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METFORMIN TREATMENT DURING PREGNANCY

Metabolic and immunological aspects

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Akademisk avhandling

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Abstract
Background: Randomized controlled trials have shown that metformin treatment slows down gestational weight gain (GWG) and reduces the risk of preterm birth in women with polycystic ovary syndrome (PCOS), but have not investigated why metformin produces these effects. Metformin treatment has previously been evaluated against insulin treatment for gestational diabetes mellitus (GDM). However, these assessments have generally combined results from participants treated with metformin alone with results from those who also required supplemental insulin, which makes it difficult to assess effects of metformin *per se*, and evaluations against diet and lifestyle treatment are lacking. **Aim:** The objectives of this thesis were to explore the potential metabolic and immunological mechanisms by which metformin slows down GWG, affects fetal growth, and reduces the risk of preterm birth in women with PCOS, and to assess the risk of neonatal hypoglycemia following metformin-treated, insulin-treated, and diet-and-lifestyle-treated GDM. In Papers I-III, metformin was evaluated against placebo. In Paper IV, metformin alone was evaluated separately from combined treatment with insulin. **Results:** Women with excessive GWG were more leptin resistant throughout pregnancy, and displayed a lower physiological serum allopregnanolone increase in late pregnancy than women who maintained a healthy weight gain (Paper I). Metformin treatment improved leptin sensitivity and counteracted excessive GWG in women with PCOS (Paper I). This treatment effect was not correlated with placental leptin and leptin-receptor mRNA expression (Paper II). Placental leptin mRNA expression correlated positively with the birthweight/placental weight ratio in the placebo-treated women with PCOS (Paper II). PCOS status was associated with enhanced maternal decidual immune-cell mobilization, and altered placental IL-5 and IL-18 mRNA expression (Paper III). Metformin treatment was associated with greater abundance of decidual $CD56^{+}$ cells, downregulated placental IL-4 and IL-18 mRNA expression, and altered placental cytokine mRNA expression profiles compared with placebo in women with PCOS (Paper III). Offspring exposed *in utero* to only metformin had similar risk of neonatal hypoglycemia to diet and lifestyle treatment alone, and lower risk than offspring whose mothers received supplemental insulin, or insulin alone. (Paper IV). **Conclusion:** In women with PCOS, metformin treatment effectively reduces the risk of excessive GWG, appears to counteract pregnancy related leptin resistance, erase a positive correlation between placental leptin mRNA expression and the placental efficiency measure birthweight/placental weight ratio, and induces complex immunological alterations at the maternal-fetal interface. The similar outcome among offspring exposed to metformin and diet and lifestyle treatment alone is reassuring for the majority of metformin-treated women with GDM who sufficiently achieves glycemic control without supplemental insulin. This thesis contributes to increasing knowledge of how metformin treatment during pregnancy affects metabolic adaptations of importance for maternal weight gain and fetal growth in women with PCOS. Further, it provides some insights into how PCOS status and metformin treatment affect the immunological landscape at the maternal fetal interface; expands previous knowledge of how metformin treatment for GDM associates with neonatal hypoglycemia; and demonstrates the importance of differentiating between metformin with and without supplemental insulin when assessing treatment-associated risks.

Keywords
Metformin, polycystic ovary syndrome, leptin, sOb-R, ghrelin, allopregnanolone, AMPK, gestational weight gain, birthweight, placenta, gestational diabetes, neonatal hypoglycemia

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