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COMMENTARY

Hot Topics of the 19th International Conference on Prenatal Diagnosis and Therapy, 2015, Washington, DC, United States

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The 19th conference of International Society for Prenatal Diagnosis and Therapy was held in Washington, DC on July 12–15, 2015. This exciting meeting focused on the controversies in current approaches in prenatal diagnosis and the future directions in this field. As part of the organization's mission, the presentations contributed to the goal of "promoting the health of children, their mothers, and families by advancing the science and practice of genetics and fetal care worldwide." As a young physician who has recently joined this growing field, I was captivated by the topics discussed and their translation into patient care. Below are some highlights and controversies presented.

First Plenary Debate

Noninvasive Prenatal Testing (NIPT) Should Routinely Include Microdeletions and Microduplications

PRO: Dr. Peter Benn (University of Connecticut)

Dr. Benn emphasized that the microdeletion and microduplication conditions represented "are clinically significant and with therapeutic interventions available". He mentioned that 1.7 % of all pregnancies have small pathogenic copy-number variations (CNVs) and many of them have well-defined syndromes. He then focused on 22q11 deletion syndrome, which has an incidence of 1:1000–6000 and very variable phenotype. Dr. Benn posited that routine screening for microdeletions would "avoid the diagnostic odyssey and improve long term outcome with early intervention, especially neonatal seizures and hypocalcemia." He mentioned the study by Gross et al. [1] which showed higher positive predictive value of 14.4 % for 22q deletion with a higher depth of read. In conclusion, he stated that 22q deletion screening already shows clinical efficacy and low false positive rate and more importantly, improves the patient's outcome. Similarly, the study by Wapner et al. [2] concluded that given that significant microdeletions and microduplications may occur in >1 % of pregnancies, single-nucleotide polymorphism (SNP)-based noninvasive prenatal testing (NIPT) should be considered for the general pregnant population regardless of age.

CON: Dr. Aubrey Milunsky (Tufts University School of Medicine)

Dr. Milunsky's opening statement was a critical reflection on the goal of prenatal genetic diagnosis: "to reassure parents at risk who may, selectively, have unaffected offspring. It is not a search and destroy mission". He cited a study by Wang et al. [3] describing a wide range of discordant cytogenetic and NIPT results with variable positive predictive values (PPVs) and false positive rates (FPRs). Dr. Milunsky reminded the audience about the real biological mechanisms for discordant cell-free DNA (cfDNA) screening results, including maternal karyotypic aberrations, placental mosaicism, and maternal malignancy.

He reviewed the flaws in the validation of cfDNA screening for microdeletions emphasizing that deletions are

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of variable size and that utilizing samples spiked with known microdeletions does not satisfy requirements for validation. Dr. Milunsky then highlighted the genetic counseling challenges associated with microdeletion screening, including achieving proper informed consent, clarifying the clinical significance when the PPV is low, and the prediction of future development with such variable clinical presentations. He stressed that more field studies are needed before the routine implementation of microdeletion screening, emphasizing that "to categorically determine that a fetus was affected with a serious genetic disorder, without adequate pre-test counseling and consent, would fundamentally undermine patient autonomy and reproductive decision-making" [4].

Second Plenary Debate

Will the Fetal Exome Contribute to the Counseling and Management of the Dysmorphic or Malformed Fetus?

PRO: Dr. Lyn Chitty (University College London)

Dr. Chitty presented her position in favor of fetal exome sequencing, stressing its benefits only if it contributes to the diagnosis, counseling, and/or management. Fetal anomalies affect 3–5 % of pregnancies and diagnosis is required to offer appropriate counseling, discuss continuation or termination of pregnancy, and offer appropriate prenatal, intrapartum, and postanatal treatment. Several case reports showed that prenatal exome sequencing adds 10–25 % to the diagnostic yield for dysmorphic fetuses. In a study by Yang et al. [5], whole exome sequencing (WES) yielded a diagnosis in 11 (54.5 %) of terminated fetuses. In a case series from Great Ormond Street Hospital for Children NHS Foundation Trust and UCL Hospital, 5 of 25 (20 %) prenatal cases had causative mutations with two further indicative of a recessive disease [6].

CON: Dr. Jan Friedman (University of British Columbia)

Dr. Friedman highlighted that clinical validity, utility, or cost effectiveness of whole exome sequencing in the setting of a dysmorphic fetus has not been established. He explained that most of WES is experimental, interpretation is usually open-ended, and often uncertain until further validation or evidence becomes available. This is in stark contrast to the clinical setting, where specificity and speed are critical.

Dr. Friedman emphasized that exome sequencing does not test for CNVs, structural rearrangements, mutations other than single nucleotide variations (SNVs) or small insertions and deletions (INDELs), and mutations that lie outside protein-coding genes. He underscored that our understanding of variants at this time is limited and reminded the audience to keep in mind that WES may find variants of unknown significance involving known disease genes, variants of candidate disease genes, and incidental findings. Furthermore, even for known pathogenic mutations of known disease genes, penetrance is often incomplete or uncertain as well as has phenotypic variability.

Third Plenary Debate

Is There Value to a Nuchal Translucency (NT) Ultrasound?

PRO: Dr. Liona Poon (King's College, Fetal Medicine Foundation, London)

Dr. Poon started by acknowledging that cfDNA is superior in diagnosing trisomy 21, 18, and 13. She then clarified that although cfDNA is a superior screening test for trisomies, an ultrasound scan for dating and diagnosis of multiple pregnancies is crucial to the interpretation of its results. She then went on to present the other reasons why the 11–13 weeks scan should continue to be the best screening tool for aneuploidy: (1) cfDNA screening is too expensive to be a universal screening tool; (2) an increased NT is a marker of many chromosomal abnormalities, fetal defects, and genetic syndromes that are not assessed with cfDNA screening; (3) it is not only an NT measurement, but is also a tool for the early diagnosis of fetal structural defects, including cardiac anomalies; and (4) additional to its role as a tool for the detection for trisomies, sonogram also considers maternal risks, based on age, body-mass index, ethnicity, obstetric history, and personal medical history. This, in combination with maternal serum markers and other sonographic parameters like uterine artery pulsatility index, represents a window to aid in the prevention of poor obstetrical outcome, like pre-eclampsia, fetal growth restriction, and preterm birth.

CON: Dr. Alessandro Ghidini (Inova Alexandria Hospital and Georgetown University Hospital)

Dr. Ghidini opened his remarks by emphasizing that the following conditions were not the subject of this debate: (1) The value of the NT in the context of combined or sequential genetic screen as alternative to NIPT; (2) the value of the NT in the context of NIPT performed contingent on abnormal results at combined or sequential screen; (3) the value of cystic hygroma as a congenital abnormality of the lymphatic system.

He then turned his attention to highlight the current recommendations of the American College of Obstetricians and Gynecologists' recent Committee Opinion which states that "parallel or simultaneous testing with multiple screening methodologies for aneuploidy is not cost effective and should not be performed" [7]. Also, the American College of Medical Genetics' Policy Statement established that "NIPS [Noninvasive prenatal screening] does not replace the utility of a first-trimester ultrasound examination, which has been proven to be useful for accurate gestational dating, assessment of the NT region to identify a fetus at increased risk for a chromosome abnormality, identification of twins and higher-order pregnancies, placental abnormalities, and congenital anomalies." [8]. The Board of the International Society for Prenatal Diagnosis states that "in some practices, an early ultrasound examination for fetal abnormalities is carried out, and postponing cfDNA until this is completed is a consideration." [9].

In summary, Dr. Ghidini suggested that after cfDNA test, NT does not provide additional benefit.

Selections from the "ISPD Top Abstracts"

Noninvasive Prenatal Testing and Incidental Detection of Occult Maternal Malignancies [10]

Speaker: Dr. Diana Bianchi (Tufts Medical Center)

According to Dr. Bianchi, 0.2 % of abnormal NIPT results are discordant with the fetal or neonatal karyotype, and some of the explanations include confined placental or maternal mosaicism, co-twin demise, maternal organ transplant, and maternal malignancy. Although cancer during pregnancy is rare (1 in 1000), the aims of this study were to understand the relationship between aneuploidy detection with NIPT and occult maternal malignancies; whether malignancy is an explanation for false positive NIPT results; and if earlier detection would improve maternal clinical care and outcome. The other main objective was to evaluate massively parallel sequencing (MPS) data for patterns of copy number variations that might prospectively identify occult maternal malignancies.

This study was a case series of 125,426 NIPT test results from asymptomatic pregnant women from 2012 through 2014. Overall, 18 % of cases with multiple aneuploidies had a subsequent cancer diagnosis (95 % CI, 7.5–33.5 %). A positive NIPT was matched with the diagnosis of ten patients with the following malignancies: B-cell lymphoma, T-cell leukemia, Hodgkin lymphoma, leiomyosarcoma, neuroendocrine, colorectal, anal, and unspecified adenocarcinoma. The mean maternal age of patients diagnosed with cancer was 35 years (23–39 years), the mean gestational age at NIPT was 13.9 weeks (10–20 weeks), and the cancer diagnoses ranged from early-stage to metastatic disease.

All cancer cases were characterized by extensive CNVs that involved many chromosomes. A higher risk for malignancy was associated with a pattern of multiple aneuploidies or a single autosomal monosomy. These results are presumably due to the cfDNA that is released into the plasma from apoptotic malignant cells.

As Dr. Bianchi concluded, the limitations of study are due to the retrospective design and small sample size. She suggested a prospective study to determine the pattern of genomic imbalance that is most closely associated with a risk of cancer and how would this translate into clinical care for subsequent early diagnosis and treatment.

Fetal Precision Medicine: Prenatal Treatment of Down Syndrome

Speaker: Dr. Diana Bianchi (Tufts Medical Center)

The closing presentation by Dr. Bianchi brought to our attention the innovative vision of treating Down syndrome in the prenatal period, where "not treating prenatally is a lost opportunity to improve neurogenesis and positively impact brain development and connectivity."

Dr. Bianchi presented the idea that there are distinct fetal neurologic phenotypes associated with Down syndrome, including decreased frontothalamic distance, decreased transcerebellar diameter, and decreased cerebellar volume. These findings could perhaps be the end result of decreased cell proliferation and increased cell death, confirmed by transcriptomic analysis that suggests increased oxidative stress. After defining the phenotype of the Ts1Cje mouse model for trisomy 21, treatment was given to the affected mice with protective neuropeptides, known by the acronym NAP/SAL, showing improved spatial learning in affected adult mice. The second treatment was given with choline supplementation, which is key in the production of acetyl choline, cell membrane formation, and epigenetic regulation. This therapy produced improvement in "cognition, attention, and emotional regulation." The third therapy was prenatal epigallocatechin-3-gallate (EGCG), which showed increased neuronal density. The fourth treatment modality was with prenatal fluoxetine, which showed long term improvement of cognitive performance by restoring "overall cellularity and connectivity in multiple locations in the brain."

The ongoing work by Dr. Faycal Guedj focuses on the effects of prenatal treatment with apigenin, which is a potent antioxidant that crosses the blood–brain barrier and has been demonstrated to promote adult neurogenesis. So far, it has shown to normalize expression in many genes at

the embryonic stage, in neonates shortens the time it takes to achieve developmental milestones, and in adulthood has shown improvement in open field test and in memory. The next challenge is to prepare a clinical trial after identifying a compound that is safe for pregnant women and their fetuses, which crosses the placenta to achieve fetal therapeutic levels and has demonstrated benefits after birth. In conclusion, the vision for the future in our field is to use prenatal diagnosis as an opportunity for fetal treatment, hopefully with long-term or even permanent benefits.

Conclusion

The field of prenatal screening, diagnostics and fetal therapy is rapidly evolving and the next year promises continued innovation and improvements in patient care. I look forward to the 20th meeting of ISPD (2016), where we can continue to combine our efforts globally in order to promote knowledge and advocate improved health worldwide.

Compliance with ethical standards

Conflict of interest None.

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