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Research Article

Enoxaparin and Low Dose Aspirin Improve Outcomes in High-Risk Pregnancies Complicated Further by Unexplained Low Maternal Serum Pregnancy-Associated Plasma Protein-A

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Abstract

Objective: To evaluate the effect of enoxaparin and low dose aspirin on outcomes of high-risk pregnancies complicated by unexplained low maternal serum PAPP-A (LPAPP-A) in comparison to similarly high-risk patients with normal maternal serum PAPP-A (NPAPP-A).

Methods: We examined 1430 high-risk gestations; 210 experienced LPAPP-A in addition to preexisting high-risk conditions and 1220 had NPAPP-A (≥ 0.5 MOM). All patients were under treatment with enoxaparin and low dose aspirin for pro-thrombotic and pre-existing high-risk conditions. We compared incidence of prematurity, birth weight < 10% (IUGR), early pregnancy loss < 20 weeks (EPL), fetal demise (FD) ≥ 20 weeks, neonatal death, preterm PROM (pPROM), abruption, and preeclampsia.

Results: Gestational age at birth was marginally different (37.4 ± 0.12 vs 37.8 ± 0.04, p=0.05). Prematurity was higher in the LPAPP-A vs. NPAPP-A group (13.6% vs 8.2%, p = 0.02). The incidence of IUGR was not different (p = 0.2). Two EPL happened in LPAPP-A (0.9%) and 16 in the normal group (1.3%), p = 0.22. There were two FDs in the NPAPP-A and none in the LPAPP-A group (1.4/1000). pPROM was similar (0.5% vs 0.0%, p = ns). Mild preeclampsia happened in 3 (0.24%) patients in the NPAPP-A group and none in the LPAPP-A group. There was no case of early severe preeclampsia.

Conclusion: Treatment with enoxaparin and low dose aspirin in high-risk patients with LPAPP-A improves clinical outcomes and obviates the difference in comparison to high-risk patients with NPAPP-A. Complications such as pPROM, abruption, fetal demise, neonatal death, preeclampsia, early pregnancy loss, and incidence of IUGR were similar in the two groups. Importantly, all such complications were significantly less frequent than previously reported in low-risk patients with LPAPP-A.

Keywords: *pregnancy; PAPP-A; IUGR; preeclampsia; pregnancy loss; fetal demise; prematurity; pPROM; enoxaparin*

Introduction

Pregnancy-associated plasma protein-A (PAPP-A) was first identified several decades ago and ever since, it has been studied extensively [1]. PAPP-A has been a very useful screening tool in the detection of aneuploid fetuses during the late first trimester [2-7]. It has been found to be a reliable screening methodology in combination with free-beta-human chorionic gonadotropin (hCG) and fetal nuchal translucency yielding detection rates of as high as 95%. After the methodology was applied to everyday practice for the detection of fetuses with Down syndrome and other aneuploidies, it became apparent that there are a number of pregnancies with abnormally low PAPP-A levels but with chromosomally normal fetuses. This condition has been termed "unexplained low PAPP-A" in otherwise normal pregnancies.

Pregnancies with unexplained low PAPP-A were found to be at higher risk than otherwise would be expected for pregnancy related complications such as preterm birth, pre-eclampsia, growth restriction, miscarriage, and fetal death [8-13]. Various studies attempted to quantify the relationship between low PAPP-A, and adverse pregnancy outcomes. It seems that in the earlier stages of the clinical application of the methodology there was some controversy as to whether low PAPP-A constitutes a risk factor for adverse outcomes. However, a large number of recent studies have clearly shown that if PAPP-A values are ≤ 0.5 MOM, the risk for adverse perinatal outcomes are significant to require our attention into finding a treatment for such pregnancies [14]. So far, it has not been possible to identify the pathology that causes low PAPP-A, in chromosomally normal fetuses; this lead to speculation that unexplained low PAPP-A is the result of quantitative and/or qualitative trophoblastic deficiency. This is appropriate since all the adverse outcomes that have been described in the international literature are outcomes usually caused by placental insufficiency.

Enoxaparin and unfractionated heparin are known to improve outcomes in high-risk patients with pro-thrombotic conditions and poor perinatal histories [15-23]. Enoxaparin treatment in a randomized clinical trial reduced the incidence of severe early preeclampsia by 88% and fetal growth restriction by 77.5% in patients at risk to develop the condition [24]. Furthermore, enoxaparin restored physiological vascular changes in women with angiotensin-converting enzyme D/D polymorphism and improved uterine artery compliance in comparison with the control group. Enoxaparin and unfractionated heparin exert angiogenic effects on placental villi *in vitro* preparations of human placenta. Such angiogenic effects lead to increased vascularization and villus formation [25]. Patients treated with enoxaparin for recurrent pregnancy loss achieved better outcomes when the anti-Xa was higher in comparison to patients with lower anti-Xa levels [23].

In our center, we collect prospectively all the important outcomes data for the purpose of internal quality analysis and quality improvement. Once a year, we analyze our outcomes against nationally acceptable averages for all serious pregnancy complications as reported by the Centers for Disease Control (CDC). We have noted that our patients with abnormally low PAPP-A levels were not experiencing as many of the complications reported in the literature and their outcomes were similar to those of pregnancies with normal PAPP-A levels. This study is a retrospective analysis of all singleton high-risk pregnancies that underwent first trimester screening for aneuploidy in our practice and examines the differences in the major complications between patients with normal PAPP-A levels and those with unexplained low PAPP-A levels. This study also compares the outcomes of our high-risk cohort with unexplained low PAPP-A in comparison with the outcomes reported in peer-reviewed journals in low risk unselect patients with unexplained low PAPP-A.

Materials and Methods

We reviewed our prenatal ultrasound database from January 1st 2010 to December 31st 2013 and extracted all singleton pregnancies, which underwent first trimester screening for aneuploidy in our practice and who were treated with anticoagulants for preexisting high-risk conditions, Table 1. We identified 1488 such pregnancies. Complete outcomes were available in 1430 and this group formed the study sample. All pregnancies were viable at the first trimester visit during which the aneuploidy study was done. We excluded singleton gestations not treated with anticoagulants and twin or higher order multiple pregnancies. The study design was reviewed by the institutional review board (IRB) and was approved. The high-risk conditions for which all patients were referred to our center is presented in Table 1.

All patients screened positive for genetic, acquired, or combined thrombophilia prior to the nuchal translucency (NT) visit. We treated these patients with anticoagulants because of the pro-thrombotic conditions identified in addition to the prior high-risk factors. (Table 1) All patients were treated with enoxaparin and low dose Aspirin. The initial enoxaparin dosage was 40 mg/day and subsequently, it was increased according to the maternal serum anti-Xa level. The goal of the treatment was to maintain an anti-Xa level between 0.3 and 0.6 ng/ml. [23] Anti-Xa levels were examined every four weeks until 34 weeks gestation. The aspirin was discontinued at 35 weeks gestation and enoxaparin was replaced by Heparin at 37 weeks gestation and continued until delivery.

High Risk Conditions	Number	Percent of Total
Assisted reproductive technologies	376	26.4%
Fetal Demise	83	5.8%
Poor Obstetrical history*	403	27.9%
Recurrent pregnancy loss	568	39.9%
Entire cohort	1430	100%

Table 1: *High-risk conditions for which all patients were treated with anticoagulants.*

**Patients who experienced one or more of the following complications during previous pregnancies: preeclampsia, preterm birth, preterm PROM, and IUGR.*

All patients underwent umbilical artery Doppler, ductus venosus Doppler and uterine artery Doppler (left and right uterine arteries) at the time of NT testing; we measured the pulsatility index (PI) of each vessel. In addition, all patients underwent umbilical artery Doppler studies as well as both uterine arteries at the time of the level II ultrasound between 20 and 23 weeks gestation. For the analysis of the uterine artery Doppler we used the mean arterial pulsatility (PI) index of both uterine arteries because it reflects the totality of uteroplacental blood supply.

All collected outcomes data were tabulated accordingly. The hospital charts were reviewed for additional information that was not available in our practice's records. Demographic data as well as delivery outcomes from the in-hospital records were crosschecked with our prospectively collected outcomes data and confirmed for completeness and accuracy. Data were analyzed for prematurity, intrauterine growth restriction (IUGR), preeclampsia, abruptio placentae, fetal death, neonatal death, premature rupture of membranes (pPROM), and early pregnancy loss (EPL). We also compared the sequential Doppler findings between patients with normal and unexplained low PAPP-A.

Preterm birth was defined as any birth < 37 weeks. Intrauterine growth restriction (IUGR) was defined as birth weight at < 10^{th} % for gestation. Preterm PROM was defined as rupture of the amniotic membranes in the absence of labor before 37 weeks gestation. Early pregnancy loss was defined as a spontaneous fetal loss between the time of NT testing and 20 weeks gestation. Fetal demise was defined as any spontaneous fetal death after 20 completed weeks. Preeclampsia was defined according to the criteria of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy, adapted by ACOG [26].

NTD laboratories did the analysis of all blood samples for PAPP-A and beta-hCG. The methodology used has been described previously [27]. All NT studies were performed by qualified and certified technicians and physicians according to the standards promoted by Fetal Medicine Foundation. All patients with chromosomally normal fetuses and with PAPP-A values of ≤ 0.5 MOM were classified as abnormal and constitute the group of patients with unexplained low PAPP-A.

Statistical analysis was done by means of JMP statistical analysis software, SAS Inc., Carry North Carolina. We performed descriptive statistical analysis, simple regression, and one-way analysis of variance for comparison of the means. Analysis of categorical data was done by means of X^2 testing. Statistical significance was set at p value of < 0.05

Results

We analyzed in total 1430 patients with complete data sets after we excluded 58 patients who delivered in other hospitals and data were not available. In 210 patients, PAPP-A was ≤ 0.5 MOM and in 1220 it was > 0.5 MOM. The value of 0.5 MOM is below the 10^{th} % for our population.

Maternal age at time of study was similar in both groups (32.6 ± 0.3 vs 32.8 ± 0.1, p = 0.5) and fetal size by CRL was similar (59.9 ± 0.5 vs 60.5 ± 0.2, p = 0.4). We found no differences in racial distribution between patients with normal and abnormal PAPP-A (p = 0.8), gravidity (p = 0.3), and parity (p = 0.4) Mean gravidity was 3.2 ± 1.7 (range 1-10) and mean parity was 1 ± 1.1 (range 0-5).Human

chorionic gonadotropin (hCG) was lower in patients with low PAPP-A (0.9 ± 0.04 vs 1.2 ± 0.02, p < 0.0001). The mean MOM of PAPP-A value in the low PAPP-A group was 0.38 ± 0.04 vs 1.2 ± 0.02 in the normal PAPP-A group, p < 0.0001). In the entire cohort, 376 (26.4%) patients experienced infertility prior to the index pregnancy and they conceived by means of in-vitro fertilization (IVF). Gravidity was similar in the two groups (3.1 ± 1.2 vs. 3.2 ± 0.05, p = 0.28).

All neonates born alive in both groups were discharged home. The spontaneous EPL rate was similar between the low PAPP-A group and the normal group (0.95% vs 1.29%, p = 0.22). There were twenty (1.4%) spontaneous pregnancy losses in the entire cohort; eighteen losses happened at < 20 weeks (1.26%). There were two fetal demises after 20 weeks in the entire cohort for a demise rate of 1.4/1000 births; both demised fetuses belonged to the normal PAPP-A group and were normally grown; their death was presumed to be the result of umbilical cord accident due to the presence of umbilical cord entanglement in the absence of other pathology.

Two patients (0.9%) in the low PAPP-A group experienced pPROM and 9 patients (0.7%) in the normal group (p = 0.30). One patient (0.5%) in the low PAPP-A experienced both, oligohydramnios and abruptio placentae. There was no case of abruptio placentae in the normal PAPP-A group. There were no cases of severe early preeclampsia (prior to 34 weeks gestation) in any of the two groups; there were 3 cases of preeclampsia in the normal PAPP-A group and they all happened between 36 and 39 weeks gestation (0.2%).

Mean gestational age at time of delivery was statistically marginally different between the low and normal PAPP-A groups (37.4 ± 0.12 and 37.8 ± 0.04, p < 0.05). However, this difference is clinically insignificant and non-existed. The incidence of prematurity however was higher in the low PAPP-A group in comparison with the normal PAPP-A group (13.6% vs 8.2%, p = 0.02). Birth weight in the low PAPP-A group was lower than in the normal group (2972.3 ± 37 vs 3180.7 ± 15, p < 0.0001). The incidence of IUGR was similar in the two groups; in the normal PAPP-A group it was 2.64% and the low PAPP-A group 4.17% (p = 0.26). In the entire cohort, the incidence of IUGR was 2.85%. The mean PAPP-A MOM value was significantly lower in fetuses that subsequently developed IUGR in comparison to fetuses with normal birth weight (0.79 ± 0.10 vs 1.17 ± 0.02, p < 0.0001); PAPP-A level between preterm and term fetuses was not different (1.03 ± 0.07 vs 1.16 ± 0.02, p = 0.056).

We identified significant differences in the Doppler findings. The uterine artery Doppler PI was higher in patients with LPAPP-A in comparison to NPAPP-A, while the Doppler PI of the umbilical artery and ductus venosus were similar. The difference in the uterine artery Doppler PI persisted until 22 weeks gestation. In contrast to the uterine artery, umbilical artery Doppler PI was similar in the two groups in the first and second trimesters. Furthermore, in fetuses that were destined to develop IUGR, the umbilical artery Doppler PI was significantly different than fetuses with normal growth. Doppler measurement comparisons between LPAPP-A and NPAPP-A groups are presented in Table 2 and comparisons between IUGR fetuses are presented in Table 3. Because of the lack of an untreated low-risk control group with LPAPP-A to compare the outcomes of our high-risk treated subjects to, we utilized summarized published perinatal outcomes of low-risk patients with LPAPP-A that were not treated with anticoagulants [14]. This comparison is presented in Table 4.

Discussion

This study reviews the outcomes of a cohort of high-risk pregnant patients treated with anticoagulants that underwent first trimester screening for aneuploidy in our high-risk practice. We compared the clinical outcomes according to PAPP-A value (MOM) at the first trimester aneuploidy screening. This study differs from the previous ones in several ways. First, all patients suffered from pre-existing high-risk conditions with significant inherent risks for poor perinatal outcomes in contrast to previous studies that were population based unselect patients with low overall risk for adverse outcomes. Second, all patients were treated according to a protocol based on the preexisting high-risk pathology. Third, all patients received anti-coagulation treatment due to genetic and/or acquired pro-thrombotic conditions in addition to the preexisting high-risk pathology. Fourth, the majority of this cohort experienced multiple pregnancy complications and pregnancy failures while treated with existing "standard" therapeutic schemes prior to the current pregnancy.

Despite early controversies on the relationship between low PAPP-A and adverse pregnancy outcomes, it seems that there is enough evidence that low PAPP-A in the presence of a genetically normal fetus is a high-risk condition associated with poor perinatal outcomes [10,12,13,28-31]. Various studies looked at associations between low PAPP-A, and placental size or uterine artery Doppler or both, and pregnancy outcomes. In patients with very low PAPP-A (≦ 0.3 MOM) and small placenta size at the time of the NT study, fetal demise affected17% of the fetuses and prematurity affected 46% of the pregnancies. In the same study, the high incidence of poor outcomes was further amplified in high-risk patients in comparison to low risk patients [28]. In our study, mean birth weight in the low PAPP-A group was decreased in comparison to normal PAPP-A. However, this is misleading because the birth weight in this group was influenced from higher incidence of prematurity due to indicated preterm delivery; the incidence of IUGR was similar in both groups. Therefore, the decreased birth weight in the low PAPP-A group is in part the result of prematurity. The rest of the outcomes in both groups were similar.

The resistance of the uterine artery in the first trimester along with PAPP-A measurements has been evaluated in relation to pre-eclampsia and IUGR but the results have been inconsistent [11,30,32-35]. Such studies described abnormal uterine arterial resistance during the first trimester in patients destined to develop preeclampsia and/or IUGR. Prior studies did not evaluate the resistance of the umbilical arteries in the same patients. Our Doppler findings are in agreement in regards to uterine arteries between low PAPP-A and normal PAPP-A groups at 11-13 weeks; furthermore, we present evidence that the difference in the uterine artery Doppler PI persisted until 22 weeks gestation. In contrast to the uterine artery, umbilical artery Doppler PI was similar in the two groups in the first and second trimesters (Table 2). Increased resistance in the uterine arteries in patients with LPAPP-A reflects an incomplete remodeling process of the uterine spiral arteries, pathology common to most placenta-related pregnancy complications. Our findings corroborate previous studies regarding uterine artery resistance in the first trimester in patients with LPAPP-A, and expanded further with documentation of persistent uterine artery abnormalities into the second trimester, in the absence of umbilical artery pathology. When we compared the umbilical artery Doppler PI, at 22 weeks, between fetuses destined to grow normally vs. fetuses destined to develop IUGR (Table 3), we found that the umbilical artery resistance was higher in fetuses destined to develop IUGR. This finding indicates that IUGR development was the consequence of first trimester uteroplacental pathology and the abnormality of the umbilical artery Doppler was a secondary event further compromising placental function. Since uterine artery oxygen content affects trophoblastic development in the placenta after 11-13 weeks gestation, decreased uterine artery compliance between first and second trimester might be responsible for the decreased compliance we found in the umbilical artery in the second trimester in fetuses with IUGR.

Doppler Vessel Examined	Low PAPP-A	Normal PAPP-A	*p-value*
Ductus Venosus PI	1.04 ± 0.01	1.02 ± 0.005	P = ns
Umbilical Artery PI at 11 weeks	2.2 ± 0.03	2.1 ± 0.01	P = ns
Umbilical Artery PI at 22 weeks	1.06 ± 0.01	1.05 ± 0.006	P = ns
Mean Uterine Artery PI at 11 weeks	1.62 ± 0.03	1.51 ± 0.01	P = 0.001
Mean Uterine Artery PI at 22 weeks	0.85 ± 0.01	0.77 ± 0.006	P < 0.001

Table 2: *Comparisons of Doppler Pulsatility Index (PI) in fetal and maternal vessels between patients with low PAPP-A and normal PAPP-A values.*

In a comprehensive review of the existing literature, Gagnon., *et al*. [14] revealed that the incidence of intrauterine growth restriction, preterm birth, fetal death at > 24 weeks gestation, pre-eclampsia, and spontaneous abortion were two to three-fold higher in unselect low-risk pregnancies complicated by low PAPP-A in comparison to similar risk pregnancies with normal PAPP-A values [14].

Our high-risk patients with unexplained low PAPP-A experienced significantly reduced incidence of obstetric complications in comparison to low-risk patients with unexplained low PAPP-A as summarized by Gagnon *et al* in the international literature Table 4 [14].

Doppler Vessel Examined	IUGR	NORMAL	*p-value*
Ductus venosus PI (Mean ± SE)	1.05 ± 0.03	1.02 ± 0.05	P = ns
Umbilical artery Doppler PI at 11 weeks	2.12 ± 0.01	2.22 ± 0.07	P = ns
Umblical artery Doppler PI at 22 weeks	1.14 ± 0.03	1.04 ± 0.00	P = 0.003
Mean uterine artery PI at 11 weeks	1.73 ± 0.06	1.51 ± 0.01	P < 0.0001
Mean uterine artery PI at 22 weeks	0.93 ± 0.03	0.77 ± 0.01	P < 0.0001

Table 3: *Doppler measurements in foetuses with IUGR in comparison to normally grown foetuses.*

Poor Outcomes	Low-risk patients with low PAPP-A (%)*	Present Study (%) ++	Reduction of Incidence of poor outcomes (%)
Birth Weight < 10% (IUGR)	19	4.17	79
Fetal Death > 20 weeks (%)	5.2	0.0	100
Neonatal Death (%)	6.1	0	100
Preterm PROM (pPROM) (%)	3.0	0.9	70
Early Pregnancy Loss < 20 weeks (EPL) (%)	4.6	0.95	80
Abruption (%)	5.0	0.5	90
Preeclampsia (%)	9.3	0.0	100

Table 4: *Outcomes in low-risk patients with unexplained low PAPP-A in comparison to outcomes in our high-risk cohort with unexplained low PAPP-A.*

**These percentages are averages of the incidence of poor outcomes as reported by Gagnon., et al. [].*

++Incidence of outcomes in our high-risk patients with low PAPP-A treated with anticoagulants for pre-existing high-risk condition.

It is a weakness of our study that due to the nature of our practice we could not have our own controls to compare outcomes between low-risk patients with low PAPP-A vs. our high-risk patients with low PAPP-A. We instead used the summarized risks calculated from the review of the international literature as done by Gagnon., *et al*. [14] Accordingly and despite the lack of untreated low-risk controls, our study demonstrates a comprehensive and significant reduction in the incidence of preeclampsia, IUGR, pPROM, fetal death, neonatal death, abruption, and early pregnancy loss regardless of how one looks at it. Accordingly, one would have expected our findings to be even more impressive have we had the opportunity to compare our high-risk treated LPAPP-A patients with a group of low-risk untreated LPAAP-A patients. We speculate that in addition to the antithrombotic benefit of enoxaparin the prevention of serious complications in our high-risk cohort and the subgroup of patients with unexplained low PAPP-A is the result of the combined effects of enoxaparin including anti-thrombotic, angiogenic, and its effect on angiotensin production [24,25,36,]. With the exception of fetal and neonatal death, events that are usually rare in low risk patients, our study had enough power to identify any significant difference in the other complications. Despite the limitations of the study, the findings are significant enough to prompt further research on the use of enoxaparin and low dose aspirin in pregnancies complicated by unexplained low PAPP-A as well as in pregnancies at significant risk for adverse perinatal outcomes secondary to placental insufficiency.

Conclusion

In conclusion, our study demonstrates a significant reduction of preeclampsia, IUGR, pPROM, abruption, early pregnancy loss, fetal demise, and neonatal death in patients at risk for such complications due to pre-existing high-risk conditions complicated further by unexplained low PAPP-A. Our study also provides evidence that enoxaparin and low dose aspirin exert a significant reduction in the incidence of such severe pregnancy complications in patients at risk due to prior poor history with normal maternal serum PAPP-A. Controlled studies in the future will enhance our understanding of the precise utility of such anti-thrombotic treatments in the prevention of serious obstetrical complications.

Conflict of Interest

The authors declare that they do not have any conflict of interest.

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