Maternal hypomagnesaemia causes placental abnormalities that may contribute to fetal and postnatal mortality

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Background: Magnesium (Mg) is essential for development and the maintenance of normal cellular processes. However, it is estimated that more than 20% of women are Mg deficient either during pregnancy or the preconceptional period, largely due to an inadequate dietary intake. Numerous clinical studies have demonstrated that maternal nutrient deficiencies during pregnancy can adversely affect fetal development and the subsequent health of the offspring. Studies in transgenic animals have also shown that the Mg channels and transporters TRPM6, TRPM7 and MagT1 are crucial for normal development. However, the effect of altered Mg levels during pregnancy on placental and embryonic development has yet to be directly examined. In this study, we used a dietary model to investigate how moderate and severe maternal Mg deficiency affects placental and fetal development, and the regulation of Mg transporters during gestational Mg deficiency.

Methods: Female CD1 mice (N=7 to 12 dams per group) received a control (0.2% w/w Mg), moderately Mg deficient (MMD; 0.02% w/w Mg) or severely Mg deficient (SMD; 0.005% w/w Mg) diet for 4 weeks prior to mating and then throughout pregnancy. A subset of dams was euthanized at embryonic day (E) 18.5 for tissue collection. The expression of Mg transporters TRPM6, TRPM7, and MagT1 was measured in whole placentas by qPCR. Placental MagT1 expression was also localized by *in situ* hybridization. Placental glycogen deposition and cross-sectional areas of the spongiotrophoblast and labyrinth layers were measured histologically.

Results: At E18.5, maternal plasma and bone Mg levels were significantly reduced in Mg deficient groups. Maternal hypomagnesaemia led to dose-dependent fetal loss (approximately 70% in SMD embryos), early postnatal mortality (failure to thrive in SMD offspring by PN10), and caused fetal growth restriction (reductions in body weight of 10% and 5% in SMD and MMD respectively at E18.5) Maternal hypomagnesaemia was associated with significant morphological changes in the placenta, evident by increased placental glycogen deposition and reduced placental spongiotrophoblast cross-sectional area. Gross abnormalities (*e.g.* large vacuole-like structures) were present in ~25% of SMD placentas. There were no differences in mRNA expression levels of Mg channels TRPM6 and TRPM7 in the placenta. In contrast, MagT1 mRNA expression was increased in Mg deficient groups and was localized to the placental spongiotrophoblast layer. After birth, offspring in both Mg deficient groups failed to thrive (reductions in body weight of ~50% and 10% in SMD and MMD at PN7). Animals in the SMD were not viable after P10.

Conclusions: Dietary Mg intake plays an important role in fetal health and outcomes. Our study shows that maternal hypomagnesaemia leads to altered placental morphology, growth restriction, and fetal and neonatal loss. These changes placental development are likely to have profound effects on fetal growth and may influence the long-term health of the offspring. Our results highlight the crucial nature of Mg for neonatal health, emphasizing the importance of maintaining adequate Mg levels throughout preconceptional and gestational periods.