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Calcium, phosphorus, and bone metabolism in the fetus and newborn☆

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ABSTRACT

The placenta actively transports minerals whereas the intestines and kidneys may be nonessential for fetal mineral homeostasis. Mineral concentrations are higher in fetal blood than in adults in order for the developing skeleton to accrete adequate mineral content. Fetal bone development and serum mineral regulation are dependent upon parathyroid hormone (PTH) and PTH-related protein (PTHrP), but not calcitriol, fibroblast growth factor-23, calcitonin, or the sex steroids. After birth, a switch from fetal to neonatal regulatory mechanisms is triggered by loss of the placental calcium infusion, onset of a breathing, and a postnatal fall in serum calcium and rise in phosphorus. This is followed by an increase in PTH, then a rise in calcitriol, and developmental changes in kidneys and intestines. Serum calcium increases and phosphorus declines over days. The intestines become the main source of mineral, while kidneys reabsorb mineral, and bone turnover contributes additional mineral to the circulation.

Contents

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1. Introduction

Neonatal mineral and skeletal homeostasis represents a state of transition between fetal physiology, in which the placenta dominates to deliver and remove minerals, and adult physiology, in which the calciotropic hormones coordinate mineral handling by the intestines, kidneys, and bone. In order to understand this transition, it is first necessary to review the regulation of fetal mineral homeostasis, and then discuss the progressive changes that are provoked at birth.

The reader is referred to the author's much more comprehensive and detailed review that contains more than 750 citations of the primary data described herein [1]. Allotted space permits this brief monograph to serve only as a synopsis of the longer article.

2. Fetal calcium, phosphorus, and bone metabolism

The endochondral skeleton begins forming in the embryo, but it is not until the third trimester that substantial bone is formed and mineralized. The average human fetus has 30 g of calcium by term, with 80% of that accreted during the third trimester. Although the kidneys and intestines control the delivery and excretion of minerals in the adult, they are relatively unimportant for the normal fetus. Instead, it is the placenta that actively transports minerals from the maternal circulation, and returns excess minerals and waste products back to the mother. Physiological studies in animals, and limited human data, have shown that the placenta is usually capable of extracting adequate mineral for the fetus even when maternal mineral concentrations are low. More marked maternal hypocalcemia from severe hypoparathyroidism, for example, is required to cause fetal hypocalcemia and reduced skeletal mineral content.

2.1. Serum minerals and calciotropic hormones

The normal fetal circulation is characterized by serum mineral concentrations that are raised significantly higher than maternal and normal adult values. Serum calcium and ionized calcium are usually increased 0.30–0.50 mmol/L, serum phosphorus is about 0.5 mmol/L higher, while serum magnesium is typically only 0.05 mmol/L greater. This “fetal hypercalcemia” has been demonstrated as early as 15 weeks of gestation. Despite a high calcium × phosphorus product in the circulation, the normal fetus does not develop widespread calcifications, likely because of rapid uptake of mineral into the developing skeleton, and the comparatively short duration of gestation.

The purpose of high calcium and phosphorus concentrations is uncertain. However, studies in genetically manipulated murine fetuses indicate that a high serum calcium concentration is not necessary for fetal survival to term, but it is required for full mineralization of the fetal skeleton. If the fetal serum calcium is reduced to the normal adult level, the skeleton is undermineralized at term. The high serum calcium may also benefit the neonate during the first 48 h after birth, because the serum calcium will fall with the onset of breathing and cutting of the umbilical cord. A higher fetal serum calcium value may protect against a postnatal calcium that falls low enough to provoke tetany, arrhythmias, or seizures.

Parathyroid hormone (PTH) is typically suppressed to very low levels in fetal or cord blood as compared to maternal and normal adult values. These low values arise from synthesis within the fetal parathyroids; maternal PTH does not cross the placenta. The calcium sensing receptor responds to the high fetal serum calcium concentration to keep PTH suppressed. Calcitriol also circulates at low levels, and must derive from 1α-hydroxylase activity in the fetal kidneys and placenta because it too does not cross the placenta from the mother. Low PTH, high serum calcium and phosphorus, and fibroblast growth factor-23 (FGF23), each contribute to suppression of 1α-hydroxylase expression and calcitriol synthesis. The low calcitriol levels are not due to inadequate availability of substrate, since 25-hydroxyvitamin D readily crosses the placenta to reach 75–100% of the maternal value in cord blood. High 24-hydroxylase activity in the placenta causes much 25-hydroxyvitamin D to be converted to 24,25-dihydroxyvitamin D, a form that cannot be converted to calcitriol.

A longstanding puzzle about human cord blood was that it contains low immunoreactive intact PTH concentrations, but high levels of PTH-like bioactivity as measured in cytochemical bioassays. This discrepancy is explained by high circulating concentrations of PTH-related protein (PTHrP), which mimics many of the N-terminal actions of PTH. When PTH and PTHrP are both expressed in equivalent units (pmol/L), the concentration of PTHrP in human cord blood is typically 2 to 4 pmol/L, or up to 15-fold higher than the simultaneous PTH values (0.2 to 0.5 pmol/L).

Limited human data indicate that intact FGF23 circulates at less than one-third the normal adult value, whereas the concentration of the inactive C-terminal fragment of FGF23 is 2-fold the normal adult value. FGF23's co-receptor Klotho circulates at 6-fold adult and neonatal values. It is unclear whether these values imply decreased, normal, or increased FGF23-attributable activity in the fetal circulation as compared to the adult.

Calcitonin is synthesized in the fetal thyroid and placenta, and circulates at about twice the maternal level in human fetuses.

Placental-derived human chorionic gonadotropin and the fetal pituitary gonadotropins can stimulate sex steroid production by the ovaries and testes. In addition, the fetal adrenals synthesize sex steroids. Although there is a spike in testosterone production from the testes in the first trimester, serum levels of testosterone and estradiol remain low until term, and are similar between male and female fetuses.

In a few studies the cord blood testosterone, estradiol, or both have been reported to be equal to or higher than the maternal concentrations. This appears to result when the umbilical vein or mixed cord blood have been sampled, since the placenta aromatizes maternal androgens and converts them into estrogens. In fact, by the third trimester the placenta accounts for nearly all of the estradiol, estrone, and estriol in the maternal circulation. The concentrations of estradiol or conjugated estrogen is the umbilical artery are significantly lower than in the umbilical vein, and are more likely to reflect systemic fetal concentrations of sex steroids.

Overall, the circulation of human fetuses typically displays high levels of calcium, phosphorus, and magnesium, low concentrations of PTH, calcitriol, and the sex steroids, and high levels of PTHrP and calcitonin.

2.2. Regulation of fetal serum mineral concentrations

Animal models have elucidated the roles of the calciotropic hormones in regulating fetal serum mineral concentrations. PTHrP is a key regulator since deletion of its gene in murine fetuses (*Pthrp* null) results in hypocalcemia and hyperphosphatemia. But despite its low circulating levels, PTH remains important because deletion of its gene (*Pth* null) causes a similar degree of hypocalcemia and hyperphosphatemia. PTHrP and PTH appear to have additive roles in regulating serum calcium, with loss of both hormones leading to more marked hypocalcemia than caused by absence of either alone.

These results predict that human babies lacking either PTHrP or PTH will be hypocalcemic and hyperphosphatemic at birth. Due to the sporadic nature of congenital hypoparathyroid disorders, no cord blood calcium or phosphorus measurements have been reported.

Calcitriol is not required to regulate serum minerals since animal fetuses with severe vitamin D deficiency, absence of the vitamin D receptor in mice (*Vdr* null), and absence of 1α-hydroxylase to form calcitriol (*Cyp27b1* null), each have normal serum calcium and phosphorus, renal mineral excretion, and concentrations of the remaining calciotropic hormones. Human data from randomized clinical trials and observational studies of severe vitamin D deficiency, and case reports of