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Review

Risk management in obstetrics: how to reduce the risk?

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Abstract

In this paper the authors examined the most important factors that in the pre-conception period can interfere in the evolution of pregnancy. They also reported a method that since the first trimester of pregnancy is able to identify women at higher risk of developing preeclampsia.

Keywords

Lifestyle, folate supplementation, thyroid function, PCOS, first trimester screening.

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Introduction

It is known that the intrauterine life plays an important role in the health of the person from the birth until adulthood [1]. The physiological evolution of pregnancy (P) requires a good mother's health starting by the menstrual cycles preceding the fecundation up the term of P. In this regard it is important to remember the role of folic acid intake since the menstrual cycles prior to fertilizing. In addition to that, it is crucial even before P to evaluate thyroid function (TF), such as metabolic, infectious diseases that could affect the health of the fetus and the mother. This is particularly true when the mother is not young anymore, since with ageing there is a reduction of the ovarian reserve. In this period, in addition to the high prevalence of chromosomal alterations for damages of oocytes [2, 3], it is important to assess the overall health of the woman. It is well known that the increasing age predisposes to metabolic and vascular dysfunctions, as demonstrated in animal studies [4]. In these cases, there are difficulties in the embryo implant with deleterious effects on placental function and a high risk of preeclampsia (PE), intrauterine growth restriction (IUGR) and preterm delivery (PD) [5]. In the recent years efficacious contraceptive methods permit that the women could chose the time of their first P, so that the evaluation of the general mother's health is mandatory prior the onset of P. During the first trimester (1st tr.) of P, there are methods to examine the risk of several complications. This work tried to synthesize the approach to P with the aim both to prevent and to reduce the main pathologies dangerous for the well-being of newborn and mother.

Folate supplementation

Several studies documented the preventive effects of maternal folate supplementation on the occurrence of neural tube defects [6, 7]. A recent meta-analysis study evaluated the association between maternal folate supplementation and the risk of congenital heart defects (CHDs) [8]. This study evidences a significant decreased risk of CHDs with maternal preconception intake of folate. The common daily dosage of folate intake is 0.4 mg [9] from preconception (4-12 weeks) until the end of the 1st tr. of P (8-12 weeks). High risk mothers with recognized pathologies (including epilepsy, insulin dependent diabetes, obesity with BMI > 35 kg/m^2) require increased dietary intake of folate-rich foods and daily supplementation with 5 mg folic acid, beginning at least three months before conception and continuing until 10 to 12 weeks post conception. From 12 weeks post-conception and continuing throughout P and the postpartum period (4-6 weeks or as long as breastfeeding continues), supplementation should consist of a multivitamin complex with folic acid (0.4-1.0 mg) [10]. In the recent years there is also the proposal to insert folate in the hormonal contraceptives, with the guarantee to obtain a sufficient folic supplementation at the end of contraception [11, 12].

Lifestyle

Obesity is a very important problem since it is known the deleterious effect on the reproduction. However, these problems will be not evaluated in the present paper. Another problem is the awareness about the dangers deriving from the alcohol and smoke before and during the P.

Alcohol and pregnancy

Alcohol exerts teratogenic effects in all the gestation times, with peculiar features in relationship to the trimester of P in which alcohol is assumed. Alcohol itself and its metabolites modify DNA synthesis, cellular division, cellular migration and the fetal development. The characteristic facial appearance of babies affected by feto-alcoholic syndrome depends on the alcohol impact on skull facial development during the 1st tr. of P. There also are cerebral damages with defects of brain development that can get to fetal death. Serious consequences on fetal health also depends on the dangerous effects of alcohol exposure in the organogenesis of the heart, the bone, the kidney, sensorial organs, and other organs. Binge drinking is a high factor risk of mental retardation and of delinquent behavior in adulthood. Unfortunately, a lower alcohol intake also exerts deleterious effects on fetal health. In several countries of the world there is a high alcohol use, and this habit is increased in the women. Therefore, correct information has to be given to avoid alcohol use by women in the preconception time and during the pregnancy [13].

Smoke

The active smoke before and during P has been demonstrated to be deleterious for the fetal health [14]. The fetuses of women smoking during

P are estimated to have a higher risk of low birth weight compared with those of non-smokers. The decrement in birthweight appears to be primarily due to IUGR in relationship to disorders in endothelial functions of maternal vessels [15]. In addition to active smoking, environmental tobacco smoke exposure seems to exert negative effects on fetal growth [16-18]. Some studies showed a moderate increased risk of environmental tobacco smoke exposure and PD [19, 20]. Maternal smoking or environmental tobacco smoke exposure have shown greater effects in older women [21, 22]. During pre-conception it is important to highlight the negative effects of active and passive smoking on the outcome of P and this is even more important in women older than 35 years [23]. Furthermore, there are many evidences that nicotine is a neural teratogen. In fact, the exposure of fetal and neonate brain to nicotine through maternal smoking, exerts deleterious effect on cholinergic modulation of brain development [24].

Evaluation of woman's health

Thyroid function

The development of the brain proceeds soon after the conception with the composition of the three main part of the brain [25]. Thyroid hormones (TH) play a key role in the cytoarchitecture of the brain [26]. An insufficiency or an excess of TH during the first weeks of P may lead to disorders in the morphology of several brain regions, such as changes in the neurotransmitters [27]. Since the fetus is able to synthesize TH only by the second trimester (2nd tr.) of P, a lack or an excess of TH can exert adverse effect on fetal brain development. It is known that TH pass through the placenta [28], with deleterious consequences in the presence of maternal thyroid diseases. These reasons induce to screen the TF prior the conception [29]. However, during P the TF has to be evaluated also in euthyroid women. In fact, maternal TF changes throughout P in relationship to changes in the endocrine placenta function. TSH levels are low during the 1st tr. of P in relationship to stimulation of thyroidal thyrotropin receptors and thyroxine (T4) exerted by human Chorionic Gonadotropin (hCG) [30]. An increase of triiodothyronine (T3) and T4 levels begin with the increase of estrogens that stimulate thyroxin-binding-globulin (TBG). During P the use of trimester-specific range for TF is recommended. TSH is the most sensitive indicator of thyroid status in P with the following ranges: 0.1-2.5 mIU/L in the 1st tr.; 0.2-3.0 mIU/L in the 2nd tr; 0.3-3.0 in the third trimester (3rd tr.) of P [31]. During P increases the iodine's request in relationship to increased TH production, increased renal iodine losses, and transplacental transfer of iodine to the fetus [32]. The World Health Organization (WHO) recommends approximately 250 mg of iodine intake daily for pregnant women, higher than the 150 mg/day recommended for nonpregnant women [33]. It is important to remember that maternal iodine deficiency is associated with unfavorable outcomes of pregnancy and maternal TF [34].

Hyperandrogenism and polycystic ovary syndrome

Polycystic ovary syndrome (PCOS) is characterized by hyperandrogenism, ovarian dysfunction and polycystic ovarian morphology. PCOS is a reproductive disorder associated with metabolic disorders that can impair woman's health during the entire life [35]. A recent review [36] concludes that the risk of PE/pregnancy-induced hypertension (PIH) and gestational diabetes mellitus (GDM) is 1.5 and 2 times higher, respectively, in women with compared with women without PCOS. These complications of P depend on the low inflammation grade (LIG) that occurs in PCOS women, mainly in those in which obesity and the visceral obesity are associated with the PCOS characteristics [36]. In PCOS there is a strict relationship between hyperandrogenism and hyperinsulinemia. In a high percentage, at least 50%, of PCOS women, even in those with a normal weight, there is insulin resistance (IR), favoring metabolic disorders and stimulating adipose tissue. This condition is the *primum movens* for the metabolic syndrome in which the LIG plays a key role in the impairment of endothelium [37] and the consequent poor placentation, cause of the negative outcomes of P, such as PE, intrauterine growth retardation (IUGR), PD [38, 39]. In women with PCOS the oral glucose tolerance test (OGTT) is mandatory to evaluate the insulin-glucose metabolism. The American Diabetes Association has included the PCOS among the criteria for testing type 2 diabetes in asymptomatic women at the first prenatal visit [40], the same screening was recommended by the International Association of Diabetes and Pregnancy Study Groups [41]. The IR can be treated with metformin or with other treatments, such as the inositol, the antioxidant

compound [42]. Recently, the role of vitamin D (vtD) on metabolic disorders of PCOS has been evaluated. The gene encoding vtD receptors interferes on genes regulating glucose, lipid and blood pressure [43]. Although few studies are available on vtD supplementation in women with PCOS, it has been shown that in PCOS women low levels of vtD correlate with obesity and IR [44].

First trimester of pregnancy

During the first stage of P, the placental epithelium completely surrounds the embryo. At the end of the 1st tr., the gestational sac occupies the uterine cavity and the chorion is differentiates in the definitive placenta. The placenta contains the tertiary villi connected to embryo throughout the umbilical cord. They grow and differ throughout the P, forming the mature placenta. The extravillous throphoblast (EVT) invades the endometrium throughout the 1st tr. of P [45]. A part of EVT proliferates within the spiral arterioles and it is called endovascular trophoblast (EV). The EVT cells occlude the arterioles in the decidua spirals to avoid that the maternal blood enter the space intervillous developing [46]. The block of the arterioles is limited to the site of installation and, therefore, maintains a hypoxic environment for fetoplacental angiogenesis in the tertiary villi [47]. The activity of EV directs the size of the latest plate and placental chorionic final. This phase is crucial to ensure a proper size of the placenta so that fetal growth could be normal. Then there is the interstitial EVT whose cells preferentially surround spirals arterioles replacing the muscular artery wall with a matrix-like fibrinoid passively dilated to create channels that carry blood to the intervillous spaces [48]. The invasion of interstitial EVT is greater and continued during the 2nd tr. [49]. The myometrium is invaded by interstitial EVT to a depth of 3-5 mm. In P complicated by PE this invasion is limited to only 2 mm [50]. The placental angiogenesis is essential for a smooth development of the placenta. Growth and vascular remodeling are considered crucial in the placental and fetal growth [51]. Angiogenesis is regulated by various pro- and anti-angiogenic factors, including the family of the Vascular Endothelial Growth Factor (VEGF). VEGF is expressed by several cells; on the contrary, Placental Growth Factor (PlGF) is mainly produced by the placenta and is present in the circulation at high concentrations in normal P [52]. The PlGF levels increase approximately until the 32nd week, then decreasing until the end of P. In a P complicated by PE before the 37th week, the levels of PlGF are significantly lower because, in response to oxidative stress and inflammation, the placenta increases the release of the s-receptor Flt1, which, tying the PlGF, reduces the circulating free PlGF levels. PlGF may be a predictive marker of abortion during the first trimester of P: its levels are lower in women with miscarriage in comparison with those of women with at term P [53]. PlGF is used as a predictive marker of PE, which is characterized by abnormal patterns of angiogenic and anti-angiogenic factors [54]. Our recent studies show that PlGF levels are lower than the cut-off values for all women with PD without known causes [39]. In cases with values less than PlGF cut-off for gestational age, histology of the placenta showed clear signs of chronic hypoxia [39]. P-associated plasma protein-A (PAPP-A) plays a fundamental role in the regulation of Insulin Growth Factor (IGF) through local proteolysis of IGF Binding Protein-4 (IGFBP-4) [55]. The IGFBP-4 binds to IGF-I and IGFII with a high affinity, limiting their interaction with cellular receptors for IGF, a mechanism involved in the inhibition of fetal growth [56, 57]. In fact, it is known that the IGF system plays an important role in the development and placental growth; therefore, it is not surprising that low serum levels of PAPP-A may be associated with a higher incidence of PE [58]. The early identification of pregnancies with high risk for developing PE can reduce the prevalence of PE through therapeutic interventions as the prophylactic use of low-dose aspirin [59, 60]. A new system in which the assay of PlGF is associated in those of PAPP-A, βhCG and αfetoprotein (AFP) permits to give an early screening of PE if these parameters are associated with the measurement of median blood pressure, ultrasound examination with Doppler flussimetry of uterine arteries and the medical history of the woman.

Conclusion

Many elements should be considered to reduce the obstetrician risk. In this short paper we tried to examine the most indicative to reduce the risk in the prenatal period and during the early stages of P with the aim to give adequate preventive therapeutic measures addressed to antagonize negative outcomes of P.

Declaration of interest

The Authors declare that there is no conflict of interest.

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