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ORIGINAL ARTICLE

Low PAPP-A: the impact of ultrasound to evaluate fetal growth

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ABSTRACT

Objective Our objective was to describe utilization and impact of sonographic growth assessment in pregnancies with low pregnancy-associated plasma protein-A (PAPP-A).

Methods Singleton pregnancies with PAPP-A ≤5th percentile and no other risk factors for fetal growth restriction from January 2011–June 2013 were included. Antepartum and delivery data were obtained by reviewing medical records. Outcomes of pregnancies referred for sonographic growth assessment were compared with those not referred for ultrasound. Fisher's exact test, chi-square analysis, and Mann–Whitney U were used for statistical comparison.

Results Two hundred ninety-five patients were included. Of 285 pregnancies reaching the third trimester, 77.5% were referred for ultrasound, with the initial scan at a median gestational age of 28 weeks [26–29]. Referral for growth scans was associated with earlier gestational age at delivery and higher rates of delivery for fetal indications. Those who did not undergo growth scans were more likely to deliver a small for gestational age infant at term, 20.7% versus 35.0% ($p = 0.04$). There was one third-trimester fetal demise, occurring in a patient who had been undergoing growth scans.

Conclusion Growth scans in those with low PAPP-A were associated with delivery at earlier gestational age, with higher rates of delivery for fetal indications and lower rates of small for gestational age newborns at term. No significant differences in neonatal outcomes were observed. © 2015 John Wiley & Sons, Ltd.

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INTRODUCTION

Biochemical markers of open neural tube defects and fetal chromosomal abnormalities are widely used in prenatal screening. Abnormal analyte levels, such as high maternal serum alpha-fetoprotein or low pregnancy-associated plasma protein-A (PAPP-A), have been associated with poor perinatal outcomes in the absence of structural or chromosomal abnormalities.[1–3] While the association between abnormal serum analyte levels and adverse obstetric outcomes has been recognized, there are no evidence-based interventions shown to improve outcome.[4]

In pregnancies considered at high-risk for adverse fetal outcomes, such as intrauterine growth restriction (IUGR) or stillbirth, it is common to recommend fetal assessment in addition to maternal evaluation of fetal activity.[5] Because abnormal serum analytes are considered risk factors, fetal assessment could be recommended in these pregnancies. In the absence of any guidelines or recommendations from organizations such as the American College of Obstetricians and Gynecologists or the Society for Maternal-Fetal Medicine, however, other practitioners may not recommend fetal assessment. Currently, neither American College of Obstetricians and Gynecologists nor Society for Maternal-Fetal Medicine has any specific recommendations for fetal evaluation in pregnancies with low PAPP-A.[4]

Our objective was to evaluate the use of ultrasound assessment of fetal growth in pregnancies with low PAPP-A and to determine whether sonographic growth assessment is associated with higher rates of delivery for fetal indications and different outcomes compared with pregnancies with clinical assessment of fetal growth only.

METHODS

This was a cohort study that included singleton pregnancies with low PAPP-A undergoing combined first-trimester risk assessment for chromosomal abnormalities at the Weill Cornell Medical Center from January 2011 through June 2013. Review of laboratory results identified all pregnancies with PAPP-A ≤5th percentile during the study period, and ultrasound records were reviewed to exclude multifetal pregnancies. Pregnancies with abnormal fetal karyotype were excluded. PAPP-A was measured at 9–13 weeks as part of risk assessment for fetal chromosomal abnormalities. All laboratory testing was performed by Perkin Elmer Labs/NTD (Melville, NY).

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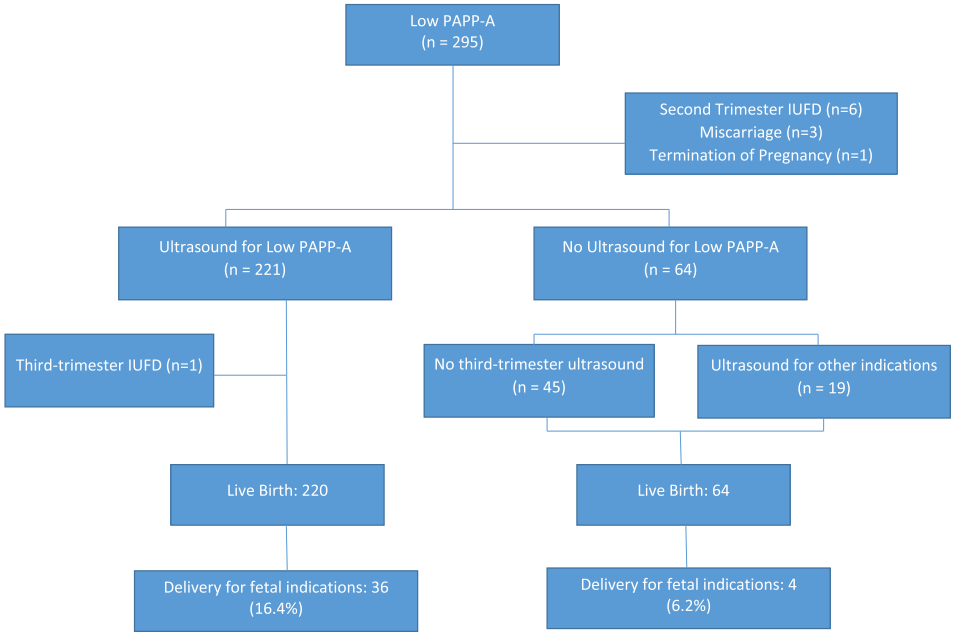

Figure 1 Selected obstetrics outcomes of patients with low PAPP-A

Referring obstetricians were provided with reports describing the multiples of median of PAPP-A and percentiles, both adjusted for gestational age, maternal weight, and ethnicity. These reports describing maternal age-related risk and adjusted risk of Down syndrome and Trisomy 18/13 did not highlight abnormal levels of PAPP-A or free beta-hCG and contained no recommendations for follow-up. Follow-up for low PAPP-A was thus at the discretion of individual obstetricians.

When ultrasound indicated abnormal growth, recommendations for follow-up care were based on sonographic findings and clinical factors, including gestational age. When normal growth was identified in a patient referred for low PAPP-A, the timing and frequency of subsequent growth scans were at the discretion of individual obstetricians. All ultrasound examinations were performed by sonographers accredited by the American Registry for Diagnostic Medical Sonography under the supervision of maternal-fetal medicine physicians.

Antepartum and delivery data were obtained by reviewing medical records. Those referred for ultrasound to evaluate fetal growth who had risk factors for IUGR besides low PAPP-A, such as hypertension or pre-gestational diabetes, were excluded. Small for gestational age (SGA) was defined as a birthweight below the 10th percentile based on a US growth curve.[6]

The primary outcome was the rate of delivery for fetal indications. Secondary outcomes included gestational age at delivery and perinatal outcomes, including stillbirth, Apgar scores, and neonatal intensive care unit (NICU) admission. Though only lower rates of adverse perinatal outcomes, such as stillbirth, would represent a clear benefit to fetal surveillance, we did not choose these as primary outcomes as they occur with relatively low prevalence.

Fisher's exact test, chi-square analysis, and Mann–Whitney U were used for statistical comparison. Continuous data are presented as median (interquartile range). Institutional review board permission to review medical records was obtained.

RESULTS

During the study period, there were 9208 patients who underwent combined first-trimester risk assessment, with low PAPP-A noted in 407 (4.4%). After excluding twin pregnancies ($n=18$), chromosomal abnormalities ($n=34$), pregnancies with other risk factors for growth restriction ($n=37$), and pregnancies lost to follow-up ($n=23$), there were 295 patients who met inclusion criteria.

The median maternal age was 33 years [30–36]. PAPP-A was in the 5th percentile in 125 patients (42.4%), the 2.5th percentile in 38 (12.9%), the 2nd percentile in 50 (16.9%), the 1st percentile in 41 (13.9%), and <1st percentile in 41 (13.9%). Selected outcomes of included patients are described in Figure 1. Fetal demise occurred in six pregnancies (2.0%) in the second trimester. Three women (1.0%) miscarried in the second-trimester. One woman, with PAPP-A in the 0.1st percentile, underwent abortion at 22 weeks after prenatal diagnosis of fetal growth restriction with intracranial hemorrhage.

Of the remaining 285 patients, 221 (77.5%) were referred for growth scans because of low PAPP-A, with the initial scan at a median gestational age of 28 weeks [26–29]. Women referred for growth scans were older, with no significant difference in maternal weight, ethnicity, or distribution of PAPP-A percentiles in those referred for ultrasound versus those who were not. (Table 1) In those referred for growth scans, the median number of scans was three, and 17 women (7.7%) underwent five or more growth scans. Most patients who were referred for growth scans were also referred for nonstress tests prior to the estimated due date, while relatively few women not referred for growth scans underwent nonstress tests (74.2% vs 20.3%; $p<0.001$).

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Table 1 **Baseline characteristics**

	Growth scans ($N = 221$)	No growth scans ($N = 64$)	p-value
Maternal age (years)	33 (30–36)	32 (30–34)	0.003[a]
Maternal weight at time of PAPP-A measurement (pounds)	137 (122–152)	131 (121–146)	0.39[a]
Ethnicity			
White	57.5%	64.1%	0.15[b]
Black	10.9%	7.8%	
Hispanic	5.9%	9.4%	
Asian	25.8%	17.2%	
Other	0.0%	1.6%	
Median PAPP-A percentile	2.5 (1–5.0)	2.5 (1–5.0)	0.68[a]
Number of growth scans	3 (2–4)	0 (0–1)	<0.001[a]

[a]Mann–Whitney U.
[b]Chi-Square.

Those under the care of maternal-fetal medicine physicians were more likely to be referred for growth scans for low PAPP-A compared with those managed by general obstetrician/gynecologists (93% vs 73%; $p = 0.001$). Patients with Medicaid insurance were less likely to be referred compared with those with private insurance (62.0% vs 80.0%; $p = 0.03$).

Of 284 live births, 36 (12.7%) were delivered prior to term. There were 11 preterm births performed for fetal indications, ten in the group referred for growth scans because of low PAPP-A. In the group referred for growth scans, ultrasound was consistent with IUGR in eight of these cases. In the two cases without suspected IUGR, preterm delivery was due to nonreassuring fetal heart rate monitoring, performed because of decreased fetal movement in one case and cholestasis of pregnancy in the other. All but one of these ten patients referred for growth scans because of low PAPP-A had other indications for fetal assessment, including uterine size less than dates and preeclampsia. The single case of preterm birth for a fetal indication in those not referred for growth scans due to low PAPP-A was due to suspected IUGR in a patient referred for fetal assessment due to gestational hypertension.

There was one intrauterine fetal demise in the third trimester, at 31 weeks' gestation in a woman who had been undergoing growth scans. The timing of and indications for delivery for the remaining 284 patients are seen in Table 2. The median gestational age at delivery was 39 1/7 weeks (38 0/7–40 0/7), and the median gestational age at birth was five days earlier in those referred for growth scans ($p = 0.02$). The rate of delivery for fetal indications was significantly higher in those undergoing growth scans, 16.4% versus 6.2% ($p = 0.04$). Of 40 deliveries for fetal indications, 35 were for suspected IUGR (87.5%).

In 284 live births, 77 newborns (27.1%) were SGA. Fifty-five of these were in the group referred for growth scans, and IUGR was suspected in 27 of them (49.1%). The median interval between the final growth scan and delivery of a SGA newborn was significantly longer in the 27 unsuspected compared with the 28 suspected cases, 26 days (18–48) versus 3 days (0–11); $p < 0.001$. While there was no significant association between the rate of SGA newborns and referral for growth scans, those who did not undergo growth scans were more likely to deliver an SGA infant at term (35.0% versus 20.7%; $p = 0.04$). (Table 2).

Table 2 **Growth scans versus no growth scans**

	Growth scans ($N = 220$)	No growth scans ($N = 64$)	p-value
Gestational age at delivery	272 days (263–279)	277 days (268–285)	0.02[a]
Preterm birth	14.5%	6.2%	0.09[b]
Cesarean delivery	30.9%	29.1%	1.0[b]
Birthweight	3028 g (2679–3452)	3088 g (2663–3497)	0.88[a]
Delivery for fetal indications	16.4%	6.2%	0.04[b]
SGA at birth (all births)	25.0%	34.4%	0.15[b]
SGA at Birth (term birth)	20.7%	35.0%	0.04[b]
1-minute Apgar	9 (9–9)	9 (9–9)	0.19[a]
5-minute Apgar	9 (9–9)	9 (9–9)	0.41[a]
Neonatal intensive care unit admission	10.0%	3.1%	0.12[b]

SGA, small for gestational age.
[a]Mann–Whitney U.
[b]Fisher's exact test.

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There were no significant differences in Apgar scores or rates of NICU admission between the two groups. (Table 2). Prematurity and low-birth weight were the most common indications for NICU admission.

DISCUSSION

In our population of patients with low PAPP-A, we saw significant variation in referral for growth scans based on insurance and provider type. Patients referred for growth scans were delivered at earlier gestational ages, with higher rates of delivery for fetal indications and lower rates of SGA newborns at term. There were no differences in neonatal outcomes. In most preterm births for fetal indications, there were clinical indications for fetal evaluation besides low PAPP-A, such as size/dates discrepancy or preeclampsia.

The pathophysiology of obstetric complications associated with low PAPP-A involves abnormal placental function, and lesions associated with malperfusion are more prevalent in affected pregnancies.[7–9] Histologically, low PAPP-A appears to be associated with defective syncytiotrophoblast formation and function.[10] In addition to growth restriction, low PAPP-A has also been associated with stillbirth, preeclampsia, abruptio placenta, and preterm birth.[1,8] There is currently no evidence to support any change in obstetric management to prevent these conditions in the patient with low PAPP-A.[4]

Despite the association between abnormal analyte levels and adverse outcomes, they are not good screening tests, with low sensitivity and poor positive predictive value (PPV) for stillbirth (sensitivity 10.53%; PPV 0.58%), IUGR (sensitivity 10.45%; PPV 18.71%), and preeclampsia (sensitivity 7.85%; PPV 3.46%).[1,2] Despite this, low PAPP-A is recognized as a risk factor for poor outcomes, and in our population led to fetal surveillance in most cases. This surveillance was associated with a higher rate of delivery for fetal indications, without evidence of improved outcome.

Measurements of PAPP-A as a screening test for chromosomal abnormalities may be less prevalent in the future. Biochemical risk assessment is not indicated in patients who have undergone chorionic villus sampling and is not warranted in patients undergoing noninvasive prenatal testing with cell-free fetal DNA assessment, a superior screening test for chromosomal abnormalities.[11,12] It is not clear to what extent obstetricians should be concerned that foregoing PAPP-A measurement will deprive them of important information, though there is no evidence that evaluating PAPP-A levels to assess risk of IUGR or other adverse outcomes leads to interventions that improve perinatal outcome.

An obvious limitation of this study is the retrospective design. In the absence of evidence-based guidelines, we do not recommend any specific management when low PAPP-A is identified. Many obstetricians are aware of the association between low PAPP-A and adverse outcomes, however, and most patients were referred for ultrasound to evaluate growth as well as for fetal testing for no other apparent indication. While we did not find any difference in PAPP-A levels or other baseline characteristics between the two groups, it is possible that the group referred for third trimester ultrasound was at higher risk, and that fetal surveillance leading to earlier delivery prevented some adverse outcomes.

The higher rate of small for gestational age term newborns in pregnancies not referred for fetal surveillance due to low PAPP-A could indicate that this population was exposed to a higher risk of stillbirth or other poor outcomes unlikely to be observed in a small study population. Our study clearly lacked power to compare stillbirth rates, however. Dugoff et al. described a rate of intrauterine fetal demise of 0.58% associated with PAPP-A ≤5th percentile.[1] To have 80% power to discern a 50% decline in this rate to 0.29%, in a population like ours in which three-fourths of patients underwent growth scans, would require a total study population of 24 660 with low PAPP-A. It should be noted that studies evaluating aggressive screening for fetal growth restriction[13] or early delivery for suspected fetal growth restriction[14] have not documented improved outcomes.

CONCLUSION

We did not identify any clear benefit of ultrasound to evaluate fetal growth in those with low PAPP-A and no additional risk factors for IUGR. While those not evaluated by ultrasound had higher rates of SGA newborns, we did not see any difference in neonatal outcomes. Though this retrospective study cannot exclude the possibility that fetal surveillance prevented bad outcomes, there remains no good evidence that fetal surveillance leads to beneficial interventions in pregnancies with low PAPP-A.

WHAT'S ALREADY KNOWN ABOUT THIS TOPIC?

- The association between low PAPP-A and intrauterine growth restriction is well described.

WHAT DOES THIS STUDY ADD?

- This study evaluated outcomes in pregnancies with low PAPP-A by comparing groups referred for growth scans due to low PAPP-A with those not referred. It reinforces the fact that any benefit to fetal assessment in this population remains unproven.

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