Pregnancy Outcomes and Low PAPP-A

Date of Search: 05/10/2016-06/10/2016
Sources Searched: Medline, Embase, DynaMed, TRIP, NICE Evidence Search.

Search History:
1. Medline; "Pregnancy associated plasma protein A".ti,ab; 1283 results.
2. Medline; exp PREGNANCY-ASSOCIATED PLASMA PROTEIN-A/; 1517 results.
3. Medline; "PAPP-A".ti,ab; 1383 results.
4. Medline; 1 OR 2 OR 3; 1964 results.
5. Medline; (first adj2 trimester*).ti,ab; 19805 results.
6. Medline; exp PREGNANCY TRIMESTER, FIRST/; 14239 results.
7. Medline; 5 OR 6; 26193 results.
8. Medline; low*.ti,ab; 3129662 results.
9. Medline; 4 AND 7 AND 8; 383 results.
10. Medline; (low* OR abnormal).ti; 328118 results.
11. Medline; 4 AND 7 AND 10; 54 results.
12. Medline; ("PAPP-A" adj2 low*).ti,ab; 169 results.
13. Medline; ("PAPP-A" adj2 ("fifth percentile" OR "5th percentile")).ti,ab; 5 results.
14. Medline; ("Pregnancy associated plasma protein A" adj2 ("fifth percentile" OR "5th percentile")).ti,ab; 4 results.
15. Medline; (low* adj2 "Pregnancy associated plasma protein A").ti,ab; 44 results.
16. Medline; 12 OR 13 OR 14 OR 15; 194 results.
17. Medline; 7 AND 16; 156 results.
18. EMBASE; "Pregnancy associated plasma protein A".ti,ab; 1704 results.
19. EMBASE; exp PREGNANCY-ASSOCIATED PLASMA PROTEIN-A/; 2429 results.
20. EMBASE; "PAPP-A".ti,ab; 2110 results.
21. EMBASE; 18 OR 19 OR 20; 3094 results.
22. EMBASE; (first adj2 trimester*).ti,ab; 25852 results.
23. EMBASE; exp PREGNANCY TRIMESTER, FIRST/; 34742 results.
24. EMBASE; 22 OR 23; 41607 results.
25. EMBASE; (low* OR abnormal).ti; 392782 results.
26. EMBASE; (outcome* adj2 pregna*).ti,ab; 31370 results.
27. EMBASE; exp PREGNANCY OUTCOME/; 44935 results.
28. EMBASE; 26 OR 27; 56238 results.
29. EMBASE; 21 AND 24 AND 25 AND 28; 48 results.
30. EMBASE; ("PAPP-A" adj2 low*).ti,ab; 219 results.
31. EMBASE; ("PAPP-A" adj2 ("fifth percentile" OR "5th percentile")).ti,ab; 7 results.
32. EMBASE; ("Pregnancy associated plasma protein A" adj2 ("fifth percentile" OR "5th percentile")).ti,ab; 2 results.
33. EMBASE; (low* adj2 "Pregnancy associated plasma protein A").ti,ab; 46 results.
34. EMBASE; 30 OR 31 OR 32 OR 33; 239 results.
35. EMBASE; 24 AND 28 AND 34; 84 results.
36. EMBASE; 35 not 29; 43 results.
37. EMBASE; *PREGNANCY ASSOCIATED PLASMA PROTEIN A/; 1069 results.

38. EMBASE; *FIRST TRIMESTER PREGNANCY/; 9677 results.
39. EMBASE; 28 AND 37 AND 38; 72 results.
1. EMBASE; exp PREDICTIVE VALUE/; 104949 results.
2. EMBASE; exp FIRST TRIMESTER PREGNANCY/ AND *PREGNANCY ASSOCIATED PLASMA PROTEIN A/; 506 results.
3. EMBASE; 1 AND 2; 43 results.
4. Medline; exp SENSITIVITY AND SPECIFICITY/; 476253 results.
5. Medline; exp PREGNANCY-ASSOCIATED PLASMA PROTEIN-A/; 1517 results.
6. Medline; exp PREGNANCY TRIMESTER, FIRST/; 14239 results.
7. Medline; 4 AND 5 AND 6; 188 results.
8. Medline; decreas*.ti; 64400 results.
9. Medline; 5 AND 6 AND 8; 5 results.
10. EMBASE; decreas*.ti; 81654 results.
11. EMBASE; 2 AND 10; 5 results.
12. Medline; (early adj2 pregnancy).ti,ab; 19328 results.
13. Medline; 4 AND 5 AND 12; 16 results.

Title: Pregnancy outcomes with extremely low pregnancy-associated plasma protein A

Author(s): Halik I., McCarthy F., Rozette C., Sankaran S., Pasupathy D., Kyle P., Kent E.

Language: English

Abstract: Introduction Our aim was to evaluate the outcomes of pregnancies with a pregnancy-associated plasma protein A (PAPP-A) below 0.1 multiples of the median (MoM) at first-trimester screening. Methods A retrospective cohort study was performed between 1 May 2010 and 14 October 2015. Pregnancies with PAPP-A <0.1 MoM were identified. The rates of karyotypic abnormality and adverse pregnancy outcome were calculated. Results Of 43 752 women undergoing first-trimester screening during the study period, 0.07% (n = 32) had PAPP-A <0.1 MoM. Fetal karyotype was available for 24 fetuses, of which 87.5% were abnormal. The commonest chromosomal abnormality was triploidy (45.8%, n = 11). Other aneuploidies were trisomy 18 (25%, n = 6), trisomy 13 (12.5%, n = 3) and trisomy 21 (4.2%, n = 1). Outcome data were available on 29 pregnancies, with three pregnancies still ongoing. Eight women opted for pregnancy termination and 55% of pregnancies (n = 16) resulted in first trimester or second-trimester miscarriage. Of the five babies delivered alive, there was one neonatal death, one baby born with multiple congenital abnormalities and one case of preterm prelabour rupture of membranes and preterm delivery. Just 7% (n = 2) of the cohort was delivered at term without complications. **Conclusion First-trimester PAPP-A levels <0.1 MoM are associated with a very poor prognosis in pregnancy, with very high rates of aneuploidy and pregnancy loss. This should be considered when counselling women with low PAPP-A and may inform decisions regarding further prenatal testing options and pregnancy management.**

Publication Type: Journal: Conference Abstract

Source: EMBASE

Full Text:

Title: An obstetric outcome audit of pregnancies complicated by low first-trimester maternal serum pregnancy-associated plasma protein A levels at Barking, Havering and redbridge university teaching hospitals NHS trust

Citation: BJOG: An International Journal of Obstetrics and Gynaecology, April 2016, vol./is. 123/(73), 1470-0328 (April 2016)

Author(s): Thompson M., Murray R., Madipola N., Power M., Otigbah C., Spencer K.

Language: English

Abstract: Objectives Low maternal serum pregnancy-associated plasma protein A (PAPP-A) levels in the first trimester are associated with poor pregnancy outcomes; miscarriage, intrauterine deaths, antepartum haemorrhage, stillbirth, fetal growth dysfunction and pregnancy hypertensive disorders. We audited outcomes in pregnancies complicated by low maternal first-trimester serum PAPP-A. Methods A retrospective audit of pregnancies with low PAPP-A levels between March 2014 and May 2015. The reference standard was a cutoff of <0.415 multiples of the median from RCOG guidelines. Results There were 260 affected pregnancies with low PAPP-A among 8900 screened. In 201 of these pregnancies there were antenatal concerns regarding placental abruption, intrauterine growth restriction (IUGR), pregnancy hypertension, preeclampsia, and haemolysis, elevated liver enzymes and low platelet count (HELLP) syndrome. There were 60 emergency caesarean deliveries in the same group, 53.3% of which were for fetal compromise or uteroplacental complications, higher than in the local caesarean section audit. Compared with the background obstetric population, the pre-eclampsia rate of 1.2% was not as high as the background prevalence of 2.3% during this period, 7.44% babies were small for gestational age below the 10th centile, and there were five stillbirths, 1.9% versus 0.08% in the background population. There were 22 premature births, of which eight were severe early preterm births at <34 weeks of gestation. The induction rate of 2.7% for reduced fetal movements at term was low, but 23.4% of the inductions of labour were for fetal compromise, antepartum haemorrhage, IUGR, pregnancy-induced hypertension and pre-eclamptic toxaemia. **Conclusion A low maternal serum PAPP-A in the first trimester is associated with a very high risk of uteroplacental complications and such pregnancies deserve closer surveillance**.

Publication Type: Journal: Conference Abstract

Source: EMBASE

Full Text:

Title: Pregnancy-associated plasma protein A levels and pregnancy outcome an audit with outcome data of 8000 pregnancies

Citation: BJOG: An International Journal of Obstetrics and Gynaecology, April 2016, vol./is. 123/(80-81), 1470-0328 (April 2016)

Author(s): Maudlin L., Maxey V., Evans A., Chipchase A., Smith R.

Language: English

Abstract: Introduction National guidelines state that low pregnancy associated plasma protein A (PAPP-A) of <0.415 multiples of the normal median (MoM) in the first trimester should be considered as a major risk factor for delivery of a small-for-gestational-age (SGA) baby and therefore these women should be referred for serial ultrasound scans from 26 to 28 weeks of gestation. The aim was to see if the guideline was followed (standard: 100%) and to review outcome data for miscarriage, prematurity and stillbirth. Methods Data were collected from all women with low PAPP-A (<0.4 MoM) from 2012 to 2014. Of 8761 women undergoing screening, 194 (2.2%) had low PAPP-A. Outcome data were available on 191 (98.4%) of which three patients did not continue care at our hospital; 183 (96%) had at least one additional growth scan. Results Pregnancy outcomes showed that 11 (5.7%) resulted in miscarriage. Four (2.2%) resulted in stillbirth (of which all were SGA); 53 (27.3%) delivered babies that were <10th centile on customised growth charts; 39 (21.6%) delivered before 37^{+0} weeks (of which 27 were SGA); and 19 (9.8%) were induced for suspected SGA, of which 16 (85%) were subsequently small. **Conclusion Our outcome data are in keeping with larger studies for positive predictive value for detection of SGA and increased stillbirth rates above the general population. Of those stillbirths; one had a termination for severe growth restriction around 20 weeks, one occurred before serial scans were initiated, one had a placental abruption at 35 weeks and one delivered at 41 weeks with a disparity between estimated and actual fetal weight.**

Title: The outcome of pregnancies complicated by a low PAPP-A value

Author(s): Wickens O., Crosfill F.

Language: English

Abstract: Introduction: The aim of this study to determine whether the combined test biochemical marker, PAPP-A, is a reliable predictor of women at high risk of developing adverse obstetric outcomes. Methods: A retrospective study was carried out on 200 singleton pregnancies having undergone combined test screening. Data were collected for 100 women with normal PAPP-A value (>0.415 MoM) and 100 women with low PAPP-A value (<0.415 MoM). The low PAPP-A group was divided into two groups; very low PAPP-A (<0.350 MoM) and low PAPP-A (<0.415 but >0.350 MoM). To compare groups, maternal factors (smoking status, ethnicity, parity, BMI), pregnancy-related complications (pre-eclampsia, gestational hypertension, placental abruption, miscarriage) and fetal factors (gestational age, fetal sex, mode of delivery (MOD), preterm delivery, induction of labour (IOL), stillbirth, chromosomal abnormalities, birth centiles) were recorded. Results: The groups were similar in BMI, maternal age, parity, ethnicity and smoking status. Although not statistically significant there was an increased incidence of preterm delivery, IOL, pre-eclampsia, gestational hypertension and caesarean section rate in pregnancies with low PAPP-A. There was an increased incidence of male fetuses (P < 0.05), low birthweight infants (P < 0.001) in women with PAPP-A < 0.415 MoM. A greater incidence of small-for-gestational age infants (P < 0.001) and babies born at a

lower gestational age (P < 0.05) in women with PAPP-A < 0.350 MoM. One stillbirth, one miscarriage and one termination for Down syndrome pregnancy were recorded in the low PAPP-A groups. **Conclusion: Low PAPP-A in the first trimester is associated with adverse pregnancy outcomes: small-for-gestational age infants, reduced gestational age and low birthweight infants and a greater incidence of male fetuses. Although a low value can identify a high-risk group of women for obstetric complications, its sensitivity and specificity as an individual marker is low. Greater research into using surveillance techniques to improve detection rates is required, allowing for appropriate intervention before complications arise.**

Publication Type: Journal: Conference Abstract

Source: EMBASE

Full Text:
Available from *John Wiley and Sons* in [BJOG: An International Journal of Obstetrics and Gynaecology](#)

Title: Correlation of first-trimester serum levels of pregnancy-associated plasma protein A with small-for-gestational-age neonates and preterm births.

Citation: International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics, May 2016, vol. 133, no. 2, p. 159-163, 1879-3479 (May 2016)

Author(s): Gundu, Shridevi, Kulkarni, Mohan, Gupte, Sanjay, Gupte, Asmita, Gambhir, Maitreyee, Gambhir, Prakash

Abstract: To analyze the relationship between first-trimester levels of pregnancy-associated plasma protein A (PAPP-A) and small-for-gestational-age (SGA) neonates and preterm births, and to assess predictive utility for these events. A prospective study was conducted among women undergoing first-trimester screening between January 1, 2012, and December 31, 2013, at two centers in Pune, India. Serum PAPP-A levels, pregnancy course, and outcome were assessed. Overall, 1474 women were included. An association was found between the lowest quintile of PAPP-A levels (<0.4 multiples of median) for both SGA (<10th centile; 20.9% of cases in this PAPP-A quintile) and preterm birth (<37weeks; 15.8%). Women in the lowest quintile of PAPP-A concentration had a significantly increased risk of SGA (<10th centile) than did those with higher concentrations (adjusted odds ratio 2.92, 95% confidence interval 2.00-4.27). Their risk of preterm birth (<37weeks) was also increased (adjusted odds ratio 1.84, 95% confidence interval 1.25-2.72). The predictive sensitivities of the lowest quintile of PAPP-A were 35.85% for SGA (<10th centile) and 27.92% for preterm birth (<37weeks). **Low levels of PAPP-A were associated with SGA and preterm births; however, poor predictive sensitivity could restrict clinical utility of this marker when used alone**. Copyright © 2016 International Federation of Gynecology and Obstetrics. Published by Elsevier Ireland Ltd. All rights reserved.

Source: Medline

Title: Outcome of pregnancies with low PAPP-A in a district general hospital

Citation: BJOG: An International Journal of Obstetrics and Gynaecology, April 2015, vol./is. 122/(56-57), 1470-0328 (April 2015)

Author(s): Nachimuthu P., Nejad A.

Abstract: Introduction The aim was to evaluate the outcome of pregnancies with PAPP-A <0.40 Mom during routine first trimester screening. Methods It is a retrospective study done over 1 year period from January to December 2013. Results In total we identified 36 pregnancies with a PAPP-A level below the cut off including 35 singleton pregnancies and 1 twin pregnancy. About 80% of women were multipara and 20% were primipara. The vast majority 91% were between the age groups of 20-40 years, whilst 1 woman was <20 and 2 were over 40 years. 25% came under the high risk category in the combined screening. Out of them 33% had confirmed aneuploidy and 55% declined further testing. Anomaly scan confirmed anomaly in 4 (11%) of them. 3 (8.3%) pregnancies were terminated and there were 34 live births. There were 29 (80%) term births and (20%) preterm births. There was a 13% (4) association with PET. The incidence of low birthweight babies under 2500 g was 15% and a further 20% of babies weighed between 2500-3000 g. 79% of babies were male and 21% were female. 18% of babies were admitted to special care and there was 1 neonatal death. Discussion **In conclusion low PAPP-A level seem to be associated with poor pregnancy outcome. There is clearly a higher incidence of aneuploidies and anomalies compared to the background rate. It was also found that there is a significantly higher association with preterm births almost 3 times compared to the background rate. There is also a slightly higher association with pre-eclampsia. The rate of low birthweight babies was found to be significantly higher and there is also a higher rate of admission to special care. This study though small does re-emphasis the results shown in other studies that PAPP-A does have an important role in predicting pregnancy outcome.**

Title: How low is too low: Does the percentile of low PAPP-A affect pregnancy outcomes?

Author(s): Foroutan J., Lewis D., Herrera K., King L., Bimson B.

Abstract: INTRODUCTION: When screening for aneuploidy, the definition of a low pregnancy-associated plasma protein-A (PAPP-A) depends on the percentile cut-off used. We sought to determine whether a lower percentile cut-off is associated with worse pregnancy outcomes. METHODS: A retrospective cohort study was performed using maternal serum analyte results from first trimester and sequential screening tests from January 2002-December 2012. Low PAPP-A, <5th percentile, was defined as <0.4 MOM (multiples of the median). A PAPA-A <1st percentile was defined as <0.33 MoM and the 2-5th percentile was defined as 0.34- 0.40 MoM. Patients were excluded if they had known structural and/or chromosomal anomalies, multiple gestations, and pre-gestational diabetes. Women were placed into 2 groups: Group 1, 2-5th percentile and Group 2, <1st percentile. Low birth weight was defined as <2500g and intrauterine growth restriction (IUGR) was defined as estimated fetal weight or abdominal circumference <10% on ultrasound. Statistical analysis was performed using Wilcoxon signed-rank test and Fisher's exact test to compare pregnancy outcomes among the 2 groups. RESULTS: A total of 11,958 patients had screening tests

performed during this time period and 263 patients had a low PAPP-A. Ten patients were excluded, leaving 253 patients for analysis. See table below. (Table Presented) **CONCLUSIONS: A PAPP-A <1st % does not appear to have worse pregnancy outcomes when compared to the 2-5th %. Using a lower cutoff does not appear to have any clinical significance.**

Publication Type: Journal: Conference Abstract

Source: EMBASE

Title: Outcome of pregnancy with low PAPP-A

Citation: Archives of Disease in Childhood: Fetal and Neonatal Edition, June 2014, vol./is. 99/(A169), 1359-2998 (June 2014)

Author(s): Imcha M., Egbase E., Ross G.

Language: English

Abstract: Background PAPP-A is a biochemical marker in first trimester screening undertaken at 11-13 weeks gestation. Studies have shown that low levels of it (<0.4 MoM) are descriptive of poor early placentation and can be an independent risk factor of complications associated with adverse obstetric outcomes. Objective Review existing management and pregnancy outcome of women with low PAPP-A levels and formulate guidelines to establish uniform standard practice for better outcomes. Method Following parameters were retrospectively analysed from case notes from January to December 2011: Maternal Age Parity Miscarriage PAPP-A levels Aspirin Uterine artery Doppler Growth scan Hypertension Delivery time Stillbirth APGAR SCBU admission Results 81 identified with low PAPP-A 90% received counselling 46% commenced on low dose aspirin 88% had uterine artery doppler 75% had growth scans 66% had no growth restriction 66% had further dopplers 38% received steroids 64% had no adverse outcomes 60% of babies born had weight greater than 3kg 25% had SCBU admission 36% had adverse outcomes **Conclusion Low PAPP-A levels have limited value as a one-time single marker test and is poorly sensitive. Likelihood of an adverse outcome increases as PAPP-A level decreases. For pregnant women with a low PAPP-A level, monitoring of fetal growth and doppler indices can help identify high risk of adverse obstetric outcomes. Even if the ultrasound examination is normal it does not rule out an adverse outcome. Increased surveillance during pregnancy and low dose aspirin with uterine artery doppler were introduced in the guidelines for management of pregnant women with low PAPP-A.**

Publication Type: Journal: Conference Abstract

Source: EMBASE

Full Text:
Available from *Highwire Press* in [Fetal and Neonatal](#)

Title: Association of first trimester PAPP-a with small for-gestational age infant and other adverse pregnancy outcomes

Citation: Journal of Maternal-Fetal and Neonatal Medicine, June 2014, vol./is. 27/(138), 1476-7058 (June 2014)

Author(s): Cervino Gomez E., Gonzalez Rodriguez L., Cernadas Pires S., Gonzalez Boubeta R., Lopez Ramon y Cajal C.N.

Language: English

Abstract: Brief Introduction: The PAPP-A is produced by the placental syncytiotrophoblasts and works as a protease for IGF binding protein 4. IGF plays a major role in the fetal growth, mediating in the trophoblastic invasion and the glucose and aminoacids transport across the placenta. Levels of PAPP-A<0.4 MoM in the first trimester screening, have been linked to an increasingly frequent adverse perinatal outcomes. The early identification of fetuses at risk of SGA may improve the gestational surveillance and optimize the moment of birth. The objective is ascertain the clinical usefulness of a low level of PAPP-A in the first trimester screening, as a SGA predictor at birth and if there are differences for other adverse perinatal outcomes. Materials & Methods: Type of study: cases and controls. Inclusion criteria: Spontaneous, single pregnancies, in <38 yearold women subjected to first trimester screening for aneuploidies between week 11 and 13 + 6 at University Hospital Complex Vigo, between January 2012 and June 2013. Exclusion criteria: twin pregnancy, maternal illness, in vitro fertilization, chromosomal aneuploidy or fetal malformation. The cut-off point for a low PAPP-A is set at MoM<0.4, in accordance with the 5st percentile of our center. Population: 4879 pregnant women subjected to first trimester screening over this period. Cases: 259 patients with low PAPP-A (<0.40 MoM) in first trimester screening over the same period. Controls: 259 patients in the control group (PAPP-A>0.41 MoM) are selected on a pairing basis. Statistical analysis: Conducted with a SSPS 19 pack for Windows. A P value<0.05 was deemed to be statistically significant. Clinical Cases or Summary Results: 225 pregnant women were included in the cases group (34 of those 259 were excluded) and 228 in the control group (31 of those 259 were excluded). There were no differences of statistical relevance regarding the age, race, BMI or cigarette smokers. We found relevant differences as for the number of SGA and preterm delivery (p<0.05). 30.9% of newborns with low PAPP-A were SGA (54.36% of those SGA featured a weight below 5st percentile), as opposed to 11% in the controls group. 73% of SGA born during our study featured a low PAPP-A, coming up to 80.4% in SGA below 5st percentile. The incidence of preterm birth was 9.5% in the cases group, compared to 3.6% in the controls group. We did not find differences with regard to adverse outcomes such as preeclampsia, gestational diabetes or intrauterine fetal birth. Perinatal outcomes were pretty similar concerning the type of birth, Apgar and pH. The number of admissions of newborns was higher in cases group, 13.6% compared to 2.7%. It was somewhat noticeable, though, that there were 3 fetal deaths before week 24 in the cases group as opposed to none in the control group. **Conclusions: Low levels of maternal serum PAPP-A are associated with an increased risk of SGA (RR 4.2 for SGA below 5st percentile, RR 2 below10st percentile), preterm delivery (RR 2.6) and admission in neonatal care unit (RR 5). The association for SGA of PAPP-A levels below the 5st percentile suggests that patients within this group may benefit from increased surveillance for this condition.**

Full Text:
Available from *Taylor & Francis* in [Journal of Maternal-Fetal and Neonatal Medicine, The](#)

Title: Predicting SGA neonates using first-trimester screening: influence of previous pregnancy's birthweight and PAPP-A MoM.

Author(s): Krauskopf, Alexandra Lara, Knippel, Alexander Johannes, Verde, Pablo Emilio, Kozlowski, Peter

Abstract: Investigating the proportions of anamnestic and biochemical variables of the previous and current pregnancies for the prediction of small for gestational age (SGA) neonates in the current pregnancy. In this observational retrospective study, 45 029 pregnancies were examined, including 3862 patients with more than one pregnancy. Odds ratios for SGA using anamnestic parameters and pregnancy-associated plasma protein A (PAPP-A) values from all pregnancies were estimated by using a logistic regression model. There were 2552 (5.7%) SGA neonates. Two threshold PAPP-A values were identified at 0.15 MoM and 0.33 MoM with probabilities for SGA of 23% and 17%, respectively. A previous SGA < 10th centile and a current PAPP-A MoM value < 5th centile result in odds ratios of 4.8 (95% CI: 3.5-6.5) and 3.0 (95% CI: 1.8-5.0), respectively. The parameters' combined odds ratio is 14.1 (95% CI: 3.9-50.3) with a number needed to screen of ten for one SGA neonate at a detection rate of 37%. **Information on previous pregnancies affected by SGA and a current pregnancy's low PAPP-A value are reliable predictors for a SGA delivery. First-trimester biochemical analysis should be maintained to detect women at risk for delivering a SGA neonate.**

Source: Medline

Full Text:
Available from *Taylor & Francis* in [Journal of Maternal-Fetal and Neonatal Medicine, The](#)

Title: Can first trimester serum pregnancy associated plasma protein A (PAPP-A) predict adverse pregnancy outcome? Retrospective cohort study

Author(s): Bilagi A., Burke D., Mills I., Riley R., Kilby M.D., Morris R.K.

Language: English

Abstract: Objective To investigate the relationship between maternal serum pregnancy-associated plasma protein-A (PAPP-A) in first trimester and pre-eclampsia (PE), small-for gestational age (SGAbirthweight <10th customised centile), miscarriage, stillbirth, perinatal and neonatal death and preterm delivery <37 weeks (PD). Method A retrospective cohort study examining singleton pregnancies in women delivering at Birmingham Women's Hospital between 2011 and 2015 with first-trimester combined screening. Fetuses with aneuploidy were excluded. Maternal medical, antepartum, pregnancy outcome and neonatal data were obtained. Unadjusted and multivariable logistic regression with adjustment for known prognostic factors and confounders was conducted. Additional adjusted analyses also adjusted for nuchal translucency (NT) and crown-rump length (CRL) as potential prognostic factors. Results 12 592 pregnancies with 852 (6.8%) PD, 352 (2.8%) PE, 1824 (14.5%) SGA, 73 (0.6%) miscarriages, 37 (0.3%) stillbirths, 73 (0.6%) perinatal deaths and 38 (0.3%) neonatal deaths. There were statistically significant lower odds of SGA, PD, PE and stillbirth as PAPP-A increases in adjusted analyses [SGA odds ratio (OR) 0.87 (95% CI 0.85-0.90) P < 0.0001, PD OR 0.92 (95% CI 0.90-0.96) P = 0.001; PE OR 0.91 (95% CI 0.85-0.97) P = 0.004); stillbirth OR 0.72

(95% CI 0.53-0.99) P = 0.04]. There were no statistically significant associations between miscarriage, perinatal or neonatal death with PAPP-A. With additional adjustment for NT and CRL, there remained statistically significant associations between PAPP-A and SGA, PD and PE. **Conclusion Low PAPP-A is a risk factor for adverse pregnancy outcomes, especially SGA. Further work needs to consider which threshold should be chosen combined with other risk factors to give accurate prediction.**

Publication Type: Journal: Conference Abstract

Full Text:
Available from *John Wiley and Sons* in [BJOG: An International Journal of Obstetrics and Gynaecology](#)

Title: Low pregnancy associated plasma protein - A (PAPP-A) in the first trimester - Is it a predictor of poor perinatal outcome?

Author(s): Karim J., Sau A., Percival S.

Language: English

Abstract: Aim: To examine the predictive value of pregnancy associated plasma protein (PAPP-A) for various markers of poor pregnancy outcome. Method Databases at University Hospital Lewisham were used retrospectively to identify all singleton pregnancies which underwent first trimester combined screening between July 2008 and April 2010 and who were found to have levels of PAPP-A<0.4 MOM. The perinatal courses of these pregnancies (n=256) were evaluated for signs of adverse outcome (spontaneous abortion, stillbirth, preterm labour, intrauterine growth restriction (IUGR), early onset pre-eclampsia, late-onset preeclampsia, gestational hypertension and placental abruption) and were compared to the outcomes of a matched control group of pregnancies (n=277) with normal PAPP-A levels. Results: Women with low serum PAPP-A were 5.0 times more likely to suffer fetal loss than those in the control group with an increased incidence of spontaneous abortion (RR 1.7) and of stillbirth (RR 2.3). The overall relative risk of IUGR was 2.2. However, IUGR was 4.3 times more prevalent in pregnancies with PAPP-A<0.2 than in pregnancies from the control group. Results: indicated that women with low PAPP-A were also at increased risk of preterm birth (RR 1.9), early pre-eclampsia (RR 2.0), late pre-eclampsia (RR 1.9) and gestational hypertension (RR 1.3). There were no incidences of placental abruption in live birth pregnancies from either group. **Conclusions: This study shows that serum PAPP-A is an important marker for poor pregnancy outcome and that women with low serum PAPP-A levels would benefit from increased monitoring of their pregnancies.**

Publication Type: Journal: Conference Abstract

Full Text:
Available from *Highwire Press* in [Fetal and Neonatal](#)

Title: Lack of association between low pregnancy-associated plasma protein (PAPP-A) in the first trimester with pregnancy outcomes

Author(s): Ranganathan A., Johnson H., Bastin J., Sarkar P.

Language: English

Abstract: Introduction Low levels of pregnancy-associated plasma protein A (PAPP-A) in the first trimester have variably been shown to be associated with adverse fetal outcomes such as small for date and preterm birth. The objective of this study was to examine fetal outcomes in pregnancies with low PAPP-A to assist in the antenatal management. Methods This is a hospital-based, retrospective study on pregnancies with low PAPPA in the first trimester. Low PAPP-A is defined as <0.4 multiples of median (MoM) and were measured between 11 weeks and 13 + 6 weeks. 5275 women underwent first trimester screening over the study period of 17 months from April 2012 to August 2013, of which 147 women were identified to have a low PAPP-A (<0.4 MoM). Three women with early miscarriage, 4 with chromosomal abnormalities and 2 with multiple pregnancies were excluded from the analysis. 16 pregnancies were lost to follow-up. Thus, 122 pregnancies with normal karyotype were included in the study. Other variables included in the analyses were hCG expressed as MoMs, nuchal translucency (mm) and combined risk expressed numerically. Fetal outcome measures were taken as birthweight and gestation at delivery. Data were analysed on SPSS 19. Spearman's rho was used for non-parametric correlations, and multinomial logistic regression to identify significant correlations. Subgroup analyses were undertaken with birthweights of U 2500 g and with gestation at delivery of <37 weeks. Results The median PAPP-A MoM was 0.339 with interquartile (IQR) between 0.286 +/-0.374. The minimum PAPP-A value was 0.004 and the maximum 3.780. Birthweight was normally distributed with a mean of 3006 g (SD = 696.25). The gestational range was 18 weeks (24-42 weeks) with a median at 39 weeks. No significant correlation could be identified with either birthweight or gestational age and PAPP-A. Logistic regression analysis confirmed the lack of significant correlations (beta = 0.228, P = 0.308 ns, n = 122). Subgroup analyses with birthweight U 2500 g (n = 21) and with gestational age at birth <37 weeks (n = 12) could not establish significant associations between PAPP-A and outcomes within these subgroups. Conclusion **This study could not identify a significant correlation between PAPP-A measured between 11 and 13 + 6 weeks with either birthweight or gestational age at delivery. Cut-off levels of 0.4 MoMs may have lesser sensitivity as a screen for identifying low birthweight and preterm delivery.**

Full Text:
Available from *John Wiley and Sons* in [BJOG: An International Journal of Obstetrics and Gynaecology](#)

Title: Low versus normal first-trimester maternal PAPP-A levels and pregnancy outcome

Author(s): Rahkonen L., Ulander V.-M., Hamalainen E., Alfthan H., Markkanen H., Heinonen S., Stefanovic V., Kaijomaa M.

Language: English

Abstract: Introduction: Pregnancy-associated placental protein A (PAPP-A) is a glycoprotein produced by the placental syncytiotrophoblasts, and it is detectable in the maternal circulation from early pregnancy. PAPP-A is responsible for the cleavage of insulin-like growth factor binding protein-4 (IGFBP-4) from insulin-like growth factor (IGF), and thus it contributes to the regulation of fetal growth. PAPP-A is used as part of the first-trimester combined screening (FTS) for Down's syndrome but has also been studied as an independent marker for adverse pregnancy outcome. The risks of aneuploidy, hypertensive disorders, spontaneous abortion, small for gestational age births, prematurity and stillbirths have been shown to increase with decreasing PAPP-A levels. Still, the value of PAPP-A as an individual marker is debatable, and different cut-off values for low PAPP-A have been used in previous studies. The objective of our study was to estimate the clinical significance of low PAPP-A (50.3 MoM) in our routinely screened population in the Helsinki University District area. Materials and methods: A cohort of 961 pregnant women with low PAPP-A levels (50.3 MoM) and 961 age-matched women with normal PAPP-A levels (0.9-1.1 MoM) were followed over a four year period (2009-2012).The reference group selection was based on the assumption that the exposure related to decreased PAPP-A production would be absent in women with PAPP-A level close to 1.0 MoM (0.9 - 1.1 MoM). The FTS was performed according to the guidelines of the Finnish Ministry of Social Affairs and Health and the NT measurement was performed according to the Fetal Medicine Foundation protocol. Patients were considered screen positive with NT >3mm or a FTS risk >1/250, and genetic counseling with chromosomal analysis was offered in these pregnancies. Pregnancyinduced hypertension (PIH) was identified as a normal blood pressure in the early pregnancy and a measurement >145/90mmHg at least twice during pregnancy. Increased blood pressure with proteinuria 4300 mg/ 24 h was identified as preeclampsia. A spontaneous abortion was identified as a loss of the pregnancy or fetal viability before completed 22 pregnancy weeks, and preterm delivery as any delivery before completed 37 pregnancy weeks. Fetal death before delivery and after completed 22 pregnancy weeks was identified as stillbirth (SB), and small for gestational age (SGA) was identified as a gender-specific birth weight less than -2 SD. The prevalence of adverse pregnancy outcomes was determined. This included aneuploidies, fetal structural abnormalities, hypertensive disorders of pregnancy, spontaneous abortion, PTD, SB and SGA births. Clinical cases and summary results: Compared to the reference, the overall incidence of pregnancy failure (OR 17.8, p <0.001) was increased in the group with low PAPP-A. In the study group, the risk of aneuploidies (OR 116.1) and spontaneous abortion (OR7.7) was significantly higher (p<0.001), but no difference was detected in the incidence of major structural abnormalities (p=0.738). The incidences of preterm delivery (OR 2.5), PIH (OR 1.9), preeclampsia (OR 10.9) and small for gestational age births (OR 4.9) were all significantly higher in the group with low PAPP-A. Nine cases (0.9 %) of stillbirth occurred in pregnancies with low PAPP-A whereas there were none in the reference group. **Conclusion: Low PAPP-A and the associated adverse outcomes reflect poor placental function. However, due to controversial data, a low positive predictive value and a lack of follow-up consensus, PAPP-A can not be considered suitable for routine screening of adverse pregnancy outcome. Still, low PAPP-A is clearly a warning sign and risks should to be considered in planning the follow-up scheme of pregnancies with low PAPP-A. On the contrary, normal PAPP-A appeared to be reassuring with a very low risk of adverse outcome.** (Table Presented).

Full Text:
Available from *Taylor & Francis* in [Journal of Maternal-Fetal and Neonatal Medicine, The](#)

Title: Association of first-trimester pregnancy-associated plasma protein A levels and idiopathic preterm delivery: A population-based screening study

Author(s): Pummara P., Tongsong T., Wanapirak C., Sirichotiyakul S., Luewan S.

Language: English

Abstract: Objective: This study aims to determine the strength of relationship between pregnancy-associated plasma protein A (PAPP-A) concentrations, using a Thai-specific reference range, and rates of idiopathic preterm delivery. Materials and methods: A retrospective cohort study was conducted on consecutive singleton pregnancies, undergoing first-trimester screening for fetal Down syndrome, between January 2007 and July 2012, at our network hospitals in the northern part of Thailand. The prospective database was assessed for the records with complete outcome information, including PAPP-A concentrations, gestational age at delivery, medical and obstetric complications, and fetal and pregnancy outcomes. Pregnancies with potential causes of preterm delivery were excluded. The recruited women were assigned to two groups; a group with normal PAPP-A levels (>10th percentile) and a group with low PAPP-A levels (<10th percentile). The main outcome was the rate of idiopathic preterm births in the two groups. Results: Of 6867 screened women, 3830 were available for analysis and 670 were excluded because of potential confounders. Of the remaining 3160, 302 had low PAPP-A levels and 2858 had normal PAPP-A levels. The rates of spontaneous preterm births at <36 weeks, <34 weeks, and <32 weeks of gestation were significantly higher in women with low PAPP-A levels (7.6% vs. 17.9%, 3.1% vs. 11.9%, and 2.2% vs. 11.9%, respectively), with a relative risk of 2.37, 3.79, and 5.41 for preterm birth, respectively. **Conclusion: A PAPP-A level of <10th percentile was significantly associated with an increased risk for idiopathic preterm birth. Therefore, pregnant women with low PAPP-A levels in the first trimester should be considered at a high risk of preterm delivery.** Copyright © 2016 .

Publication Type: Journal: Article

Source: EMBASE

Full Text:
Available from *Free Access Content* in Taiwanese Journal of Obstetrics and Gynecology

Title: The relationship between first-trimester pregnancy-associated plasma protein-A levels and intrapartum fetal distress development.

Author(s): Avşar, Ayşe Filiz, Seçen, Elçin İşlek, Akçay, Gülin Feykan Yeğin, Keskin, Hüseyin Levent, Taş, Emre Erdem, Dalgacı, Ahmet Ferit

Abstract: To investigate the relationship between the development of intrapartum fetal distress and serum pregnancy-associated plasma protein-A (PAPP-A) levels measured during first-trimester

aneuploidy screening tests. This retrospective study included 283 uncomplicated pregnancies that resulted in full-term live births via spontaneous labor or with the induction by oxytocin. Cases were divided into two groups based on whether their first-trimester PAPP-A multiple of the median (MoM) levels were ≤0.5 (Group 1, n=75) or >0.5 (Group 2, n=208). As primary end points, the rate of cesarean section (C/S), the rate of C/S due to fetal distress, and the umbilical artery blood pH values in cases of C/S for fetal distress were compared between the two groups. Statistical analyses were performed using the Chi-square test and independent samples t-test. P≤0.05 were considered statistically significant. The mean gestational age at birth and the birth weights were significantly lower in Group 1 than in Group 2 (p=0.002 and p=0.007, respectively). Although the rate of C/S was similar between the groups (p=0.823), the rate of C/S due to fetal distress was significantly higher in Group 1 than in Group 2 (68.4% vs. 42%, respectively; p=0.050) and the mean umbilical artery blood pH value for C/S deliveries indicated by fetal distress was lower (p=0.048) in Group 1 than in Group 2. When the mode of delivery was analyzed according to the application of labor induction, both the C/S delivery rates (31.6% in Group 1 and 31.7% in Group 2; p=0.992) and C/S delivery rates due to fetal distress (66.7% in Group 1 and 46.2% in Group 2; p=0.405) were similar in both groups**. Low PAPP-A levels (≤0.5 MoM) in the first trimester are associated with the risk of intrapartum fetal distress development and the likelihood of C/S for fetal distress. Nonetheless, this risk is not affected by labor induction.**

Source: Medline

Full Text:
Available from *National Library of Medicine* in [Journal of the Turkish German Gynecological Association](#)
Available from *ProQuest* in [Journal of The Turkish German Gynecological Association](#)

Title: Role of first trimester maternal serum pregnancy associated plasma protein a with adverse outcome of pregnancy

Citation: Indian Journal of Clinical Biochemistry, December 2015, vol./is. 30/(S65), 0974-0422 (December 2015)

Author(s): Shruthi R., Kusuma M.R., Belle V.S., Varashree B.S.

Language: English

Abstract: Although the primary aim of first trimester screening is to identify pregnancies at risk of aneuploidy, first trimester findings such as Pregnancy associated plasma protein-A(PAPP-A) and free betahuman chorionic gonadotropin (beta-hCG) may give insight into other adverse pregnancy outcomes. Studies have shown that decreased levels of serum PAPP-A is associated with adverse pregnancy outcomes. This study is done to compare the serum PAPP-A levels with the outcome of pregnancy like Premature Rupture Of placental Membrane (PROM), Intra Uterine Growth Retardation (IUGR) and Fetal distress. The objective was to compare serum PAPP-A levels with the outcome of pregnancy like PROM, IUGR and Fetal distress. After obtaining approval from Institutional Ethical committee, 224 pregnant women (group 1-83 without complications, group 2-141 with complications) were included for the study. Further group 2 was subdivided based on age:- group 2a age <30 years, group 2b age >30 years. Serum PAPP-A levels were measured by immunoassay method. Median values of PAPP-A were found to be decreased in group 2. Similar results were found in group 2b. The values of PAPPA were decreased significantly in patients with PROM, IUGR and fetal distress. **A low serum PAPP-A level may be the descriptive of poor early**

/abnormal placentation as the root cause. Serum PAPP-A is a marker for poor pregnancy outcome and would benefit by early identification of adverse outcome of pregnancy.

Title: Pregnancy outcome in women detected with low PAPP-A level following antenatal screening for Down syndrome

Author(s): Gilchrist C., Lalrinawmi L., Sinha A.

Language: English

Abstract: Introduction Pregnancy associated plasma protein A (PAPP-A) is a large glycoprotein first described in 1974. In normal pregnancy, the majority of circulating PAPP-A is produced by trophoblasts and decidua. Recent studies have suggested that low PAPP-A level in the first trimester is associated with poor pregnancy outcomes, even in singleton pregnancies with chromosomally normal fetuses. Low levels of PAPP-A is postulated to affect the release of insulinlike growth factor, leading to abnormal trophoblastic invasion and placentation, which can ultimately culminate in poor pregnancy outcome. Methods This is a retrospective cohort study carried out at Great Western Hospital, United Kingdom. The study population consisted of all antenatal women detected with low PAPP-A level during routine antenatal screening for Down syndrome between April 2012 and March 2014. Low level of PAPP-A was defined as 0.25 multiples of the median. Pregnancy outcomes were analysed by review of individual maternity case notes and electronic database, Maternity Medway, used in the department. Results The uptake of antenatal screening for Down syndrome during the study period was 63% of all pregnant women booked within the hospital catchment area. Out of these, 55 women were identified to have low PAPP-A levels and included in this study. These women were aged between 17 and 44 years, with an average age of 30.5 years. Five (9.1%) women in the study population were smokers and 25 (45.5%) were overweight with body mass index of more than 25. Fifteen (27.3%) women underwent genetic testing either as chorionic villous sampling or amniocentesis, and out of these, eight (53.3%) had termination of pregnancies due to confirmed fetal chromosomal abnormalities. Two (3.6%) women miscarried in the second trimester. Forty-five (81.8%) women went on to deliver live babies and out of these, 13 (28.9%) babies were small for gestational age. Eight (17.8%) babies required admission to neonatal unit and one (2.2%) baby was born with oesophageal atresia not diagnosed antenatally. Five (9.1%) women developed gestational hypertension and Preeclampsia, two (3.6%) developed gestational diabetes and one (1.8%) developed obstetric cholestasis. **Conclusion Low PAPP-A level is well established as an indicator of fetal chromosomal abnormality. It is also a marker for both fetal and maternal pregnancy complications attributable to abnormal placentation and placental insufficiency. Our data supports current evidence and these women should be regarded as high-risk pregnancies. There is a growing need for robust guidelines regarding additional fetal and maternal surveillance.**

Title: Correlation of neonatal weight with maternal serum levels of pregnancy-associated plasma protein-A during the first trimester of pregnancy: a retrospective study.

Author(s): Giudice, Ivana, Benintende, Gianfranco, Di Nicolò, Anna Maria, Mangiameli, Daniela, Carrara, Grazia, Randazzo, Claudia, Sapuppo, Irene Maria, Gulisano, Antonio

Abstract: Evaluate the relationship between neonatal weight and pregnancy-associated plasma protein-A. Retrospective study on 2564 singleton pregnancies with healthy term neonates in three groups of women with different values of pregnancy-associated plasma protein-A who underwent the combined test during the first trimester. Non-parametric test and correlation analysis for statistical elaboration were carried out. There exists a correlation between the serum levels of pregnancy-associated plasma protein-A in the first trimester of pregnancy and neonatal weight. Values of pregnancy-associated plasma protein-A lower than the 25th percentile are associated with neonatal weight in a significant way. There was no significant association between pregnancy-associated plasma protein-A values above 1.50 MoM and neonatal weight. This study confirms the positive correlation between circulating concentrations of pregnancy-associated plasma protein-A and fetal growth. Low neonatal weight and factors that can cause this could be determined from the first trimester by measuring the concentrations of pregnancy-associated plasma protein-A in maternal serum. Even if the association between the levels of pregnancy-associated plasma protein-A and a low neonatal weight has been demonstrated, however, we have to say that the sensitivity of a such screening method for the prediction of low birth weight and perinatal complications seems to be rather low. **The variations of pregnancy-associated plasma protein-A during the first trimester cannot be used as a marker of excessive fetal growth.**

Title: Maternal serum PAPP-A as an early marker of obstetric complications?

Author(s): Quattrocchi T., Baviera G., Pochiero T., Basile F., Rizzo L., Santamaria A., Corrado F., D'Anna R.

Abstract: Objective: The aim of this study was to investigate whether low first-trimester PAPP-A levels are associated with an adverse pregnancy outcome. Materials and Methods: A retrospective case-control study was carried out using a Down's syndrome assays database over a 6-year period, between the 8th and 11th week of pregnancy. There were 164 women with PAPP-A multiples of median (MoM) levels <0.3 and 1,640 women with PAPP-A MoM levels >0.3 who served as a control group. Outcome measures were the prevalence of miscarriages, gestational hypertension,

preeclampsia, pre-term delivery, gestational diabetes and intrauterine growth retardation in both groups. Results: The two groups significantly differed only for miscarriages: 29 (17.7%) vs. 159 (9.7%), p = 0.04, OR 1.7; gestational hypertension: 15 (9.1%) vs. 74 (4.5%), p = 0.02, OR 2.1, and preeclampsia: 9 (5.5%) vs. 29 (1.8%), p = 0.02, OR 2.5. **Discussion: Even if in this study the PAPP-A cutoff considered was lower and was assayed in an earlier period compared with other studies, the detection rate for adverse pregnancy outcomes did not improve**. Copyright © 2014 S. Karger AG, Basel.

Publication Type: Journal: Article

Source: EMBASE

Full Text:
Available from *ProQuest* in [Fetal Diagnosis and Therapy](#)

Title: Pregnancy-associated plasma protein a levels are decreased in obstetric cholestasis.

Citation: Clinical and experimental obstetrics & gynecology, Jan 2015, vol. 42, no. 5, p. 617-618, 0390-6663 (2015)

Author(s): Hançerlioğullari, N, Aktulay, A, Engin-Üstün, Y, Ozkan, M Ş, Oksuzoglu, A, Danişman, N

Abstract: Obstetric cholestasis is a cholestatic disease usually commencing in the third trimester of pregnancy and characterized by pruritus, elevation of liver enzymes, and increase in bile acids. The objective of this study was to compare the first trimester serum indicators of obstetric cholestasis with normal pregnancies. Thirty-five patients diagnosed with obstetric cholestasis in a three-year period with first trimester biochemical assessment available were included in the study. Seventy patients with concordant pregnancy weeks, matched-age normal pregnancies were included as the control group. Pregnancy-associated plasma protein A (PAPP-A) and free beta-human chorionic gonadotropin (beta-hCG) levels were analyzed. No difference was observed between the two groups in terms of age and week of pregnancy. While the mean PAPP-A level was 0.76 ± 0.31 multiples of the medians (MoM) in the obstetric cholestasis group, it was determined to be 1.5 ± 0.84 in the control group (p = 0.0001). Among the two groups, the hCG levels were found to be higher in the obstetric cholestasis group (1.2 ± 0.79 MoM vs. 0.98 ± 0.53, p = 0.041**). In this study, the first trimester PAPP-A levels in the obstetric cholestasis cases were found to be significantly lower than the control group. Low PAPP-A levels should be a warning for obstetric cholestasis.**

Source: Medline

Title: Abnormal blood biomarkers in early pregnancy are associated with preeclampsia: a meta-analysis.

Citation: European journal of obstetrics, gynecology, and reproductive biology, Nov 2014, vol. 182, p. 194-201, 1872-7654 (November 2014)

Author(s): Allen, Rebecca E, Rogozinska, Ewelina, Cleverly, Kirsty, Aquilina, Joseph, Thangaratinam, S

Abstract: Our aim was to evaluate the strength of association between abnormal levels of first trimester maternal blood biomarkers and the risk of preeclampsia. We searched MEDLINE, EMBASE and Cochrane databases from inception until April 2013. Studies that assessed the association

between any abnormal maternal blood biomarker in the first trimester and preeclampsia were included. Two independent reviewers selected studies, extracted data and assessed the quality. Results were summarized as pooled odds ratios with 95% confidence intervals. From 1071 citations, we identified 30 studies (65,538 women) for inclusion. Twenty four studies assessed preeclampsia of any onset, 10 studied early onset preeclampsia and seven evaluated late onset preeclampsia (after 34 weeks of gestation). The biomarkers PAPP-A (OR 2.1, 95% CI 1.6, 2.6), PP13 (OR 4.4, 95% CI 2.9, 6.8), sFlt-1 (OR 1.3, 95% CI 2.9, 6.8), pentraxin (OR 5.3, 95% CI 1.9, 15.0) and inhibin-A (OR 3.6, 95% CI 1.7, 7.6) were significantly associated with any preeclampsia. The odds of early onset preeclampsia were significantly increased when the biomarkers PlGF (OR 3.4, 95% CI 1.6, 7.2), PAPP-A (OR 4.8, 95% CI 2.5, 22.5), PP13 (OR 7.5, 95% CI 2.5, 22.5), soluble endoglin (OR 18.5, 95% CI 8.4, 41.0) and inhibin-A (OR 4.1, 95% CI 1.9, 8.8) were abnormal. Two biomarkers, soluble endoglin (OR 2.1, 95% CI 1.9, 2.4) and inhibin-A (OR 1.9, 95% CI 1.4, 2.8) were significantly associated with late onset preeclampsia. **Abnormal maternal blood biomarkers in early pregnancy are significantly associated with preeclampsia, particularly early onset disease**. Copyright © 2014 Elsevier Ireland Ltd. All rights reserved.

Source: Medline

Title: Low pregnancy-associated plasma protein A level in the first trimester.

Author(s): Huynh, Lise, Kingdom, John, Akhtar, Sabrina

Abstract: To review the recent evidence behind the association of low levels (ie, below the fifth percentile) of pregnancy-associated plasma protein A (PAPP-A) with adverse perinatal outcomes and to integrate new findings with the recommendations made by the Society of Obstetricians and Gynaecologists of Canada in 2008. A review of recently published articles revealed that current evidence is sparse and mixed for the association of low PAPP-A level with small size for gestational age, preterm delivery, hypertensive disorders of pregnancy, and stillbirth. There is limited evidence that suggests an association between low PAPP-A levels and spontaneous pregnancy loss. Recent studies suggest that low PAPP-A levels are associated with abnormal placentation, which might be the root cause of the adverse perinatal outcomes of interest. The evidence behind the association of low PAPP-A levels with adverse perinatal outcomes is both lacking and mixed. However, recent data do suggest an association between low PAPP-A levels and abnormal placentation. **This emerging topic currently lacks strong evidence-based guidelines, yet has potential important implications for perinatal outcomes. Collaboration with obstetric specialists regarding pregnant women who have low PAPP-A levels in the context of normal first-trimester aneuploidy screening results might aid clinical decision making about pregnancy and placental surveillance. While the clinical meaning of a low PAPP-A level detected in the context of normal fetal aneuploidy screening remains under debate, pregnant patients with such results should be counseled that at present no strong evidence exists to justify an ongoing ultrasound surveillance program.** Copyright© the College of Family Physicians of Canada.

Source: Medline

Full Text:
Available from *National Library of Medicine* in Canadian Family Physician
Available from *Highwire Press* in Canadian Family Physician

Title: Preterm delivery in women with low PAPP-A at first trimester screening

Citation: Tehran University Medical Journal, October 2014, vol./is. 72/7(457-462), 1683-1764 (01 Oct 2014)

Author(s): Jafari R.M., Maasomi M.T., Najafian M., Saadati N.

Language: Persian

Abstract: Background: Previous investigations have shown that pregnancy-associated plasma protein-A (PAPP-A) levels are associated with adverse pregnancy outcomes including intrauterine growth restriction (IUGR) fetuses as well as preterm delivery. The aim of this study was to determine the rate of preterm delivery in women with low PAPP-A and at intermediate risk for chromosomal abnormalities in the first trimester screening.Methods: A total of 137 women who underwent Down syndrome screening between 11 to 14 weeks of gestation were studied from September 2011 to September 2013 at Perinatal Care Clinic, Imam Khomeini Hospital, Ahvaz, Iran. From those, 52 patients had low PAPP-A. Inclusion criteria were singleton pregnancies, at 11 to 14 weeks of gestation, at intermediate risk for Down syndrome (risk in 1:101 to 1:1000). The intermediate risk was estimated based on maternal parameters, maternal serum markers (PAPP-A and beta-hcG), and nuchal translucency (NT) using fetal medicine foundation (FMF), UK) software. The power of the study was 90%. The sample size was estimated based on prevalence of preterm delivery in pregnancies with low PAPP-A in the first trimester screening. Patients were followed-up until delivery to observe pregnancy outcomes. We evaluated the variables such as level of PAPP-A, outcomes of delivery, age, beta-hCG, and gestational age.Results: Among 137 normotensive pregnant women at intermediate risk for Down syndrome, 52 cases (38%) had low PAPP-A (<0.4 MoM). Of 52, 14 cases (27%) had pre-term delivery. None of our patients had pregnancy related or non related diabetes, pree-clampsia, or chromosomal anomalies. 45 cases (86%) from 52 patients were equal or less than 35 years, while 7 patients were more than 35 years. Among 52 followed-up patients, 48 patients (92.4%) were at low-intermediate risk (risk in 1:251 to 1:1000), and 4 cases (7.6%) were at high-intermediate risk (risk in 1:101 to 1:250).**Conclusion: We found high frequency of preterm delivery in pregnant women with low PAPP-A level at the first trimester screening. Hence, this group of patients needs special and early preventive management. Furthermore, we suggest that future researches to be conducted with larger sample size and also cervix length measurement to be included**. Copyright © 2014 Tehran University of Medical Sciences (TUMS). All rights reserved.

Publication Type: Journal: Article

Source: EMBASE

Title: Low maternal serum PAPP-A in the first trimester and adverse pregnancy outcome: An experience over one year from a University Hospital

Citation: Archives of Disease in Childhood: Fetal and Neonatal Edition, June 2014, vol./is. 99/(A164-A165), 1359-2998 (June 2014)

Author(s): Sadrudin F., Lacey L., Mukherjee S.

Abstract: Introduction Maternal serum pregnancy associated plasma protein A (PAPP-A) is derived from the placenta and is a component of combined screening. When combined with maternal age, fetal nuchal translucency and maternal serum free beta-hCG it has a detection rate of 85-90% for trisomy 21 (1). PAPP-A levels are influenced by other factors including ethnicity, smoking status and mode of conception (e.g. IVF). Previous studies have correlated low PAPP-A with adverse pregnancy outcomes including pre-eclampsia, pregnancy induced hypertension, small for gestational neonates and late pregnancy losses (1,2,3). Aims We identified cases of low PAPP-A at our university hospital to review pregnancy outcomes. Methods We conducted a retrospective study of the case notes of 64 women with a PAPP-A level less than 1.0 MoMs who had high risk combined screening results. Results Twenty-six women had a PAPP-A of <0.5 MoMs and thirty-eight women had a PAPP-A of 0.5-<1.0 MoMs. Table 1 summarises our findings. (Table presented) **Conclusion Low PAPP-A levels were associated with an increase in adverse pregnancy outcomes. 14% of the patients in our study had small for gestational age babies. As expected the chromosomal anomaly rate in our group was much higher than the background rate**.

Full Text:
Available from *Highwire Press* in [Fetal and Neonatal](#)

Title: Variation of Papp-A level in the first trimester of pregnancy and its clinical outcome

Author(s): Patil M., Panchanadikar T.M., Wagh G.

Abstract: Introduction: Abnormalities in maternal serum marker levels and fetal measurements obtained during the first trimester screening can be a marker not only for certain chromosomal disorders and anomalies in the fetus but also for specific pregnancy complications. In particular, low maternal serum pregnancy-associated plasma protein-A (PAPP-A), at 11-13 weeks of gestation, is associated with stillbirth, infant death, intrauterine growth restriction, preterm birth, and pre-eclampsia in chromosomally normal fetuses, while a raised nuchal translucency is associated with specific structural abnormalities and genetic syndromes. We have studied the serum Papp-A level in 560 pregnant patients (11-13 weeks gestation) registered at Bharati Hospital and Research Centre, Pune. All patients undergoing testing were followed till the delivery and their neonatal outcome was also taken into consideration. Aims and Objectives: Our aim is to study the pregnancy outcome in relation to the variations of Papp-A level in the first trimester of pregnancy. Materials and Methods: Every patient visiting the antenatal OPD was counseled for testing of First Trimester Screening to assess fetal well-being. Patients who were registered for delivery at our hospital were taken into the trial. Blood samples were taken at 11-13 weeks of pregnancy and sent to the PerkinElmer lab for analysis. Results were expressed in Multiple of Median and patients having MOM value less than 0.5 were carefully observed till the delivery, and a thorough neonatal examination was done by a pediatrician. Observations: 524 patients were included in the trial out of which 452 patients were found to have a normal Papp-A level of >0.5 MOM. All these patients were followed further during

the antenatal period where 18 patients developed preterm labor and few patients developed pregnancy-induced hypertension. The obstetric outcome of patients with a normal Papp-A level was fairly uneventful as compared to others with a low Papp-A level. **Conclusions: Though Papp-A level in the first trimester of pregnancy (11-13 weeks) is an important predictor of future obstetric outcome, it has poor positive predictive value. Patients having a Papp-A level less than 0.5 MOM have a high risk for preterm delivery, fetal growth restriction, and stillbirths along with increased incidence of hypertensive disorders of pregnancy. A low Papp-A level is a useful indicator of risk of preterm delivery and future chance of development of pregnancy-induced hypertension.** © Federation of Obstetric & Gynecological Societies of India 2013.

Publication Type: Journal: Article

Source: EMBASE

Full Text:
Available from *National Library of Medicine* in [Journal of Obstetrics and Gynaecology of India](#)
Available from *Springer Link Journals* in [Journal of Obstetrics and Gynecology of India, The](#)

Title: Low first trimester PAPP-A and predictability of small for gestational age

Citation: BJOG: An International Journal of Obstetrics and Gynaecology, April 2014, vol./is. 121/(39-40), 1470-0328 (April 2014)

Author(s): Shanmugasundaram L., Bhavani

Language: English

Abstract: Introduction Low first trimester PAPP-A values in first trimester is associated with increased risk of small for gestation, pre-eclampsia and preterm delivery. There is no known adverse association for elevated PAPP- A. The aim of this study is to identify the role of low PAPP-A and a cut-off that would detect at least 70% of small for gestational age fetuses among twin and singleton gestation. Methods This is a retrospective case series. A random group of 150 double marker reports where pregnancy outcome details were available. Parturition register reviewed and gestation, birthweight details correlated with first trimester PAPP-A values in MoMs. All PAPP-A samples were processed at the same lab (SRL Diagnostics, Mumbai). All PAPP-A samples were all obtained in the first trimester 11 weeks + 4 days - 13 weeks + 6 days gestation in the study period March 2012-January 2013. 15 samples were excluded, as the women moved out of area for delivery and had follow-up at our institute only until early part of the third trimester. Two further cases were excluded as miscarriage occurred <24 weeks. Results from 133 PAPP-A and birthweight pairs have been analysed for this study. Results Total eligible study group = 133 Total SGA = 17 (<5th% Mediscan, Chennai). Among 17 SGA pregnancies 12 had PAPP-A < 0.7. This includes 9 preterm SGA & 3 term SGA. In total 32/133 had <0.7 PAPP-A. Conclusion PAPP-A levels of <0.7MoM, in this study population, gave a positive predictive value of 0.73 and negative predictive value of 0.93 for SGA**. Hence, as reported in current literature there is role for PAPP-A in risk prediction for small for gestational age fetus. In our study population a cut off of 0.7 MoM helped identify most of the at-risk women.**

Publication Type: Journal: Conference Abstract

Source: EMBASE

Title: Low first trimester PAPP-A does not predict adverse pregnancy outcome in high risk women

Author(s): Florio K., Peng Y., Catov J., Parks W.T., Parviainen K.

Language: English

Abstract: INTRODUCTION: Low maternal serum concentrations of pregnancyassociated plasma protein A (PAPPA) in the first trimester has been attributed to suboptimal placentation and associated with higher incidence of adverse pregnancy outcomes, including preeclampsia and fetal growth restriction. Women with pre-existing medical co-morbidities are at higher risk for these complications and more intensive surveillance is typically recommended. METHODS: We conducted a retrospective cohort study of women with singleton pregnancies and pre-existing medical co-morbidities (pregestational diabetes, renal disease, collagen vascular disease or chronic hypertension) who underwent first trimester screening and delivered at Magee-Womens Hospital 2006-2012. Adverse pregnancy outcome was defined as a composite of hypertensive disorders of pregnancy (gestational hypertension, preeclampsia, HELLP or eclampsia), intrauterine growth restriction (<10% by birthweight), intrauterine fetal death or placental abruption. Low PAPP-A was defined as below 10th% (<0.57 MOM). The chi^2 and Fisher's Exact tests were utilized for statistical analysis. RESULTS: Of 479 women meeting inclusion criteria, 18% of the women had low PAPP-A on first trimester screen. 26% of these women went on to experience an adverse composite outcome as compared to 16% of women with normal PAPP-A (p=.395) . Maternal age, parity, race, BMI, and smoking status did not differ between the groups. Additional analysis utilizing a lower threshold PAPP-A of <5% did not improve discrimination. The category of maternal co-morbidity did not impact the results. **CONCLUSIONS: Low first trimester PAPP-A does not reliably identify women with medical co-morbidities at risk for adverse pregnancy outcome. The mechanisms for hypertensive disorders of pregnancy and fetal growth restriction are potentially different.**

Publication Type: Journal: Conference Abstract

Source: EMBASE

Title: First trimester pregnancy-associated plasma protein a (PAPP-A) and placental size in women with adverse pregnancy outcomes

Author(s): Florio K., Park W.T., Peng Y., Catov J., Parviainen K.

Language: English

Abstract: INTRODUCTION: PAPP-A is a metalloprotease that cleaves insulinbinding protein 4 and thereby regulates the availability of insulin-like growth factor (IGF-1), a mitogenic peptide that facilitates multiple cell functions, including trophoblast invasion and placental growth. In addition to

aneuploidy, low concentrations of PAPPA in the first trimester have been associated with disorders of impaired placentation. We sought to evaluate the relationship between first trimester PAPP-A, placental size at delivery and select adverse pregnancy outcomes. METHODS: We conducted a retrospective cohort study of women with singleton pregnancies who underwent first trimester screening, delivered at Magee-Womens Hospital and had placenta sent for pathologic evaluation 2006-2012. Women with pregestational diabetes, renal disease, collagen vascular disease or chronic hypertension were excluded. Adverse pregnancy outcome was defined as a composite of hypertensive disorders of pregnancy (gestational hypertension, preeclampsia, HELLP or eclampsia), intrauterine growth restriction (<10% by birthweight), intrauterine fetal death or placental abruption. Low PAPP-A was defined as below 10th% (<0.57 MOM). Placental size was designated small if placental weight was < 10th percentile, adjusted for gestational age at delivery. The chi^2 and Fisher's Exact tests were utilized for statistical analysis. RESULTS: Of 2928 women meeting inclusion criteria, 328 (14%) of these women had low PAPP-A on first trimester screen. 124 (38%) of these women met criteria for the composite outcome; 51 (34%) if small placental size and 69 (63%) if normal size (p<.001). In subgroup analysis, small placental size was associated with hypertensive disorders (p<.001) and IUGR (p<.001). Abruption was not impacted by placental size; there was only 1 fetal demise in the cohort. Maternal age, parity and smoking status did not differ between the groups, but race (p=.002) differed significantly. **CONCLUSIONS: Women with low PAPP-A and normal placental size at delivery had lower incidence of adverse outcome compared to women with small placental size. This finding could be explained by recovery from transient first trimester placental dysfunction.**

Publication Type: Journal: Conference Abstract

Source: EMBASE

Title: Association between first-trimester maternal serum pregnancy-associated plasma protein-A and obstetric complications.

Citation: Prenatal diagnosis, Sep 2013, vol. 33, no. 9, p. 839-847, 1097-0223 (September 2013)

Author(s): D'Antonio, Francesco, Rijo, Claudia, Thilaganathan, Basky, Akolekar, Ranjit, Khalil, Asma, Papageourgiou, Aris, Bhide, Amar

Abstract: This study aimed to investigate the relationship between maternal serum pregnancy-associated plasma protein-A (PAPP-A) in the first trimester of pregnancy and the development of preeclampsia (PE), early PE, small-for-gestational age (SGA) fetus and preterm delivery (PD). This is a retrospective study of 12,355 pregnant women that delivered between 2008 and 2011. We define the first, third and fifth percentiles of maternal serum PAPP-A multiples of the median (MoM). The primary outcome measures were the occurrence of PE, early PE (PE requiring delivery before 34 weeks), SGA fetus (birth weight < 5th centile) and PD. The Mann-Whitney U-test and chi-squared test were used to analyze continuous and dichotomous variables, respectively. Maternal serum PAPP-A was significantly lower in women with PE, early PE, SGA fetus and PD (0.91, 0.74, 0.80 and 0.84 MoM, respectively) than in the study population (0.99 MoM) (p < 0.05). The lower the MoM percentile of PAPP-A, the higher are the odds ratio (OR) to develop PE, early PE, SGA fetus and PD. Maternal serum PAPP-A levels are lower in women who develop preeclampsia, those with SGA fetus and those who deliver preterm. However, on its own, maternal serum PAPP-A performs poorly (OR for PE between 1.76 and 2.41 with the lower percentile of PAPP-A) as a screening test for these conditions. © 2013 John Wiley & Sons, Ltd.

Title: First trimester maternal serum pregnancy-associated plasma protein-A is a predictive factor for early preterm delivery in normotensive pregnancies.

Citation: Gynecological endocrinology : the official journal of the International Society of Gynecological Endocrinology, Jun 2013, vol. 29, no. 6, p. 592-595, 1473-0766 (June 2013)

Author(s): Dane, Banu, Dane, Cem, Batmaz, Gonca, Ates, Seda, Dansuk, Ramazan

Abstract: In this study, we investigated whether the concentrations of pregnancy-associated plasma protein-A (PAPP-A) or free β-hCG (fβhCG) in the first trimester can identify women at increased risk of subsequent preterm delivery in the absence of hypertensive disorders. Preterm and early preterm deliveries are defined as those deliveries before completing 37 and 34 weeks, respectively. A total of 868 women were enrolled into this study. According to the level of the markers, the patients were evaluated in three groups: 1 - maternal serum level ≤ 5 th percentile, 2 - between 5th and 95th percentiles, 3 - ≥ 95 th percentile. In the group of patients with a PAPP-A level ≤ 5 th percentile [≤ 0.35 multiples of the median (MoM)], mean gestational age (GA) at delivery, mean birth weight and the number of the cases with early preterm delivery were significantly lower than the others. Mean level of PAPP-A was significantly lower in cases with early preterm than term deliveries (0.58 ± 0.32 versus 1.09 ± 0.69; p = 0.01). Maternal serum level of fβhCG did not show significant difference between these groups (0.84 ± 0.45 versus 1.17 ± 0.77; p = 0.15**). Low levels of maternal serum PAPP-A (≤ 0.35 MoM) (Odds ratio = 7; 95% confidence interval 1.8-27.7; p = 0.0048) significantly predicted early preterm delivery in normotensive pregnancies. Women with low levels of PAPP-A at first trimester have a higher risk of early preterm delivery even in the absence of hypertensive disorders.**

Title: Audit of pregnancy outcomes and complications in euploid pregnancies with a low PAPP-A (0.3 MoM) at first trimester screening

Citation: BJOG: An International Journal of Obstetrics and Gynaecology, June 2013, vol./is. 120/(145), 1470-0328 (June 2013)

Author(s): Alldred S.K., Valjalo B., Bricker L., Alfirevic Z., Agarwal U.

Language: English

Abstract: Objective Low first trimester serum PAPP-A is associated with adverse obstetric outcomes, including intrauterine growth restriction (IUGR), preterm labour, fetal death in utero (FDIU), pre-eclampsia and miscarriage. Presently there is no standard national guidance for the management of chromosomally normal pregnancies with a low first trimester serum PAPP-A. We have audited pregnancy outcomes for women with a low first trimester serum PAPP-A in our trust to gain baseline information with the aim of producing a local guideline. Method Retrospective audit of hospital case

notes and electronic maternity records (Meditech) from 1st January 2012 to 8th November 2012. Results Sixty women with low PAPP-A were identified. Thirty-six women had a documented pregnancy outcome, 24 women have not yet delivered and are therefore excluded from analysis. Four women had a chromosomal abnormality and are therefore excluded (two miscarriages and two terminations). of the remaining 32 women, there were two miscarriages (6%) and two mid-trimester losses (6%) with normal karyotype. Twenty-eight women had livebirths, there were no fetal deaths in utero. The mean birthweight was 3126 g. There were no babies with IUGR (birthweight <5th centile for gestation). There were six preterm deliveries (<37 weeks) (18.75%) but none at <34 weeks. It is of note that there were a number of women with preterm inductions of labour due to diabetes in pregnancy. Four women (12.5%) developed pre-eclampsia, including one eclamptic seizure. No significant neonatal abnormalities or early neonatal deaths were observed in the 28 live births. **Conclusion The adverse obstetric outcomes in our trust are comparable to those noted in a systematic review of pregnancy outcomes associated with a low first trimester serum PAPP-A, with the exceptions that there were no cases of IUGR and FDIU in our patient population. Our preterm labour rate was marginally higher but may be confounded by preterm induction of labour for diabetes in two of our patients. This is a small patient population, and larger numbers are needed for a true reflection of complication rates. These findings warrant the development of a standard protocol in our trust, for monitoring and minimising the risks associated with the pregnancies, which may include aspirin prophylaxis for pre-eclampsia, serial growth scans and timing of induction of labour. A UK survey of current practice is currently in progress.**

Publication Type: Journal: Conference Abstract

Source: EMBASE

Full Text:
Available from *John Wiley and Sons* in [BJOG: An International Journal of Obstetrics and Gynaecology](#)
Available from *John Wiley and Sons* in [BJOG: An International Journal of Obstetrics and Gynaecology](#)

Title: The relationship of low maternal PAPP-A at 11-13+6 weeks of gestation with smallfor-gestational age newborns and stillbirths

Author(s): Antsaklis P., Iliescu D., Theodora M., Papanicolaou T., Daskalakis G., Mesogitis S., Papantoniou N., Antsaklis A.

Language: English

Abstract: OBJECTIVE: To assess whether low PAPP-A (Pregnancy associated plasma protein-A) at 11-13+6 weeks of pregnancy is related to bad obstetrical outcome and more specifically small for gestational age newborns and stillbirths. METHODS: A retrospective study, from 2 university hospitals (Athens University-Greece and Craiova University-Romania), which included all women who attended for the first trimester screening for chromosomal abnormalities (Nuchal Translucency, free-shCG and PAPP-A). The study included all women with singleton pregnancies. In total there were 9533 women, while complete data and pregnancy outcome were available in 4012 women. Low PAPP-A (<0,3 MoM) was found in 215 women, while complete data and pregnancy outcome was available in 103 of these pregnancies. RESULTS: From the 9533 pregnancies we identified 215 (2.2%) with low PAPP-A (0,3 MoM). Complete data and outcome of the pregnancy was available for 103 of these pregnancies. From the 103 pregnancies with low PAPP-A we excluded 11 cases who

underwent termination of pregnancy for abnormal karyotype. From the remaining 92 pregnancies there were 8 cases of small for gestational age and 2 cases of intrauterine fetal death. There were also 3 cases of preterm delivery and 4 cases of late miscarriage (after 16 weeks). **CONCLUSION: Low PAPP-A (< 0,3 MoM) during the first trimester of pregnancy seems to be related with an increased risk of adverse obstetrical outcome and more specifically with small for gestational age fetuses and stillbirth. Pregnancies with low PAPP-A values, even when the risk for chromosomal abnormalities is low should be managed as high-risk pregnancies.**

Publication Type: Journal: Conference Abstract

Source: EMBASE

Title: Low pregnancy associated plasma protein-A in the 1st trimester: Is it a predictor of poor perinatal outcome?

Citation: Journal of Obstetrics and Gynaecology, May 2013, vol./is. 33/4(351-354), 0144-3615;1364-6893 (May 2013)

Author(s): Karim J.N., Sau A.

Language: English

Abstract: The objective of the study was to examine the predictive value of pregnancy associated plasma protein-A (PAPP-A) as a marker of poor pregnancy outcome. Databases at the University Hospital Lewisham, were used retrospectively to identify singleton pregnancies, which underwent 1st trimester combined screening between July 2008 and April 2010 and were found to have PAPP-A levels < 0.4MoM. The perinatal courses of these pregnancies (n = 315) were evaluated for signs of adverse perinatal outcome and compared with a matched control group of pregnancies (n = 330) with normal PAPP-A levels. Results showed that women with low serum PAPP-A were at increased risk of adverse pregnancy outcome compared with the control group (OR 2.4, p = 000.1). They were also more likely to suffer fetal loss (OR 6.2, p = 0.001) in the form of miscarriage (OR 2.7, p = 0.110) and stillbirth (OR 2.4, p = 0.001). **It was concluded that serum PAPP-A is a marker for poor pregnancy outcome and women with low serum PAPP-A levels would benefit from increased monitoring of their pregnancie**s. © 2013 Informa UK, Ltd.

Publication Type: Journal: Article

Source: EMBASE

Full Text:
Available from *Taylor & Francis* in Journal of Obstetrics and Gynaecology

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Title: First trimester PAPP-A MoM values predictive for breech presentation at term of pregnancy.

Citation: Gynecological endocrinology : the official journal of the International Society of Gynecological Endocrinology, May 2013, vol. 29, no. 5, p. 503-507, 1473-0766 (May 2013)

Author(s): Londero, Ambrogio P, Salvador, Stefania, Fruscalzo, Arrigo, Bertozzi, Serena, Biasioli, Anna, Ceraudo, Maria, Visentin, Silvia, Driul, Lorenza, Marchesoni, Diego

Abstract: Our aim was to state the role of first trimester pregnancy-associated plasma protein A (PAPP-A)-multiple of the median (MoM) value as a predictor for breech presentation at term of pregnancy. In this retrospective study, we present data for 1100 singleton full-term deliveries that took place in a third-level hospital setting in northeast Italy between January 2004 and July 2007. For each case, PAPP-A, free beta-human chorionic gonadotropin and nuchal translucency were measured during prenatal trisomies screening (between 11 weeks and 13 weeks and 6 d). A wide range of predictive factors for breech presentation at term of pregnancy and other confounding elements were considered. Of the 1100 singleton deliveries at term considered in our study, 40 babies were in breech presentation. Using bivariate analysis and multivariate logistic regression, a lower PAPP-A MoM than 0.63 (first quartile of our distribution) in the first trimester (OR 2.41, CI.95 1.25-4.67), and placental index at term higher than the median value (OR 2.04, CI.95 1.00-4.17) were proven to be associated with breech presentation at term. **A low PAPP-A during the first trimester was a predictive factor for breech presentation at term of pregnancy. Acknowledging and acting on this predictor could enable improved management of breech foetuses in the future.**

Source: Medline

Title: Low maternal serum PAPP-A in the first trimester and pregnancy outcome: An experience over 3 years

Author(s): Weaver A., Nanda S., Rozette C., Kyle P., Sankaran S.

Language: English

Abstract: Introduction Maternal serum PAPP-A (pregnancy associated plasma protein-A) is a part of combined screening. Previous studies have shown correlation between low PAPP-A and adverse pregnancy outcome. Objective The aim of this study is to establish the positive predictive value of low-PAPP-A in prediction of adverse pregnancy outcomes - pre-eclampsia (PET), pregnancy induced hypertension (PIH), delivery of small for gestational age neonates (SGA) and late pregnancy losses. Materials and Methods 16690 women underwent combined screening from 1/8/2008 to 1/8/2011. 326 women with low PAPP-A (=<0.3 MoM) were identified (1.95%). The median PAPP-A of the screening population was 1.074 MoM. Within this group of pregnancy with low PAPP-A, maternal serum PAPP-A was compared between the subgroups of adverse pregnancy outcome and normal-outcome. (Table Presented) **Conclusion In our screening population, median PAPP-A MoM was higher compared to some previous studies. Maternal serum PAPP-A in pregnancies with adverse outcome was significantly lower than those that resulted in a normal outcome. Compared to the pregnancies with low-PAPP-A but normal outcome, median PAPP-A MoM was significantly lower in pregnancies ending in delivery of small-for-gestational age neonate (customised BW < 10th-centile), and showed a trend towards a decrease in those ending in late-pregnancy losses (>24 weeks).**

Publication Type: Journal: Conference Abstract

Source: EMBASE

Full Text:
Available from *Highwire Press* in [Fetal and Neonatal](#)

Title: First trimester PAPP-A levels correlate with sFlt-1 levels longitudinally in pregnant women with and without preeclampsia.

Citation: BMC pregnancy and childbirth, Jan 2013, vol. 13, p. 85., 1471-2393 (2013)

Author(s): Saxena, Aditi R, Seely, Ellen W, Rich-Edwards, Janet W, Wilkins-Haug, Louise E, Karumanchi, S Ananth, McElrath, Thomas F

Abstract: First trimester Pregnancy Associated Plasma Protein A (PAPP-A) levels, routinely measured for aneuploidy screening, may predict development of preeclampsia. This study tests the hypothesis that first trimester PAPP-A levels correlate with soluble fms-like tyrosine kinase-1 (sFlt-1) levels, an angiogenic marker associated with preeclampsia, throughout pregnancy. sFlt-1 levels were measured longitudinally in 427 women with singleton pregnancies in all three trimesters. First trimester PAPP-A and PAPP-A Multiples of Median (MOM) were measured. Student's T and Wilcoxon tests compared preeclamptic and normal pregnancies. A linear mixed model assessed the relationship between log PAPP-A and serial log sFlt-1 levels. PAPP-A and PAPP-A MOM levels were significantly lower in preeclamptic (n = 19), versus normal pregnancies (p = 0.02). Although mean third trimester sFlt-1 levels were significantly higher in preeclampsia (p = 0.002), first trimester sFlt-1 levels were lower in women who developed preeclampsia, compared with normal pregnancies (p = 0.03). PAPP-A levels correlated significantly with serial sFlt-1 levels. Importantly, low first trimester PAPP-A MOM predicted decreased odds of normal pregnancy (OR 0.2, p = 0.002**). Low first trimester PAPP-A levels suggests increased future risk of preeclampsia and correlate with serial sFlt-1 levels throughout pregnancy. Furthermore, low first trimester PAPP-A status significantly predicted decreased odds of normal pregnancy**.

Source: Medline

Full Text:
Available from *BioMed Central* in BMC Pregnancy and Childbirth
Available from *National Library of Medicine* in BMC Pregnancy and Childbirth
Available from *ProQuest* in BMC Pregnancy and Childbirth
Available from *National Library of Medicine* in BMC Pregnancy and Childbirth

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Title: Maternal level of pregnancy-associated plasma protein A as a predictor of pregnancy failure in threatened abortion.

Citation: The Malaysian journal of pathology, Dec 2012, vol. 34, no. 2, p. 145-151, 0126-8635 (December 2012)

Author(s): Hanita, O, Roslina, O, Azlin, M I Nor

Abstract: Threatened miscarriage is a common complication of pregnancy. Despite initial viability confirmation by ultrasound scan, some of these patients had further spontaneous abortion. A highly sensitive and specific biomarker would be useful to determine the outcome of pregnancy and to prevent emotional impact to these women. A prospective 14-month cohort study was conducted in the Obstetrics and Gynaecology Department of Universiti Kebangsaan Malaysia Medical Centre to determine whether low serum levels of pregnancy-associated plasma protein A (PAPP-A) measured in early pregnancy can predict the outcome of threatened abortion. 42 pregnant women between 6 to 22 weeks of gestation with threatened abortion and 40 controls were enrolled. Serum samples were collected at presentation and PAPP-A was assayed by electrochemiluminescent immunoassay

technique. Pregnancies were followed-up until 22 weeks of gestations and the outcome documented. Nine patients (11%) developed spontaneous abortion and 73 patients (89%) had successful pregnancy. The median PAPP-A level was significantly lower in patients with spontaneous abortion compared to those who had successful pregnancies in the threatened abortion group: 0.78 MoM (0.41-1.00 MoM) vs 1.00 MoM (1.00-2.0 MoM) respectively ($p < 0.05$). The best sensitivity of 44% and specificity of 93% were obtained at the cut of value of 0.66 MoM (95% CI, 0.561-0.773). **In conclusion, low PAPP-A value in threatened abortion women is associated with pregnancy failure, although the use of PAPP-A as a one-time single marker has limited value**.

Source: Medline

Full Text:
Available from *ProQuest* in Malaysian Journal of Pathology, The
Available from *Free Access Content* in Malaysian Journal of Pathology

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Title: First trimester pregnancy associated plasma protein a as a marker for preterm labor in patients with rupture of membranes

Author(s): Fatela-Cantillo D., Gomez-Arias J., Munoz-Carmona V., Fernandez-Suarez A., Macias-Blanco C., Diaz-Iglesias J.

Language: English

Abstract: Background: Preterm labor is one of the most common reasons for hospitalization of pregnant women, but identifying women with preterm contractions who will deliver preterm is an inexact process. Moreover, infants born between 36 and 38 weeks continue to experience increased morbidity and mortality and thus constitute a population at risk. Induction of labor or cesarean delivery in the absence of labor should be scheduled only after 39-0/7 weeks' gestation because maternal and infant morbidity and mortality are significantly lower after 39-0/7 weeks'. The purpose of this study was to determine whether pregnancy associated plasma protein A (PAPP-A) can be used to identify pregnancies at risk for preterm labor before 39-0/7 weeks' among patients with rupture of membranes. Methods: The study population that was available for this analysis included 90 singleton pregnancies whom PAPP-A level, free beta subunit human chorionic gonadotropin (fBhCG), nuchal translucency, and pregnancy outcome data were available from combined first trimester screening over a 1-year period. Blood samples were analyzed for PAPP-A level (mUI/mL) with an immunoassay system (Immulite 2000, Siemens, Germany). We excluded pregnancies with aneuploidy, major anomalies, fetal infection, or second trimester premature rupture of membranes (PPROM). Rupture of membranes (ROM) was defined as the rupture of the membranes before the onset of labor between 37 and 38 weeks of pregnancy. We chose the fifth and twenty fifth PAPP-A percentiles as categorical marker for low PAPP-A which correspond to approximately 0.27 and 0.52 MoM, respectively. First, a series of statistical tests were performed to assess relationships with each marker and, in addition, with ROM. Fisher's exact test and chi-squared test were used for categorical variables and Mann-Whitney test was used for continuous variables. Results: The mean maternal age at time of blood sampling was 30.9 +/- 4.95 years, with a range of 17 to 42 years. All of women were white. Fourteen pregnancies in our study presented ROM between 37 and 38 weeks of pregnancy and thirty after 39-0/7 weeks'. There were no significant relationships between PAPP-A levels and ROM (p=0.790). PAPP-A levels in pregnancies with rupture of membranes before 39-0/7 weeks were lower than pregnancies with rupture of membranes after 39-0/7 weeks, nevertheless

this relationship was not significant (p= 0.186). **Conclusions: Low pregnancy associated plasma protein A levels in the first trimester were not associated with rupture of membranes between 37 and 38 weeks of pregnancy in our study. However, we found a trend towards an increased rate of premature rupture membranes in pregnancies with PAPP-A below the twenty fifth percentile.**

Publication Type: Journal: Conference Abstract

Source: EMBASE

Full Text:
Available from *Free Access Content* in Clinical Chemistry
Available from *ProQuest* in Clinical Chemistry

Title: Efficiency of first-trimester growth restriction and low pregnancy-associated plasma protein-A in predicting small for gestational age at delivery.

Citation: Prenatal diagnosis, Aug 2012, vol. 32, no. 8, p. 724-729, 1097-0223 (August 2012)

Author(s): Carbone, Jeanine F, Tuuli, Methodius G, Bradshaw, Rachael, Liebsch, Julie, Odibo, Anthony O

Abstract: To evaluate the efficiency of first-trimester fetal growth restriction (FGR), low pregnancy-associated plasma protein A (PAPP-A), and their combination for predicting small for gestational age (SGA) at delivery. Retrospective cohort study of women undergoing first-trimester aneuploidy screening. Fetal crown-rump lengths (CRLs) were at 10 to 14 weeks' gestation and converted to gestational age adjusted Z-scores. Low PAPP-A was defined as levels<5th percentile for GA. Receiver-operating characteristic curves were used to assess screening efficiencies. Among 3269 pregnancies meeting the inclusion criteria 185 (5.7%) infants were SGA. CRL Z-score< -1.0 standard deviation was identified as the optimal definition of early FGR. Using either CRL Z-score< -1.0 standard deviation or PAPP-A<5th percentile had the highest sensitivity (33%) with a specificity of 82.1% when screening for SGA. Using a combination resulted in an increased association (adjusted odds ratio 4.23[confidence interval 1.37-13.03]) at the expense of significantly reduced sensitivity (3.13%). **First-trimester FGR and PAPP-A<5th percentile are associated with delivery of an SGA infant. Neither of these parameters or the combination of the two are sufficient powerful predictors of SGA to be clinically useful screening tools.** © 2012 John Wiley & Sons, Ltd.

Source: Medline

Full Text:
Available from *John Wiley and Sons* in Prenatal Diagnosis
Available from *John Wiley and Sons* in Prenatal Diagnosis

Title: Decreased PAPP-A is associated with preeclampsia, premature delivery and small for gestational age infants but not with placental abruption

Citation: European Journal of Obstetrics Gynecology and Reproductive Biology, July 2011, vol./is. 157/1(48-52), 0301-2115;1872-7654 (July 2011)

Author(s): Ranta J.K., Raatikainen K., Romppanen J., Pulkki K., Heinonen S.

Abstract: Objective: To investigate links between first trimester Down's syndrome screening markers and adverse pregnancy outcomes; preeclampsia (PE), small for gestational age (SGA), preterm delivery (PD) and placental abruption (PA) in spontaneous, chromosomally normal pregnancies. Study design: Cohort study in a university hospital. Data during pregnancy were routinely collected from a total study population of 2844 pregnant women between 2005 and 2007. Four study groups were pregnancies with PE (N = 175), PA (N = 17), PD (N = 213) and SGA (N = 275) plus a reference group with normal outcome (N = 2164). The median MOMs of maternal serum concentrations of pregnancy associated plasma protein A (PAPP-A) and free beta human chorionic gonadotropin (fbeta-hCG) were compared using two-tailed pooled t-tests, continuous variables were compared using Student's two-way t-tests, and Chi-square tests were used to analyse dichotomous variables. Fisher's exact test was used when there were fewer than five units in any of the classes. Results: The median MOM of maternal serum PAPP-A was significantly lower in women with PE, PD and SGA (0.79, 0.80 and 0.79 MOM, respectively) than in the reference group (0.99 MOM) (p < 0.01). The median MOM of maternal serum fbeta-hCG was also significantly lower in the SGA group (0.90 MOM) and in the PE and PD groups (0.86 and 0.92 MOM) than in the reference group (0.99 MOM, p = 0.02). There was no detectable difference between the biochemical markers in the PA group and the reference group. No statistical difference was found between NT MOMs in the reference and study groups. **Conclusion: The concentrations of first trimester screening (FTS) serum markers were lower in pregnancies where PE, PD and SGA occurred. In the latter two cases, there was an inverse association between incidence and PAPP-A and fbeta-hCG values. However, the development of PA during pregnancy could not be predicted from biochemical marker concentrations. The mechanism behind PA is probably less dependent on the placenta than on the decidua**. © 2011 Elsevier Ireland Ltd.

Title: First trimester pregnancy-associated plasma protein-A in pregnancies complicated by subsequent gestational diabetes.

Author(s): Beneventi, Fausta, Simonetta, Margherita, Lovati, Elisabetta, Albonico, Giulia, Tinelli, Carmine, Locatelli, Elena, Spinillo, Arsenio

Abstract: To compare routine first trimester biochemical and ultrasound markers in pregnancies complicated by gestational diabetes with those of a control group. First trimester data including the screening test for Down syndrome were retrieved from a computer data base. Clinical data were recorded at delivery. A multivariate quantile regression model was used to analyze the association between first trimester data and subsequent clinical outcomes in a case-control study design. In the group of women who developed second trimester gestational diabetes, both first trimester median (1494 vs 2225 mU/L, P < 0.001) and adjusted multiple of median pregnancy-associated plasma protein-A (PAPP-A) concentrations (1.2 vs 0.7, P < 0.001) were significantly lower than in the control group. Differences between observed and expected crown-to-rump length expressed in mm was lower in women destined to develop gestational diabetes than in the control group (0.2 vs 1.4 mm, P < 0.005). In multivariate models, first trimester maternal PAPP-A concentrations correlated

independently and inversely to pregestational body mass index (BMI, P = 0.004), subsequent gestational diabetes (P < 0.001) and pregnancy complications (P = 0.036). **First trimester PAPP-A concentrations were lower among pregnant women with subsequent gestational diabetes than in the control group**. Copyright © 2011 John Wiley & Sons, Ltd.

Source: Medline

Full Text:
Available from *John Wiley and Sons* in [Prenatal Diagnosis](#)
Available from *John Wiley and Sons* in [Prenatal Diagnosis](#)

Title: PAPP-A and free β-hCG measured prior to 10 weeks is associated with preterm delivery and small-for-gestational-age infants.

Citation: Prenatal diagnosis, Feb 2011, vol. 31, no. 2, p. 171-175, 1097-0223 (February 2011)

Author(s): Kirkegaard, Ida, Henriksen, Tine Brink, Tørring, Niels, Uldbjerg, Niels

Abstract: To evaluate whether measuring pregnancy-associated plasma protein A (PAPP-A) and free β-human chorionic gonadotrophin (β-hCG) before 10 weeks of gestation affect the association between these biomarkers and adverse pregnancy outcomes. Singleton pregnant women (9450) who attended the prenatal screening program, Aarhus University Hospital, Denmark, were included. Maternal serum levels of PAPP-A and free β-hCG were measured between week 8 and 13 weeks and 6 days. The risk of preterm delivery (<37 weeks) and small for gestational age (SGA) (<the fifth centile) was evaluated in relation to PAPP-A and free β-hCG < 0.4 multiples of the median, stratified according to early (<10 weeks) or late (≥ 10 weeks) biochemical testing. A stronger association between low PAPP-A and SGA was found with early serum sampling compared to late, but the difference was not statistically significant [odds ratio (OR) 3.2 vs 1.8; P value = 0.11]. This difference did not apply to PAPP-A and preterm delivery. For free β-hCG, a stronger association with preterm delivery was found with early testing (OR 1.9 vs 1.1; P value = 0.31), whereas this difference was not found regarding SGA. Biochemical testing before 10 weeks does not affect the association between low PAPP-A and free β-hCG and adverse pregnancy outcomes. Whether the association is actually stronger with early testing, requires further study. Copyright © 2011 John Wiley & Sons, Ltd.

Source: Medline

Full Text:
Available from *John Wiley and Sons* in [Prenatal Diagnosis](#)
Available from *John Wiley and Sons* in [Prenatal Diagnosis](#)

Title: First-trimester umbilical vein blood flow in pregnancies with low serum pregnancy-associated plasma protein-A levels: an early predictor of fetal growth restriction.

Citation: Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology, Oct 2010, vol. 36, no. 4, p. 433-438, 1469-0705 (October 2010)

Author(s): Rizzo, G, Capponi, A, Pietrolucci, M E, Capece, A, Arduini, D

Abstract: To investigate umbilical vein blood flow (UVBF) during the first trimester in pregnancies with low serum pregnancy-associated plasma protein-A (PAPP-A) levels and to relate umbilical vein

(UV) diameter, time-averaged maximum velocity (TAMXV) and UVBF values to the subsequent development of fetal intrauterine growth restriction (IUGR). UVBF assessment was performed at 11 + 0 to 13 + 6 weeks' gestation in 102 singleton pregnancies with PAPP-A concentrations of < 0.3 multiples of the median. UV diameter, UV-TAMXV and UVBF were calculated and analyzed in relation to pregnancy outcome. Pregnancy outcomes were: 51 pregnancies with birth weight ≥ 10(th) centile (Group A), 30 pregnancies with birth weight < 10(th) centile with normal Doppler in the umbilical artery throughout gestation (Group B) and 21 pregnancies with birth weight < 10(th) centile and abnormal umbilical artery Doppler later in gestation (Group C). No differences were found in PAPP-A levels between groups. Group C fetuses exhibited significantly lower values of UV-TAMXV (z-score - 1.99 SDs, t = 8.527, P ≤ 0.0001) and UVBF (z-score - 0.97 SDs, t = 7.420, P ≤ 0.0001) **in comparison with normal reference ranges, while no differences were found in Groups A or B. Decreased UV-TAMXV and UVBF at 11 + 0 to 13 + 6 weeks' gestation identify fetuses at risk of developing IUGR among pregnancies with low levels of PAPP-A.** Copyright © 2010 ISUOG. Published by John Wiley & Sons, Ltd.

Source: Medline

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Available from *John Wiley and Sons* in [Ultrasound in Obstetrics and Gynecology](#)
Available from *Wiley-Blackwell Free Backfiles NHS* in [Ultrasound in Obstetrics and Gynecology](#)
Available from *John Wiley and Sons* in [Ultrasound in Obstetrics and Gynecology](#)

Title: Low maternal PAPP-A is associated with small-for-gestational age newborns and stillbirths.

Citation: Acta obstetricia et gynecologica Scandinavica, Sep 2010, vol. 89, no. 9, p. 1226-1228, 1600-0412 (September 2010)

Author(s): Marttala, Jaana, Peuhkurinen, Sini, Laitinen, Paivi, Gissler, Mika, Nieminen, Pentti, Ryynanen, Markku

Abstract: We investigated the association of first trimester low maternal serum pregnancy-associated plasma protein-A (PAPP-A) levels with small-for-gestational age (SGA) newborns and stillbirths (SBs) in a retrospective national population-based register study. The study group comprised 921 women with the lowest 5% PAPP-A levels (< or =0.3 MoM) and the control group comprising 18,615 women with PAPP-A levels >0.3 MoM. In the study group there were 35 (3.8%) and in the control group 213 SGA newborns (1.1%), respectively (OR, 3.41; 95% CI, 2.37-4.91). There were 9 (1.0%) and 51 (0.3%) cases of SBs in the study and control groups, respectively (p < 0.002; OR, 3.59; 95% CI, 1.76-7.32). Low PAPP-A is a risk factor for SGA and SB.

Source: Medline

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Title: Low PAPP-A in the first trimester is associated with reduced fetal growth rate prior to gestational week 20.

Citation: Prenatal diagnosis, Jun 2010, vol. 30, no. 6, p. 503-508, 1097-0223 (June 2010)

Author(s): Salvig, J D, Kirkegaard, I, Winding, T N, Henriksen, T B, Tørring, N, Uldbjerg, N

Abstract: To evaluate the association between maternal pregnancy-associated plasma protein-A (PAPP-A) and fetal growth from the first to the second trimester. A prospective cohort study including 8347 pregnant women attending prenatal care at Aarhus University Hospital were conducted. PAPP-A was measured during 8 to 14 gestational weeks. Fetal growth between the two scans in the first and second trimesters was estimated by (GA(20)- GA(12))/Days(calendar), where GA(12) reflects gestational age in days calculated from crown-rump length at a 12-week scan, GA(20) reflects gestational age in days calculated from biparietal diameter at a 20-week scan, and Days(calendar) reflects the number of calendar days between the two scans. Fetal growth rate from the first to the second trimester was correlated with PAPP-A, with a regression coefficient of 0.009 (95% CI, 0.007-0.012, P < 0.001). **PAPP-A below 0.30 MoM was associated with a fetal growth rate below the tenth centile, with an adjusted OR of 2.05 (95% CI, 1.24-3.38). Low levels of PAPP-A are associated not only with low birth weight at term but also with slower fetal growth prior to 20 weeks of gestation.**

Source: Medline

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Title: Association of first-trimester low PAPP-A levels with preterm birth.

Author(s): Goetzinger, Katherine R, Cahill, Alison G, Macones, George A, Odibo, Anthony O

Abstract: To determine the association of, and predictive ability of, pregnancy-associated plasma protein A (PAPP-A), free beta-human chorionic gonadotrophin (beta-hCG), and nuchal translucency (NT) with preterm birth (PTB). A 5-year retrospective cohort study of women who underwent first-trimester combined screening was performed. Maternal medical, antepartum, and pregnancy outcome data were obtained. PAPP-A and beta-hCG were converted to multiples of the median (MoM), and primary exposure was defined as < or =10th percentile MoM for PAPP-A. Secondary exposures were defined as > or = 90th percentile MoM for beta-hCG and NT values of > or = 20 and 25 mm. The primary outcome was PTB before 35 weeks and the secondary outcome was PTB before 32 weeks. Univariate, bivariate, multivariate, and receiver-operator analyses were used. Of the 2231 patients meeting inclusion criteria with complete outcome data available, 222 had a PAPP-A level < or =10th percentile MoM. Abnormally low PAPP-A was associated with an increased risk for PTB < 35 weeks [adjusted odds ratio (aOR) 2.0, 1.0-3.8] and < 32 weeks (aOR 2.7, 1.1-6.4), even after adjusting for prior PTB, tobacco exposure, chronic hypertension, and body mass index. PAPP-A < or =10th percentile was not sufficiently predictive of PTB < 35 weeks (area under curve = 0.63, 95% CI 0.53-0.72). Neither abnormally high beta-hCG nor increased NT was associated with an increased risk for PTB. **PAPP-A < or =10th percentile is associated with an increased risk for PTB, but is not sufficiently predictive to be used clinically**. Copyright (c) 2010 John Wiley & Sons, Ltd.

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Title: First trimester pregnancy associated plasma protein-A as a marker for poor pregnancy outcome in patients with early-onset fetal growth restriction.

Author(s): Fox, Nathan S, Chasen, Stephen T

Abstract: To determine whether pregnancy associated plasma protein-A (PAPP-A) can be used to identify pregnancies at risk for poor perinatal outcomes among patients with second trimester fetal growth restriction (FGR). We analyzed outcomes for singleton pregnancies of patients with evidence of FGR in the second trimester who also had first trimester serum PAPP-A measured for aneuploidy risk assessment. We excluded pregnancies with aneuploidy, major anomalies, fetal infection, or second trimester premature rupture of membranes (PPROM). One hundred and ninety eight pregnancies with second trimester FGR and first trimester serum PAPP-A measurements were identified. PAPP-A below the fifth percentile was associated with an increased rate of third trimester SGA (50% vs 11%, p = 0.012), preterm birth (33.3% vs 8%, p = 0.039), NICU admission (33.3% vs 8%, p = 0.039), intrauterine or neonatal death (20% vs 0%, p = 0.002), smaller median birth weight (2975g vs 3085g, p = 0.026), and earlier median gestational age at delivery (38.14 weeks vs 39.86 weeks, p = 0.004). **PAPP-A values below the 10th percentile and below the 25th percentile were also associated with poor outcomes. PAPP-A appears to be a useful marker for neonatal outcome in patients diagnosed with second trimester FGR.** Copyright (c) 2009 John Wiley & Sons, Ltd.

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Title: Pregnancy outcome in the setting of extremely low first trimester PAPP-A levels.

Author(s): Scott, Fergus, Coates, Anne, McLennan, Andrew

Abstract: Serum pregnancy-associated plasma protein-A (PAPP-A) is part of first trimester Down syndrome screening. Low levels have been associated with adverse outcome as well as chromosomal abnormality. To assess the incidence of adverse outcome when PAPP-A levels are at or below 0.2 multiples of the median (MoM). Data on consecutive patients attending a first trimester screening program were collected. Those with PAPP-A levels < or = 0.2 MoM were divided into three groups: < or = 0.1 MoM; 0.11-0.15 MoM; and 0.16-0.2 MoM. Screening 44 535 patients resulted in 197 with PAPP-A levels < or = 0.2 MoM. The incidence of karyotypic abnormality increased with decreasing PAPP-A levels. In the absence of chromosome abnormality, pregnancy outcomes were defined as 'normal' in at least 30% and 'good' in at least 60%, with both percentages increasing as the PAPP-A level rose. The PAPP-A levels were significantly lower in the group with a poor outcome. The incidence of prematurity was similar in the three groups, but higher than the statewide average, while the incidence of extreme prematurity appeared to be related to reducing PAPP-A levels. The incidence of growth restriction in the three groups was similar, but was still double the incidence in the normal population. **If the PAPP-A level is < or = 0.2 MoM and the karyotype is normal, there is an increased risk of adverse outcome. Even with PAPP-A below 0.1 MoM, a good outcome can be**

expected in 60% of cases. Careful morphological assessment is suggested and later monitoring of fetal growth and well-being.

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Available from *Australian and New Zealand Journal of Obstetrics and Gynaecology* in [Patricia Bowen Library and Knowledge Service West Middlesex university Hospital](#)

Title: Pregnancies conceived using assisted reproductive technologies (ART) have low levels of pregnancy-associated plasma protein-A (PAPP-A) leading to a high rate of false-positive results in first trimester screening for Down syndrome.

Citation: Human reproduction (Oxford, England), Jun 2009, vol. 24, no. 6, p. 1330-1338, 1460-2350 (June 2009)

Author(s): Amor, D J, Xu, J X, Halliday, J L, Francis, I, Healy, D L, Breheny, S, Baker, H W G, Jaques, A M

Abstract: First trimester screening (FTS) for Down syndrome combines measurement of nuchal translucency, free beta-human chorionic gonadotrophin and pregnancy-associated plasma protein-A (PAPP-A). The aim of this study was to undertake a detailed analysis of FTS results in singleton pregnancies conceived using assisted reproductive technologies (ART) and non-ART pregnancies. A record linkage study compared outcomes in 1739 ART-conceived and 50 253 naturally conceived pregnancies. Overall, significantly lower PAPP-A levels were detected in ART pregnancies (0.83 multiples of median, MoM) than in controls (1.00 MoM) (t-test $P < 0.001$). This difference remained after excluding complicated pregnancies. Analysis of factors affecting PAPP-A levels suggested fresh compared with frozen embryo transfers and use of artificial cycles compared with natural cycles for frozen transfers were associated with lower values. The adjusted odds ratio (AdjOR) for receiving a false-positive result was 1.71 (95% CI 1.44-2.04; $P < 0.001$) for ART pregnancies compared with non-ART pregnancies, and this leads to a higher AdjOR (1.24, 95% CI 1.03-1.49; $P = 0.02$) for having a chorionic villous sampling (CVS) or amniocentesis. ART pregnancies have reduced FTS PAPP-A levels leading to an increased likelihood of receiving a false-positive result and having a CVS/amniocentesis. Lower PAPP-A may reflect impairment of early implantation with some forms of ART.

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Available from *Highwire Press* in [Human Reproduction](#)

Title: First-trimester maternal serum pregnancy-associated plasma protein-A and pre-eclampsia.

Author(s): Poon, L C Y, Maiz, N, Valencia, C, Plasencia, W, Nicolaides, K H

Abstract: To examine the relationship between low maternal serum pregnancy-associated plasma protein-A (PAPP-A) and uterine artery pulsatility index (UtA-PI) at 11+0 to 13+6 weeks with subsequent development of pre-eclampsia (PE). UtA-PI and serum PAPP-A were measured in women attending for routine care at 11+0 to 13+6 weeks of gestation. In the population, 156 (1.9%) women developed PE, including 32 (0.4%) in whom delivery was before 34 weeks (early PE) and 124 (1.5%) with delivery at 34 weeks or more (late PE); 7895 (98.1%) women had no PE. Regression analysis was used to examine which of the factors amongst maternal characteristics, log PAPP-A multiples of the median (MoM) and log UtA-PI MoM contributed to the prediction of PE. The median PAPP-A MoM was 1.002 (interquartile range (IQR), 0.685-1.411) in the unaffected group, 0.555 (IQR, 0.463-0.922) in early PE and 0.911 (IQR, 0.580-1.247) in late PE. Serum PAPP-A was below the 5th centile in 21.9% of early PE and 6.5% of late PE cases. The PAPP-A-related patient-specific risk for PE was strongly influenced by maternal characteristics. There was a significant association between log UtA-PI MoM and log PAPP-A MoM (P=0.001), and the detection rate of screening for PE by maternal variables and UtA-PI was not improved by inclusion of PAPP-A. Regression analysis was used to establish tables that allow modification of the maternal history and PAPP-A-related patient-specific risk for PE by the measurement of UtA-PI. **Low PAPP-A is a marker for subsequent development of PE. The PAPP-A-related patient-specific risk for PE can be modified by the measurement of UtA-PI.** Copyright (c) 2008 ISUOG.

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Available from *John Wiley and Sons* in [Ultrasound in Obstetrics and Gynecology](#)

Title: First trimester predictors of adverse pregnancy outcomes

Author(s): Brameld K.J., Dickinson J.E., O'Leary P., Bower C., Goldblatt J., Hewitt B., Murch A., Stock R.

Language: English

Abstract: Aim: To identify first trimester indicators of adverse pregnancy outcomes. Method: Data were obtained from the statewide evaluation of first trimester screening for Down syndrome in Western Australia which included 22 695 pregnancies screened between August 2001 and October 2003. Screening data were linked with pregnancy outcome information from the Hospital Morbidity Database and the Birth Defects Registry. The odds ratios (OR) of adverse outcomes were analysed for combined risk incorporating maternal age, nuchal translucency (NT) and biochemical parameters and then separately for each parameter (pregnancy-associated plasma protein-A (PAPP-A), free beta human chorionic gonadotropin (beta-hCG) and NT). Results: Risk assessments for first trimester

combined screening are derived from maternal age, ultrasound measurement of fetal NT, maternal serum free -hCG and PAPP-A. Increased combined risk for Down syndrome was significantly (P <0.01) associated with spontaneous loss at or before 24 weeks gestation (OR 13.51), birth defects (OR 6.58) and preterm birth at or before 32 weeks gestation (OR 3.2). Maternal serum PAPP-A below the 5th centile was associated with Down syndrome (OR 8.43), spontaneous loss before 24 weeks (OR 5.04) and later than 24 weeks (OR 4.50), preterm delivery before 32 weeks (OR 3.11) and before 37 weeks (OR 2.24). NT above the 95th centile was associated with Down syndrome (OR 43.91), birth defects (OR 4.02) and spontaneous loss before 24 weeks (OR 6.24). Low levels of free beta-hCG and increased NT were less consistently associated with adverse outcomes and high levels of free beta-hCG showed limited use as an indicator. The detection rates for all outcomes other than Down syndrome were less than 40%. **Conclusion: Biochemical indicators and NT that are measured during first trimester screening for Down syndrome show a number of associations with adverse outcomes, but do not show appropriate performance characteristics for screening tests. These data are consistent with the view that the individual components, specifically low PAPP-A levels alone, do not provide an effective screening tool for adverse pregnancy outcomes.** © 2008 The Royal Australian and New Zealand College of Obstetricians and Gynaecologists.

Publication Type: Journal: Article

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Available from *Australian and New Zealand Journal of Obstetrics and Gynaecology* in [Patricia Bowen Library and Knowledge Service West Middlesex university Hospital](#)

Title: Low levels of maternal serum PAPP-A in early pregnancy and the risk of adverse outcomes

Citation: Prenatal Diagnosis, November 2008, vol./is. 28/11(1029-1036), 0197-3851;1097-0223 (November 2008)

Author(s): Spencer C.A., Allen V.M., Flowerdew G., Dooley K., Dodds L.

Language: English

Abstract: Objectives To determine if low maternal serum level of pregnancy associated plasma protein A (PAPP-A) measured in early pregnancy can predict adverse pregnancy outcomes and to examine the gestational age (GA) sampling interval for these outcomes. Methods This was a nested case-control study from a prospective cohort of women recruited at <20 weeks of gestation in Halifax, NS. Cases (n = 248) were defined as women who had a fetal loss or developed preeclampsia, severe pregnancy-induced hypertension (PIH), or small for gestational age infant (SGA). Controls (n = 244) were frequency matched to cases by GA at the time of serum sampling (6 to <20 weeks GA). Participant information was obtained from questionnaires and medical chart reviews. Results Women with a low PAPP-A measure [<0.4 multiples of the median (MoM)] had an adjusted odds ratio of 2.1 [95% confidence interval (CI) 1.3-3.6] compared to others (>0.4 MoM). However, performance as a screening test was poor [sensitivity = 38.7%; specificity = 81.6%; positive likelihood ratio (LR) = 2.1; negative LR = 0.75]. In the adjusted model, the 10- to 14-week GA period was the only time period where low PAPP-A was significantly associated with adverse outcomes. **Conclusions**

Women with a low PAPP-A early in their pregnancy have twice the risk of an adverse outcome, though PAPP-A as a one-time single marker test has limited value. Copyright © 2008 John Wiley and sons, Ltd.

Publication Type: Journal: Article

Source: EMBASE

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Title: Obstetrical complications associated with abnormal maternal serum markers analytes.

Citation: Journal of obstetrics and gynaecology Canada : JOGC = Journal d'obste´trique et gyne´cologie du Canada : JOGC, Oct 2008, vol. 30, no. 10, p. 918-949, 1701-2163 (October 2008)

Author(s): Gagnon, Alain, Wilson, R Douglas, Audibert, François, Allen, Victoria M, Blight, Claire, Brock, Jo-Ann, Désilets, Valerie A, Johnson, Jo-Ann, Langlois, Sylvie, Summers, Anne, Wyatt, Philip, Society of Obstetricians and Gynaecologists of Canada Genetics Committee

Abstract: To review the obstetrical outcomes associated with abnormally elevated or decreased level of one or more of the most frequently measured maternal serum marker analytes used in screening for aneuploidy. To provide guidance to facilitate the management of pregnancies that have abnormal levels of one of more markers and to assess the usefulness of these markers as a screening test. Perinatal outcomes associated with abnormal levels of maternal serum markers analytes are compared with the outcomes of pregnancies with normal levels of the same analytes or the general population. The Cochrane Library and Medline were searched for English-language articles published from 1966 to February 2007, relating to maternal serum markers and perinatal outcomes. Search terms included PAPP-A (pregnancy associated plasma protein A), AFP (alphafetoprotein), hCG (human chorionic gonadotropin), estriol, unconjugated estriol, inhibin, inhibin-A, maternal serum screen, triple marker screen, quadruple screen, integrated prenatal screen, first trimester screen, and combined prenatal screen. All study types were reviewed. Randomized controlled trials were considered evidence of the highest quality, followed by cohort studies. Key individual studies on which the recommendations are based are referenced. Supporting data for each recommendation are summarized with evaluative comments and references. The evidence was evaluated using the guidelines developed by the Canadian Task Force on Preventive Health Care. The evidence collected was reviewed by the Genetics Committee of the Society of Obstetricians and Gynaecologists of Canada. The benefit expected from this guideline is to facilitate early detection of potential adverse pregnancy outcomes when risks are identified at the time of a maternal serum screen. It will help further stratification of risk and provide options for pregnancy management to minimize the impact of pregnancy complications. The potential harms resulting from such practice are associated with the so called false positive (i.e., uncomplicated pregnancies labelled at increased risk for adverse perinatal outcomes), the potential stress associated with such a label, and the investigations performed for surveillance in this situation. No cost-benefit analysis is available to assess costs and savings associated with this guideline. SUMMARY STATEMENTS: 1. An unexplained level of a maternal serum marker analyte is defined as an abnormal level after confirmation of gestational age by ultrasound and exclusion of maternal, fetal, or placental causes for the abnormal level. (III) 2. Abnormally elevated levels of serum markers are associated with adverse pregnancy outcomes in twin pregnancies, after correction for the number of fetuses. Spontaneous or planned mutifetal reductions may result in abnormal elevations of serum markers.

(II-2) RECOMMENDATIONS: 1. In the first trimester, an unexplained low PAPP-A (< 0.4 MoM) and/or a low hCG (< 0.5 MoM) are associated with an increased frequency of adverse obstetrical outcomes, and, at present, no specific protocol for treatment is available. (II-2A) In the second trimester, an unexplained elevation of maternal serum AFP (> 2.5 MoM), hCG (> 3.0 MoM), and/or inhibin-A (> or =2.0 MoM) or a decreased level of maternal serum AFP (< 0.25 MoM) and/or unconjugated estriol (< 0.5 MoM) are associated with an increased frequency of adverse obstetrical outcomes, and, at present, no specific protocol for treatment is available. (II-2A) 2. Pregnant woman with an unexplained elevated PAPP-A or hCG in the first trimester and an unexplained low hCG or inhibin-A and an unexplained elevated unconjugated estriol in the second trimester should receive normal antenatal care, as this pattern of analytes is not associated with adverse perinatal outcomes. (II-2A) 3. The combination of second or third trimester placenta previa and an unexplained elevated maternal serum AFP should increase the index of suspicion for placenta accreta, increta, or percreta. (II-2B) An assessment (ultrasound, MRI) of the placental-uterine interface should be performed. Abnormal invasion should be strongly suspected, and the planning of delivery location and technique should be done accordingly. (III-C) 4. A prenatal consultation with the medical genetics department is recommended for low unconjugated estriol levels (<0.3 MoM), as this analyte pattern can be associated with genetic conditions. (II-2B) 5. The clinical management protocol for identification of potential adverse obstetrical outcomes should be guided by one or more abnormal maternal serum marker analyte value rather than the false positive screening results for the trisomy 21 and/or the trisomy 18 screen. (II-2B) 6. Pregnant woman who are undergoing renal dialysis or who have had a renal transplant should be offered maternal serum screening, but interpretation of the result is difficult as the level of serum hCG is not reliable. (II-2A) 7. Abnormal maternal uterine artery Doppler in association with elevated maternal serum AFP, hCG, or inhibin-A or decreased PAPP-A identifies a group of women at greater risk of IUGR and gestational hypertension with proteinuria. Uterine artery Doppler measurements may be used in the evaluation of an unexplained abnormal level of either of these markers. (II-2B) 8. Further research is recommended to identify the best protocol for pregnancy management and surveillance in women identified at increased risk of adverse pregnancy outcomes based on an abnormality of a maternal serum screening analyte. (III-A) 9. In the absence of evidence supporting any specific surveillance protocol, an obstetrician should be consulted in order to establish a fetal surveillance plan specific to the increased obstetrical risks (maternal and fetal) identified. This plan may include enhanced patient education on signs and symptoms of the most common complications, increased frequency of antenatal visits, increased ultrasound (fetal growth, amniotic fluid levels), and fetal surveillance (biophysical profile, arterial and venous Doppler), and cervical length assessment. (III-A) 10. Limited information suggests that, in women with elevated hCG in the second trimester and/or abnormal uterine artery Doppler (at 22-24 weeks), low-dose aspirin (60-81 mg daily) is associated with higher birthweight and lower incidence of gestational hypertension with proteinuria. This therapy may be used in women who are at risk. (II-2B) 11. Further studies are recommended in order to assess the benefits of low-dose aspirin, low molecular weight heparin, or other therapeutic options in pregnancies determined to be at increased risk on the basis of an abnormal maternal serum screening analyte. (III-A) 12. Multiple maternal serum markers screening should not be used at present as a population-based screening method for adverse pregnancy outcomes (such as preeclampsia, placental abruption, and stillbirth) outside an established research protocol, as sensitivity is low, false positive rates are high, and no management protocol has been shown to clearly improve outcomes. (II-2D) When maternal serum screening is performed for the usual clinical indication (fetal aneuploidy and/or neural tube defect), abnormal analyte results can be utilized for the identification of pregnancies at risk and to direct their clinical management. (II-2B) Further studies are recommended to determine the optimal screening method for poor maternal and/or perinatal outcomes. (III-A).

Source: Medline

Title: First-trimester pregnancy-associated plasma protein A and subsequent abnormalities of fetal growth.

Author(s): Peterson, Suzanne E, Simhan, Hyagriv N

Abstract: The purpose of this study was to describe the relationship between first-trimester pregnancy-associated plasma protein A (PAPP-A) and birthweight along its continuum and at its extremes. This was a retrospective cohort of 1371 women who underwent first-trimester screening for fetal aneuploidy and who delivered at our hospital. First-trimester PAPP-A has a positive relationship with birthweight. As PAPP-A decreases, the risk of small-for-gestational-age (SGA) infants increases. PAPP-A of <10%, <5%, and <1% were associated with an increasing adjusted odds ratio for SGA infants (2.0 [95% CI, 1.2-3.5; P = .012]; 2.4 [95% CI, 1.2-4.7; P = .015]; 9.3 [95% CI, 3.4-25.5; P = .001], respectively). PAPP-A levels of >90% were associated with an adjusted odds ratio for birthweight of >4500 g of 2.9 (95% CI, 1.02-8.17; P = 0.046). First-trimester PAPP-A is a marker of placental function that correlates with birthweight along its continuum and at its extremes. **The strong association between low PAPP-A and SGA warrants further investigation of its usefulness as a screening tool.**

Source: Medline

Title: Use of the combined first-trimester screen result and low PAPP-A to predict risk of adverse fetal outcomes.

Author(s): Barrett, Sandie L, Bower, Carol, Hadlow, Narelle C

Abstract: To investigate associations between combined first-trimester screen result, pregnancy associated plasma protein-A (PAPP-A) level and adverse fetal outcomes in women. Pregnancy outcomes for 10,273 women participating in a community based first-trimester screening (FTS) programme in Western Australia were ascertained by record linkage to birth and birth defect databases. A first-trimester risk cut-off of > or = 1 in 300 defined screen positive women. Screen positive pregnancies were more likely to have Down syndrome and birth defects (chromosomal or nonchromosomal) than screen negative pregnancies. When birth defects were excluded, screen positive pregnancies were at increased risk of pregnancy loss, low birth weight and preterm birth. Pregnancies with low PAPP-A (< or =0.3 multiples of the median (MoM)) had higher risk of chromosomal abnormality, birth defect, preterm birth, low birth weight, or pregnancy loss, compared to those with PAPP-A > 0.3 MoM**. In pregnancies without birth defects, low PAPP-A was a stronger predictor of preterm birth, low birth weight or pregnancy loss than a screen positive result. Women with positive screen or low PAPP-A were at increased risk for some adverse fetal outcomes. The sensitivity of these parameters was insufficient to support primary screening, but increased surveillance during pregnancy may be appropriate.**

Source: Medline

Full Text:

Title: Low levels of maternal serum PAPP-A in the first trimester and the risk of pre-eclampsia.

Author(s): Spencer, Kevin, Cowans, Nicholas J, Nicolaides, Kypros H

Abstract: Low levels of pregnancy associated plasma protein-A (PAPP-A) have been previously shown to be associated with pregnancies that subsequently develop pre-eclampsia. The objective of this study was to establish the relative risk for pre-eclampsia at various PAPP-A levels as an aid to counselling and follow up of pregnancies. Maternal serum PAPP-A and free ss-human chorionic gonadotropin (ss-hCG) levels at 11 to 13 weeks of gestation from 224 singleton pregnancies that subsequently developed pre-eclampsia were compared to those from 47,770 normal singleton pregnancies resulting in live births after 37 weeks with birth weight greater than or equal to the 10th centile of normal for gestation. In all cases, the measured PAPP-A and free ss-hCG levels were expressed as multiple of the median (MoM). The association between metabolite levels and the incidence of pre-eclampsia was assessed by comparing the relative incidence at a number of MoM cut-offs and at various centiles. At various marker levels, the likelihood ratio for pre-eclampsia was also calculated. In the pre-eclampsia group the median PAPP-A MoM was significantly reduced (0.772 MoM, $p < 0.0001$) whilst the median free beta-hCG MoM was not different from controls (0.981 MoM, $p = 0.26$). With decreasing levels of PAPP-A, the likelihood ratio for pre-eclampsia increased. At the 5th centile of normal (PAPP-A MoM 0.415) the odds ratio was increased 4-fold and at this cut-off 15% of cases of pre-eclampsia would be identified. **The graphical presentation of a likelihood ratio curve for pre-eclampsia at any PAPP-A MoM level is likely to be useful in counselling women with low levels of PAPP-A and a normal karyotype. Use of low levels of PAPP-A for selecting women for further follow-up with uterine artery Doppler may further improve the clinical discrimination.**

Source: Medline

Full Text:

Title: Obstetrical Complications Associated With Abnormal Maternal Serum Markers Analytes

Author(s): Wilson R.D., Audibert F., Allen V.M., Blight C., Brock J.-A., Desilets V.A., Gagnon A., Johnson J.-A., Langlois S., Summers A., Douglas Wilson R., Wyatt P.

Language: English

Abstract: Objective: To review the obstetrical outcomes associated with abnormally elevated or decreased level of one or more of the most frequently measured maternal serum marker analytes used in screening for aneuploidy. To provide guidance to facilitate the management of pregnancies that have abnormal levels of one of more markers and to assess the usefulness of these markers as a screening test. Options: Perinatal outcomes associated with abnormal levels of maternal serum

markers analytes are compared with the outcomes of pregnancies with normal levels of the same analytes or the general population. Evidence: The Cochrane Library and Medline were searched for English-language articles published from 1966 to February 2007, relating to maternal serum markers and perinatal outcomes. Search terms included PAPP-A (pregnancy associated plasma protein A), AFP (alphafetoprotein), hCG (human chorionic gonadotropin), estriol, unconjugated estriol, inhibin, inhibin-A, maternal serum screen, triple marker screen, quadruple screen, integrated prenatal screen, first trimester screen, and combined prenatal screen. All study types were reviewed. Randomized controlled trials were considered evidence of the highest quality, followed by cohort studies. Key individual studies on which the recommendations are based are referenced. Supporting data for each recommendation are summarized with evaluative comments and references. The evidence was evaluated using the guidelines developed by the Canadian Task Force on Preventive Health Care. Values: The evidence collected was reviewed by the Genetics Committee of the Society of Obstetricians and Gynaecologists of Canada. Benefits, Harms, and Costs: The benefit expected from this guideline is to facilitate early detection of potential adverse pregnancy outcomes when risks are identified at the time of a maternal serum screen. It will help further stratification of risk and provide options for pregnancy management to minimize the impact of pregnancy complications. The potential harms resulting from such practice are associated with the so called false positive (i.e., uncomplicated pregnancies labelled at increased risk for adverse perinatal outcomes), the potential stress associated with such a label, and the investigations performed for surveillance in this situation. No cost-benefit analysis is available to assess costs and savings associated with this guideline. Summary Statements: 1.An unexplained level of a maternal serum marker analyte is defined as an abnormal level after confirmation of gestational age by ultrasound and exclusion of maternal, fetal, or placental causes for the abnormal level. (III)2.Abnormally elevated levels of serum markers are associated with adverse pregnancy outcomes in twin pregnancies, after correction for the number of fetuses. Spontaneous or planned mutifetal reductions may result in abnormal elevations of serum markers. (II-2). Recommendations: 1.In the first trimester, an unexplained low PAPP-A (< 0.4 MoM) and/or a low hCG (< 0.5 MoM) are associated with an increased frequency of adverse obstetrical outcomes, and, at present, no specific protocol for treatment is available. (II-2A) In the second trimester, an unexplained elevation of maternal serum AFP (> 2.5 MoM), hCG (> 3.0 MoM), and/or inhibin-A (>22.0 MoM) or a decreased level of maternal serum AFP (< 0.25 MoM) and/or unconjugated estriol (< 0.5 MoM) are associated with an increased frequency of adverse obstetrical outcomes, and, at present, no specific protocol for treatment is available. (II-2A)2.Pregnant woman with an unexplained elevated PAPP-A or hCG in the first trimester and an unexplained low hCG or inhibin-A and an unexplained elevated unconjugated estriol in the second trimester should receive normal antenatal care, as this pattern of analytes is not associated with adverse perinatal outcomes. (II-2A)3.The combination of second or third trimester placenta previa and an unexplained elevated maternal serum AFP should increase the index of suspicion for placenta accreta, increta, or percreta. (II-2B) An assessment (ultrasound, MRI) of the placental-uterine interface should be performed. Abnormal invasion should be strongly suspected, and the planning of delivery location and technique should be done accordingly. (III-C)4.A prenatal consultation with the medical genetics department is recommended for low unconjugated estriol levels (<0.3 MoM), as this analyte pattern can be associated with genetic conditions. (II-2B)5.The clinical management protocol for identification of potential adverse obstetrical outcomes should be guided by one or more abnormal maternal serum marker analyte value rather than the false positive screening results for the trisomy 21 and/or the trisomy 18 screen. (II-2B)6.Pregnant woman who are undergoing renal dialysis or who have had a renal transplant should be offered maternal serum screening, but interpretation of the result is difficult as the level of serum hCG is not reliable. (II-2A)7.Abnormal maternal uterine artery Doppler in association with elevated maternal serum AFP, hCG, or inhibin-A or decreased PAPP-A identifies a group of women at greater risk of IUGR and gestational hypertension with proteinuria. Uterine artery Doppler measurements may be used in the evaluation of an unexplained abnormal level of either of these markers. (II-2B)8.Further research is

recommended to identify the best protocol for pregnancy management and surveillance in women identified at increased risk of adverse pregnancy outcomes based on an abnormality of a maternal serum screening analyte. (III-A)9.In the absence of evidence supporting any specific surveillance protocol, an obstetrician should be consulted in order to establish a fetal surveillance plan specific to the increased obstetrical risks (maternal and fetal) identified. This plan may include enhanced patient education on signs and symptoms of the most common complications, increased frequency of antenatal visits, increased ultrasound (fetal growth, amniotic fluid levels), and fetal surveillance (biophysical profile, arterial and venous Doppler), and cervical length assessment. (III-A)10.Limited information suggests that, in women with elevated hCG in the second trimester and/or abnormal uterine artery Doppler (at 22-24 weeks), low-dose aspirin (60-81 mg daily) is associated with higher birthweight and lower incidence of gestational hypertension with proteinuria. This therapy may be used in women who are at risk. (II-2B)11.Further studies are recommended in order to assess the benefits of low-dose aspirin, low molecular weight heparin, or other therapeutic options in pregnancies determined to be at increased risk on the basis of an abnormal maternal serum screening analyte. (III-A)12.Multiple maternal serum markers screening should not be used at present as a population-based screening method for adverse pregnancy outcomes (such as preeclampsia, placental abruption, and stillbirth) outside an established research protocol, as sensitivity is low, false positive rates are high, and no management protocol has been shown to clearly improve outcomes. (II-2D) When maternal serum screening is performed for the usual clinical indication (fetal aneuploidy and/or neural tube defect), abnormal analyte results can be utilized for the identification of pregnancies at risk and to direct their clinical management. (II-2B) Further studies are recommended to determine the optimal screening method for poor maternal and/or perinatal outcomes. (III-A). Copyright © 2008 Society of Obstetricians and Gynaecologists of Canada.

Publication Type: Journal: Article

Source: EMBASE

Title: Low maternal serum levels of pregnancy-associated plasma protein-A during the first trimester are associated with subsequent preterm delivery with preterm premature rupture of membranes.

Citation: Taiwanese journal of obstetrics & gynecology, Sep 2007, vol. 46, no. 3, p. 242-247, 1875-6263 (September 2007)

Author(s): She, Bo-Quing, Chen, Su-Chee, Lee, Fa-Kung, Cheong, Mei-Leng, Tsai, Ming-Song

Abstract: To assess the relationship between the first-trimester maternal serum pregnancy-associated plasma protein-A (PAPP-A) levels and pregnancies complicated by preterm delivery. The correlation between PAPP-A levels and gestational age at delivery was analyzed by linear regression. The probabilities of low PAPP-A multiples of the median (MoM) levels between preterm delivery and control population were analyzed by logit model. A positive correlation was noted between the first-trimester PAPP-A MoM levels and gestational age at delivery between 34-38 weeks (p < 0.001). Lower PAPP-A MoM level had a significantly higher likelihood of preterm delivery (p < 0.05). When preterm premature rupture of membranes (PPROM) and preterm labor (PTL) were analyzed separately, there was an increasing likelihood of PPROM with decreasing PAPP-A MoM levels (p < 0.05), but not for PTL with intact membranes. **Low maternal serum PAPP-A levels during the first trimester may reflect a trophoblast invasion defect in the maternal-fetal interface, resulting in subsequent preterm delivery, particularly in those of PPROM.**

Title: Association between first trimester maternal serum pregnancy associated plasma protein-A and adverse pregnancy outcome.

Citation: The Australian & New Zealand journal of obstetrics & gynaecology, Dec 2003, vol. 43, no. 6, p. 438-442, 0004-8666 (December 2003)

Author(s): Kwik, Michele, Morris, Jonathan

Abstract: To investigate whether low pregnancy associated plasma protein-A (PAPP-A) levels in the first trimester of pregnancy are associated with subsequent intrauterine fetal growth restriction, stillbirth and preterm delivery. A retrospective review of pregnancy outcomes was undertaken in women who had PAPP-A carried out in the first trimester of pregnancy at the time of nuchal translucency scan. Pregnancy outcomes were assessed by the review of medical records, and postal questionnaires. Delivery details were collected, including livebirth, neonatal birthweight and gestational age at delivery. The chi2 test was used to investigate the association between low first trimester serum PAPP-A levels and adverse fetal outcomes. Unpaired t-test was used for continuous variables. Sensitivities and specificities were then calculated. A total of 894 women who had blood collected for PAPP-A were identified, and data was obtained for 827 deliveries. Each had a normal karyotype. There were six intrauterine deaths, 13 babies with birthweights below the 3rd centile, 55 babies weighing below the 10th centile, and 96 women who delivered prematurely. Four of six intrauterine deaths had low PAPP-A levels (<0.5 multiples of the median), with a relative risk of 13.75. **Low PAPP-A levels were associated with fetal weight below the 10th centile (P = 0.01) but not the 3rd centile. There was no statistically significant association between low maternal serum PAPP-A levels and preterm delivery. At 11-13 weeks' gestation, low maternal serum PAPP-A levels are associated with fetal death in utero and birthweight below the 10th centile. First trimester PAPP-A may be a useful tool for identifying pregnancies at risk of adverse fetal outcomes.**

Title: Decreased first trimester PAPP-A is a predictor of adverse pregnancy outcome.

Citation: Prenatal diagnosis, Sep 2002, vol. 22, no. 9, p. 778-782, 0197-3851 (September 2002)

Author(s): Yaron, Yuval, Heifetz, Sigal, Ochshorn, Yifat, Lehavi, Ofer, Orr-Urtreger, Avi

Abstract: Low levels of maternal serum pregnancy associated plasma protein-A (PAPP-A) have been linked to chromosome anomalies such as trisomy 21, 13 and 18, triploidy and sex chromosome aneuploidy. Low levels of PAPP-A have also been implicated in spontaneous miscarriage. The

purpose of this study was to evaluate whether low levels of first trimester PAPP-A are predictive of other adverse pregnancy outcomes. The study included patients with singleton pregnancies who underwent combined first trimester screening using nuchal translucency (NT) and maternal serum free beta-human chorionic gonadotrophin (free beta-hCG) and PAPP-A at 10-13 weeks' gestation. Patients with chromosome aberrations or fetal anomalies were excluded. Serum marker levels were expressed as gestational age-specific multiples of the median (MoMs). The incidences of various adverse pregnancy outcomes (spontaneous preterm labor, fetal growth restriction (FGR), proteinuric and non-proteinuric pregnancy induced hypertension (PIH), intrauterine fetal demise, oligohydramnios, spontaneous miscarriage and placental abruption) were evaluated, according to maternal PAPP-A MoM levels. Of the 1622 patients in the study, pregnancy complications were observed in 184 (11.3%). Patients with PAPP-A < or =0.25 MoM had significantly higher rates of FGR (RR = 3.12), proteinuric PIH (RR = 6.09), spontaneous miscarriage (RR = 8.76). No statistically significant differences were noted for other adverse outcomes evaluated Women with PAPP-A < or =0.50 MoM also had significantly higher rates of FGR (RR = 3.30) and spontaneous miscarriage (RR = 3.78**). We conclude that decreased levels of first trimester maternal serum PAPP-A are predictive not only of chromosome anomalies but also of adverse pregnancy outcome.** Copyright 2002 John Wiley & Sons, Ltd.

Source: Medline

Full Text:
Available from *John Wiley and Sons* in [Prenatal Diagnosis](#)

Title: Early pregnancy levels of pregnancy-associated plasma protein a and the risk of intrauterine growth restriction, premature birth, preeclampsia, and stillbirth.

Citation: The Journal of clinical endocrinology and metabolism, Apr 2002, vol. 87, no. 4, p. 1762-1767, 0021-972X (April 2002)

Author(s): Smith, Gordon C S, Stenhouse, Emily J, Crossley, Jennifer A, Aitken, David A, Cameron, Alan D, Connor, J Michael

Abstract: The risk of adverse perinatal outcome among 8839 women recruited to a multicenter, prospective cohort study was related to maternal circulating concentrations of trophoblast-derived proteins at 8-14 wk gestation. **Women with a pregnancy-associated plasma protein A (PAPP-A) in the lowest fifth percentile at 8-14 wk gestation had an increased risk of intrauterine growth restriction [adjusted odds ratio, 2.9; 95% confidence interval (CI), 2.0-4.1], extremely premature delivery (adjusted odds ratio, 2.9; 95% CI, 1.6-5.5), moderately premature delivery (adjusted odds ratio, 2.4; 95% CI, 1.7-3.5), preeclampsia (adjusted odds ratio, 2.3; 95% CI, 1.6-3.3), and stillbirth (adjusted odds ratio, 3.6; 95% CI, 1.2-11.0). The strengths of the associations were similar when the test was performed before 13 wk gestation or between 13 and 14 wk gestation.** In contrast, levels of free beta-human CG, another circulating protein synthesized by the syncytiotrophoblast, were not predictive of later outcome in multivariate analysis. PAPP-A has been identified as a protease specific for IGF binding proteins. We conclude that control of the IGF system in the first and early second trimester trophoblast may have a key role in determining subsequent pregnancy outcome.

Source: Medline

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