Maternal depletion syndrome

**Abstract**

The term of maternal depletion syndrome (MDS) is frequently used to state the poor health status of the mother and fetus in developing countries. The syndrome was assigned to the nutritional stress induced by successive and too close pregnancies and deliveries or by early pregnancies. MDS was studied in terms of two assumptions: poor nutritional status of large multiparous with a short interval between deliveries and early pregnancy, in which it exists a competition for nutrients to satisfy the maternal and fetal growth. An adequate availability of the macronutrients during the pregnancy is probably the only and most important factor that influences the course of pregnancy. Folic acid and iron are the key micronutrients involved in physiological processes during pregnancy. If the folic acid and iron status before the conceptions is weak, this can lead to multiple negative effects for both mother and fetal development. This paper is a review of physiopathology and studies from literature regarding the effects of the micronutrients depletion on the maternal and fetal body, in the context of maternal depletion syndrome.

**Keywords:** maternal depletion syndrome, nutritional status, short interval between deliveries, early pregnancies

**Introduction**

The term maternal depletion syndrome (MDS) is frequently used to state the poor health status of the mother and fetuses in the developing countries. The syndrome was attributed to the nutritional status induced by successive pregnancies and childbirth, to lactation and includes anemia, osteomalacia, goiter, edema, inadequate weight gain during pregnancy and deliveries of infants with low birth weight for gestational age. Unfortunately, if this syndrome occurs only following the childbearing pattern or it occurs following a combination of factors (i.e. childbearing, prolonged poverty, inadequate nutrition) remains unclear.

Two hypotheses have been proposed towards investigating the MDS: (I) women with high parity show a poor nutritional status compared to women with low parity, (II) short intervals between deliveries are associated with poor maternal health and poor pregnancy outcome. MDS should be studied separately for each reproductive cycle, being characterized by a negative change in the nutritional status during pregnancy, change that emphasizes the nutritional repletion with shortening of the periods.

Breastfeeding can also contribute in the association between the short interval between pregnancies and fetuses born with low birth weight, given the involvement of breastfeeding in the MDS. Lactogenesis is a process that involves consumption of very high amount of energy and increased mobilization of nutrients from the maternal stores. Prolonged breastfeeding lowers the maternal bone density, the maternal calcium deposits being reverted to normal only after at least 12 months, in terms of an adequate food intake or a supplementation of the diet with calcium. Occurrence of pregnancy while breastfeeding accentuates depletion of nutrients from maternal reserves, this leading to an increased maternal exhaustion and therefore, to adverse effects on the fetus.

An adequate availability of the nutrients during pregnancy is probably the only and the most important factor influencing the course of pregnancy. Although many models of physiological and metabolic adjustments have been tempted to improve the nutrient use during pregnancy, it has been shown that they are often inadequate for women with poor nutritional status before conception. Therefore an appropriate source of nutrients to maintain the frail equilibrium between the needs of the mother during pregnancy and the fetus is needed. An inadequate source of nutrients can lead to a biological competition between the mother and the embryo, thus bodies being jeopardized.

It was largely discussed in several studies that poor prognosis of the pregnancies are arising from young women with very short interval between pregnancies. Some authors attribute an increased risk of poor pregnancy outcomes in case of the combination of maternal age or short interval between pregnancies with additional factors (i.e. socio-economic status, stress, lifestyle, proper prenatal care).

Others, attribute the poor results to an independent factor, related to some aspects of the physiology of women, such as biological immaturity in case of pregnancy that occurred in very young women or the competition for nutrients or incomplete recovery, anatomical and physiological modifications in case of short intervals between pregnancies.

**Pathophysiology**

The information discussed above was focused on the influence of food restriction (i.e. protein-energy maternal depletion) on pregnancy outcome. Macronutrients can be defined as required substances in increased amount for proper pregnancy development and fetal growth. This category includes carbohydrates, proteins, lipids and water.
From the pathophysiological point of view, the micronutrients model and the impact of their depletion in further development of pregnancy has been studied. The micronutrients mobilized from the maternal reserves must meet the needs of pregnancy and lactation and should be replaced during intervals between pregnancies. If the intervals are too short or if there is a competition between maternal and fetal growth, it results in deficiency of these nutrients, which can lead to an unfavorable prognosis after pregnancy. Folic acid and iron are the key micronutrients involved in the physiological processes during pregnancy. If folic acid and iron status before conception is weak, this may result in multiple negative effects for both mother and fetal development (4).

**Folic acid**

Folic acid is especially important for the normal fetal development. Once absorbed, the folic acid acts as a cofactor for many essential cellular responses, including the transfer of the single bonds of carbon. Folic acid is also necessary for the cell division given its role in deoxyribonucleic acid (DNA) synthesis (3). Folic acid is also the substrate for a variety of reactions that affect the metabolism of some amino acids, including the pathways for trans-methylation and trans-sulfuration (5).

The interference with DNA synthesis leads to abnormal cell division. Rapidly dividing cells, such as those of the hematopoietic system are most susceptible to occurrence of irregularities in DNA production. Thus, one of the first clinical manifestations of folate deficiency is the hypersegmentation of neutrophils, later followed by the constitution of megaloblastic bone marrow cells, macrocytic erythrocytes and subsequently macrocytic anemia. Abnormalities in the epithelial cell division and the gonads follow this progression (4). A central feature of the fetal development is represented by the sustained cell division. As a result of its role in nucleic acids synthesis, folic acid needs are increased during the periods of rapid growth of tissues (6).

### Table 1: Influence of the folic acid on the outcome of pregnancy (5)

<table>
<thead>
<tr>
<th>Author</th>
<th>Study design</th>
<th>Number of subjects</th>
<th>Associated pathology</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scholl et al. (6)</td>
<td>Prospective study of folate and serum folate</td>
<td>832</td>
<td>-</td>
<td>Women with low folate intake (≤240 μg/d) had more than three times greater risk for preterm delivery/infant LBW than women with folate intake &gt;240 μg/d (P &lt;0.05). Risk of preterm delivery without premature rupture of membranes increased three times (P &lt;0.05). Odds of preterm delivery increased 1.5% per unit decrease in serum folate (P &lt;0.05).</td>
</tr>
<tr>
<td>deVries et al. (7)</td>
<td>Uncontrolled study (postload homocysteine)</td>
<td>62</td>
<td>Non-hypertensive women with history of: plaental abruption, fetal demise, IUGR</td>
<td>Hyperhomocysteinemia prevalence 24% compared with 2-3% expected for Dutch population</td>
</tr>
<tr>
<td>Leeda et al. (8)</td>
<td>Case series evaluated for hyperhomocysteinemia (methionine load) at 10 weeks postpartum</td>
<td>207</td>
<td>History of: preeclampsia, IUGR</td>
<td>17.7% of preeclamptic women (n = 181) 19.2% of women with a history of IUGR (n = 26) tested positive for hyperhomocysteinemia. In a subsequent pregnancy (n = 14) with supplementation (folic acid, vitamin B6, and aspirin): birth weight increased from 1088 ± 570 to 2867 ± 648 g, pregnancy length increased from 29.5 ± 3.7 to 36.7 ± 2.2 wk. The proportion with preeclampsia decreased from 78.6% to 50% (no statistical testing).</td>
</tr>
</tbody>
</table>

**Maternal depletion syndrome**

Bigiu et al.
<table>
<thead>
<tr>
<th>Author</th>
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<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frelut et al.</td>
<td>Case-control study</td>
<td>21</td>
<td>IUGR diagnosed at 27 ± 3 weeks pregnancy</td>
<td>Positive bivariate correlation (week 32) between maternal RBC folate and infant birth weight ($r = 0.48, \ P &lt; 0.02$).</td>
</tr>
</tbody>
</table>
| Malinow et al.    | Observational study of plasma homocysteine and serum folate in healthy nulliparas at delivery (37-42 wk) | 35                 | -                    | High maternal homocysteine correlated negatively with:  
  - low infant birth weight ($r = -0.36, \ P < 0.05$) and  
  - short pregnancy duration ($r = -0.42, \ P < 0.05$).  
High maternal serum folate correlated positively with:  
  - increased birth weight ($r = 0.47, \ P < 0.01$) and  
  - pregnancy duration ($r = 0.23, \ P < 0.05$).  
Homocysteine and serum folate were negatively correlated ($r = -0.54, \ P < 0.001$).                                                                 |
| Rondo et al.      | Case-control study                                                             | 356                | IUGR                 | More growth-restricted infants (25.7%) than control infants (19.9%; $P < 0.01$) had abnormally low RBC folate in cord blood.  
No significant difference in maternal RBC folate (at delivery).                                                                                                    |
| Iyengar et al.    | Nonrandomized trial  
  - iron level alone (60 mg/dL)  
  - in combination with folate (500 μg/dL) | 189                | -                    | Folic acid group had ($P < 0.001$) higher:  
  - infant birth weight (~200 g)  
  - placental weight (~61 g).                                                                                                                                     |
| Rolschau et al.   | Paired trial:  
  - age  
  - parity,  
  - smoking  
  - pregravid weight with allocation to iron (200 mg Fe) or multivitamins  
  - with folic acid (5 mg)  
  - without folic acid |                     | -                    | Among folic acid group subjects:  
  - infant birth weight was increased by 400 g ($P < 0.01$)  
  - placental weight was greater by ≈50 g (NS).                                                                                                                  |
| Czeize et al.     | Randomized controlled trial (periconceptional supplementation with folic acid - containing multivitamins) |                     | -                    | The folic acid group had:  
  - more multiple pregnancies (3.8% compared with 2.7%, $P < 0.05$) and  
  - girls (50.1% compared with 48.1%) than did the trace mineral group (the difference was not statistically significant ($P = 0.18$).  
A significant excess of LBW infants among  
  - folic acid-supplemented subjects (5.8%) compared with  
  - Trace mineral group (4.2%) ($P < 0.05$).  
Among singleton pregnancies, rate of LBW was:  
  - 4.3% (folic acid group)  
  - 3.5% (trace mineral group) ($P = 0.17$).                                                                                                                     |
During pregnancy, processes depend of folic acid concentration include the increased erythrocytes mass, expanding of the uterus, placental and fetal growth. Serum folate is a sensitive indicator of the folate level available for replication of cells with a high rate of transformation[7]. A metabolic effect of folate deficiency is the increased homocysteine levels. Hyperhomocysteinemia may also occur due to folic acid deficiency when the dietary intake of folic acid is decreased. In other cases, certain genetic factors or interactions between genes and the environment can increase the folate metabolic demand[8-13].

Various observational studies on the levels of folate during pregnancy suggest a potential significant benefit of adequate folate status on fetal growth and pregnancy[12].

The folic acid has an important role in DNA synthesis and cell replication suggesting that its deficit could influence the length of pregnancy and the fetal growth[14]. Folate deficiency also interferes with maternal erythropoiesis, with the uterus and mammary gland growth and the growth of the placenta[15].

All studies have shown that decreased intake of folic acid from food or supplements was associated with maternal characteristics reflecting a poor nutritional status, including a low energy intake, inadequate pregnancy growth and increased incidence of macrocytic anemia upon entry into the prenatal care. Low intake of folate (<240 ng/day) was associated with a three times higher risk of giving birth to infants with low birth weight or premature birth, after being checked a number of other factors involved like maternal age, parity, smoking, ethnicity, energy and other nutrients (i.e. iron, zinc, vitamins) intake.

Iron

Iron is another micronutrient that is mobilized from the maternal stores during pregnancy, iron reserves tend to remain low several months after birth[16]. Iron-deficiency anemia is a common problem especially among teenage pregnant women[17] and it is often associated with premature birth and low birth weight. Excessive rate of premature births in women with a short interval between births can be caused by the insufficient deposits repletion after a previous pregnancy or during the growth increased needs in case of adolescents[16].

Iron-deficiency anemia is widespread globally, being estimated at 40-50% in women of reproductive age. Previous studies brought inconclusive evidence regarding the association between maternal iron deficiency anemia and intrauterine growth restriction. There are several plausible biological mechanisms linking maternal anemia to growth restriction. Low levels of hemoglobin restrict the oxygen circulation, leading to a chronic hypoxia thus creating a propitious environment for subsequent oxidative stress that can cause fetal growth restriction. Another possible mechanism of involvement of maternal anemia is the increased production of the norepinephrine stimulated by low levels of iron, which subsequently leads to an increase in the level of corticotropin-releasing hormone, apparently involved in limiting the fetal growth[18].

Literature remains inconclusive regarding the association of maternal iron deficiency anemia and the maternal and fetal mortality and morbidity. A meta-analysis conducted by Stoltzfus et al. estimated a 28% lower risk of perinatal mortality with each rise of 10 g/L in hemoglobin level [RR = 0.72 (95% CI: 0.62-0.89)][18,20]. However, Zhang Q et al. did not find any relationship between the two, in a large study conducted in 2009 on a prospective cohort of 163,313 live births[21]. Numerous studies have reported a relationship of „U” shape between maternal hemoglobin and premature birth or the birth of fetuses with low birth weight[22]. Another meta-analysis carried out by Xiong et al. revealed a significant association between anemia, determined in the first 2 trimesters of pregnancy and the risk of preterm birth [OR = 1.32 (95% CI: 1.01-1.74)] but did not find any link between hemoglobin level <100-110 g/L and fetal growth restriction. However, the meta-analysis included only 3 studies[23].

Zinc

The zinc deficiency in pregnant laboratory animals leads to fetal growth limitation and if it is severe, it may even have teratogenic effects. Although human studies are not numerous, similar results were observed in women with low zinc reserves. It seems that severe zinc deficiency has dangerous effects on pregnancy outcome.

The first evaluation of the maternal zinc status was reported by Jameson in 1976[24]. He conducted a study on 316 pregnant women and found that 60% of women who gave birth to fetuses with various congenital anomalies had low serum zinc levels in the first trimester. There have been several studies conducted in order to evaluate the relationship between maternal zinc status and fetal weight at birth. Because the birth weight is a continuous variable, this can be measured in smaller batches then other variables such as pregnancy induced hypertension, maternal hemorrhage or congenital anomalies. Between 1977 and 1994, it were published a total of 41 studies regarding the relationship between zinc status and birth weight. They were reviewed by Tamura and Goldberg, seven of the studies reporting a significant relationship between maternal zinc status and incidence of intrauterine fetal growth restriction[24,25].

Vitamin D

Vitamin D deficiency continues to be a major public health problem, especially among women of reproductive age, showing an upward trend of the deficit rates in the recent years[44]. Vitamin D is unique among the essential micronutrients, which can be produced by the body in the subcutaneous tissue under the influence of ultraviolet rays. Vitamin D receptors have been identified in tissues spread throughout the body, allowing a wide range of parts to form the biologically active hormone
Table 2 Maternal zinc status determinants during pregnancy

<table>
<thead>
<tr>
<th>Investigator</th>
<th>Location</th>
<th>Year</th>
<th>Number of subjects</th>
<th>Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crosby et al. (27)</td>
<td>United States</td>
<td>1977</td>
<td>182</td>
<td>Mid pregnancy plasma Zn level correlated with birth weight</td>
</tr>
<tr>
<td>Atinmo et al. (28)</td>
<td>Nigeria</td>
<td>1980</td>
<td>50</td>
<td>Plasma Zn level correlated with birth weight</td>
</tr>
<tr>
<td>Meadows et al. (29)</td>
<td>United Kingdom</td>
<td>1981</td>
<td>238</td>
<td>Leukocyte Zn level decreased in mothers with small for gestational age infants</td>
</tr>
<tr>
<td>Meadows et al. (30)</td>
<td>United Kingdom</td>
<td>1983</td>
<td>90</td>
<td>Leukocyte Zn level decreased in mothers with intrauterine growth restriction infants</td>
</tr>
<tr>
<td>Patrick et al. (31)</td>
<td>Canada</td>
<td>1982</td>
<td>13</td>
<td>Leukocyte Zn level correlated with birth weight</td>
</tr>
<tr>
<td>Ghosh et al. (32)</td>
<td>Hong Kong</td>
<td>1985</td>
<td>437</td>
<td>Birth weight positively correlated with serum Zn level and negatively correlated with hair Zn level</td>
</tr>
<tr>
<td>Simmer and Thompson (33)</td>
<td>United Kingdom</td>
<td>1985</td>
<td>79</td>
<td>Leukocyte Zn level decreased in mothers with small for gestational age infants</td>
</tr>
<tr>
<td>Mameesh et al. (34)</td>
<td>Iran</td>
<td>1985</td>
<td>57</td>
<td>Serum Zn level correlated with birth weight, length, and head circumference</td>
</tr>
<tr>
<td>Wells et al. (35)</td>
<td>United Kingdom</td>
<td>1987</td>
<td>70</td>
<td>Leukocyte Zn concentrations predicted LBW</td>
</tr>
<tr>
<td>Singh et al. (36)</td>
<td>India</td>
<td>1987</td>
<td>92</td>
<td>Decreased serum Zn level correlated with reduced birth weight and number of LBW infants</td>
</tr>
<tr>
<td>Higashi et al. (37)</td>
<td>Japan</td>
<td>1988</td>
<td>228</td>
<td>Decreased level of serum Zn in 3rd trimester associated with more LBW infants</td>
</tr>
<tr>
<td>Mbofung and Subbarav (38)</td>
<td>Nigeria</td>
<td>1990</td>
<td>22</td>
<td>Placental Zn level correlated with birth weight</td>
</tr>
<tr>
<td>Neggers et al. (39)</td>
<td>United States</td>
<td>1990</td>
<td>476</td>
<td>Serum Zn level correlated with adjusted birth weights</td>
</tr>
<tr>
<td>Yosodhara et al. (40)</td>
<td>India</td>
<td>1991</td>
<td>176</td>
<td>Decreased serum Zn level and higher cord blood Zn level associated with larger birth weights</td>
</tr>
<tr>
<td>Jeswani and Vani (41)</td>
<td>India</td>
<td>1991</td>
<td>60</td>
<td>Decreased cord blood Zn level in small for gestational age and preterm infants</td>
</tr>
<tr>
<td>Speich et al. (42)</td>
<td>France</td>
<td>1992</td>
<td>66</td>
<td>Erythrocyte and plasma Zn levels predicted birth weight</td>
</tr>
<tr>
<td>Kirksey et al. (43)</td>
<td>Egypt</td>
<td>1994</td>
<td>29</td>
<td>Serum Zn level in 2nd trimester - 20% of variance in birth weight</td>
</tr>
</tbody>
</table>
1,25-dihydroxyvitamin D 25(OH)D. Maternal vitamin D deficiency is associated with a wide range of pregnancy complications including premature birth, preeclampsia and intrauterine growth restriction (40).

Several observational studies have established a connection between serum levels of 25(OH)D and the risk of intrauterine growth restriction in obstetrics. Most of the literature is based on observational studies, but determining the causality of this association can only be achieved through randomized clinical trials (41).

Circulating concentrations of other nutrients like vitamin A, vitamin B6 and vitamin B12 also decrease during pregnancy, but these micronutrient concentrations return to normal shortly after birth, suggesting that is less likely that they will be involved in the negative, maternal and fetal, maternal depletion syndrome.

Conclusions

Short interval between births or early occurrence of pregnancy (less than two years since menarche) increases the risk of premature birth or the birth of fetuses with intrauterine growth restriction. MDS has been proposed as a possible cause for these pathologies. Maternal exhaustion, protein-energy, resulting from short intervals between pregnancies or early pregnancy leads to an alteration of maternal nutritional status at conception and also to a modified prognosis of pregnancy outcome. Sharing protein deposits and available energy between maternal and fetal dyad is influenced by the initial grade of the maternal malnutrition. The population at risk for MDS may benefit of supplementation of food and micronutrients during pregnancy and also between pregnancies.

References