



Center For Advanced Fetal Care Newsletter

Volume 3 Issue 3
Summer of 2012
Tripoli – Lebanon

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Maximalism in Minimalism...

Proteomics. Metabolomics. Neural crest cells. Cell free DNA. mRNA. Time lapse in ART. Neurocranium. Viscerocranium. The fetus as a terrorist controlling the maternal cardiovascular system. Non-invasive prenatal diagnosis (NIPD). Inverting the pyramid of antenatal care from 12 weeks to 1-8 weeks...These are but a few of the highlights of the 11th World Congress of the Fetal Medicine Foundation held in Kos, the birthplace of Hippocrates, commemorating the 20th anniversary of the introduction of the nuchal translucency measurement. And how far we have come since then! Over the course of 5 intense 12-hour days, over 1500 delegates from 80 countries were reminded of their sacred vows dating back to Hippocrates, in addition to being presented with the latest in minimalism in medicine, the penultimate of maximalism, unraveling further the secrets of human life. And that is precisely why the venue was chosen as such: in order for Professor Geroulanos, president of the International Hippocratic Foundation in Kos, to present a magnificent lecture chronicling the life and contributions of the father of medicine, Hippocrates, with his genius. He brilliantly reminded us that even today, Hippocrates' teachings hold even more value as one is breathlessly overwhelmed with all that is yet to come, and with the challenges of how to assimilate and apply the minimalism in order to maximize the beneficence to our patients while minimizing the undue anguish that shall inevitably accompany the introduction of all these new minimalistic/maximalistic trends. We thus dedicate this issue to the maximalism in minimalism where we become less and less invasive with our needles, yet more and more invasive at the cellular molecular level...We present highlights from select presentations at the 11th World Congress of the Fetal Medicine Foundation, share with you the historic presentation of Professor Geroulanos, in addition to our usual quarterly features. And as we venture into the mysteries of today's unknown, we close by quoting Professor Geroulanos in his excerpts from Hippocrates' writings:



Dr. Eugene Pergament, Kos

"Life is short,

Medicine is a long-term art,

Rescuing the patient is urgent,

Experience is deceiving, and

Correct judgment is difficult"



www.ihfk.gr

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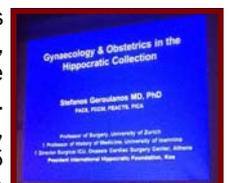
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Fetal Personalized Medicine: Progress & Challenges

Having been a pioneer in taking NIPD from the bench to clinical practice (Bianchi et al. Obstet Gynecol 2012; 119: 890-901), Bianchi brings us a comprehensive overview on fetal personalized medicine (Nature Medicine 2012; 18: 1041-1051). In this exceptional review, Bianchi projects that enabled by the most recent advances in fetal genome sequencing, together with the evolving understanding of underlying fetal physiology utilizing gene expression arrays, a personalized approach to fetal treatment is a possibility for diseases that the fetus may be at risk for in life. Nonetheless, there are great challenges to be faced as these modalities are introduced, their results interpreted and these must be accompanied by adherence to strict ethical principles. And Bianchi thus concludes that though the primary goal of prenatal diagnosis has been providing the parents with informed choices, today at this turning point in fetal medicine, and armed with the armamentarium of genetic, genomic and transcriptomic data, we are crossing the threshold of translating these insights into therapeutic personalized fetal medicine...

Gynaecology & Obstetrics in the Hippocratic Collection

A must see lecture for all of us in Ob/Gyn detailing the contributions of Hippocrates to our specialty. This lecture was presented by Stefanos Geroulanos, MD, PhD, president of the International Hippocratic Foundation (www.ihfk.gr), on 25 June 2012, at the 11th World Congress of the Fetal Medicine Foundation in Kos, Greece. The lecture, which is 31 minutes in length, was video-taped by our editor-in-chief, and permission to upload the lecture was granted by Professor Geroulanos on 25 July 2012. The lecture, in its available format, can be viewed on laptops/desktops (but not tablets/smart phones) at <http://www.cfafc.org/index.php?page=fmf2012>



Stefanos Geroulanos, MD

Highlights from the 11th World Congress of the Fetal Medicine Foundation Held in Kos-Greece, 24-28 June 2012



A most unique congress in its approach to fetal medicine, in accordance with Dr. Eugene Pergament's call to invert the pyramid of care to weeks 1-8, in that a full day was dedicated to the pre-implantation days in ART, another to all the non-invasive prenatal testing modalities, in addition to new applications in in-utero and post-natal surgery...We hereby include select vignettes from specific presentations covering the entire span of fetal maternal medicine from preimplantation to postnatal care. With this, we hope to highlight the critical need for clear guidelines as well as extreme caution as we incorporate these various modalities into clinical practice in order to safeguard against the effect of "The Amazing Spiderman" ...

Preimplantation Screening and Diagnosis. D. Wells.

One of the greatest challenges being faced in fetal medicine today is higher order gestations as a result of assisted reproduction. And at the forefront of the great advances to help control this phenomenon and to aid in the selection of the optimal embryos is "time lapse observation" or morphokinetics. Here the tri-gas IVF incubator is equipped with a built in camera that acquires images of the dividing embryos to try and identify any errors or hallmarks that may hinder implantation, such as cleavage time, blastomere size and multinucleation. This shall further enhance embryo classification to maximize implantation and minimize the need for embryo reduction (Meseguer et al. Hum Reprod. 2011; 26: 2658-2671).

Implantation and Obstetric Complications. C. Simon.

In the on-going quest against prematurity with all its morbidities and mortality, success has been met in identifying a genetic cause for preterm labor and birth. Hiriyoto et al (J Clin Invest. 2010; 120: 803-815) have been able to validate that either uterine-specific deficiency of transformation-related protein 53 which encodes p53, or a heightened uterine target of rapamycin complex 1 (mTORC1) signaling, may promote preterm birth in mice by causing premature uterine decidual senescence and even death of the pups. As such the authors call for focusing more and more on the maternal decidua and the dysregulation of genes in order to investigate further various underlying mechanisms of obstetrical pathologies such as preeclampsia, preterm birth and recurrent pregnancy loss...

Liver-to-Thoracic Volume Ratio (LiTR) by MRI in Fetuses with Congenital Diaphragmatic Hernia (CDH). J. Jani

Another of Jani et al's distinguished work was presented on the role of fetal MRI, utilizing the LiTR (Ultrasound Obstet Gynecol 2008; 32: 627-632), in predicting postnatal survival in fetuses with isolated CDH. The study included 30 expectantly managed fetuses, and 31 fetuses who had undergone fetoscopic endoluminal tracheal occlusion (FETO). The effects on postnatal survival of observed-to-expected (O/E) ratio of total fetal lung volume (TFLV), LiTR, GA at delivery, side of CDH, intrathoracic position of the liver, GA at FETO and occlusion duration (for FETO group) were compared. In 19 fetuses with FETO, a post-FETO MRI was available and the proportionate increase in O/E ratio of TFLV at 3-8 weeks post FETO was compared with pre-FETO, and correlated with pre-FETO LiTR. A significant inverse relationship was found between the pre-FETO LiTR and lung response. LiTR was predictive of postnatal survival at discharge in both groups. In the FETO group, the LiTR was predictive of the lung response post-FETO.

Open Fetal Surgery: Results of the MOMS Trial. A. Flake.

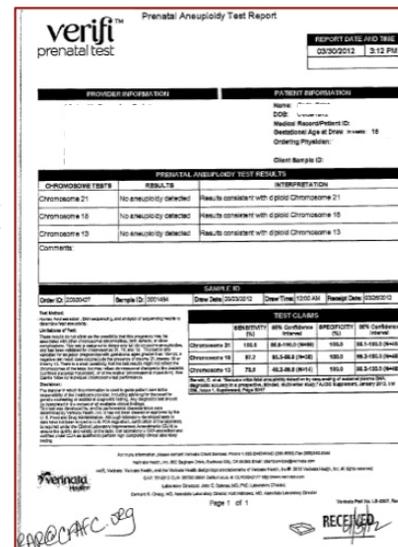
Professor Flake presented the results of the MOM's trial (Scott Adzick et al. NEJM. 2011; 364: 993-1004) with its great promise. This randomized trial was conducted on fetuses with a myelomeningocele at levels T1-S1 with hindbrain herniation and a normal karyotype at 19-25 weeks. Fetuses were randomized to in-utero open repair versus postnatal repair. There was a significant improvement in fetuses who had an in-utero open repair over those who were repaired postnatally with respect to shunting (50% reduction at 12 months), and independent ambulation (twice as many were independently ambulatory and 1/2 the number were wheelchair bound). However, there were significant maternal complications: pulmonary edema (6%), chorioamniotic membrane separation (28%), abruptions (6%) and uterine dehiscence (9%), in addition to 21% of fetuses with RDS in the in-utero treated group versus 6% in the postnatally treated group. MOMS II is currently underway to determine whether there is any impact on adaptive behavior at 5-8 years of age. And the great promise is in tissue engineering of a fluid permeable tissue layer which can be placed via fetoscopy under ultrasound guidance to simplify the in-utero repair and minimize the co-morbidities.

Metabolomics in Aneuploidies and Preeclampsia. R. Bahado-Singh.

Metabolomics is the systemic cataloguing and quantification of metabolites. With the recent advances, it is now feasible to carry out a comprehensive analysis of cellular metabolites in order to further characterize cellular activity in certain conditions, such as preeclampsia. Bahado-Singh et al. (J Matern Fetal Neonatal Med. 2012; April 28 [Epub ahead of print]) carried out a case control study of maternal plasma samples from 30 women who later developed early preeclampsia at less than 34 weeks and compared them to 60 normal controls. Subsequently genetic computing and standard statistical analysis were employed to predict the development of preeclampsia from the various metabolite concentrations, with and without the pulsatility index of the maternal uterine artery (UtA PI). A combination of 4 metabolites (citrate, glycerol, hydroxyisovalerate and methionine) had a 75.9% sensitivity at a false positive rate of 4.9% for predicting preeclampsia. There was marked improvement if these 4 metabolites were combined with the UtA PI and the fetal crown-rump length yielding a sensitivity of 82.6% and a false positive rate of 1.6%. The authors concluded that there is a profound change in the metabolites in the first trimester, and that these algorithms proved to be highly sensitive in the first trimester. In addition, similar algorithms utilizing metabolomics are being investigated for the early prediction of trisomy 21.

CF AFC's Technical Recommendation: Non-Invasive Prenatal Diagnosis (NIPD) Utilizing Maternal Blood

Prenatal diagnosis, as we have come to know it, will soon be obsolete...It is quite a challenge to keep up with the various modalities: no sooner do we feel comfortable with the techniques, let alone the counseling and result-interpretation of a method, than we have to start re-learning all over again. So what now of all that we have been doing? What about the NT, NB, DV, TR, FMFA and double test? What is their role now, on the 20th anniversary of the NT, after the recent introduction of NIPD as of 1 March 2012? The commercial test is currently available in the USA for women at 10-22 weeks (a sample report is on the right hand side belonging to one of our patients who travelled from Lebanon to the USA to have it done). The test has a reported sensitivity of 100% for trisomy 21, 97.2% for trisomy 18 and 78.8% for trisomy 13 (Bianchi et al. *Obstet Gynecol* 2012; 119: 890-901). It will be more widespread world-wide in the next few months. Utilizing NIPD in high-risk women is expected to decrease the rate of invasive testing to 0.005% (oral communication, Rossa Chiu MD, FMF Kos 2012). The role of the first trimester scan remains critical for the re-selection of the high risk group, however, that role will decrease with time as more experience is gained with NIPD. And as technology advances, this will inevitably be accompanied by a tremendous increase in the world-wide incorporation of a full anatomy scan in the first trimester. Today, it is possible to determine fetal sex, RhD and common chromosomal aneuploidies by NIPD. In addition, the principles for single gene disorders and non-invasive fetal genome assembly have been established. We are moving at such a rapid rate and it is expected that in the foreseeable future, non-invasive fetal karyotyping will be a possibility (oral communication, Rossa Chiu MD, FMF Kos 2012). As such, the need for global dedicated centers with well-trained certified medical professionals, in accordance with proper guidelines, has never been as urgent as it is now, at this turning point in maternal and fetal medicine...



THIS AND THAT

AIUM Abstract Submission

Abstract submission is open till September 27 for the AIUM's Annual Convention to be held April 6-10 in New York. For details and instructions on abstract submission, as well as an outstanding educational experience, visit the new vibrant AIUM website at www.aium.org



SANA's 1st Year in Review

SANA Medical NGO has just completed its first year of medical and educational missions in North Lebanon and would like to share its accomplishments with all who may be interested. A report on the first year is available at www.sanango.org. With great lessons learnt, SANA is excited about its upcoming year with much that is planned especially on the educational front, and we thank our supporters at the forefront of which is ISUOG and ISUOG Outreach ...



ISUOG Annual Congress

The annual congress of ISUOG is planned for September 9-12 in Denmark. Several new features shall be introduced including special session for beginners and sonographers. Details at www.isuog.org



Recommended App: Fetal Cardiac Z-Scores

Another innovative app from the Fetal Diagnostic Centers which is educational, practical and easy to navigate through. This app elegantly reviews the complicated concept of Z-scores in a simple manner, and is heavily illustrated with both schematic drawings as well as corresponding sonographic images. It clearly explains and illustrates where to obtain each cardiac measurement in addition to when in the cardiac cycle. Measurement may then be displayed utilizing various biometric options. This app is highly recommend for anyone wishing to evaluate the fetal heart in depth, beyond just obtaining the standard views that are necessary for ascertaining cardiac structure.



Lebanese Society of Ob/Gyn

Building on the success of its past congresses, the Lebanese Society of Ob/Gyn's annual congress on "Controversies in Women's Health" will be November 15-17 at the Movenpick in Beirut. Exciting pre-congress workshops in addition to a rich program covering maternal fetal medicine, reproductive endocrinology as well as gyn oncology, with international world-renowned speakers, are planned. Abstract submission deadline is 30 September. Details at www.isog2012.com



Prenatal Diagnosis of Congenital Heart Disease in Lebanon. R Abu-Rustum, MF Ziade, A Kesrouani, M Nassar, N Helou and S Abu-Rustum. Presented as OP35.08 ISUOG September 2011, and as P153 at the 11th World Congress of the Fetal Medicine Foundation, Kos Greece, June 2012.

Objective: To determine the prenatal diagnosis rate (PDR) of congenital heart disease (CHD) in a pediatric population age ≤ 5 years.

Methods: Prospective study at 3 pediatric cardiology clinics on 74 consecutive patients at age ≤ 5 years. Patients were questioned about family history (FHx), if they were scanned prenatally and if an abnormality was suspected prenatally. The presence of other structural/chromosomal abnormalities, age at diagnosis, final diagnosis and the need for surgical/medical intervention was established. Data was analyzed using chi square and non-parametric z approximation. Scans were performed by a single pediatric cardiologist. No background information was available on other patients who may have been prenatally diagnosed, who may have terminated or who may have had a spontaneous in utero fetal demise.

Results: 74 patients with 94 structural cardiac lesions were enrolled. FHx was positive in 18.9%. All were scanned prenatally and 86.5% were scanned at each prenatal visit. The PDR was 21.2%. Mean age at diagnosis was 13.4 months. The most prevalent lesions in our population were ventricular septal defects 32.4%, pulmonary artery stenosis 12.2%, patent foramen ovale 9.5%, tetralogy of fallot 8.1% and dysplastic mitral valve 6.8%. Of all cases 39.2% already had or would require surgical intervention and 21.2% needed medical therapy. Of 6 with a known karyotype, 4 had trisomy 21, 1 had DiGeorge syndrome and 1 was normal. Of the 94 total lesions, 56.4% were amenable to prenatal diagnosis by a 4 chamber view but only 18.9% were diagnosed prenatally. Prenatal diagnosis was considered critical in 26/94 (27.7%) and of those, 26.9% were diagnosed prenatally versus in 10.3% of those with non-critical lesions ($p=0.043$).

Conclusion: Even though 100% of patients being evaluated by a pediatric cardiologist were scanned prenatally, and 56.4% of lesions were amenable to detection by a 4CV, the PDR for CHD was only 21.2%, and 26.9% in those in whom prenatal diagnosis is critical. This calls for urgent implementation of basic training in fetal echo to maximize the utility of our machines and enhance our prenatal diagnostic rates.

Lesions Diagnosable by 4 Chamber View	Total Number	Prenatally Diagnosed
Ventricular Septal Defect	24	2 (8.3%)
Tetralogy of Fallot	6	1 (16%)
Dysplastic Mitral Valve	5	0
Atrioventricular Septal Defect	4	2 (50%)
Tricuspid Atresia	3	0
Pulmonary Atresia	3	1 (33%)
Dysplastic Tricuspid Valve	2	1 (50%)
Dextrocardia	1	1 (100%)
Total Anomalous PVR	1	0
Isomerism	1	0
Hypoplastic Right Heart	1	1 (100%)
Single Ventricle	1	0
Situs Inversus	1	1 (100%)
Diagnosable by 4CV	53/94 (56.4%)	10/53 (18.9%)



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CFAFC would like to thank Drs. Diana Bianchi, Linda Daou, Gregory DeVore, Ishraq Dhaifalah, Faysal El-Kak, Stefanos Geroulanos, Nabil Helou, Jacques Jani, Assaad Kesrouani, Anwar Nassar, Malek Nassar, Mark Skalnsky and Fouad Ziade for their contributions to this issue.



For any interesting case reports, comments, suggestions or announcements to be included in our newsletter, please send an e-mail to rar@cfafc.org.

Scoring System for Coarctation of the Aorta

The critical in utero diagnosis for coarctation (CoA) has remained a major challenge. And though there have been several sonographic markers described over the years, these have had low sensitivities and high false positive rates. The need for a scoring system utilizing the various markers was addressed at the ISUOG in 2011 (oral communication, Abu-Rustum et al, <http://isuog.conference2web.com/content/3078>). This has now been accom-



Figure 1



Figure 2

plished by the recent retrospective work of Gomez-Montes et al (Ultrasound Obstet Gynecol, 29 June 2012 [Epub ahead of print]) in which they describe a multiparametric scoring system on 85 fetuses with ventricular (Figure 1) and great vessel (Figure 2) disproportion, utilizing fetal gestational age of \leq or $>$ 28 weeks, and various sonographic markers. The likelihood ratios for z-score of the ascending aorta (AAo) ≤ -1.5 , pulmonary valve/aortic valve ratio ≥ 1.6 , and z-score of the aortic isthmus in the 3 vessels-trachea view ≤ -2 were utilized to calculate post-test probability of coarctation, which were found to be higher in fetuses with CoA. In fetuses at ≤ 28 weeks, a rate of growth of the aortic valve ≤ 0.24 mm/week was 100% specific. The authors conclude that this objective scoring system is simple to incorporate by echocardiologists when evaluating fetuses with suspected CoA.

Upcoming Congresses

COURSE TITLE	DATES	LOCATION	WEBSITE ADDRESS
22nd World Congress of the International Society of Ultrasound in Obstetrics and Gynecology	Sept 9-12, 2012	Denmark, Copenhagen	www.isuog.org/WorldCongress/2012/
Hot Topics in Perinatal Medicine	Sept 15, 2012	Beirut, Lebanon	www.aub.edu.lb/fm/cme/activities/Documents/Perinatal-Medicine.pdf
National Conference on Ob/Gyn Ultrasound	Sept 28-30, 2012	Chicago, IL	www.iame.com/conferences/obgyn_ultrasound/
2nd Fetal Echocardiography Symposium at UCLA	Oct 20, 2012	Los Angeles, CA	www.cme.ucla.edu/courses/event-description?event_id=2046283
2nd Central-Eastern European Symposium on Free Nucleic Acids in NIPD	Oct 25-26, 2012	Olomouc, Czech	www.prenat2012.upol.cz
2nd Global Congress of Maternal and Infant Health	Oct 25-28, 2012	Shanghai, China	www.comtecmed.com/gmih/2012
Third Annual Fetal Echocardiography: Normal and Abnormal Hearts	Oct 28-29, 2012	Las Vegas, NV	www.edusymp.com/meetingview.asp?productid=5121
Patient Safety in Obstetrics 2012: Reducing Risk and Improving Outcomes	Nov 1-3, 2012	Las Vegas, NV	www.edusymp.com/meetingview.asp?productid=5127
Obstetrical Ultrasound in the High Risk Patient	Nov 9-11, 2012	Las Vegas, NV	www.iame.com/conferences/obstetric_ultrasound/
Annual Congress of the Lebanese Society of Obstetrics & Gynecology	Nov 15-17, 2012	Beirut, Lebanon	www.lisog2012.com
15th Mid-Atlantic Ultrasound Symposium	Nov 16-17, 2012	Virginia Beach, VA	www.evms.edu/continuing-medical-education/continuing-medical-education.html