Original Article

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The Effect of Fetal Gender on the Delivery Outcome in Primigravidae Women with Induced Labours for all Indications

Obstetrics and Gynaecology Section

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ABSTRACT

Introduction: There is increasing evidence of a gender-related phenomenon where the presence of a male fetus may have an adverse effect on the outcome of pregnancy.

Aim: The aim of this study was to investigate the effect of fetal gender on the delivery outcome in primigravidae women with induced labours.

Materials and Methods: This was an observational cohort study of primigravidae women who had Induction Of Labour (IOL) for all indications during a two-year period. Women with breech vaginal deliveries, stillbirths, multiple pregnancies and elective Caesarean Section (CS) were excluded.

Results: Of the 936 eligible patients identified, 493(52.6%) gave birth to male neonates and 443(47.4%) to female neonates. Age, ethnicity, Body Mass Index (BMI) and smoking were similar between women that delivered male and female neonates. More than half of all women were induced for post-date pregnancies. In women who gave birth to male neonates, the CS delivery rate was higher than in those with female neonates (23.7% vs 17.8%; p=0.029). Though emergency admission rates to the neonatal Intensive Care Unit (ICU) and arterial/venous pH from umbilical cord sampling immediately after birth were similar between male and female neonates, nevertheless male neonates had lower Apgar scores of <7 at 1 minute after birth (p=0.02).

Conclusions: This study has shown that, male gender fetuses have a higher CS delivery rate in primigravidae women undergoing IOL and may be more vulnerable to fetal compromise when in labour.

Keywords: Caesarean section, Induction of labour, Male

INTRODUCTION

Induction Of Labour (IOL) is a relatively common procedure in Obstetrics with rising rates throughout the world [1]. In the United Kingdom for the year 2011-2012 the IOL rate was 22.1% with a mean Caesarean Section (CS) delivery rate of 30.2% for primiparous and 13.2% for multiparous women with induced labours [2,3]. It is suggested that, IOL should be offered when it is likely that a better outcome will result if labour is initiated than if the pregnancy continues [4]. The reason for this recommendation is that women who are offered IOL are twice as likely to be delivered by a caesarean section as women with a spontaneous onset labour [5].

There are reports in the literature that have focused on certain risk factors in the attempt to determine the success of the IOL process, such as parity and the cervical score [1]. There are recent studies that have highlighted the role of fetal gender as a significant risk factor for CS delivery in induced labour [6-9]. These studies however, involved either nulliparous women induced for post-date pregnancies [6,7] or a mixed cohort of both primigravidae/multigravidae women induced for all indications [8].

The purpose of this study was to establish the fetal gender effect in delivery outcome in a cohort of primigravidae only women with induced labour and to provide the most recent literature updates on possible underlying mechanisms that could explain this gender effect.

MATERIALS AND METHODS

This was an observational cohort study of primigravidae only women induced for various medical reasons at the Maternity Unit of the Shrewsbury and Telford Hospitals (SaTH) NHS Trust, between January 2011 and December 2012. Inclusion criteria were women with singleton cephalic presentation deliveries induced for post-date pregnancy (gestational age>41 weeks), reduced fetal movements, fetal growth restriction, preeclampsia/eclampsia, gestational diabetes, term (>37 weeks) pre-labour rupture of membranes for more than 24 hours and any other medical condition. Exclusion criteria involved women with breech vaginal deliveries, stillbirths, fetal congenital abnormalities, multiple pregnancies and elective CS. Data were collected from the obstetric electronic database of the hospital and maternal data, labour/delivery data and neonatal data were all recorded.

The data that were recorded and included maternal age, Body Mass Index (BMI), ethnicity (white European, non-white European) and smoking. Other data also identified were the gestational age at delivery, route of birth (vaginal/CS delivery), epidural analgesia and liquor appearance (normal, meconium stained). Neonatal variables including fetal gender (male, female), birth weight, head circumference, Apgar scores (at 1 and 5 minutes), cord gases taken at delivery (arterial, venous) and admission to the neonatal intensive care unit were also obtained.

A literature review was conducted by searching the MEDLINE and EBSCO databases for the years 2000-2016 with the use of the following text words: fetal gender, induced labour, caesarean section, pregnancy outcome. The references of the relevant articles were also searched so as to capture any other reports that were not already identified in the electronic search.

STATISTICAL ANALYSIS

Quantitative variables were expressed as mean values and standard deviations. Qualitative variables were expressed as absolute and relative frequencies. Student's t-test and Fisher's exact test were used to compare mean values and proportions respectively. Multiple logistic regression analysis was used to identify whether or not the fetal gender was an independent risk factor for CS delivery after adjusting for confounding factors. All reported p-values were two-tailed. Statistical significance was set at p<0.05 and analyses were conducted using SPSS statistical software (version 19.0). This research study was approved by the local institutional review board.

RESULTS

A total of 936 primigravidae women met the inclusion criteria over the two-year study period. These women gave birth to 493(52.6%) male neonates and 443(47.4%) female neonates [Table/Fig-1]. Between the two subgroups of women there was no difference in their demographic data in terms of maternal age, ethnicity, body mass index and smoking. More than half of all women were induced for post-date pregnancies. During labour the occurrence of meconium stained liquor and the use of epidural analgesia was also similar between the two subgroups.

	Female (n=443)	Male (n=493)	p-value
	N(%)	N(%)	
Mothers age at delivery (years), mean (SD)	27(6.3)	26.7(6.2)	0.40‡
Ethnicity			
White Europeans	389(88%)	448(90.8%)	0.16*
Non-white Europeans	53(12%)	45(9.2%)	
Smoking	53/430(12.3%)	62/493(12.6%)	1.00*
Body mass index, mean (SD)	26.3(5.7)	26.6(5.8)	0.34‡
Post-date pregnancy	216/435(49.7%)	260/493(52.8%)	0.35*
Gestation in days, mean (SD)	282(13)	283(12)	0.18‡
Caesarean section delivery	79/443(17.8%)	117/493(23.7%)	0.029*
Meconium stained liquor appearance	79/443(17.9%)	70/493 (14.2%)	0.15*
Epidural use	183/343(41.3%)	228/493 (46.2%)	0.13*
Babies Birth Weight, mean (SD)	3328(619)	3523(556)	<0.001‡
Head circumference at birth (cm)	34.4(1.7)	35.2(1.5)	<0.001‡
Apgar score <7 at 1 minute	36/436 (8.3%)	63/489 (12.9%)	0.02*
Apgar score <7 at 5 minutes	3/436(0.7%)	4/489 (1.8%)	1.00*
Cord gases taken at delivery Arterial pH			
<7.20	50/178(28.1%)	53/210(25.2%)	0.65*
<7.25	88/178(49.4%)	103/210 (49%)	1.00*
Cord gases taken at delivery Venous pH			
<7.20	17/178(9.6%)	23/220(10.5%)	0.83*
<7.25	43/178 (24.2%)	46/220 (20.9%)	0.46*
Admitted to NNU	22/388(5.6%)	29/433(6.7%)	0.56*

[Table/Fig-1]: Association of fetal gender with patient demographics and induced labour and neonatal characteristics.
*Fishers-exact test; ‡ Student's test.

The CS delivery rate was higher in primigravidae women who gave birth to male neonates in comparison to those with female neonates (23.7% vs 17.8%;p=0.029) thus, providing an unadjusted Odds Ratio of OR=1.48 (95%CI:1.07-2.04;p=0.016). Male gender fetuses had greater mean values of birth weight and head circumference in comparison to female neonates (p<0.001), even though gestational age at delivery was similar. Multiple logistic regression analysis after adjusting for birthweight and head circumference showed that, this gender-related difference in CS delivery rates was no longer significant. This indicates that, the higher rate of CS delivery in males when compared to female neonates could be explained by the increased birth weight and head circumference of male fetuses.

Emergency admissions to the neonatal Intensive Care Unit (ICU) following delivery were similar between male and female neonates. The mean values of arterial/venous pH from the umbilical cord sampling immediately after birth were also similar between male and female neonates. However, male neonates had lower Apgar scores of <7 at 1 minute after birth (p=0.02) in comparison to females.

DISCUSSION

Since, Hall and Carr-Hill first described in 1982 a 17% increase in CS in the presence of a male fetus [1], there have been several studies reporting on this gender-related phenomenon. An extensive review [10] published in 2007 that summarised the available evidence from these studies concluded that, the male fetal gender should be considered an independent risk factor for an adverse pregnancy outcome. Large population-based studies [11-19] from different countries reporting on the delivery outcome in relation to fetal gender have further quantified that the risk of CS delivery for male fetuses is increased by 8-48% [Table/Fig-2]. Other smaller cohort-based studies investigating the same male gender-effect on CS delivery rates have found that, the risk is increased by 25-47% in women with spontaneous onset labour [20,21] and by 83%-251% in women with induced labour [6-8]. There are few studies however, that failed to show any such association between fetal gender and the increased risk of CS delivery [22,23]. The lack of association between male fetal sex and increased risk of CS delivery or the varying magnitude of the male-gender effect on CS rates that has been observed could be explained by the different parturient populations across the various study designs described in the literature [23].

Study	N (Study Period)	Onset of labour (spontaneous vs induced)	Delivery outcome	Does the male gender effect on CS delivery remain after adjusting for birth weight?
Schildberger et al., [11], 2016 (Austria)	n=444,685 (2008-2013)	All deliveries	CS: 55.7% males vs 44.3% females*	Not reported**
Liu et al., [12], 2016 (Northern China)	n=65,173 (2011)	All deliveries	OR=1.087 (95%CI:1.052-1.123)	Yes
Weissmann-Brenner et al., [13], 2015 (Israel)	n=37,327 (2004-2008)	All deliveries	OR=1.18 (95%CI:1.12-1.24)	Yes
Hou et al., [14], 2014 (Mainland China)	n=109,722 (2011)	All deliveries	OR=1.1 (95%CI:1.1-1.1)	Yes
Khalil et al., [15], 2013 (North Africa-Libya)	n=29,140 (2009-2010)	All deliveries	OR=1.10 (95%CI:1.05-1.16)	Yes
Aibar et al., [16], 2012 (Spain)	n=29,530 (2003-2009)	All deliveries	OR=1.34 (95%CI:1.21-1.59)† OR=1.39 (95%CI:1.09-1.65)‡	Yes
Melamed et al., [17], 2010 (Israel)	n=66,387 (1995-2006)	All deliveries	OR=1.12 (95%CI:1.07-1.17)	Yes
Sheiner et al., [18], 2004 (Israel)	n=108,995 (1988-1999)	All deliveries	OR=1.2 (95%CI:1.2-1.3)	Yes
Bekedam et al., [19], 2002 (Netherlands)	n=423,303 (1990-1994)	All deliveries	OR=1.48 (95%CI:1.44-1.51)‡	Yes

[Table/Fig-2]: Population-based studies reporting on the delivery outcome in relation to fetal gender. Odds ratios along with 95% confidence intervals are presented for the risk of CS delivery in male versus female fetuse [11-19].
*OR's not calculated.
** The authors of the article did not adjust their findings for birthweight.
† CS delivery for failure to progress in labour.
‡ CS delivery for fetal distress.

This study has shown that, male gender fetuses in comparison to females have a 48% higher risk of CS delivery in primigravidae women with induced labour (unadjusted OR=1.48;95% CI:1.07-2.04; p=0.016). However, when adjusting for birthweight and head circumference this male-gender effect on the CS delivery rates was no longer existant. There are studies in the literature in support of our finding that the increased CS rate in males no longer persists after adjusting for birthweight [20,24]. Nevertheless, all the large population-based studies [Table/Fig-2] have shown that the male gender effect on CS delivery still remains after adjusting

for birthweight [11-19] thus, indicating the existence of other underlying biological mechanisms beyond fetal weight itself that could account for this gender-related phenomenon.

There have been many explanations provided in the literature as to why male neonates have a higher CS delivery rate when compared to their female counterparts with the indication for operative delivery being labour dystocia or fetal distress. First, male neonates are heavier than females as shown by higher birthweights and higher rates of macrosomia (>4kg) [10,11,17,18,25], which could explain the higher CS rates due to labour arrest [20,24]. Second, increased rates of CS delivery due to fetal distress have been reported in male-bearing pregnancies [16,19,24,25]. It has been contemplated that, this may be the result of intrinsic gender-related differences in the fetal response to hypoxia. When hypoxia occurs during labour the release of catecholamines from fetuses is considered to be an important defense mechanism [24]. It has been postulated that, this catecholamine surge improves the ability of the fetus to withstand the effects of hypoxia [26,27]. Nevertheless, it has been demonstrated that, males have lower levels of catecholamines after asphyxia which may explain the worse outcome for males after a hypoxic event [28].

A third explanation comes from more recent studies that have shown that, male and female fetuses are different in terms of growth and development in utero due to sex-biased gene expression leading to divergent growth patterns [29]. It has been demonstrated that male fetuses grow faster in utero and they have smaller placentas than females relative to their birthweight [30,31]. The consequence of this is that when male fetuses are subjected to the stress of labour they have less placental reserves to use when sub-optimal conditions appear [29]. This may explain the finding why male fetuses have a higher incidence of fetal distress as reflected in being more likely to have abnormal fetal blood sampling and lower Apgar scores [8,12,18,19,21,24]. In our study, male neonates also had increased rates of lower Apgar scores of <7 at 1 minute after birth in comparison to females.

On review of the literature, there are only a few studies reporting on the association between fetal gender and pregnancy outcome in women with induced labour [6-8]. [Table/Fig-3] shows that, women being induced in comparison to those with spontaneous onset labours have a relatively higher risk of CS delivery even after adjustment for birthweight (83%-251% vs 25-47%) [6,7,20-23,25]. The physiological explanation given in the literature for the male gender effect in induced labour, in addition to the three pathophysiological mechanisms described earlier, is that there are different steroidal pathways regarding the onset of induced labour between female and male fetuses [6] and different fetoplacental responses to the induction of labour process between the fetal genders which could explain the higher IOL failure rates in male fetuses [7].

The main strength of this study is that, it has the largest to date sample size of 936 primigravidae women investigating the gender effect on delivery outcome in cases of induced labour. Second, the confounding effect of parity [32] in the induction of labour process was eliminated by including primigravidae only women. Third, all cases that were analysed in this study were from a single center and therefore, were managed according to the same clinical guidelines and protocols.

LIMITATION

The limitations of this study include its retrospective nature of data collection and the inability to retrieve data about the cervical status of women when being induced. It is well-established in literature that cervical scoring in terms of the Bishop score is a key factor to the success of IOL [1,33,34]. For this reason, this variable could not be incorporated in the data analysis and therefore, adjust for any confounding effect.

Study	N (Study Period)	Onset of labour (spontaneous vs induced)	Delivery outcome	Does the male gender effect on CS delivery remain after adjusting for birth weight?
Antonakou et al, 2016 (Index study in United Kingdom)	n=936 primigravidae (2011-2012)	Induced labour	OR=1.48 (95%CI:1.07-2.04)	No
Dunn et al., [25] 2015 (Australia)	n=9,223 primiparous (2001-2011)	All deliveries	OR=1.24† OR=1.38‡	Yes
Toricelli et al., [6], 2013 (Italy)	n=376 nulliparous (2004-2012)	Induced labour	OR=1.88 (95%CI:1.87-2.98)	Yes
Toricelli et al., [7], 2013 (Italy)	n=492 (2004-2011)	Induced labour	OR=2.51 (1.67-3.78)	Not reported*
Nasri et al., [22], (Iran)	n=1,537 (2008)	All deliveries	No gender effect	----------
Agarwal et al., [8], 2009 (United Kingdom)	n=658 (2001-2003)	Induced labour	OR=1.83 (95%CI:1.26-2.64)	Yes
Viegas et al., [20], 2008 (Malaysia)	n=4,644 nulliparous (2007)	Spontaneous labour	OR=1.25 (95%CI:1.07-1.43)	No
Lurie et al., [23], 2004 (Israel)	n=2,581 (2001)	All deliveries	No gender effect	----------
Eogan et al., [21], 2003 (Ireland)	n=8,075 primigravidae (1997-2000)	Spontaneous labour	OR=1.47 (95%CI:1.20-1.79)	Yes

[Table/Fig-3]: Cohort-based studies reporting on the delivery outcome in relation to fetal gender. Odds ratios along with 95% confidence intervals are presented for the risk of CS delivery in male versus female fetuses [6,7,20-23,25].
*The authors of the article did not adjust their findings for birthweight.
† CS delivery for failure to progress in labour. 95%CI were not provided.
‡ CS delivery for fetal distress. 95%CI were not provided.

CONCLUSION

This study has shown that male gender fetuses have a higher CS delivery rate in primigravidae women undergoing induction of labour and may be more vulnerable to fetal compromise when in labour. It has confirmed the findings from the previous few studies that reported on women with induced labour even though the male gender effect on the CS delivery rate in this study was much less than previously estimated.

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