High-throughput untargeted plasma metabolomics unravels gender dimorphic metabolic trajectories in naturally conceived and ICSI prepubertal children

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Background

Assisted reproductive technologies (ART) influence the metabolic physiology of the offspring, with a higher predisposition to metabolic disorders.

Long-term metabolomic studies that separately consider males and females conceived with intra-cytoplasmic sperm injection (ICSI) vs. naturally conceived (NC) children are needed.

Previously, we had reported that ICSI-conceived prepubertal girls exhibit significant alterations in their metabolic profiles.

Objectives

In this study, we expand our metabolomic analyses on the effect of ICSI on the metabolic physiology of prepubertal boys and conduct comparative analyses of both genders in NC and ICSI children.

Methods

Blood plasma samples of 14 ICSI & 14 NC strictly matched boys were analyzed 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 (*Fig 1*).

Results

Combining metabolomic & biochemical measurements differentiated the ICSI & NC groups in both genders, with this difference being more prominent in the girls *(Fig 2).*

Gender-based metabolic profile comparison of the two genders revealed that the primary clustering is gender-based rather than way of conception based. *(Fig 2-4).*

The most significant differences in metabolite concentrations were sorbitol & 3 aromatic amino acids (tyrosine, phenylalanine & tryptophan) potentially correlated with brain & liver disorders.

Gender dimorphism of the metabolic profile was evident, highlighting the amino acid & lipid metabolism together with the Cori cycle as the main metabolic pathways that are different between prepubertal boys & girls.

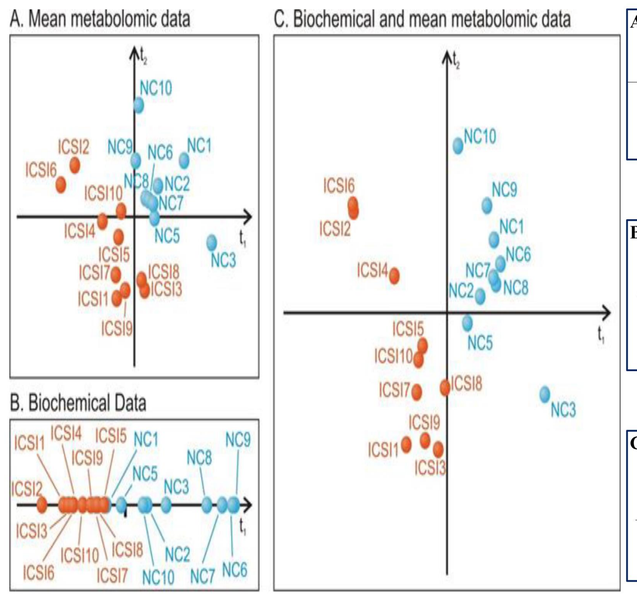

Figure 2. PLS-DA graphs for (A) the mean metabolic profiles, (B) the biochemical profile data and (C) the biochemical combined with the mean metabolic profile data. In all cases, the analysis indicates a fair discrimination between the control (9 girls) and the ICSI (10 girls) groups.

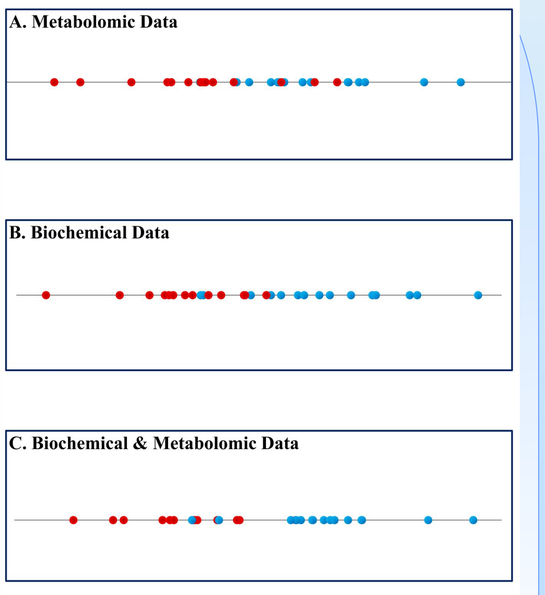

Figure 3. PLS-DA graphs for (A) the mean metabolic profiles, (B) the biochemical profile data and (C) the biochemical combined with the mean metabolic profile data. In all cases, the analysis indicates a fair discrimination between the control (15 boys) and the ICSI (10 boys) groups.

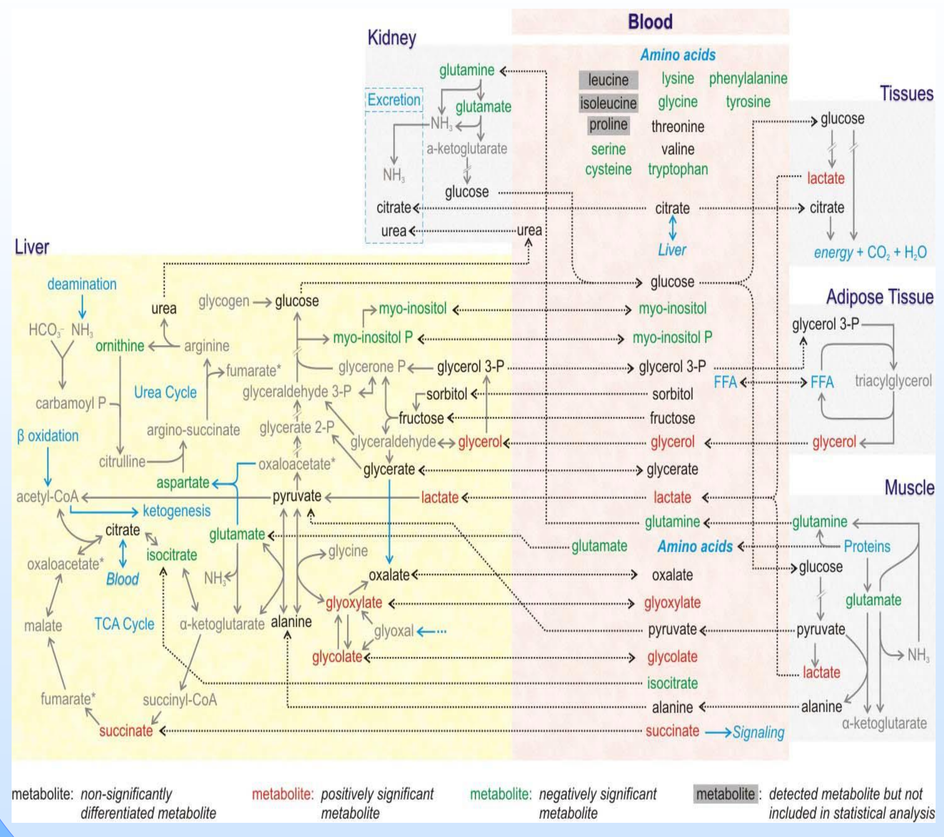

Figure 1. Inter-organ metabolic network

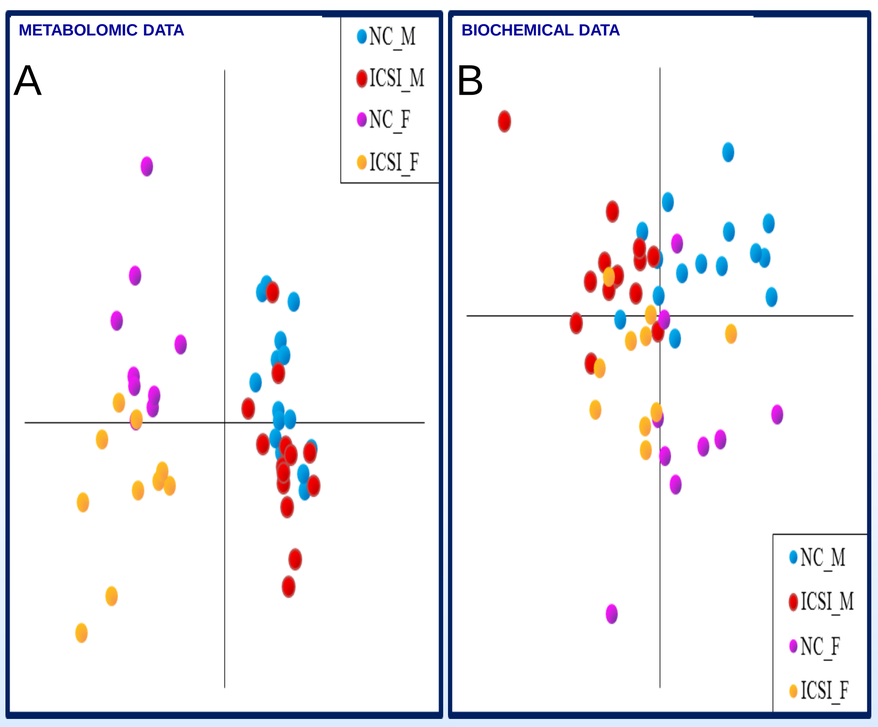

Figure 4. PLS-DA graphs for (A) the mean metabolic profiles, (B) thebiochemical profile data and (C) the biohemical combined with the mean metabolic profile data. In all cases, the analysis indicates a fair discrimination between the control and the ICSI groups.

Conclusions

- High-throughput untargeted metabolomics in combination with conventional biochemical analyses provide a detailed fingerprint of the metabolic physiology in both genders & the epigenetic metabolic aberrations due to ICSI.
- Both methods indicate a profound effect of gender on the metabolic profile.
- A better understanding of the mechanisms underlying metabolic sexual dimorphism and adverse effects of ART would provide insight to improve the management of metabolic diseases and to implement prevention of the long-term effects of ART before they become clinically manifested.

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