13 THE EFFECT OF FETAL PROGRAMMING ON THE EXPRESSION OF GENES INVOLVED IN ADULT VASCULAR FUNCTION

OBJECTIVE: Endothelial nitric oxide synthase (NOS3) is involved in the vascular adaptations to pregnancy. We have previously reported that mice born to mothers lacking NOS3 gene have fetal growth abnormalities and abnormal vascular function in later life. This study investigate the potential mechanisms involved in the fetal programming of adult vascular function by evaluating expression of relevant genes in this animal model of fetal programming induced by an unfavorable uterine environment.

STUDY DESIGN: Homozygous NOS3 knockout (C57BL/6J-NOS3-/-KO) and wild type mice (NOS3 +/+WT) were cross-bred to produce litters grown in a maternal environment lacking NOS3 (NOS3 -/-KO) and maternally-heterozygous (NOS3 +Pat/-Mat) and litters grown in normal maternal environment, paternally-derived heterozygous (NOS3 +Mat/-Pat) and wild type (NOS3 +/+WT). Female offspring at 7-8 weeks of age (n = 4-5/group) were sacrificed. The aorta was isolated and total RNA extracted. TaqMan and appropriate probes for neuronal (NOS1), inducible (NOS2), and cyclooxygenases 1 and 2 (COX1 and COX2) and for pre-developed 18S rRNA probe were used for real-time RT-PCR. mRNA quantification was expressed as relative value (ratio to its own 18S rRNA). One-way ANOVA followed by post-hoc test was used for statistical analysis.

RESULTS: In the aorta, the NOS1, NOS2, and COX1 mRNA expressions were significantly lower in NOS3 -/-KO and NOS3 +Pat/-Mat female mice compared with NOS3 +/+WT (P < .005). COX2 expression was not different between the groups (Table).

CONCLUSION: Fetal programming and altered vascular function in adult offspring developing in an unfavorable uterine environment are associated with downregulation of genes active in maintaining normal vascular function.

Relative value

<table>
<thead>
<tr>
<th>Gene</th>
<th>NOS1 (mean ± SD)</th>
<th>NOS2 (mean ± SD)</th>
<th>COX1 (mean ± SD)</th>
<th>COX2 (mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NOS3 +/+/KO</td>
<td>1.43 ± 0.001</td>
<td>1.27 ± 0.01</td>
<td>1.16 ± 0.01</td>
<td>1.49 ± 0.002</td>
</tr>
<tr>
<td>NOS3 +Pat/-Mat</td>
<td>1.35 ± 0.02</td>
<td>1.26 ± 0.004</td>
<td>1.11 ± 0.009</td>
<td>1.42 ± 0.01</td>
</tr>
<tr>
<td>NOS3 +Mat/-Pat</td>
<td>1.49 ± 0.03</td>
<td>1.30 ± 0.01</td>
<td>1.19 ± 0.01</td>
<td>1.46 ± 0.02</td>
</tr>
<tr>
<td>NOS3 +/+/WT</td>
<td>1.50 ± 0.03</td>
<td>1.30 ± 0.005</td>
<td>1.23 ± 0.02</td>
<td>1.46 ± 0.02</td>
</tr>
</tbody>
</table>

14 EFFICACY OF ENOXAPARIN FOR IMPROVING PREGNANCY OUTCOMES AND UTEROPLACENTAL BLOOD FLOW IN WOMEN WITH THROMBOPHILIA AND RECURRENT PREGNANCY LOSS

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OBJECTIVE: Maternal thrombophilia is associated with recurrent pregnancy loss (RPL). Prophylaxis with low-molecular-weight heparin can benefit women with thrombophilia and RPL. There is little information about the effect of such treatment on uteroplacental blood flow. The purpose of this study was to evaluate the efficacy of two doses of enoxaparin for improving pregnancy outcomes and to investigate the effect on uteroplacental blood flow.

STUDY DESIGN: This multicentre, prospective, randomised, open-label study compared pregnancy outcome in women with thrombophilia and recurrent pregnancy loss (3 losses in first trimester, 2 losses in second trimester or 1 loss in third trimester) receiving enoxaparin 40 mg/day or 80 mg/day (40 mg twice daily). Women were enrolled at 5-10 weeks gestation and received enoxaparin throughout pregnancy and post-partum. The primary efficacy endpoints were the delivery of a live, healthy infant and Doppler indices in the uterine and umbilical arteries.

RESULTS: Prophylaxis with enoxaparin significantly increased the rate of live birth (84.3% vs 28.2% for 40 mg/day, 78.3% vs 28.3% for 80 mg/day; P = .001), decreased the rate of pre-eclampsia (3.4% vs 6.7% for 40 mg/day, 4.4% vs 14.3% for 80 mg/day; P = .001) and decreased the rate of placental abruption (4.5% vs 13.5% for 40 mg/day, 3.3% vs 8.8% for 80 mg/day; P = .002) compared with patients historical rates. The pulsatility index was significantly lower in the uterine arteries of women who received 80 mg/day compared to those receiving 40 mg/day, between 30-34 weeks (1.2 ± 0.8 vs 1.5 ± 0.15, respectively P < .05). No other significant differences in efficacy or safety were observed between the two enoxaparin groups.

CONCLUSION: Enoxaparin increased the rate of live births in thrombophilic women with recurrent pregnancy loss. A dose of 40 mg/day was sufficient to significantly improve pregnancy outcome. Improved uteroplacental blood flow in the group receiving the higher dose of enoxaparin suggests that this dose should be considered in women with multiple thrombophilic defects.

15 THE INFLUENCE OF PRIOR ROUTE OF DELIVERY: POSTPARTUM MATERNA L AND NEONATAL OUTCOMES

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OBJECTIVE: Accurate risk/benefit information is needed to counsel an increasing number of women requesting elective cesarean section. The purpose of this study was to assess maternal and neonatal postpartum outcomes associated with previous method of delivery.

STUDY DESIGN: We analyzed prospectively collected singleton maternal and neonatal data from 7/2002-12/2003 in four MemorialCare hospitals. Birth data were collected into a dedicated perinatal database and combined with coded data from a MedAI database of postpartum maternal and neonatal procedures and outcomes. Patients were subdivided in four groups: (1) Nulliparous; (2) Prior vaginal; (3) Prior Cesarean (CS) without trial of labor (TOL); and (4) Prior CS with TOL. Results were compared by chi square analysis with significance at P < .05.

RESULTS: During the study period there were 77,406 births fitting the above criteria. Compared to prior vaginal delivery, patients with prior CS had significantly increased risks of morbidity. The subgroup of prior CS patients without a TOL were more likely to require blood transfusion (P < .001, OR 3.1), ICU admission (P < .001, OR 4.5), and readmission within 30 days (P < .025, OR 1.7) than patients with prior vaginal deliveries. Prior CS with TOL patients did not have these increased risks but were more likely to receive aminoglycosides for postpartum infection (P < .01, OR 1.81). Term neonates born to mothers with previous CS were more likely to have postoperative hospitalization (>7 days) in both groups: no TOL (P < .001, OR 6.69) and TOL (P < .05, OR 2.51). There were no significant differences based on prior delivery route for neonatal mortality within the first 28 days of life, neonatal seizures or encephalopathy.

CONCLUSION: Prior cesarean delivery is a significant risk factor for important postpartum morbidities of the mother and neonate. These risks and benefits should be carefully discussed with women considering elective cesarean section.