Gestational diabetes mellitus is associated with an altered placental glucocorticoid receptor isoform profile, increased human placental lactogen mRNA expression and placental glycogen accumulation

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Background: Gestational diabetes mellitus (GDM) occurs in up to 16% of all pregnant women and increases the risk of a range of maternal and fetal complications. The placenta secretes hormones including Human placental lactogen (hPL), encoded by CSH1 and CSH2 to alter maternal glucose homeostasis to ensure adequate glucose availability for the growing fetus. GDM occurs when the maternal system does not adapt appropriately to these endocrine changes or as a consequence of placental dysfunction. Glucocorticoid signalling has been implicated in placental dysfunction and glucocorticoid exposure is known to alter secretion of hPL, increase glycogen accumulation and alter glucose transport, all of which have been implicated in GDM. However to date, the role of glucocorticoid signalling in GDM is not well characterized. The glucocorticoid receptor (GR) is encoded by a single gene, Nr3c1 which forms at least 8 different GR isoforms in the human placenta. Recent studies have demonstrated that the GR isoform profile regulates tissue-specific glucocorticoid sensitivity and is implicated in poor birth outcomes. The aim of this study was to determine how glucocorticoid sensitivity may be altered in placentae of women with GDM.

Methods: Placentae were collected from healthy women and from women with GDM at term, ensuring all other parameters were matched. For initial analysis, only male placentae were analysed while analysis of female placentae is ongoing. RNA was extracted for qPCR analysis and cytoplasmic and nuclear protein fractions were extracted for Western blotting (GR) and enzymatic assay analysis. Placental glycogen content was determined using a commercially available enzymatic assay.

Results: Within male placentae from women with GDM, there was a significant increase in the expression of cytoplasmic GRα-A ($P<0.05$), and an uncharacterized GR immunoreactive band at 69kDa ($P<0.05$), while GRα-D expression was reduced ($P<0.05$).Within the nuclear fraction, the expression of the 69kDa band and GRα-D were significantly reduced ($P<0.05$). Additionally, male placentae from women with GDM had a significant increase in Csh1 expression ($P<0.05$) accompanied by an increase in glycogen deposition ($P<0.05$).

Discussion/Conclusion: The findings from the current investigation support the hypothesis that altered glucocorticoid sensitivity is implicated in GDM. The alterations in the GR isoform profile in placentae from women with GDM are consistent with previous studies investigating placental dysfunction in maternal asthma and dexamethasone exposure. The direct relationship between expression levels of specific GR isoforms and the increased hPL and glycogen content requires further investigation. Future studies will manipulate GR isoform patterns in placental cells to investigate if glucocorticoid signalling is the primary defect of if other factors such as maternal glucose are likely to contribute to altered GR isoform patterns in GDM.