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Pregnancy: Metabolic Adaptations and Nutritional Requirements

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Introduction

Pregnancy is a dynamic anabolic state with increased nutritional requirements to support growth and metabolism of maternal and fetal tissues, nutrient storage in the fetus, and preparation of maternal tissues for lactation. Although these additional nutrient needs may be met by increased maternal dietary intake, part of the increased demands is met by complex physiological adjustments and changes in nutrient metabolism that evolve continuously throughout pregnancy according to the changing requirements at different stages of gestation.

Metabolic adjustments depend on each nutrient and may include uptake and accretion in new tissues, deposition in maternal stores, redistribution among tissues, and increased turnover or rate of metabolism. For certain nutrients, physiological adjustments favor a more efficient utilization of the nutrient from the diet by increased intestinal absorption and/or reduced excretion through urine or the gastrointestinal tract. For each nutrient, more than one adjustment may be acting (Table 1).

Metabolic and physiological adjustments during pregnancy respond to the hormonal changes during gestation, the fetal nutrient demands, and the maternal nutrient supply through diet or mobilization of nutrient reserves. Adjustments vary widely between women depending on several factors such as lifestyle behavior, genetic background, habitual diet, use of supplements, and prepregnancy nutritional status.

Within the physiological capacity of adaptation, the developing fetus is protected from nutrient deficiency or excess in the maternal diet. However, a limit in the capacity for adjustment of the maternal organism during pregnancy may be reached depending on complex factors and interactions not yet fully studied. Limited access to a variety of foods, intense physical activity, adolescent motherhood, poor nutritional status prior to pregnancy, and environmental exposure to toxic substances (i.e., mercury, lead, pesticides, and dioxins) or infectious agents (i.e., foodborne pathogens such as listeria as well as salmonella, tuberculosis, malaria, intestinal parasites, and HIV) impose additional stress on the physiological capacity of adaptation during pregnancy. When this capacity is exceeded, fetal growth and development and pregnancy outcome may be impaired. If undernutrition or excess of certain nutrients affects the fetus, there may be short-term and lifelong adverse health effects.

Changes in Maternal Physiology and Metabolism during Pregnancy

Hormonal Changes

Changes in maternal hormone secretion during pregnancy contribute to maintain the pregnancy state and to modify the utilization of nutrients (especially carbohydrates, fat, and protein) in order to stimulate maternal tissues to make greater use of lipids as energy-yielding substrates and to increase the availability of glucose, amino acids, and micronutrients for fetal growth. Hormonal changes also contribute to ensure that maternal lean tissues are conserved and spared for providing energy or amino acids for the fetus.

Soon after implantation, the corpus luteum and the placenta secrete hormones to ensure the maintenance of pregnancy and to influence metabolism in preparation for the developing fetus. Serum human chorionic gonadotropin increases rapidly during the first 2 weeks of gestation, reaches a peak at about 8 weeks, and then gradually declines but remains elevated until delivery. Serum human placental lactogen increases continuously throughout pregnancy parallel to the increase in placental mass, reaching a concentration at term about 20 times higher than before conception. This hormone affects the metabolism of carbohydrates and lipids, antagonizing the action of maternal insulin and stimulating maternal lipolysis, thus contributing to direct energy-yielding substrates to the fetus.

The corticotropin-releasing hormone (CRH) is produced by the placenta by 8 weeks after conception but remains usually undetectable in maternal serum until the last trimester of pregnancy when there is a gradual increase to about 50-fold. Placental CRH stimulates the production of fetal cortisol that in turn blocks the inhibitory effect of progesterone on placental synthesis of CRH and fetal cortisol. Maternal serum CRH is increased in preeclampsia and by maternal stress and infections and is associated with higher risk of preterm delivery.

Progesterone and estrogens serum concentrations rise progressively throughout pregnancy increasing over fivefold and tenfold, respectively, from 10 to 40 weeks of pregnancy. After 8–10 weeks of gestation, the main source of these hormones is the placenta although estrogens are also originated in the fetus and other maternal tissues. Progesterone stimulates maternal respiration and relaxes smooth muscle contributing to the atony of the uterus and the urinary and gastrointestinal tracts.

Table 1 Metabolic and physiological adaptations affecting nutrition utilization during pregnancy

<table>
<thead>
<tr>
<th>Adaptation</th>
<th>Example of nutrients affected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased tissue uptake</td>
<td>Amino acids, iodine, folate, iron</td>
</tr>
<tr>
<td>Redistribution among tissues</td>
<td>Zinc, iron, calcium, vitamin A, vitamin D,</td>
</tr>
<tr>
<td>Increased turnover/metabolism</td>
<td>Protein (amino acids), zinc, folate, calcium,</td>
</tr>
<tr>
<td>Increased maternal stores</td>
<td>iodine, vitamin D</td>
</tr>
<tr>
<td>Increased intestinal absorption</td>
<td>Fat</td>
</tr>
<tr>
<td>Reduced endogenous losses</td>
<td>Iron, calcium, zinc</td>
</tr>
<tr>
<td></td>
<td>Protein (nitrogen), zinc</td>
</tr>
</tbody>
</table>
Estrogens (estradiol, estrone, and estriol) influence carbohydrate and lipid metabolism, increase the rate of maternal bone turnover, stimulate the conversion of maternal pituitary somatotroph cells into prolactin-secreting cells (in preparation for lactation), and help prepare the uterine muscle cells for delivery.

**Blood Volume and Composition and Other Physiological Changes**

As gestation progresses, several maternal organ systems adapt to the changing needs. The size of the heart increases by about 12% and cardiac output increases by about 40% in response to the increased oxygen demands. Although lung capacity is reduced by about 5% (due to elevation of the diaphragm by the enlarged uterus), alveolar ventilation increases as pregnancy progresses resulting in a more efficient gas exchange. Gastrointestinal motility is reduced, and consequently, transit time is longer allowing for increased nutrient absorption. The kidneys increase slightly in size, and renal plasma flow and glomerular filtration rate increase by about 75% and 50%, respectively, resulting in an increased urinary excretion not only of metabolic end products but also of certain nutrients. Maternal blood volume gradually expands with a modified cell and plasma composition that serves to increase the tissue supply of oxygen and nutrients and also to prepare for blood loss at delivery.

Compared to the nonpregnant state, total blood volume increases 35–40% during pregnancy, mainly by expansion of plasma volume (45–50%) and proportionally less expansion of red cell mass (15–20%). As a result of this ‘hemodilution of pregnancy,’ hemoglobin concentration and hematocrit values decrease especially at midpregnancy (20–30 weeks), when there is the largest increase in plasma volume, but increase slightly again in the third trimester. For these reasons, the recommended hemoglobin and hematocrit cutoff values for screening for anemia in pregnant women are trimester-specific and lower than for nonpregnant women.

Plasma volume starts to increase at 6–8 weeks of gestation, expands rapidly up to 30–34 weeks, and tends to plateau thereafter. By the end of pregnancy, the total increase in plasma volume is about 1500 ml. Red cell mass increases by about 200–250 ml during pregnancy driven by the increase in maternal erythropoietin production. The increase in red blood cell mass is greater with the use of iron supplements. Total white blood cell count increases during pregnancy although within the normal range. Neutrophils are the major type of leucocytes increased, possibly due to reduced apoptosis, and have increased oxidative metabolism. Monocyte-to-lymphocyte ratio markedly increases during pregnancy. Platelet count decreases particularly during the third trimester, a condition named ‘gestational thrombocytopenia.’

Plasma concentration of total protein, particularly albumin and γ-globulin, most amino acids, some minerals, and water-soluble vitamins, decreases during pregnancy due in part to hemodilution, increased glomerular filtration rate, and/or changes in turnover or metabolism. In contrast, plasma concentration of α1-, α2-, and β-globulins, lipid fractions (particularly triacylglycerol and also VLDL, LDL, and HDL), and fat-soluble vitamins usually increases during pregnancy. Most of these changes occur during the first 10 weeks of gestation.

For those nutrients that have a decreased concentration during pregnancy, reduction is much less than the 40-fold increase in plasma volume. Therefore, the total amount of energy-yielding substrates, vitamins, and minerals in the maternal circulation increases during pregnancy.

**Fetal Demands**

The demand for nutrients gradually evolves during gestation both in total amount and in particular nutrients required. Three main physiological stages of fetal development are usually described during pregnancy: implantation, organogenesis, and growth. Animal studies indicate that the presence or absence of certain nutrients particularly at the early stages of gestation is critical for normal development. The total amount of nutrients needed becomes critical during the second half of gestation when most of the fetal growth occurs.

During implantation and up to 2 weeks of gestation, the fertilized ovum embeds in the uterine wall and receives nutrients directly provided by the uterine secretions. At this stage, there are specific nutritional needs, but quantitative requirements are negligible.

During tissue differentiation and organogenesis, mostly occurring from 2 to 6 weeks of gestation, nutrients are provided from the maternal circulation. At this stage, lack or excess of certain nutrients can cause specific congenital abnormalities. For example, evidence from animal studies indicates that folate, vitamin B12, vitamin A, and niacin deficiencies cause defects in the central nervous system; vitamin B6 and manganese deficiencies impair neuromotor development; riboflavin deficiency affects the formation of the skeleton; and zinc deficiency or excess of vitamin A causes multiple organ malformations and embryonic death. In contrast, much less is known about the effects of specific nutrient deficiencies on organogenesis in humans. Only folate has been clearly recognized as a critical micronutrient for the prevention of neural tube defects.

During the remaining 30–32 weeks of pregnancy, most fetal growth occurs, initially by hyperplasia (rapid increase in the number of cells), later by simultaneous increase in cell size, and finally by hypertrophy (cells growing mostly in size). Critical nutrients for cell division are folate, vitamin B12, and zinc, while sufficient supply of amino acids, vitamin B6, and glucose is required for cell growth. During this rapid growth period, nutrients are delivered from mother to fetus through the placenta. Some nutrients are transferred across the placenta by simple diffusion (e.g., free fatty acids, cholesterol, and fat-soluble vitamins) whereas others by facilitated (carrier-mediated) diffusion (e.g., glucose) or active transport (e.g., amino acids, most water-soluble vitamins, calcium, iron, and zinc). In the latter case, nutrient concentrations are usually higher in fetal than in maternal circulation. Similarly to the phase of organogenesis, little is known on the effect of specific nutrient deficiencies during fetal growth in humans, although there is strong evidence that nutritional deficiency during this phase causes intrauterine growth retardation and low birth weight and increased risk of impaired immune function. However, inadequate nutrition at this stage will not cause developmental abnormalities.
Changes in Maternal Body Composition and Weight Gain

Gestational weight gain usually follows a sigmoid curve. Approximately 5% of the total weight gain occurs during the first trimester of pregnancy and the remainder 95% is gradually gained at an average rate of about 0.45 kg per week during the second trimester and 0.40 kg per week during the third trimester. The average total weight gain in full-term healthy primigravidas is about 12 kg although the amount of weight gain varies widely among women. Total weight gain is inversely related to maternal prepregnancy body mass index. Mean total weight gain during a full-term pregnancy ranges between 10 and 16.7 kg in normal weight adult women and is lower than 11 kg in overweight and obese women. Higher total weight gains normally occur in adolescent women, in thin women, and in twin or multiple pregnancies. Current recommendations of weight gain during pregnancy are set according to prepregnancy maternal weight for height categories. A normal weight gain during pregnancy is more likely to be associated with optimal reproductive outcome, fetal and infant growth, and development.

Two major components contribute to weight gain during pregnancy: the products of conception (fetus, amniotic fluid, and placenta) and the accretion of maternal tissues (expansion of blood volume and extracellular fluid, enlargement of uterus and mammary glands, and increased adipose tissue). Of the total weight gain, the fetus accounts for ~27%, amniotic fluid 6%, and the placenta 5%. Maternal tissue accretion contributes mainly with fat deposition (average 27%, although highly variable between women). The majority of the maternal fat deposited during pregnancy is subcutaneous. In healthy pregnant women, fat appears to be deposited mainly in the hips, back, and upper thighs. This pattern of fat deposition appears to be unique of pregnancy. Fat deposition occurs mainly during the first 30 weeks of gestation under progesterone stimulation. This early fat deposit acts as an energy store for late pregnancy and during lactation. The increase in fat-free mass during pregnancy represents mainly an increase in body water. The amount and pattern of gestational weight gain are strongly influenced by changes in maternal physiology and metabolism and by placental metabolism.

Nutritional Requirements during Pregnancy

Approaches for Estimating Nutritional Needs during Pregnancy

Assessment of nutritional requirements during pregnancy is challenging due to the continuous alteration in nutrient metabolism and turnover that affect concentrations in tissues and fluids and the gradual shift in the efficiency of nutrient utilization that contributes to attain homeostasis.

For most nutrients, including energy, protein, and minerals, requirements during pregnancy have been assessed using the factorial approach. This involves estimates of the total amount of the extra energy and nutrient accumulated in the mother (blood, breast, uterus, and adipose tissue) and the products of conception (fetus, placenta, and amniotic fluid) during the whole pregnancy, above the nonpregnant nonlactating state, and correction by a factor to cover for the inefficient nutrient use for tissue growth. This approach relies on indirect data and does not allow for estimates of requirements by gestational stage.

For protein and some minerals, balance studies have been used to assess nutrient retention at different stages during pregnancy. In these studies, measurement of the nutrient intake and losses from the body is done as precisely as possible during a period of time (in general during 3 weeks), and the difference is taken to indicate net retention (or loss) during the assessed period. Because not all possible sources of body losses are measured, balance studies tend to overestimate intake and underestimate losses. Also, because balance studies are carried out over short periods of time at specific stages of pregnancy, results cannot be extrapolated to the entire pregnancy.

For a few nutrients, such as folate, evidence has been obtained from experimental human studies on the amount of intake needed to attain adequate tissue concentrations (e.g., erythrocytes) and nutrient-dependent functions (e.g., enzyme activity). For many vitamins and minerals, observational studies and intervention trials have related maternal intakes to pregnancy outcomes.

Recommended nutrient intakes during pregnancy are set by expert scientific committees of different countries or organizations, based on the interpretation of the available evidence on nutritional requirements during pregnancy. The most widely used set of nutrient recommendations are those developed by the Food and Agriculture Organization/World Health Organization (FAO/WHO) and by the Institute of Medicine (IOM) for the United States and Canada (Dietary Reference Intakes, DRIs). The percent increase of recommended daily nutrient intake during pregnancy over the nonpregnant nonlactating state differs between nutrients and may differ between scientific organizations (Figure 1).

Specific Nutrient Metabolism and Requirements

Energy

Theoretical estimations of the overall energy cost of pregnancy in well-nourished women have been done based on the contribution of three main components: (1) the energy deposited as new tissue in the products of conception (placenta, uterus, amniotic fluid, fetus, mammary glands, and expansion of blood volume), approximate cost 5000 kcal; (2) the energy deposited in fat, approximate cost 36000 kcal; and (3) the energy required to maintain the new tissues, approximate cost 36000 kcal.

Several longitudinal studies have measured changes in basal metabolic rate (BMR), energy expenditure, and energy deposition during pregnancy in different populations, thus providing experimental evidence for estimating requirements. These studies have shown that energy requirements during pregnancy have a large variability within individuals and between populations and are influenced by several factors, including prepregnancy body weight, body mass index and body fat, maternal age, BMR, and level of physical activity.

Estimated energy requirements (EERs) during pregnancy by the FAO/WHO have been based on multiples of BMR and the level of physical activity. For each trimester of pregnancy, studies indicate that the average increase in BMR is 5%, 10%, and 25%, and the average increase in total energy expenditure (TEE) is 1%, 6%, and 17%, respectively, over prepregnancy values. EERs during pregnancy have been also derived from studies using the double-labeled water technique. EER is
estimated as the sum of TEE of the nonpregnant woman plus the estimated median change in TEE of 8 kcal per gestational week, plus 180 kcal per day for energy deposition in maternal and fetal tissues during pregnancy. Taken together, these approaches translate into recommended increases of energy intake of 340 kcal per day in the second trimester and 452 kcal per day in the third trimester.

The capacity for physiological adaptation in energy metabolism during pregnancy is complex and highly variable. Adequate maternal weight gain and fetal growth are good indicators that maternal energy intake is adequately meeting energy requirements during pregnancy.

Protein

Adaptation in maternal nitrogen metabolism starts early during pregnancy and favors nitrogen conservation and protein deposition in the fetus and maternal tissues. There is a shift in the partitioning of amino acids for oxidation and protein synthesis favoring the latter. Maternal urea synthesis is reduced, therefore, with less utilization of amino acids as energy substrates. The rate of transamination of branched-chain amino acid is also reduced. During the second half of pregnancy, insulin secretion increases associated with greater insulin resistance. Thus, there is an increase in circulating glucose available for transfer to the fetus that indirectly spares amino acids for protein synthesis. Isotopic studies indicate that protein turnover increases during pregnancy and that the increase in protein synthesis is about 25% by late pregnancy compared to the nonpregnant state. There is evidence that metabolic changes in amino acid utilization during pregnancy may be limited by micronutrient status.

Using the factorial approach, the estimated total protein accretion during a full-term normal pregnancy is 925 g. Most of protein is accrued in the fetus (42%) and also in the uterus (17%), blood (14%), placenta (10%), and mammary tissue (8%). Balance studies in women before and during pregnancy indicate that nitrogen retention increases gradually during gestation particularly from the second to third trimesters. The increase in nitrogen retention during pregnancy is due to a reduction in urinary nitrogen excretion, with no change in fecal and integumental losses.

The recommended increase in protein allowance during pregnancy over the nonpregnant requirement varies (±25 g per day, the United States and Canada; ±6 g per day, the United Kingdom and FAO/WHO). Most pregnant women worldwide consume at least the recommended intake. Moreover, there is little evidence that healthy women already consuming an adequate amount of protein need to consume more during pregnancy.

Iron

Pregnancy has a marked impact on iron metabolism due to the expansion of maternal erythrocyte mass that is proportional to the increased need for oxygen transport. Besides the iron need for the additional synthesis of hemoglobin (450 mg), tissue formation (placenta, 50 mg), and restitution of blood loss during delivery (250 mg), there is a need of 200–400 mg to be transferred from mother to fetus in order to ensure infant iron stores during the first months of life. Therefore, it is estimated that iron requirements over the course of pregnancy may reach 1000 mg, not equally distributed over its duration. The average requirement for iron absorption increases from

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**Figure 1** Percent changes in recommended nutrient intakes during pregnancy over the nonpregnant state. The FAO/WHO recommends taking iron supplements up to 100 mg to all pregnant women. For the FAO/WHO, percent change over nonpregnant nonlactating women was calculated considering the average recommended intake throughout pregnancy.
about 0.8 mg per day at early pregnancy to about 3–8 mg per day during the third trimester.

Maternal–fetal transfer of iron is especially increased during the last two-thirds of pregnancy and involves serum iron binding to transferrin receptors in placenta. Maternal serum transferrin increases almost twofold over nonpregnant values during pregnancy, possibly to facilitate iron uptake by the placenta. Hepcidin is a systemic regulator of iron metabolism that controls the efflux of iron into plasma through ferroportin regulation and therefore may have an important role on iron homeostasis during pregnancy. Liver production of hepcidin is simultaneously regulated by circulating and stored iron, erythropoietic activity, and inflammation. The limited evidence from studies during pregnancy indicates lower concentrations of hepcidin compared to the nonpregnant state and also a decrease in circulating hepcidin as pregnancy progresses with the lowest levels observed in the third trimester.

During the initial phase of pregnancy, cessation of menstrual iron losses contributes to meeting iron requirements and preserves maternal iron. Thereafter, mobilization of maternal iron stores is stimulated and theoretically could make a significant contribution. During the second and third trimesters, there is also a marked increment in the efficiency of intestinal iron absorption with an average increase of two- to threefold, or more, over nonpregnant values. It is estimated that women would need an iron store of ~500 mg at conception in order to ensure meeting the iron demands of pregnancy together with the iron supplied in the diet. However, almost half of women worldwide enter pregnancy with no iron reserves, therefore requiring increased iron intakes. The IOM recommends an increase of iron intake from 18 mg per day for nonpregnant women to 27 mg per day during pregnancy, a level difficult to achieve from food intake, therefore requiring the use of iron supplements. The WHO recommends iron supplementation 30–60 mg per day of elemental iron during pregnancy. However, recent studies indicate that the benefits of iron supplementation on maternal and infant health are inconsistent across populations and may have side effects such as reduced absorption of nonheme iron and other minerals and increased oxidative stress. Therefore, iron supplements during pregnancy may not be universally recommended.

**Zinc**

The additional zinc requirement during pregnancy estimated by the factorial approach is about 100 mg, more than half accrued in the fetus (57%), and the remainder in the uterus (24%), placenta (6.5%), expanded blood volume (6.5%), mammary tissue (5%), and amniotic fluid (<1%). This requirement corresponds to about 5–7% of the total body zinc in a healthy nonpregnant adult woman.

There is a physiological decline of 15–35% in plasma zinc concentration as a result of hemodilution, increased urinary zinc excretion, increased zinc uptake by maternal tissues, and transfer to fetus. However, the total amount of circulating zinc rises due to the increased blood volume and the increased (10–15%) erythrocyte zinc concentration. Transfer of sufficient zinc to the fetus is dependent on the maternal serum zinc concentrations. It appears that placenta zinc uptake adapts to fetal needs, being higher in periods of rapid growth and also when maternal zinc status is low. The efficiency of intestinal zinc absorption increases from early to late pregnancy, especially when habitual zinc intake is low. Renal zinc conservation is an additional adaptation in pregnant women accustomed to low-zinc diets.

It is estimated that an additional zinc intake of 2–10 mg per day is needed during pregnancy, depending on zinc bioavailability in the diet (FAO/WHO). The IOM recommends an additional 3 mg daily for both adult (from 8 to 11 mg per day) and adolescent (from 9 to 12 mg per day) pregnant women.

**Calcium**

During pregnancy, there is a marked increase in maternal calcium demand for fetal skeletal mineralization. Fetal calcium accumulation rate varies from about 2–3 mg per day in the first trimester, 50 mg per day at midgestation, to 250–300 mg per day in the third trimester. This implies in a total fetal calcium accrual of 20–30 g.

The additional calcium is obtained primarily from increased efficiency of intestinal absorption that usually doubles during pregnancy and may be more efficient when maternal calcium intake is low. Concomitantly, there is an increased expression of enterocyte Ca-binding protein. The increase in calcium absorption starts early in pregnancy and therefore precedes fetal calcium needs for bone growth. This is consistent with some calcium storage on maternal skeleton for future mobilization. Bone turnover is increased during pregnancy, as indicated by several markers of bone resorption and bone formation, especially during the last trimester. Although bone turnover may contribute to maintaining calcium dynamics, it results in very little or no net calcium loss from bones during this period. Urinary calcium excretion is increased as a consequence of the higher intestinal uptake and glomerular filtration rate. When corrected by creatinine clearance, fasting calcium excretion is normal or decreased.

Evidence from different studies indicates that the physiological adaptations for providing calcium to the fetus are largely independent of maternal calcium intake. Therefore, recommended calcium intakes during pregnancy are not increased over those for nonpregnant nonlactating women (IOM and FAO/WHO). However, special consideration should be given to adolescent mothers and women habitually consuming very low-calcium diets.

**Iodine**

Physiological alterations in thyroid function include the requirement of an increased production of thyroid hormone that, in turn, depends on thyroid integrity and adequate availability of dietary iodine. Regulation of thyroid function during pregnancy includes a marked increase in serum thyroxine-binding globulin, increased renal clearance of iodine, and stimulation of the thyroid gland by human chorionic gonadotropin. Iodide (the reduced form of iodine) pool of the body is constituted by iodide from diet and from catabolism of thyroid hormones. In the nonpregnant state, and conditions of adequate intake (150 μg per day), this pool is in dynamic equilibrium with the thyroid gland and kidneys. During pregnancy, renal iodide clearance increases 30–50% and iodide requirement for thyroid hormone production increases by 50%, from the first weeks of gestation. Later in gestation, iodide is transferred from the maternal circulation to the fetus by placenta.
Increased iodide uptake and glandular hypertrophy are the main mechanisms by which the thyroid gland adapts to increased requirement and/or decreased supply. In situations of iodine deficiency, the thyroid gland is able to adjust hormone synthesis to the increased needs reaching a steady state, as a physiological adaptation of pregnancy. In contrast, with restricted iodine supply, pregnancy may lead to an excessive glandular stimulation. Depending on severity of iodine deficiency, pathological alterations may occur resulting in different degrees of impairment in fetal neural system development.

Iodine intake recommendation is based on estimated daily thyroid iodine uptake of ~75 μg per day by the fetus and the thyroid iodine content of the newborn, together with data on iodine balance during pregnancy and studies of iodine supplementation that prevent increased thyroid size. Compared to the nonpregnant state, both the IOM and the FAO/WHO recommend an additional intake of 70 μg per day during pregnancy.

**Folate**
Pregnant women have a high folate requirement as a result of increased folate utilization, catabolism, and urinary excretion. 5-Methyltetrahydrofolate (5-MTHF) is the biologically active folate metabolite that affects DNA synthesis, amino acid metabolism, and methylation of genes, proteins, and lipids via S-adenosylmethionine-mediated one-carbon transfer reactions.

Circulating 5-MTHF can be transported into cells either by the reduced folate carrier, a facilitative anion-exchange carrier, or by an endocytic process mediated by folate receptors. Folate receptors are expressed in the neural folds during the neurulation phase of embryonic development, demonstrating the importance of folate uptake for proper neural tube development. Adequate folate nutrition, especially in the periconceptional period, is thus necessary to prevent neural tube defects besides other congenital defects.

Serum 5-MTHF is the main determinant of placental transfer to the fetus. A critical concentration >7 nmol l⁻¹ appears to ensure adequate folate fetal transfer. Serum folate concentrations decline in pregnant women as a physiological response to pregnancy, although mechanisms have not been fully elucidated. Erythrocyte folate concentration is an indicator of long-term folate status and tissue stores during pregnancy. A physiological decline in erythrocyte folate concentration is observed at early pregnancy followed by a slight increase at midpregnancy.

The IOM and FAO/WHO recommend an intake of 400 μg dietary folate equivalents (DFEs) per day for all women of reproductive age. This is based on strong evidence that ensuring an adequate folate intake for women who are capable of becoming pregnant contributes to reduce the risk of neural tube defect occurrence. During pregnancy, both organizations recommend an additional 200 μg of DFEs daily. In the United Kingdom, recommendations are substantially lower, with an additional 100 μg per day of folate during pregnancy over the 200 μg per day recommended for nonpregnant, nonlactating women.

**Vitamin B₁₂**
Vitamin B₁₂, or cobalamin, is a crucial nutrient for fetal development due to its role in DNA synthesis. Maternal serum cobalamin concentrations begin to decline in the first trimester of pregnancy, more than would be expected from hemodilution alone, and continue to decrease to about half the nonpregnant concentrations until the end of second trimester. Despite this decrease, serum homocysteine is not elevated as would be expected in vitamin B₁₂ deficiency. A concomitant increase in erythrocyte cobalamin and decrease in saturation of cobalamin-binding serum proteins suggest a redistribution of cobalamin during pregnancy. Transcobalamin I and transcobalamin III increase during the second and third trimesters, and transcobalamin II, considered the best biomarker of active or available B₁₂, increases sharply in the third trimester to about one-third of nonpregnant values.

During pregnancy, absorption of vitamin B₁₂ remains unchanged or increased due to an increase in the number of intrinsic factor–B₁₂ receptors in response to placental lactogen. Newly absorbed vitamin B₁₂ is preferably concentrated in the placenta and then transferred to the fetus down a concentration gradient so that serum vitamin B₁₂ concentrations in the newborn are about twice the level found in mother, although correlated with each other. Maternal liver stores contribute less to the placental–fetal transference of vitamin B₁₂.

Total fetal vitamin B₁₂ requirement during pregnancy is estimated to be 50 μg, while maternal stores may reach >1000 μg in healthy women with mixed diets. The estimated deposition rate of vitamin B₁₂ in fetal liver during intrauterine life is 0.2 μg per day and is the basis for current recommendations. An intake of 2.6 μg per day of vitamin B₁₂ is recommended by both the IOM and the FAO/WHO during pregnancy, corresponding to an 8% increase compared to the nonpregnant state. Meeting fetal demands may be difficult for pregnant women consuming diets restricted in animal food sources as in many developing regions of the world and in the case of vegetarians.

**Vitamin A**
During pregnancy, an extra amount of vitamin A is required for tissue growth and also to ensure fetal stores to be used after birth. Requirements are highest during the third trimester, when fetal growth is most rapid. The absence or excess of active vitamin A metabolites (isomers of retinoic acid) at critical periods of gestation can lead to abnormal development of the embryo and the placenta.

The major maternal circulating forms of vitamin A are retinol bound to retinol-binding protein and retinyl esters packaged in chylomicrons and their remnants. Changes in maternal status and/or dietary vitamin A intake affect these circulating retinoid levels and thus the amount of vitamin A available to cross the placenta. Maternal serum homeostatic mechanisms involving lecithin–retinol acyltransferase activity and binding proteins contribute to maintain fetal acquisition of vitamin A relatively stable over a wide range of maternal dietary vitamin A intake. Maternal serum retinol concentrations <0.7 μmol l⁻¹ and >3 μmol l⁻¹ indicate deficiency or excess, respectively.

In less developed countries, providing pregnant women with adequate amounts of vitamin A contributes to reduce maternal and infant mortality due to infection. In contrast, in developed countries, the potential adverse effects of excessive consumption of vitamin A associated with fetal malformation are the main concern. The risk of fetal abnormalities due to vitamin A toxicity is higher during the first trimester of
gestation and associated with excessive retinol (and not β-carotene) intake from supplements.

Vitamin A requirements during pregnancy are based on adequate fetal liver vitamin A content at birth, assuming that the liver contains approximately half the body’s vitamin A when liver stores are low, as in the case of newborns. Considering an efficiency of maternal vitamin A absorption of 70% and an estimated increased requirement of 50 μg per day during the last trimester, vitamin A DRI for pregnancy is increased by 10% over the nonpregnant state, totaling 770 μg RAE (retinol activity equivalents) per day. The recommended safe intake by the FAO/WHO is increased from 500 to 800 μg RE (retinol equivalents) per day.

**Vitamin D**

The main circulating form of vitamin D, 25-hydroxyvitamin D, is transferred from mother to fetus through the placenta in relatively small amounts that do not appear to cause maternal depletion. Serum concentration of 25-hydroxyvitamin D does not generally change during pregnancy, although there are physiological changes affecting both transport and metabolism of vitamin D by mechanisms not fully understood. Changes include increased circulating levels of vitamin D-binding protein and 1,25-dihydroxyvitamin D₃, the major active vitamin D metabolite.

Compared to prepregnancy state, 1,25-dihydroxyvitamin D serum concentration increases two- to threefold starting in the first trimester and reaching a maximum in the third trimester. Although this increase is mainly due to maternal synthesis by the renal 1α-hydroxylase, there is also contribution from increased placental and decidual 1α-hydroxylase activity. During pregnancy, parathyroid hormone (PTH)–related peptide (rather than PTH), which is produced in fetal parathyroid glands and placental tissues, could be a potential signal for placental synthesis of active vitamin D and consequently for placental calcium transfer. Although closely related, the increase in intestinal calcium absorption during pregnancy cannot be explained solely by the increased 1,25-dihydroxyvitamin D because intestinal calcium absorption doubles early in pregnancy, well before the increase in free 1,25-dihydroxyvitamin D concentrations late in pregnancy.

Given that the available evidence does not suggest that pregnant women are at increased risk of vitamin D deficiency compared with nonpregnant women, recommended intakes are not increased during pregnancy compared to the nonpregnant state [IOM and FAO/WHO]. However, recommended intakes of vitamin D (cholecalciferol) for nonpregnant women are set higher by the IOM (15 μg per day) than by the FAO/WHO (5 μg per day).

**Conclusion**

The complex physiological adjustments and changes in nutrient metabolism during pregnancy appear to be highly integrated for maintaining homeostasis and ensuring that fetal and maternal needs are met. Studies investigating these adjustments in different populations and under different conditions in relation to dietary intake have provided the basis for establishing nutritional requirements during pregnancy. However, much remains to be known on the interacting effects of factors such as nutritional status prior to pregnancy, maternal immaturity, habitual diet, physical activity, genetic background, and environmental exposure to toxic substances and infectious agents, on the capacity for physiological/metabolic adaptation during pregnancy. Understanding the limits of this capacity is crucial for warranting fetal and maternal health in the short and long term.

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**See also:** Calcium: Physiology; Dietary References: US; Energy Metabolism; Folic acid and Folates: Physiology and Health Effects; Food and Agriculture Organization of the United Nations; Hypovitaminosis A; Iodine: Physiology; Iron: Physiology of Iron; Pregnancy: Dietary Guidance for Pregnancy; Protein Quality and Amino Acids in Maternal and Child Nutrition and Health; Retinol: Physiology; World Health Organization; Zinc: Physiology and Health Effects.

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**Further Reading**


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**Relevant Websites**


http://www.iom.edu/ – Institute of Medicine of the National Academies.