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# Combined Effect of Fetal Sex and Advanced Maternal Age on Pregnancy Outcomes

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**Background:** Fetal sex and maternal age are each known to affect outcomes of pregnancies. The objective of the present study was to investigate the influence of the combination of maternal age and fetal sex on pregnancy outcomes in term and post-term singleton pregnancies.





**Material/Methods:** This was a retrospective study on term singleton pregnancies delivered between 2004 and 2008 at the Chaim Sheba Medical Center. Data collected included maternal age, fetal sex, and maternal and neonatal complications. The combined effect of fetal sex and maternal age on complications of pregnancy was assessed by multivariable logistic regression models.

**Results:** The study population comprised 37,327 pregnancies. The risk of operative deliveries increased with maternal age  $\geq 40$  and in pregnancies with male fetuses. The risk of maternal diabetes and of longer hospitalization increased as maternal age increased, and in women  $< 40$  carrying male fetuses. The risk of hypertensive disorders increased in pregnancies with males as maternal age advanced. The risk of shoulder dystocia and neonatal respiratory complications increased in male neonates born to women  $< 40$ . The risk of neonatal hypoglycemia increased in males for all maternal ages.

**Conclusions:** Risk assessment for fetal sex and advanced maternal age were given for different pregnancy complications. Knowledge of fetal sex adds value to the risk assessment of pregnancies as maternal age increases.

**MeSH Keywords:** **Cesarean Section • Gender Identity • Maternal Age • Pregnancy Outcome • Vacuum Extraction, Obstetrical**

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## Background

Fetal sex and maternal age are each known to affect outcomes of pregnancies. Women carrying male fetuses were reported to be at increased risk of preterm deliveries, preeclampsia, fetal distress, labor dystocia, operative deliveries, and perinatal mortality [1–8]. Hyperemesis gravidarum and hypertension-related growth retardation were significantly more common in pregnancies with female fetuses [9–12]. In recent decades more women delay family planning or continue childbirth after the age of 40. Increased maternal age was reported to be associated with diabetes mellitus, preeclampsia, preterm delivery, low birth weight, stillbirth, increased rates of cesarean section, and post-partum hemorrhage [13–20]. The combined impact of both maternal age and fetal sex on the outcomes of pregnancy has not been evaluated yet.

With the increase in maternal age during recent decades [14–16] and the increased interest in the influence of fetal sex on pregnancy outcomes [1,5], our objective was to investigate the influence of the combination of advanced maternal age ( $\geq 40$ ) and fetal sex on the pregnancy outcomes in term and post-term singleton pregnancies in a large tertiary center, in order to improve the prenatal follow-up and counseling, especially in the group of pregnant patients over age 40 years.

## Material and Methods

A retrospective study was performed on all consecutive live singleton pregnancies delivered at term and post-term between 1 July 2004 and 30 September 2008 at Chaim Sheba Medical Center, Tel HaShomer, a large tertiary referral center at the center of Israel with over 10,000 deliveries per annum. The study was approved by the Institutional Review Board of the Chaim Sheba Medical Center no. 5407.

Gestational age was determined by first trimester ultrasound measurements in most cases. Last-menstrual-period dating was used for those women for whom 1<sup>st</sup> trimester sonography was not performed.

Term birth was defined as birth at or after 37 completed weeks of gestation.

The department's patient admission database was screened for the period 1 July 2004 to 30 September 2008. Antenatal follow-up test results and pregnancy outcomes were routinely entered into the database at admission to delivery and following delivery.

The variables assessed in the study were: maternal age, gestational age at delivery, mode of delivery, birth weight, fetal sex, Apgar scores, number of days of maternal hospitalization, and

pregnancy complications. Maternal complications included gestational and pre-gestational diabetes, post-partum hemorrhage, extensive perineal lacerations including grade 3 and 4 lacerations and cervical tears, hypertensive disorders of pregnancy (including gestational hypertension and preeclampsia), and placental abruption. Neonatal complications included shoulder dystocia, hypoglycemia (defined as blood glucose  $< 40$  mg%), and respiratory complications. Respiratory complications of the neonates consisted of transient tachypnea of the newborn, aspiration including meconium aspiration, respiratory distress syndrome, asphyxia, and need for oxygenation or intubation.

Duration of hospitalization of 5 days or more and operative deliveries were also considered as adverse pregnancy outcomes.

Advanced maternal age was defined as maternal age of  $\geq 40$  years at delivery.

The sex of the infant was analyzed in the study. We chose to use the words "fetal sex" because the goal of the study was to improve prenatal care and follow-up of pregnant patients. Therefore, knowledge of fetal sex may add value to the risk assessment of pregnancies, allowing for optimal care of the patients.

Exclusion criteria included multiple fetuses or preterm deliveries.

## Statistical analysis

Differences in the study parameters between male and female neonates were tested using the chi-square test for categorical variables. Student's t-test was used for comparison of continuous parameters between neonatal sex and between the 2 categories of maternal age:  $< 40$  and  $\geq 40$ . The combination of sex and maternal age category was defined ( $< 40$ , male;  $< 40$ , female;  $\geq 40$ , male;  $\geq 40$ , female). Logistic regression models were used to assess the effect of sex and maternal age on maternal and neonatal complications, controlling for gestational age, birth weight, diabetes mellitus, and mode of delivery. Multivariate logistic regression was performed to explore factors associated with mode of delivery (cesarean section versus normal vaginal delivery, and vacuum or forceps delivery versus normal vaginal delivery). Odds ratios (OR) and corresponding 95% confidence interval were derived, and considered significant if excluding unity. In the case of outcomes in which the outcome rates are  $< 5\%$ , the OR approximate the rate ratios. A p-value of 0.05 or less was considered statistically significant.

## Results

During the study period 37,327 singleton neonates were delivered at or after 37 weeks' gestation at the Chaim Sheba Medical Center; 51.1% were boys and 48.9% were girls.

**Table 1.** Distribution of deliveries (singletons, week > 36) by selected characteristics and gender.

	Total N=37,327		Boys N=19,108		Girls N=18,219		P
<b>Mother's age (years)</b>							
Mean ±SD	30.9±4.9		30.9±4.9		30.9±5.0		0.8
Median	31		31		31		
Range	16–59		16–59		17–56		
<b>Gestational age (weeks)</b>							
Mean ±SD	39.3±1.2		39.2±1.2		39.3±1.2		0.0003
Median	39		39		39		
Range	37–43		37–43		37–43		
37–40 weeks, %	84.2		84.7		83.8		
41–43 weeks, %	15.8		15.3		16.3		
<b>Birth weight (grams)</b>							
Mean ±SD	3297±423		3362±437		3229±417		<0.0001
Median	3285		3350		3220		
Range	1727–6585		1727–6585		1800–4990		
<b>Apgar 5</b>							
Mean ±SD	9.85±0.77		9.85±0.75		9.85±0.78		0.9
Apgar 5 <7, %	1.6		1.6		1.7		0.4
Apgar 5 ≥7, %	98.4		98.4		98.3		
<b>Duration of hospitalization (days)</b>							
Mean ±SD	2.74±2.24		2.77±1.83		2.72±2.60		0.03
Median	2		2		2		
Range	1–183		1–73		1–183		
Hospitalization 1–4 days, %	93.5		93.2		93.8		
≥5 days, %	6.5		6.8		6.2		0.02
<b>Mode of delivery n, %</b>							
<b>Normal vaginal delivery</b>	26,811	71.8	13,371	70.0	13,440	73.8	<0.001
<b>Cesarean section</b>	8,030	21.5	4,325	22.7	3,705	20.4	
<b>Forceps</b>	271	0.73	158	0.83	113	0.62	
<b>Vacuum extraction</b>	2,215	5.9	1,254	6.6	961	5.3	

The characteristics of the study population are presented in Table 1. The average birth weight of male fetuses was significantly higher than female neonates. Women who delivered male neonates underwent significantly more operative deliveries and their hospitalization was longer. Significantly more pregnancies carrying female fetuses delivered post-date.

There were 1490 deliveries (4%) among women aged 40 years and more. The ratio between male and female fetuses was close to 1 both in mothers aged ≥40 and <40. The comparison of pregnancy outcomes in male and female fetuses according to maternal age is presented in Table 2. For both male and female

pregnancies, as maternal age increased more women had diabetes, both gestational and pre-gestational, with no difference according to fetal sex (from <2% among women aged <25 to more than 11% among women ≥40). The risk of hypertensive disorders increased in mothers aged ≥40 both carrying male and female fetuses, but with statistical significance only in male fetuses, and borderline significance in female fetuses. The rate of shoulder dystocia and respiratory problems was higher in males than in females, with statistical significance in patients aged <40.

There were statistically more cesarean sections in women aged ≥40 and in women carrying male fetuses. In mothers aged ≥40,

**Table 2.** Distribution of deliveries (singletons, gestational age  $\geq 37$ ) by complications, maternal age and gender.

	Maternal age <40		Maternal age >40		p for maternal age		p for gender	
	Boys N=18,368 %	Girls N=17,469 %	Boys N=740 %	Girls N=750 %	Boys	Girls	<40	40+
<b>Maternal complications</b>								
Diabetes	4.4	3.8	11.5	13.2	<0.001	<b>&lt;0.0001</b>	0.002	0.3
Extensive perineal tears	0.41	0.36	0	0	0.13	0.5	0.5	
Post partum hemorrhage	0.45	0.39	0.54	0.13	0.6	0.5	0.4	0.2
Hypertensive disorders	0.97	1.04	1.76	1.73	0.04	0.07	0.5	0.9
Placenta abruption	0.23	0.20	0.27	0	0.7		0.6	
Duration of hospitalization (>5 days)	6.6	5.9	12.6	13.3	<0.001	<b>&lt;0.001</b>	0.006	0.7
Mode of delivery					<0.001	<b>&lt;0.001</b>	<0.001	<0.001
Cesarean section	21.7	19.3	47.1	44.5				
Vacuum/forceps	7.5	6.0	5.1	3.6				
<b>Neonatal complications</b>								
Shoulder dystocia	0.86	0.66	0.68	0.53	0.6	0.7	0.035	0.8
Neonatal hypoglycemia	2.35	1.67	4.19	2.13	0.001	0.3	<0.001	0.002
Neonatal respiratory problems	1.86	1.04	1.62	0.93	0.6	0.8	<0.001	0.2
Apgar 5<7	1.5	1.7	2.3	1.3	0.07	0.5	0.2	0.2

statistically more patients were hospitalized for more than 5 days, both with male and female neonates.

Table 3 presents the combined effect of sex and maternal age on adverse pregnancy outcomes. Arbitrarily, fetal female sex and maternal age <40 were chosen to have an odds ratio (OR) of 1. The odds ratio of other combinations of maternal age and fetal sex were calculated.

In multivariable logistic regression analysis, we found that maternal age and fetal sex were significant risk factors for neonatal hypoglycemia and respiratory problems controlling for gestational age, birth weight, maternal diabetes, and mode of delivery. Diabetes was significantly associated with neonatal hypoglycemia (OR=3.53 95%CI=2.87–4.34).

Neither maternal age nor fetal sex was found to be associated with hypertensive disorders of pregnancy, while birth weight, gestational age, diabetes, and mode of delivery were predictors of these complications.

Both sex and maternal age were associated with mode of delivery. Women aged  $\geq 40$  carrying male fetuses were at an almost 3-fold risk to give birth by cesarean section compared with younger women for both fetal sexes.

## Discussion

During the last 2 decades, several studies have reported an association between fetal sex and pregnancy outcome, and between increased maternal age and complications of pregnancies. The present study examined the combined effect of both maternal age and fetal sex on pregnancy outcomes in term singleton pregnancies. We presented the odds ratio for different outcomes of pregnancy according to fetal sex and to maternal age. We arbitrarily chose fetal female sex and maternal age <40 to have the odds ratio of 1 and calculated the OR of the other combinations accordingly.

More women with advanced age at pregnancy have pre-pregnancy chronic medical conditions that may have an impact on

**Table 3.** Effect of maternal age and gender of new born on maternal and neonatal complications.

	Maternal age	Gender	OR*	95%CI	p
<b>Maternal complications</b>					
Hypertensive disorders	<40	Female	1.0		
	<40	Male	0.92	0.75–1.14	0.5
	>40	Male	1.58	0.89–2.79	0.12
	>40	Female	1.53	0.86–2.71	0.15
Duration of hospitalization (>5 days)	<40	Female	1.0		
	<40	Male	1.12	1.03–1.23	<b>0.01</b>
	>40	Male	2.16	1.70–2.75	<b>&lt;0.001</b>
	>40	Female	2.27	1.79–2.87	<b>&lt;0.001</b>
<b>Mode of delivery</b>					
Cesarean section vs. normal	<40	Female	1.0		
	<40	Male	1.18	1.12–1.24	<b>&lt;0.001</b>
	>40	Male	3.59	3.07–4.18	<b>&lt;0.001</b>
	>40	Female	3.06	2.63–3.57	<b>&lt;0.001</b>
Vacuum/Forceps vs. normal delivery	<40	Female	1.0		
	<40	Male	1.32	1.21–1.43	<b>&lt;0.001</b>
	>40	Male	1.34	0.95–1.88	0.09
	>40	Female	0.86	0.58–1.28	0.5
<b>Neonatal complications</b>					
Shoulder dystocia	<40	Female	1.0		
	<40	Male	1.31	1.03–1.66	<b>0.03</b>
	>40	Male	1.01	0.41–2.48	0.98
	>40	Female	0.79	0.29–2.16	0.65
Hypoglycemia	<40	Female	1.0		
	<40	Male	1.39	1.19–1.61	<b>&lt;0.001</b>
	>40	Male	2.15	1.46–3.15	<b>&lt;0.001</b>
	>40	Female	1.02	0.61–1.70	0.95
Respiratory problems	<40	Female	1.0		
	<40	Male	1.80	1.50–2.16	<b>&lt;0.001</b>
	>40	Male	1.53	0.85–2.76	0.16
	>40	Female	0.87	0.41–1.86	0.72

Adjusted for presence of maternal diabetes.

pregnancy outcomes [21–24]. The increased risk of diabetes as maternal age increased was reported before [16,24,25], as well as the elevated risk for diabetes in pregnancies carrying male fetuses [3,5]. The present study demonstrates that, in younger women, significantly more pregnancies carrying male fetuses have diabetes. Furthermore, the risk of diabetes increases as maternal age advanced in both male- and female-carrying pregnancies. Diabetes may account for excessive fetal weight, leading to increased risk for difficult deliveries,

operative vaginal deliveries, cesarean sections, and neonatal complications such as shoulder dystocia and neonatal hypoglycemia [8], all found in our study to be increased in pregnancies carrying male fetuses.

Maternal age did not have any statistical impact on neonatal shoulder dystocia and respiratory problems, but male sex did. The risk of neonatal hypoglycemia in our study increased in males for all maternal ages.

Another pre-pregnancy chronic condition that may be more frequent as maternal age advances is hypertension [26]. Indeed, our study demonstrated an increased risk of hypertensive disorders in mothers aged  $\geq 40$  of both male and female fetuses, but with statistical significance only in male fetuses. The effect of sex on hypertensive disorders of pregnancies has been evaluated previously. Studies that did find differences between male and female fetuses attributed these differences to hormonal influences on infiltration by extravillous trophoblasts into the placental bed [10,11] and differences in maternal blood plasma volume expansion [27]. Contrary to these studies, we did not find a significant association between fetal sex and hypertensive disorders of pregnancy.

Previous studies reported an increased risk of cesarean section in women  $\geq 40$  [21,22], and in pregnancies carrying male fetuses [3]. There were statistically more cesarean sections in pregnancies carrying male fetuses and when maternal age was  $\geq 40$ . The combined effect of maternal age and fetal sex on the mode of delivery has not been reported yet. Sheiner et al. [3] attributed the increased risk of cesarean section in pregnancies with male fetuses to the higher birth weight of males, leading to prolonged and more complicated deliveries. Indeed, and similar to previous studies [1,3,5], the birth weight of male neonates was significantly higher than in females. Since fetal macrosomia is an important risk factor for prolonged and operative deliveries [4,28], our study too found an increased rate of both operative vaginal deliveries and cesarean sections in pregnancies carrying male fetuses. Although we did not differentiate between the causes of the cesarean sections, these results are in agreement with Liberman et al. [29] who hypothesized that while the increased rate of cesarean section due

to dystocia in pregnancies carrying male fetuses was related to the larger size of males, the increased risk of cesarean section for fetal distress might be the result of intrinsic sex-related differences in the fetal response to hypoxia.

One of the outcomes of increased rates of diabetes, hypertensive disorders, and operative deliveries is longer hospitalization. We found that in mothers aged  $\geq 40$ , statistically more patients were hospitalized for more than 5 days, both with male and female neonates. In women  $< 40$ , the duration of hospitalization was longer in patients carrying male fetuses.

We acknowledge limitations of our study, especially the retrospective nature of the analysis. Nevertheless, the fact that clinical findings were entered into the database by an experienced team at delivery, as well as the large size of our study cohort, both increase the reliability of our findings.

## Conclusions

In the last 3 decades the prevalence of delaying family planning significantly increased [23,30]. Since increased maternal age and male fetal sex have each elevated risks for pregnancy complications, the combination of increased maternal age and male fetal sex may augment these risks. The obstetrician needs to evaluate pre-pregnancy medical conditions of every pregnant woman and monitor the pregnancy according to the known risk factors along with the possible adverse situations of each woman. We demonstrated that knowledge of fetal sex adds value to the risk assessment of pregnancies, allowing for optimal follow-up and management of every pregnancy and delivery.

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