Vitamin D has been a hot topic in the medical world for the last decade. The classical and non-classical pathways of this hormone affect calcium metabolism, the immune system, cell proliferation and differentiation, infection. Vitamin D insufficiency and deficiency among pregnant women is frequent in many populations over the world. Research indicates that the adequate vitamin D level in pregnancy is optimal for maternal, fetal, and child health. Vitamin D deficiency is prevalent in Ukraine. There are few data from Ukraine about the prevalence of hypovitaminosis D in pregnancy and in the newborn. Adverse health outcomes during pregnancy are preeclampsia, gestational diabetes mellitus, and caesarean section. Consequences in newborns are low birth weight, neonatal rickets, risk of neonatal hypocalcemia, asthma, and/or type 1 diabetes mellitus. Vitamin D deficiency during pregnancy is the origin of a host of future perils for a child, especially it affects the neurodevelopment and immune system. Some of this damage caused by maternal vitamin D deficiency gets evident after 3–5 years. Therefore, the prevention of vitamin D deficiency among pregnant women is essential. The currently recommended supplementation amount of vitamin D is not sufficient to maintain a value of 25(OH)D above 30 ng/ml during pregnancy. Studies are underway to establish the recommended daily doses of vitamin D in pregnant women. Clearly, further investigation is required to study the effects of vitamin D, vitamin D supplementation for improvement in human health generally and mothers and children specifically. This review discusses vitamin D metabolism, dietary requirements and recommendations, and implications of vitamin D deficiency during pregnancy and lactation.

Keywords: vitamin D; pregnancy; child health; review

Vitamin D deficiency is a preventable health problem. Concerns about vitamin D have resurfaced in medical and scientific literature owing to its multiple effects on human health. We are beginning to learn that it plays a much wider role in health and disease prevention. The classical and non-classical pathways of this hormone affect calcium metabolism, the immune system, cell proliferation and differentiation, infection [1]. The question scientists have been working on for almost a decade is why and how vitamin D is affecting conception, pregnancy, and the health of the newborn [2]. Also, the media has been taking increasing interest, and public expectations have been raised regarding the enhanced public health. Some of this damage caused by maternal vitamin D deficiency gets evident after 3–5 years. Therefore, the prevention of vitamin D deficiency among pregnant women is essential. The currently recommended supplementation amount of vitamin D is not sufficient to maintain a value of 25(OH)D above 30 ng/ml during pregnancy. Studies are underway to establish the recommended daily doses of vitamin D in pregnant women. Clearly, further investigation is required to study the effects of vitamin D, vitamin D supplementation for improvement in human health generally and mothers and children specifically. This review discusses vitamin D metabolism, dietary requirements and recommendations, and implications of vitamin D deficiency during pregnancy and lactation.

Abstract. Vitamin D has been a hot topic in the medical world for the last decade. The classical and non-classical pathways of this hormone affect calcium metabolism, the immune system, cell proliferation and differentiation, infection. Vitamin D insufficiency and deficiency among pregnant women is frequent in many populations over the world. Research indicates that the adequate vitamin D level in pregnancy is optimal for maternal, fetal, and child health. Vitamin D deficiency is prevalent in Ukraine. There are few data from Ukraine about the prevalence of hypovitaminosis D in pregnancy and in the newborn. Adverse health outcomes during pregnancy are preeclampsia, gestational diabetes mellitus, and caesarean section. Consequences in newborns are low birth weight, neonatal rickets, risk of neonatal hypocalcemia, asthma, and/or type 1 diabetes mellitus. Vitamin D deficiency during pregnancy is the origin of a host of future perils for a child, especially it affects the neurodevelopment and immune system. Some of this damage caused by maternal vitamin D deficiency gets evident after 3–5 years. Therefore, the prevention of vitamin D deficiency among pregnant women is essential. The currently recommended supplementation amount of vitamin D is not sufficient to maintain a value of 25(OH)D above 30 ng/ml during pregnancy. Studies are underway to establish the recommended daily doses of vitamin D in pregnant women. Clearly, further investigation is required to study the effects of vitamin D, vitamin D supplementation for improvement in human health generally and mothers and children specifically. This review discusses vitamin D metabolism, dietary requirements and recommendations, and implications of vitamin D deficiency during pregnancy and lactation.

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of that damage may be permanent, that is, it cannot be fully reversed by taking vitamin D after birth. Vitamin D is a misnomer. It is structurally similar to estrogen, testosterone, progesterone, and all the steroid hormones. Because of its steroid structure and function, vitamin D plays an important role in priming cells for other hormones to do their action [6].

Vitamin D itself is devoid of any biological activity, but enzymatic conversion to 1α,25-dihydroxyvitamin D (1,25(OH)₂D) generates the hormonal form with diverse biological activities [7]. The active form of vitamin D (1,25-dihydroxyvitamin D₃, 1,25(OH)₂D₃) has well-established effects on bone metabolism and mineral homeostasis. However, recently it has become clear that 1,25(OH)₂D₃ has potent anti-proliferative and immunomodulatory actions that are not immediately linked to its role as a skeletal regulator [8]. The actions of 1,25(OH)₂D₃ are mediated through specific, high affinity binding to the vitamin D receptor (VDR), which is present in multiple tissues.

Important changes occur in the maternal concentration of vitamin D and in calcium metabolism to provide the calcium needed for fetal bone mineral accretion during pregnancy. Calcium is transported from the mother to the fetus through the placenta. Approximately 25–30 g of calcium is transferred to the fetal skeleton by the end of pregnancy, most of which is transferred during the last trimester. The requirement for vitamin D in maintaining normal calcium metabolism throughout pregnancy and lactation in mothers, fetuses, and newborn infants is still controversial. It is clear, however, that vitamin D requirements are increased in mothers during pregnancy and lactation. Established as the placenta at the end of the first trimester, villous tissues secrete multiple hormones that maintain pregnancy and regulate placental physiology [9]. The synthesis, metabolism, and function of vitamin D compounds during pregnancy are complex. Data suggest that 1,25(OH)₂D₃ aids implantation and maintains normal pregnancy, supports fetal growth through the delivery of calcium, controls secretion of multiple placental hormones, and limits the production of proinflammatory cytokines.

Obesity is also associated with significant increases in the odds of maternal and neonatal vitamin D deficiency [10]. Certain medications like steroids, antiepileptic medications, cholesterol-lowering drugs, and some diuretics reduce the absorption of vitamin D from the intestines. It is difficult to make recommendations for health practitioners to follow when they give advice about supplementation particularly during pregnancy. It is clear from inferences gained from the research to date that pregnant women who are both obese and vitamin D deficient should not only be concerned about their own health but that of their offspring and that having sufficient vitamin D will improve their long-term health outlook. Interventions in this area, once more clearly understood, will improve intergenerational health and prenatal conditions, which are of vital importance, and surely this will involve further research, preconceptional care, and a population-wide public health intervention such as universal supplementation of vitamin D during pregnancy.

New research suggests that women who take high doses of vitamin D during pregnancy have a greatly reduced risk of complications, including gestational diabetes, preterm birth, and infection [11]. This recommendation may be controversial because very high doses of vitamin D have been long believed to cause birth defects.

Various human studies are done so far involving pharmacological doses of vitamin D during pregnancy. A study in human subjects involved the administration of 100,000 IU vitamin D per day (2.5 mg/day) throughout pregnancy to hypoparathyroid women to maintain serum calcium with no fatal outcome. Hypoparathyroid patients have completed many pregnancies while receiving ergocalciferol, it is unlikely that material vitamin D, 25(OH)D₃, or 24,25(OH)₂D₃ per se are teratogens [12].

Most prenatal vitamins have around 400 IU of vitamin D, and most health groups are recommended for taking no more than 2,000 IU of the vitamin in supplement form daily. Eventually, as circulating 25(OH)D increases to toxic concentrations, the classic situation of hypercalcemia, hypercalciuria, and, finally, extraskelatal calcification becomes evident. Hypercalciuria due to excessive vitamin D intake is always accompanied by circulating 25(OH)D concentrations >100 ng/ml [13]. Maternal vitamin D concentration at term, gestational diabetes, adverse effects, and low birth weight were not reported in any trial or reported only by one study [13].

To attain circulating 25(OH)D concentrations that exceed 100 ng/ml, a daily vitamin D intake well in excess of 10,000 IU/d (250 µg/d) for several months would be required. However, hypervitaminosis D has never occurred when physiologic amounts of vitamin D are ingested. In addition, no case of hypervitaminosis D from sun exposure has ever been reported. This is supported by the recent finding from a randomized, double-blind, placebo-controlled trial examining the effects of a single annual megadose of vitamin D₃ (500,000 IU, equivalent to approximately 1,370 IU/d) on fall and fracture outcomes in community-dwelling elderly women with a history of fall or fracture [14].

Adequate vitamin D intake is essential for maternal and fetal health during pregnancy, and prevention of adverse outcomes. Recent work emphasizes the importance of non-classical roles of vitamin D in pregnancy and the placenta. Vitamin D deficiency during pregnancy is associated with the non-classical actions of this hormone, being linked with preeclampsia, insulin resistance, gestational diabetes mellitus, bacterial vaginosis, and an increased risk for caesarean section delivery [15]. Women who have vitamin D deficiency do not usually feel any different but in some may have muscle weakness and weakened bones. Pregnancy does not exacerbate hypocalcemia and secondary hyperparathyroidism in people with pre-existing vitamin D deficiency.

A new study finds that women who develop severe preeclampsia tend to have lower blood levels of vitamin D than healthy pregnant women raising the possibility that the vitamin plays a role in the complication. Preeclampsia rates elevate during the winter months when sunlight-dependent 25(OH)D productions are reduced. Vitamin D supplementation reduces preeclampsia risk, compared to unsupplemented controls [16]. Two clinical trials support the potential role of vitamin D in the prevention of preeclampsia, although neither of these treated with vitamin D supplements alone. In an uncontrolled trial, supplementation with a multivitamin/mineral supplement and halibut liver oil (containing 900 IU/d vitamin D) provided at the 20th week of gestation reduced the odds of preeclampsia by 32% (95% CI, 11–47%) [17]. Vitamin D supplementation in early pregnancy should be explored for preventing preeclampsia and promoting neonatal well-being.
Vitamin D is known to influence insulin secretion. 1,25(OH)₂D regulates insulin secretion by pancreatic β-cells and thereby affects circulating glucose levels [18]. As expected, a low concentration of 25(OH)D is a risk factor for insulin resistance, glucose intolerance, and features of metabolic syndrome in normoglycemic subjects. Vitamin D deficiency during early pregnancy significantly increases the risk for gestational diabetes in later pregnancy [19].

Vitamin D may influence the course of infectious diseases during pregnancy. Low 25(OH)D levels correlate with increased bacterial vaginosis in the first trimester. Bacterial vaginosis is more prevalent in black women, who typically have lower serum 25(OH)D concentrations and have a six-fold higher chance of vitamin D deficiency compared with white women. Vitamin D exerts an impact on the immune system, cytokines, and antibacterial peptides that are likely to regulate the bacterial flora. Nutritional vitamin D status has very recently been linked to the human innate immune system and its ability to contain Mycobacterium tuberculosis [20].

VDR and 1,25(OH)₂D₃ normally increase skeletal muscle function. Conversely, vitamin D deficiency results in proximal muscle weakness and decreased lower extremity muscle function, perhaps contributing to the risk for caesarean section. The Cochrane Library issued a review of vitamin D supplementation during pregnancy and identified 7 relevant studies. The Cochrane review concluded that there is not enough evidence to evaluate the requirements and effects of vitamin D supplementation during pregnancy. Data from three trials involving 463 women show a trend for women who receive vitamin D supplementation during pregnancy to less frequently have a baby with a birth weight below 2,500 grams than those women receiving no treatment or placebo, although the statistical significance was borderline [15, 21].

Because the poor vitamin D stores of the mother may impair vitamin D state in the infant, it is important to know whether rickets can be prevented in breast-fed infants by supplementation of the mother [22]. The Canadian Paediatric Society recommended 2,000 IU of vitamin D₃ for pregnant and lactating mothers with periodic blood tests to check levels of 25(OH)D and calcium [23]. The American Academy of Pediatrics recommendations focus on supplementing the infant and make no specific recommendations about universally supplementing breastfeeding mothers. A sufficient supply of vitamin D to the breast-fed infant is achieved only by increasing the maternal supplementation up to 2,000 IU/day. As such a dose is far higher than the daily dietary allowance recommended for lactating mothers its safety over prolonged periods is not known and should be examined. Other suggestions of vitamin D supplementation of 400 IU/day to breast-fed infants is the most secure way of preventing rickets in infants [24].

Adequate maternal vitamin D levels are also important for fetal and child health. Fetal vitamin D concentrations are mainly dependent on maternal concentration, and maternal deficiency may lead to adverse outcomes in offspring. Vitamin D deficiency in mothers has significantly increased the risk of infantile rickets due to inadequate maternal — fetal transfer of 25-hydroxyvitamin D [25]. Recent retrospective studies found a significant and previously undetected association of maternal vitamin D deficiency with rickets-associated infant heart failure and with acute lower respiratory tract infection [26], a serious complication often associated with sepsis without clinical signs of rickets.

Vitamin D supplementation in pregnancy has previously been associated with a reduced risk of wheezing and type 1 diabetes [27]. A few studies have observed that maternal vitamin D concentrations are related to offspring birth weight and growth during the postnatal years. Lower maternal vitamin D status was associated with lower bone mineral concentration and impaired glucose homeostasis in newborn infants [28]. Maternal vitamin D deficiency also has been associated with craniotabes [29], a softening of skull bones that is one of the earliest signs of vitamin D deficiency, in a case study with neonatal seizures of a hypocalcemic infant and with impaired skeletal development in utero. Interestingly, vitamin D deficiency during pregnancy is also associated with risks of health problems later in childhood, including improper bone development at 9 years of age, asthma, dental cavities, schizophrenia, and type 1 diabetes mellitus [30]. The concept that maternal nutritional status influences the risk of chronic disorders in the offspring has attracted interest over the past 2 decades.

The Cochrane review has recently pointed out that the topic of maternal vitamin D requirements during pregnancy has been poorly studied. The reality is that the actual vitamin D requirement during pregnancy is not known. For that matter, the requirement for the general population is not known either. There is no dietary recommended intake for vitamin D. What is known today is that for a pregnant woman, the adequate intake for vitamin D is 200 IU per day. However, this recommended level, which was largely arbitrarily set, seems to be less helpful to improve the nutritional vitamin D status of pregnant women. National Osteoporosis Foundation recommends 400—800 IU of vitamin D for pregnant women. A recent systematic review concluded that antenatal vitamin D supplementation is effective in improving the vitamin D status of Asian and white women, improves growth in the first year of life in South Asian babies, and therefore may contribute to reducing the incidence of rickets in this latter group, without evidence of harm [31]. Current NICE guidance states clearly that pregnant women are informed, at their first antenatal booking, of the importance of adequate vitamin D during pregnancy and after, to maintain their own and their baby’s health. These women are advised to take 10 micrograms per day in the form of a multivitamin supplement. It is crucial to ensure that at-risk women are aware of this need. Current U.S. guidelines call for pregnant women to get 400—600 IU. However, research in recent years has been challenging those ideas on what is enough and what is too much. For now, though, 600 IU in prenatal vitamins remain the recommended daily intake for pregnant women. However, getting 25(OH)D₃ levels consistently above 30 ng/ml may require at least 1,500—2,000 IU/day of vitamin D. If a mother is vitamin D deficient, breast milk is not a good source of vitamin D, so infants need to be given vitamin D supplementation until they are weaned. Also, women are encouraged to continue to take vitamin D supplements after pregnancy to help protect against health problems such as osteoporosis. It was recently shown that maternal supplementation of vitamin D at
a dose of 2,100 IU/day was needed, when administered during the period of lactation, in order to observe an increase in serum levels of 25(OH)D in the breast-fed infants compared to those observed in children given 400 IU/day.

Conclusions
Vitamin D has emerged as something of a wonder supplement, according to the claims of dozens of studies published in the past few years. The current lack of evidence of benefit for women at lower risk of vitamin D deficiency points to the need for further research into vitamin D supplementation in pregnant women with clinical neonatal and infant end-points. There is a similar gap in the knowledge base for optimal dosing, as there is little empirical robust evidence to support 600–800 IU/day. Further research is required, particularly to establish the dose needed to supplement pregnant women with pre-existing deficiency and the optimal gestation at which vitamin D supplementation should be started. Recommendations should be made on informing women of the importance of maintaining adequate vitamin D stores in pregnancy, particularly for those at greatest risk of vitamin D deficiency. Future studies are essential to determine the true vitamin D requirement during pregnancy not only for maternal skeletal preservation and fetal skeletal formation, but also for fetal “imprinting” that may affect neurodevelopment, immune function, and chronic disease susceptibility soon after birth as well as later in life.

Conflicts of interests. Author declares the absence of any conflicts of interests and their own financial interest that might be construed to influence the results or interpretation of their manuscript.

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Дефіцит вітаміна D во время беременности также рассма-
при рождении, рахіт новонароджених, ризик гіпокальціємії
последствам для новонароджених относят низьку масу тела
ционный сахарный диабет и кесарево сечение. К негативным
для здоровья во время беременности являются гестоз, геста-
Неблагоприятными последствиями дефицита витамина D
повитаминоз D во время беременности и у новорожденных.
существует недостаточно данных о распространенности ги-
В Украине распространен дефіцит вітаміну D, в той же
ляется оптимальным для здоровья матери, плода и ребенка.
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Наслідки дефіциту вітаміну D під час вагітності та лактації

Резюме. Вітамін D залишається актуальною темою серед
медичної громадськості протягом останніх 10 років. Класич-
ні та некласичні ефекти цього гормону впливають на метабо-
лізм кальцію, імунну систему, проліферацію та диференціацію
клітин, інфекцію. Недостатність і дефіцит вітаміну D серед
вагітних жінок спостерігаються в багатьох країнах світу.
Дефіцит вітаміну D під час вагітності також розглядається як
фактор ризику виникнення в подальшому порушень фізич-
ного розвитку та імунної системи. Ці ураження, зумовлені
недостатністю вітаміну D у матері, стають очевидними через
декілька років. Тому профілактика дефіциту вітаміну D серед
вагітних має важливе значення. Наразі рекомендована доза до-
даткового призначення вітаміну D недостачі для підтримки
рівня 25(OH)D понад 30 нг/мл під час вагітності. Тривають до-
слідження з метою встановлення рекомендованих добових доз
вітаміну D у вагітних. Очевидно, що необхідне подальше дослі-
дження впливу вітаміну D, додаткового його призначення для
поліпшення здоров’я людей в цілому, а також матерів та дітей.
В огляді обговорюється метаболізм вітаміну D, добра потреба
та рекомендації спосібно профілактики негативних наслідків
дефіциту вітаміну D під час вагітності та лактації.
Ключові слова: вітамін D; вагітність; здоров’я дитини; огляд

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Последствия дефицита витамина D во время беременности и лактации

Резюме. Витамин D остается актуальной темой среди
медико-общественности в течение последних 10 лет. Класи-
ческие и неклассические эффекты этого гормона влияют на мета-
бoliczь кальция, иммунную систему, пролиферацию и дифференциацию
клеток, инфекцию. Недостаточность и дефицит витамина D у
вагинальных является оптимальным для здоровья матери, плода и ребенка.
Дефект витамина D під час вагітності також розглядається як
фактор ризику виникнення в подальшому порушень фізич-
ного розвитку та імунної системи. Ці ураження, зумовлені
недостатністю вітаміну D у матері, стають очевидними через
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вагітних має важливе значення. Наразі рекомендована доза до-
даткового призначення вітаміну D недостачі для підтримки
рівня 25(OH)D понад 30 нг/мл під час вагітності. Тривають до-
слідження з метою встановлення рекомендованих добових доз
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дження впливу вітаміну D, додаткового його призначення для
поліпшення здоров’я людей в цілому, а також матерів та дітей.
В огляді обговорюється метаболізм вітаміну D, добра потреба
та рекомендації спосібно профілактики негативних наслідків
дефіциту вітаміну D під час вагітності та лактації.
Ключові слова: вітамін D; вагітність; здоров’я дитини; огляд

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