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Nutritional challenges during pregnancy

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ABSTRACT

Nutrition and lifestyle during pregnancy and preconceptional period represent a major public health challenge, influencing the development of the embryo, fetus, and placenta, with considerable potential to influence not only maternal health but also that of future generations.
However, the risk of inadequate maternal nutrition is high both in underdeveloped and in industrialized countries, where inflammation due to maternal obesity, stress and pollution seems to play a major role in mediating maternal, perinatal and long-term adverse outcomes.
These dietary inadequacies are due to complex socio-cultural and economic interacting factors and it is to date mandatory to incorporate in clinician's appointment brief nutrition discussions supported by easy questionnaires and to propose simple and personalized multidisciplinary interventions.

INTRODUCTION

Nutrition and lifestyle during pregnancy and preconceptional period represent a major public health challenge, influencing the development of the embryo, fetus, and placenta [1, 2], and affecting not only women's health, but also that of future generations [3, 4].
However, the risk of an inadequate nutrition before and during pregnancy is high both in underdeveloped and in industrialized countries [4-6].
Moreover, the risk of not reaching the adequate nutrient supply is increased for selected groups of women of childbearing age: those following exclusion diets, underweight or overweight/obese, smokers and adolescents [7]. Understanding the relationship between maternal nutrition, pregnancy, inflammation and birth outcomes may provide a basis for developing nutritional interventions that will improve birth outcomes and long-life health of the newborn, improving the quality of life and reducing mortality, morbidity, and health-care costs.

RECOGNIZED ROLE OF MATERNAL NUTRITION ON SHORT- AND LONG-TERM OUTCOMES

A woman's nutritional health and lifestyle, before and during pregnancy, can influence clinically important pregnancy and offspring outcomes, since diet is recognized as one of the major environmental factors influencing the development of embryo, fetus, placenta, and maternal tissues [1, 2, 8].

Poor maternal nutritional status and lifestyle, along with maternal body composition, metabolism and placental nutrient supply, are the main factors that can negatively or positively influence fetal development and have been strictly related to adverse pregnancy outcome and expression of fetal genetic potential [4].

An adequate Body Mass Index (BMI), is crucial even in the periconceptional period [9]: a preconceptional BMI < 18.5 kg/m^2 increases the risk of intrauterine growth restriction (IUGR), preterm birth and iron deficiency anemia [10], while a pre-conceptional BMI > 25 kg/m^2, and especially preconceptional obesity, increases the risk of infertility, hypertensive disorders of pregnancy [11], gestational diabetes mellitus (GDM) [12], structural anomalies, large for gestational age infants or IUGR [13], preterm birth [14], fetal and neonatal death[15], caesarean delivery [16], poor lactation practices [17]. Furthermore, and equally importantly, excessive maternal BMI perpetuates the obesity epidemic, since children of obese women are more likely to be obese themselves and to suffer from chronic cardiovascular diseases [18].

Moreover, during pregnancy it is mandatory to obtain an adequate gestation weight gain (GWG) [19]: a lower GWG is associated with decreased birthweight and failure to initiate breastfeeding [20], while an excessive GWG is associated with increased birthweight, caesarean delivery rate and postpartum weight retention. In addition, excessive GWG is associated with subsequent obesity and long-term comorbidity associated [20], with the odds of overweight in offspring at age of 7 years old increased by 3% for every 1 kg of gestational weight gain [21].

Women should also be advised that their energy intake needs in the beginning of pregnancy do not significantly increase from pre-pregnancy levels [22, 3]; they should focus on eating well for pregnancy, and not eating more [23], with an ideal balance of macronutrients that is distributed between proteins (10-35%), carbohydrates (45-60%) and fats (20-35%), while micronutrients requirements increase more than the dietary energy requirements [24].

Inadequate maternal macro and/or micronutrient status has significant potential to adversely affect many developmental processes with both immediate and longer-term consequences on both mother and fetus [25-27].

Negative effects in term of weight and length of the newborn at birth could be associated to insufficient protein [28], folate [29], iron [30] and vitamin D intake, while excessive weight of the newborn, insulin-resistance, glucose intolerance and inadequate weight control are associated to an excessive amount of high glycemic index carbohydrates [31]. The risk of stillbirth and fetal growth restriction could be associated with inadequate protein [32] or vitamin D [33] or folate intake, while the risk of preterm birth could be associated with inadequate protein intake, with low n-3 PUFAs [34] or iron [30] intake.

Fetal brain and retinal development are influenced by *n*-3 PUFAs: DHA is the major of the *n*-3 polyunsaturated fatty acid contained in the human brain and retinal rods and, thus, is essential for brain and retinal development of the fetus during pregnancy and it plays a major role in the psychomotor neurodevelopment also in the first months of life [35].

Iodine intake is critical for maternal and fetal thyroid function and fetal neurological development, leading, in case maternal untreated hypothyroidism, to "iodine deficiency disorders" (abortion, congenital anomalies, deafness, neurological cretinism, neurocognitive delay, mental retardation, as well as attention deficit hyperactivity disorders) [36].

It has been recently demonstrated that periconceptional folate intake and status significantly correlate with embryo growth [29], birth weight and adverse pregnancy outcomes; folate inadequate intake can cause megaloblastic anemia, leucopenia and thrombocytopenia, hyperhomocysteinemia, and can increase the risk in the offspring of neural tube defects [37], congenital heart disease [38], placental vascular disorders [39].

As for the risk of developing hypertensive disorders of pregnancy, it is demonstrated to be influenced by low calcium [40] or Vitamin D [41] intake.

With regards to long term outcomes, nutrients are involved in enzymes, signal transduction, transcription pathways, oxidative stress and epigenetic modifications, since the periconceptional period [26].

Some of these effects occur via epigenetic mechanisms [42] such as DNA methylation or histone acetylation, heritable stable changes in gene expres-

sion not mediated by alterations of the DNA sequence, but susceptible to environmental influences, that can modify the growth and metabolic trajectory and that can be passed across generations [43].
Such environmental influences include both under- and over-nutrition, maternal hyperglycemia, dietary deficiency or imbalance of nutrients (such as folate, vitamin B12, vitamin B6, and choline which are involved in the methylation cycle), inflammation and lifestyle creating a cycle of passing "health capital" from one generation to the next [3]. Macro- and micronutrients affect the availability of methyl donors, substrates and transcription factors which are direct regulators of DNA stability and gene expression [44]. By this mechanism, nutrients are able to influence the complex biological pathways involved in gametogenesis, embryogenesis, as well as in placental and fetal growth, also impacting future health status, not only in terms of perinatal survival status, but by permanently modulating gene expression [10] and altering developmentally plastic systems, with implications in term of predisposing or not the fetus to non-communicable diseases (NCDs) in later life by influencing physiological thresholds of energy balance regulation [45]. This is of pivotal importance considering that NCDs, including obesity, metabolic syndrome, cardiovascular disease and type 2 diabetes mellitus, represent the leading causes of illness and mortality in the world (**Figure 1**).
Of note, the influence of the male partner's health should also not be neglected. Testis is formed when the male is a fetus, and the germ cells from which sperm ultimately differentiate are sequestered in fetal life, so it is possible that the father's sperm can be affected by environmental factors from his conception through to the production of mature sperm [46]; as for female germ cells, obesity, poorly controlled diabetes, and micronutrient deficiencies in males can affect sperm quality and fertility, thus affecting future offspring health [47].

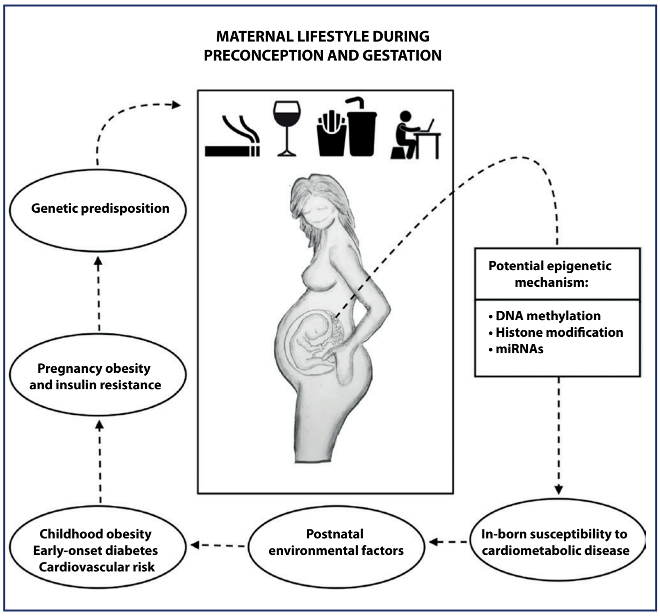

Figure 1. *Maternal lifestyle during preconception and gestation.*
Figure adapted from Moholdt T, Hawley JA. Maternal Lifestyle Interventions: Targeting Preconception Health. Trends Endocrinol Metab. 2020;31(8):561-9. Picture courtesy Anneliese Olsson.

CURRENT MATERNAL NUTRITION IS INADEQUATE BOTH IN UNDERDEVELOPED AND IN INDUSTRIALIZED COUNTRIES

The association between maternal nutrition and short- and long-term outcomes is quite complex and influenced by different biologic, socioeconomic, and demographic factors, which vary widely in different populations, but the overall risk of an inadequate diet, in the preconception period and throughout pregnancy, is high both in underdeveloped [48] and in industrialized countries [49].
Good nutrition is defined as a well- balanced diet that provides all essential nutrients in optimal amounts and proportions, whereas malnutrition is the state produced by an inadequate intake of a good quality diet, and this can refer to an inadequate intake of macronutrients such as calories and protein (*i.e.* undernutrition), to an inadequate intake or increased losses of specific or multiple vitamins and minerals (*i.e.* micronutrient malnutrition) because of an unbalanced diet or to an intake of too many macronutrients (*i.e.* overnutrition), or to an excessive amounts of inappropriate substances (as alcoholism) [26].
It is important to note that under- and over-nutrition can occur at the same time in sections of a population, and over time in the same person as circumstances change [50]. There are many well-known factors contributing to such change, including socioeconomic progress, urbanization, and adoption of a "Western lifestyle" [51] leading to a "nutrition transition" that creates a double burden indicated by high prevalence of childhood undernutrition as well as adiposity-related chronic diseases [52, 53], that is a key concern in many low- and middle-income countries, including India, that are currently undergoing nutrition and epidemiological transition [54] (**Figure 2**).

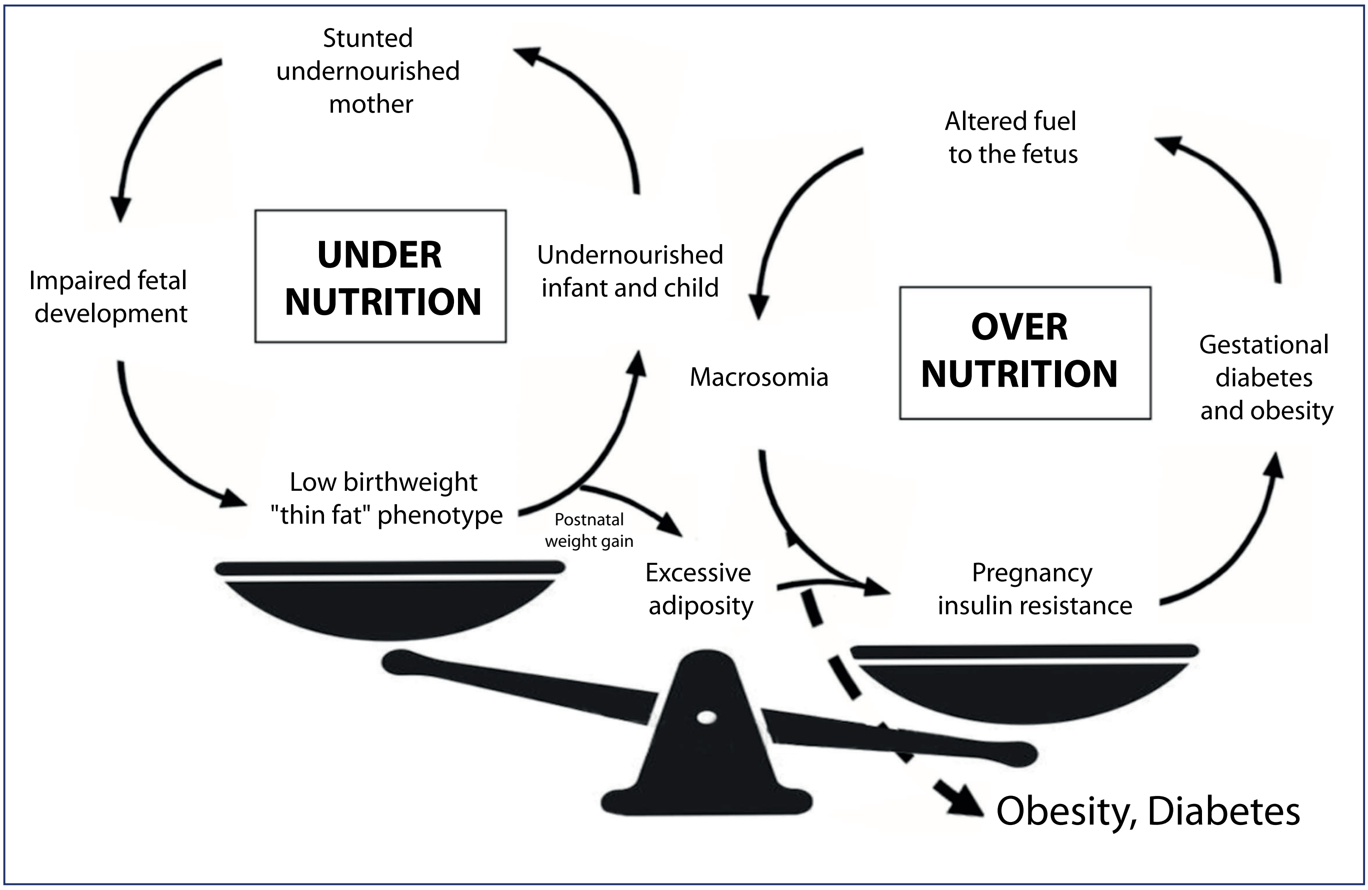

Figure 2. *Maternal nutrition and fetal programming.*
Figure adapted from Yajnik CS. Nutrient-mediated teratogenesis and fuel-mediated teratogenesis: Two pathways of intrauterine programming of diabetes. Int J Gynecol Obstet. 2009;104(Suppl):S27-31.

In underdeveloped countries undernutrition still causes the death of almost 1.5 million women [55] and children every year, and is usually associated with inadequate nutrient intake that occurs because of food shortage [56], increased nutritional requirements or losses, for example because of rapid growth or menstrual bleeding, parasitic or other infections (malaria, helminths, HIV), or inflammation [3]. Women living in under-resourced environments in low-and middle-income countries are likely to be deficient in a number of macro- and especially micro-nutrients, including iron, iodine, selenium, vitamin D, calcium, zinc and folate, which can lead to anemia [57] (the iron deficiency is the leading single-nutrient deficit, affecting over two billion people worldwide) stunting, to underweight and wasting, to reduced resistance to infections, to weaken their reproductive performance and to a greater risks of complications during pregnancy like low birthweight, preterm delivery and preeclampsia [58]. There is increasing evidence on the effects of maternal undernutrition on neonatal outcomes and long-term effects on intellectual, physical, and social development of the offspring, and the exposure to undernutrition in utero is connected to congenital anomalies, stunting in childhood, shorter adult height [59]. Studies have also shown an association between low birth weight resulting from undernutrition and increased risk of long-term impaired cognition, delayed motor development, obesity and NCDs in later life, as reported in individuals exposed to the Dutch famine of 1944-45 [60, 61].

Despite the availability of economic and nutritional resources, most women fail to meet the right energy, macronutrient and micronutrients needs also in industrialized countries [6, 62], where dietary patterns, typified by fast foods, snacking, breakfast skipping, soft drinks and energy-dense convenience foods rich in sugars and oils are nutritionally unbalanced and fail to meet recommended daily allowance for micronutrient [5]. More specifically, several studies have shown that iron, iodine, folic acid and vitamins D and B12 intake are consistently below national nutrient recommendations in most developed geographic regions [27, 63]. The switch to a high-fat and low-quality diet in developed countries, as previously commented, also causes maternal overnutrition and obesity producing a range of health risks for the woman, including hypertensive disorders of pregnancy, gestational diabetes mellitus (GDM), and obstructed delivery and risks for the fetus including macrosomia, high blood glucose/glucose intolerance, high blood insulin and neonatal hypoglycemia, congenital anomalies, preterm birth, stillbirth/ infant death, and development of childhood excessive weight and later NCDs in offspring, contributing to the obesity pandemic [64].

INCREASED INFLAMMATION DUE TO OBESITY, STRESSFUL LIFE, POLLUTION

Pregnancy is considered a natural inflammatory state. In early pregnancy, coordinated release of interleukin (especially IL-10 and IL-11) regulates trophoblast differentiation and invasion, being therefore crucial in the establishment of pregnancy [65]. Meanwhile, the immune system plays a key regulatory role across pregnancy and is characterized by unique, pregnancy-specific adaptations that protect the developing fetus from the maternal immune system and support the tissue remodeling necessary to pregnancy. Moreover, pregnancy is a state of profound metabolic changes characterized by increased fat mass, insulin resistance, and mild hyperlipidemia, where phospholipids, total, LDL and HDL cholesterol, and triglycerides significantly increase [66].

Potentially, these metabolic changes become pathologically exacerbated by pregestational obesity, a medical condition characterized by insulin resistance, hyperglycemia, hyperlipidemia and a low-grade chronic inflammation and oxidative stress [4, 67]. Recent studies suggest that this heightened inflammatory response, both locally (adipose tissue, placenta, and vascular endothelium) [68] and systemically (circulating plasma concentrations), may also be involved in mediating maternal, perinatal and long-term adverse outcomes, including gestational hypertension, diabetes, preeclampsia [69], fetal demise [70], preterm delivery [71], congenital anomalies, both impaired fetal growth and macrosomia [72], caesarean section and instrumental delivery [73], and might be responsible for metabolic imprinting in the offspring [74], predisposing offspring to possibly cognitive defects [75] and to NCDs as obesity and cardiovascular diseases [76].

In obesity, expansion of adipose tissue mass is associated with increasing inflammation and insulin resistance [67]: adipose tissue can recruit macrophages and promote inflammation, undergo necrosis, and express high levels of pro-inflammatory cytokines, including tumor necrosis factor (TNF)-alpha, interleukin (IL)-6, monocyte chemotactic protein (MCP)- 1, inducible nitric oxide synthase, transforming growth factor (TGF)-beta, and pro-coagulant proteins such as plasminogen activator inhibitor type 1, tissue factor and factor VII [77]. Recent studies also reported increased mitochondrial DNA and hepcidin levels in obese pregnant mothers, significantly correlating with pre-gestational BMI [78, 79], thicker and less efficient placentas in overweight [80] and obese [81] women (suggesting that an unbalanced pregestational nutritional status can decrease the placental efficiency in maternal-fetal exchanges). Moreover metabolomic analyses showed differences in placental metabolites involved in antioxidant defenses, nucleotide production, as well as lipid synthesis, LC-PUFA biomagnification and energy production, supporting a shift towards higher placental metabolism [82].

Inflammatory activity and immune and neuroendocrinal dysregulation are also associated with a "toxic" stress exposure, as occurs with prolonged exposure to adverse life circumstances, such as discrimination, economic hardship and different kind of violence or intense physical stress. Higher prenatal stress is associated with increased circulating levels of cortisol and pro-inflammatory markers (IL6, TNFα and IL1β), and lower anti-inflammatory marker (IL10), greater pregnancy virus reactivation [83] and reduced cellular immune competence. Several studies have demonstrated that maternal stress is associated with low birthweight [84], preterm birth [83], gestational diabetes, preeclampsia and postpartum mental health disorders [85].

It is conceivable that stressors experienced prior to conception could also affect immune cell gene expression during pregnancy, with a few studies highlighting the link between preconception stressful life events and poor obstetric outcomes, including low birthweight and preterm birth [86], but to date, the role of stress exposure before pregnancy in humans is controversial [87].

Finally, one of the major environmental health threat to pregnant women and their offspring is ambient pollution. Exposure to air pollution, especially to ultra-fine particles (< 1 μm), has been shown to induce oxidative stress and inflammation and recent studies have shown that different size inhaled particulate matter (PM) can enter the circulation and reach the human placenta and damage trophoblast with activation of endoplasmic reticulum stress, growth inhibition, oxidative stress and inflammation [88]. These still largely unknown effects on human placental function are related to a higher risk of preeclampsia, low birth weight and pre-term births [89]. Pollution acts on the woman health not only directly by particulate matter but also indirectly by polluter food due to the endocrine disruptors, exogenous substances able to mimic or to interfere with the endocrine system [90], found in high concentration in several everyday products including plastic bottles and food containers [91] that could be easily absorbed by dietary intake and that could negatively impact fetal and placental health by interfering with the embryonic developing epigenome [92] and potentially contributing to the onset of severe gestational conditions as preeclampsia [93], fetal growth restriction [94] and gestational diabetes [95].

HOW TO ADDRESS THE PROBLEM

Despite the recognized role of nutrition in improving maternal and child health and reducing the global burden of non-communicable diseases, several studies have shown inadequacies within women's dietary intakes in pregnancy worldwide [96-98]. The causes of this lack of adherence to recommended healthy dietary intakes for pregnancy are complex and remain, to date, object of debate and partially unexplained.

Women may not receive nutrition advice during pregnancy [99] or, when received, nutrition advices are often self-sourced, too general, inadequate, impersonalized or limited to addressing specific pregnancy issues (such as anemia and food safety) [100]. This may have a negative effect on behavior change, as demonstrated by previous studies showing that women may be less likely to follow generic advice [96], which moreover overlap with mistaken or false beliefs and conflicting messages, when searching for further advices from other sources then physicians [101].

Patients' craving and nausea, eating disorders, lack of resources, lack of healthcare professionals training and lack of time are other significant barriers to address nutrition changes in clinical practice [102] (**Figure 3**).

All these difficulties coexist in a global situation where even countries in which healthy diets originated, as the Southern Europe concerning the Mediterranean diet (rich of vegetables, fruits, cereals and fish and olive oil as the main fat sources and a moderate amount of red wine, and offering protection against cardiovascular diseases, some types of cancer and neurodegenerative diseases) [103] are rapidly withdrawing from their traditional eating pattern orienting their food choices towards products typical of the Western diet (which is rich in refined grains, saturated fats, sugars, red and pro-

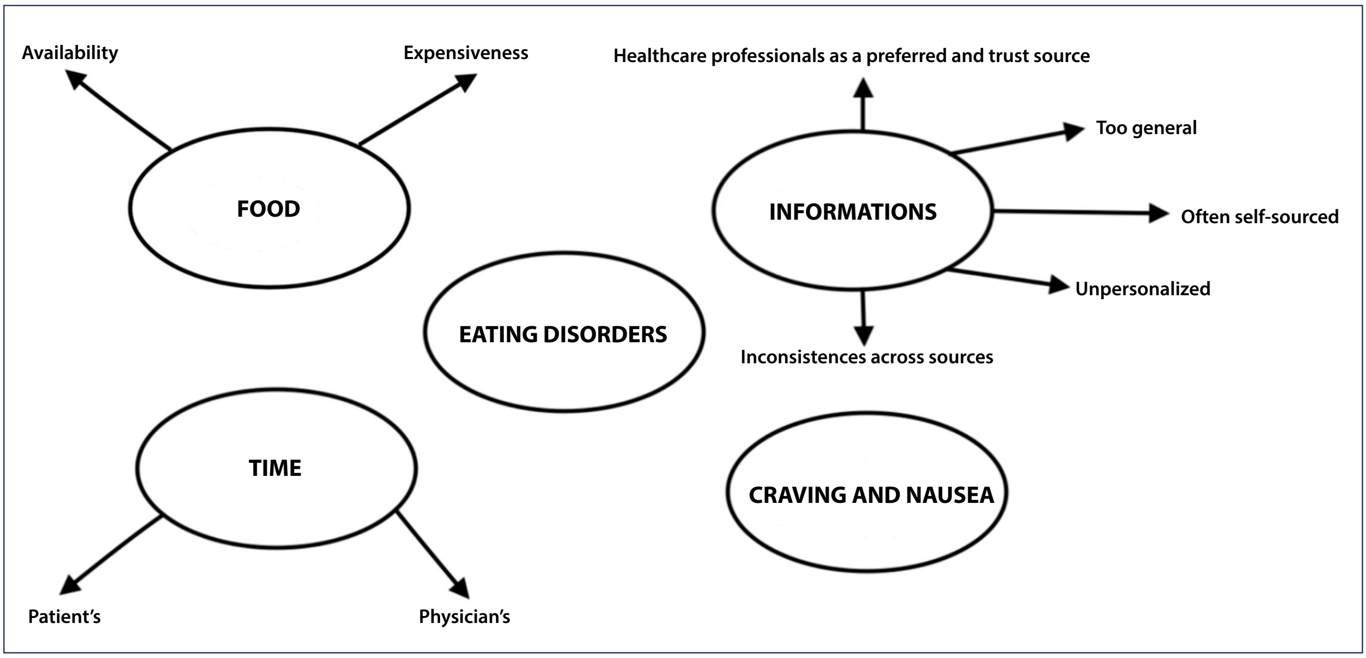

Figure 3. *Barriers influencing nutritional changes in clinical practice.*
Figure adapted from Killeen SL, Callaghan SL, Jacob CM, Hanson MA, McAuliffe FM. "It only takes two minutes to ask"-a qualitative study with women on using the FIGO Nutrition Checklist in pregnancy. Int J Gynaecol Obstet. 2020;151 Suppl 1(Suppl 1):45-50.

cessed meat and associated with several pregnancy adverse outcomes like birth defects, gestational diabetes mellitus, hypertensive disorders and offspring non-communicable diseases) [104].

One of the reasons of this diet transition has been imputed to the cost of some products typical of the Mediterranean diet, that has lead people to give up this eating pattern in favor of less-expensive foods [105]. This corroborates the evidence that diet quality follows a socio-economic gradient [106] where higher-income, older and better-educated women have a greater adherence to Mediterranean diet-like eating patterns, as recently demonstrated by the MOLI-SANI study [107], and to dietary guidelines or nutritional recommendations [98].

In this complex scenario it is mandatory to develop simple and effective methods to assess dietary behaviors and nutritional status during pregnancy to support the gestational weight gain assessments (that can determine if caloric intake is adequate, but cannot estimate adequacy of intake of specific nutrients or food groups) and the valid biochemical indices, thus promoting an healthy lifestyle, identifying women who may benefit from dietary intervention, and indeed closer fetal surveillance to prevent pregnancy complications [3].

As single food items and micronutrients, without considering the composite biological interactions between nutrients, have shown inconclusive associations with complex health outcomes [108], measures of the overall diet quality have been developed for adults by different international organizations [109, 110], explaining the full complexity of the diet by including both food and nutrient component, with an increasing number of pregnancy-specific dietary adaptations to reflect current nutritional recommendations for pregnancy and different national dietary guidelines [96, 109]. Dietary assessment tools such as food records, multiple 24-hour dietary recalls or food-frequency questionnaires can be used to assess diet quality in a reproducible way; a meaningful interpretation of diet quality is thus possible after a simplification of the multidimensional results into a unique composite score.

This evaluation of the quality of maternal intakes should start in the early pregnancy [9, 26], especially for the first-time mothers [96], and should be supported by nutrition scores that include those nutrients that are of a paramount importance in pregnancy for maternal and neonatal outcomes [111].

A simple, free, clinical practice tool specifically designed for obstetricians and gynecologists, as the FIGO (Federation of Gynecology and Obstetrics) Nutrition Checklist, is a potential solution to start conversations related to general healthy nutrition and weight in antenatal care: this checklist is in fact designed to facilitate quick and relevant nutrition discussions between women and their healthcare professional in a personalized and consistent manner [96], paving the way for further dietary and medical interventions (**Table 1**).

In this setting, a recent study demonstrated that first trimester nutritional score, based on the FIGO Nutritional Checklist recommendations and measuring the adherence to a healthy diet and lifestyle in pregnancy, is significantly associated with early biochemical and ultrasound markers of placental development, independently of pregestational BMI [97]. Higher first trimester maternal nutritional scores (reflecting adherence to healthy diet and lifestyle in pregnancy) were associated with increased PAPP-A concentrations, lower Uterine Arteries mean Pulsatility Index, decreased placental volumes at the first trimester screening ultrasound. These results may have a clinical impact on pregnancy, since a reduced first trimester placental volume has been shown to be predictive of preeclampsia and low birthweight [112]. Authors also underlined the possible positive effect of early nutritional counselling addressing women with an abnormal BMI, as required by local obstetric care protocols, in the improvement of nutritional habits during pregnancy.

In conclusion, during pregnancy women may be more motivated to make diet or lifestyle changes [3]: pregnant women welcome diet, weight, and nutrition-related discussions [113] and show desire for nutrition to be addressed as "part of the process" in antenatal care [96], considering diet as one of the factors that are in their control and that can help protect their health and that of the future child [114].

To promote these changes, and since most pregnant women consider doctors to be the most reliable source for nutrition information [101] and wish for nutrition and weight to be addressed during routine antenatal appointments [96], clinicians have the responsibility to incorporate brief nutrition and weight discussions as part of their standard appointment [96], giving their patients a chance for periodic reflections on nutritional health and lifestyle and proposing simple but personalized multidisciplinary interventions [115].

Table 1. *Demographic characteristics.*

1). DO YOU HAVE ANY SPECIAL DIETARY REQUIREMENTS (E.G. VEGETARIAN, VEGAN, ALLERGIES)?		
If yes, please list:	....	
2). WHAT IS YOUR:		
a. Weight	.... **kgs**	
b. Height	.... m	
c. (Health care professional to complete): Your BMI is	.... kg/m^2	
3). QUALITY OF DIET:		
i) Do you eat meat or chicken 2-3 times per week?	Yes	No
ii) Do you regularly eat more than 2 - 3 portions of fruit or vegetables per day?	Yes	No
iii) Do you eat fish at least 1-2 times per week?	Yes	No
iv) Do you consume dairy products (such as milk, cheese, yogurt) every day?	Yes	No
v) Do you eat whole grain carbohydrate foods (brown bread, brown pasta, brown rice or other) at least once a day?	Yes	No
vi) Do you consume packaged snacks, cakes, pastries or sugar-sweetened drinks less than 5 times a week?	Yes	No
4). WHAT IS YOUR:		
i) If you are pregnant, did/do you take folate/folic acid supplements in pre-pregnancy and in early pregnancy (first 12 weeks)?	Yes	No
ii) Do you get regular exposure to the sun (face, arms and hands for at least 10-15 mins per day)?	Yes	No
iii) Has the doctor/nurse tested your haemoglobin (level of iron in the blood)?	Yes	No
(Health care professional to complete): If yes, is it more than 110 g/l?	Yes Enter the value: ....**g/l**	No
If you have answered No to any of the questions in section 3 or 4 your nutritional status may need to be assessed in **more detail.**		

Table adapted from Hanson MA, Bardsley A, De-Regil LM, et al (2015) The International Federation of Gynecology and Obstetrics (FIGO) recommendations on adolescent, preconception, and maternal nutrition: "Think Nutrition First". Int J Gynecol Obstet. 131:5213-5253.

COMPLIANCE WITH ETHICAL STANDARDS

Authors contribution

All the authors contributed equally to this work.

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Study registration

N/A.

Disclosure of interests

The authors declare that they have no conflict of interests.

Ethical approval

N/A.

Informed consent

N/A.

Data sharing

Data are available under reasonable request to the corresponding author.

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