M4 MAXIMUM VASODILATORY RESERVE IS NEGATIVELY CORRELATED WITH BMI AND WAIST CIRCUMFERENCE IN WOMEN WITH POLYCYSTIC OVARIAN SYNDROME

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Polycystic Ovarian Syndrome (PCOS) is associated with insulin resistance, increased risk of NIDDM and possibly with hypertension and cardiovascular risk. We have previously shown impaired microvascular vasodilatory reserve (MVR) in subjects with NIDDM and "prediabetic" glucose intolerance. In the latter MVR was inversely correlated with fasting insulin.

In this study we compared MVR in 19 women with PCOS (oligo/amenorrhoea with either hirsutism, ultrasound evidence of PCOS, and/or raised androgens) and 19 age- and BMI-matched women with normal menses. MVR in response to local heating was assessed using laser Doppler flowmetry. There were no significant differences between PCOS and controls with respect to MVR (1.53 (1.0 - 2.76) vs 1.61 (0.9 - 2.43) V median (range), p = 0.93), age, BMI, blood pressure or fasting glucose. However, in the PCOS group MVR was negatively correlated with BMI (R = -0.56, p = 0.013) and waist circumference (R = -0.61, p = 0.006). No such relationship was observed in controls.

Although MVR in PCOS did not differ significantly from controls, there was a strong negative correlation with anthropometric indices associated with insulin resistance and cardiovascular risk. In this group of women increasing BMI and visceral adiposity may be associated with deterioration in MVR in the absence of glucose intolerance.

M5 A POSSIBLE ASSOCIATION BETWEEN A SPECIFIC MUTATION IN THE CYP 17 (17a-HYDROXYLASE/17-20 LYASE) GENE AND ALTERED PLASMA GONADAL STEROID HORMONE CONCENTRATIONS

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It is possible that premenstrual syndrome (PMS) and polycystic ovarian syndrome (PCOS) could both have a genetic basis related to polymorphic variants for specific enzymes involved in the steroid hormone pathway. In the present study, a specific mutation (T-34C) in the gene for one of the rate-limiting enzymes in the pathway, CYP17 (17a-hydroxylase/17-20-lyase), was investigated in patients with PCOS and/or PMS. This mutation consisting of a single base change in the promoter region close to the start of transcription creates a potential site for Sp1 transcription factor binding, which may alter gene expression. Blood samples were obtained from 12 women diagnosed with PMS alone and 4 women with PMS and PCOS. Genomic DNA was extracted, amplified using PCR, and the products digested using MspA I restriction enzyme.

The luteal phase plasma progesterone concentration was significantly greater in the 3 PMS patients with at least one affected (A2) allele compared with the other unaffected patients (45.6±3.1 and 10.8±2.8 nmol/l respectively, P = 0.02), as was the plasma 17α-hydroxy-progesterone concentration (9.4±1.2 and 4.4±0.9 nmol/l respectively, P = 0.05). Interestingly, one of the PMS/PCOS patient with the A2 allele had a markedly raised plasma testosterone concentration (2.7 nmol/l) compared with the patients with PMS alone (1.47±0.32 nmol/l). These results if confirmed would provide evidence for a specific gene mutation influencing steroid hormone production in more than one disease state.

M6 THE METABOLIC MAP OF THE LIVER LOBULE IN DIABETIC KETOACIDOSIS

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A new method of detailed mapping of metabolism along the radius of the hepatic lobule (Burns, SP et al Biochemical Journal 319:377-383, 1996) was used to compare perfused livers from normal rats with those from animals with severe (systemic blood pH<7.0) diabetic ketoacidosis (DKA) induced by streptozotocin 48h previously. The perfusate contained 1.3 mM lactate and 0.8 mM palmitate bound to albumin. Normal livers were perfused at pH 7.4 and DKA livers at pH 6.8; some normal livers were also perfused at pH 6.8. In normal livers, approximately 25% of glucose synthesized peripherally is taken up by the more terminal perivenous cells. In DKA livers, this perivenous uptake disappears and is replaced by gluconeogenesis at a greater rate than peripherally. In normal livers perfused at pH 6.8, perivenous uptake of glucose is decreased, but the distribution of glucose output and uptake otherwise resembles that at pH 7.4. In normal livers, perfused at pH 7.4, pHj, measured by 31P-NMR, is 7.4-7.7 in the most perivenous cells and declines to <7.25 peripherally. The pattern is reversed in DKA, the most periporal cells having a pHj of 7.5-8.0, and markedly in the most perivenous cells. 3-hydroxybutyrate is synthesized throughout the lobule, but in normal liversperfused at pH 6.8 and in DKA livers, approximately 20-50% of that synthesized in the most perivenous 30% of the lobular volume is derived from acetocacetate derived peripherally and transported down the sinusoid. The low pH, peripherally in DKA may be due to ketogenesis, and is likely to inhibit gluconeogenesis which shifts to the perivenous region, which is more alkaline. These results demonstrate major plasticity of metabolic function within the hepatic lobule.

M7 ORAL CALCIUM LOADING IN NORMAL AND INSULIN DEPENDENT DIABETIC (IDD) PREGNANCY

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Infants of IDD mothers are at risk of hypocalcaemia yet calcium (Ca) handling in IDD pregnancy is little understood. We measured serum ionized Ca (iCa) (ion-selective electrode), intact parathormone (PTH) [2-site immunoassay] & urinary Ca excretion (UreCa) (Roche Cobas Integra 700) at 21 (19-23) wks gestation in 20 normal and 20 IDD women before and for 4 hrs after 1 g oral Ca citrate. 15 of each returned postnatally (iPTH - not lactating. Values are median (quartiles) or means ± SEM. Analysis of variance (AVG) with post-hoc T test or Kruskal Wallis AVG and post hoc Mann Whitney were used to detect time-related differences. Basal PTH was unchanged during normal pregnancy but in IDD pregnancy was suppressed(p<0.01) falling even further(p<0.05) after oral Ca (table 1).

Outside pregnancy fasting Ca, PTH and UreCa were similar in both groups. Within 3h of Ca in pregnancy PTH was suppressed(p<0.01) in both groups and remained so for 4 hrs with greater suppression in the IDD group at 24 hrs (p<0.05). Ca rose(p<0.01) hourly in each group without plateauing by 4hrs. UreCa rose 5-fold by 3hrs (p<0.01).

Basal Ca & UreCa were the same in normal and IDD pregnant women;after oral Ca, Ca rose from 1.16 (0.9-0.7) to 1.25 (1.03-1.25) mmol/l in IDD & from 1.19 (0.9-1.0) to 1.25 (1.03-1.25) mmol/l in controls. Ca rose(p<0.01) hourly in each group without plateauing by 4hrs. UreCa rose 5-fold by 3hrs (p<0.01). Table 1

<table>
<thead>
<tr>
<th>PTH (pmol/l)</th>
<th>Control (n=20)</th>
<th>IDD (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting</td>
<td>2.7 (2.0-3.5)</td>
<td>2.0 (1.6-2.3)**</td>
</tr>
<tr>
<td>1 hr post Ca</td>
<td>1.2 (1.2-1.9)</td>
<td>1.2 (1.1-1.9)</td>
</tr>
<tr>
<td>3 hr post Ca</td>
<td>1.4 (0.9-1.9)</td>
<td>0.8 (1.1-1.9)**</td>
</tr>
<tr>
<td>4 hr post Ca</td>
<td>1.3 (1.2-1.3)</td>
<td>1.0 (1.1-1.3)</td>
</tr>
<tr>
<td>IPM fasting</td>
<td>3.7 (2.7-5.1)</td>
<td>2.7 (1.9-3.3)**</td>
</tr>
</tbody>
</table>

* p<0.01 (below detection limit of assay)
We confirm that pregnancy is not a state of