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Evaluation of the impact of vegan-vegetarian diets on maternal-fetal health in pregnancy: our experience

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Alla mia famiglia

1. Introduction

1.1 Nutrition in pregnancy

Maternal nutrition plays an important role during pregnancy. An adequate nutritional status of the mother, even before the onset of pregnancy, as well as proper nutrition during gestation, are essential prerequisites for the prevention of most maternal-fetal pathologies. Pregnancy is a period of intense fetal growth and development and adequate intake of macronutrients and micronutrients during pregnancy promotes these processes, while undernutrition and overnutrition can be associated with adverse pregnancy outcomes [1-5].

Diet and lifestyle are important determinants of health of both mother and offspring, starting from the preconceptional period. Therefore, it is important to evaluate and make changes, when required, to improve maternal nutrition before and during pregnancy. The effects of inadequate or excessive intake of some nutrients can be observed in the short-term and also in the long-term. Both fetal undernutrition and overnutrition, including development in an obesogenic environment, can lead to permanent changes of fetal metabolic pathways and thereby increase the risk of childhood and adult diseases related to these pathways. The energy intake requirements in pregnancy are often overestimated by women in the western world, and it is crucial for doctors to provide correct information, advising them on adequate nutrition, aimed at the optimal development of the fetal organs, according to the current recommendations. The popular belief that it is necessary to "eat for two" is unfortunately still widespread, while literature data indicate that the increase in basal metabolic rate during pregnancy is actually minimal [6].

1.2 Adaptation of the maternal body to pregnancy: changes related to weight gain

During pregnancy, important changes occur in the maternal organism, aimed at creating a suitable environment for fetal growth and preserving the health of the mother until the moment of delivery. These changes concern both the genital system and extra-genital organs and systems. Some of these changes are closely related to nutritional status and weight gain during pregnancy.

Significant variations in the composition of body fluids and circulating plasma mass occur during pregnancy. The increase in lean mass is mainly represented by the fetal component (42%), the uterus (17%), the placenta (10%), the erythrocyte mass (14%) and the breast tissue (8%). The deposition of fat mass consists of 76% subcutaneous tissue, which accumulates mainly in the second trimester, with the aim of guarantee an energy reserve for the last phase of pregnancy and while breastfeeding [7-9].

Also, pregnancy is characterized by profound haematological changes, aimed at ensuring adequate perfusion of the fetal-placental unit and preparation for maternal blood loss during delivery [8]. The most significant haematological changes include hemodilution, with related physiological anemia, neutrophilia and changes in the coagulation structure, with an increase in pro-coagulating factors and a decrease in fibrinolysis.

1.3 Metabolic changes: carbohydrates, lipids and proteins

During pregnancy, glucose metabolism is characterized by impaired glucose tolerance, with progressive decrease in fasting glycemia and a slight increase in post-prandial glycemia, a reduction in peripheral insulin sensitivity and an increase in blood glucose, insulin secretion by pancreatic beta cells. Pregnancy is therefore, even in physiological conditions, "diabetogenic". These changes are due to several factors: the increase in plasma volume, the increase in the utilization of glucose (both fetus-placental and maternal, the latter secondary to the increase in beta-cell function) and inadequate hepatic gluconeogenesis. This leads to an increase in the basal and re-active insulin secretion, also because the glucose, once absorbed and taken up preferentially by those maternal organs (uterus, muscles, heart), which require greater consumption, in part is directed towards the fetal placental unit, the other part is eliminated in the urine due to the increase in the glomerular filtration index and the decrease in tubular reabsorption, with a decrease in the glucose reabsorption threshold and consequent intermittent glycosuria. The increase in insulin secretion is not only secondary to the development of peripheral resistance to it, but also to the effect of the increasing placental activity that neutralizes insulin by means of the HPL, which is continuously increasing. A greater need for glucose is therefore evident and gluconeogenesis contributes only in part (30%).

Obesity causes a further decrease in insulin sensitivity in the liver. Starting from the 20th week, the rise in the HPL hormone and the ever higher level of estrogen and progesterone determine an increasingly marked resistance to insulin, which makes peripheral use of glucose limited. As a result of insulin resistance, the pancreas releases higher amounts of insulin, without however resolving its resistance, therefore:

• in the first half of pregnancy, fasting glucose levels are lower, but the administration of an oral load does not lead to a marked increase in blood glucose, as the high sensitivity to insulin promotes synthesis and glycogen storage, the accumulation of storage fats, the cellular metabolism of amino acids, and the decrease in glycosylated hemoglobin (HbA1c).

• after the 20th week, as resistance develops, the plasma insulin level increases compared to the previous period: the administration of a glucose load leads not only to a higher increase in insulin than in the previous period, but also an increase in blood sugar.

• at the end of pregnancy, blood sugar remains at high levels after meals while it remains lower in fasting than in extra-pregnancy conditions, despite the 30% increase in gluconeogenesis. The increase in peripheral insulin resistance (the peak is at the 32nd week) remains constant until the end of pregnancy. As a result, there is a decrease in the use of glucose, the induction of glycogenolysis and gluconeogenesis and the energy use of fats. Ketosis develops rapidly, especially during labor.

Fats are absorbed from the intestine more slowly during pregnancy, due to reduced entero-hepatic circulation. In the first half of pregnancy, fats are accumulated as a deposit in the maternal organism (mostly in mother and primiparous women), while in the second half of pregnancy they are mainly used to produce the energy necessary for fetal growth, saving carbohydrates. At the beginning of pregnancy, the maternal organism is more sensitive to the action of insulin and this leads to an increase in lipoprotein-lipases which reduce the accumulation of fat. Subsequently, by increasing peripheral resistance to insulin, insulin itself increases and consequently tissue lipase, which induces fat mobilization and secondary lipolysis; on the other hand, hepatic lipase decreases, while cholesterol, triglycerides and phospholipids increase. Total cholesterol, after an initial decrease in the first eight weeks, increases until the end of pregnancy, with values ranging from 25 to 200% (VLDL 35%; LDL 50-90%; HDL 10-25%). Triglycerides progressively increase from the onset of pregnancy, overall in an interval between 90 and 500%.

Starting from the 36th week, both triglycerides and cholesterol reach their maximum peaks, however, from this moment the production of plasma steroids can be so high (500 mg/24h), to consume all available cholesterol reserves thus explaining the progressive decrease. The increase in lipids in the first half of pregnancy aims to increase fat reserves, which will be used in the second half and in the puerperium, in the form of fatty acids used by the mother. Changes in the lipid profile during pregnancy, although not of the atherogenic type, must be carefully monitored.

Hyperlipidemia in pregnancy is not so much influenced by diet as by endocrine factors:

• insulin, which facilitates fat deposits

• estrogen / progesterone, which stimulate synthesis of cholesterol and triglycerides by the liver

• HPL, which favors the accumulation of lipids in maternal deposits in the postprandial period, while fasting induces lipolysis.

Non-esterified fatty acids (NEFA) also increase in pregnancy and are progressively converted into triglycerides and cholesterol, incorporated into phospholipids and oxidized to CO_2 or ketone bodies. Slowly, cholesterol and triglycerides decrease in the puerperium, when elevated levels of prolactin (PRL) induce an increase in breast lipoprotein lipases: this allows the local synthesis of fatty acids and the delivery of 200-400 calories in the form of lipids with milk.

Pregnancy involves an anabolic condition, with reduced synthesis of urea due to decreased hepatic uptake of blood amino acids (AA): after the meal these increase in the blood, but to a lesser extent than in the extra-pregnancy condition, especially for as regards the AAs involved in gluconeogenesis, probably conveyed towards the fetal-placental unit, both for fetal growth and as an energy source. The concentration of total serum proteins, in particular albumin, decreases during pregnancy, while increasing liver synthesis.

Pre-pregnancy BMI and gestational weight gain have independent, but cumulative, effects on infant birth weight and possibly in the gestational duration. The incidence of pregnancy complications is higher at the upper and lower extremes of weight gain. At the beginning of pregnancy, it is advisable for the doctor to evaluate the nutritional status of the woman and her body mass index (BMI), adjusting the energy and nutritional intake during pregnancy based on the pre-pregnancy BMI and the WHO recommendations. In women who intend to seek pregnancy, it is good to encourage the achievement or maintenance of a BMI within the normal limits.

It is good to inform women about the real increase in calories needs during pregnancy, much lower than what women generally believe, by encouraging physical activity [10-12]. Nutritional counseling is also mentioned in the WHO Recommendations on Nutrition in Pregnancy (table 1).

Table 1: Summary list of WHO recommendations on antenatal care (ANC) for a positive pregnancy experience

These recommendations apply to pregnant women and adolescent girls within the context of routine ANC

A. Nutritional interventions		
	Recommendation	**Type of recommendation**
Dietary interventions	**A.1.1:** Counselling about healthy eating and keeping physically active during pregnancy is recommended for pregnant women to stay healthy and to prevent excessive weight gain during pregnancy.[a]	Recommended
	A.1.2: In undernourished populations, nutrition education on increasing daily energy and protein intake is recommended for pregnant women to reduce the risk of low-birth-weight neonates.	Context-specific recommendation
	A.1.3: In undernourished populations, balanced energy and protein dietary supplementation is recommended for pregnant women to reduce the risk of stillbirths and small-for-gestational-age neonates.	Context-specific recommendation
	A.1.4: In undernourished populations, high-protein supplementation is not recommended for pregnant women to improve maternal and perinatal outcomes.	Not recommended

1.4. Nutritional intake requirements and energy balance in pregnancy

Pregnancy involves a modest increase in caloric requirements for healthy women, who are normal weight and with a moderately active lifestyle, which varies according to the trimester considered, which can be achieved by increasing the consumption of macronutrients, i.e. maintaining the balance between carbohydrates, fats and proteins, in the quantitative ratios recommended by the Nutritional Guidelines. The excess of calories during pregnancy can be just as harmful as their deficiency, especially in overweight women and obese, for which the risk of adverse outcomes increases, as well as the vulnerability of the unborn child to the development of metabolic pathologies in adulthood. Pregnant women of normal weight with a singleton pregnancy need to increase daily caloric intake by 340 and 450 additional kcal/day in the second and third trimesters, respectively, for appropriate weight gain, but they do not need to increase energy intake in the first trimester.

1.5. Macronutrients

Proteins

The fetal/placental unit utilizes approximately 1000 g of protein during pregnancy, with the majority of this requirement in the last six months. The recommended intake levels of high-quality protein for the population, which correspond to 54 g/day for an adult woman, should be increased by 1 g/day in the first trimester of gestation, 8 g/day in the second trimester and 26 g/day in the third trimester [13].

Carbohydrates

Carbohydrates are the main source of energy in the general population as well as in pregnancy; with an intake of 45-60% of the total daily energy. The daily amount of carbohydrates should not be less than 175 g to ensure adequate supply to both the maternal and fetal brain. When choosing foods, it is useful to give preference to whole grains to ensure an adequate intake of fiber. The consumption of simple carbohydrates (mono and disaccharides) should be limited to 10% of carbohydrates and have to be related to the physical activity performed [14,15].

Lipids

The quality of the lipids consumed with the diet is fundamental to guarantee the correct development and growth throughout the developmental age, starting from the prenatal period up to the first months of life, thanks to an adequate supply ensured by the placenta during intrauterine life and by breast milk after birth [16].

Essential fatty acids and their long-chain polyunsaturated derivatives (PUFAs) are important structural components of membranes, therefore fundamental in the formation of new tissues. They are called "essential" as the human body is unable to synthesize them, therefore an adequate dietary intake is essential, especially in pregnancy. Since neurocognitive development occurs mostly in the 3rd trimester, during this period the mother most needs these nutrients. Docosahexaenoic acid (DHA) is an omega 3 fatty acid, particularly important for the development of the nervous system and the retina. It plays an essential role in numerous biological processes and is an important precursor of molecules such as prostaglandins, leukotrienes and thromboxanes, responsible for regulating utero-placental flow.

For this reason, its possible role in the duration of pregnancy, in pre-eclampsia and IUGR has been hypothesized. Excessively low plasma levels of DHA have been found in women who take exclusively vegetarian diets or who do not have an adequate intake of fish, or in particular populations, such as that of mothers who maintain the habit of smoking. The need for DHA increases by 100-200 mg per day during pregnancy [17-20].

1.6. Micronutrients

Micronutrients, necessary in small quantities in the diet, consist of vitamins and minerals and they play a fundamental role in many biological functions; this role is even more important during pregnancy. In fact, during gestation the need for micronutrients increases more than that of macronutrients. An inadequate intake of micronutrients, and a low nutritional quality of the diet, can have important negative consequences both for the mother and for the development of the fetus [21]. Recommendations for daily intake of vitamins and minerals during pregnancy and lactation are shown in the table 2.

Recommended dietary allowances, or adequate intakes, and tolerable upper limits for adult pregnant and lactating women

	RDAs		ULs for pregnant and lactating women
	Pregnant women*	Lactating women*	
Fat-soluble vitamins			
Vitamin A	770 mcg	1300 mcg	3000 mcg
Vitamin D	600 international units (15 mcg)	600 international units (15 mcg)	4000 international units (100 mcg)
Vitamin E	15 mg	19 mg	1000 mg
Vitamin K¶	90 mcg	90 mcg	ND
Water-soluble vitamins			
Vitamin C	85 mg	120 mg	2000 mg
Thiamin	1.4 mg	1.4 mg	ND
Riboflavin	1.4 mg	1.6 mg	ND
Niacin	18 mg	17 mg	35 mg
Vitamin B6	1.9 mg	2 mg	100 mg
Folate	600 mcg	500 mcg	1000 mcg
Vitamin B12	2.6 mcg	2.8 mcg	ND
Minerals			
Calcium	1000 mg	1000 mg	2500 mg
Phosphorus	700 mg	700 mg	4000 mg
Iron	27 mg	9 mg	45 mg
Zinc	11 mg	12 mg	40 mg
Iodine	220 mcg	290 mcg	1100 mcg
Selenium	60 mcg	70 mcg	400 mcg

RDA: recommended dietary allowance; AI: adequate intake; UL: (tolerable) upper limit; ND: not determinable, due to lack of data of adverse effects and concern with regard to lack of ability to handle excess amounts.
* Females over 18 years old.

Well-nourished women may not need multiple-micronutrient supplements to satisfy these daily requirements, but without a careful evaluation by a nutritionist, it is important to recommend them. Individual adjustments should be made based on the woman's specific needs.

Vitamin A

Vitamin A is a fat-soluble vitamin that can be taken in two forms: as retinoids through foods of animal origin (dairy products, liver, fish liver oils), or as provitamin (carotenoids), present in numerous plant foods (fruits and vegetables). Vitamin A is essential for embryogenesis, growth, immune function and normal cell development and differentiation. Vitamin A deficiency during pregnancy increases the risk of maternal night blindness, anemia, infections, prematurity and can be the cause of congenital malformations. It also appears to be essential for the expression of genes involved in hematopoiesis, already in the early gestational period, promoting the hemogenic program in the aorto-gonad-mesonephros area, stimulating erythropoiesis in the fetal liver and activating the expression of erythropoietin. An excess of vitamin A can have teratogenic effects, with a higher incidence of malformations of the brain, spine and heart valves. Vitamin A supplementation is not necessary where the usual daily intake is greater than three times the Recommended Daily Allowance (RDA) (for example, 8000 international units or 2400 μg of retinol equivalent), i.e. in most developed countries [22,23].

Folic acid

Folate is a water-soluble vitamin complex belonging to group B, mainly contained in green leafy vegetables, fresh fruit, cereals and offal, however the bioavailability of the folate contained in food is very variable. The role of this vitamin in DNA synthesis, cell replication processes, regulation of gene expression and metabolism of amino acids, make it essential for health. Inadequate levels of folate in the diet can lead to anemia, leukopenia and thrombocytopenia. The rapid use of folate during pregnancy, for the constitution of fetal cells and tissues, causes the need for these compounds to increase during the periconceptional period. Maternal folic acid supplementation is therefore widely recommended for all women of childbearing age wishing to become pregnant, especially due to the reduction of the risk of neural tube defects. Recent studies suggest benefits associated with folic acid supplementation also for reducing the risk of congenital heart disease and developing placenta. The reference intake levels in pregnancy are increased by 50% for pregnant women compared to other women of childbearing age (600 vs 400 µg/day).

National and international guidelines recommend the intake of 400 µg/day of folic acid at least thirty days before conception and up to at least three months of gestation. Folic acid supplementation is recommended at a dose of 4-5 mg/day for women who have given birth to fetuses with neural tube defects, suffer from malabsorption, celiac disease, or are taking antiepileptic drugs, have familiarity for neurological diseases/malformations, have pre-gestational diabetes or obesity.

In conclusion, during pregnancy, a varied and balanced diet, which meets the needs of other essential nutrients, contains sufficient quantities of B vitamins. It is recommended to take 5 portions a week of fruit and vegetables, two portions a week of legumes, occasionally taking dried fruit and preferring whole grains [24-27].

Vitamin C

Vitamin C (L-ascorbic acid) is involved in numerous processes such as the biosynthesis of collagen, carnitine, catecholamines, peptide hormones, bile salts, as well as in the catabolism of tyrosine, in the regulation of oxygen levels in response to hypoxia and ultimately in epigenetic control. In addition, it promotes the synthesis of endothelial nitric oxide (NO), which has protective functions at the level of the vascular system. In the digestive system, vitamin C prevents the transformation of nitrites present in food into nitrosamines, which are carcinogenic compounds. In addition, it promotes the absorption of non-heme iron by reducing ferric iron to ferrous iron, which is the most bioavailable form. Vitamin C is present in fresh fruits and vegetables, especially peppers, citrus fruits, kiwis, strawberries, tomatoes, chicory and broccoli. Cooking involves a loss of about 50% of the vitamin; it is advisable to use steam cooking or cooking in a little water. In many products, vitamin C is added as an antioxidant additive and to replenish treatment losses. The ascorbate concentration decreases in maternal plasma during pregnancy due to haemodilution and active transport to the fetus, but the amount of vitamin C transferred to the fetus is not well defined. In case of a correct nutritional attitude, supplementation of vitamin C during pregnancy is not recommended [17,23].

Vitamin D

Vitamin D is synthesized in the body following exposure to the sun, while endogenous synthesis is influenced by various factors, partly linked to the characteristics of the individual, such as sex and phenotype, partly of type environmental activity, such as physical activity, weight, time of exposure to sunlight, latitude, season, pollution, use of sunscreens and taking supplements. Diseases that induce intestinal malabsorption, such as celiac disease, Crohn's disease, cystic fibrosis, ulcerative colitis, renal failure and some drugs, can contribute to the development of a vitamin D deficiency. In obese subjects a vitamin D deficiency develops more easily than in normal weight subjects, as vitamin D is deposited in the adipose tissue and therefore the circulating levels are found in reduced quantities.

Vitamin D3 is the predominant form in maternal blood. In the first phase of gestation, vitamin D is involved in the modulation of the immune system, by regulating the release of various cytokines, helping to favor embryonic implantation, as well as regulating the secretion of various hormones.

The main sources of vitamin D are milk and derivatives, eggs and fish (especially fatty fish such as herring and salmon).

According to a recent systematic review of the literature, maternal supplementation during pregnancy reduces the risk of pre-eclampsia, as well as preterm delivery and low birth weight. NICE recommends a supplement of 10 μg/day of vitamin D during pregnancy and breastfeeding in all women. However, vitamin D supplementation in Italy does not seem to be necessary in all women and can be recommended, after a case-by-case evaluation, only in those at risk of hypovitaminosis for environmental reasons or with food deficiencies[12, 28-30].

Iron

Meat and fish, but also legumes and green leafy vegetables, are the main dietary sources of iron.

The need for iron during pregnancy progressively increases up to the third month, parallel to its accumulation in the fetal tissues. During gestation, iron deficiency can impair fetal growth and development, increase the risk of preterm delivery and low birth weight. According to some recent studies, inadequate iron levels during pregnancy are associated with an increased cardiovascular risk for the unborn child in adulthood. Postpartum hemorrhage also seems to correlate with an insufficient intake of iron.

Hemoglobin concentrations below 11 g / dl in the first trimester and <10.5 g/dl beyond the 28th week should be evaluated and treated appropriately to optimize pre-partum hemoglobin concentration and reduce the risk of transfusions. Oral ferrous iron supplementation (60-120 mg/day) is the treatment of first choice in case of iron deficiency anemia. It is necessary to inform women on how to improve the intake of ferrous iron with food and on the factors that interfere with iron absorption. The indications in terms of recommended intake levels vary from 27 mg per day, for all pregnant women of the Reference Nutrient Intake Levels, to the WHO 30-60 mg [12, 31].

Iodine

Iodine is a component of thyroid hormones and therefore directly or indirectly influences the metabolism of glucose, proteins, lipids, calcium, phosphorus and thermogenesis. In the body, iodine is found above all linked to thyroglobulin. In pregnancy, iodine deficiency can cause miscarriage, increased perinatal mortality, the risk of congenital anomalies and neurodevelopmental disorders. The National Academy of Medicine recommends daily iodine intake of 220 mcg during pregnancy and 290 mcg during lactation; the World Health Organization (WHO) recommends iodine intake of 250 mcg for both pregnant and lactating women [32].

Calcium

Calcium is essential for neonatal development. The need for this mineral increases significantly during pregnancy and breastfeeding; in fact, the fetal requirement varies from 50 mg / day in the middle of pregnancy up to 330 mg / day at the end.

WHO recommends an intake of 1.5-2.0 g/ day of calcium from the twentieth week until the end of pregnancy, especially for women at risk of hypertension [12].

Zinc

Zinc is an essential mineral for embryogenesis, fetal growth, lactation. A substantial deficiency of this element, although rare, can lead to defects in growth, delay in the maturation of bone and sexual characteristics, damage to immune system. Zinc is mainly found in foods such as fish, red meats and seafood. The bioavailability of this nutrient in the body is limited by the high amount of fiber contained in these foods. Reference levels for zinc in adult women are estimated at 8 mg/day. The additional requirement for pregnant women is minimal in the first trimester, and subsequently increases to reach 0.7 mg / day in the last period before childbirth. The upper level intake for zinc for the adult and pregnant population was established at 25 mg / day [33].

1.7 Vegan-vegetarian diets and pregnancy

Diets low in animal-based foods are gaining global attention as being beneficial to human (for their effects on cardiovascular diseases, metabolic syndrome and cancer diseases) and planetary health. Vegetarian diets exclude any meat, fish, seafood, or animal by-product but include milk, cheese and eggs. Vegan diets are free of all flesh food, eggs, dairy products, and even honey.

In details, vegetarian diets frequently are grouped as follows:

- Semi-vegetarian – People who consume meat, fish or chicken in their diet on occasion. Some people who follow such a diet may not eat red meat, but may eat fish and perhaps chicken.

● Pescatarian – Vegetarian whose diet includes fish on occasion in addition to eggs, milk, and milk products, but no other animal meats.

● Lacto-ovo-vegetarian (LOV)– Eggs, milk, and milk products (lacto = dairy; ovo = eggs) are included, but no meat is consumed.

● Lactovegetarian (LV) – Milk and milk products are included in the diet, but no eggs or meat are consumed.

● Macrobiotic – Whole grains, especially brown rice, are emphasized and vegetables, fruits, legumes, and seaweeds are included in the diet. Locally-grown fruits are recommended. Animal foods limited to white meat or white-meat fish may be included in the diet once or twice a week.

● Vegan – All animal products, including eggs, milk, and milk products, are excluded from the diet. Some vegans do not use honey. They also may avoid foods that are processed or not organically grown.

● Fruitarian – Vegan diet based on fruits, nuts and seeds. Vegetables classified botanically as fruits (avocado, tomatoes) are commonly included in fruitarian diets; all other vegetables, grains, beans and animal products are excluded.

Vegan and vegetarian diets are rich in cereals, fruit, vegetables, legumes, which reduce the intake of saturated fats and cholesterol and therefore have protective properties against various chronic diseases, including cardiovascular ones. However, these effects are only positive when the diet is well planned in order to avoid possible deficiencies. To balance these diets, nuts, flax seeds and oily fruit must not be missing. The consumption of vegetable proteins, such as soy, tofu and legumes, combined with cereals, also guarantee the intake of noble proteins with a high biological value, such as those of meat. Therefore, vegetarians and vegans must not limit themselves to eliminating foods of animal origin and/or their derivatives, but it is important that they replace these foods with others of plant origin that can provide the necessary nutrients. For these reasons, vegetarian and vegan diets can have a different impact on health in relation to socio-economic status. In developing countries, these diets are more likely to lead to deficiencies. In Italy 6.7% of people are vegetarians while 2.2% are vegan (3% in 2017, 1% in 2016, 0,2% in 2015, 0,6% in 2014). The data are extrapolated from the last Eurispes report that every year takes a picture of the evolution and changes in the lifestyles and behavior of Italians. In 2020, therefore, with 8.9% of the indications, vegetarians and vegans are increasing compared to 2019 and 2018, when this percentage was respectively 7.3% and 7.1%. In the last 5 years, the total of those who have decided not to consume meat and derivatives is quite constant, remaining between 6 and 8%. The Academy of Nutrition and Dietetics in 2009 established that appropriately planned vegetarian diets, including total vegetarian or vegan diets, are healthful, nutritionally adequate, and may provide health benefits in the prevention and treatment of certain diseases. Well-planned vegetarian diets are appropriate for individuals during all stages of the life cycle, including pregnancy, lactation, infancy, childhood, and adolescence, and for athletes. Pregnancy is a unique and particular situation since the body has to cope not only with the nutritional needs of the mother but also with the regular growth of the fetus. Adequate nutrition is therefore one of the most important aspects to better enjoy this moment. The growing use of vegan-vegetarian diets in "rich" populations requires the need to evaluate their risks and benefits during pregnancy since the data in the literature are rather scant and heterogeneous with very contrasting results. North et al. in 2000, after enrolling about 8,000 children, reported an increased risk of hypospadias in children of vegetarian mothers (adjusted odds ratio, aOR 4.99, 95% confidence interval, 95% CI 2.1-11.88). Therefore the risk of hypospadias needs further investigation to identify potential confounding factors, and should be mentioned in counselling with patients. Also, vegetarian women can suffer from calcium, zinc, DHA, vitamin B12 and iron deficiency. DHA contributes to normal brain and eye development in the fetus and breast-fed infant and its requirement in pregnancy is increased by 100-200 mg per day [34-53].

The data on the impact of LOV and vegan diets on the gestational age at delivery, the incidence of preterm delivery, as well as on birthweight [54–57], are inconsistent. The mentioned studies were performed in different countries with heterogenous social, cultural, and dietary patterns, which could influence and cause inconsistent results. In addition, since vegan women are reportedly at risk of deficiencies of various vitamin levels, such as B12 and D, their newborns may also sustain similar deficiencies. Adequate counseling for women on a vegetarian or vegan diet should include discussion on the introduction of foods reinforced with B12 and iron and the need for any supplementation.

2. Aim of the study

The aim of our study was to perform a prospective observational study to evaluate the safety and efficacy of vegan-vegetarian diets on maternal-fetal health during pregnancy within population living in Italy, in the Apulia region (Foggia city), increasing the available scientific evidence. In particular, our main goal was to highlight if vegetarian or vegan diets could be considered safe for the mother's health and for offspring during pregnancy and lactation. We also aimed to determine the association between specific maternal diet and pregnancy outcome, especially small for gestational age fetuses and preterm birth, by comparing women who followed vegan diet to women who followed different diets. We also focused on the effect of these dietary patterns on the lack of micronutrients in order to find a target therapy that could avoid fetal complications.

3. Materials and methods

Women with low-risk pregnancies were prospectively recruited from the Institute of Obstetrics and Gynecology, University of Foggia, Foggia, Italy between March 2018 and March 2021. The inclusion criteria included age 18-45 years and singleton pregnancies accurately dated by ultrasound. Only women who maintained the same diet for at least 3 months prior to and throughout the current pregnancy were enrolled. Women with a prior medical indication for a specific restrictive diet, previous bariatric procedures or other bowel resections, concurrent medical disorders, psychiatric illness, HIV infection, COVID-19 infection or hepatitis B infection were excluded. Eligible women were asked to fulfill a structured self-completed food questionnaire containing 41 items in order to evaluate their food habits and diet (omnivorous, vegetarian, semi-vegetarian, vegan, Islamic raw food vegan, fruitarian) and to assess nutrients loss and their implementation. The items included: eating habits and length of following a specific diet, maternal age, medical and obstetric history, vitamins and supplementations taken, body mass index (BMI) at the time of conception, gestational weight gained during pregnancy, mode of delivery and gestational age at delivery.

We did not offer any dietary consultation to prevent interference with the results. We did not exclude women based on consumption or not of vitamin supplementation, though most of the women consumed vitamin supplementation.

Information on delivery details and antenatal pregnancy complications was obtained from the hospital maternity records. Primary outcomes were preterm birth (delivery prior to 37 weeks) and incidence of small-for-gestational- age (SGA: birthweight below the 10% percentile).

We also evaluated these maternal-fetal outcomes:

- Percentage of intrauterine fetal deaths
- Weight of the newborn
- Maternal weight
- Hypertensive disorders in pregnancy
- Proteinuria
- Gestational diabetes
- Gestational age at birth
- Hemoglobin value at the end of pregnancy
- Nutritional deficiencies in the mother or fetus found during pregnancy, at birth or few weeks after delivery

Subjects enrolled

All subjects were informed of the purpose of the study and signed the informed consent form at recruitment. They were informed that their participation was completely voluntary. No compensation of any kind was offered to study participants.

Statistical analysis

Descriptive statistics of demographic and clinical characteristics have been carried out using SPSS® statistics 24.0 software (IBM, Chicago, IL). Comparison between continuous variables was performed using Student's T-test or Mann Whitney's test and expressed as mean ± standard deviation of the mean (SD) or median (Interquartile Range, IR). Nominal and categorical variables were analyzed by the Chi-Square test and expressed as n (%). A multivariable logistic regression was used to control the potential confounding effect of age, parity, BMI. We calculated the risk for vegan mothers to have preterm birth, SGA fetuses, lower mean gestational weight gain compared to omnivorous mothers. P value of 0.05 was considered statistically significant.

4. Results

A total of 266 surveys were collected from women attending our maternity outpatient clinic: 245 (92.1 %) omnivores (O), 17 (6.4 %) lacto-ovo-vegetarians (LOV), and 4 (1.5%) vegan (V). The demographic characteristics of the patients are provided in Table 3.

TABLE 3. Demographic Characteristics of patients recruited according to diet

Values are given as number (percentage) or mean (±SD)

Vegan-vegetarian	**Omnivorous**
European 21 (100%)	European 245 (100%)
Age (years) 32.05 (±5.13)	Age (years) 32.56 ± 4.02
BMI (kg/m^2) 25.6 (±3.1)	BMI (kg/m^2) 26.8 (±3.42)
Parity 0.85 (±1.85)	Parity 0.93 (±2.05)

BMI body mass index at pregnancy onset

Our data showed a great increase in the percentage of vegan and vegetarian food styles (7.9%) in a region of Italy (Apulia) with a relatively high incidence of omnivorous eating habits (92.1%). Also they confirmed the nutritional deficiencies (vitamin B12 and iron) reported in previous studies and an increase of preterm birth delivery (23.8%). The incidence of SGA newborns was 9.5%. Complete results are reported in table 4.

TABLE 4. Main maternal and fetal outcomes in vegan-vegetarian and omnivorous patients

Outcomes	Vegan-vegetarian (21)	Omnivorous (245)	p
Spontaneous delivery	18 (85.7%)	214 (87.3%)	0.79
C-section	3 (14.3%)	31 (12.7%)	0.61
Iron deficiency	13 (61.9%)	25 (10.2 %)	*0.031*
Vit. B12 deficiency	7 (33.3%)	12 (4.9%)	*0.038*
Gestational weight gain (Kg)	11.6 ±4.21	14.31 ± 4.77	*0.002*
Gestational diabetes	2 (9.5 %)	22 (9%)	0.32
Gestational age at birth	37.1 weeks (±1.75)	39.82 ± 1.47	0.46
Hemoglobin value at the end of pregnancy	10.4 g/dl (±1.25)	10.9 g/dl (±1.45)	0.08
Weight of the newborn	3092 g (±365)	3328 g ± 595.8	0.06
Small for gestational age fetuses	2 (9.5%)	4 (1.6%)	*0.002*
Preterm birth	5 (23.8%)	20 (8.2%)	*0.004*

Intrauterine fetal deaths	none (0%)	none (0%)	
Hypertensive disorders in pregnancy	3 (14.3%)	34 (13.9%)	0.546
Proteinuria	1 (4.7%)	10 (4%)	0.065
Nutritional deficiencies in the mother or fetus (at birth or few weeks after delivery)	none (0%)	none (0%)	

Comparing vegan-vegetarian with omnivorous patients, we found that vegan-vegetarian groups presented higher prevalence of Iron and vitamin B12 deficiency (61.9 % vs 10.2 % and 33.3 vs 4.9%, P=0.031 and 0.038), higher prevalence of preterm birth (23.8% vs 8.2%, p=0.004), higher prevalence of SGA (9.5% vs 1.6%, p=0.022), and lower mean gestational weight gain **(**11.6 ± 4.21vs 14.31 ± 4.77; p=0.002) compared with omnivorous patients. No other statistically significant differences were found.

In multivariate logistic regression, women with vegan-vegetarian were associated to higher risk of preterm birth (OR 3.56, 95% CI 1.19–10.6, p=0.02), SGA newborns (OR 6.66, 95% CI 1.47–30.06, p=0.01), lower mean gestational weight gain (OR 2.82, 95% CI 1–7.92, p=0.049).

5. Discussion

We aimed to evaluate the safety and efficacy of vegan-vegetarian diets on maternal-fetal health during pregnancy within population living in Italy, in Apulia area, increasing the available scientific evidence. Especially, our main goal was to highlight if vegetarian or vegan diets could be considered safe for the mother's health and for offspring during pregnancy and lactation. We also aimed to determine the association between specific maternal diet and pregnancy outcome, especially small for gestational age fetuses and preterm birth, by comparing women who followed vegan-vegetarian diet to women who followed omnivorous diets.

Our study showed that vegan-vegetarian patients have iron and vitamin B12 deficiency, higher incidence of preterm birth delivery and SGA newborns, lower gestational weight gain.

Vegetarians-vegans in our study gained less weight during pregnancy compared to omnivores. This could explain the increased risk for SGA neonates. The most interesting data of our study is certainly the increased risk of preterm birth which is in contrast with the current literature [47-58].

The strength of our study is that it is one of the largest study carried out in a region of Italy (Apulia) with a relatively high incidence of omnivorous eating habits. We recruited women in different stages of their pregnancy in order to maintain heterogenicity. Also, women recruited followed the same diet for at least 3 months prior to their pregnancy up to delivery in order to avoid bias. Among the limitations of our study we can include the relatively small number of vegan-vegetarian group which presents limited generalizability. Also we were not able to stratify other demographic characteristics, such as ethnicity (all the patients were European) social status and smoking. Therefore, further larger studies are necessary to give more strength to our preliminary results because clinically relevant associations may still have been missed.

6. Conclusions

Our findings suggest that a vegan-vegetarian diet is associated with an increased risk for preterm birth and SGA newborns with lower gestational weight gain and also nutritional deficiencies (vitamin B12 and iron). Therefore, vegan-vegetarian women should be encouraged to maintain a healthy diet and to undergo regular follow-up of maternal weight and to undergo specific diet consultation. Adequate counseling should include discussion on the introduction of foods reinforced with B12 and iron and the need for any supplementation.

7. Future research

Pregnancy is a crucial time for the development of a new individual. Lifestyle and maternal nutrition, placental functioning and fetal genotype interact synergistically in a three-compartment model, in order to ensure adequate development intrauterine and a good pregnancy outcome [58].

The demonstration of a relationship between nutritional habits and pregnancy outcome parameters would have a strong impact in clinical practice and could explain whether there is a specific point in pregnancy in which a change in diet might influence the outcomes.

Preliminary studies have provided the first evidence of an association between maternal nutritional habits, first trimester markers of placental function, and gestational age at birth, laying the foundations for future intervention strategies starting as early as the first trimester of pregnancy. A large ongoing multicenter Italian study **(SIMPLE STUDY)** on both low and high-risk pregnancies is going to provide a more accurate picture of the current nutritional habits in pregnancy, as well as more reliable evidence of the detected association.

OGGETTO:"Studio prospettico, multicentrico per valutare l'associazione tra score nutrizionale periconcezionale, markers di funzionalità placentare del primo trimestre di gravidanza ed outcomes materno-neonatali" prot. SIMPLE Study

La Struttura diretta dalla S.V. è autorizzata a condurre. lo studio clinico citato in oggetto.

Lo studio dovrà essere condotto in rispetto alla normativa vigente nonché in ottemperanza del regolamento aziendale sulle sperimentazioni e studi osservazionali e alle prescrizioni del Comitato Etico.

La S.V. comunicherà al Comitato Etico l'inizio e la conclusione dello studio con rapporto finale ed eventuali interruzioni ed eventi avversi che si verifichino durante lo studio.

Tutta la documentazione relativa allo studio dovrà essere archiviata a cura della S.V. per un tempo non inferiore a 3 anni dalla conclusione dello studio..

Le ulteriori documentazioni dello studio (emendamenti, eventi avversi ecc. dovranno essere notificate al C.E. da parte dello sponsor per il tramite dello sperimentatore principale.

Nelle comunicazioni si prega di citare sempre il protocollo di approvazione del Comitato Etico **(43/CE/2021** del **31.3.2021)** e la Delibera del Commissario Straordinario **(DCS n. 220 del 8.4.2021).**

DELIBERAZIONE DEL COMMISSARIO STRAORDINARIO

Nominato con Deliberazione della Giunta Regionale n. 1892 del 30/11/2020

N. 220 del 08/04/2021

OGGETTO

Autorizzazione alla conduzione dello studio osservazionale no profit "Studio prospettico, multicentrico per valutare l'associazione tra score nutrizionale periconcezionale, markers di funzionalità placentare del primo trimestre di gravidanza ed outcomes materno neonatali" prot. SIMPLE Study da effettuarsi presso la struttura di Ostetricia Ginecologia Univ. – Promotore ASST Fatebenefratelli Sacco Milano - Sperimentatore prof. Luigi Nappi

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