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Original Research Article

Association of low pregnancy-associated plasma protein A with the timing of delivery in babies with intrauterine growth restriction, babies showing suboptimal growth on serial scans, and well-grown babies

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ABSTRACT

Background: The ideal timing for delivering babies with pre-eclampsia or small for gestational age is clear. There is agreement on delivering babies with pre-eclampsia and small for gestational age, but not for normally growing babies with low pregnancy-associated plasma protein A (PAPP-A). The study aimed to investigate the association of low PAPP-A with adverse pregnancy outcomes and ideal delivery timing in a well-grown baby with low PAPP-A as a risk factor.
Methods: A retrospective study analyzed 3240 singleton pregnancies with first-trimester Down syndrome screening at local hospitals from January 2022 to April 2023. Among these, 130 singleton pregnancies had PAPP-A levels at the 5th centile, along with risk estimations and documentation.
Results: In NCIC trust births, 3280 women were assessed for low PAPP-A. Of these, 130 had low PAPP-A levels. It revealed that 46.9% used Aspirin, with a high down screen risk found in 11.5%. In this study, 13.1% experienced pregnancy induced hypertension (PIH). 2 resulted in intrauterine fetal death (1.5%). 9 women (6.9%) experienced pre-term births. The study identified 8 newborns (6.25%) with birth weights below the 10th centile after >39+6 weeks, and 6 (4.6%) <3rd centile after 37+6 weeks.
Conclusions: The study linked low PAPP-A to poor APGAR scores, stillbirth, growth issues, and special care unit admissions. Babies with low PAPP-A showed higher morbidity and mortality after 41 weeks. The findings indicate that delivery should occur between 40+0 and 40+6 weeks. Further research is needed to create an antenatal protocol for optimal delivery timing for babies with low PAPP-A.

Keywords: Papp-A, IUGR, Suboptimal growth, Stillbirth, APGAR <7, SCBU admissions

INTRODUCTION

The encoding gene for pregnancy-associated plasma protein-A (PAPP-A), a protease that is a member of the matrix metalloproteinase family, is found on chromosome 9q33.1.[1] Soon after blastocyst implantation, PAPP-A can be detected in the early stages of pregnancy. From then on, its levels rise steadily until delivery, when it reaches its maximum concentration at term.[2] Low levels of PAPP-A may be a sign of poor placental function and implantation since maternal serum PAPP-A concentrations are a good measure of placental volume. Reduced PAPP-A production is caused by smaller placentas and malfunctioning syncytiotrophoblasts.[3] PAPP-A levels below the threshold for the first-trimester screening can be a distinct risk factor for several unfavorable pregnancy outcomes, including low birth weight, preeclampsia, fetal growth restriction, preterm delivery, stillbirth, gestational hypertension, intrauterine fetal death after 24 weeks, and spontaneous fetal loss before 24 weeks.[4,5]

In a previous study, it was stated that the maternal plasma PAPP-A concentrations between 8- and 14-week gestation are a strong predictor of a poor perinatal outcome in a

subsequent pregnancy. Before 13 weeks of gestation, there was a comparable degree of correlation between PAPP-A and the outcome. These statistics suggest that a negative pregnancy outcome is predetermined in the first trimester for a certain percentage of women.[6]

In 2010, a retrospective cohort study was carried out to find out the association of first trimester low maternal serum PAPP-A levels with small-for-gestational-age (SGA) newborns and stillbirths (SBs). In this study of 19.536 women, a statistically significant ($p<0.002$*) association between PAPP-A levels below the fifth percentile and rates of stillbirth was noticed.[7]

In cases when the estimated fetal weight (EFW) is <3rd centile and there are no additional risk factors, labor and/or delivery should commence at 37+0 weeks gestation and no later than 37+6 weeks gestation. If the fetus with an EFW falls between the 3rd and the <10th centile, 39+0 weeks should be the estimated time of delivery. 39+6 weeks should be the goal for birth. The NICE guidelines for inducing labor should be adhered to in cases involving uncomplicated pregnancies. Women should always be given a thorough explanation of the reasons behind the induction offer, together with a discussion of the advantages, disadvantages, and other options.[8]

At 39+0 weeks gestation and beyond, induction of labor is not linked with an upsurge in cesarean section, instrumental vaginal birth, fetal morbidity, or admission to the neonatal intensive care unit.[9]

The best time to deliver a baby with difficulties such as pre-eclampsia or small for gestational age is widely agreed upon, but the best time to deliver a regularly growing baby with a low PAAP-A risk factor is less certain.

While there is broad agreement over when to deliver a newborn with pre-eclampsia and small for gestational age issues, there is less agreement regarding when to deliver a regularly growing child whose risk factor is low PAAP-A.

The present study has been taken up to look at the care provided to pregnant women with a low PAPP-A, the review which was done antenatally, delivery plan and to assess the outcomes for mothers and babies.

This study aims to see the association of low PAPP-A with adverse pregnancy outcomes and ideal timing of delivery in a well-grown baby with low PAPP-A as a risk factor.

METHODS

This is a single-center retrospective observational study of 3240 singleton pregnancies that underwent first-trimester combined screening for Down syndrome between January 2022 and April 2023 at West Cumberland Hospital and Cumberland Infirmary under North Cumbria Integrated Care Trust. Pregnancy outcome data were collected until April 2023. From this cohort of women, 130 singleton pregnancies with PAPP-A levels ≤0.415 MoM (corresponding to the 5th centile) were identified from the electronic badger net database with documentation and risk estimates of first-trimester screening. Additional data regarding maternal characteristics, biomarkers, ultrasound measures, and pregnancy outcomes were also collected. This included maternal age, weight, body mass index (BMI), smoking status, ethnicity, parity, PAPP-A in MoM, pregnancy-induced hypertension, high down screening risk, serial growth scans, umbilical artery Doppler studies as well as outcomes including gestational age (GA) at delivery, mode of delivery, birth weight (live births), APGAR scores and baby special care unit admission.

Miscarriage was defined as fetal loss before 24 weeks of gestation. Preterm birth was defined as birth before 37 completed weeks of gestation (and after 24 weeks of gestation), which could be either iatrogenic or due to spontaneous preterm labor, and early preterm birth was defined as that before 34 weeks of gestation. Pre-eclampsia was defined, according to the guidelines of the International Society for the Study of Hypertension in Pregnancy as the occurrence of gestational hypertension with proteinuria of 300 mg or more in 24hrs or two readings of elevated blood pressure and at least 2+ on the urine dipstick analysis 6 hours apart. SGA was defined as a birth weight below the 10th centile for gestational age. Definition of FGR in a current pregnancy: defined as either of the following: EFW or abdominal circumference (AC) <3rd centile, EFW or AC <10th centile with evidence of placental dysfunction (either), bnormal uterine artery Doppler (mean pulsatility index >95th centile 38), earlier in pregnancy (20–24 weeks) and/or, abnormal umbilical artery Doppler (absent or reversed end diastolic flow or pulsatility index >95th centile).

Statistical analysis

The demographic data and clinical parameters obtained were subjected to descriptive statistical analysis and by using statistical package for the social sciences (SPSS) (version 20), the data is stated as frequencies (n), and percentages (%) in tabulated form. Student t-test was performed to test the significance of the difference between study parameters. In all the cases p value ≤0.05* is considered as statistically significant.

RESULTS

The present study shows that a total of 3280 women were enrolled in the present study. Out of these 3280 women, those who had low PAPP-A among all the antenatal women during the study period were taken as the target study population. The consumption of Aspirin in the study population, where it can be noted that around 46.9% (n=61) consumed aspirin. The uterine Doppler test was done on pregnant women, where only one woman has gone through it, two of them had no information or record, and the rest 127 (97.7%) didn't undergo the uterine Doppler.

Table 1 depicts high down screen risk with low PAPP-A, where 11.5% (n=15) of patients had a high down screen risk with low PAPP-A, in pregnancy-induced hypertension in pregnant women, where 13.1% (n=17) of women were having PIH, the number of patients having an intrauterine device, it can be noticed that out of 130 patients, only two (1.5%) had an IUD. Of the pre-term deliveries, nine (6.9%) were having pre-term deliveries, respectively.

Table 2 portrays the <10 centile birth weight at >39+6 weeks, where it can be observed that eight babies (6.25%) were with <10 centile birth weight at >39+6 weeks, it also represents the <3 centile birth weight after 37+6 weeks, where it can be observed that six babies (4.6%) were with <3 centile birth weight after 37+6 weeks.

Table 3 is about the normal growth of babies born at 39, 40, and 41 weeks, a majority (n=16, 12.3%) of them were born at 39 weeks, followed by babies with normal growth at 40 weeks (n=12, 9.2%) and least were born at 41 weeks (n=7, 5.4%), respectively and it also depicts the babies with low PAPP-A tailing of growth born at 39, 40, and 41 weeks, in which a majority (n=20, 15.4%) of them were born at 39 weeks, followed by babies with tailing growth at 40 weeks (n=07, 5.4%) and least were born at 41 weeks (n=03, 2.3%), respectively.

In the present study, women with low PAPP-A delivered at 39, 40, and 41 weeks were focused. It was revealed that most of the women (n=19) after induction delivered at 39+0 to 39+6 gestation at birth and when not induced the majority of women (n=21) delivery took place at the same gestation period i.e. 39+0 to 39+6, respectively. A statistical significance was observed in the correlation of study parameters (p=0.04*) (Table 4).

In this study, babies with normal growth born at 39, 40, and 41 weeks were examined. It was observed that most (n=08) of the babies were born after induction at 40+0 to 40+6 gestation period and when not induced the majority (n=11) of babies were born at 39+0 to 39+6 gestation period, respectively. A statistical significance was not observed in the correlation of study parameters (p=0.06) (Table 5).

In this study, babies with tailing growth born at 39, 40, and 41 weeks were observed. It was noted that most (n=11) of the babies were born after induction at a 39+0 to 39+6 gestation period and when not induced the majority (n=09) of babies were born at 39+0 to 39+6 gestation period, respectively.

A statistical significance was not found when the correlation of the study parameters was carried out (p=0.78) (Table 6).

Table 1: High down screen risk with low PAPP-A, patients with PIH in current pregnancy, IUD, and pre-term deliveries.

Variables	Frequency (N)	Percentage (%)
High down screen risk with low PAPP-A		
Patients with a high down screen risk with low PAPP-A	15	11.5
Patients without a high down screen risk with low PAPP-A	115	88.5
Patients with PIH in current pregnancy		
With PIH	17	13.1
Without PIH	113	86.9
IUD		
Yes	02	1.5
No	128	98.5
Pre-term deliveries		
<37 weeks	09	6.9

Table 2: <10 centile birth weight at >39+6 weeks and <3 centile birth weight after 37+6 weeks.

Variables	Frequency (N)	Percentage (%)
<10 centile birth weight at >39+6 weeks		
Babies born with <10 centile birth weight at >39+6 weeks	08	6.2
Babies born without <10 centile birth weight at >39+6 weeks	122	93.8
<3 centile birth weight after 37+6 weeks		
Babies born with <3 centile birth weight after 37+6 weeks	06	4.6
Babies born without <3 centile birth weight after 37+6 weeks	124	95.4
Total	130	100

Table 3: Babies with normal growth born at 39, 40, and 41 weeks and babies with low PAPP-A tailing of growth born at 39, 40, and 41 weeks.

Variables	Frequency (N)	Percentage (%)
Babies with normal growth born at 39, 40, and 41 weeks		
Babies with normal growth born at 39 weeks	16	12.3
Babies with normal growth born at 40 weeks	12	9.2
Babies with normal growth born at 41 weeks	07	5.4
Babies without normal growth born at 39, 40, and 41 weeks	95	73.1
Babies with low PAPP-A tailing of growth born at 39, 40, and 41 weeks		
Babies with tailing of growth born at 39 weeks	20	15.4
Babies with tailing of growth born at 40 weeks	07	5.4
Babies with tailing of growth born at 41 weeks	03	2.3
Babies without tailing of growth born at 39, 40, and 41 weeks	30	76.9
Total	130	100

Table 4: Women with low PAPP-A delivered at 39, 40, and 41 weeks; APGAR <7 at 5 mins - women with low PAPP-A delivered at 39, 40, and 41 weeks and SCBU admissions - women with low PAPP-A delivered at 39, 40, and 41 weeks.

IoL and gestation at birth	Total delivery (women)	Stillbirth	P value
Induced			
39+0 to 39+6	19	0	
40+0 to 40+6	14	0	
41+0 to 41+6	02	0	
Not induced			
39+0 to 39+6	21	0	
40+0 to 40+6	09	0	
41+0 to 41+6	09	01	
		APGAR <7	
Induced			
39+0 to 39+6	19	0	
40+0 to 40+6	14	0	
41+0 to 41+6	02	0	
Not induced			
39+0 to 39+6	21	01	0.04*
40+0 to 40+6	09	0	
41+0 to 41+6	09	01	
		SCBU	
Induced			
39+0 to 39+6	19	0	
40+0 to 40+6	14	01	
41+0 to 41+6	02	0	
Not induced			
39+0 to 39+6	21	0	
40+0 to 40+6	09	0	
41+0 to 41+6	09	01	
Total	74	02	

*Statistically significant.

Table 5: Babies with normal growth born at 39, 40, and 41 weeks; APGAR <7 at 5 mins- babies with normal growth born at 39, 40, and 41 weeks and SCBU admissions- babies with normal growth born at 39, 40, and 41 weeks.

IoL and gestation at birth	Total delivery (women)	Stillbirth	P value
Induced			
39+0 to 39+6	05	0	0.06

Continued.

IoL and gestation at birth	Total delivery (women)	Stillbirth	P value
40+0 to 40+6	08	0	
41+0 to 41+6	01	0	
Not induced			
39+0 to 39+6	11	0	
40+0 to 40+6	04	0	
41+0 to 41+6	06	01	
Total	35	01	
		APGAR <7	
Induced			
39+0 to 39+6	05	0	
40+0 to 40+6	08	0	
41+0 to 41+6	01	0	
Not induced			
39+0 to 39+6	11	01	
40+0 to 40+6	04	0	
41+0 to 41+6	06	01	
Total	35	02	
		SCBU	
Induced			
39+0 to 39+6	05	0	
40+0 to 40+6	08	01	
41+0 to 41+6	01	0	
Not induced			
39+0 to 39+6	11	0	
40+0 to 40+6	04	0	
41+0 to 41+6	06	0	
Total	35	01	

Table 6: Babies with tailing growth at 39, 40, and 41 weeks; APGAR <7 at 5 mins- babies with tailing growth at 39, 40, and 41 weeks and SCBU admissions- babies with tailing growth at 39, 40, and 41 weeks.

IoL and gestation at birth	Total delivery (women)	Stillbirth	P value
Induced			
39+0 to 39+6	11	0	
40+0 to 40+6	05	0	
41+0 to 41+6	0	0	
Not induced			
39+0 to 39+6	09	0	
40+0 to 40+6	02	0	
41+0 to 41+6	03	0	
		APGAR <7	
Induced			
39+0 to 39+6	11	0	
40+0 to 40+6	05	0	
41+0 to 41+6	0	0	0.78
Not induced			
39+0 to 39+6	09	0	
40+0 to 40+6	02	0	
41+0 to 41+6	03	0	
		SCBU	
Induced			
39+0 to 39+6	11	0	
40+0 to 40+6	05	0	
41+0 to 41+6	0	0	
Not induced			

Continued.

IoL and gestation at birth	Total delivery (women)	Stillbirth	P value
39+0 to 39+6	09	0	
40+0 to 40+6	02	0	
41+0 to 41+6	03	0	
Total	30	0	

DISCUSSION

Aski et al, in the year 2024, in their research aimed to analyze and compare the levels of PAPP-A in gestational women exhibiting intrauterine growth restriction (IUGR) versus those not affected by this condition during the gestational period of weeks 11 to 14. The findings revealed a statistically significant variance in the median PAPP-A levels, with women experiencing IUGR demonstrating a level of 0.64, in contrast to a level of 1 in those without IUGR; furthermore, a threshold value of 0.73 for PAPP-A was identified, exhibiting a sensitivity of 72.2% and a specificity of 60.5% in the prediction of adverse pregnancy outcomes.[10]

Jindal et al, in their research undertaken at Lok Nayak Hospital in New Delhi, India, determined that females exhibiting diminished levels of PAPP-A necessitate more rigorous monitoring due to the heightened likelihood of severe pregnancy outcomes, thereby underscoring the critical nature of early identification and surveillance during the initial trimester. Diminished PAPP-A levels (defined as less than 0.4 MoM) during the first trimester of gestation are correlated with detrimental outcomes including pre-eclampsia, IUGR, intra-uterine fetal demise, pregnancy-related hypertension, and a variety of other pregnancy-associated complications.[11]

Silva et al, in the year 2023 in their retrospective study stated that the study demonstrated a notable increase in umbilical artery pulsatility index (UA PI) prevalence in cases with maternal PAPP-A levels <0.45 MoM during the first trimester, relative to those with levels ≥0.45 MoM (12.7% versus 5.4%). Furthermore, a significantly elevated incidence of cesarean deliveries was noted in cases with PAPP-A levels <0.45 MoM compared to those with levels ≥0.45 MoM (42.7% versus 30.1%).[12]

Middleton et al, in the year 2020, concluded that the initiation of labor in women diagnosed with gestational hypertension or mild pre-eclampsia after 36 weeks of gestation exhibited a reduced incidence of severe hypertension in contrast to expectant management. The research findings indicated that the induction of labor did not yield a statistically significant variation in adverse neonatal outcomes relative to expectant management.[13]

The study's sample size may limit the generalizability of the findings. A larger sample size is essential for validating results across a wider population. Constraints in the study population, including twins and babies with anomalies, alongside the single-centre design, further restrict applicability.

CONCLUSION

The current study concludes that low PAPP-A is linked to low APGAR scores, stillbirth, foetal growth restriction, suboptimal newborn growth, and baby admission to a special baby care unit. After 41 weeks, well-grown newborns showed higher neonatal morbidity and mortality when low PAPP-A was the only risk factor. Consequently, it is possible to draw the conclusion from the data that these patients must be delivered between 40+0 and 40+6 weeks. To create an antenatal protocol for the timing of delivery in fully developed newborns with low PAPP-A, larger research is necessary to design antenatal protocol for the timing of delivery in well-grown babies with low PAPP-A.

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