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

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Abstract

Objective 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.

Quality of evidence 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.

Main message 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.

Conclusion 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.

EDITOR'S KEY POINTS

- There is no strong evidence to suggest an association between low first-trimester pregnancy-associated plasma protein A (PAPP-A) levels and adverse perinatal outcomes, nor does the evidence suggest the need to perform routine ultrasonography surveillance.
- Current evidence does suggest an association between low PAPP-A level and abnormal placentation.
- Women with low first-trimester PAPP-A levels should continue to be routinely screened for background medical risk factors that might affect placental health.
- Collaboration with obstetric experts might be warranted for women with low PAPP-A levels to aid in guiding individual pregnancy surveillance for fetal and placental health.

POINTS DE REPÈRE DU RÉDACTEUR

- Il n'y a pas de données probantes convaincantes laissant supposer des liens entre de faibles taux de protéines A plasmatiques associées à la grossesse au premier trimestre et des issues périnatales indésirables. Les données probantes ne font pas valoir non plus la nécessité de procéder à une surveillance systématique par échographie.
- Les données scientifiques actuelles indiquent bel et bien une association entre un faible taux de PAAP-A et une placentation anormale.
- Il faut continuer de dépister systématiquement, chez les femmes ayant de faibles taux de PAAP-P au premier trimestre, des facteurs de risque médicaux antécédents qui pourraient nuire à la santé placentaire.
- Il y aurait lieu de collaborer avec des experts en obstétrique dans les cas de femmes ayant de faibles taux de PAAP-A pour aider à orienter la surveillance de la santé fœtale et placentaire dans chaque grossesse particulière.

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Cet article a fait l'objet d'une révision par des pairs.
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Faibles taux de protéines A plasmatiques associées à la grossesse au premier trimestre

Résumé

Objectif Examiner les récentes données probantes concernant les liens entre de faibles taux (c.-à-d. en-deçà du cinquième percentile) de protéines A plasmatiques associées à la grossesse et des issues périnatales

indésirables, et intégrer les nouvelles constatations aux recommandations produites par la Société des obstétriciens et gynécologues du Canada en 2008.

Qualité des données Une révision des articles récemment publiés a révélé que les données probantes sont insuffisantes et mitigées concernant l'association entre de faibles taux de PAAP-A et une petite taille pour l'âge gestationnel, un accouchement avant terme, des troubles d'hypertension gestationnelle et la mortinatalité. Des données probantes limitées font valoir qu'il existe un lien entre de faibles taux de PAPP-A et un avortement spontané. De récentes études indiquent que de faibles taux de PAPP-A sont associés avec une placentation anormale, ce qui pourrait être à la source des issues périnatales indésirables en cause.

Message principal Les données probantes étayant une association entre de faibles taux de PAPP-A et des issues périnatales indésirables sont à la fois peu nombreuses et partagées. Toutefois, de récentes données indiquent bel et bien une association entre de faibles taux de PAPP-A et une placentation anormale. Il manque actuellement des guides de pratique fondés sur des données probantes convaincantes sur ce sujet émergent qui a pourtant des répercussions importantes sur les issues périnatales. Une collaboration avec des spécialistes de l'obstétrique concernant les femmes enceintes ayant de faibles taux de PAPP-A observés dans le contexte des résultats du dépistage normal de l'aneuploïdie au premier trimestre pourrait aider à la prise de décisions cliniques entourant la surveillance placentaire et de la grossesse.

Conclusion Bien que la signification clinique d'un faible taux de PAPP-A détecté dans le cadre du dépistage normal de l'aneuploïdie fœtale demeure controversée, les patientes enceintes ayant de tels résultats devraient être informées qu'à l'heure actuelle, il n'y a pas de données probantes convaincantes justifiant un programme de surveillance continue à l'échographie.

In July 2011, the Society of Obstetricians and Gynaecologists of Canada (SOGC) and the Prenatal Diagnosis Committee of the Canadian College of Medical Geneticists reiterated the recommendation that all pregnant women in Canada, regardless of age, should be offered prenatal screening for the most common clinically important fetal aneuploidies through an informed counseling process.[1] Currently available noninvasive screening options include maternal age combined with 1 of the following: first-trimester screening (FTS) for nuchal translucency and maternal serum biochemical markers, second-trimester maternal serum screening for maternal serum biochemical markers, or 2-step integrated prenatal screening (IPS), which includes first- and second-trimester serum screening with or without nuchal translucency (**Table 1**). Among other maternal serum biochemical markers, FTS and IPS in Canada both measure pregnancy-associated plasma protein A (PAPP-A) levels in the first trimester.[1] Pregnancy-associated plasma protein A is a protease that participates in the local release of insulinlike growth factors. Since the mid-1990s the established association of low levels of PAPP-A with Down syndrome has led to wide use of PAPP-A measurement as a part of aneuploidy screening.[1] However, certain pregnancies might have negative screening results for the most common aneuploidy (trisomy 21) despite a low level of PAPP-A. This occurs especially in women younger than 30 years, or in pregnancies with low nuchal translucency values (< 1.5 mm), as these characteristics confer a low risk of Down syndrome. Several studies have investigated the relationship in such cases between low levels of PAPP-A in early pregnancy and other adverse obstetric outcomes. This article aims to review the current evidence behind the association between low first-trimester PAPP-A level and the following adverse perinatal outcomes: small size for gestational age (SGA), preterm labour, hypertensive disorders of pregnancy, spontaneous abortion, and stillbirth.

Table 1. Current screening tools for aneuploidy involving the use of PAPP-A

TEST	MARKERS	TRIMESTER
FTS	NT, free β-hCG, PAPP-A, MA	First
IPS	NT, PAPP-A, AFP, uE3, free β-hCG or total hCG, inhibin A, MA	First and second
IPS without inhibin A	NT, PAPP-A, AFP, uE3, total hCG, MA	First and second
Serum IPS	PAPP-A, AFP, uE3, free β-hCG or total hCG, inhibin A	First and second

AFP—α-fetoprotein, FTS—first-trimester screening, hCG—human chorionic gonadotropin, IPS—integrated prenatal screening, MA—maternal age, NT—nuchal translucency, PAPP-A—pregnancy-associated plasma protein A, uE3—unconjugated estriol.

Quality of evidence

In October 2008, the SOGC published a technical update reviewing key publications investigating the association between low levels of PAPP-A and adverse pregnancy outcomes. This review concluded that low PAPP-A levels were statistically significantly associated with increased risk of intrauterine growth restriction (IUGR), preterm delivery, fetal death after 24 weeks, preeclampsia, and spontaneous abortion ($P < .05$).[2] The review summarized several key population studies including a 2006 landmark Scottish multicentre prospective cohort study of

8483 women showing odds ratios of 2.8 for SGA, 1.9 for preterm delivery, and 2.2 for stillbirth in women with PAPP-A levels lower than the fifth percentile.[3] Since 2008, a number of studies have been published on this topic[4-13] contributing to the body of evidence behind association between low PAPP-A levels measured in the first trimester and adverse perinatal outcomes including SGA, IUGR, preterm delivery, preeclampsia, spontaneous abortion, and stillbirth (**Table 2**).

Main message

Fetal weight: SGA and IUGR. Since 2008, 6 studies of varied designs have investigated the relationship between low PAPP-A level and fetal weight or growth.[4-9] Four of the 6 studies, involving a total of 24 668 women, reported statistically significant relationships between PAPP-A levels below the fifth percentile or less than 0.4 multiples of the median (MoMs) and SGA or IUGR ($P < .05$).[4-7] One of these, a retrospective cohort study involving 3269 women, investigated the predictive value of PAPP-A levels below the fifth percentile for SGA. Their results yielded a positive predictive value of 2.97 (95% CI 1.1 to 6.4) of a PAPP-A level below the fifth percentile for SGA. However, the authors believed that a positive predictive value of 2.97 was not strong enough to consider the use of PAPP-A level to screen for SGA.[4] Another 2 of the 6 recent studies included a 2012 retrospective case-control study, which found that a PAPP-A level below the 10th percentile was not significantly associated with SGA,[8] and a 2011 retrospective cohort study involving 28 566 women, which found no predictive value of PAPP-A level below the fifth percentile for low birth weight.[9] The current evidence for an association between PAPP-A level below the fifth percentile and SGA remains mixed.

Preterm delivery. Four recent studies have investigated the relationship between low PAPP-A and preterm delivery.[8-11] Of these, 2 retrospective cohort studies that included a combined total of 11 681 women found a statistically significant association between low PAPP-A level (below the 10th percentile in one study and below the 5th percentile in another) and preterm delivery.[10,11] It is notable that the study that found an association between PAPP-A level below the 10th percentile and preterm delivery did not find a strong enough association to endorse the use of PAPP-A level to screen for preterm delivery.[10] The other 2 recent studies included a retrospective case-control study of 663 women that did not find an association between PAPP-A level below the 10th percentile and preterm delivery,[8] and a 2011 retrospective cohort study of 28 566 women that concluded a PAPP-A level below the fifth percentile was not predictive of preterm labour.[9] The current evidence for an association between low PAPP-A levels and preterm labour remains mixed, and no evidence exists to support the measurement of low PAPP-A level as a test for preterm delivery.

Hypertensive disorders of pregnancy. There have been 4 recent studies investigating a link between hypertensive disorders of pregnancy—specifically preeclampsia—and low PAPP-A levels.[8,9,12,13] Two of the prospective cohort studies found an inverse relationship between measured PAPP-A levels and preeclampsia:

Table 2. Definition of commonly used terms

TERM	DEFINITION
IUGR	Designates a fetus that has not reached its growth potential owing to genetic or environmental factors, with an estimated fetal weight below the 10th percentile (usually measured via ultrasound)
SGA	Designates a born infant whose weight is below the 10th percentile for its gestational age—usually the result of IUGR
Preterm labour and preterm delivery	Onset of active labour and delivery before 37 weeks' gestation
Spontaneous abortion	The ending of a pregnancy resulting in an expulsion of the fetus before it has reached a viable gestational age of 20 weeks, typically with a weight of ≤ 500 g
Stillbirth	Fetal death after 20 weeks' gestational age. If gestational age is unknown, it is defined by a fetal weight of > 500 g
Hypertensive disorders of pregnancy	Refers to hypertension during pregnancy. There are 3 important types: • Preeclampsia—new onset of hypertension with proteinuria after 20 weeks' gestation in a previously normotensive woman • Eclampsia—development of generalized tonic-clonic seizures in a woman with preeclampsia in the absence of other neurologic conditions that can account for the seizures • Chronic or pre-existing hypertension—hypertension (SBP > 140 mm Hg and DBP > 90 mm Hg) that predates pregnancy or that is present before 20 weeks' gestation

DBP—diastolic blood pressure, IUGR—intrauterine growth restriction, SBP—systolic blood pressure, SGA—small size for gestational age.

- In a prospective cohort study of 45 women (20 in the control group and 25 with 1 or more of fetal growth restriction [n=7], gestational hypertension [n=7], and preeclampsia [n=13]), placental abnormalities were found in all cases in the study group but not in the control group. Abnormal placentation was found to be associated with a lower mean (SD) PAPP-A level of 0.7 (0.3) MoM in the test group versus 1.1 (0.5) in the control group (P=.03).[12]
- In a prospective screening study of 8051 women, median PAPP-A MoMs were 1.002 in normal pregnancies and 0.555 and 0.911 in pregnancies with early and late preeclampsia, respectively. Logarithmic analysis of the median PAPP-A levels revealed significantly lower values in women presenting with both early (P<.01) and late (P<.03) preeclampsia compared with the control group.[13]

The remaining 2 studies were both retrospective cohort studies involving 663 and 28 566 women that investigated the association between a PAPP-A level lower than a specific cutoff point (10th percentile and 5th percentile, respectively) and the development of preeclampsia.[8,9] These studies found no association with preeclampsia and no predictive value of a low PAPP-A level for preeclampsia. The evidence is once again mixed regarding an association between low PAPP-A levels and the risk of preeclampsia.

Spontaneous abortion. Two recent studies have investigated the relationship between low PAPP-A levels and subsequent second-trimester spontaneous pregnancy loss.[9,14] In 2012, Hanita et al conducted a prospective cohort study of 42 women with threatened miscarriage and 40 controls.[14] From the total of 82 women, the authors found that the mean PAPP-A level was significantly lower in the group with threatened miscarriages who subsequently progressed to spontaneous abortions compared with the control group (0.78 MoMs vs 1.00 MoMs; P<.05).[14] In 2011, the cohort study of 28 566 women found a low PAPP-A level below the fifth percentile was predictive of subsequent miscarriage (odds ratio 14.53; 95% CI 10.44 to 20.22).[9] These recent studies suggest that low PAPP-A levels might be associated with subsequent pregnancy loss before fetal viability.

Stillbirth. Three studies have recently investigated the association between low PAPP-A level and the rate of stillbirth.[5,9,15] In 2010, a retrospective cohort of 19 536 women found a statistically significant association between PAPP-A levels below the fifth percentile and rates of stillbirth (P<.002).[5] However, the 2011 large historical cohort study of 28 566 women found no predictive value of a low PAPP-A level (below the fifth percentile) for stillbirth.[9] A 2009 study found that among women with low PAPP-A levels (below 0.3 MoMs), a higher risk of stillbirths was found when an abnormal placenta was seen on ultrasound, potentially explaining the link between a low PAPP-A level and rates of stillbirth.[15] Current evidence regarding the relationship of low PAPP-A levels with stillbirth rates remains conflicting, and additional studies are required to elucidate the relationship between a low PAPP-A level and rates of stillbirth, and the mechanism that would lead to stillbirth in such cases.

Abnormal placental morphology: the root cause? Although some evidence supports a positive association between low PAPP-A levels and adverse perinatal outcomes, there remains a relative paucity of high-quality population-based studies to determine the strength of the association and to understand which additional factors (such as multiple abnormal FTS or IPS values, clinical risk factors, or abnormal ultrasound findings) modify this risk. Therefore, it might be more helpful to shift our focus to study the likely pathogenesis behind these cases of adverse outcomes—abnormal placentation. Several recent studies have investigated the relationship between low PAPP-A levels and placentation. A small study in 2011 used Doppler ultrasound to compare "vascularization" in the placentas of 12 women with low PAPP-A levels (lower than 0.3 MoMs) with the placentas of 11 women in a control group.[16] This study found a statistically significant difference in placental vascularization that correlated with reduced number of capillary vessels per villus cross section (P=.005) and smaller capillary diameters (P=.041) in women with low PAPP-A levels. In 2009, a study showed that in women with low levels of PAPP-A, uterine artery Doppler ultrasound results (as a surrogate marker for uteroplacental vascular resistance) at 22 weeks' gestational age could be used to predict an increased risk of preterm delivery, SGA, and low birth weight.[17] Two recent studies investigating the relationship between low PAPP-A levels and preeclampsia found that low PAPP-A levels were significantly associated with abnormal placental morphology (P=.03) and abnormal uterine artery Doppler scan results (P=.001).[12,13] A 2009 study evaluated ultrasound assessment of placental function at 19 to 22 weeks in 90 women with low PAPP-A levels (below 0.3 MoMs); abnormal placental morphology was found in 19 women (21%), which was significantly associated with IUGR, preterm delivery, and stillbirth, while abnormal uterine artery Doppler scan results were of less value (P<.05).[15]

Conclusion

Although data are sparse and often conflicting, a review of the recent literature reveals some evidence of an association between low PAPP-A levels in the first trimester and adverse pregnancy outcomes including SGA, IUGR, preterm delivery, hypertensive disorders of pregnancy, and stillbirth in low-risk populations. Studies

published since 2008 demonstrate that a PAPP-A level below the fifth percentile is significantly associated with an increased chance of spontaneous abortion before the age of viability ($P<.05$).[4-9] Larger studies investigating the relationship between adverse pregnancy outcomes and low PAPP-A levels will require capture of placental pathology to test the hypothesis that abnormal placentation is the root cause. While the clinical meaning of low PAPP-A levels 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 ongoing ultrasound surveillance. All patients should continue to be screened for risk factors that might contribute to placental damage (**Box 1**). A previous complex obstetric history (**Box 2**), such as a pregnancy complicated by hypertension or IUGR, or sonographic abnormalities of the placenta or membranes, should raise further suspicion for risk of adverse pregnancy outcomes. Serial Doppler ultrasound surveillance in this subgroup of women with low PAPP-A levels might be justified.[18,19] Finally, as the intervention required to prevent stillbirth in the late third trimester is delivery, normally by induction of labour, providers might consider vaginal examination at 40 weeks in women with low PAPP-A levels to evaluate readiness for induction at 41 weeks as per the recent SOGC recommendation for all pregnancies.[20]

Box 1. Background medical risk factors for placental damage

The following are risk factors for placental damage:

- Insulin-dependent diabetes
- Substantial obesity (body mass index > 35 kg/m^2)
- Advanced maternal age (> 40 years)
- Chronic hypertension
- Previous venous thromboembolism
- Renal disease
- Autoimmune disease

Box 2. Complex obstetric history that should raise suspicion of placental damage

The following complex obstetric histories should raise suspicion of placental damage:

- Previous unexplained placental loss after 16 weeks' gestation
- Previous stillbirth after 20 weeks' gestation
- Previous delivery before 34 weeks' gestation owing to hypertension, preeclampsia, or HELLP (hemolysis, elevated liver function, and low platelet count) syndrome
- Previous intrauterine growth restriction due to placental disease, or abnormal results on uterine or umbilical artery Doppler scan

Consultative support from local obstetric providers might help guide individual pregnancy surveillance for fetal and placental health.

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Contributors

All authors contributed to the literature review and interpretation, and to preparing the manuscript for submission.

Competing interests

None declared

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