Adverse Pregnancy Outcomes after a False - Positive Second Trimester Serum Screen for Down Syndrome in Thai Pregnant Women

Sukit Sritippayawan, MD*,
Chalie Vachirasrisoontra, MD*

** Department of Obstetrics and Gynecology, Charoenkrung Pracharuk Hospital*

Objective: *To determine whether a false-positive second trimester serum screen for Down syndrome in Thai pregnant women is predictive of adverse pregnancy outcomes.*
Material and Method: *The relationship between adverse pregnancy outcomes in women and a false-positive screening for Down syndrome was investigated in a case-control study. The Double-marker maternal serum screening for Down syndrome (alpha-fetoprotein and free β-hCG) was performed on Thai pregnant women between 14 and 21 weeks' gestation at Charoenkrung Pracharuk Hospital from March 1998 to August 2002. The pregnancy outcomes of 165 women having false positive serum screening (risk ratio at least 1:270; study group) were compared to the outcomes of 165 control patients having negative serum screening results (control group). The outcome indices analyzed were preterm delivery, low birth weight newborn, small-for-gestational age newborn, preeclampsia, placenta previa, and fetal death.*
Results: *The incidence of adverse pregnancy outcomes was 18.2% in the study group and 15.2% in the control group (odds ratio = 1.244; 95% confidence interval = 0.696, 2.225; p = 0.46). Women in the study group delivered at a significantly lower birth weight of newborns than women in the control group did (3088.1 ± 543.9 versus 3229.1 ± 454.6 g, respectively; p = 0.011). No significant differences in adverse outcomes was discovered after the comparisons between the study group and the control group: preterm delivery 11 of 165 (6.6%) versus 5 of 165 (3%), p = 0.124; low birth weight newborn 11 of 165(6.6%) versus 6 of 165 (3.6%), p = 0.213; small for gestational age newborn 4 of 165 (2.4%) versus 0 of 165 (0%), p = 0.123; preeclampsia 16 of 165 (9.7%) versus 12 of 165 (7.3%), p = 0.429; placenta previa 4 of 165 (2.4%) versus 4 of 165 (2.4%) , p = 1; fetal death 1 of 165 (0.6%) versus 0 of 165 (0%), p = 1.*
Conclusion: *The present findings revealed no apparent increase in the adverse pregnancy outcomes analyzed in women with false positive Down syndrome screening test.*

Keywords: *False-positive Down syndrome screening test, Adverse pregnancy outcomes*

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Second-trimester double marker maternal serum screening for Down syndrome in Asian population has been widely used in prenatal care in some countries in Asia[1,2]. By using a multivariate risk algorithm combining maternal serum alpha-fetoprotein (MSAFP), free β-hCG, and maternal age, 56.5-83% of Down syndrome cases can be detected with a 5.3-7.5% false positive rate[3,4]. Whether false positive maternal serum screening results for Down syndrome indicate an increased risk of adverse pregnancy outcomes has been evaluated in previous studies[5-9]. However, the results of these studies are inconsistent. Furthermore, race has been reported to be a significant independent factor in predicting risk for adverse pregnancy outcome[10]. Therefore, the authors conducted a case-control study enrolling Thai pregnant women who had been underwent second-trimester serum screening for Down syndrome to assess the association between

Correspondence to : Sritippayawan S, Department of Obstetrics and Gynecology, Charoenkrung Pracharuk Hospital, Bangkok 10120, Thailand.

adverse pregnancy outcomes and false positive maternal serum screening results.

Material and Method

Double-marker maternal serum screening for Down syndrome (alpha-fetoprotein and free β-hCG) was performed on 1,820 Thai pregnant women between 14 and 21 weeks' gestation at Charoenkrung Pracharuk Hospital from March 1998 to August 2002. The quantitative AFP levels were measured with a radioimmunoassay (AFP RIA; CIS bio international, France). Measurement of free beta-hCG in maternal serum was carried out by using a solid-phase two-site immunoenzymatic assay (FβHCG ELACT; CIS Ltd., Gif-sur-yvette Cedex, France). The positive result for Down syndrome screening was defined as a second-trimester risk of 1:270 or greater. The current study used information collected for this database. This program achieved a term Down syndrome detection rate of 83%, with a false positive rate of 7.5%[3].

Pregnancies with multiple gestations (n = 12), overt maternal diabetes (7), women with fetuses affected with Down syndrome (n = 6), known fetal chromosomal abnormalities (n = 5), neural tube or abdominal wall defects, or fetal anomalies detected by ultrasound at the time of screening (n = 14), positive neural tube defect screening results (n = 51), uninterpretable screening results (n = 36), another hospital delivery (n = 658), bad past medical history or obstetric history or family history (n = 701: family history of medical illness with a hereditary tendency; maternal history, family history, or previous child with a known genetic disease; history of previous congenital anomaly or mental retardation; history of substance abuse eg. tobacco smoking, alcohol abuse, and illicit drug use; history of previous stillbirth, > 2 miscarriages; radiation exposure) were excluded from the study. After excluding women for one or more of the reasons cited above, 330 women remained in the study. Pregnancy outcome information was obtained from the delivery records registered at Charoenkrung Pracharuk Hospital. The study group included 165 women with false positive serum screening for Down syndrome. The control group included 165 women with negative serum screening results. The authors evaluated the possible confounding factors that may affect the serum levels of AFP, free β-hCG, or the risk ratio calculated from Down syndrome screening the authors used. The factors the authors assumed included maternal age and parity. The study and control groups were matched for similar date of screening (0-30 days before or after: to minimize the assay result variation), maternal age, and parity. The pregnancy outcomes of the study group were compared to the outcomes of the control group. The adverse pregnancy outcomes recorded for analysis included preterm delivery(before 37 weeks' gestation); low birth weight newborn, defined as birth weight under 2,500g; small for gestational age (SGA) newborn, defined as birth weight below the tenth percentile for gestational age[11]; preeclampsia which was considered to be present in patients who had hypertension (blood pressure greater than 140/90 mmHg) after 20 weeks' gestation with generalized edema or proteinuria; placenta previa; and fetal death after 28 weeks' gestation.

The data were analyzed by using the statistical software package. Dichotomous variables were analyzed with Chi-square test and Fisher exact test, as appropriate. Continuous variables were analyzed with the unpaired Student t test. Odds ratios (OR) and 95% confidence intervals (CI) were calculated when appropriate. $P < 0.05$ was considered statistically significant when testing hypotheses.

Results

Table1 summarizes details of the study and control populations. The mean maternal age, mean gestational age at screening, mean gestational age at delivery and parity of the study and control groups were without significant difference. Family and pregnancy histories were unremarkable for both groups. The mean birth weight of the study and control groups were significant difference.

Table2 compares the adverse pregnancy outcomes of the study group with those of the control one. There was no significant difference in the incidence of preterm delivery, low birth weight newborn, SGA newborn, preeclampsia, placenta previa, and fetal death between both groups. Complications with higher risks in the study group included preterm delivery, low birth weight newborn and preeclampsia. However, except for the risk of preterm delivery, the differences in the risk of devolping other complications between the two groups were less than twofold. The adverse pregnancy outcome occurred in 30 of 165 women in the study group, compared with 25 of 165 in the control group (OR = 1.244, 95%CI = 0.696, 2.225; p = 0.46) but not with significant difference.

As shown in Table-3, 30 from 165 cases of false positive group had adverse pregnancy outcomes. Women who had adverse pregnancy outcomes delivered at a significantly earlier gestational age than

Table 1. Demographic factors in case and control groups

Demographic factors	Case (False-positive screen) n = 165	Control group (Negative screen) n = 165	p-value
Maternal age (yrs):mean (SD)	34.5 (6.4)	33.7 (5.2)	0.219
Gestational age at Screening (wks): mean (SD)	17.4 (2.0)	17.1 (2.0)	0.174
Gestational age at Delivery (wks): mean (SD)	38.5 (2.0)	38.8 (1.2)	0.079
Parity, nulliparous	67	56	0.210
Birth weight (g): mean (SD)	3088.1 (543.9)	3229.1 (454.6)	0.011

* $p < 0.05$ was considered statistically significant

Table 2. The risk of adverse pregnancy outcomes in case and control groups

Complications	False-positive screen (165) n (%)	Control Group (165) n (%)	Odds ratio	95%CI	p-value
Adverse pregnancy outcome*	30 (18.2)	25 (15.2)	1.244	0.696, 2.225	0.46
Preterm delivery	11 (6.6)	5 (3.0)	2.286	0.776, 6.731	0.124
Low birth weight	11 (6.6)	6 (3.6)	1.893	0.683, 5.245	0.213
SGA	4 (2.4)	0 -	-	-	0.123
Preeclampsia	16 (9.7)	12 (7.3)	1.369	0.627, 2.992	0.429
Placenta previa	4 (2.4)	4 (2.4)	1.0	0.246, 4.067	1.0
Fetal death	1 (0.6)	0 -	-	-	1.0

* Patients had at least one of the listed adverse outcomes

Table 3. Demographic factors in women with false positive Down syndrome screening result (n = 165)

Demographic factors	With adverse outcome (n = 30)	Without adverse outcome (n = 135)	p-value
Maternal age (yrs): mean (SD)	35.3 (5.5)	34.3 (6.6)	0.434
Gestational age at Delivery (wks): mean (SD)	36.7 (3.6)	38.8 (1.0)	<0.001*
Parity, nulliparous	14	53	0.455
Birth weight(g):mean(SD)	2617.3 (848)	3192.7 (381.8)	<0.001*

* $p < 0.05$ was considered statistically significant

those with normal outcomes, and their newborns had a lower birth weight ($p < 0.05$).

Discussion

When a woman receives a false positive Down syndrome screening result, both she and her antenatal care provider are eager to know whether the positive result has other adverse pregnancy outcome. The present study results showed that after a false-positive screen for Down syndrome based on double markers(MSAFP and hCG),one in five women with a singleton gestation and no relevant history experienced an adverse pregnancy outcome. The risk was 1.244 times greater than a control population (but not with significant difference). However, except for the risk of preterm delivery, other complications (low birth weight newborn, small for gestational age newborn, preeclampsia, placenta previa, and fetal death after 28 weeks' gestation) between the two groups were less than twofold. The authors also found that the mean birth weight was significantly lower in the study group. The association between adverse pregnancy outcomes and elevated maternal serum hCG has been attributed to early uteroplacental underperfusion[12,13]. The reduced oxygen supply to the syncytiotrophoblasts may result in hyperplasia of the cells and increase in production of hCG. An impaired uteroplacental perfusion resulted in poor delivery of substrate to the fetus, and thus suboptimal growth.

Table 4. Literature review on the association of maternal serum beta-hCG and adverse pregnancy outcomes

Reference	Conclusion
Pergament et al[8] (1995)	(Triple marker; risk cut-off value > 1:250; 174 cases) One in three women with a false-positive screen for Down syndrome may experience an adverse pregnancy outcome (Preterm delivery, Preterm PROM, Abruptio placentae, Preeclampsia, SGA and Fetal death).Odds ratio for total adverse outcome was 3.5, 95%CI 1.6-7.8; $p < 0.01$
Chapman et al[7] (1997)	(Triple marker; risk cut-off value > 1:190; 1,135 cases) Women > age 30 with a false - positive screen for Down syndrome are not at increased risk for adverse pregnancy outcomes (DFU, Preterm delivery, SGA)
Hsieh et al[5] (1997)	(Double marker; Asian; risk cut-off value >1:270; 5,885 cases) No apparent increase in the adverse perinatal outcomes analyzed in Taiwanese women under 35 years of age having false-positive screen for Down syndrome (Postterm pregnancy, Preeclampsia, Abruptio placentae, Placenta previa, and Polyhydramnios)
Ogle et al[6] (2000)	(Double marker; risk cut-off value > 1:250; 544 cases) The incidence of adverse pregnancy outcomes was 11.9% in the study group and 8.6% in the control group. These data identify no evidence for a strong association between a false positive Down syndrome screening test result and subsequent adverse perinatal outcomes (Preeclampsia, IUGR, Preterm labour, and DFU)
Summers et al[9] (2003)	(Triple marker; risk cut-off value 1:385; 23,098 cases) The risks of obstetric complications in women who screened positive or negative for Down syndrome were similar (Preeclampsia, APH, SGA, DFU, and Preterm delivery). The differences in the risks of developing complications between the two groups were less than two fold. Odds ratio was 1.20 (95%CI = 1.11, 1.30)

CI, Confidence intervals; PROM, premature rupture of membranes; SGA, small for gestational age; DFU, death fetus in utero; IUGR, intrauterine growth retardation, APH, antepartum hemorrhage

The authors also revealed that the present study identify no evidence for a strong association between a false positive Down syndrome screening test result and the subsequent adverse pregnancy outcomes in the general population. The results of studies on the association between false positive Down syndrome screening results and adverse pregnancy outcomes have been controversial. Pergament et al[8] found that women with false positive Down syndrome screening results significantly differed from their matched controls in the incidence of preterm delivery, preeclampsia, and SGA newborns. Ogle et al[6] also found no evidence of association either. A study by Summers et al[9] demonstrated that the risk of developing obstetric complications in the case group was slightly higher (OR = 1.20, 95%CI = 1.11, 1.30). Complications included pregnancy-induced hypertension, preeclampsia, antepartum hemorrhage, SGA newborn, spontaneous fetal loss, and preterm delivery. However, except for the risk of spontaneous fetal loss, the differences in the risk of devolping other complications between the two groups were less than twofold. Hsieh et al[5] studied in Taiwanese women with false positive Down syndrome screening results. They found that the adverse perinatal outcomes which did not reach a level of statistically significant difference included postterm pregnancy, preeclampsia, abruptio placentae, placenta previa, and polyhydramnios.

The discordant results may be accounted for by differences in sample size, race, demographics of the population, serum biochemical markers used for screening, and different cut-off values. Further studies are needed to clarify these differences. A large prospective case-controlled study is required to verify the present findings and extend them to a large and more heterogeneous population. However, the results of the present study provided important information for the counseling of women with positive screen results for Down syndrome for prediction and prevention of pregnancy adverse outcomes.

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ผลลัพธ์อันไม่พึงประสงค์ของการตั้งครรภ์ในสตรีไทยที่มีผลบวกลวงจากการตรวจกรองกลุ่มอาการดาวน์ในไตรมาสที่สองของการตั้งครรภ์

สุกิจ ศรีทิพยวรรณ, ชาลี วชิรศรีสุนทรา

วัตถุประสงค์: *เพื่อศึกษาว่าผลบวกลวงจากการตรวจกรองกลุ่มอาการดาวน์ในไตรมาสที่สองของการตั้งครรภ์โดยใช้การตรวจระดับของอัลฟาฟีโตโปรทีน และฟรีเบต้าเอชซีจีในเลือดมารดา สามารถคาดการณ์ผลลัพธ์อันไม่พึงประสงค์ของการตั้งครรภ์ในสตรีไทยได้หรือไม่*

วัสดุและวิธีการ: *เป็นการวิจัยเชิงวิเคราะห์ชนิดย้อนหลัง เพื่อศึกษาความสัมพันธ์ระหว่างผลบวกลวงจากการตรวจกรองกลุ่มอาการดาวน์ในไตรมาสที่สองของการตั้งครรภ์ โดยใช้การตรวจระดับของอัลฟาฟีโตโปรทีน และฟรีเบต้าเอชซีจีในเลือดมารดา กับผลลัพธ์อันไม่พึงประสงค์ของการตั้งครรภ์ ศึกษาในสตรีตั้งครรภ์ที่ได้รับการตรวจกรองกลุ่มอาการดาวน์ที่โรงพยาบาลเจริญกรุงประชารักษ์ ระหว่างเดือนมีนาคม พ.ศ. 2541 ถึง สิงหาคม พ.ศ. 2545 โดยเปรียบเทียบผลลัพธ์ของการตั้งครรภ์ในสตรี 165 คนที่มีผลบวกลวงจากการตรวจกรองกลุ่มอาการดาวน์ กับผลลัพธ์ของการตั้งครรภ์ในสตรี 165 คนที่มีผลเลือดปกติจากการตรวจกรองกลุ่มอาการดาวน์ ผลลัพธ์ของการตั้งครรภ์ที่ศึกษาได้แก่ การคลอดก่อนกำหนด ทารกแรกเกิดที่มีน้ำหนักตัวน้อยกว่า 2,500 กรัม ทารกแรกเกิดที่มีน้ำหนักตัวต่ำกว่าเปอร์เซ็นต์ไทล์ที่ 10 ที่อายุครรภ์นั้น ๆ ภาวะครรภ์เป็นพิษ ภาวะรกเกาะต่ำ และภาวะทารกตายในครรภ์*

ผลการศึกษา: *สตรีที่มีผลบวกลวงจากการตรวจกรองกลุ่มอาการดาวน์ และสตรีที่มีผลเลือดปกติจากการตรวจกรองกลุ่มอาการดาวน์ พบอุบัติการณ์ของผลลัพธ์อันไม่พึงประสงค์ของการตั้งครรภ์ ร้อยละ18.2 และร้อยละ 15.2 ตามลำดับ ทารกแรกเกิดของสตรีที่มีผลบวกลวงมีน้ำหนักน้อยกว่าทารกแรกเกิดของสตรีที่มีผลเลือดปกติอย่างมีนัยสำคัญทางสถิติ (3088.1 $\pm$ 543.9, 3229.1 $\pm$ 454.6 กรัม; $p = 0.011$) ไม่พบความแตกต่างอย่างมีนัยสำคัญทางสถิติในผลลัพธ์อันไม่พึงประสงค์ของการตั้งครรภ์ของสตรีทั้งสองกลุ่ม*

สรุป: *จากการศึกษาครั้งนี้แสดงให้เห็นว่าไม่พบผลลัพธ์อันไม่พึงประสงค์ของการตั้งครรภ์มากขึ้นในสตรีที่มีผลบวกลวงจากการตรวจกรองกลุ่มอาการดาวน์*

เอกสารอ้างอิง

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