Disorders of Calcium Homeostasis in the Fetus and Neonate

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ABSTRACT

The physiological mechanisms involved in the alterations in calcium homeostasis during pregnancy are complex. The fetal acquisition of calcium, for skeletal growth, is obtained by an increase in intestinal calcium absorption in the mother with transplacental calcium transfer to the fetus. The regulation of calcium homeostasis during the transition from the intrauterine to the extrauterine environment is complex and poorly understood. Within the first few hours of life the serum calcium concentration begins to fall progressively reaching a "trough" value by the second or third day of life and then increases to normal values by the tenth day of life. In some neonates the fall in calcium concentration is sufficient to be associated with either tetany or convulsions. Hypocalcemia is probably the commonest disturbance of calcium homeostasis that occurs in the neonate and can be subdivided into three main groups on the basis of the etiological mechanism involved. Other disorders of calcium homeostasis that may affect the neonate include hypoparathyroidism, either congenital or acquired, pseudohypoparathyroidism, and vitamin D deficiency. Hypercalcemia may occur, but is a relatively rare occurrence in the neonate.

This review covers those disorders of calcium homeostasis that may affect either the fetus or the neonate. For the purposes of this review, the term 'neonate' will be used to indicate infants up to six months of age.

Normal Calcium Homeostasis in Pregnancy

The skeleton of a full-term newborn infant contains 20 to 30 grams of calcium, the majority of which is acquired during the third trimester. To prepare for this process and also for the losses of calcium that occur during lactation, maternal calcium accretion begins early in gestation. During normal pregnancy, there is a significant fall in the maternal plasma concentrations of calcium, total protein and albumin, and an increase in alkaline phosphatase activity when the values obtained at 34 to 40 weeks are compared with those...
of 10 to 15 weeks. The change in plasma calcium concentration in the women studied was not significant after correction for the simultaneous reduction in albumin concentration. The latter is a feature of the normal physiological hemodilution of pregnancy.

The physiological mechanisms involved in the alterations in calcium homeostasis during pregnancy are complex. The fetal acquisition of calcium is not at the expense of the maternal skeleton but is obtained by an increase in intestinal calcium absorption in the mother with transplacental calcium transfer to the fetus. The increase in maternal intestinal calcium absorption is associated with an increase in serum 1,25-dihydroxycholecalciferol concentration. In those studies, it was also reported that at birth the placental venous concentrations of 1,25-dihydroxycholecalciferol were low and bore no relationship to the maternal values. It was suggested that the low 1,25-dihydroxycholecalciferol values in-utero indicated that there was no need for intestinal fetal calcium absorption. At 24 hours after birth, the neonatal serum 1,25-dihydroxycholecalciferol values had increased to within the normal adult range. The postnatal increase probably reflects an increase in the renal production rate of this sterol hormone to meet the extrauterine need for calcium absorption to allow skeletal growth.

Intrauterine Disorders

There is relatively little information available on the intrauterine diagnosis of disorders affecting either calcium homeostasis or the skeleton. Most of the information that is available deals with those disorders that can be diagnosed by radiographic examination of the fetus. The prenatal diagnosis of hypophosphatasia, an inborn error of metabolism with inadequate calcification of the skeleton, can be made using amniotic fluid samples and radiological techniques. In that study, the authors reported that ultrasonography, alkaline phosphatase determination in the amniotic fluid cell culture, and radiography of the fetus appeared to be reliable for the prenatal diagnosis of hypophosphatasia.

Intrauterine hyperparathyroidism is a benign, self-limited condition whose sole manifestation is abnormal bone density. This syndrome, also called congenital hyperparathyroidism, occurs in infants born to mothers with persistent hypocalcemia or hypoparathyroidism. The major complications are bone fractures during birth and hypercalcemia in the early neonatal period. The latter is due to parathyroid hyperplasia in the infant, a consequence of the maternal hypocalcemia. The development in recent years of various biological metabolites of vitamin D for the treatment of hypoparathyroidism in the mother should avoid this particular complication of pregnancy. The treatment of a pregnant woman suffering from idiopathic hypoparathyroidism with calcitriol (1,25-dihydroxycholecalciferol) has resulted in the delivery of normocalcemic twin infants who showed no ill effects from the treatment.

Hypocalcemia

By strict definition, hypocalcemia should be considered as a reduction in the physiologically active serum component,—the ionized calcium concentration. The more usual definition is a reduction in total serum calcium concentration after making an allowance for a variation in the simultaneously measured albumin concentration. A consideration of these definitions is of importance in the newborn where variations in calcium binding by proteins may account for the occasional occurrence of clinical signs of hypocalcemia that correlate poorly with the measured serum calcium concentration. The development, and widespread availability in recent
years, of ion specific electrodes for the routine measurement of the ionized calcium concentration should help resolve these occasional, apparently conflicting, clinical dilemmas and be of value in the assessment of hypocalcemia in the newborn. As a general rule, the clinical signs of hypocalcemia occur in the newborn when the ionized calcium concentration is less than 2.5 mg per dl and are often present at concentrations between 2.5 and 3.0 mg per dl.

The causes of hypocalcemia in the newborn to be reviewed here are listed in table I. In addition to these causes, the possibility of artifactual hypocalcemia must be considered whenever the clinical findings are not consistent with the measured serum calcium. Apparent hypocalcemia can be produced by contamination of the sample with calcium chelators (such as ethylenediamine tetraacetic acid and oxalate which are used as anticoagulants) and when either colorimetric or fluorometric assay methods are employed. In many of these methods, a variety of other interferences (e.g., bilirubin, hemoglobin, and lipemia) can produce apparent hypo- or hypercalcemia. The availability of atomic absorption methods for serum calcium using only small volumes of serum allows resolution of these problems in almost all cases.

**TABLE I**

<table>
<thead>
<tr>
<th>Causes of Hypocalcemia in the Newborn and Neonate</th>
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<tr>
<td>Neonatal hypocalcemia</td>
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<td>Early</td>
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<tr>
<td>Late</td>
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<td>Maternal hyperparathyroidism</td>
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<td>Congenital hypoparathyroidism</td>
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<tr>
<td>Pseudohypoparathyroidism</td>
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<td>Type I</td>
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<td>Type II</td>
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<td>Vitamin D deficiency</td>
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<td>Magnesium deficiency</td>
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Neonatal hypocalcemia

Neonatal hypocalcemia, probably the most common disturbance of calcium homeostasis in the newborn, may be subdivided into three main groups—early, late, and in association with maternal primary hyperparathyroidism.

*Early Neonatal Hypocalcemia.* This type of hypocalcemia occurs in the first 48 hours of life. The regulation of calcium homeostasis during the transition from the intrauterine to the extrauterine environment is complex and poorly understood. In the normal infant at birth, the calcium concentration in cord blood is higher than in the maternal circulation. Within the first few hours, the serum calcium concentration begins to fall progressively, reaching a “trough” value by the second or third day, and then increases to normal values by the tenth day of life. The fall in calcium concentration is greater in infants who are either not fed or who receive cow’s milk than in those who are breast fed. The fall is greatest in infants who are premature, anoxic, acidotic, of low birth weight, have suffered birth trauma, or who are born to diabetic mothers. In some neonates, the fall in calcium concentration is sufficient to be associated with either tetany or convulsions.

The incidence of early neonatal hypocalcemia is higher in “sick” infants than in normal full-term infants. In their study of calcium metabolism in newborn infants, David and Anast reported that parathyroid secretion is normally low in the early newborn period and that impaired parathyroid function, with low or undetectable hormone concentrations, occurs in most infants with neonatal hypocalcemia. The latter may, therefore, be regarded as being due to a state of functional parathyroid immaturity. David and Anast also concluded that additional unknown factors appeared to contribute to the reduction in serum calcium concentration in neonatal hypocalcemia. Amongst these contrib-
utory factors, hypomagnesemia appears to play an important role.

The incidence of neonatal hypocalcemia is significantly increased in the infants of diabetic mothers even when gestational age and perinatal complicating factors are taken into consideration. The pathogenesis of the hypocalcemia in this particular situation has been attributed to a relative state of maternal hyperparathyroidism that may induce fetal hypoparathyroidism.

Late Neonatal Hypocalcemia. This type of hypocalcemia occurs either in normal full-term, of average or above average weight, or occasionally in premature infants who are artificially fed. In these infants, the symptoms or signs of hypocalcemia may develop between the fourth and tenth days of life or occasionally after several weeks. The occurrence of hypocalcemia in this group is not associated with a history of perinatal problems. The mechanism for the hypocalcemia in this group has been attributed to the high phosphate content of the artificial feed used.

The high phosphate content of artificial feeds has a dual role in the pathogenesis of hypocalcemia. A major effect is the induction of hyperphosphatemia. The phosphate content of cow’s milk, from which all artificial feeds are prepared, ranges from 56 to 112 mg per 100 ml compared with 6 to 26 mg per 100 ml for human breast milk. The calcium to phosphate ratio of a foodstuff is important in the availability of calcium for absorption from the intestinal tract. An increase in the calcium content of artificial foods has been reported to abolish their hypocalcemic effect. It is possible that an additional factor in the pathogenesis of hypocalcemia in these infants is some degree of functional immaturity of the parathyroid glands. In this situation, the infants would be unable to respond normally to the challenge of a phosphate load.

In addition to the hypocalcemic role of phosphates in artificial feeds, attention has also been drawn to the potential role of fatty acids. Hanna and his colleagues reported that infants receiving human breast milk absorbed between 50 and 60 percent of dietary calcium whilst those on artificial feeds only absorbed 25 to 30 percent. The disparity in these absorption rates was attributed to the fatty acid composition of the artificial feeds. The precise role of dietary fat and the efficiency of fat absorption in the etiology of hypocalcemia in the newborn together with their interrelationship with calcium absorption remains to be clarified.

Maternal Hyperparathyroidism. Hypocalcemia in a neonate owing to parathyroid gland suppression, with a physiological state of transient hypoparathyroidism, is a well recognized complication of maternal primary hyperparathyroidism. Tetany in the neonate may very often be the first clinical indication of the disease process in an asymptomatic mother. In some infants with hypocalcemia induced by maternal primary hyperparathyroidism, there is associated hypomagnesemia. It can be speculated that in this situation hypomagnesemia either induces target-organ resistance to the actions of parathyroid hormone or inhibits secretion, and that this plays a further major role in maintaining the hypocalcemia. The occurrence of the combination of asymptomatic maternal primary hyperparathyroidism with neonatal hypocalcemia is sufficient to justify the determination of serum calcium concentration in all mothers of infants with neonatal hypocalcemia.

Congenital Hypoparathyroidism

Congenital hypoparathyroidism is a rare disorder. It may occur sporadically or with a familial incidence. There is some evidence that in this familial disorder, the primary abnormality is a defect in parathyroid hormone biosynthesis. The parathyroid glands arise from pharyngeal pouches III and IV. Congenital aplasia or
hypoplasia of the parathyroid glands may occur either as a solitary defect or in combination with defects in development of the other structures that arise from the same pharyngeal pouches. One type is the III/IV pharyngeal pouch syndrome (Di-George Syndrome) that includes hypoplasia of the thymus and parathyroid glands, impairment in cellular immunity, and characteristic facies. The great vessels of the heart also arise from the same pharyngeal pouches and developmental defects in these structures also occur as a feature of this syndrome. The hypocalcemia of the DiGeorge Syndrome is associated with T-cell deficiency. An infant has been reported in whom there was transient hypocalcemia with T-cell deficiency. This patient presented with convulsions at six weeks of age associated with marked T-cell deficiency; by 32 weeks of age the infant was normocalcemic with a normal percentage of T-cells.

The age at presentation of congenital hypoparathyroidism is dependent on whether there is either hypoplasia or aplasia of the parathyroid glands. The neonate with aplasia is likely to present within a few days of birth with hypocalcemic convulsions. In those children with hypoplasia, the clinical presentation may not occur until later in infancy or childhood when a calcium stress situation cannot be met by the hypoplastic parathyroid glands. The early aplastic presentation is likely to be initially confused with early or late neonatal hypocalcemia, while the hypoplastic presentation is likely to be initially diagnosed as acquired hypoparathyroidism.

ACQUIRED HYPOPARATHYROIDISM

The term "acquired" is used to differentiate between those lesions present at birth and those that develop in the post-delivery period. In the older infant, young child, or adult, the term "acquired hypoparathyroidism" is used to denote either autoimmune lesions or damage to the parathyroid glands following either surgical trauma to the neck or irradiation. Although it is a very rare occurrence, acquired hypoparathyroidism may occur in the first six months of life. In idiopathic hypoparathyroidism, there is a solitary endocrine lesion as distinct from the genetic autoimmune form which may be characterized by the presence of insufficiency of other endocrine glands and evidence of multiple sites of autoimmune tissue injury. In an infant, it may be difficult or even impossible to differentiate between the acquired form described under this heading and congenital hypoplasia of the parathyroid glands.

Genetic autoimmune hypoparathyroidism has an autosomal recessive mode of inheritance. In addition to parathyroid insufficiency, there is commonly a linked autoimmune disturbance in adrenocortical function. In some patients there is also a disturbance in thyroid function, and other rare endocrine disorders may occur. The adrenal insufficiency does not necessarily present concurrently with the hypoparathyroidism, and it may be delayed for some years. Severe intestinal malabsorption with steatorrhea is a striking feature in this disorder. Steatorrhea is normally a feature of idiopathic hypoparathyroidism but is particularly severe in the genetic autoimmune form. This supports the concept of autoimmune intestinal-cell tissue injury. In further support of this concept is the fact that this group of hypoparathyroid patients may develop antibodies to gastric parietal cells resulting in intrinsic factor deficiency and pernicious anemia. The most striking diagnostic feature of this form of hypoparathyroidism is the associated severe muco-cutaneous moniliasis. These patients lack an immune reaction to Candida with a consequent severe intractable moniliasis of their skin, nails and mucous membranes. In some there is either partial or total alopecia, also a consequence of autoimmune tissue injury.
Pseudohypoparathyroidism

This rare disorder is characterized by the biochemical features and symptoms of hypoparathyroidism and an absent phosphaturic response to exogenous parathyroid hormone together with, in some patients, the presence of characteristic physical and skeletal stigmata. Thyroid dysfunction may occur as a feature of pseudohypoparathyroidism and possibly reflects a defect at either the level of the hypothalamus or above, while in others it may be due to a defect within the thyroid gland. The symptoms of hypoparathyroidism may begin at an early age but are usually not present at birth. The physical and skeletal stigmata in the older child or young adult include short stature, round face, and brachydactyly. The biochemical features of the disorder are characterized by the failure of parathyroid hormone, which is secreted in either normal or increased amounts, to effect an adequate response of its target tissues with consequent hypocalcemia and hypophosphatemia. The failure of the renal tubules to respond to exogenous parathyroid hormone, as assessed by an increment in urinary cyclic adenosine monophosphate (AMP) excretion, has allowed the disorder to be further subdivided into Types I and II.

Type I pseudohypoparathyroidism is characterized by the presence of the specific physical and skeletal stigmata together with the lack of an increase in urinary cyclic AMP excretion following an intravenous infusion of parathyroid hormone. Pseudohypoparathyroidism Type I is an inherited disorder with an autosomal dominant pattern, although cases may occur sporadically. Among the kindreds of patients with this disorder, cases may be found who exhibit the characteristic physical and skeletal stigmata but who do not have a disturbance in calcium homeostasis (pseudopseudohypoparathyroidism).

It has been proposed that the response to parathyroid extract in patients with pseudohypoparathyroidism is dependent on their vitamin D status. This proposal was based on the absence of a phosphaturic response following the administration of parathyroid extract in a patient with pseudohypoparathyroidism while hypocalcemic. A normal phosphaturic response was found after the plasma calcium concentration had been raised by the administration of large doses of vitamin D₂. It has, however, been recognized for a long time that large doses of vitamin D are needed for the therapeutic management of these patients. The need for large dose therapy is consistent with a defect in one or more of the hydroxylation steps in the formation of the biologically active metabolites of vitamin D rather than a primary deficiency state. In a child with pseudohypoparathyroidism a physiological dose of 1,25-dihydroxycholecalciferol rapidly corrected the hypocalcemia and increased the intestinal calcium absorption. In the same patient, a pharmacological dose of 25-hydroxycholecalciferol was, however, required to cause a similar effect. These findings are consistent with a defect in the renal 1α-hydroxylation of 25-hydroxycholecalciferol and formation of the biologically active sterol.

Patients with Type II pseudohypoparathyroidism differ from those with Type I. Despite the absence of a phosphaturic response, they show a normal increase in urinary cyclic AMP hormone. A major clinical diagnostic difference between the two types of pseudohypoparathyroidism is the absence of the physical and skeletal stigmata in patients with the Type II form.

Vitamin D Deficiency

Hypocalcemia in vitamin D deficiency involves at least two mechanisms; firstly, an impairment in intestinal calcium absorption, and secondly, unresponsiveness to the actions of endogenous parathyroid hormone.
In the neonate, a state of vitamin D deficiency can be induced as the result of a defect in the hepatic or renal hydroxylation activation steps of the steroid hormonal form or from an inadequate dietary intake of vitamin D in the presence of simultaneous lack of endogenous synthesis. Hypocalcemia from a dietary deficiency of vitamin D, with associated clinical symptoms, is nowadays a relatively rare phenomenon in early infancy, although it may occur in infants born to mothers with a poor vitamin D status owing to the nature of the mother's diet. In the extreme situation of a mother with osteomalacia owing to a dietary deficiency of vitamin D, the newborn may show clinical signs or rickets. In one of the reviewers' experience, hypocalcemia has, however, been relatively common in infants born to immigrant Indian and Pakistani women in England with a poor vitamin D status. In this group, the vitamin D deficiency was of a multifactorial etiology: (1) inadequate exposure to bright sunlight, owing to social traditions and also to the northern latitude of England, combined with (2) a diet low in vitamin D content whilst having a high content of phytate. The latter appears to act either by reducing the availability of calcium for intestinal absorption or by interfering with the intestinal absorption of vitamin D metabolites, particularly from the enterohepatic circulation. Hypocalcemia owing to vitamin D deficiency may occur in infants at three months or more of age who are receiving cow's milk that has not been supplemented with vitamin D. Hypocalcemia and rickets may also develop in low birth weight artificially fed premature infants. In this situation, the vitamin D that is normally added to these artificial feeds is inadequate either because of the small volume that the infants receive or more probably because the "normal" amount of D supplementation in the milk is inadequate for the skeletal calcium demands of the premature infant. Defects in either the hepatic or renal hydroxylation steps in the formation of the active hormonal form of vitamin D may occur in infancy. Defective 25-hydroxylation with consequent hypocalcemia can occur in association with congenital atresia of the bile ducts and/or neonatal hepatitis. Hypocalcemia and rickets have been reported as common complications of neonatal hepatitis. A defect in renal 1α-hydroxylation is the probable mechanism involved in vitamin D-dependent rickets; a feature of this syndrome is hypocalcemia. It would, however, be unlikely for a patient to present with hypocalcemia owing to this disorder within the first six months of life.

Magnesium Deficiency

Severe magnesium depletion is associated with hypocalcemia. The mechanism for hypocalcemia in this deficiency state involves either a failure of the actions of parathyroid hormone on its target tissues or a block in the synthesis and/or secretion of the hormone from the parathyroid glands. A rare disorder which involves a specific defect in intestinal magnesium absorption has been described in male infants. This disorder may present in the first few weeks of life with convulsions and hypocalcemia with severe hypomagnesemia.

Hypercalcemia

In the older infant and adult, there are many disorders that may cause severe hypercalcemia. The most common of these disorders are malignancy and primary hyperparathyroidism; treatment with thiazide diuretics is the most common cause of mild hypercalcemia. In the fetus and neonate, as defined for this review, there are relatively few causes of hypercalcemia (Table II).
TABLE II
Causes of Hypercalcemia in the Newborn and Neonate

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<thead>
<tr>
<th>Primary hyperparathyroidism</th>
<th>Idiopathic hypercalcemia</th>
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<tbody>
<tr>
<td>Mild</td>
<td>Severe</td>
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PRIMARY HYPERPARATHYROIDISM

Hyperparathyroidism with the onset of symptoms either at birth or in the early neonatal period is a rare but well recognized phenomenon. The importance of the recognition and diagnosis is that the disorder may be fatal if it is not promptly treated. The diagnosis of these neonates has occurred with an increasing frequency following the recognition of the familial incidence of primary hyperparathyroidism. Neonatal primary hyperparathyroidism has both autosomal dominant and autosomal recessive modes of inheritance. The usual finding on histological examination of the parathyroids is diffuse chief cell hyperplasia of all four glands necessitating total parathyroidectomy. Familial primary parathyroid hyperplasia is a feature of the syndrome of multiple endocrine adenomatosis Types I and II, and within each kindred there may also be some members with the syndrome of familial hypocalciuric hypercalcemia.

IDIOPATHIC HYPERCALCEMIA

Idiopathic hypercalcemia in the neonate occurs in two main forms that probably represent two different disease processes. The mild form occurred mainly in England during the late 1940's and early 1950's; the incidence has markedly declined since that time. In these infants the hypercalcemia presented with clinical symptoms, with a rapid onset, at approximately three months of age. The infants had a history of a normal delivery and normal developmental progress up to that date. All were artificially fed on a national dried milk that was fortified with vitamin D. The pathogenesis appears to have been related to the excessive vitamin D content of the artificial milk. Since hypercalcemia did not occur in all infants on this artificial feed, it would, however, suggest that hypersensitivity to vitamin D may have been an additional factor in those who became hypercalcemic. The decline in the incidence of this syndrome has corresponded with a reduction in the vitamin D content of the artificial milk.

The severe form of idiopathic hypercalcemia is rare and consists of a syndrome characterized by elfin-like facies, mental retardation, osteosclerosis, hypercalcemia, hypercalciuria, nephrocalcinosis, and uremia. The infants are often of low-birth weight, and some of the symptoms and signs can either be recognized at birth or be dated back to birth. These observations are consistent with the view that the disorder has its onset during intrauterine life. Neonates with this syndrome often have cardiovascular abnormalities, the commonest of which are supravalvular aortic or pulmonary stenosis, coarctation of the aorta, and peripheral stenoses in systemic or pulmonary arteries.

Conclusion

Hypocalcemia is the commonest disturbance of calcium homeostasis in the neonate and is predominantly of the early type. This type of hypocalcemia appears to represent a state of functional immaturity of the parathyroid glands. A state of functional hypoparathyroidism may occur in the neonate as a consequence of maternal primary hyperparathyroidism; tetany in the neonate may be the first manifestation of the maternal disease. Neonatal hypoparathyroidism of either the congenital or acquired types is a rare occurrence. In recent years, the rare disorder of pseudohypoparathyroidism has been subdivided into either Types I or II on the basis of the response of the renal tubules to
exogenous parathyroid hormone, as assessed by urinary cyclic adenosine monophosphate excretion. Hypocalcemia owing to dietary deficiency vitamin D is a relatively rare occurrence; it may, however, occur in some specific population groups and in countries with endemic problems of malnutrition. Hypocalcemia owing to defects in either the hepatic or renal hydroxylation stages of vitamin D may occur as a feature of some disease states. In the fetus and neonate, there are relatively few causes of hypercalcemia. The further elucidation of the disorders of calcium homeostasis in this age group will undoubtedly be enhanced in the near future with the recent development and availability of assay methods for the various di- and tri-hydroxymetabolites of cholecalciferol.

References

23. ROSENTHAL, T., YAHAV, J., TEICHER, A., FRAND, M., and ROTEK, Y.: A case of maternal...