THE PROSPECT TRIAL: LOOKING FOR ANSWERS FOR PRETERM BIRTH PREVENTION IN MULTIPLE GESTATIONS
By Joseph Biggio, MD and Jennifer McIntosh, MD

Preterm birth prevention has had some big steps forward in the past decade. Cervical length screening can identify women at risk and progesterone can be used to decrease preterm birth. These two tools alone have been widely implemented across the country, thanks to efforts from ACOG and SMFM. In spite of these advances, one area where unanswered questions remain is preterm birth prevention for multiple gestations - there are no evidenced-based interventions to offer women with twins who have a short cervix. With multiple gestations on the rise, searching for this answer is an important priority. The “Trial of Pessary and Progesterone for Preterm Prevention in Twin Gestation with a Short Cervix”, or PROSPECT trial, was created in hopes of answering these important questions.

Previous intervention trials in unselected twin pregnancies have failed to demonstrate any benefit to intramuscular progesterone or vaginal progesterone. At the time PROSPECT was initially conceived, no pessary studies in twins had been published, though several studies have been published since then demonstrating lack of effect in unselected twins. Based on the association between short cervical length in singletons and risk for subsequent spontaneous preterm birth, PROSPECT creators proposed to evaluate the utility of vaginal progesterone and the Arabin pessary for the prevention of preterm birth in twins with a short cervix. Several subgroup analyses of other studies suggested that if there were a subgroup of multiple gestations that might benefit from either vaginal progesterone or Arabin pessary, it would be those with a short cervix. PROSPECT chose 30 mm, or the 20th percentile, as the threshold for qualifying enrollment based on analysis of the distribution of cervical length measurements in women with twins in the MFMU Preterm Prediction Study.

Women with twin gestations are eligible to undergo cervical length screening at 16 weeks - 23 weeks, and exclusion criteria include monoamniotic twins or a diagnosis of twin twin transfusion syndrome. Women with uncomplicated diamniotic twin gestations and a cervical length < 30 mm are eligible for randomization to one of three study arms: Arabin pessary, 200 mg daily of vaginal progesterone (gel capsules), or an identical appearing placebo. PROSPECT plans to enroll 210 women per group with an overall enrollment of 660 women, and all study subjects are followed by research staff monthly.

The primary outcome is delivery or death of one or both fetuses prior to 35 weeks gestation. Multiple secondary analyses are also planned including assessment of effectiveness based on cervical length at randomization, fetal fibronectin concentration, as well as an examination of neonatal outcomes.

PROSPECT has been open for enrollment for approximately 1 year and it will likely take 2-3 additional years to reach the target enrollment.

Providers interested in referring patients for potential participation in the trial can contact their nearest MFMU center (see mfmu.bsc.gwu.edu for a listing) or can contact Joseph Biggio (jbiggio@uabmc.edu) to connect you with the MFMU research staff at a site near you. While some sites require delivery to occur at the MFMU hospital, this is not mandated at sites. The results of this study are eagerly anticipated!
THE FIRST TRIMESTER INTRACRANIAL TRANSLUCENCY: FAST FACTS
By Reem S. Abu-Rustum, MD

Background Information
Since the introduction of nuchal translucency (NT) assessment, approximately 70% of women present for evaluation at this critical point in gestation. With the improvement in the resolution of the sonographic equipment, it is possible to carry out full fetal anatomic assessment at 11-14 weeks with a 51% detection rate of major structural abnormalities. Nonetheless, the early detection of open spina bifida remains a challenge with a 14.3% detection rate and no clear guidelines on how to rule it out in the first trimester. Several first trimester markers have been described as first trimester screening modalities among which are the intracranial translucency (IT) in 2009, brain stem/brain stem occipital bone in 2011, and the ratio of the biparietal diameter to the transabdominal diameter in 2015.

Intracranial Translucency: What is it?
The IT was introduced in 2009 by Chaoui et al as a first trimester marker for open spina bifida. It represents the fourth ventricle and can be visualized in the same mid-sagittal plane utilized for NT measurement and nasal bone visualization (Figure 1). It is bordered by the brain stem anteriorly and the choroid plexus of the fourth ventricle posteriorly; the choroid plexus of the fourth ventricle sits between the IT and the cisterna magna (Figure 2). In the setting of open spina bifida, the fourth ventricle may be compressed by caudal displacement of the brain, as early as the first trimester, leading to a poorly visualized IT (Figure 3).

Intracranial Transluceny: How to Assess for its Presence?
In order to properly visualize the IT, the fetus must be captured in the mid-sagittal plane utilized for NT assessment employing magnification. The following fetal landmarks should be visualized: nasal bone, palate, mandible, NT, thalamus, midbrain, brainstem and medulla oblongata with the IT recognizable as the echolucent space between two echogenic lines (Figure 2).

Intracranial Transluceny: Recent Data
Several retrospective and prospective studies have reported on the sensitivity and specificity of the IT as a first trimester marker for early detection of open spina bifida. A meta-analysis by Meruotti et al in 2016 systematically reviewed 9 studies including a total of 21070 fetuses. The authors conclude that though the IT is a highly specific first trimester marker for early detection of open spina bifida (specificity 99.7%), it has a sensitivity of only 53.5%.

Conclusion
Open spina bifida remains a challenging first trimester diagnosis with various sonographic markers described for early screening. With the IT’s high specificity, families with a prior affected child and a visualized IT can be reassured early in gestation. Because of the high risk of false positive results, however, caution must be exercised to avoid over-diagnosis. Multi-center prospective trials are needed to determine the best combination of first trimester markers to effectively screen for open spina bifida.

Reference:
FIGURE 1: Mid-sagittal plane demonstrating the nuchal translucency (NT), nasal bone (NB) and intracranial translucency (IT).

FIGURE 2: Mid-sagittal plane demonstrating the NB, palate (P), mandible (MN), thalamus (T), sphenoid bone (solid black line), midbrain (M), brain stem (BS), medulla oblongata (MO), fourth ventricle/intracranial translucency (IT), choroid plexus of the IT (*), cisterna magna (CM), the occipital bone (dotted line) and nuchal translucency (NT).

FIGURE 3: A 12w1d fetus with open spina bifida. Note the abnormal posterior fossa with a widened brain stem (BS) and unclear IT/CM.
GOODBYE FRIEND
By Mark Tomlinson, MD

With the recent passing of Julian T (Bill) Parer many of us lost a friend while our specialty lost an enthusiastic clinician, teacher, and investigator. His presence at regional and national meetings will be sorely missed. Whenever he stepped to the podium either to question the presenter or present himself, his comments were guaranteed to be not only insightful but challenging, encouraging and always delivered with a smile. Outside of medicine he had a great love for the outdoors that was infectious. Bill was able to share this passion with countless others. An example is his legendary “birding” expeditions at the annual Pacific Coast OB/Gyn Society meetings.

Born in Australia, Dr. Parer’s investigative career began there in the early 1960’s where he completed a Masters degree. He then moved to the US developing a love for the Northwest and California. He earned a PhD in Physiology from Oregon State University in 1965 where he studied cardiorespiratory function and blood acid base balance. As one would expect, he published numerous papers using sheep and rhesus monkey models. More interesting however was a series of studies involving a wide variety of other mammalian species including the echidna and platypus, baboons and chimpanzees, young lion and tiger, camel, and even elephants. In 1971 Dr. Parer completed his MD degree at the University of Washington and went on to residency at University of Southern California during the early days of electronic fetal monitoring (EFM). This was to become the major focus of his career combining basic science and clinical research. After completing residency he joined the faculty at University of California, San Francisco (UCSF) where he remained for more than 30 years.

While Dr. Parer’s long and illustrious career is marked by accomplishments too numerous to mention, his tireless efforts to teach EFM interpretation and management deserves special attention. From the first publications in the late 1960s, EFM was rapidly adopted into clinical practice with nearly 70% of pregnancies in the United States utilizing the technology by 1989, increasing to more than 85% over the next decade. In fact, it is the only form of intrapartum surveillance most obstetricians practicing today have ever experienced. Despite the widespread use, the commonly held early belief that EFM could eliminate fetal acidemia and its sequelae was not realized. There has been little reduction in cerebral palsy rates while the cesarean section rate increased dramatically leading some to call for an abandonment of the technology. Embracing the challenge Dr. Parer advocated for standardizing nomenclature, interpretation, and management recognizing that tremendous variability in the approach to EFM was contributing to the problem. For nearly 35 years he directed the Antepartum and Intrapartum Management (AIM) postgraduate course at UCSF. He chaired the NICHD Work Group tasked with developing “standardized and unambiguous definitions for fetal heart rate tracings”. At his Presidential address for the Pacific Coast Obstetric and Gynecologic Society in 2010, Dr. Parer admitted his disappointment that another lesser known goal of the NICHD work group, to develop a consensus for management of the FHR tracing was not achieved. Despite the disappointment he persevered with publication in 2007 of a 5-tier system based on FHR patterns and their risk of acidemia as well as the risk of progression to acidemia. A second NICHD work group published its proceedings in 2010 affirming and updating the definitions from the 1997 report and adopting a 3-tier system for categorizing FHR tracing over the 5-tier system in part attempting to maintain simplicity. The limitations Category II were quickly recognized prompting some to adopt the 5-tier system to subdivide the indeterminate tracings while others developed other similar independent modifications. Smart phone apps have even been developed to aid in interpretation and management. In the same presidential address he acknowledged and encouraged these efforts.

Electronic Fetal Monitoring is here for the foreseeable future. The Fetal Monitoring Credentialing (FMC) honors Bill’s vision and legacy by striving for consistent knowledge and interpretation. Thanks for the memories my friend.
GEM was developed by a source you can trust and is designed to help improve the efficiency and satisfaction in prenatal clinics by providing mobile education for routinely offered prenatal genetic screening and diagnostic testing options:

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