NEWSLETTER

This newsletter centers on reproductive topics with a genetics focus. If there is an organization or upcoming webinar you'd like me to include in a future newsletter, please feel free to reach out at genetics@modernreproduction.org.

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Webinars:

AMBRY GENETICS: CURRENT STATE OF PRENATAL WHOLE EXOME SEQUENCING

On Demand

ONCOFERTILITY CONSORTIUM

Topics include:

- Conservative Management of Gynecologic Cancers and Fertility
- Preserving Fertility After Colorectal Cancer
- Reproductive Hormones & Fertility Throughout the Lifespan in Klinefelter Syndrome

On Demand

NEWSLETTER

The little lit review

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Impact of trophectoderm biopsy for preimplantation genetic testing on obstetric and neonatal outcomes: a meta-analysis

Di Mao, PhD; Jian Xu, MD; Ling Sun, MD

OBJECTIVE: This study aimed to investigate whether trophectoderm biopsy for preimplantation genetic testing is associated with an increased risk of adverse obstetrical and neonatal outcomes compared with conventional in vitro fertilization or intracytoplasmic sperm injection without preimplantation genetic testing.

DATA SOURCES: Entries between January 1990 and August 2022 were searched using MEDLINE, Embase, Web of Science, the Cochrane Library, and Google Scholar.

STUDY ELIGIBILITY CRITERIA: Publications comparing the outcomes of pregnancies after preimplantation genetic testing using trophectoderm biopsy and in vitro fertilization or intracytoplasmic sperm injection were included. Only human studies with a cohort or case-control design or randomized controlled trials were eligible for inclusion.

METHODS: The study selection process was performed independently by 2 investigators. The quality of the observational studies was assessed using the Newcastle-Ottawa Scale, and the Cochrane risk-of-bias tool version 2 was used to grade the level of bias in randomized controlled trials. The pooled odds ratio and 95% confidence interval were calculated using a random-effects model when substantial heterogeneity occurred (indicated by I^2 of >50% and P<.1). Otherwise, a fixed-effects model was used.

How do you counsel patients about the risk of the trophectoderm biopsy?

RESULTS: This meta-analysis included 13 studies involving 11,469 live births after preimplantation genetic testing treatment with trophectoderm biopsy before embryo transfer and 20,438 live births after in vitro fertilization or intracytoplasmic sperm injection only. The odds ratio of preterm delivery was higher in the trophectoderm-biopsied group than in the routine in vitro fertilization or intracytoplasmic sperm injection group (pooled odds ratio, 1.12; 95% confidence interval, 1.03–1.21); however, the difference did not exist after sensitivity analysis (odds ratio, 0.97; 95% confidence interval, 0.84–1.11). The risk of low birthweight did not increase among the biopsied pregnancies (pooled odds ratio, 1.01; 95% confidence interval, 0.85–1.20). No marked difference was observed in the risk of other obstetrical or neonatal outcomes between the biopsy and control groups. Furthermore, no difference was noted in the perinatal outcomes between trophectoderm-biopsied and nonbiopsied groups in the subgroup analyses by intracytoplasmic sperm injection, frozen-thawed transfer, or single embryo transfer.

CONCLUSION: Trophectoderm biopsy for preimplantation genetic testing treatment did not alter the risk of obstetrical or neonatal outcomes compared with conventional in vitro fertilization or intracytoplasmic sperm injection without preimplantation genetic testing. However, this study was limited by the large observational evidence base, and more randomized controlled trials are needed to further confirm these findings.

"Infertility status was another crucial confounder in these comparisons. It has been postulated that the underlying infertility disorders leading patients to assisted reproductive technology (ART) are more likely to ac- count for adverse pregnancy outcomes than the ART procedure"

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NEWSLETTER

The little lit review

Noninvasive single-cell-based prenatal genetic testing: A proof of concept clinical study

Michelle Bellair | Elisabete Amaral | Mason Ouren | Cameron Roark | Jaeweon Kim | April O'Connor | Adrianna Soriano | Margaret L. Schindler | Ronald J. Wapner | Joanne L. Stone | Nicola Tavella | Audrey Merriam | Lauren Perley | Amy M. Breman | Arthur L. Beaudet

The article explores the development and assessment of the Luna Prenatal Test, a non-invasive genetic test aimed at detecting fetal abnormalities using circulating trophoblasts from maternal blood. Unlike invasive methods like amniocentesis and CVS, the Luna test poses no risk of pregnancy loss. While cell-free non-invasive prenatal testing (cfNIPT) exists, it has limitations in detecting certain chromosomal anomalies.

The Luna test isolates fetal trophoblasts from maternal blood by sequencing maternal blood and comparing informative SNPs. It then analyzes the cells genetic content using next-generation sequencing (NGS). Clinical studies show promising results, with high success rates in recovering trophoblast cells and concordance with invasive methods for detecting chromosomal abnormalities. Challenges such as placental mosaicism and technical limitations remain, warranting further research to enhance the test's clinical utility.

Every cell subjected to NGS analysis was given one of three scores for deletion/duplication (del/dup) and/or aneuploidy as below by a genomics specialist:

1. **Scorable for aneuploidy and 1.5Mb del/2.0Mb dup resolution:** had very high-quality NGS data and very few putative gains or losses called by the NxCsoftware
2. **Scorable for aneuploidy only**: cells in the S phase of the cell cycle where numerous small genomic segments not yet replicated cannot be distinguished from small deletions
3. **Unscorable, not used for further analysis**: Unscorable cells were either apoptotic, lost in processing, had very low mappable reads, or had data unsuitable for analysis for unknown reasons.

TABLE 6 Summary of 243 cases attempting to compare the Luna test with CVS or amniocentesis.[a]

Agreement (179)	
Luna test	**CVS/amnio**
160 normal	160 normal
9 Trisomy 21	9 Trisomy 21, one both twins + mosaic 2 in one
3 Trisomy 18	3 Trisomy 18
1 Trisomy 13	1 Trisomy 13
1 47,XXX	1 47,XXX
1 MZ twin all cells Williams S.	Amnio Williams deletion both fetuses
4 opposite sex twins normal	4 opposite sex twins normal
Failed or incomplete information but no conflict (55 new + 6 above)[a]	
1 del PMP22	Karyotype not informative for del
10 twin + 6 above	10 twin + 6 above
7 samples rejected	
22 no cells recovered	
10 all cells unscorable	
6 no CVS or amniocentesis	
9 + 1 above Mosaicism or rare autosomal trisomy (9 new + 1 above)[b]	
243 Total	

[a]See the text of Results for further explanation.
[b]Some cases are listed twice indicated as counted above.

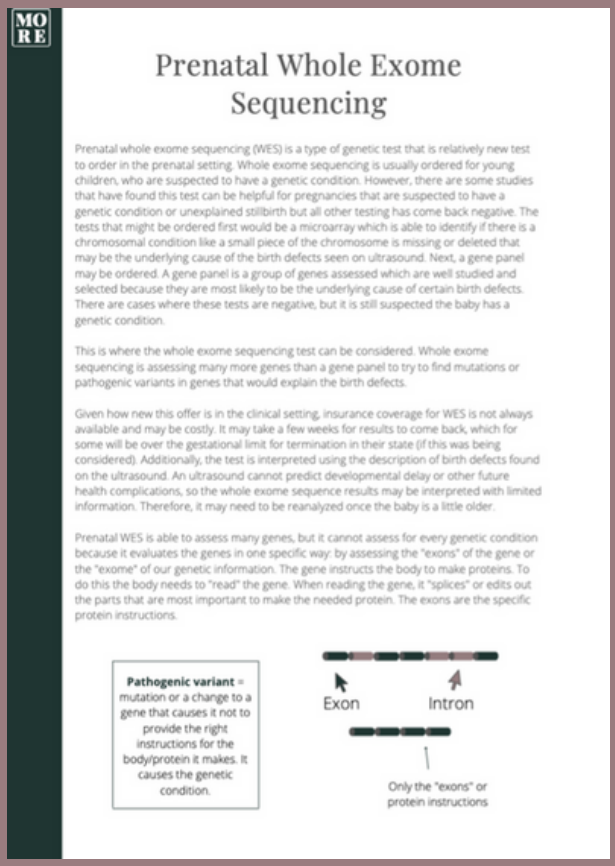
NEWSLETTER

Community Content:

Follow on LinkedIn as well!

Modern Reproduction Content:

Handouts and brochures are available on the site such as this prenatal whole exome handout :D


MO RE

Prenatal Whole Exome Sequencing

Prenatal whole exome sequencing (WES) is a type of genetic test that is relatively new test to order in the prenatal setting. Whole exome sequencing is usually ordered for young children, who are suspected to have a genetic condition. However, there are some studies that have found this test can be helpful for pregnancies that are suspected to have a genetic condition or unexplained stillbirth but all other testing has come back negative. The tests that might be ordered first would be a microarray which is able to identify if there is a chromosomal condition like a small piece of the chromosome is missing or deleted that may be the underlying cause of the birth defects seen on ultrasound. Next, a gene panel may be ordered. A gene panel is a group of genes assessed which are well studied and selected because they are most likely to be the underlying cause of certain birth defects. There are cases where these tests are negative, but it is still suspected the baby has a genetic condition.

This is where the whole exome sequencing test can be considered. Whole exome sequencing is assessing many more genes than a gene panel to try to find mutations or pathogenic variants in genes that would explain the birth defects.

Given how new this offer is in the clinical setting, insurance coverage for WES is not always available and may be costly. It may take a few weeks for results to come back, which for some will be over the gestational limit for termination in their state (if this was being considered). Additionally, the test is interpreted using the description of birth defects found on the ultrasound. An ultrasound cannot predict developmental delay or other future health complications, so the whole exome sequence results may be interpreted with limited information. Therefore, it may need to be reanalyzed once the baby is a little older.

Prenatal WES is able to assess many genes, but it cannot assess for every genetic condition because it evaluates the genes in one specific way: by assessing the "exons" of the gene or the "exome" of our genetic information. The gene instructs the body to make proteins. To do this the body needs to "read" the gene. When reading the gene, it "splices" or edits out the parts that are most important to make the needed protein. The exons are the specific protein instructions.

Pathogenic variant = mutation or a change to a gene that causes it not to provide the right instructions for the body/protein it makes. It causes the genetic condition.

Exon Intron

Only the "exons" or protein instructions