RESEARCH PAPERS

Maternal-Fetal Relationships of Copper, Manganese, and Sulfur in Ruminants. A Review

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ABSTRACT
Placental transfer and localization of copper, manganese, and sulfur in the ruminant are described. The fetus is completely dependent upon the dam for its supply of these minerals.

Numerous studies have shown significant correlations between fetal and maternal tissue copper concentration. Because copper is essential for development of the central nervous system of the embryonic lamb, an acute maternal hypocuprosis can cause gross brain lesions in the fetal or neonate lamb.

Manganese deficiency in the gestating ruminant has deleterious effects on the developing embryo; inadequate dietary manganese induces an abnormal development of the epiphsial fetal cartilage.

This review provides information on partition of dietary sulfur between maternal tissues, fetus, and placenta. Sulfur may be transferred to the ruminant fetus in a variety of organic forms as well as in the inorganic form.

INTRODUCTION
Early in this century the long effects of malnutrition were shown to depend upon the stage of life during which malnutrition occurred. Stillborn and immature fetuses were produced by cows fed calcium deficient diets (22, 26). Since that time many studies have demonstrated a variety of alterations in fetus and newborn when excesses or deficiencies of several mineral elements were fed to pregnant and lactating females.

Systematic studies of effects of alterations in dietary mineral supplies have been hampered by complicating factors including interrelationships among minerals or with other dietary components. As well, analytical methodology in many cases has been tedious, and only in the past two decades have techniques for studying transfer and metabolism in vitro been refined. In spite of these limitations a substantial number of studies of copper and manganese in pregnant ruminants have been undertaken, particularly in relation to development of deficiency diseases of newborn. More recently sulfur metabolism in the dam and fetus has been studied for several species, including sheep and cattle.

This review outlines knowledge of maternal-fetal relationships of copper, manganese, and sulfur, particularly for ruminants, and points out areas requiring further research.

COPPER
Cattle and sheep diseases associated with deficiency of copper (Cu) have been reported from different parts of the world. In cattle effects of Cu deficiency usually are postnatal while in sheep and goats symptoms of Cu deficiency often occur in utero. In sheep and goats dramatic changes in Cu metabolism during gestation may have profound effects upon normal growth and development of the fetus.

PRENATAL COPPER DEFICIENCY
Adequate maternal intake of Cu is essential for development of the central nervous system (CNS) of the embryonic lamb. Consequences of Cu deficiency during intrauterine life may include gross brain lesions, with affected lambs born dead or dying shortly after birth. Enzootic ataxia of the unborn or the unweaned lamb is primarily from Cu deficiency (5), a degeneration of myelin in the spinal cord being responsible for the ataxia that frequently affects the hind limbs. Histologically, the pathological process
of enzootic ataxia of lambs suggests a disorder of nervous parenchyma in myelination areas in the form of a spongy inhibition associated with functional vascular disorders (58). Ewes deficient in copper give birth to lambs characterized by a partial herniation of the cerebellum such that anteriorly the fissura prima lay beneath the tentorium cerebelli and posteriorly formed a "tail" in the foramen magnum (59).

Lesions in the brain and spinal cord characteristic of enzootic ataxia could be detected as early as 99 days postconception in fetal lambs whose dams were grazing on land where enzootic ataxia (swayback) occurred (57). However, it is the opinion of Lewis et al. (42) that the characteristic lesion of delayed swayback is not present at birth but develops in the postnatal period. This controversy is of considerable importance in relation to the timing and effectiveness of measures of control of the disease. Administration of therapeutically effective amounts of copper to the ewe could be delayed until the last month of pregnancy and still be effective in preventing swayback in the offspring (45). It appears that an inadequate supply of copper to the fetus during the last 3 or 4 wk of gestation can cause swayback (11). Innes and Shearer (36) concluded on pathological grounds that the disease process is initiated at a late stage of gestation.

In guinea pigs deficient of Cu that showed gross brain changes at birth, it was postulated that the supply of copper was inadequate during fetal development to maintain the necessary oxidase activity (17). Moreover, the deficiency of copper also might limit synthesis of phospholipid (20). Because of high demand for copper by the developing embryo, the Cu-deficient ewe is unable, apparently, to maintain a Cu reserve adequate for normal functional purposes during late gestation. However, in some cases Cu-deficient ewes give birth to an unaffected lamb; in these ewes more Cu crosses the placenta than in the ewe giving birth to an affected lamb.

**COPPER TRANSFER TO THE FETUS**

There is constant increase in copper deposition throughout the fetal period and, therefore, an increasing demand for copper by the fetus (66). The pregnant ewe appears to be equipped poorly to protect her lamb against effects of a dietary deficiency of copper. Her blood and plasma copper falls during pregnancy and again after parturition, perhaps from the physiological disturbances that accompany pregnancy, such as an increase in blood volume and demands of the developing fetus (8).

When Cu is absorbed by the ewe, it is transferred to the liver and converted into hepatocuprein and then into haemocuprein for liberation into the blood stream. It may be that the hepatocuprein or other Cu complexes in the liver govern transfer of Cu from dam to fetus (56).

Work by Scheinberg et al. (55) and later by Widdowson (65) showed a markedly higher maternal blood concentration of ceruloplasmin than that of the fetus. Presumably only the nonceruloplasmin fraction passes over to the fetus, and it is not until after birth that the neonate acquires the ability to synthesize ceruloplasmin for itself.

The relationship of fetal content of Cu to body weight is approximately allometric (69) for lambs and is fitted by the regression equation: \( \ln (\text{Cu mg}) = 1.16 \ln (\text{w.kg}) + 0.667 \) (RSD + .19) in which the regression coefficient is approximately equal to the mean of the ratios of the specific ratio. Williams et al. (69) calculated that between days 80 and 144 of gestation the rate of Cu deposition increased exponentially and that at the end of pregnancy there was .24 mg Cu in the triplet fetus.

The daily amount of Cu deposited in the total products of conception of the ewe during the first, second, and third trimester averaged 15, 85, and 186 mg/day (48). The placenta contained 1.5 mg Cu; fluids .96 mg Cu, and fetus 11.34 mg Cu after 136 days gestation.

**Copper Concentrations in Tissues**

**Bovine.** Copper contents in all fetal tissues were similar to adult concentrations (Table 1) with the exception of higher Cu in fetal liver (52). Low Cu in both maternal blood and liver and in the fetal liver have been demonstrated conclusively and constantly in all cases of bovine Cu deficiency (6, 5).

McCosker (44) showed that Cu in the liver of newborn calves was significantly higher than that of their dams. There were no significant correlations between Cu in dams and their
TABLE 1. Copper concentration in bovine tissues of cows, fetus, and neonate (ppm dry matter).

<table>
<thead>
<tr>
<th></th>
<th>Liver</th>
<th>Other tissues</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fetus 263</td>
<td>Fetus</td>
</tr>
<tr>
<td>Pryor (29)</td>
<td>Dam 164</td>
<td></td>
</tr>
<tr>
<td>McCosker (22)</td>
<td>Fetus 430</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cows at calving</td>
<td></td>
</tr>
<tr>
<td>Cunningham (8)</td>
<td>17.1 ± 2.55a</td>
<td></td>
</tr>
<tr>
<td>Pryor (29)</td>
<td>9.8 ± 1.7</td>
<td></td>
</tr>
<tr>
<td>McCosker (22)</td>
<td>316 ± 33</td>
<td></td>
</tr>
<tr>
<td></td>
<td>329 ± 58</td>
<td></td>
</tr>
<tr>
<td>Difference: calf and cow</td>
<td>344 ± 33**</td>
<td>319 ± 57**</td>
</tr>
</tbody>
</table>

Other tissues

| Fetus | Brain: 10.4, kidney: 10.8, pancreas: 2.8, Spleen: 10.7, and lung: 5.9 |

*Mean ± standard deviation.

**P<.01.

offspring. However, no systematic attempt has been made to study copper content of bovine fetuses at varying ages or to relate this to the copper status of the dam over pregnancy. Van Der Grift (51) observed the liver Cu of pregnant cows decreased during the last 4 mo of gestation and that administration of Cu to the dam during this period enhanced transfer of Cu to the fetus. It was reported by Cunningham (9) that there was more copper in the liver of the newborn than of the fetal calf.

Parenteral administration of CuSO₄ or Cu-glycine to the cow 1 to 4 mo prepartum significantly increased the concentration of liver Cu in the newborn calf relative to that of the maternal liver (2). However, there was no quantitative relationship between the dosage of Cu administered to the cow and Cu concentration in the neonatal calf liver. Field (19) showed that calves born to cows given 10 g of CuSO₄ orally at 14-day intervals during pregnancy had higher Cu in their livers than did calves from cows deficient in Cu.

Ovine. Copper concentration in the liver can be used to assess the incidence of Cu deficiency in sheep (1), with liver Cu concentrations of less than 30 ppm being classes as Cu deficient (Table 2).

Suttle and Field (59) recorded marked variations in liver Cu of newborn lambs born from Cu depleted ewes. They found that variation in the degree of Cu depletion in the newborn was related to plasma Cu in the ewe during the last 2 mo of pregnancy.

Low Cu in the liver could occur without any sign of clinical abnormality (49) even with large differences in Cu content livers of normal and Cu deficient sheep and lambs.

Copper in other fetal tissues (49) was much lower than in the ewe, which is in contrast to the work of Pryor (52) with calves. Copper of newborn lambs from unsupplemented ewes was 7.1 ± 1.1 ppm and 10.9 ± .6 ppm from Cu-supplemented ewes (59), which compares favorably to the 9 to 18 ppm range suggested as normal for ruminants (29). Mean Cu concentrations in the kidney were 16.8 ± 3.3 ppm and 17.9 ± 7.05 ppm and in the heart 8.9 ± .75 and 12.3 ± .78 ppm DM for unsupplemented and supplemented lambs. These data demonstrate that Cu supplementation can alter Cu of specific tissues differently and that “normal” varies considerably among different tissues.

Blood Copper

From the work of Beck (4), under normal conditions transfer of Cu to the ovine fetus can occur without altering maternal blood Cu. Eden (15) suggested that blood Cu was highly variable
between sheep but also in the same animal
sampled in different times. Extreme means had
no relation to state of health of the animals.
Changes in blood Cu during pregnancy occurred
within the normal range of variation for non-
pregnant sheep and were not related to the
particular stage of pregnancy. Decreases in
blood Cu were as frequent as increases and may
alternate in successive months of pregnancy.
Possible physiologically important increases in
maternal blood are inadequate to satisfy
demands of the fetus, but evidence of this is
meager. The normal wide range of variation
makes difficult any quantitative studies of any
physiological changes specifically associated
with pregnancy.

According to McCosker (44), fetal and
newborn sheep have lower blood Cu than
normal adults because of low ceruloplasmin in
the blood of fetal and newborn lambs. Transition
from newborn to adult blood Cu occurs rela-
tively rapidly in sheep, taking place within 3
days after birth.

Interference with assimilation of Cu by the
ewe does not appear to be reflected in lowering
Cu in the liver or blood to an extent consistent
with any recognizable pathogenic effect.
Transfer of adequate amounts of Cu from ewe
to developing fetus appears to be a fundamental
necessity for correct myelin formation, and
impaired Cu transfer to the fetus is manifested
in development of deficiency symptoms in the
animal at birth.

Dramatic changes in metabolism of copper
associated with pregnancy have been docu-
mented for many animals (62). These changes
are summarized. 1) Maternal serum cerulo-
plasmin and Cu concentrations increase during
pregnancy and decrease postpartum; 2) Neo-
natal serum ceruloplasmin and Cu concen-
trations are low, only about 20% of the mater-
nal; 3) Liver Cu in the newborn is high. Further,
the dam must provide the fetus with adequate
Cu. If this hypothesis is correct, the elevated
maternal ceruloplasmin represents an overpro-
duction of Cu to ensure adequate amounts for
the fetus. Whether the fetus can derive Cu direct-
ly from maternal ceruloplasmin is not known.

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Table 2. Copper concentration in tissues of ovine (ppm dry matter).

<table>
<thead>
<tr>
<th></th>
<th>Liver</th>
<th>Kidney</th>
<th>Brain</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Deficient&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Normal&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Deficient</td>
</tr>
<tr>
<td></td>
<td>X</td>
<td>SD</td>
<td>X</td>
</tr>
<tr>
<td>1 Ewe</td>
<td>7.3</td>
<td>1.22</td>
<td>473</td>
</tr>
<tr>
<td>Neonate</td>
<td>6.1</td>
<td>.78</td>
<td>218</td>
</tr>
<tr>
<td>2 Ewe</td>
<td>17.5</td>
<td>5.7</td>
<td>470</td>
</tr>
<tr>
<td>Neonate</td>
<td>9.2</td>
<td>1.6</td>
<td>71</td>
</tr>
<tr>
<td>3 Fetus</td>
<td>136</td>
<td>15.6</td>
<td>9.0</td>
</tr>
<tr>
<td>4 Ewe</td>
<td>103</td>
<td>12</td>
<td>134</td>
</tr>
<tr>
<td>Neonate</td>
<td>157</td>
<td>15</td>
<td>239</td>
</tr>
</tbody>
</table>

<sup>a</sup>Copper status.
Cu. In hepatic cells Cu is stored and incorporated into ceruloplasmin whereas excretion from the body is via bile (28). Incorporation of Cu into ceruloplasmin is a vital function of the liver since Cu is transported to the extrahepatic tissues in the form of ceruloplasmin. The concentration of Cu in the mammalian liver is higher at birth than at any other time during life (46). More than 50% of the total Cu in the body of most newborn lambs is in the liver (69).

Much of the copper in fetal bovine liver is in the mitochondria as a copper-protein complex called "neonatal hepatic mitochondrialcuprein", which contains about 40 mg Cu/kg (51). Between 15 and 35% of the total hepatic Cu of the sheep fetus, corresponding to most of the cytosol Cu, is in the metallothionein-containing fraction (68, 69).

Williams and Bremner (68) found that copper concentrations in liver increased towards the end of gestation in ewes. They reported 14 ± 1.2 g Cu/g fresh liver in the 80-day-old fetus and 54 ± 5.8 g Cu/g fresh liver in the 140-day-old fetus. This agrees with McDougall (45). Liver Cu begins to decrease soon after birth, presumably from mobilization to meet the needs of other tissues of the growing animal. The substantial store of Cu in the liver of newborn animals would be of advantage when the sole source of exogenous Cu is milk, which is usually low in copper.

COPPER-IRON INTERACTIONS

Copper functions in utilization of iron at an early stage of hematopoiesis (16, 27). Brückmann and Zonkeck (7) reported that Cu influences mobilization of Fe deposits and its transformation into hemoglobin. It generally is believed that congenital Cu defect is related to this function.

Placental and maternal serum Fe and Cu are compared in Table 3. Means of Cu were considerably higher in maternal blood than in placental blood whereas the converse was true for serum Fe. It seems strange, however, that the high Cu content of the fetal tissues should be associated with a low fetal plasma Cu, whereas the high Fe content of the fetal tissues is accompanied by a high serum Fe in the fetus (18). In fetal ruminants hepatic Cu and hepatic Fe are correlated, which suggests that these elements antagonize each other (43). It is possible that competition for transport systems is involved (60, 61).

MANGANESE

In ruminants manganese (Mn) deficiency produces a number of striking symptoms in the fetus or neonate. Increased numbers of abortions and births of calves or lambs with deformed limbs have been reported when dams were fed fodder low in Mn or containing substances reducing Mn utilization.

Placental Transfer of Manganese

There have been few studies of movement of Mn across the placenta. Following intravenous administration of $^{52}$Mn, concentration of radioactivity in the rat fetus increased slowly over 16 h (53). During early development of the mouse embryo, $^{52}$Mn concentrations were low, particularly in comparison to placental tissue concentrations, but the concentration of Mn in the embryo increased during development (41). In the early stages of embryonic development $^{52}$Mn was retained primarily in trophoderm and decidua, whereas in later stages its retention was limited to villi of well-developed placenta.

The amount of Mn transferred across the placenta in 60-, 80-, and 110 days was higher in fetal tissues on the high Mn diet. Transfer of $^{52}$Mn was higher in the low diet. Thus, the percentage of available Mn transferred to the fetus was greater in the low diet, but the actual amount was less (50). Following administrations of $^{54}$Mn to pregnant ewes, the concentration of radioactivity in the placenta peaked 12 h postinjection with the placental concentration representing more than 50% of the total $^{54}$Mn concentration in the fetal compartment (23). After 168 h, more than half of the $^{54}$Mn had

<table>
<thead>
<tr>
<th></th>
<th>Placental</th>
<th>Maternal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma Cu</td>
<td>$75 \pm 14^a$</td>
<td>$260 \pm 42$</td>
</tr>
<tr>
<td>Serum Fe</td>
<td>$165 \pm 71$</td>
<td>$75 \pm 32$</td>
</tr>
</tbody>
</table>

$a$ Mean ± standard deviation.

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accumulated in the fetus with placental concentration decreasing to about 25% of the total fetal compartment $^{54}$Mn content. These data suggest that Mn was transferred readily and comparatively rapidly from ewe to fetus.

Manganese Deficiency and Fetal Malformation

The largest fetal reservoir of Mn appears to be bone (21). A dietary deficiency of Mn during pregnancy may result in several types of skeletal abnormalities in the offspring.

Relationships between a low Mn intake by pregnant cows and an increased incidence of deformed calves was reported (12). Cows fed low Mn rations during gestation gave birth to calves that had skeletal deformities, including enlarged joints, stiffness, twisted legs, as well as a general physical weakness. In these calves breaking strength and length of the humerus also were reduced (13). Manganese deficiency in the pregnant quinea pig prevents normal development of epiphyseal cartilages of bones of their fetuses (63). The cartilage in the Mn-deficient fetus has a reduced mucopolysaccharide content, which suggests an active role for manganese in bone matrix formation.

Uronic acid and sulphur amino acids are higher in epiphyseal cartilage of newborn lambs from ewes supplemented with 60 ppm Mn than in cartilage from those born to ewes fed diets containing 5 ppm Mn (32). A tendency for higher hexosamine was in the organic matrix of lambs from the manganese-supplemented ewes, whereas serine, histidine, and lysine were higher in cartilage from the Mn-depleted group. Thus, effectiveness of Mn in prevention of joint abnormalities may be from the influence of Mn on mucopolysaccharide content, which suggests an active role for manganese in bone matrix formation.

Tissue Manganese Concentrations

According to Jarvinen and Ablstrom (37) the concentration of Mn was higher in livers of pregnant rats with the highest Mn intake whereas in nonpregnant animals dietary Mn had no appreciable effect on Mn concentration in the liver. Liver Mn concentrations were highest in the offspring of dams given the largest amount of Mn.

In newborn kids from goats fed a diet of low (1.9 ppm) Mn, Anke et al. (43) found that some tissues such as kidney, spleen, heart, brain, and hair depleted faster than some other tissues (Table 4). The newborn lamb preferentially stores Mn (30) in the liver, and the livers of neonate lambs from ewes fed an Mn-supplemented diet contain higher concentrations of Mn than those of lambs born to ewes fed a diet low in Mn (Table 4). The concentration of manganese in the liver of newborn lambs (30) appears to be useful for assessing the Mn status of the dam. Howes and Dyer (33) reported a higher concentration of Mn in newborn calf liver and muscle when the dam had received Mn supplementation (Table 4).

Neonate calves born to dams on low Mn diets exhibited reduced Mn in liver and kidney (54). The liver-Mn content of neonate calves born to cows fed 25 ppm Mn(H) was 12 ppm Mn (dry matter basis) compared with 7 ppm Mn for calves born to cows fed 16 ppm Mn(L) during pregnancy. The kidney of the H calves contained 2.52 ppm Mn compared with 1.17 ppm for the L calves.

Manganese Interaction with Other Minerals

As the study of trace element metabolism has advanced in recent years nutritionists have become aware of many biological interactions among these nutrients. Information on quantitative distribution of these substances in the fetus becomes a necessity in the study of a dietary deficiency. Knowledge of the intimate relationships between manganese and various other trace elements is just beginning to emerge.

In the Mn-deficiency neonatal kid, Anke et al. (32) reported that the heart, kidney, liver, and skeletal muscle contained more phosphorus than similar organs of control animals. In the Mn-deficient kid all tissues studied showed elevated Cu. Hidiroglou et al. (31), working with newborn lambs, found that for lambs born to Mn-supplemented ewes, calcium content was higher in all tissues analyzed. Higher magnesium

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**TABLE 4.** Manganese (Mn) concentrations in the tissues of fetus and neonate ruminant (ppm dry matter).

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Anke et al. (42)</th>
<th>Hidiroglou et al. (47)</th>
<th>Hansard (46)</th>
<th>Howes and Dyer (51)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.9/90.0</td>
<td>5.0/60.0</td>
<td>3.0/13.0</td>
<td>13.0/21.0</td>
</tr>
<tr>
<td>Liver</td>
<td>6.4/1.6</td>
<td>12.19/1.09</td>
<td>3.30/1.00</td>
<td>4.48/0.19</td>
</tr>
<tr>
<td>Kidneys</td>
<td>2.5/1.8</td>
<td>4.52/1.13</td>
<td>0.50/0.10</td>
<td></td>
</tr>
<tr>
<td>Spleen</td>
<td>1.9/4.0</td>
<td>1.68/1.14</td>
<td>0.68/0.18</td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>1.5/6.0</td>
<td>1.17/0.34</td>
<td>0.37/0.18</td>
<td></td>
</tr>
<tr>
<td>Heart</td>
<td>1.1/6.0</td>
<td>0.60/0.25</td>
<td>0.47/0.19</td>
<td></td>
</tr>
<tr>
<td>Skeletal</td>
<td>1.3/4.0</td>
<td>0.82/0.12</td>
<td>0.28/0.26</td>
<td>1.10/0.11</td>
</tr>
<tr>
<td>Femur</td>
<td>8.4/2.0</td>
<td>12.1/5.1**</td>
<td>3.56/1.00 (shaft)</td>
<td></td>
</tr>
<tr>
<td>Rib</td>
<td>6.9/2.0</td>
<td>10.3/3.3</td>
<td>3.00/0.72 (shaft)</td>
<td></td>
</tr>
<tr>
<td>Carpal</td>
<td>6.2/1.3</td>
<td>9.9/5.8</td>
<td>0.50/0.20</td>
<td></td>
</tr>
<tr>
<td>Brain</td>
<td>2.7/7.7</td>
<td>7.7/1.8</td>
<td>0.6/0.20</td>
<td></td>
</tr>
<tr>
<td>Spinge</td>
<td>3.6/7.7</td>
<td>5.5/6.0</td>
<td>4.68/0.9</td>
<td>4.89/0.18</td>
</tr>
<tr>
<td>Hair</td>
<td>3.2/6.0</td>
<td>3.0/2.1**</td>
<td>0.37/0.18</td>
<td></td>
</tr>
</tbody>
</table>

*P<.05.

**P<.01.
(Mg) was recorded in tissues of lambs born to ewes on low Mn diets (38). Because of the similarity in chemistry between Mn and Mg and because they can replace each other in several biochemical systems (67), it is possible that with a reduction in dietary Mn, dietary Mg was utilized to a greater extent by the body.

In rats the Fe concentration in fetuses of dams fed large amounts of Mn is nearly equal to that in the offspring of dams on a low iron diet, which suggests antagonism between Mn and Fe (37). However, in the ovine fetus this is not the case (31). Not only was Fe in the maternal tissues not affected by dietary Mn, but lambs born to ewes fed the low Mn diet had significantly less Fe in the liver and in the lung. This anomaly is difficult to rationalize.

The biological and physiological significance of many mineral changes in tissue are not readily apparent. It is suggested that a dietary deficiency of Mn in the fetus results in altered utilization of other mineral elements in the fetus and these interactions may be of biological importance. As shown with rats during gestation, fetal malformation arising from maternal dietary manganese deficiency may be caused by indirect effects of mineral interactions rather than by the direct effect of the low Mn in the body of the developing embryo (35).

**SULFUR**

The role of sulfur (S) has been studied extensively in relation to various aspects of nutrition and metabolism. Only a few studies, however, have been devoted to maternal-fetal relationships of inorganic S or S-containing organic compounds. Studies of S metabolism have been hampered to some extent by the complexity of the metabolic role of S and the many interrelationships of S with other compounds. It is of importance, therefore, to recognize that in dealing with S in particular measurement of S alone may be sufficient to characterize maternal-fetal relations of this element.

Transfer to the Fetus

At 45 days of pregnancy in the ewe (24) the placenta contained 90% of the total $^{35}$S in the products of conception; as gestational age increased to 140 days, the fetus accumulated progressively more $^{35}$S until at 140 days the fetus contained 77.2% of the total dose and the placenta 16%. The fetal percentage of total dose of $^{35}$S administered to ewes increased markedly with advancing fetal age, which reflects partially increased fetal utilization as well as increased fetal size. Further observations by these workers (24) indicate that following $^{35}$S administration to ewes, maximum tissue $^{35}$S was within 4 h of dosing while the fetal content continued to increase in activity for 7 days, although uptakes of $^{35}$S by different fetal tissues differed. In a later study with cattle (25) continually increasing fetal $^{35}$S concentrations were observed for 7 days following Na$_2$SO$_4$ administration to heifers. Hansard and Mohammed (25) observed that with heifers at 90 days of gestation 76% of the $^{35}$S in the products of conception was in the placenta.

Dziewistkawski (14) recorded that older rat embryos retained more $^{35}$S from Na$_2$SO$_4$ and suggested that since a large proportion of the $^{35}$S was used in tissue anabolism, the increased $^{35}$S uptake of the older embryo was simply a result of increased fetal growth.

Sulfur may be transferred to the fetus in a variety of organic forms, as well as the inorganic form. In studies with swine equipped with maternal fetal indwelling cannulas, Knipfel et al. (40) observed that transfer of $^{35}$S-methionine was dependent upon the extent and duration of maternal blood methionine. In further studies with ewes (30), increasing $^{35}$S-methionine loads to the ewe resulted in significantly greater $^{35}$S-methionine elevations in the fetus. Elevated methionine and its metabolites in the fetal blood or in amniotic fluid were not reduced readily and represented a potentially toxic accumulation.

**Fetal S Metabolism**

Sulfate S crossing the rat placenta is used largely in tissue synthesis (14). Cartilage contained high $^{35}$S, and it was proposed (14) that sulfate S in the embryo was a prominent component of chondroitin sulfate in skeletal cartilage. A number of other tissues also contained appreciable amounts of $^{35}$S, and a few days before birth evidence of secretion of a sulfur containing mucopolysaccharide was seen, although the role of such a compound is unknown. Hansard and Mohammed (25, 14) reported that for both sheep and cattle $^{35}$S-
sulfate appeared in highest concentrations in the most metabolically active tissues, the internal organs and bone, of the ovine and bovine fetus.

Knight et al. (38) and McGarry and Roe (47) studied effects of salicylamide and indole on sulfate incorporation by fetal rats as these compounds are excreted as sulfate conjugates. Both compounds reduced fetal sulfate retention but did not impair fetal growth in the earlier study, but in the study of McGarry and Roe (47) skeletal deformities in the fetus resulted from administration of salicylamide. These workers concluded that salicylamide reduced placental transfer of sulfate and impaired the incorporation of sulfate into glycosaminoglycans. A number of other compounds such as tolbutmaine and phenyl-butazone have affected sulfate incorporation.

In a number of species, the fetus has had limited, or nonexistent mechanisms, for catalyzing sulfur amino acids; the various essential products of the transulfuration pathway for methionine catalysis reach the fetus following maternal catalysis. Under conditions where large doses of methionine or cysteine are given, for example, as stimulants to wool production (10), accumulation of methionine or its metabolites in the fetus might affect adversely fetal growth and development. Fetal growth in rats is reduced following high methionine, and fetal amino acid patterns and postnatal behavior have been altered following methionine loading of ewes (39).

In view of the many roles of S in metabolism both pre- and postnatailly, the range of effects arising from maternal-fetal relationships of S is extremely wide. The occurrence of S in a variety of compounds and its ready interconversion makes study of maternal-fetal relationships difficult.

In addition, while interactions between sulfur and other minerals are known, the extent to which these are functionally important in pregnant female and fetus remain largely unknown. Hurley (34) summarized studies from their laboratory indicating that the effect of prenatal Mn deficiency on skeletal abnormalities was at least partially due to rearrangement of mucopolysaccharine synthesis, which suggests a possible interaction of Mn with S.

A review of literature concerning maternal-fetal relationships of minerals in general, and in particular Cu, Mn, and S in ruminants, raises a number of points. First, there is little information to suggest that the developing fetoplacental unit in the ruminant is markedly, if at all, different from that of nonruminant animals. If, in fact, this is the case, then a considerable body of knowledge from other species may be applicable to ruminants. Second, it is difficult to draw firm conclusions regarding effects of minerals such as those covered in this review since interactions among such minerals and with other components of the diet are numerous and intricate. Third, there is a lack of information regarding quantification of transplacental passage of all nutrients in vitro, which must be satisfied before much of the information now available can be utilized adequately. It is hoped that this review will stimulate further activity in fetal-maternal relationships of minerals and other compounds.

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