초청강연

좌장 : 김종덕 (전북의대)

Korean Journal of Fetal Medicine
Vol. 3 No. 2 June 2007

Screening for gestational diabetes: Beyond the glucose challenge

Brian Koos

UCLA, USA

Maternal hyperglycemia increases placental transfer of glucose to the fetus, which, in turn, triggers fetal hyperinsulinism and other metabolic perturbations that lead to disproportionately increased truncal adiposity and increased risk for shoulder dystocia and birth trauma. Fetal hormonal adjustments associated with this disorder predispose to childhood obesity, impaired glucose tolerance, and metabolic syndrome. These complications provide a compelling rationale to normalize glycemia in gravidas with gestational diabetes mellitus (GDM), but standard glucose tolerance screening for GDM has suboptimal reproducibility and accuracy. We have recently explored whether the putative insulin mediators myo-inositol (myo-I) and D-chiro-inositol (chiro-I) could be used to identify GDM. Our study comprised 46 normal pregnant women who were screened for GDM by a 1-h, 50-g glucose load at 24-28 weeks of gestation. The 21 gravidas with GDM were compared to 25 with normal screening (NG), who were matched by age, gestational age, body mass index, and race/ethnicity. Mean random urinary chiro-inositol concentrations were significantly less ($p < 10^{-3}$) for GDM compared to NG, but myo-inositol levels were similar. The mean myo-inositol/D-chiro-inositol concentration ratio was 12.7 times that for NG, with results virtually identical for random and 24-h urine collections. With urinary inositol ratio for discrimination, the observed sensitivity and specificity were both 100%. Using a log-scale Gaussian distribution model, the urinary inositol ratio is predicted to have a sensitivity of 93.0%, specificity of 91.1%, and accuracy of 92.0% for GDM. The myo-inositol/D-chiro-inositol ratio in random urine samples is an exceptionally good marker for GDM that is projected to have greater accuracy than conventional screening.

Korean Journal of Fetal Medicine
Vol. 3 No. 2 June 2007

Adenosine: A common mediator of fetal behavioral and cardiovascular responses to hypoxia

Brian Koos

UCLA, USA

Fetal survival during acute hypoxia depends upon the redistribution of cardiac output that increases blood flow (and thus O_2 delivery) to critical organs (e.g., brain, heart) with a reduction in flow to less important tissues. Another key adaptation is the reduction in O_2 consumption, which involves decreased heart rate, movements, growth, and regulated O_2 metabolism. Plasma and brain levels of adenosine rapidly rise during hypoxia, and these increased extracellular adenosine concentrations appear to be a crucial mediator of many fetal responses to hypoxia. Studies in chronically catheterized fetal sheep have shown that the adenosine A_{2A} receptor subtype is involved triggering peripheral arterial chemoreflexes that mediate hypoxia-induced fall in heart rate and rise in mean arterial pressure. The hypoxia-induced decrease in cerebral vascular resistance, which increases brain blood flow, is also largely mediated by adenosine. Hypoxia inhibits fetal breathing movements via a neuronal circuit that involves the parafascicular nuclear complex of the posteromedial thalamus. The rise in brain adenosine levels during hypoxia inhibits breathing via activation of central adenosine A_{2A} receptors. In summary, hypoxia-induced rise in tissue adenosine levels activates A_{2A} receptors that are involved in crucial adaptations to acute O_2 deprivation. This mechanism is the physiologic basis for fetal assessment of that involves fetal heart rate, Doppler velocimetry, and ultrasound imaging.

Korean Journal of Fetal Medicine
Vol. 3 No. 2 June 2007

Tocolysis: Is it time to challenge current practice?

G C Di Renzo, M.D., Ph.D.

Centre of Perinatal and Reproductive Medicine & Department of Obstetrics and Gynecology, University of Perugia, Perugia, Italy

Preterm birth remains one of the serious problems in perinatal medicine and is associated with an increased risk of perinatal complications and long-term morbidity. Although each day that delivery is delayed between 22 and 28 weeks'gestation increases neonatal survival by 3%, since most spontaneous preterm labors occur between 28 and 34 weeks'gestation, this is of secondary concern; the primary goal of delay is to improve the function of certain systems in the fetus and to balance the risks of a hostile intrauterine environment with the complications of extrauterine preterm life.

Perceptions of uterine contractions have always been interpreted by pregnant women as evidence for impending preterm labor. The majority of these women will present to their local hospitals for assessment of labor, resulting in over half being admitted, treated and released without delivering after a few days. With the use of biochemical markers (particularly fetal fibronectin) and sonographic evaluation of the cervix, it is possible to identify the majority of women who are not in preterm labor.

Standardization of assessment and disposition of patients presenting with the signs and symptoms of preterm labor will: 1) allow for timely interventions for preterm labor; 2) maintain maternal-fetal safety; 3) minimize the need for hospitalization only for those patients at greater risk of preterm delivery; and 4) promote effective transport of preterm labor patients to higher, more appropriate levels of care.

Tocolysis is the first therapeutic approach in the treatment of preterm labor.

Therefore, the primary aims of tocolytic therapy are to delay delivery to allow the administration of a complete course of antepartum glucocorticosteroids in order to primarily reduce the incidence and severity of idiopathic respiratory distress syndrome and intraventricular hemorrhage and to arrange in utero transfer to a center with neonatal intensive care unit facilities.

The secondary aim of tocolytic therapy is to delay delivery to reduce the perinatal mortality and morbidity associated with severe prematurity. A full comparison of costs has not been reported but this should also take into account the costs of administering each drug against any benefits or adverse effects, primarily the costs of preterm birth itself, savings on neonatal intensive care and the comparison of obstetric and tocolytic budgets to other hospital budgets.

In Europe, the most widely used tocolytic agents are: prostaglandin-synthetase inhibitors (PGI), calcium-antagonists (CA), β-mimetics (BM), and oxytocin-antagonists (atosiban, AT). The first three categories of drugs have been related

to severe maternal adverse effects (tachycardia, nausea, vomiting, trembling, giddiness, even pulmonary edema), fetal (tachycardia, bradycardia, sudden death) e neonatal (morbidity and hospital stay in intensive care). Their use nowadays should be discouraged also considering that PGI and CA are unlicensed. The efficacy and safety of AT versus BM, in the treatment of preterm labor, have been studied in a randomised, multicentric, controlled, double-blind trial showing a net advantage of AT over BM.

Atosiban represents an advance in currently available tocolytics, and should be considered a first-line tocolytic for the management of preterm labour, as recently stated by RCOG and EAPM giudelines. Experiences like ours on the prolonged use of AT in early gestational ages, such in case of multiple pregnancy or premature rupture of membranes before 28 weeks, has confirmed optimal compliance and safety of the drug, allowing to reach a gestational age with less perinatal risks.

Korean Journal of Fetal Medicine
Vol. 3 No. 2 June 2007

Non invasive prenatal diagnosis: Fetal cells and free fetal DNA

G C Di Renzo, M.D., Ph.D.

Centre of Perinatal and Reproductive Medicine & Department of Obstetrics and Gynecology, University of Perugia, Perugia, Italy

During the past 15 years advances in molecular techniques and embryo-fetus knowledge have changed the possibilities for screening and prenatal diagnosis of fetal abnormalities. At present, however, fetal samples can be obtained only after invasive procedures as amniocentesis or chorionic villus sampling (CVS).

Amniocentesis (15-18 weeks of gestation) and CVS procedures (10-12 weeks) carry a risk of fetal loss around 1% and for this reason they can be offered only to women at risk of children with chromosomal abnormalities or at advanced age. Unfortunately about 0.7% of live infants from low-risk mothers are born with a congenital abnormality.

On the contrary, to decrease undesirable or deleterious effect in respect to mother and fetus, it would be necessary to develop non-invasive means to identify all pregnant at risk. Therefore, a better prenatal screening test should be simple, easy, least aggressive or painful, sensitive and specific. Besides, results of a screening of non-invasive test depend especially on "the cut-off point" that affects sensitivity and specificity.

Unfortunately until now, none of the routine non-invasive screening test for congenital abnormalities can detect all kind of anomaly and not reach the "ideal requirements" such as sensitivity (100%) and specificity (100%): obviously the best are those that are closest to achieved optimal values.

Recent results from studies of non-invasive prenatal diagnosis screening by using biochemical serum markers such as triple test for Down's syndrome detection show an high false positive rate (about 8.5%); 100 women with normal fetus, 8/9 of these undergo amniocentesis. For this reason, it seems that the maximum screening efficiency is not achieved by this test.

An alternative strategy that could be utilized to overcome the sensitivity and specificity of triple test for a non-invasive prenatal screening test may be the use of fetal cells and free fetal nucleic acids present in peripheral maternal circulation during pregnancy.

Some studies have demonstrated the presence of fetal cells (such erythroblasts and stem-cells) in maternal blood and some methods have emerged for isolation of these, thus providing a promising approach for non-invasive prenatal diagnosis of genetic abnormalities.

Moreover, the availability of genome sequences, the possibility to amplify minimum DNA quantity and determine alterations in gene dosage with Real-Time Polymerase Chain Reaction (RT-PCR) or to detect abnormality in chromosome number of non dividing-cells with FISH technique (Fluorescence In Situ Hybridisation), have transformed the limit of

prenatal diagnosis and for these reasons non-invasive techniques using fetal cells could represent a new real method capable to evaluate a wide spectrum of fetal genetic issues with a high profit.

Another possibility of non invasive prenatal diagnosis began in 1997, when Lo et al. showed the presence of free fetal DNA in maternal plasma and serum.

The studies following this discovery have proved that fetal DNA is present in maternal circulation from the first weeks of gestation and it degrades in few hours after delivery; therefore it cannot interfere with prenatal diagnosis of subsequent pregnancies.

Many authors have demonstrated the feasibility of the detection of Y-specific sequences in maternal blood from early gestation and showed that the sensitivity can reach 100% by using real time PCR. The limit of this approach is the low concentration of free fetal DNA in maternal plasma: for this reason, it is important to discover a method with high sensitivity for DNA dosage.

Until now, the principal approaches, in which fetal cells have been tested in non invasive prenatal diagnosis, are the detection of fetal trisomies and the determination of fetal gender by using FISH technique. Free fetal DNA has been assessed, principally, in prenatal screening of fetal gender and fetal RhD genotyping by using real time PCR technique.

On the basis of this knowledge, we are investigating the sensitivity and specificity of employing Real-Time PCR technique for non-invasive prenatal screening of fetal gender and fetal RhD genotyping.

Moreover, we are carrying out a study on non-invasive prenatal screening test (SAFE test) which consists in a genetic analysis of fetal stem cells isolated from peripheral maternal blood useful to detect the majority of the fetus affected by trisomies 13, 18 and 21, which are the most frequent diseases in born alive.

This test could be an interesting approach for a future non-invasive prenatal diagnosis, safe for the fetus, available for all pregnant women and not only for those with a risk of getting a fetus affected by genetic abnormalities.

The SAFE test will be discussed in detail at the session.