Title:

INTRAUTERINE PROGRAMMING OF POLYCYSTIC OVARY SYNDROME: EVIDENCE FROM CORD BLOOD GLOBAL METHYLATION ANALYSIS

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Objective:

Polycystic ovary syndrome (PCOS) affects 5-15% of women. PCOS is a heterogeneous disorder displaying endocrine, metabolic, reproductive dysfunction and cardiovascular risk manifestations. Evidence of heritability exists, but only a portion of the genetic transmission is identified by genome-wide association studies and linkage studies, suggesting that epigenetic influences play a role. Evidence implicates intrauterine influences in the genesis of PCOS. The study aims to identify unique epigenetic reprogramming of cord-blood gene networks in progeny
of PCOS mothers by comparing global DNA methylation patterns in cord blood of neonates of infertile women with and without PCOS.

**Design:**

Prospective cohort study

**Material and Methods:**

This single-center study included patients undergoing in vitro fertilization (IVF) for infertility included anovulatory PCOS women diagnosed by Rotterdam criteria (n = 6) and a control group of ovulatory non-PCOS women (n = 6) matched for age and body mass index (BMI). Umbilical cord blood was collected at delivery of the placenta, DNA extracted and methylation analysis performed.

**Results:**

Nine hundred and eighteen genes differentially methylated CpG dinucleotides were detected. Seventy-eight percent (n=720) mapped into 10 gene networks. Key features of the primary network were hormonal regulation (ESR1), mitochondrial activity (APP, PARK2), and glucose metabolism (INS). Other significantly altered networks were dominated by genes involved in the G-protein coupled receptor signaling pathway (interacting with the insulin receptor signaling pathway and regulatory metabolic function), lipid metabolism, cardiovascular system development, and inflammation.

**Conclusion:**

The results of this pilot study suggest that maternal PCOS significantly influences the fetal gene networks involving carbohydrate, lipid and inflammation processes in PCOS pregnancy. The existence of a putative “super PCOS epigenomic pathway” is suggested, and an epigenetic at risk PCOS “signature” may exist and be identifiable at birth.