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Untargeted Plasma Metabolomics in Prepubertal ICSI & naturally conceived Children Unravels Gender - dimorphic Metabolic Trajectories after ICSI

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Background

Intracytoplasmic sperm injection (ICSI) is an assisted reproduction technique (ART) mainly used to overcome male infertility.
Nowadays, ICSI is employed frequently due to its high success rate, despite it being highly invasive (i.e. epigenetic risk).
Recent studies in ART offspring show a higher incidence of cardio-metabolic risk than in naturally-conceived (NC) controls.
Thus, in our prior untargeted metabolomic study between ICSI and NC prepubertal girls, we demonstrated insulin resistance in the former.

Objectives

Untargeted plasma metabolomic analysis of ICSI and NC prepubertal boys was performed to detect possible gender-dimorphic metabolic differences with respect to the girl study group.

Methods

Blood plasma samples of strictly matched ICSI and NC boys were analysed by Gas Chromatography - Mass Spectrometry (GC-MS) metabolomics.
Both metabolomic and biochemical data were analyzed using multivariate statistics and compared with the corresponding results of the girl ICSI and NC groups.
The results were visualized on a reconstructed inter-organ metabolic network (*Figure 1*).

Results

Combining metabolomic and biochemical measurements differentiated the ICSI and NC groups in both genders, with this difference being more prominent in the girls (*Figure 2*).
However, the discriminatory metabolites were gender-specific (*Figure 2-4*).
Whereas in both sexes a significantly higher concentration in insulin resistance associated metabolites was observed in the ICSI group, in the ICSI boys the largest difference relatively to the NC group was the significantly smaller concentration of the aromatic amino acids, potentially correlated with brain and liver abnormalities.

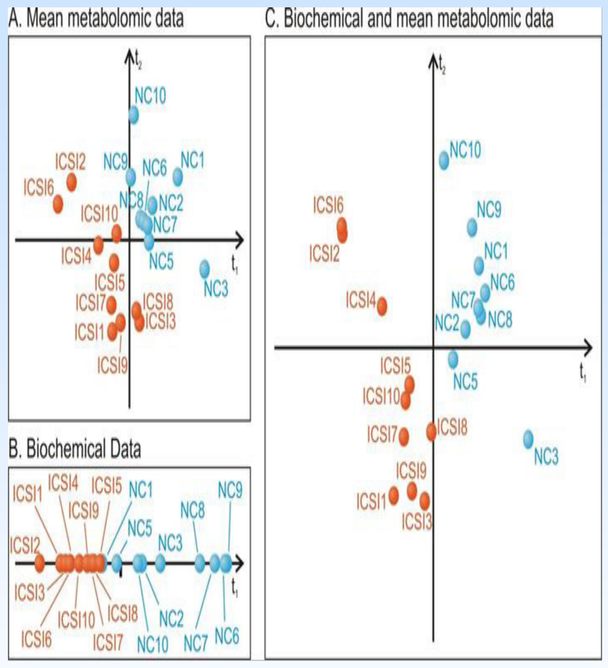


*Figure 2. PLS-DA graphs for (A) the mean metabolic profiles, (B) the biochemical profile data and (C) the biochemical combined with the mean metabolic profile data.
In all cases, the analysis indicates a fair discrimination between the control (9 girls) and the ICSI (10 girls) groups.*

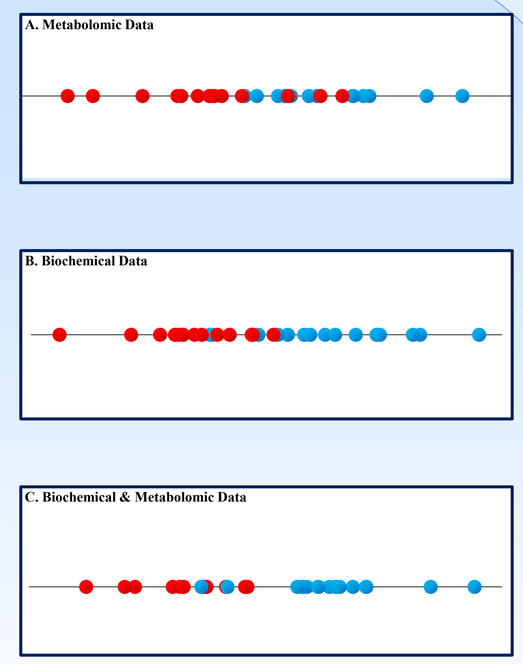


Figure 3. PLS-DA graphs for (A) the mean metabolic profiles, (B) the biochemical profile data and (C) the biochemical combined with the mean metabolic profile data. In all cases, the analysis indicates a fair discrimination between the control (15 boys) and the ICSI (10 boys) groups.

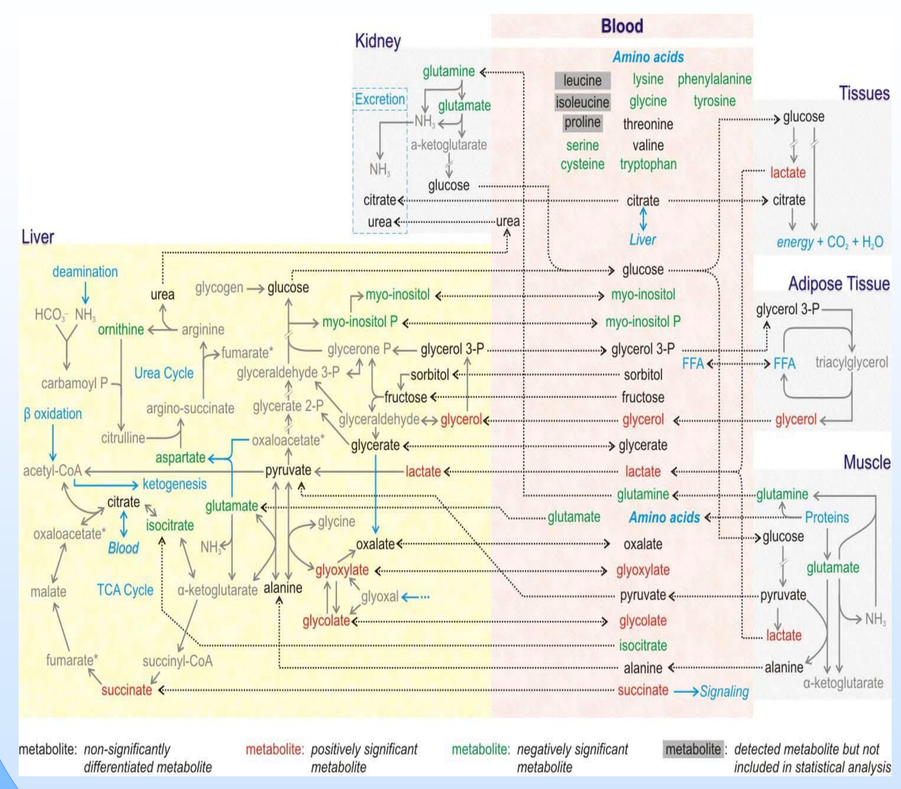
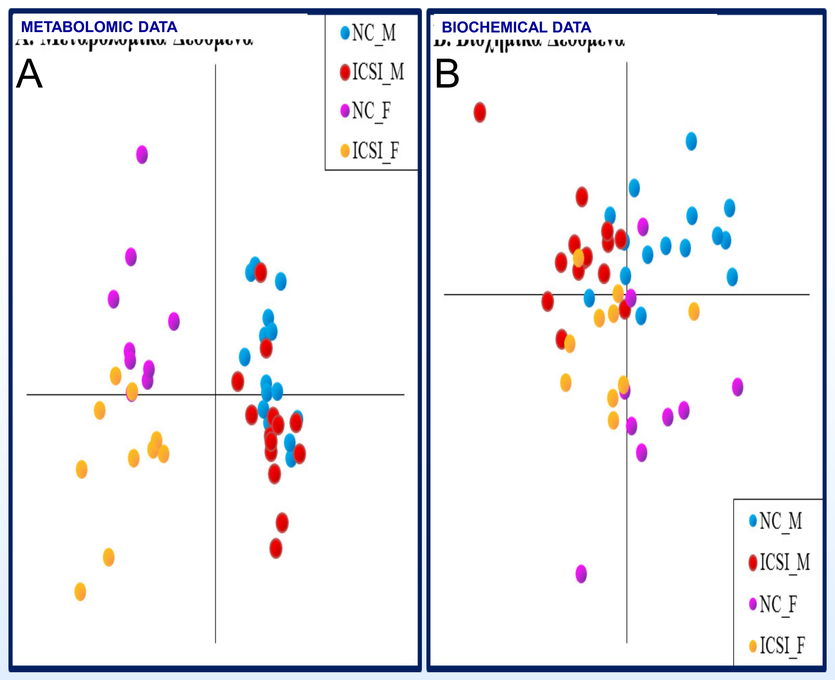


Figure 1. Inter-organ metabolic network



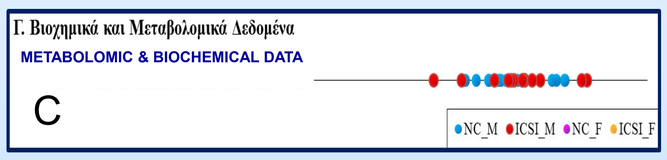


Figure 4. PLS-DA graphs for (A) the mean metabolic profiles, (B) thebiochemical profile data and (C) the biohemical combined with the mean metabolic profile data. In all cases, the analysis indicates a fair discrimination between the control and the ICSI groups.

Conclusions

Our results suggest an increased risk for metabolic disorders as a result of ICSI in both boys and girls. By providing a high resolution perspective of the metabolic state in pre-pubertal children, metabolomics might help develop gender-specific tests and treatments.

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