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Update on Early Prenatal Screening in 2025

Ken Seethram, MD

Advances in prenatal screening over the last three decades have delivered methods which broadly focus on genetics, fetal well-being, and preeclampsia screening, offering early insights in pregnancy to enable better risk management and planning strategies.

Key Takeaways
• First trimester is the critical window for comprehensive screening.
• NIPT is powerful but should not replace ultrasound or PE screening.
• Combining tools improves detection and allows earlier intervention.
• Patients benefit most from integrated screening with same-day risk disclosure when possible.
• Don’t skip ultrasound even with normal NIPT — 1.1% of anomalies will be missed.
• Low-dose aspirin is proven to reduce preterm PE by 62% if started by 14 weeks.
• NIPT is not suitable for vanishing twins or triploidy.
• Screening tools are complementary, not interchangeable.

Background

Prenatal screening has undergone tremendous evolution over the past 100 years. In 1933, Penrose[1] was the first to identify the association between Trisomy 21 (Down syndrome) and advanced maternal age. The discovery of the human diploid chromosome number 46 by Tijo and Levanin in 1956,[2] along with the development of metaphase karyotyping, enabled the precise correlation of the Trisomy 21 genotype with its clinical phenotype. This breakthrough opened the possibility for diagnostic testing, leading to the deployment of procedures such as amniocentesis and chorionic villus sampling (CVS).

Moving from Diagnostics to Screening

Amniocentesis and CSV are referred to as invasive diagnostic tests, each carrying an estimated 1% risk of miscarriage. In the mid-1980's the introduction of double and triple marker screening enabled the possibility of triaging pregnancies for invasive testing. Triple marker screening also expanded the scope of screening goals beyond Trisomy 21, to include other abnormalities such as aneuploidy and neural tube defects. While double and triple marker screening offered improved performance over age-based screening alone, they were associated with high false positive rates, and results which were delayed until 18–20 weeks of gestation.

By the late 1980's, prenatal screening was beginning to expand from a singular emphasis for detecting Trisomy 21 to a broader one on general fetal wellness. As well, consumer interest was changing, which drove the demand for prenatal screening options available as early as possible in pregnancy.

Three Advancements of Prenatal Screening

There have been three major developments in prenatal screening since 1990. These include advances in early ultrasound techniques and the description of markers for aneuploidy, the introduction of non-invasive prenatal testing (NIPT), and the development of preeclampsia (PE) screening.

Ultrasound

The early 1990s marked the dawn of a new era in screening with the development of ultrasound as a driving tool for prenatal screening. Nuchal Translucency (NT), (**Figure 1**), first described by Kypros Nicolaides,[3] became an early screening tool between 11–14 weeks of gestation. It offered an improved detection rate (versus serum screening) and a lower number of screen-positive results. When NT measurement was combined with serum markers such as serum pregnancy associated plasma protein-A (PAPP-A), and human chorionic gonadotropin (hCG), the screening achieved detection rates of 85%, with a 5% screen-positive rate, all prior to prenatal week 14. Subsequently, the correlation with nasal bone (NB) assessment,[4] followed by the addition of ductus venosus (DV) flow evaluation brought the "First trimester screen (FTS)" detection rates to 96% with a 3% screen-positive rate.[5] In addition, the ultrasound examination provided the added benefit of identifying fetal defects involving the spine, brain, cardiac, gastrointestinal, bladder, and limbs. DV flow has been linked to a 6.9-fold increase in the risk of congenital heart disease.[6] As such, DV assessment provides a functional screening tool to identify fetuses at a risk of congenital heart defects. Contemporary FTS screening between 11–14 weeks now includes five key factors for risk assessment: NT, NB, DV, serum PAPP-A and serum beta hCG.

The Fetal Medicine Foundation maintains the largest database of NT, NB, and DV measurements. To address quality assurance, access to this database is restricted to individuals accredited by the Fetal Medicine Foundation.[7] These users can connect through a variety of software platforms which then generates the risk assessment profiles for each patient. This process supports effective counselling to determine risk levels and discussions about further diagnostic testing options when indicated.

Ultrasound has evolved a multifaceted approach to screening, including aneuploidy screening via markers, anatomy assessment, pregnancy dating, and cardiac evaluation. This approach has expanded the focus of screening toward a broader view of fetal health.

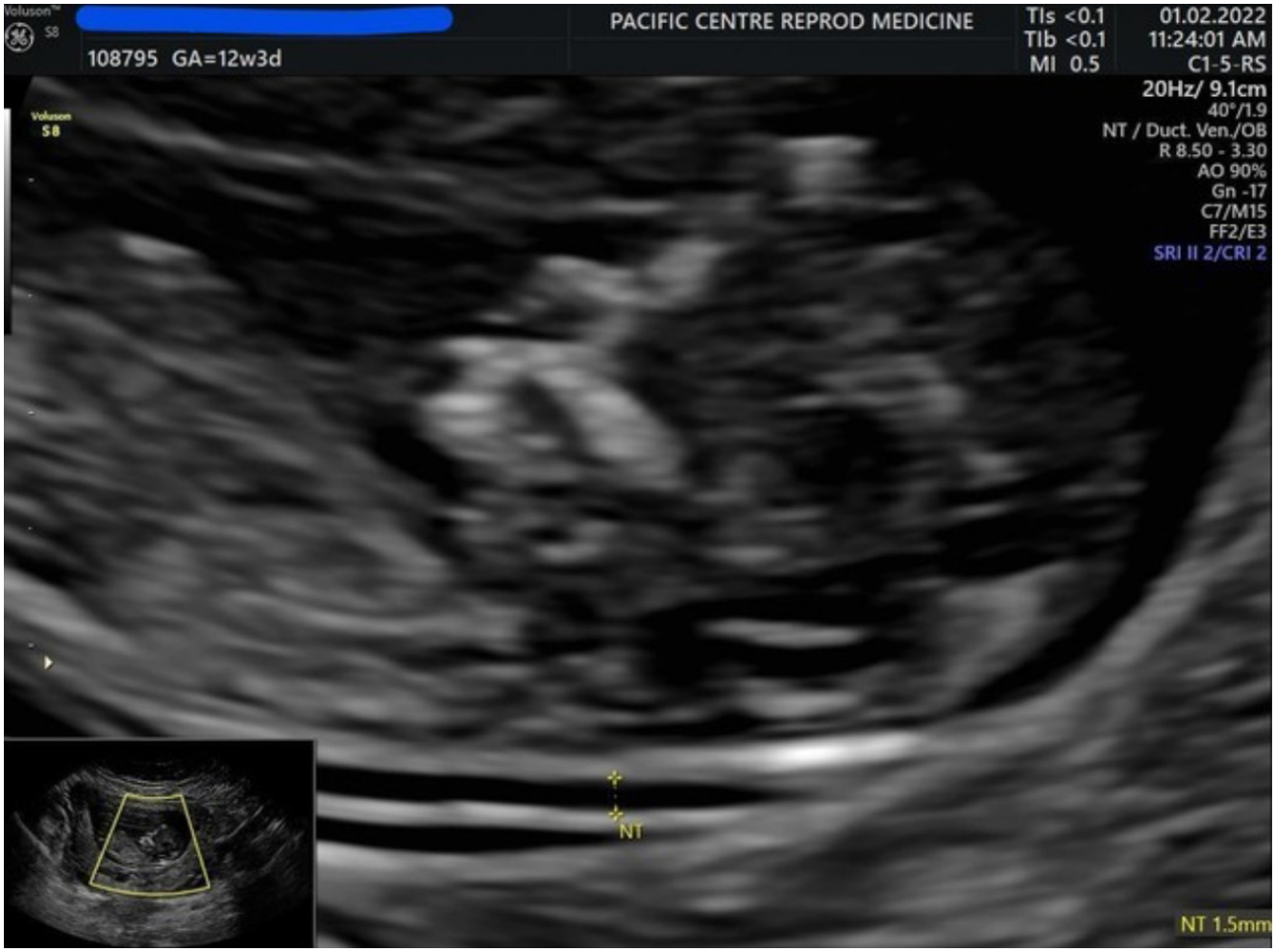

Figure 1. Nuchal translucency measurement at 12 weeks and 3 days of gestation; *courtesy of Ken Seethram, MD.*

Non-Invasive Prenatal Testing/Screening

Since 1997, it has been recognized that we can recover fragments of placental DNA[8] (small, typically under 1000 Kilo-base pairs) that can be detected in the maternal blood stream as early as 8 weeks of gestation. These fragments can be compared against the human genome library to reassemble the fetal genome and detect aneuploidies. Over time, various methods have emerged, including those targeting selective regions or individual mutations. Despite the expansion of some panels to include rare disease detection, the focus of NIPT remains the detection of aneuploidy.

NIPT aneuploidy (Trisomy 21, 13, 18) achieves detection rates higher than 99%. However, several notes and limitations prevent NIPT from serving as a standalone prenatal screening tool:

1. Approximately 1–3% of results yield a "no-call" or a "redraw request" often due to a low 'fetal fraction' (the proportion of placental versus maternal DNA), and can be linked with increased risks of aneuploidy, placental mosaicism, maternal malignancy, or technical issues. A redraw will yield a result in most cases.
2. Failed NIPT – options to consider include detailed anatomy ultrasound, genetic counseling referral including a discussion about invasive testing.
3. False positive rates remain below 1%.
4. NIPT is not applicable in cases of vanishing twins.
5. All NIPT methods (apart from SNP-based methods) do not detect triploidy.
6. Because NIPT analyzes placental cells, it may not reflect the current viability of the fetus.

Introduced in 2011, NIPT has since evolved to include screening for microdeletions and microduplications.[9] These types of mutations are quite rare but have broadened the scope and appeal of the test. In addition, the ability to determine fetal sex through NIPT has contributed to its growing popular appeal.

Pre-Eclampsia (PE) Screening

PE affects 2–8% of pregnancies and is a global contributor to 46,000 maternal deaths, and 500,000 fetal or newborn deaths. It is associated with primigravida status, multifetal pregnancy, obesity, and other medical conditions.[10] PE stems from imperfect implantation and placental development, wherein the lack of proper trophoblastic invasion and vascular recruitment lead to impaired placental bed perfusion. This compromised blood flow can manifest in fetal growth restriction and oligohydramnios during the second or third trimester. This impaired perfusion can then result in maternal physiological adaptations resulting in hypertension. In the short term, the hypertensive response is of benefit by improving placental perfusion. Over the longer term, the increase in maternal blood pressure can adversely affect end-organs, including the liver, bone marrow, and brain. Early detection of impaired placentation offers both clinical and therapeutic advantages, such as prompting closer surveillance, and timely initiation of low-dose Aspirin (ASA). The efficacy of ASA in reducing the risk of PE has been demonstrated in several trials. The 2017 ASPRE trial,[11] which used first trimester PE screening followed by randomized treatment with ASA versus placebo, demonstrated that administering 150 mg/day of ASA from 11–14 weeks until 36 weeks reduced the incidence of preterm preeclampsia by 62% in those at high risk of PE.

Early PE screening can consist of several elements including:

1. A detailed maternal history
2. Blood pressure measurements (two measures, simultaneously in both arms, repeated 5 minutes apart) to calculate the mean arterial pressure (MAP)
3. Uterine artery Doppler measurement
4. Serum proteins such as PAPP-A and Placental Growth Factor (PIGF)

Due to the accuracy and simplicity of screening, combined with the morbidity and mortality of PE, the International Federation of Gynecology and Obstetrics released a global initiative in 2019 to promote standardized PE screening strategies.[12]

Logistics of Early Testing

All of the early screening components described above can be completed prior to the end of the first trimester. The window for FTS screening is 11–14 weeks of gestation, (or a 45–84 mm of Crown rump length). Serum analytes used in PE screening can be processed using the same analyzer that processes chemical assays for beta hCG and PAPP-A. Several algorithms are available to support this integrated approach to screening:

1. NIPT alone. This can be performed as early as 8 gestational weeks.
2. NIPT combined with FTS. In this algorithm, venipuncture is performed prior to the FTS ultrasound. The serum is analyzed for biochemical markers, often within 35 minutes. This allows for an integrated risk assessment of markers with biochemistry, allowing for result disclosure immediately following the ultrasound. The plasma can also be used for NIPT, with turn-around-times ranging from 7–10 days depending on the provider. Alternately, patients may undergo a blood draw 7 days prior to the ultrasound, permitting a full disclosure of both FTS and NIPT results at the time of the ultrasound.
3. FTS with PE screening. This approach involves a combination of maternal history, sequential blood pressures, uterine artery Doppler assessment, and rapid analysis of placental growth factor. A results disclosure for both PE and FTS screening can be provided at the conclusion of the ultrasound visit.
4. A comprehensive approach that combines FTS with PE screening and NIPT.

Why Combine Screening Tools?[13]

NIPT reflects the genetic profile of placental DNA. Several studies have shown that approximately 5% of fetuses with low-risk NIPT had abnormal marker findings on first trimester ultrasound. As well, relying on low-risk NIPT results without ultrasound would miss approximately 1.1% of major structural anomalies. The inherent value of PE screening and the relative ease of adding it to FTS screening makes it a very appealing tool to help reduce downstream mortality and morbidity.

Patient Triaging Algorithm

Possible outcomes following early prenatal screening incorporating FTS, PE screening, and NIPT:

1. **Low-risk results across FTS, NIPT, and PE screening**
   a. These patients typically require prenatal care with minimal intervention.
2. **High risk findings on FTS or NIPT**
   a. These patients benefit from referral to Maternal Fetal Medicine for consideration of diagnostic testing such as CVS or amniocentesis.
3. **Abnormal DV flow:** if reversed DV flow is observed despite normal genetic assessment, fetal echocardiography is advised.
4. A **4-chamber cardiac view** is also recommended during the 11-14w scan.
5. **High Risk PE screening**
   a. These patients benefit from the administration of low-dose ASA (162 mg) nightly.
   b. As well, enhanced surveillance may include home BP monitoring, fetal growth surveillance, and other supportive measures.

Costs of Screening and Availability

In the Canadian health system, access to prenatal screening can vary across provinces and territories. At a minimum, patients should receive some form of risk assessment beyond maternal age to determine whether diagnostic procedures such as amniocentesis or CVS is advised. In the best-case scenario, comprehensive screening incorporates all available modalities. Many managed health systems have explored tiered screening, wherein an abnormal NIPT result is followed up with FTS screening, or vice versa, which offers effective screening at a low cost. However, a more integrated and thorough screening strategy in the first trimester may provide women with earlier, more complete information, and opportunities for downstream risk reduction. In this way, greater investments in early screening could provide reduced healthcare costs and improved outcomes later in pregnancy.

Summary

Over the last 30 years prenatal screening has undergone a remarkable evolution, enabling providers and their patients greater insight into fetal and maternal health. Advancements in genomics and NIPT, along with improvements in ultrasound markers, fetal anatomic assessment, and preeclampsia screening, have led to an unprecedented opportunity to provide more meaningful information early in pregnancy. These evolving tools offer an opportunity to change the way we provide prenatal care in the future.

Appendix: Summary Tables

1. Initial Time Window
All prenatal screening should ideally be completed before 14 weeks gestation. The optimal window is between 11–14 weeks, when the crown-rump length (CRL) measures between 45–84 mm.
2. Screening Options and What to Know
Option A: NIPT Alone
• Detects Trisomy 21, 18, and 13 with high sensitivity (>99%).
• May miss structural anomalies and is not useful in vanishing twins or triploidy.
• Best for patients who decline ultrasound but want early genetic screening.
Option B: NIPT + First Trimester Screening (FTS)
• Combines genetic risk data from NIPT with anatomic and functional screening from ultrasound and biochemistry.
• Ultrasound includes nuchal translucency (NT), nasal bone (NB), ductus venosus (DV) flow, and markers like PAPP-A and beta hCG.
• Allows immediate disclosure of results when bloodwork is pre-drawn.
• This is a preferred option for comprehensive early assessment.
Option C: FTS with Pre-Eclampsia (PE) Screening
• Adds risk prediction for preeclampsia using maternal history, blood pressures (both arms, repeated), uterine artery Doppler, and placental markers (PAPP-A and PlGF).
• Enables timely initiation of low-dose aspirin (162 mg at bedtime) for high-risk patients, which has been shown to reduce preterm preeclampsia by up to 62%.
Option D: Full Integration (Best Practice)
• Combines NIPT, FTS, and PE screening.
• Offers the most complete picture of fetal and maternal risk early in pregnancy.
• Can often be done in a single visit with appropriate timing and logistics.
3. What to Do with Results
• If all results are low-risk (FTS, NIPT, and PE), continue with routine prenatal care.
• If there are high-risk findings on NIPT or FTS, refer to Maternal-Fetal Medicine for consideration of diagnostic testing like CVS or amniocentesis.
• If ductus venosus flow is abnormal (e.g., reversed flow), recommend fetal echocardiography, even if genetic tests are normal.
• If PE screening shows high risk, start ASA 162 mg nightly and consider enhanced surveillance including home blood pressure monitoring and serial fetal growth assessments.

Screening Modalities Overview

Screening Modality	Timing	Purpose	Who Should Get It
FTS (Ultrasound + Biochemistry)	11–14 weeks	Trisomy screening, structural anomalies, cardiac defects	All patients; baseline screen
NIPT (cfDNA blood test)	As early as 8 weeks	High sensitivity screen for trisomy 21/18/13, fetal sex	All patients, esp. maternal age >35, prior aneuploidy, or high-risk ultrasound
PE Screening (BP, Doppler, PAPP-A, PIGF)	11–14 weeks	Predict preeclampsia; ID high-risk for aspirin	All patients, especially primigravida, obesity, twins, or medical comorbidities

Results and Recommended Actions

Result	Recommended Action
Low-risk FTS, NIPT, PE	Continue routine prenatal care
High-risk NIPT or FTS	Refer to Maternal-Fetal Medicine; consider CVS or amniocentesis
Abnormal ductus venosus flow (e.g., reversed flow)	Recommend fetal echocardiogram
High-risk PE screen	Start ASA 162 mg nightly, monitor BP, fetal growth surveillance

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Financial Disclosures

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