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Hypomagnesaemia and pregnancy

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Abstract

Hypomagnesaemia is common in pregnancy, particularly in developing countries and low-income communities. Despite the frequent therapeutic use of magnesium in pregnancy, and the evidence regarding the association of hypomagnesaemia with adverse pregnancy outcomes in animal studies, it remains unclear whether hypomagnesaemia is associated with complications in human pregnancy. Three case reports of pregnancies complicated by moderate–severe hypomagnesaemia are presented and magnesium physiology in pregnancy is discussed. The evidence as to whether hypomagnesaemia may represent a direct cause, a consequence of other disease processes or an epiphenomenon in adverse pregnancies outcomes is reviewed.

Keywords

Hypomagnesaemia, physiology, adverse pregnancy outcomes, hypertensive disorders of pregnancy, diabetes mellitus, premature labour, small for gestational age, Gitelman syndrome, jejunoileal bypass

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Introduction

Magnesium (Mg), the fourth most abundant cation in the body, has been described as the 'forgotten' electrolyte in medicine. Mg infusions were previously used in pregnancy for tocolysis, and continue to be used for fetal neuroprotection in the setting of prematurity and prevention of eclampsia, as well as oral supplementation for prevention of leg cramps. Maternal hypomagnesaemia (hypoMg) has been reported in 16% of pregnant women in Nigeria and 40–60% of pregnant women in South Asia.[1,2] Murine studies have shown maternal hypoMg is associated with impaired placental development, impaired fetal growth and increased mortality.[3,4] The evidence that hypoMg is a cause of adverse pregnancy outcome or that supplementation is beneficial in humans remains unclear. Three cases of pregnancies complicated by hypoMg are described. Mg physiology in pregnancy is reviewed, and the possible relationship between hypoMg and adverse pregnancy outcomes discussed.

Case 1

A 31-year-old gravida 2 para 1 was referred for antenatal care at 12 weeks' gestation. Diabetes mellitus had been diagnosed at age 20 with hypoMg, mild renal dysfunction and renal cysts, confirmed on genetic testing to be due to hepatonuclear factor 1 beta heterozygosity (HNF1-β). Her first pregnancy had resulted in the birth of a 3400 g live male infant at 37 weeks' gestation. The patient's medications included metformin, insulin, folic acid, aspirin and calcium. Sulphonylurea therapy had previously been ineffective. The patient's body mass index preconception was 29.7 kg/m^2. Investigations revealed HbA1c of 5.3% and serum creatinine was 84 µmol/l with eGFR 80 ml/min/1.73 m^2. During the pregnancy, serum Mg (se Mg) ranged between 0.4 and 0.5 mmol/l (non-pregnant reference interval 0.7–1.0). Serum potassium (se K) was normal. No Mg supplementation was given. The current pregnancy was complicated by fetal macrosomia, a healthy 4413 g infant male born at 37 weeks' gestation who was euglycaemic in the neonatal period.

Case 2

A 38-year-old gravida 5 para 2 was noted to have a se Mg of 0.2 mmol/l on blood tests performed for investigation of arthralgias at 32 weeks' gestation. Se K^+ was 3.9 mmol/l (normal third trimester 3.2–4.6), serum calcium was 2.39 mmol/l (normal 2.0–2.4) and 25-hydroxy vitamin D was 112 nmol/l (normal 50–150). The patient was asymptomatic. The woman's first successful pregnancy had been complicated by pre-eclampsia at 35 weeks' gestation and her second pregnancy was uncomplicated. Se Mg had not been tested previously. The woman's past history was significant for osteosarcoma treated with surgery and chemotherapy including cisplatin at age 19 years. In this pregnancy, gestational diabetes mellitus (GDM) had been diagnosed at 28 weeks and she was treated with metformin and insulin with satisfactory glycaemic control. During the pregnancy se Mg ranged between 0.2 and 0.4 mmol/l. Twenty-four-hour urine Mg was inappropriately elevated at 4.1 mmol/day (normal 3–5) and 24 h urine calcium was 1.0 mmol/day (non-pregnant reference range 1.2–7.5). At 32 weeks' gestation serum aldosterone was 5830 pmol/l (normal third trimester 415–2800) and plasma renin activity was 138 mU/l (normal 66–660). Urinary amino acids were of normal pattern. Gene testing for HNF1-β was negative. Genetic testing for Gitelman syndrome (GS) is pending. Her electrocardiogram showed normal PR and QRS duration, and the QTc interval was 456 ms. The pregnancy was otherwise uncomplicated, the mother delivering a healthy 3436 g female infant by planned caesarean section at 38 weeks' gestation. No neonatal electrolytes were performed. The previous cisplatin therapy is the most likely cause of the hypoMg in this case. Cisplatin therapy may cause long-term renal Mg wasting as well as hypocalciuria.[5] The main differential diagnosis in this case is GS, which may also cause hypoMg secondary to hypermagnesuria, hypocalciuria and hyperreninaemic hyperaldosteronism.

Case 3

A 35-year-old El Salvadorian woman, gravida 5 para 0, was noted to have a se Mg of 0.3 mmol/l and se K of 3.1 mmol/l on routine blood tests at 16 weeks' gestation. The patient was asymptomatic. GDM was diagnosed at 11 weeks' gestation, and her past history was significant for hypothyroidism, vitiligo and non-alcoholic fatty liver disease. She denied using proton pump inhibitors (PPIs), diuretics or herbal treatments, and denied pica or excess caffeine intake. Her se K had been

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3.0 mmol/l six years earlier. Her family history was unknown. Twenty-four-hour urine electrolyte excretion was Mg 5.4 mmol/day, calcium 6.6 mmol/day and K 75 mmol/day (normal second trimester 10–40). Urine amino acid pattern was normal. Serum aldosterone was 2610 pmol/l and plasma renin activity 188 mU/l. Antitransglutaminase antibody performed in view of hypothyroidism and vitiligo was negative. As renal ultrasound and function were normal, testing for HNF1-β mutation was not performed. Mg aspartate 1 g three times a day was prescribed; however, se Mg remained unchanged. GDM was managed with basal-bolus insulin. A healthy 4179 g boy was delivered at 37 weeks by elective caesarean section. The mother was lost to follow-up post-partum.

The woman did not have ocular or renal manifestations suggestive of familial hypoMg with hypercalciuria and nephrocalcinosis. Although testing for seven genes associated with Bartter syndrome was negative, this condition is associated with a multitude of gene mutations, some of which are not tested for routinely, and there may be many unrecognised mutations.[6,7] Bartter syndrome was thought to be the most likely cause of hypoMg in this case.

In summary three cases of different aetiologies of significant hypoMg in pregnancy are presented. Despite the severity of hypoMg no maternal or fetal complications other than GDM were noted.

Mg physiology

Distribution of Mg. The normal adult human body contains approximately 1000 mmol of Mg.[8,9] The predominant sites of distribution of Mg are in bone (53%), muscle (27%), soft tissue (19%) and red blood cells (RBCs) (0.5%), with only 0.3% of total body Mg in serum.[10] Thirty per cent of the stores of Mg in bone is exchangeable and functions to stabilise the serum concentration. Of se Mg, 20% is protein bound, 65% is ionised and the remainder is complexed with anions including phosphate and citrate. Acid–base disturbances have minimal effect on the distribution of Mg. Intracellular Mg concentrations range from 5 to 20 mmol/l of which 1–5% is ionised.

Mg absorption. Mg absorption occurs primarily in the ileum and colon. Fractional intestinal absorption is dependent mainly on Mg status and tends to be inversely related to intake with 65% absorption at low and 11% at high intake.[9] Mg intake depends on the Mg concentration in drinking water and foods. Green leafy vegetables, grain, cereal, nuts and legumes are rich in Mg. Intermittent concentrations of Mg are found in fruit, meat and fish, and low Mg concentrations are present in dairy products. Refining and cooking of foods result in significant loss of Mg.[11] A review of six studies performed in the United States found that Mg intake during pregnancy ranged from 30 to 50% of the recommended daily intake of 355 mg/day.[12] Intake was particularly inadequate in low-income women.

Intracellular Mg homeostasis is regulated by transport mechanisms and homeostatic factors, which are encoded by Mg-sensitive genes. TRMP6 and TRMP 7 are Mg-sensitive genes localised in the colon and renal distal convoluted tubules. It is thought they play an important role in regulating whole-body Mg homeostasis. Increased expression of TRMP6 at 12 weeks' gestation has been demonstrated compared with non-pregnant controls indicating an increased demand for Mg in pregnancy.[13]

Mg excretion. Ninety-five per cent of Mg filtered by the kidneys is reabsorbed, predominantly in the thick ascending loop of Henle.[9,14] Reduced absorption, and thus increased Mg excretion, occurs with increased plasma Mg concentration, increased glomerular filtration rate, hypophosphataemia and hypercalcaemia. Several hormones including parathyroid hormone, calcitonin, insulin, glucagon and antidiuretic hormone also affect urinary excretion of Mg. Normal Mg excretion in the non-pregnant adult is 3–5 mmol/day. Urinary excretion of Mg rises by approximately 25% during pregnancy.[15] In the presence of hypoMg, Mg excretion of greater than 1 mmol/day is consistent with renal Mg wasting. Mg excretion of less than 0.5 mmol/day is suggestive of Mg deficiency.[11]

Assessment of Mg status. Measurement of se total Mg levels may be affected by delay in separating serum, high phosphate levels, lipaemia, hyperbilirubinaemia and haemolysis. Se Mg does not correlate with tissue pools nor reflect total body or intracellular Mg content.[9] Measurement of ionised Mg is possible although susceptible to false results without very well-defined sample handling, and probably has little value in addition to se total Mg levels.[16–21] RBC Mg does not correlate well with total body Mg or other measures of Mg status.[22] Lymphocyte Mg may be a better reflection of skeletal and muscle Mg stores; however, the measurement is technically difficult and has high intra-individual variation.[23] Mg loading/tolerance tests are a sensitive measure to detect Mg deficiency in individuals with normal renal function.[24,25] Nuclear magnetic resonance spectroscopy is useful as a research tool to measure intracellular Mg without requiring skeletal muscle or bone biopsy.

Mg levels in pregnancy. Se Mg declines from a preconception mean of 0.93 mmol/l to a nadir mean of 0.63 mmol/l in the third trimester.[15,26–30] Trimester-specific reference intervals for Mg in pregnancy depend on the assay used and the population studied.

Published reference intervals are as follows[31]:

	Preconception	First trimester	Second trimester	Third trimester
Se Mg (mmol/l)	0.62–0.95	0.65–0.9	0.62–0.9	0.45–0.9

Similarly ionised and RBC Mg, and intracellular free Mg in brain and muscle are lower in pregnancy than in non-pregnant controls when measured by NMR spectroscopy.[32,33]

Transplacental passage of Mg. After the fifth month of gestation, increasing amounts of Mg are transported from mother to fetus, averaging approximately 4.5 mg/day.[34] Fetal Mg levels are higher than maternal Mg levels consistent with a transplacental gradient. Little is known about the mechanism and regulation of placental Mg flux.[35] It has been postulated that maternal–fetal Mg gradient is due to an active transport mechanism, as the gradient is not due to differences in protein binding between mother and fetus.[36] The gradient, however, is insufficient to protect the fetus from Mg deficiency in the setting of chronic maternal Mg deprivation.

Hypomagnesaemia and pregnancy complications

HypoMg has been implicated as a potential contributing factor in hypertensive disorders of pregnancy, GDM, preterm labour and intrauterine growth restriction.

Hypertensive disorders of pregnancy. Meta-analyses have shown an inverse relationship between dietary Mg intake and the risk of hypertension, stroke, heart failure and diabetes mellitus in the general population.[37–39] A meta-analysis of 14 studies revealed women with pregnancy-induced hypertension had lower levels of se Mg, zinc and calcium than healthy pregnant women.[40] There is an overexpression for the gene SLC41A1, a Na/Mg exchanger, in placenta from women with preeclampsia (PET) compared with normal placentas, suggesting a change in Mg homeostasis may contribute to the development of PET.[41] Twenty-four-hour urine excretion of Mg and calcium is significantly lower in second and third trimester in women with mild pregnancy-induced hypertension than in normotensive controls.[42]

Major methodological difficulties in the interpretation of intervention studies into the role of Mg supplementation in prevention of hypertensive disorders of pregnancy include variations in dietary

intake of Mg, doses of Mg used and the bioavailability of individual Mg preparations used (e.g. Mg citrate has better bioavailability than Mg oxide or Mg chloride).[43–45] High doses of supplemental Mg may result in diarrhoea. A review of the Cochrane Pregnancy and Childbirth Group's trial register found that Mg supplementation during pregnancy was not associated with a reduction in perinatal mortality, small for gestational age (SGA) or preeclampsia compared with a control group.[46] Mothers taking Mg were less likely to require hospitalisation during pregnancy. Mg supplementation was associated with significantly fewer babies with Apgar score of less than 7 at 5 min, meconium-stained liquor, late fetal heart decelerations and mild hypoxic–ischaemic encephalopathy. A multicentre randomised double-blind clinical trial, the Brazilian Magnesium trial, is examining the effect of Mg citrate 150 mg twice a day versus placebo commenced at 12–20 weeks' gestation on adverse pregnancy outcomes in women at higher risk of placental dysfunction.[47]

A recent randomised controlled trial of low-risk pregnant women in Iran with se Mg less than 0.78 mmol/l at 12–14 weeks' gestation found that supplementation with an effervescent 200 mg Mg preparation for one month together with a multimineral preparation containing 100 mg Mg until the end of pregnancy was associated with lower risks of PET, intrauterine growth restriction, preterm birth, low birth weight and GDM.[48]

Mouse models of moderate dietary maternal hypoMg did not find programming for neonatal nephron deficit or later cardiovascular function at six months of age, suggesting no long-term adverse outcomes for the cardiovascular health on offspring of hypoMg mothers.[49]

GDM. The analysis of a possible relationship between se Mg and the development of GDM has yielded inconsistent results in observational studies.[50] Studies comparing serum ionised and total Mg between GDM and controls have revealed lower, similar and elevated levels.[51–54] Infants of mothers with GDM have lower whole blood Mg levels at 24 h of life than matched controls and are at increased risk of neonatal hypocalcaemia.[55]

A double-blind placebo-controlled trial of 70 women with Mg deficiency and GDM randomised to 250 mg Mg oxide or placebo per day found that those receiving Mg therapy had a significant reduction in fasting plasma glucose and serum insulin concentration and improvement in insulin sensitivity, and a lower incidence of neonatal hyperbilirubinaemia and newborn hospitalisation.[56] No difference was seen in the requirement for insulin therapy, polyhydramnios, preterm delivery, newborn birth size or neonatal hypoglycaemia. In one study of post-partum women following pregnancies complicated by GDM, lower se Mg was associated with increased risk of developing T2DM.[57]

Preterm labour. Several studies have demonstrated lower se and RBC Mg levels in women with preterm delivery or preterm labour.[58–62]

SGA. Lower cord blood intracellular platelet Mg levels in SGA neonates suggest that intrauterine Mg deficiency may result in SGA and potentially programme insulin resistance after birth, leading to increased risk of metabolic syndrome in later life.[63] The pooled estimation from three trials found that Mg supplementation was associated with a 30% reduction in the rate of SGA infants.[64] Similarly pooled results from four trials found a 33% reduction in low birth weight with Mg supplementation, and that overall newborns in Mg supplementation group weighed 51 g more than the newborns of non-supplemented mothers.

Medical conditions that cause hypoMg and pregnancy outcomes

The major causes of hypoMg relevant to pregnancy are summarised in Table 1. Diabetes mellitus is likely to be the most common cause of hypoMg in pregnancy. A Medline review using the terms 'hypomagnesaemia', 'magnesium' and 'pregnancy' indicated that GS was the most common condition associated with hypoMg in case studies. Older literature reported hypoMg occurring with thiazide diuretic therapy during pregnancy as well as in pregnancies following jejunoileal bypass surgery for obesity. PPIs, increasingly being prescribed for gastro-oesophageal reflux in pregnancy, may be associated with hypoMg; however, this usually occurs with long-term use and to date no cases have been described in pregnancy.

Table 1. Causes of hypomagnesaemia relevant to pregnancy.

Gastrointestinal
• Decreased intake – malnutrition, alcohol excess
• Malabsorption – steatorrhoea, small bowel bypass surgery, proton pump inhibitors, ketogenic diets
• Secretory loss – chronic diarrhoea
Renal
• Congenital tubular defects – Gitelman syndrome, Bartter syndrome, familial hypomagnesaemia with hypercalciuria and nephrocalcinosis, autosomal dominant hypomagnesaemia, HNF1-β mutations
• Drug induced – loop/thiazide diuretics, calcineurin inhibitors, previous cisplatin therapy, alcohol
• Reduced NaCl reabsorption – hyperaldosteronism, hypercalcaemia
• Osmotic polyuria – poorly controlled diabetes mellitus
• Leptospirosis
Miscellaneous
• Post-parathyroidectomy
• Excessive lactation

1. *Type 1 diabetes mellitus (T1DM).* Renal clearance of Mg increases during hyperglycaemia in individuals with T1DM independently of insulin levels from the time of diagnosis.[65,66] Hypermagnesiuria and hypoMg tend to be greater in female than male individuals with the same glycaemic control. Severity of hypoMg is greater in diabetic patients with microalbuminuria or overt nephropathy than in normoalbuminuric individuals.[67,68] A relationship between maternal se Mg at approximately nine weeks' gestation and adverse pregnancy outcome (spontaneous miscarriage, congenital malformation) was examined in 96 pregnancies to 84 women with T1DM.[69] Maternal blood glycohaemoglobin was significantly higher, and se Mg lower in the group of women with adverse pregnancy outcomes. There was no significant correlation between se Mg and glycohaemoglobin. Amniotic fluid Mg levels were lower in pregnant women with T1DM compared with gestation-matched controls.[70,71]

   Neonatal hypoMg was demonstrated in 40% of offspring of mothers with T1DM.[72] These infants did not display the normal increase in se Mg in the first week of life seen in normomagnesaemic infants. Neonatal hypoMg was related to severity of maternal diabetes mellitus, prematurity and lower maternal gravidity. It is postulated that lower fetal Mg levels may result in impaired release and resistance to the action of parathyroid hormone resulting in neonatal hypocalcaemia. Less strict glycaemic control during pregnancy in women with T1DM was associated with a higher rate of neonatal hypocalcaemia and lower neonatal se Mg than in women with strict control.[73] Similarly se Mg was lower in venous cord blood in 44 pregnancies to women with diabetes mellitus (27 T1DM, 17 insulin-treated GDM) compared with non-pregnant controls and non-pregnant women with T1DM. Urine excretion of Mg and calcium is lower in children of mothers with T1 DM, possibly related to intrauterine programming of renal bivalent cation handling.[74]

2. *GS.* GS is an autosomal recessive salt-losing tubulopathy due to a mutation of genes encoding the sodium chloride co-transporters and Mg channels in the thiazide-sensitive segments of the distal convoluted tubule. The prevalence of GS has been estimated to be 1:40,000 women with heterozygote frequency of 1% in

Caucasians.[75] Characteristic biochemical features include hypoMg, hypokalaemia, hyperreninaemic hyperaldosteronism, kaliuresis and hypocalciuria. Thirty pregnancies to 22 mothers with GS have been reported.[76–79] Pregnancy complications included two cases of stillbirth in women with presumed GS.[77,80] The diagnosis of GS in these two cases was not definite – both women presented with symptomatic hypokalaemia following gastroenteritis, the se Mg was normal in both cases, and genetic testing was not performed. Two cases of intrauterine growth restriction, and one case of preeclampsia with haemolysis, elevated liver enzymes and low platelets have been reported in mothers with GS.[79] In addition, oligohydramnios was noted in six pregnancies that were otherwise uncomplicated.[81] Despite the treating team being unable to normalise se Mg and potassium levels in the majority of cases, pregnancy outcomes were normal leading authors to question the necessity of correcting serum electrolytes in GS pregnancies.[82–84]

3. *Thiazide diuretic therapy.* Thiazide diuretics were extensively used in the treatment of oedema and hypertensive disorders of pregnancy prior to the mid-1980s. Treatment with thiazides in non-pregnant adults was associated with hypoMg in 19.4% of 242 subjects after 1–3 weeks of treatment.[85] Thiazide diuretic use during pregnancy has been shown to be associated with marked hypokalaemia and moderate hyponatraemia; however, se Mg was not measured.[86] A Cochrane review found no difference between thiazide diuretic use in pregnancy and placebo with regard to the development of PET, perinatal death, preterm birth, gestation at delivery or caesarean section rate.[87]

4. *Jejunoileal bypass.* HypoMg occurs in up to 58% of patients following jejunoileal bypass.[88] Pregnancy following jejunoileal bypass may be associated with severe hypoMg, hypocalcaemia and hypokalaemic paralysis.[89] A review of 179 pregnancies in mothers who had previously undergone jejunoileal bypass for obesity found no increased rate of congenital malformations or perinatal mortality, though lower birth weight, shorter gestational age and a higher proportion of small-for-dates infants than expected occurred.[90] It is possible these mothers may have had other nutritional deficiencies that led to fetal growth restriction.

5. *PPIs.* HypoMg may uncommonly occur with long-term use of PPI as a result of reduced passive and active intestinal Mg absorption. While onset of hypoMg has been reported as early as 14 days after commencement of PPI, the median time of onset is after 5.5 years of PPI use, and the risk is highest in the elderly especially with concomitant diuretic use.[91,92] Short-term PPI use causes at most a 5% reduction in se Mg and a 1% reduction in intestinal absorption after one week of PPI therapy.[92] No cases of PPI-induced hypoMg in pregnancy have been reported. Studies including more than 10,000 pregnancies with maternal exposure to PPIs did not demonstrate an increased risk of congenital malformation, premature delivery, perinatal mortality, low birth weight or low Apgar scores.[93–96]

6. *Calcineurin inhibitors.* HypoMg is seen in approximately 5% of long-term renal transplant recipients, with no significant difference in those receiving cyclosporine or tacrolimus.[97] No reports of clinically significant hypoMg complicating immunosuppression have been reported in pregnancy.

Conclusion

It remains unclear whether hypoMg is a direct cause of adverse pregnancy outcomes, a consequence of underlying disorders such as poorly controlled diabetes mellitus or insulin resistance/metabolic syndrome which may lead to pregnancy complications, or an epiphenomenon in these disease processes. The pregnancy outcome in the three cases presented despite moderate–severe hypoMg, and the predominantly satisfactory pregnancy outcome in women with GS or following jejunoileal bypass argues against hypoMg as a direct cause of adverse pregnancy outcomes. The need for Mg supplementation in hypoMg pregnant women who are asymptomatic remains unanswered. Further studies examining the pregnancy and neonatal effects of Mg supplementation in women at high risk of gestational diabetes and hypertensive disorders of pregnancy, and in women with existing diabetes mellitus would be valuable to inform this issue.

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