Theme 6 / Infant of Diabetic Mother and Long-Term Consequences

PP 43
Disproportionate body composition and neonatal outcome in offspring of mothers with and without gestational diabetes
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Objective: High birth weight is associated with increased risk of neonatal complications. However, it is not known if the risk differs with body proportionality. The primary aim of this study was to determine the risk of adverse pregnancy outcome in relation to body proportionality in LGA infants (BW >90th percentile) stratified by maternal gestational diabetes. Material: Population based study of all LGA (birth weight (BW) >90th centile) infants born to women with GDM (n=1,547) between 1998-2007. The reference group comprised LGA infants (n= 83,493) born to mothers without diabetes. Data was obtained from the Swedish Medical Birth Registry. Infants were categorized as proportionate (P-LGA) if ponderal index was (PI) (BW in grams/length in cm³) \( \leq 90^{th} \) percentile and as disproportionate (D-LGA) if PI >90th percentile. The primary outcome was a composite morbidity of : fetal distress, Apgar score < 4 at 5 min, birth trauma, acute respiratory disorders, hypoglycemia or hyperbilirubinemia. Secondary outcomes included cesarean section and the above stated diagnoses analyzed separately. Logistic regression analysis was used to obtain odds ratios (OR) for adverse outcomes in relation to body proportions. The multivariate model included adjustment for maternal country of birth, age, BMI, height, smoking before pregnancy, parity, mode of delivery, pregnancy induced hypertension and preeclampsia. Results: The risk of composite neonatal morbidity were increased in pregnancies complicated by GDM versus controls but comparable between P- and D-LGA in both groups. D-LGA infants born to mothers without diabetes, had significantly increased risk of birth trauma (OR 1.19 95% CI [1.09-1.30] and hypoglycemia (OR 1.23 [1.11-1.37]. D-LGA infants in both groups had significantly increased odds of cesarean section. Conclusion: The risk of composite neonatal morbidity is significantly increased in GDM offspring compared with the reference group. In both pregnancies with and without GDM, the risk of composite neonatal morbidity is comparable between P-LGA and D-LGA.

PP 44
Circadian variation in glucose during diabetic pregnancy is associated with macrosomia in the newborn
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Introduction: Macrosomia is the commonest complication of diabetic pregnancy, often occurring despite achieving good glucose control as measured by HbA1c and home blood glucose monitoring. Although it is commonly attributed to hyperglycemia, the actual continuous glucose profile across the 24 hour day/night cycle that is associated with its development has not been described.
**Aim:** The purpose of this study was to determine the circadian glucose profile associated with macrosomia in well controlled diabetic pregnancy, utilising functional data analysis of glucose obtained by CGMS (Continuous Glucose Monitoring System) from a previous observational study.

**Methods:** We developed functional data analysis to analyse the numerous and complex data obtained by CGMS in 35 Type 1 and 14 Type 2 diabetic pregnancies. 256640 glucose measurements were made over 171 measurement sessions. Macrosomia was defined as above the 90th centile for gestation-adjusted birth-weight. **Results:** Mothers who developed macrosomic babies had a greater circadian variation in glucose with significantly higher levels of glucose during the daytime and evening, but lower levels from 1am until 9am, compared to mothers who did not develop macrosomia.

**Conclusions:** This study is the first to demonstrate, using functional data analysis, the circadian variation in glucose that is associated with the development of macrosomia in diabetic pregnancy. It confirms established evidence that postprandial hyperglycemia during the day is associated with macrosomia, but gives novel information about the contribution of nocturnal glucose control and suggests that relative hypoglycemia has an important role to play. This information is important to enable development of more accurate diagnostic and prognostic assessments, and optimize the application of new therapeutic technologies in insulin administration.

**PP 45**

**Preterm delivery in women with Type-1 diabetes mellitus and characteristics of insulin treatment**


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**Background and aims:** Preterm delivery is a complication of diabetic pregnancy. Spontaneous preterm birth is mainly associated with maternal hyperglycemia whereas elective preterm delivery intends to minimize or prevent pregnancy complications. On the other hand, myometrial contractility is impaired in diabetic women, with the underlying mechanisms being unknown. We hypothesized that maternal insulin treatment could have an influence on preterm birth and aimed to analyze its associations with insulin treatment characteristics (dose, insulin type).

**Material and methods:** We performed a retrospective cohort study in a tertiary care hospital. Inclusion criteria: Women with Type 1 diabetes mellitus and singleton pregnancy delivering in the centre between 1st January 1981 and 1st July 2009, using the same type of prandial and basal insulin since before pregnancy. Logistic regression analysis (backward method) was used to predict preterm birth (total, spontaneous, elective) using as potential predictors calendar year, fetal characteristics (presence of congenital malformation, stillbirth, large or small for gestational age) and maternal characteristics (including age, ethnicity, smoking habit, anthropometrics, diabetes duration, prior obstetric history, prandial and basal insulin type, and mean trimestral insulin dose, self-monitored capillary blood glucose and glycated haemoglobin).

**Results:** 417 women delivered in the study period. Insulin treatment characteristics: 25.4% lispro and 2.6% aspart as prandial insulin; 3.1% glargine & 34.4% pump treatment as basal insulin. Median gestational age at delivery was 38 weeks (P25 37, P75 38). Preterm delivery occurred in 22.5% of pregnancies (3.8% spontaneous, 18.5% elective). Mean insulin dose in the second trimester was one of the predictors of total preterm birth (OR 50.472, p <0.05). In the prediction of spontaneous preterm birth, mean insulin dose in the second trimester was also included (OR 43098, p <0.02), together with treatment with lispro insulin (OR 0.151, p <0.05) and glargine insulin (OR 25.603, p <0.02) among other predictors. Insulin treatment variables were not included among the predictors of elective preterm birth.

**Conclusions:** In women with Type 1 diabetes mellitus, insulin treatment variables are included among independent predictors of preterm birth, at the expense of spontaneous preterm birth. The associations warrant further analysis.
Perinatal outcomes in women with Type-2 versus Type-1 diabetes mellitus
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**Objective** was to compare perinatal outcome in pregnant women with type-2 DM vs. type-1 DM.

**Patients and methods:** In the period (2000.-2012.) 557 pregnant women with type-1 DM and 149 with type-2 DM were delivered. Following data were analyzed: age, body mass index (BMI), weight gain, HbA1c level in each trimester of pregnancy, complications of labor and delivery, newborn weight and ponderal index, perinatal mortality and morbidity. All women with type-2DM received insulin. **Results:** 557 type-1 DM women delivered 563 newborn children (4 pregnancies with twins and 1 pregnancy with triplets). 149 type-2 DM women delivered 154 newborn children (5 pregnancies with twins). No shoulder dystocia occurred.

### Table 1. Maternal and fetal/neonatal characteristics

<table>
<thead>
<tr>
<th></th>
<th>Type-1 DM (n=557)</th>
<th>Type-2 DM (n=149)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>29.3±32</td>
<td>32.8±5.5</td>
<td>&lt;0.003</td>
</tr>
<tr>
<td>BMI (kg/m2)</td>
<td>23.5±3.8</td>
<td>29.2±6.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Weight gain in pregnancy (kg)</td>
<td>13.3±5.3</td>
<td>10.1±6.5</td>
<td>&lt;0.003</td>
</tr>
<tr>
<td>Chronic hypertension n (%)</td>
<td>37 (6.5%)</td>
<td>15 (9.8%)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Diabetic nephropathy n (%)</td>
<td>40 (12.6%)</td>
<td>0 (0%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HbA1c: first trimester</td>
<td>7.42±1.6</td>
<td>7.4±1.4</td>
<td>&lt;0.018</td>
</tr>
<tr>
<td>HbA1c: second trimester</td>
<td>6.5±1.2</td>
<td>6.3±0.9</td>
<td>n.s.</td>
</tr>
<tr>
<td>HbA1c: third trimester</td>
<td>6.6±1.3</td>
<td>6.6±1.2</td>
<td>n.s.</td>
</tr>
<tr>
<td>New born weight (g)</td>
<td>3353.1±770</td>
<td>3385±824.3</td>
<td>n.s.</td>
</tr>
<tr>
<td>Ponderal index (100xg/cm3)</td>
<td>2.82±0.3</td>
<td>2.79±0.3</td>
<td>n.s.</td>
</tr>
<tr>
<td>Cesarean section n (%)</td>
<td>4 (0.7%)</td>
<td>2 (1.3%)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Fetal macrosomia n (%)</td>
<td>466 (93.5%)</td>
<td>82 (55.0%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Premature deliveries n (%)</td>
<td>174 (31%)</td>
<td>38 (24.7%)</td>
<td>&lt;0.035</td>
</tr>
<tr>
<td>Neonatal malformations n (%)</td>
<td>109 (19.7%)</td>
<td>31 (20.1%)</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

**Conclusion:** Despite a milder glycemia disturbances and better HbA1c level in first trimester women with type-2 DM had higher perinatal mortality than type-1 DM group, but fetal macrosomia and CS rate was significantly lower in type-2 DM group what can be the result of introduced insulin treatment during pregnancy.

Effects of maternal gestational diabetes mellitus and Cesarean delivery on circulating angiopoietin-like protein 4 in newborns

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Angiopoietin-like protein 4 (ANGPTL4) has been recently shown to be a potent inhibitor of lipoprotein lipase present in extrahepatic tissues and to increase adipose tissue lipolysis. Thus, higher levels of ANGPTL4 in plasma induce hypertriglyceridemia and raise plasma non-esterified fatty acids (NEFA)
levels. The expression of ANGPTL4 in different tissues is governed by peroxisome proliferator-activated receptors (PPARs) which are induced by polyunsaturated fatty acids and its concentration in plasma is decreased by insulin. Since data about ANGPTL4 in humans are still scarce and those metabolic variables are modified in the newborn, present study aimed to determine this protein in cord blood plasma of newborns known to have differences in adipose tissue lipolytic activity and insulin levels. Cord blood samples from one umbilical artery was collected in neonates of uncomplicated pregnancies born by vaginal delivery (controls, C, n=50) or by elective cesarean section (CS, n=56), or neonates of GDM mothers born by vaginal delivery (D, n= 74). Both ANGPTL4 and insulin were analyzed using ELISA kits and the other parameters were analyzed by enzymatic commercial kits. Fatty acid profile was determined by gas chromatography. No difference was found in gestational age or birth weight (BW) but both fat mass (FM) and FM/BW ratio were higher in D than in the other two groups. The changes in the concentration of the different parameters in plasma were as follows: glucose D>C>CS, insulin D=CS>C, insulin/glucose ratio CS>D>C, HOMA D>CS>C, cortisol D>C>SC, triglycerides D=CS>C, NEFA D>C>CS, glycerol C>CS=D, total saturated fatty acids (FA) C>CS>D, total monounsaturated FA C>D=CS, total n-3 FA C>D=CS, total n-6 FA C>CS>D and ANGPTL4 D>C=CS. Thus, changes in serum ANGPTL4 levels around birth varies in parallel to the lipolytic activity although in normal vaginal delivered newborns the effect is not manifested probably as a consequence of their higher insulin sensitivity which is known to decrease plasma ANGPTL4 in adults.

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PP 48
Breaking down misclassifications: not all gestational diabetes needs treatment as not all children need insulin

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Objectives: Not all the gestational hyperglycemias share the same etiology, as demonstrated in pediatric diabetology where, before the discover of the existence of monogenic forms of not autoimmune diabetes, all patients with hyperglycaemia were classified as “type 1 diabetes” and treated with insulin. The objective of the present study was to distinguish the diseases on yet by their phenotypes but by their pathogenesis providing a “taylor medicine”. Materials and methods: Two hundred and sixty four women with gestational diabetes for HAPO study criteria (fasting glycemia ≥ 92 mg/dl, and/or OGTT T60 ≥ 180 mg/dl and/or T120 ≥ 153 mg/dl) were recruited. 110 were overweight or obese (BMI >25) and were excluded by the study because patients with monogenic diabetes have low levels of insulin and generally are not overweight. One hundred and fifty four women had normal weight and continued to be enrolled. Gynecologist and Diabetologist treated all the women with low amount of CHO diet and/or insulin if the glycaemic control was not obtained. We have typed for MODY-2 and MODY-1 mothers who gave birth newborns with birthweight <2.500 Kg and their children. Results: The women who gave birth newborns with birthweight <2.500 Kg were all positive for mutation for monogenic, autosomic dominant, diabetes: four with heterozygous mutation of the GCK gene (MODY-2) and one for HNF4alpha gene (MODY-1). All the newborns were heterozygous for the same mutation of their mother. Conclusions: The treatment of a mother affected by MODY2 or 1 is the same of a mother with gestational diabetes to avoid the birth of a LGA child, due to the maternal hyperglycemia. It’s far different if both mother and child carry a MODY2 mutation: in this case the inborn has a poor insulin secretion that, if not increased by the exposure to maternal higher glycaemic levels, may determinate a
Small Gestational Age (SGA) baby. SGA newborn may be a baby with postnatal risks greater than the LGA. Intra uterine growth of the fetus has to be investigated by familial history for diabetes to suspect monogenic diabetes. In conclusion, we are confident that wider research on monogenic diabetes in pregnancy will avoid not necessary and sometimes dangerous therapies. This is the real cutting edge perspective of the modern medicine that has to pull down the categories in order to tailor the therapy on the patients and not on their disease.

PP 49
Size at birth in infants of gestational diabetes pregnancies: recent versus historical cohort comparisons
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Introduction and aims: Infants born following gestational diabetes mellitus (GDM) have greater risks for macrosomia, and later obesity and glucose intolerance. GDM management guidelines have tightened in recent years. We compared birth anthropometric outcomes between recent versus historical GDM infants, and non-GDM controls. Methods: A historical GDM infant cohort (IODM-1, N=76, 2002-2009) and a recent group (IODM-2, N=95, 2011-2012) were compared for birth weight, length and skinfold thicknesses, measured using identical protocols. Standard deviation scores (SDS) were calculated by comparison to a control population (N=601, 2001-2009). Recent GDM diagnostic criteria were OGTT glucose: 0min≥5.3, 60 mins≥10, or 120 mins≥7.8mmol/l; historically: 0min≥6.1, or 120mins≥7.8mmol/l.

Results: IODM-1 infants had greater mean±SD birth weight SDS (0.38±1.00; p=0.02), birth length SDS (0.2±1.0; p=0.02) and no difference in skinfolds (p=0.2) compared to controls. IODM-2 infants had similar mean±SD birth weight SDS (0.14±0.82), birth length SDS (0.04±0.8) to non-GDM controls, but surprisingly had lower skinfolds SDS (-0.5±0.6; p<0.0005). Only 2 infants were macrosomic (weight SDS≥2). In this recent group, 54 mothers received nutrition/ lifestyle advice, 37 additionally took medication (15 insulin, 11 metformin, 11 both) (4 unknown). Main predictors of infant adiposity for the IODM-2 group were 120min glucose and HbA1c, with no influence of maternal BMI or GDM treatment. IODM-2 vs.IODM-1 mothers had a trend to greater pre-pregnancy BMI (27.1 vs. 26.1 kg/m2) and higher 60 min glucose levels, but no difference in fasting or 120 min glucose. The recruited IODM-2 group also appears representative of the hospital GDM patient infants, with similar gestational age, and birth weight of 3.34kg. Conclusions: Contemporary IODM at our centre had similar birth weights and lengths to non-GDM controls and lower adiposity, despite no change between fasting and 120 min glucose on OGTT. We suggest that these changes likely reflect recent improvements in GDM management, rather than lower detection thresholds.

PP 50
Fetal growth in relation to gestational weight gain in women with Type 2 diabetes
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Objective: Fetal growth in relation to gestational weight gain as recommended by the Institute of Medicine (IOM) was evaluated in women with type 2 diabetes. Research Design and Methods: A retrospective cohort comprised the records of 142 singleton pregnancies in normal-weight (n=28), overweight (n=39) and obese (n=75) women with type 2 diabetes giving birth between 2008 and 2013. Birth weight was evaluated by SD-score to adjust for gestational age and sex. Results: Eighty-one women (57%) gained within or below the IOM 2009 guidelines and the remaining 61 gained more than recommended. The median (range) gestational weight gains were 7.0 kg (-4.7 to 16 kg) and 14.3 kg (9.4 to 31.8 kg), respectively. Prepregnancy BMI was 29.7 kg/m² (19.6-52.7 kg/m²) vs. 32.0 kg/m² (18.8-48.2 kg/m²), and median HbA1c was 6.6% (4.8-9%) and 6.4% (4.9-14%) at first visit and decreased to 5.9%
(4.7-9.7%) and 6.0% (5.0-9.0), in late pregnancy, respectively. Gestational weight gain within or below the IOM guidelines was associated with lower birth weight SD-score (-0.01 (-3.52-4.38) vs. 1.14 (-2.48-4.73), P=0.001), lower rates of large-for-gestational-age (LGA) infants (16 vs. 29%, P < 0.001) and macrosomic neonates > 4,000 g (3% vs 26%, P <0.001) and less perinatal morbidity (37% vs 54%, P = 0.043) compared with pregnancies with higher maternal weight gain. Maternal weight gain was a predictor of birth weight SD-score independent of prepregnancy BMI, smoking, HbA1c at last visit, ethnicity, preeclampsia and nulliparity (β = 0.11 [95% CI 0.069 to 0.149], P <0.001). Maternal weight gain increased gradually from 0 to 600 g/week. In women gaining within the IOM guidelines the median weight gain in the first half of pregnancy was 81 g/week, 114 g/week and 371 g/week in obese, overweight and normal weight women, respectively. The figures for the last part of pregnancy was 439, 427, 483 g/week, respectively. **Conclusion:** In women with type 2 diabetes, maternal gestational weight gain within or below the IOM guidelines was associated with a more proportionate birth weight and less large-for-gestational-age (LGA) infants compared to women gaining more.

**PP 51**

Ultrasound examinations near term tend to underestimate birth weight in diabetic pregnancies


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**Aim:** Accurate estimation of birth weight (BG) is crucial for planning of route of delivery in diabetic pregnancies due to the high rate of macrosomia. Risk of shoulder dystocia is twice as high as in normal pregnancies and rises with BW. It is well known that the accuracy of ultrasound to estimate BW is limited. We aimed to determine if 1.) there is a tendency either for under – or overestimation and 2.) if the degree of false estimation is influenced by maternal or fetal parameter. **Methods:** In 575 diabetic pregnancies estimated fetal weight (EFW), interval between US and delivery, maternal BMI and birth weight was obtained from medical charts. US exams were performed < 14 days delivery (mean 4.7 days). **Results:** The accuracy of BG estimation was correctly estimated within +/-10% in 59.7% of the women, underestimated by 10-20% in 22.2%, by >20% in 10.1% and overestimated by 10-20% in 7.5%, with 0.5% > 20%. In women with BMI> 30 kg/m² the percentage of correct EFW was similar as in non-obese women (61.8 vs 55.9%, p=0.205 ) but there was higher percentage of overestimation (11.8 vs 6.0%). BG > 4000 g was correctly predicted only in 43.1%, BG 3500-3999 g in 57.5% and <3500 g in 66.2% (p<0.001). BG > 4000g was underestimated by 10-20% in 34.7% and by >20% in 19.4% of the newborns. US exam 8-14 days before delivery had a lower rate of correct EFW than those performed < 7 days (52.5 vs 70.2%, p=0.01) due to a high percentage of underestimation (43.4%). However, in women with BMI> 30 kg/m² the high rate of overestimation increased (18%). **Conclusion:** US estimation tends to underestimate birth weight, specially in high birth weight with false estimates in almost 50%. This is clinically critical and should be kept in mind when planning the mode of delivery. Accuracy can be improved by a short interval between US and delivery. However, in obese women the high rate of overestimation even increased which had to be considered when indication for C-section is based on EFW.