

## OBSTETRIC AND PERINATAL OUTCOMES IN PREGNANCIES WITH POSITIVE FIRST TRIMESTER SCREENING AND NORMAL KARYOTYPE

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### ABSTRACT

**Objective:** To assess the risk of adverse obstetric and perinatal outcomes for pregnant women participating in prenatal first trimester screening of down syndrome who had a positive screening result and normal karyotype. **Methods:** This study was performed in the Fetal Medicine Unit of Imam Khomeini Hospital, Ahvaz Jundishapur University of Medical Sciences from 2013-2015. Women who underwent first trimester prenatal screening with outcome information available were included in this study. Fetuses with chromosomal abnormality were excluded. We compared the risk of adverse outcomes for all women with a positive screening result compared with a 10% random sample of women with a negative screening result. Logistic binomial regression was used to compare outcomes in screen-positive compared with screen-negative women. **Results:** We identified 138 screen-positive and 215 screen-negative pregnancies with outcome information available. Adverse outcomes significantly increased in screen positive women included spontaneous abortion and

Preterm birth. spontaneous abortion 6 (4.3%) screen-positive, 1 (.5%) screen-negative; Odds ratio .011 [CI] (1.155\_81.456), preterm labor 18 (12.9%) screen-positive, 9 (4.2%) screen-negative; Odds ratio .002 confidence interval [CI] 1.49\_7.85. Preeclampsia and still birth were higher but not significantly increased in screen positive pregnancies. Pregnancies with low PAPP-A ( $\leq 0.4$ ) multiples of the median (MoM)) had higher risk of preterm labor (p value=.00) and preeclampsia (p value=.00) compared to those with PAPP-A  $>0.4$  MoM. **Conclusion:** Among pregnancies with positive first trimester prenatal screening of down syndrome and normal karyotype provides information regarding risk across a variety of adverse pregnancy outcomes.

**KEYWORD:** First-trimester screening; adverse pregnancy outcomes; PAPP-A.

## INTRODUCTION

Prenatal screening using maternal serum samples drawn in the first- and second-trimester has been effectively used worldwide to identify women at risk for aneuploidy.<sup>[1-3]</sup>

In the first trimester of pregnancy the placentally-derived biochemical markers pregnancy-associated plasma protein-A (PAPP-A) and free  $\beta$ -human chorionic gonadotropin ( $\beta$ -hCG) are used in conjunction with the ultrasound measurement of nuchal translucency thickness (NT) as part of screening programs for trisomy 21 and other aneuploidies in which approximately 90% of such anomalies can be identified<sup>[4-10]</sup> for a false positive rate of 5%. Although the primary aim of first trimester screening is to identify pregnancies at risk of aneuploidy, first trimester findings may give insight into other adverse pregnancy outcomes.<sup>[11]</sup>

screen-positive pregnancies are at increased risk for adverse perinatal outcomes including fetal demise and preterm birth.<sup>[12,13,14]</sup> Women who screen positive for more than one condition (eg, have positive results for trisomy 21) have been shown to be at particularly high risk for poor birth outcomes.<sup>[15,16]</sup>

This study assesses the risk of adverse obstetric and perinatal outcomes in pregnant women with false-positive prenatal screening results.

## MATERIALS AND METHODS

This study was performed in the Fetal Medicine Unit of Imam Khomeini Hospital, Ahvaz Jundishapur University of Medical Sciences from 2013-2014. The study was approved by the

Ethics Committee of Department of Obstetrics and Gynecology (Ahvaz Jundishapur University of Medical Sciences (AJUMS)).

Women who participated in this study were all enrolled in the First Trimester screening of down syndrome.

The 3 first-trimester markers that were evaluated were PAPP-A level, fβhCG, and nuchal translucency. After institutional review board approval and patient informed consent were obtained, all potential subjects underwent an ultrasound examination to confirm gestational age and to measurement of nuchal translucency.

NT is measured according to the Fetal Medicine Foundation (FMF) guidelines and nuchal translucency measurement when fetal crown rump length was 45–84 mm. Women who were confirmed to have a singleton pregnancy with fetal crown-rump length between 38 and 84 mm inclusive (corresponding to 11 weeks and 13 weeks 6 days gestational age) were eligible to participate, maternal serum fβhCG and PAPP-A were measured by the Kryptor analyser and were reported as multiples of the median adjusted for gestational age, maternal weight and ethnicity.

The estimated adjusted risk at term were determined using a multivariate model and the maternal a priori background risk of having trisomy 21. Women undertaking the test were screened ‘negative’ or ‘positive’ if their risk of having trisomy 21 at term exceeded a predefined cut-off value. The term risk threshold adopted to indicate a ‘positive’ or ‘negative’ test result was 1:250. Women with screen positive were offered a diagnostic test by chorionic villus sampling (CVS) or amniocentesis. Those in which reported aneuploidies were not included and women with normal karyotype included in this study.

Demographic data, smoking status, maternal weight and height, obstetric history and the results of the NT scan were entered into a database. Adverse outcomes of pregnancies were collected from a short follow-up questionnaire given to patients after the screen trisomy 21 and obtained from them after the end of pregnancy, or from hospital records or by telephone interviews with the women. The data was used to examine the relationship between adverse obstetric complications including preeclampsia; adverse perinatal outcomes including spontaneous abortion (defined as fetal death before 20 weeks of gestation), still birth (defined as fetal death after 20 weeks of gestation), Preterm birth was defined as birth prior to

37 weeks of completed gestation and low birth weight termination (<2500 g) in screen-positive pregnancies compared with screen-negative pregnancies. Odds ratio (OR) and 95% confidence intervals (CI) were calculated in comparing outcomes between screen positive and screen negative groups and pregnancies with low PAPP-A or normal PAPP-A ( $\leq 0.4$  MoM and  $>0.4$  MoM).

## RESULT

During the 1-year study period, 2773 women with singleton pregnancies completed combined first trimester screening of down syndrome in Fetal Medicine Unit of Imam Khomeini Hospital, Ahvaz Jundishapur University of Medical Sciences.

Overall, 138 from 2773 (4.9%) had screen positive of down syndrome with normal karyotype. 138 women with singleton pregnancies and screen positive of down syndrome with normal karyotype and 8-10 percentile of screen negative (215) women with screen negative of down syndrome were participated in this study.

Maternal and fetal outcomes was obtained in all women with screen positive results ( $n=138$ ) and in screen negative women ( $n=215$ ).

The mean maternal age of screen positive women was 30.86 years and in the screen negative women was 28.9 years respectively. The mean BMI of screen positive women was  $26.4 \text{ kg/m}^2$  and in the screen negative women was  $26.1 \text{ kg/m}^2$ . Table 1

**Table 1. Maternal Characteristics: Singletons With first trimester Screening Results**

Maternal age(Y)	Screen positive	Screen negative
19 or younge	4(2.89%)	10(4.6%)
20-24	23(16.6%)	38(17.6%)
25-29	36(26.08%)	54(25.1%)
30-34	32(23.18%)	56(26.04%)
35 or older	43(31.15%)	57(26.51%)
Maternal BMI( $\text{kg/m}^2$ )	26.4	26.1

## Adverse pregnancy outcomes

Almost a fifth of screen positive women had an adverse Obstetric and Perinatal outcome. The rate of all adverse outcomes was 21.7 % in screen positive and 7 % in screen negative women. The rate of adverse maternal outcomes was 15.94 % in screen positive and 6.97% in screen negative women. And the rate of adverse fetal outcomes was 5.79 % in screen positive and .46% in screen negative women. Adverse outcomes significantly increased in screen

positive women included spontaneous abortion and Preterm birth. Preeclampsia, still birth and low birth weight were not significantly increased in screen positive pregnancies. Table2.

**Table 2: Adverse outcomes in screened pregnancies**

	Total	Screen positive(138)	Screen negative(215)	Odds ratio	95%CI
<b>Number of adverse outcome</b>	46	30(21.7%)	16(7%)	—	—
<b>Adverse maternal outcome</b>	37	22(15.94%)	15(6.97%)	-	-
Preeclampsia	7	3(2.2%)	4(1.9%)	.839	.258_5.350
Preterm labor	27	18(12.9%)	9(4.2%)	.002*	1.49_7.854
Low Birth Weight	3	1(.7%)	2(.9%)	.836	.07_8.663
Adverse fetal outcome	9	8(5.79%)	1(.46%)	-	-
Still birth	2	2(1.4%)	0(0%)	.077	.966_1.006
Spontaneous abortion	7	6(4.3%)	1(.5%)	.011*	1.155_81.456

\*Statistically significant  $p < .05$

#### **Adverse pregnancy outcomes in women with low PAPP-A**

The median PAPP-A for 2773 pregnancies were 1.12 MoM. The median PAPP-A for screen positive pregnancies was .927(.77) MoM. In comparison, the median PAPP-A for screen negative pregnancies was 1.26(.81) MoM. Low PAPP-A of  $\leq 0.4$  MoM occurred in 1.8 % of women screened down syndrome. The risk of preterm labor ( $p$  value=.000) was higher in Pregnancies with low PAPP-A also had increased risk of preeclampsia ( $p$  value=.000). table3

**Table 3: Pregnancies with low PAPP-A.**

	Low Papp_a ( $\leq 0.4$ MOM)	Normal Papp_a ( $> 0.4$ MOM)	Odd ratio	95%CI
Preeclampsia	4(9.8%)	3(1%)	.000*	2.359_50.893
Still birth	1(2.4%)	1(.3%)	.093	.469_124.715
Spontaneous abortion	4(9.9%)	3(4%)	.164	.581_16.510
Preterm labor	21(51.2%)	6(2%)	.000*	19.110_145.191
Low Birth Weight	1(4%)	2(1%)	.525	.999_1.021

\*Statistically significant  $p < .05$

#### **Pregnancy outcomes in screen positive pregnancies with low PAPP-A $\leq 0.4$**

Low PAPP-A of  $\leq 0.4$  MoM occurred in 29.7% of women with screen positive pregnancies and normal karyotype . pregnancy outcomes were determined in women with Low PAPP-A of  $\leq 0.4$  MoM and normal Papp\_a ( $> 0.4$  MOM). In women with Low PAPP-A of  $\leq 0.4$  MoM . preeclampsia, Spontaneous abortion, Preterm labor and Low Birth Weight were higher than normal Papp\_a ( $> 0.4$  MOM). But only Preterm labor was significantly higher. table4

**Table 4: Pregnancy outcomes in screen positive pregnancies with low PAPP-A $\leq$ .4 and PAPP-A $>$ .4**

	Total	Low Papp_A ( $\leq$ .4 MOM) N=41	Normal Papp_A ( $>$ .4MOM) N=97	Odd Ratio
Adverse Maternal Out Come	22(15.98%)	15(36.58%)	7(7.21%)	
Preeclampsia	3	2(4.87 %)	1( 1.03%)	.26
Preterm Labor	18	12(29.26%)	6(6.18%)	.004*
Low Birth Weight	1	1(2.43%)	0(0%)	1.83
<b>Adverse Fetal Outcome</b>	8(5.79%)	5(12.19%)	3(3.09%)	
Still Birth	2	1(2.4%)	1(1.03%)	.68
Spantaneus Abortion	6	4(9.75%)	2(2.06%)	.11

\*Statistically significant  $p < .05$

In this study the average NT thickness in all pregnant women was  $1.64 \pm .54$ mm and the average NT thickness in screen positive women was  $1.79 \pm .62$  mm. In this study 3.9% of cases had  $NT \geq 95$ th centile and .7% of women had  $NT \geq 3$ .

## DISCUSSION

We found that women with positive screening of down syndrome and normal karyotype results were at higher risk for the adverse outcomes measured including preterm birth, and spontaneous abortion and Pregnancies that screened positive for down syndrome were at particularly high risk for adverse pregnancy outcomes. Only 7 % of screen-negative pregnancies had adverse outcome compared with 21.7% of those who screened positive for trisomy 21.

These women had a rate of spantaneus abortion, a risk that was 6 fold higher than the screen-negative population. Likewise, the rate of preterm birth was 4 above the screen-negative population risk.

All women with low PAPP-A were at increased risk of adverse pregnancy outcomes such as preterm birth.

These risks remained and further increased even if all birth defects were excluded.

Studies have demonstrated conflicting data regarding an association between first-trimester PAPP-A levels and an association between preeclampsia and preterm birth.<sup>[17]</sup> In this study, PAPP-A levels of  $\leq 0.4$  MoM were predictive of increased risk of preeclampsia and premature

birth. Increased risk of low birth weight and premature birth in women with low PAPP-A has been noted by others.<sup>[18,19,20]</sup>

In contrast, other studies have found an association between low PAPP-A and increased risk of low birth weight but not with preterm birth.<sup>[21,22,23,24]</sup> Furthermore, Morssink *et al.*<sup>25</sup> concluded that PAPP-A is not associated with preterm delivery.

In this study low PAPP-A was a better predictor of preeclampsia and preterm birth than screen positive first trimester screening of down syndrome. It is well accepted that low PAPP-A is associated with pregnancy loss.<sup>[21,22,23,18,19,26]</sup> Our findings are compatible with these previous studies and demonstrated that a PAPP-A  $\leq 0.4$  MoM conveyed a significant risk of preeclampsia and preterm birth. Decreased level of PAPP-A may be an indicator of impaired placental function and implantation. It has been suggested that poor placentation could result in increased risk of adverse outcome including pregnancy loss, premature birth.<sup>[18,26]</sup>

In this study Low PAPP-A of  $\leq 0.4$  MoM occurred in 29.7% of women with screen positive pregnancies and normal karyotype and In women with Low PAPP-A of  $\leq 0.4$  MoM preeclampsia, Spontaneous abortion, Preterm labor and Low Birth Weight were higher than normal PAPP-A ( $> 0.4$  MoM). But only Preterm labor was significantly higher. Our findings are compatible with study by mohamad jafari *et al.*<sup>[27]</sup> and demonstrated that a PAPP-A  $\leq 0.4$  MoM conveyed a significant risk of preterm birth.

In this study the average NT thickness in all pregnant women was  $1.64 \pm .54$  mm and the average NT thickness in screen positive women was  $1.79 \pm .62$  mm. Our findings are compatible with previous study by Barati M *et al.* In their study the average NT thickness was 1.75 mm.<sup>[28]</sup> In this study 3.9% of cases had NT  $\geq$  95th centile and .7% of women had NT  $\geq 3$ . In the study by Zamanpoor Z *et al.*, the mean scores of NT was  $1.7 \pm 0.45$ , respectively. Besides, 1.45% of the study population had NT more than 3 MoM.<sup>[29]</sup>

In the study by Barati M *et al.*, 2.43% of the study population had NT more than 95th centile and 3 cases had spontaneous abortion and 1 case had still birth.<sup>[30]</sup>

This study found that women with a positive first trimester screen of trisomy 21 or low PAPP-A had increased risk of adverse fetal outcomes even when chromosomal birth defects were excluded. The first trimester screening of down syndrome or a low PAPP-A can be used to



stratify patients as high risk for some adverse outcomes apart from trisomy 21. However, these tests had insufficient sensitivity to be used as screening tests for these adverse outcomes.

This study provides useful information for clinicians managing high risk women with positive screening of down syndrome and normal karyotype results and ultrasound findings as data are presented on pregnancies where chromosomal birth defects have been excluded.

## CONCLUSIONS

It is important for clinicians to be aware that exclusion of chromosomal abnormality following karyotyping does not exclude increased risk of other adverse outcomes in women with a screen positive result and or in low PAPP-A result. In pregnancies with normal karyotype, a low PAPP-A was the strongest predictor of preterm birth and preeclampsia. However, a low PAPP-A or positive screening of down syndrome in first trimester does not have adequate sensitivity to stratify women into high risk groups for adverse outcomes apart from trisomy 21. Rather, a screen positive result or low PAPP-A can be used to place some women at increased risk for adverse pregnancy outcomes. Options for follow up of decreased level of PAPP-A vary with clinical practice but may include increased surveillance, fetal growth scans, cervical length at 22 weeks of gestation and uterine artery Doppler .

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