GENERAL

Abstracts 1 – 8

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1 A multicenter, prospective, masked comparison of chromosomal microarray with standard karyotyping for routine and high risk prenatal diagnosis

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OBJECTIVE: To evaluate the performance of chromosomal microarray (CMA) as an independent method for prenatal cytogenetic diagnosis

STUDY DESIGN: Villus or amniotic fluid samples from women undergoing prenatal diagnosis at 31 centers were sent to a central karyotyping lab. The samples were split; standard karyotyping was performed on one portion and the other was de-identified and sent to one of four independent microarray labs for CMA. Microarrays consisted of 84 regions of known disease association, 43 centromeric and 41 telomeric regions and a backbone of oligoneucleotides spaced 75 -125 kb with regions >1Mb reported. After a preliminary study, uncultured samples were analyzed primarily, using culture only as a back-up. Karyotype and microarray results were reported to an independent data center. Microdeletions and duplications identified exclusively by CMA were classified as "of known clinical significance" or "benign" using predefined listings. All other copy number variants (CNVs) were designated as "of uncertain clinical significance".

RESULTS: 4401 women were enrolled with indications of AMA (46%), abnormal 1st or 2nd trimester screening (18%), abnormal ultrasound (26%), and other indications (9%). Successful results were obtained by CMA in 98.7% of cases; 88% were obtained using only uncultured material. Of the 4340 samples for which results were available for comparison, 316 (7.3%) autosomal and 57 (1.3%) sex chromosome non-mosaic aneuploidies were identified by karyotype. All of these were identified by CMA however, seven (all from CVS) were reported as mosaic. Notably, 5.8% of cases with a normal karyotype and structural fetal anomalies had either a microdeletion or duplication of potential or known clinical significance, as did 1.7% of those sampled for maternal age or positive screening.

CONCLUSION: For prenatal testing, karyotyping and CMA are equally effective in identifying aneuploidy. Microarray detects additional clinically relevant information both in cases with structural anomalies and in those sampled for routine indications.

Frequency of Micro-deletions/Duplications in Pregnancies with Normal Karyotypes

Presenting Indication for Prenatal Diagnosis	Known Benign CNV (%)	CNV of Uncertain Clinical Significance**		Known Pathogenic CNV (%)	Total CNVs with Clinical Relevance (%)
		Likely Benign CNV (%)	Potential Clinical Significance (%)		
Maternal Age	31.8	2.8	1.3	0.5	1.7
Screen Positive	33.9	2.1	1.1	0.4	1.6
US Anomaly	32.2	2.5	3.2	2.6	5.8
Other*	30.0	1.6	0.8	0.5	1.4
All	32.1	2.5	1.6	0.9	2.5

*Includes: family history, previous pregnancy with abnormalities, elective

** Clinical potential determined by independent advisory committee based on size, gene content, inheritance, the literature and ultrasound findings

2 Induction of labor or expectant management for large-for-dates fetuses: a randomized controlled trial

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OBJECTIVE: To compare induction of labor with expectant management for large for dates fetuses to prevent macrosomia at birth, shoulder dystocia and the associated neonatal morbidity.

STUDY DESIGN: We conducted a randomized controlled trial in collaboration with 20 teaching hospitals, members of the GROG group, in France, Switzerland and Belgium. We included 817 women with a fetus with an estimated weight above the 95th percentile at 37 to 38 weeks of gestation. Women with diabetes treated with insulin and past history of cesarean section or shoulder dystocia were not included. The screening was first performed clinically (estimated weight above the 90th percentile), then a sonography was performed. Women were eligible if the sonographic estimated weight was above the 95th percentile. Women were randomized to induction of labor within 3 days (n=407) or expectant management (n=410). The primary outcome measure was neonatal trauma, including significant shoulder dystocia (defined as resolved by maneuvers other than McRoberts), fracture of the clavicle and brachial plexus injury, or perinatal death.

RESULTS: Baseline characteristics were similar between groups. A difference in mean birthweight of nearly 300 gr between groups was obtained (3831 gr versus 4112 gr). The risk of neonatal trauma was reduced with induction of labor (n=9, 2.2%), compared to expectant management (n=27, 6.6%) (RR: 0.34; 95%CI: 0.16 to 0.71). The likelihood of a spontaneous vaginal delivery was higher (RR 1.14; 95%CI: 1.00 to 1.29) in the induction of labor group. The risk of cesarean section was not increased after induction of labor (28.0% vs 31.7% in the induction and expectant groups, respectively). Other neonatal morbidities were similar between groups, with no recorded cases of wet lung, brachial plexus palsy and perinatal death.

CONCLUSION: Induction of labor in case of suspected large for dates fetus is associated with a lower risk of trauma at birth. This intervention does not result in an increased risk of cesarean section and improve the likelihood of a spontaneous vaginal delivery.

3 Prevention of preterm delivery after successful tocolysis in preterm labour by 17 alpha-hydroxyprogesterone caproate: a randomised controlled trial

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OBJECTIVE: Several small trials have suggested that progesterone might reduce the risk of preterm delivery among women with pre-

term labour arrested by tocolysis. This trial sought to test that hypothesis.

STUDY DESIGN: This open-label multicentre randomised controlled trial took place at 13 French university hospitals and included women with singleton pregnancies admitted at 24+0 through 31+6 weeks of gestation with a cervical length <25 mm for an episode of preterm labour that was then successfully arrested by tocolytic treatment. A course of betamethasone 12 mg, repeated after 24 hours, was given intramuscularly in all patients. Women were randomly assigned (by a centralised, computer-generated randomisation process) in a 1:1 ratio to receive either 500 mg of intramuscular 17 alpha-hydroxyprogesterone caproate (17P), started after tocolysis ended and repeated twice weekly until 36 weeks or until preterm delivery, or no treatment with 17P. Additional management in the two arms was left to the discretion of the attending physician, except that progesterone was not allowed in the control group. The primary outcome was time from randomisation to delivery, assessed according to the intention-to-treat principle.

RESULTS: A total of 188 women were randomised. The two groups were similar with respect to baseline characteristics. Outcome data were available for 184 women. There was no significant difference between the 17P and control groups in median [Q1-Q3] time to delivery (64 [42-79] and 67 [46-83] days, respectively; mean difference, -2; 95% confidence interval, -9 to +6) or in the rates of delivery before 37 (39% and 38%, p>0.99), 34 (16% and 20%, p=0.57), or 32 (9% vs 14%, p=0.35) weeks of gestation. Finally, rates of adverse perinatal outcomes did not differ significantly between the groups.

CONCLUSION: Biweekly injections of 500 mg of 17P did not prolong pregnancy significantly in women with an episode of preterm labour successfully arrested by tocolytic treatment.

4 Molecular inflammation in early pregnancy precedes structural remodeling of adipose tissue

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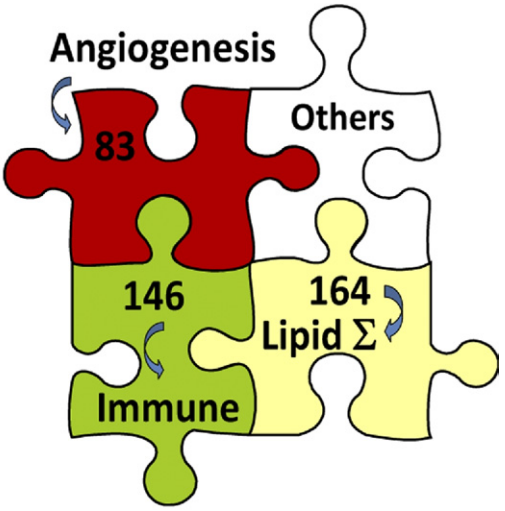
OBJECTIVE: Adipose tissue (AT) remodeling contributes to adaptations of maternal metabolic homeostasis during pregnancy. Early gestation is an anabolic condition with accrual of maternal adipose stores to meet the feto-placental and maternal later energy demands. The aim of this study was to characterize the molecular mechanisms responsible for adipose tissue remodeling in early pregnancy.

STUDY DESIGN: Women with healthy pregnancies were recruited pregravid (P) and followed-up in early (8-12 weeks) and late (36-38 weeks) pregnancy. The metabolic profile and body composition were obtained pre-gravid (P), in early (E) and late (L) pregnancy. AT biopsies were by liposuction in the subcutaneous gluteal depot. The AT transcriptome was examined by microarray profiling and RT-PCR.

RESULTS: BMI, fat mass, adipocyte volume, adipocyte cellularity and insulin resistance index were increased at L (p<0.001) and unchanged at E compared to P. The AT transcriptome encompassed 7612 genes among the 22,278 genes surveyed. The AT transcriptome exhibited significant modification at E compared to P with 15 % genes showing changes in their level of expression (645 increased and 641 decreased) between 1.5 and 10-fold. A strong activation of lipogenic pathways was indicated by genes in the lipid cluster (ATP citrate lyase, stearoyl-CoA desaturase, fatty acid synthase, lipoprotein lipase). Immune related genes pointed to the recruitment of LPS-sensing pathways (lipopolysaccharide binding protein, CD14, Toll-like receptor 4, NFkB) and macrophage activation (CD68, IL6, CSF). Enhanced angiogenesis was suggested by increased in angiopoietin, VEGFA, VCAM-1, MMP14, fibronectin.

CONCLUSION: Early pregnancy is characterized by a combination of molecular events which precedes the phenotypic changes of adipose tissue and body composition. The activation of immune pathways and angiogenic networks are novel findings. Our data suggest that early inflammation and vascular growth prepare AT remodeling in order to meet nutritional needs of mother and fetus at later stages of pregnancy. Supported by NICHD-22965-19



Gene categories over-represented
>1.5 fold in E vs. P (p<0.001)

5 Pregnancy after LEEP: results of a multicenter study

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OBJECTIVE: To assess the association between pre-pregnancy LEEP, pregnancy loss prior to 20 weeks and preterm birth.

STUDY DESIGN: A 7-year, multicenter cohort study of reproductive-aged women who underwent LEEP, PAP smear, or cervical punch biopsy without LEEP between 2000-2006. Subjects were identified by review of pathology records at 9 hospitals (both community and tertiary). Pathology records for all procedures were obtained, and all medical records for pregnancy (pre and post LEEP/Pap/punch biopsy) were obtained and reviewed in detail. Trained research nurses conducted closed-ended phone interviews with all subjects to complete historical and medical data extraction unavailable in charts. Pregnancy outcomes of women with prior LEEP were compared to 2 control groups: 1) prior Pap-only, 2) prior cervical punch biopsy using standard bivariate and multivariate techniques. We estimated a priori that we would need at least 600 women per group, based on an incidence of preterm birth <34 weeks of 4%, alpha error=0.05, beta error= 0.2, and a minimum detectable relative risk of 2.0.

RESULTS: We enrolled 625 women with a prior LEEP, 602 with a prior cervical punch biopsy, and 616 with a prior Pap smear. There were 45/616 (7.3%), 48/625 (7.7%) and 33/602 (5.5%) preterm births <34 weeks in the Pap, LEEP and punch biopsy groups respectively. There was no association between LEEP and loss prior to 20 weeks or preterm birth (Table), even after adjusting for (age, ethnicity, BMI, smoking, and prior preterm delivery).

CONCLUSION: Contrary to prior publications, in this large, well-characterized, generalizable cohort, LEEP is not associated with subsequent adverse pregnancy outcome. Subjects with prior LEEP do not