



Twins: First Trimester Evaluations

Voluson™ Ultrasound Systems

Harmony® NIPT

Twin pregnancies are more prevalent due to use of assisted reproduction technologies and have greater risk for complications compared to singleton pregnancies.¹⁻⁵ Accurate assessment of gestational age, chorionicity, structural and chromosomal anomalies in the first trimester is of particular importance in this population.¹⁻⁵ Management protocols that include properly timed detailed ultrasounds and targeted cell-free DNA analysis can allow for optimized care of these potentially complex pregnancies.¹⁻⁵

Twin pregnancies are at higher risk for perinatal morbidity/mortality, structural anomalies, and chromosomal conditions. Compared with singletons, twins are at increased risk of preterm delivery due to maternal and fetal complications.¹⁻⁵ The risk is significantly higher in monochorionic compared to dichorionic pregnancy.¹⁻⁵ The first trimester assessment presents a unique opportunity to evaluate for potential complications.

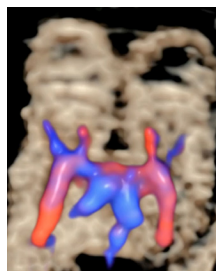


Monozygotic twins highlighted with HDlive – Image courtesy Bernard Benoit



2D image of Dichorionic twins – Image courtesy Bernard Benoit

A detailed first trimester ultrasound is recommended for accurate assessment of gestational age, and chorionicity, which allows for proper triage of pregnancies at risk for pre-term birth and twin-to-twin transfusion syndrome.¹⁻⁵ It also enables identification of increased nuchal translucency and many major structural anomalies including fetal heart defects, that can be isolated or associated with genetic, chromosomal or other malformation syndromes.⁶ This early evaluation provides information for pregnancy management including follow-up imaging and diagnostic testing options.¹⁻⁵



Monozygotic twins with STIC color applied – Courtesy of Daniel Moeglin

Data indicates that the most accurate assessment for trisomy 21 involves additional markers beyond first trimester ultrasound.¹⁻⁶ Until recently, routine screening for trisomy 21 in twins involved the combination of nuchal translucency and first trimester serum biomarkers. This method can achieve a detection rate of up to 87% in singleton gestations but may be less accurate in twins and has a 5% false positive rate.¹

Cell-free DNA (cfDNA) analysis by the Harmony test was proven to be superior to traditional serum testing for trisomy 21 in singleton gestations in 2015, based on higher detection rate (>99%) and 90-fold lower false positive rate (less than 0.1%).⁷ A low false positive rate is recognized as a major benefit of this targeted test, since false positives are associated with increased maternal anxiety, complexity of care and number of unnecessary invasive procedures.^{1,8-11}

Harmony test results in twin validation studies

Study	Trisomy 21	Trisomy 18	Trisomy 13	Euploid	Fetal Sex
Gil et al (2014)	9 of 10		1 of 1	181 of 181	
Gil et al (2019)	16 of 17	9 of 10	1 of 2	962 of 968	
Jones et al					39 of 39
Totals	25 of 27	9 of 10	2 of 3	1,143 of 1,149	39 of 39

The benefits of a low false positive rate in a population with a higher rate of Assisted Reproductive Technology (ART) conceptions and increased risk of loss after invasive testing (up to 3.8%) has led to global calls for peer-reviewed evidence supporting the use of cfDNA analysis in twin pregnancies.^{1,4,5,12-14} The Harmony test has been used in twin pregnancies since 2013 with performance evaluated in nine peer-reviewed publications.¹⁵⁻²³

Peer-reviewed Publications with the Harmony test in Twins

Year	First Author	# Twin Samples	Di-chorionic	Mono-chorionic	In vitro fertilization
2014	Gil	275	174	101	
2014	Struble	70	35	35	
2015	Stokowski	40			
2015	Bevilacqua	515*	301	67	272
2016	Sarno	438*	373	65	246
2017	Jones	51			
2019	Galeva	224*			
2019	Galeva	928*	806	122	517
2019	Gil	997	854	143	231

*included in Gil 2019

A recent meta-analysis by Dr. Mar Gil and Prof. Kypros Nicolaides et al. concluded that the performance of cfDNA analysis for trisomy 21 in twin pregnancies is comparable to that in singletons and is superior to non-cfDNA-based screening tests currently used.¹⁷

**Meta-analysis:
Pooled Weighted Performance of cfDNA for Trisomy 21 in Twins**
3,774 twin pregnancies
56 with trisomy 21

98.2%
Detection Rate

0.05%
False-Positive Rate

A combination of detailed first trimester ultrasound and targeted cfDNA analysis streamlines care of twin pregnancies. When used in combination, these screening techniques enable early detection of chromosomal conditions, structural anomalies and pregnancies at risk for twin-to-twin transfusion syndrome with low false positive rates.



Nice 3D rendering of twins



Monochorionic twins with 2 cord insertion – Image courtesy of Bernard Benoit

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Harmony is a non-invasive prenatal test (NIPT) based on cell-free DNA analysis and is considered a prenatal screening test, not a diagnostic test. Harmony does not screen for potential chromosomal genetic conditions other than those expressly identified in this document. All women should discuss their results with their healthcare provider, who can recommend confirmatory, diagnostic testing where appropriate. The Harmony Prenatal Test was developed, and its performance characteristics determined by Ariosa Diagnostics, a CLIA and CAP accredited clinical laboratory in San Jose, CA USA. This testing service has not been cleared or approved by the US FDA.

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