έδειξε ότι το άρρεν φύλο στα έμβρυα οδηγούσε σε διπλάσιο κίνδυνο καισαρικής τομής (odds ratio=2,04, 95% CI: 1,11–3,76, p=0,022). **ΣΥΜΠΕΡΑΣΜΑΤΑ** Από τη μελέτη φάνηκε ότι το άρρεν φύλο αποτελεί παράγοντα κινδύνου ο οποίος μπορεί να επιδρά στον τρόπο τοκετού σε γυναίκες με πρόκληση τοκετού. Το εν λόγω φαινόμενο που σχετίζεται με το φύλο του εμβρύου παραμένει ακόμη και μετά από προσαρμογή για το βάρος γέννησης, γεγονός το οποίο υποδηλώνει ότι υπάρχουν παράγοντες άλλοι εκτός του βάρους γέννησης που θα μπορούσαν να εξηγήσουν αυτό το φαινόμενο.

Λέξεις ευρετηρίου: Άρρεν, Βάρος γέννησης, Καισαρική τομή, Πρόκληση τοκετού, Φύλο

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