Center For Advanced Fetal Care Newsletter

Volume 1 Issue 3
Summer of 2010
Tripoli – Lebanon

INSIDE THIS ISSUE

A Leap Into The Future...

...is exactly how one would describe Professor Nicolaides' 9th World Congress of the Fetal Medicine Foundation. The contagious passion and energy portrayed served as such a propeller for all those in fetal medicine...This year's congress was coupled with Eurofetus . With over 1200 delegates from over 80 countries, it was an army of world experts tackling every single aspect of fetal medicine conceivable: from fetal surgery for diaphragmatic hernias to cardiac valvuloplasties, to in-utero cystoscopy, to open fetal surgery, to a genomic approach for fetal treatment, to the challenges of higher order gestations, to screening for aneuploidies, preterm birth and preeclampsia, to the early diagnosis of maternal diseases and birth trauma, to fetal growth restriction and fetal MRI and on and on...The packed days culminated in Professor Nicolaides' call to implementing his revolutionary vision and to "inverting the pyramid of care" in obstetrics. With this boldly-defiant step to all of our previous teachings, this foresight would select the 12 week evaluation as the pinnacle in obstetrical care: at 12 weeks, the fetus may be screened for aneuploidy, structural abnormalities, growth restriction and preterm birth and the mother may be screened for preeclampsia, diabetes, thyroid disorders and birth trauma. Those that are low risk can then be seen at 20, 32 and 41 weeks. Those that are high risk can have devised individualized plans of care for them between 16 and 32 weeks...With this issue, we also hope to "leap into a healthier and safer maternal future" by calling attention to the deplorable global state of maternal health and to two great programs: ISUOG's "Outreach" and Oxford's "Global Voices for Maternal Health" whose primary aim is decreasing maternal mortality...With this "leap into the future" we attempt to share with you all the excitement and challenges that lay ahead, hoping that this issue's contents may bring a taste of all that is yet to be, bringing us closer and closer to maternal safety and to Nicolaides' prophecy...

Determining Chorionicity by Malek Nassar, MD

Multiple pregnancies represent 1-2.5% of all pregnancies and are on the rise with the ever increasing use of assisted reproduction. Of utmost clinical importance in multiples is to determine chorionicity. Stating mono or dichorionic must precede "twin gestation" when referring to twins. Morbidity and mortality increase drastically with monochorionic gestation where closer follow up is necessitated. Several sonographic techniques may be utilized. In the first trimester counting the number of yolk sacs has been used . But the most reliable is the "lambda" sign or twin peak sign (sensitivity 97.4%, specificity 100%) for dichorionic gestations, and the T sign for monochorionic gestations (as depicted in the images). Fetal gender, number of placental masses, thickness of inter twin membrane and counting of the layers of inter twin membranes are second and third trimester markers . With advancing gestation, determining chorionicity is more challenging and less reliable, further stressing the need to look for the lambda or T sign in the first trimester and adding to the armementarium of the first trimester scan...

Indications for Fetal Surgery by Bernard Nasr, MD

As a therapeutic innovation, fetoscopic surgery has recently replaced open fetal surgery with its high fetal and maternal morbidity. In certain conditions, this has been shown to be superior with respect to fetal outcome. Fetal surgery should be offered when the natural history of the pathology is known, lethal without in-utero treatment, with severe morbidity in untreated cases or following post-natal treatment, when partial pathological correction is helpful and the therapy validated, in comparison to post-natal treatment. Laser coagulation of connecting vessels is the treatment of choice in cases of twin to twin transfusion syndrome, with survival approaching 50% of both twins and 80% of one twin. This was validated in 2004 by the Eurofetus study. Laser therapy can be offered in case of TRAP syndrome, hemangioma of the placenta, sacrococcygeal teratomas and for ablation of posterior urethral valves. A new approach of in utero treatment is embolization of the main vessel of a placental hemangioma. In cases of monochorionic twins, cord occlusion, by bipolar forceps or by laser coagulation, is helpful in cases of TRAP syndrome, severe IUGR, or a malformation in one twin. In selected cases of isolated congenital diaphragmatic hernia, tracheal occlusion by fetoscopy gives a better survival (70% versus 30%). Lower urinary tract obstruction and pleural effusion can be treated by in utero shunting. In severe aortic stenosis, which leads to hypoplastic left heart and severe pulmonary stenosis, the survival is 0%. The trial of in utero catheterization of the stenotic valve may increase the survival to 12%, nonetheless, this requires specialized skill and carries high fetal mortality. Fetal in utero transfusion has been shown to help in cases of parvovirus induced fetal anemia, following the fetal death of one of monochorionic twins and in Rhesus disease. In summary, fetal surgery provides an option in the most challenging cases and objective risk assessment must be employed together with proper counselling of the family in order to make an informed decision and to proceed with further care.

Highlights from Eurofetus and the 9th World Congress of the Fetal Medicine Foundation, Rhodes, June 20-24, 2010

Here are highlights from the Eurofetus and 9th World Congress of Fetal Medicine. Proceedings will be pulished in the January 2011 issue of the journal "Prenatal Diagnosis". In addition, the congress will soon be made available for viewing on line at the FMF website www.fetalmedicine.com and on the website of the International Society of Prenatal Diagnosis www.ispdhome.org

A Genomic Approach to Fetal Treatment by Diana Bianchi, MD

Amniotic fluid (AF) supernatant is an abundant source of cell-free fetal DNA and RNA. It has the advantage of having little contamination with maternal nucleic acids. AF can provide novel information about gene expression and functional development in the living human fetus. Using discarded AF supernatant we have identified novel differentially-regulated genes and disrupted biologic pathways in various fetal pathologies, such as twin to twin transfusion syndrome, fetal hydrops, and trisomies 21 and 18. Functional genomic analysis of second trimester fetuses with trisomy 21 suggests that oxidative stress, ion transport, and G-protein signaling are important (Slonim and Koide, *Proc Natl Acad Sci USA* 2009; 106: 9425). Significantly, very few of the differentially-regulated genes in trisomy 21 are actually located on chromosome 21. In studies of fetuses with trisomy 18, growth, ion and cation transport, neurological development, and immune molecules were significantly different from euploid fetuses. The molecular pathophysiological changes observed in cases of trisomies 18 and 21 are quite different from each other. Most recently, we have used the Connectivity Map (www.broadinstitute.org/cmap) to generate testable hypotheses regarding fetal treatment of trisomy 21 with FDA-approved drugs. The Connectivity Map "connects" disease states, biological systems disruption (as measured by pathway analysis), and pharmaceutical compounds to treat the disease. This allows a true translation from bench to bedside, and suggests a possible continuum between prenatal diagnosis and fetal therapy. If our approach is shown to be feasible it would have great relevance for many structural fetal abnormalities as well.

Non-Invasive Fetal RHD Genotyping By Paulo Chinen, MD et al

This was a prospective study, carried out on a racially mixed population of 102 D negative pregnant women, with single gestations, with or without D-antigen sensitization, analyzing fetal RHD genotype using real time PCR targeting exons 7 and 10 of the RHD gene. Genotype results were compared to cord blood phenotype obtained after delivery or at the time of the first intra-uterine transfusion. 75.5% of participants were less than 28 weeks of gestation and 87.5% had at least one relative of black ancestry. Combining the amplification of 2 exons resulted in 98% accurate genotyping, 100% sensitivity and 92% specificity. The positive likelihood ratio was 12.5 and the negative was zero. PCR confirmed the 2 false positive cases to be a pseudogene. In conclusion, determination of fetal RHD status is highly sensitive in a racially mixed population using maternal peripheral blood. For more information, this abstract has been published in the American Journal of Perinatology.

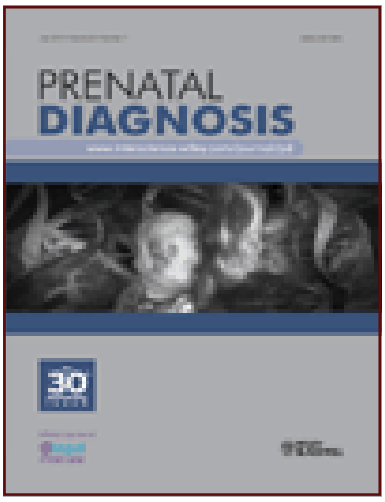
MRI in Prenatal Diagnosis By Mieke Cannie, MD & Jack Jani, MD

Although ultrasound is the screening modality of choice in obstetrics, there are circumstances during which ultrasound was reported to have some limitations such as oligohydramnios, advanced gestation due to bone ossification, fetal position, maternal abdominal wall scar and maternal obesity. Magnetic Resonance Imaging (MRI) is a technique that relies on the detection of the magnetic movements of hydrogen nuclei, present in abundance throughout our cells and tissues. Differences in the structural components of tissues translate into contrast differences on the images. Water and fat constitute the two extremes of MRI contrast, the former having high signal intensity on a T2-weighted image but low signal intensity on a T1-weighted image. The advantage of fetal MRI is that it is not limited by the same conditions limiting ultrasound. With the exception of universal restrictions of MRI, there are no limitations for its use in imaging the fetus. There are no clinical hazardous effects reported to date, using the 1.5 T magnets. Since the use of ultrafast sequences such as the single-shot fast spin-echo (SSFSE), the role of fetal MRI has increased with typical indications in central nervous system (CNS) pathologies such as in "isolated" borderline ventriculomegaly, cytomegalovirus or toxoplasmosis congenital infection, suspicion of agenesis of the corpus callosum and so on. Another indication of fetal MRI is for the assessment of pulmonary hypoplasia such as in congenital diaphragmatic hernia. Recently, MRI has been used as an alternative to classical necropsy in cases of in utero fetal death or even after termination of pregnancy, since a growing number of parents refuse classical necropsy. We will probably see in the future a growing number of indications for the use of fetal MRI in facial, thoracic, urinary pathologies, however, at the moment such indications should remain within research projects.

Clinically-Applicable Pearls from the Congress

1. In case on an increased NT and normal chromosomes, be on the outlook for orofacial clefts.
2. The fetal liver is the primary site for fetal hematopoesis in the first trimester. In trisomy 21 fetuses, at the time of the first trimester scan, there is a notable increase in hepatic artery peak systolic velocity (PSV) but a decrease in the pulsitility index (PI) to a liver with an increased volume in comparison to normals.
3. For the double screen, highest sensitivity for PAPP-A is at 9-10 weeks, with trisomy 21 detection rates approaching 90% for a FPR of 5%.
4. Late preterm birth (34w to 36w6d) constitutes 71% of all preterm births. These babies have 4X increased mortality and 3X increased risk of cerebral palsy.

CFAFC's Literary Recommendation
Prenatal Diagnosis: Special 30th Anniversary Issue



Journal of the International Society for Prenatal Diagnosis: www.ispdhome.org

Volume 30, Issue 7, July 2010. www3.interscience.wiley.com/journal/2252/home

Editor-in-Chief: Diana W. Bianchi, MD

This 30th Anniversary Issue of "Prenatal Diagnosis" is the equivalent of a textbook chronicling the evolution of prenatal diagnosis: past, present and future in all its forms: invasive, non-invasive, sonograhic (markers, 3D, the fetal heart), pre-implantation and molecular. In addition, the future direction with respect to all aspects of prenatal diagnosis, as well as fetal therapy and surgery, is addressed in this issue. This concise and thorough overview written by the pioneers in this field is a must read to all who are involved in prenatal diagnosis. It certainly is worth becoming a member of the society at a yearly cost of $200 to get access to this and other issues of the journal, not to mention the many other benefits of membership...

THIS AND THAT

ISUOG Outreach

In its continuous efforts to better maternal wellbeing globally, and decrease maternal mortality in the underserved areas of the world, ISUOG has launched its "Outreach" program, a program that even withstood the wrath in Haiti as the earthquake struck in January 2010 with its team of delegates there on an educational mission...The program is ongoing with such vision for the future, and a call for volunteers has been sent out with a workshop scheduled for Monday October 11, 2010 at 11 am as part of the annual ISUOG congress in Prague. This should be a call to all of us, respective delegates from various countries, to see how we may contribute and partake in "Outreach" by attending the workshop. And with our local governing societies, we must look to instate such regional "Outreach", as needed, in our respective countries. For more information check out the following: www.isuog.org/EducationAndTraining/Outreach+Program/

Global Voices For Maternal Health

This is a call out to all of us providing care to women in Africa, Asia, Latin America or the Middle East. The aim is to recruit and hear the voices of 10,000 healthcare workers, who provide maternal care, with the ultimate goal of finding better ways to deliver safer, affordable and more effective care to women worldwide in in an attempt to help combat one of the most neglected areas in global health: maternal mortality. Please make your voice heard by filling out the survey at www.globalvoices.org.uk/

The Fetal Heart

The importance of prenatally diagnosing fetal cardiac defects is gaining further momentum with the mounting evidence as to the improved hemodynamic status and outcome in fetuses that are diagnosed prenatally. These fetuses can then be delivered in tertiary care centers where they may be handled immediately at birth by pediatric cardiologists. And since this remains a most challenging area for the practicing obstetrician, several courses are being held to enhance the skills needed to reach these diagnoses. Two such courses are planned this coming fall: the first to be held under the direction of Professor Alfred Abuhamad in Las Vegas and the second under the direction of Professor Lindsey Allan in London. Details can be found in page 4 of the newsletter.

Non-Invasive Prenatal Diagnosis
By Marcel Achkar, Pharm D

Invasive prenatal diagnostic procedures (amniocentesis, chorionic villus sampling or cordocentesis) are offered to pregnant women to identify whether their baby will have a genetic or chromosomal disorder such as Down's syndrome, sickle cell disease, beta thalassemia ...These procedures are associated with an inherent risk of fetus loss of about 1-2%. A reliable non-invasive procedure has been sought to allow prenatal diagnosis and reduce the risk of miscarriage. Today much research is focusing on circulating cell-free fetal DNA or mRNA (cffDNA, cffmRNA) which would allow, with a simple draw of maternal blood, the diagnosis of genetic or chromosomally related disease. The presence of circulating cffDNA was demonstrated in 1997 and appears to be a physiological phenomenon associated with pregnancy. The origin of this cffDNA is the placental cell apoptosis or fetal circulating cells in maternal blood. Although the cffDNA represents only about 3 to 6 % of total cell free DNA, only alleles inherited from the father constitute readily distinguishable specific fetal sequences in maternal blood. Today available non-invasive prenatal tests are : the sex determination in X-linked disease such as Haemophilia and the fetal Rh D genotyping for Rh D negative mothers. From maternal blood at 10 weeks, the turnaround time for these tests' results is 1 day. Several techniques are under development to allow either separation of cffDNA or the use of specific cffDNA markers called epigenetics in order to allow specific fetal diagnoses. Applications for aneulpoidy have been tested in research laboratories with good results (Chiu et al 2008 ; Wright and Burton 2009; Lun et al 2008). Larger scale independent studies must be conducted to validate these applications before making them available for clinical practice.

MEDUOG

This year, the annual meeting of the Meditarranean Society of Ultrasound in Ob/Gyn will be held jointly with the Annual meeting of the Lebanese Society of Ob/Gyn, Nov 11-13, 2010 at the Bristol Hotel in Beirut. Mark your calenders as a rich program and pre-congress workshop have been organized to coincide with the opening of the Ian Donald Inter-University School of Medical Ultrasound in Lebanon . For more information: www.trust-traders.com

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CFAFC would like to thank Drs. Achkar, Bianchi, Cannie, Chahine, Chinen, Jani, Nasr and Nassar for their contributions to this issue.

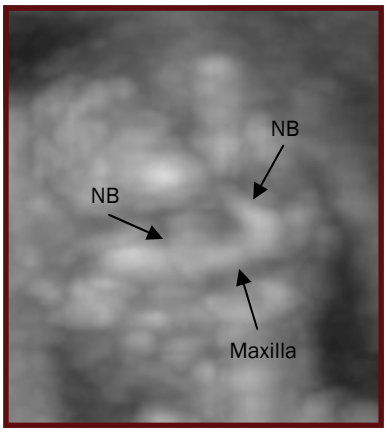
www.cfafc.org

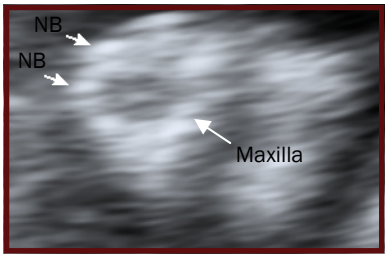
Please send us your full address and e-mail to be added to our mailing lists: rar@cfafc.org

Erratum

Retronasal Triangle

In the Spring edition of our newsletter, the image was improperly labelled as to the nasal bones. The correct labelling is on the image below. Waldo Sepulveda, MD further discussed the importance of this sonographic marker at the 9th World Congress of Fetal Medicine in the first trimester diagnosis of facial clefts. This area is the same as the premaxillary triangle seen in the second trimester and previously described by Seshadri Suresh, MBBS, RDMS who was also present at the World Congress and reiterated Prof. Sepulveda's words as to its importance as a major sonographic marker in the second trimester, as in the first, for the diagnosis of facial clefts.





Upcoming Congresses

COURSE TITLE	DATES	LOCATION	WEBSITE ADDRESS
Patient Safety in Obstetrics 2010: Reducing Risk and Improving Outcomes	September 23-25, 2010	Las Vegas, Nevada	www.edusymp.com/meetingview.asp?productid=3995
29th Annual Fetal Medicine and Surgery Society Meeting	September 25-30, 2010	Kanawaga, Japan	www.ifmss2010.org
20th World Congress of the International Society of Ultrasound in Obstetrics and Gynecology	October 10-14, 2010	Prague, Czech Republic	www.isuog.org/WorldCongress/2010/
Fetal Echocardiography: Normal and Abnormal Hearts	October 29-30, 2010	Las Vegas, Nevada	www.edusymp.com/meetingview.asp?productid=3997
6th Asia Pacific Congress in Maternal Fetal Medicine	October 29-31, 2010	Shanghai, China	www.apcmfm.hk
National Conference on Ob/Gyn Ultrasound	November 5-7, 2010	Chicago, Illinois	www.iame.com
Fetal Medicine Foundation's Advanced Ultrasound Course	November 6-7, 2010	London, UK	www.fetalmedicine.com/fmf/courses-congress/03-fmf-courses/
Obstetrical Ultrasound in the High Risk Patient	November 12-14, 2010	Las Vegas, Nevada	www.iame.com
Intensive Fetal Cardiology Course	November 13-14, 2010	London, UK	www.ichevents.com
19th Annual Ob/Gyn Update for Clinical Practice	December 2-5, 2010	Fort Lauderdale, Florida	www.cmebyplaza.com/Registrants/GoHo10/About.aspx