Hot Topics

Hot Topic 1
Weight loss in overweight and obese pregnant women (OW/OB): what is the effect on fetal growth?

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Objective: Although the IOM recommended that OW/OB gain weight during pregnancy, it has been postulated that weight loss may lower the risk of macrosomia. We evaluated the benefits of weight loss on fetal growth among OW/OB.

Study Design: Analysis of prospective multi-center data in singleton term pregnancies, in which 1195 OW/OB gained weight from their first to last prenatal visit (13.1 +/- 6.9 kg) and 46 lost weight (-5.0 +/- 4.7 kg). The 1241 OW/OB were subgrouped into 395 with normal glucose challenge test (GCT), 418 with abnormal GCT but normal oral glucose tolerance test (OGTT), and 255 with treated and 173 with untreated mild GDM. Small for gestational age (SGA) was defined as <10th centile. Fat mass (FM) and lean body mass (LBM), were assessed within 72 hrs of birth using anthropometry. Univariable and multivariable analysis was used to evaluate the association between weight loss and neonatal morphometry.

Results: Women who lost weight had higher pregravid BMI (38.7 +/- 8.9 vs. 30.7 +/- 5.3 kg/m2, p=0.0001). There was no significant difference in maternal age, smoking, parity, gestational age at delivery (EGA) or status of glucose tolerance between the two groups. Weight loss was associated with a greater risk of SGA (6/46 (13%) vs. 63/1194 (5%); adjusted OR 3.6 95% CI 1.3, 9.9; p=0.01). Neonates of OW/OB who lost weight had lower birth weight (3187 +/- 459 vs. 3445 +/- 489g, p=0.0004), FM (373 +/- 217 vs. 465 +/- 190g, p=0.001), and less LBM (2814 +/- 353 vs. 2980 +/- 345g, p=0.001). When adjusted for status of glucose tolerance, pre-pregnancy BMI, smoking, parity, study site, EGA and gender, neonates of women who lost weight had significantly lower birth weight, LBM, FM, and head circumference. There was no significant interaction among the 4 groups and weight change for SGA or other outcomes.

Conclusion: In OW/OB, weight loss is associated with SGA, decreased LBM, FM and head circumference. The significance of these findings needs to be determined because of the long-term implications for the offspring.

Hot Topic 2
Trends in incidence and serious perinatal outcomes in women with diabetes in pregnancy: A large, population-based study in Ontario, Canada 1996-2010.

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Background: Women with diabetes in pregnancy have high rates of pregnancy complications, which has increasingly important implications as diabetes prevalence in pregnancy is rising. Improved glycemic control and expert perinatal care have been associated with decreased perinatal complications. Numerous efforts to improve preconception and perinatal glycemic control and care for these women in the last decade should have led to improved outcomes. Our aims were to explore trends in incidence of diabetes in pregnancy, and examine whether the risk of serious perinatal outcomes has changed for women with diabetes in pregnancy.

Methods: We performed a population-based cohort study of 1,109,605 women who delivered in Ontario, Canada between April 1, 1996 to March 31, 2010. We categorized women as having gestational diabetes (GDM) (n=45,384), pre-gestational diabetes (pre-GDM) (n=13,278), or no diabetes (n=1,050,943). The annual
age-adjusted rates of diabetes in pregnancy were calculated, and rates of serious perinatal outcomes (congenital anomalies and perinatal mortality) were compared between groups and by year using Poisson regression. The predictors of these serious outcomes were assessed using multivariable logistic regression.

**Results:** The age-adjusted rate of women with diabetes in pregnancy doubled from 1996 to 2010 for both GDM (2.8% to 5.6%, p<0.001), and pre-GDM (0.7% to 1.5% (p<0.001)). The rate of congenital anomalies declined by 20% (from 4.6% to 3.7%, p=0.099) for women with GDM, and by 23% (from 7.1% to 5.5%, p=0.017) for women with pre-GDM, while the relative risk also significantly narrowed by 31% and 34% (p=0.003 and p=0.031). However, women with pre-GDM are still faced with an almost 1.9 fold increased risk of congenital anomalies compared to those without diabetes (RR 1.86 (95% CI 1.49-2.33)), while the RR is 1.26 (95% CI 1.09-1.45) for women with GDM. In contrast, the rate of perinatal death did not change significantly over the years. The relative risk of perinatal deaths continues to be significantly higher in women with pre-GDM (RR=2.33, 95% CI 1.59-3.43). In the stratified multivariable logistic regression, living in a rural community increased the risk of congenital anomalies and PNM in women with pre-GDM, while seeing an obstetrician reduced the risk of PNM in women with both GDM and pre-GDM.

**Conclusions:** Although congenital anomaly rates have declined over the last decade in women with pre-GDM and GDM, rates of perinatal mortality have not changed, and the risk of both these complications remains significantly elevated. With a doubling in the incidence of both GDM and pre-GDM over the last 16 years, the overall burden of diabetes in pregnancy on society is growing. Increased efforts are needed to reduce these adverse outcomes.

**Hot Topic 3**

**Complications to Bariatric surgery during pregnancy**

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To describe the obstetrical outcome in relation to the occurrence of upper abdominal pain during pregnancy in women with Roux-en Y Gastric By-pass (RYGB).

Data regarding pregnancy complications, neonatal outcome, upper abdominal pain and surgical interventions during pregnancy were collected from the medical records on 109 women with RYGB seen at Copenhagen University Hospital Hvidovre, either referred for antenatal care and delivery (n=85) or clinical evaluation of pain during pregnancy (n=24).

In 85 women followed for antenatal care, upper abdominal pain was reported in 29 (34%) during pregnancy. Additionally 24 pregnant women were referred from other hospital for evaluation of abdominal pain after RYGB. In the 53 women (29 + 24) reporting of abdominal pain, 27 (51 %) needed surgical intervention and 8 of these had or had sign of internal herniation.

Data on neonatal outcome and delivery was available in 68 women, who ended up giving birth at the department. In the 36 reporting of pain during pregnancy, the risk of premature delivery and the risk of caesarean was higher (22% versus 0 %, p<0.001), and (31% versus 19 %, p <0.05), respectively, and the mean foetal weight was lower (3020 (±515,3) versus 3255 (±374,9), p<0.05) than in the 32 women without pain. The risk of intrauterine growth retardation was identical in the two groups. None were diagnosed with HELLP (Hemolysis, Elevated Liver enzymes and Low Platelet count).

Pregnancy after a RYGB is associated with a high risk of upper abdominal pain and surgical intervention during pregnancy. Upper abdominal pain is a risk factor for premature birth but is not related to increased risk of intrauterine growth retardation. In case of upper abdominal pain pregnant women with RYGB should primarily be examined for internal hernia rather than HELLP.
Hot Topic 4
Factors associated with pre-labor urgent cesarean delivery in women with type 1 diabetes mellitus: a cohort study
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OBJECTIVE: Type 1 diabetes mellitus (DM) is associated with a three to five fold increased risk for stillbirth during pregnancy. The objective of the present study was to identify factors associated with pre-labor urgent cesarean delivery for fetal compromise in women with type 1 DM.

METHODS: We performed a nested case-control study within a prospective cohort of single pregnancies in women with type 1 DM managed with standardized protocols regarding treatment of diabetes and prenatal care. Twice-weekly home antenatal surveillance including non stress test (NST) was initiated at 32 weeks and continued until planned delivery at 38 - 39 weeks of gestation. We identified factors associated with urgent cesarean delivery for an abnormal NST. The calculated total sample size was 416 pregnancies. Independent factors and adjusted odds ratio (OR) were identified by logistic regression.

RESULTS: Among 479 pregnancies, the rate of pre-labor urgent cesarean delivery for an abnormal NST was 4%. An HbA1c at delivery of 6.4% or higher occurred in 34% of the pregnancies and was independently associated with urgent cesarean delivery (2% vs. 8%, \( P = 0.003, \text{OR} 4.16, 95\% \text{CI} 1.40 - 12.32 \)). In the univariable analysis, a low socio-economic status, smoking during pregnancy, the presence of a nephropathy and development of a polyhydramnios were not associated with urgent cesarean delivery. In the multivariable analysis, lack of preconception care and occurrence of gestational hypertension or preeclampsia were not associated with urgent cesarean delivery. The rate of stillbirth was 2 per 1000.

CONCLUSION: In women with type 1 DM, HbA1c at delivery of 6.4% or higher was associated with pre-labor urgent cesarean delivery. This suggests that tight glycemic control throughout pregnancy might reduce the risk of late fetal compromise. As glycemic control was good in 28% of the women delivered by urgent cesarean section, we suggest that fetal surveillance from 32 weeks of gestation until delivery remains a safe strategy in women with type 1 DM.

Hot Topic 5
EPO and EPOR expression in the placenta during fetal hypoxia in diabetic and hypertensive pregnancies
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Fetal hypoxia is a common problem in diabetic (DM) and hypertensive pregnancies. Elevated fetal erythropoietin (EPO) levels indicate chronic fetal hypoxia. Fetal EPO levels correlate negatively with umbilical artery (UA) pO\(_2\) and pH at birth. In the fetal lamb, the placenta becomes the main site for EPO synthesis during hypoxia. We have previously shown in type 1 DM patients that the umbilical vein (UV)/UA EPO ratio at birth correlates negatively with the UA pO\(_2\) when the amniotic fluid (AF) EPO level is >50 mU/ml suggesting that the placenta increases its EPO synthesis during fetal hypoxia also in humans. Our aim was to measure EPO gene (EPO) and EPO receptor gene (EPOR) expression in the placentae of women with DM and/or hypertensive pregnancies. We studied 17 patients with type 1 DM, 1 with insulin-treated gestational DM, 5 with type 1 DM and pre-eclampsia (PE) or gestational hypertension, 8 with PE and 9 women with normal pregnancies. All were delivered by cesarean section prior to labor. Placental biopsies were obtained and relative placental EPO and EPOR mRNA levels quantified by qPCR using TaqMan® chemistry. TATA box binding protein gene (TBP) was used as a
reference gene for normalisation. The calibrator sample consisted of pooled cDNA from women with normal pregnancies. The umbilical cord was doubly clamped and UA and UV samples were collected separately. Cord serum and AF EPO levels were measured by a chemiluminescent immunometric assay. UA samples were analyzed for pH and pO\textsubscript{2} levels at birth. In patients with UA pO\textsubscript{2} <2.0 kPa, placental EPO expression was significantly higher and EPOR expression lower than in patients with UA pO\textsubscript{2} ≥2.0 kPa (Table 1). The finding tentatively supports the hypothesis that EPO synthesis in the placenta is increased during fetal hypoxia. It is possible that EPOR expression is decreased in order to increase the transfer of EPO into the fetal circulation. Since EPO has protective effects in the central nervous system, it is tempting to assume that the fetus increases its EPO synthesis to protect its brain during chronic hypoxia. Further studies are clearly needed.

**Table 1.** Median (range) of UA and UV EPO concentrations, UA pH and pO\textsubscript{2}, and relative placental EPO and EPOR mRNA levels in patients with DM and/or hypertensive pregnancies with UA pO\textsubscript{2} <2.0 or ≥2.0 kPa. The number of subjects is presented in square brackets if different.

*Mann-Whitney U-test

<table>
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<th></th>
<th>UA pO\textsubscript{2} &lt;2.0 kPa, n=16</th>
<th>UA pO\textsubscript{2} ≥2.0 kPa, n=15</th>
<th>p-value*</th>
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<tr>
<td>UA EPO at birth (mU/ml)</td>
<td>72.9 (7.4-3190) [7]</td>
<td>64.3 (10.0-179.0) [12]</td>
<td>0.482</td>
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<tr>
<td>UV EPO at birth (mU/ml)</td>
<td>76.1 (6.1-3420) [7]</td>
<td>65.9 (10.9-187.0) [12]</td>
<td>0.536</td>
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<td>Antenatal AF EPO (mU/ml)</td>
<td>27.4 (13.4-1585.0) [7]</td>
<td>14.9 (9.6-46.4) [10]</td>
<td>0.070</td>
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<tr>
<td>UA pH at birth</td>
<td>7.25 (7.16-7.33)</td>
<td>7.28 (7.20-7.32)</td>
<td>0.060</td>
</tr>
<tr>
<td>UA pO\textsubscript{2} at birth (kPa)</td>
<td>1.55 (1.00-1.90)</td>
<td>2.50 (2.10-3.20)</td>
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<td>EPO expression (arbitrary units)</td>
<td>1.67 (0.11-8.36)</td>
<td>0.79 (0.21-2.21)</td>
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<td>EPOR expression (arbitrary units)</td>
<td>1.24 (0.60-2.22)</td>
<td>2.01 (1.35-3.44)</td>
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**Hot Topic 6**

Multipotent insulin’GLUT2’ progenitor cells are present in mouse extra-islet endocrine cell aggregates and can contribute to β-cell plasticity

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**Aims:** Beta-cell plasticity is responsible for the increase in maternal β-cell mass that occurs during pregnancy, and when this is sub-optimal it can contribute to gestational diabetes. However, after childhood the proliferation rate of mature β-cells within islets is extremely low, suggesting that there must be alternative cell compartments that can contribute to an increase in β-cell mass. Developmentally, islets arise from cells within the ductal epithelium, but the process of neogenesis of new β-cells from ducts ceases following birth. We hypothesized that additional sources of β-cell progenitors must exist within the pancreas, and that a candidate was the abundant extra-islet small endocrine cell aggregates.

**Methods:** Dispersed cells either from isolated islets or intact pancreas were studied from 7-day old RIPCre;Z/AP\textsuperscript{107} transgenic mice where the fate of β-cells could be lineage tracked through the expression of a human placental alkaline phosphatase (HPAP) reporter gene. Flow cytometry was subsequently used to sort sub-populations of β-cells. Isolated cells were cultured in medium optimized for de-differentiation of pancreatic endocrine cells to ductal epithelium (collagen matrix in the presence of EGF and cholera toxin), or for the lineage commitment and re-differentiation of de-differentiated cells to pancreatic endocrine cells, neuronal cell types, or muscle.

**Results:** Islets lost functional markers in vitro including insulin and Pdx1, whilst gaining duct and endocrine precursor markers. HPAP-expressing β-cells decreased in abundance significantly in culture, but the remaining cells de-differentiated and expressed the ductal marker cytokeratin (CK) 19. Flow
cytometry and recovery of β-cell sub-populations showed that the HPAP+ CK19+ cells had derived from insulin-positive, glucose-transporter 2- negative (Ins‘GLUT2 ) cells, representing 4% of all insulin-expressing cells, the majority of which were found outside of islets in small aggregates of 1-5 β-cells. These insulin‘GLUT2’ cells were proliferative in vivo and in vitro, and a subset of these could differentiate into endocrine, duct, neural, and muscle-cell lineages, illustrating substantial lineage plasticity. When in pancreatic endocrine re-differentiation medium, the insulin‘GLUT2’ became insulin‘GLUT2’ and demonstrated glucose-dependent insulin release. Conversely, insulin‘GLUT2’ mature β-cells from islets had no plasticity to de-differentiate or re-differentiate into a variety of cell lineages. The presence of insulin‘GLUT2’ cells within extra-islet endocrine cell aggregates persisted into adult life in mice.

Conclusions: Ins‘GLUT2’ cells represent a multi-potent, resident progenitor population located within the extra-islet endocrine cell aggregates of the pancreas throughout life in the mouse, which can contribute to β-cell plasticity. Manipulation of this progenitor population could lead to a modulation of β-cell mass.