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CASE REPORT

# Advantages of the Quadruple Screen over noninvasive prenatal testing

Nathan A. Keller & Asha Rijshinghani

Department of Obstetrics and Gynecology, Albany Medical Center, 16 New Scotland Avenue, Second Floor, MC-74 Albany, New York 12208

**Correspondence**
Nathan A. Keller, Department of Obstetrics and Gynecology, Albany Medical Center, 16 New Scotland Avenue, Second Floor, MC-74 Albany, New York, 12208.
Tel: 1-717-679-5629; Fax: 1-518-262-4942;
E-mail: kellern@mail.amc.edu

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## Key Clinical Message

Noninvasive prenatal testing (NIPT) is becoming increasingly popular with some offering it as a primary screen option in all patients in place of serum screening. Serum screening offers insight into placental function, which NIPT does not. Abnormal levels of analytes in the serum screen have been associated with pregnancy complications.

## Keywords

cell-free DNA, noninvasive prenatal testing, Quadruple Screen

## Introduction

Noninvasive prenatal testing (NIPT) is becoming increasingly popular in the United States, with increasing advocacy in the medical community. Some obstetricians now standardly offer cell-free DNA (cfDNA) to all high-risk patients [1]. One recent study concluded that cfDNA testing had significantly lower false positive rates and higher positive predictive values for trisomy 21 and 18 than standard screening with serum analytes [2]. The Quadruple Serum Screen (QUAD Screen) has been favored for reasons that it is far less expensive than cfDNA. We present a case where the QUAD Screen was very helpful in management of a high-risk pregnancy in a patient with negative cfDNA, allowing timely introduction of thromboprophylaxis and fetal surveillance. Our case also suggests a possible therapeutic role for prophylactic doses of enoxaparin on placental function.

## Case Report

A 30-year-old Gravida 5 Para 0040 at 11 + 0 weeks gestational age (GA) presented with a history of recurrent spontaneous abortions at 7, 9, and 12 weeks GA. Her fourth pregnancy was an ectopic pregnancy. Preconception workup included parental karyotypes and hysterosalpingogram, both of which were normal. Our patient's antiphospholipid antibody workup was negative, but did demonstrate Factor V Leiden (FVL) heterozygosity. The reason to test for FVL was for reasons of a positive family history. She denied smoking, alcohol, or drug abuse. Due to her past obstetrical history and FVL heterozygosity, a decision was made to start prophylactic enoxaparin 40 mg subcutaneously daily and aspirin 81 mg oral daily at 7 weeks GA.

At 14 + 2 weeks GA the patient experienced an episode of vaginal bleeding. Ultrasound examination revealed a small subchorionic bleed. Due to the ultrasound findings, enoxaparin and aspirin were discontinued.

A repeat ultrasound exam at 17 + 5 weeks GA was significant for a 2-week lag in fetal growth. At 19 + 5 weeks GA the discrepancy between GA and fetal growth was 3 weeks. Fetal anatomical examination was limited due to intrauterine growth restriction, but no obvious structural anomalies were seen and amniotic fluid volume and placental echotexture both appeared normal. Doppler flow

studies in both umbilical arteries revealed elevated resistance with S/D ratios of 8.7 and 9.3.

First trimester screen was normal with a Down Syndrome risk of 1/490 (PAPP-A: 0.45 MOM, THCG: 1.68 MOM, and Nuchal Translucency: 0.60 MOM). However, due to early onset fetal growth restriction, the patient was recommended the 2nd trimester serum screen for assessment of placental function. The results of the QUAD Screen at 17 + 5 weeks GA revealed a MSAFP of 2.61 MOM, THCG of 3.52 MOM, Inhibin-A of 3.73 MOM and uE3 of 0.40 MOM. As anticipated, the Down Syndrome risk based on the QUAD screen was 1 in 3. Free fetal DNA was obtained which was negative.

Due to the results of the serum analytes and lagging fetal growth, placental dysfunction was suspected and close maternal and fetal surveillance was initiated with weekly visits. Prophylactic doses of enoxaparin 40 mg daily and aspirin 81 mg daily were restarted at 19 + 5 weeks GA.

A repeat ultrasound examination at 23 + 5 weeks GA revealed worsening fetal growth restriction with an EFW of 272 g and UA Doppler studies revealed absent end diastolic flow (AEDF). Oligohydramnios was documented with an AFI of 5.9 cm. The patient was counseled regarding the increased risk of fetal demise.

Surprisingly, at 25 + 5 weeks GA normal end diastolic flow was documented in the umbilical arteries with S/D ratios of 3.0 and 3.5. At 27 + 6 weeks GA UA Doppler flow studies continued to be normal with S/D ratios of 2.49 and 3.08 and an EFW of 504 g. Intense fetal monitoring was initiated to assess fetal well-being in view of the interval fetal growth and fetal weight. Due to a biophysical profile (BPP) of 6/10 with nonrepetitive variable decelerations the patient was observed on labor and delivery and a course of betamethasone was administered for fetal lung maturation. The nonstress test was subsequently reactive with a reassuring BPP of 8/8 and UA S/D ratio of 3.0.

At 29 + 2 weeks GA the patient was admitted with preterm premature rupture of membranes and the betamethasone course was repeated. Two days after admission the patient went into spontaneous labor and due to a nonreassuring fetal heart rate tracing, delivery by a cesarean section was performed. Apgar scores were 5, 7, and 9 at 1, 5, and 10 min and neonatal weight was 720 g.

On the pathology report the amniotic membranes were described as dull, thin, delicate, and green tinged. The umbilical cord was trivascular with central insertion. The placenta weighed 170 g with signs of acute vasculitis, funisitis, and chorioamnionitis.

## Discussion

In recent years NIPT is becoming increasingly popular. Even in patients not at high risk of fetal aneuploidy some providers are offering NIPT [1]. However, NIPT is unable to evaluate placental dysfunction, and cannot be used for determination of risk for preterm delivery, fetal growth restriction, preeclampsia, placental abruption, intrauterine fetal demise, and perinatal death. Additionally, prohibitive cost has been identified as a major hurdle in the more routine use of NIPT in low risk patients [3]. In a cost-consequence analysis in Belgium, the authors concluded that the price of NIPT needs to be lowered substantially due to the government's limited resources for universal reimbursement [4].

In our patient due to a normal first trimester serum screen, the second trimester screen was not obtained initially. However, due to the ultrasound findings, we obtained the second trimester serum screen and all four analytes on the QUAD Screen were abnormal indicating that IUGR was probably related to placental pathology. Due to the abnormal QUAD Screen results intensive maternal and fetal monitoring was initiated which allowed us to deliver a live fetus in a timely fashion.

While NIPT may be the most accurate screening for certain aneuploidies, the American College of Obstetricians and Gynecologists and the Society of Maternal-Fetal Medicine caution that its use is solely for fetal aneuploidy and that NIPT should not be part of routine laboratory assessment, but instead should be an informed patient choice for women at high risk of fetal aneuploidy [5]. In patients who are at risk of placental-based pregnancy complications the integrated screen may be a better option for assessment of fetal chromosomal abnormalities, placental function, and fetal risks associated with placental dysfunction. In our case, the QUAD Screen results helped us in initiating an extensive surveillance of the pregnancy which may have allowed the pregnancy to reach viability.

The suspected placental dysfunction based on the serum analytes led us to restart prophylactic enoxaparin and aspirin which appears to have helped in our case. The previously abnormal UA blood flow with AEDF improved markedly following the initiation of the above medications with normalization of blood flow in the umbilical arteries. Normal UA S/D ratios were maintained until delivery and the authors believe this reversal may have been due to a "therapeutic effect" on placental blood flow from thromboprophylaxis of enoxaparin.

AEDF is considered a pathological finding associated with increased risk of perinatal death [6]. Previous authors have recognized that AEDF may rarely temporarily improve only to have subsequent worsening [7]. Further there is no evidence in the literature that once placental function has deteriorated that prophylactic doses of enoxaparin and aspirin can reverse the pathologic process. In our case, the enoxaparin and aspirin were

 

restarted due to the finding of the abnormal serum analytes. Even though prior reports do not support beneficial effects of enoxaparin once umbilical arteries reveal AEDF, in our case it appears to have had a therapeutic effect. It is our belief that if prophylactic enoxaparin had not been restarted in a timely fashion, downstream resistance of the placental circulation would have continued with a high likelihood of a fetal demise. We believe this case may also demonstrate a therapeutic role of prophylactic doses of enoxaparin.

While NIPT is a far more accurate screening tool for certain fetal aneuploidies, our case illustrates the role of the serum analytes of the QUAD Screen as markers of placental function in addition to aneuploidy screening. Abnormalities in these markers can identify patients at highest risk for poor pregnancy outcomes due to placental dysfunction with consequent modification of management of care during pregnancy [8]. In patients that undergo NIPT only, the benefit of the serum screen is lost. More recently, authors have argued in favor of offering NIPT universally to all pregnant women in place of the serum screen. Since more women have placental-based pregnancy complications, especially in the younger age group, we strongly favor the integrated serum screen over NIPT which will help identify these high-risk women and allow timely intervention.

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None.

## Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images.

## Conflict of Interest

None declared.

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