PREEXISTING MATERNAL DISORDERS – RISK FACTORS FOR NEWBORN CONGENITAL ANOMALIES

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ABSTRACT

Congenital anomalies may be determined by genetic or environmental factors or a combination of the two factors. Maternal disease can affect fetal development through specific effects of metabolic products or maternal antibody transfer. Identifying mothers and pregnancies at risk as well as providing a teratogenic risk discussion and appropriate documentation is aimed at reducing potential teratogenic effects of maternal diseases.

Keywords: maternal diseases, teratogen, congenital anomalies

Congenital anomalies may be determined by genetic or environmental factors or a combination of the two occurring during prenatal development stages. It is estimated that about 10-15% of congenital anomalies are the result of the action of environmental (internal or external) factors on fetal development (1). It means that approximately 1/250 newborn have congenital anomalies caused by an environmental factors. Teratogens are any agents (medications, drugs, chemicals, physical, environmental agent, infections, maternal diseases) that cause a permanent abnormality in structure or function, restriction of growth, or death of the embryo or fetus. (2) The effects of a teratogen on the embryo or fetus depend on the nature of the agent and some other factors (dose, route, length of exposure, the embryonic developmental stage at the time of exposure, the genetic susceptibility of the mother and embryo/fetus). During the first two weeks of gestation, teratogens commonly kill the embryo and lead to miscarriage. (3) Some women have health problems *before* they become pregnant that could lead to pregnancy complications. Maternal disease can affect fetal development through several mechanisms: specific effects of metabolic products (toxic metabolic end product, maternal underproduction of an essential metabolic product) or maternal antibody transfer.

OBESITY

Maternal obesity during pregnancy is associated with adverse outcomes that include macrosomia, hypertension, pre-eclampsia, gestational diabetes mellitus and fetal death. (4-6) Some studies indicates that maternal obesity could lead to perturbation of the normal development and maturation of the immune system of the fetus in utero. (7) Other studies have noted that children of obese mothers had a temporary accelerated development of cognition and language, followed by a rapid decline until 18 months of age, especially regarding language. (8)

DIABETES MELLITUS

Birth defects in diabetic pregnancy is 10%, higher than the general population (3%). Hyperglycemia leads to myoinositol uptake inhibition that is essential for embryonic mitosis and development of neural tube. (9,10) Maternal pregnancy-associated plasma protein-A seems to be a biomarker for maternal diabetes and large-for-gestational-age newborn. (11)

Some studies notice a correlation between elevated hemoglobin A1c (HbA1c) levels and the incidence of major congenital anomalies in infants of diabetic mothers. (12,13) HbA1c which exceed 11.5% are associated with congenital abnormalities

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in 66% of the offspring: transposition of the great vessels, ventricular septal defect (VSD), and dextrocardia are the most common heart anomalies, anencephaly, spina bifida, and hydrocephaly are the major nervous system malformations. (14) It seems that maternal diabetes affects the temporal expression pattern of gene encoding molecules involved in heart development. (15)

Rare malformations include situs inversus and caudal dysplasia, vertebral and renal anomalies, imperforate anus, radius aplasia, renal agenesis and dysplasia, and other defects. Caudal dysplasia syndrome, with varying degrees of sacral agenesis, is occasionally associated with defects of the palate and branchial arches and occurs in 1% of diabetic offspring. (16,17) In 2015, Xiang AH et al suggest a correlation between maternal diabetes and autism spectrum disorders. (18)

THYROID DISORDERS

Thyroid disorders are common in general population, much more common in the female it is to be expected that they will appear during pregnancy. Maternal hypothyroidism is mainly due to autoimmune thyroid disease. Some results showed significant differences in IQ of children of mothers who had unrecognized subclinical hypothyroidism during pregnancy, the fetus depending entirely on maternal thyroid hormones for the first 12 weeks of pregnancy when the fetal thyroid appear. (19)

Untreated hypothyroidism is associated with low birth weight and increased risk of spontaneous miscarriage and perinatal mortality. (20) Combined maternal and fetal hypothyroidism occurs mostly in regions with dietary iodine deficiency.

Hyperthyroidism during pregnancy is usually due to Basedow Graves disease. Neonatal thyrotoxicosis is transitory, lasting several months but affected children could have goiter, exophthalmos, agitation, tachycardia, periorbital edema, high appetite, hyperthermia, cardiomegaly, cardiac failure, and hepatosplenomegaly. (21)

HYPOPARATHYROIDISM

Chronic hypocalcemia is less common than hypercalcemia. The causes include chronic renal failure, congenital and acquired hypoparathyroidism, vitamin D deficiency, pseudo-hypoparathyroidism and hypomagnesemia. There is no established treatment plan for hypoparathyroidism during pregnancy because some animal studies have suggested the potential for dose-dependent fetal toxicities (for example, growth impairment, skeletal malformations and cardiovascular anomalies). (22) Infants of mothers with untreated hypoparathyroidism and low maternal calcium may have parathyroid hyperplasia and transient hyperparathyroidism during the fetal and neonatal periods. Congenital hyperparathyroidism should be considered in neonates presenting with respiratory distress, chest deformity, bone demineralization and subperiosteal reabsorption occurs in the long bones, pulmonary artery stenosis, ventricular septal defect (VSD) and muscle hypotonia. (23,24)

NUTRITIONAL DEFICIT

Folate deficiency may lead to congenital anomalies (neural tube defects, orofacial clefts, cardiac anomalies), anemia and spontaneous abortions, pre-eclampsia and intra-uterin growth retardation. Pregestational supplementation of folic acid (400 μg/day) prevents neural tube defects. (25) The high doses of folic acid in early pregnancy reduced, also, the risk of VSD. (26) However, some experimental studies support the idea that folic acid taken during the first few weeks of pregnancy is linked to epigenetic changes in fetal DNA, leading to an increased risk of childhood asthma and allergies. (27) Other studies conducted to date suggest that maternal folate exposure is not associated with children allergies. (28) Maternal iron deficiency has a direct influence on neonatal iron stores and birth weight. This deficit can lead to cognitive and behavioural problems in childhood. Calcium deficiency is associated with pre-eclampsia and intra-uterine growth restriction. (25)

DNA polymorphism-cofactor diet hypothesis development (DDCD – dietary cofactor DNA polymorphism – D) support that schizophrenia is due to fetal brain abnormalities caused by the interaction between genetic mutations and maternal nutritional co-factors (eg folate, cobalamin or pyridoxine) which are insufficient in maternal diet. (29) Retinoic acid, the active metabolite of vitamin A, plays significant signaling roles in embryogenesis. It is well known that either an excess or a deficiency of vitamin A results in congenital malformations, including eye malformations, such as rudimentary eyelids, microphthalmia, exophthalmia, external ear malformations (microtia, anotia), cardiovascular anomalies (small heart, persistent truncus arteriosus, transposition of great vessels), diaphragmatic hernia or undescended testis. (30) Poor maternal nutritional status, for example chronically undernourished Indian women with little or no in-

take of animal protein in first trimester of pregnancy had infants with significantly higher birth weights. (31)

AUTOIMMUNE DISORDERS. SYSTEMIC LUPUS ERYTHEMATOSUS

Systemic lupus erythematosus (SLE) is a systemic inflammatory autoimmune disease which can affect the mother tegumentary and musculoskeletal systems as well as the fetus. SLE is characterized by immune hyperreactivity with pathogenic autoantibody formation. For exemple, first-trimester early abortion associated with maternal antiphospholipid antibodies which include lupus anticoagulant and anticardiolipin antibodies. SLE is also associated with increased frequency of preeclampsia, prematurity, growth retardation with newborns small for gestational age. Neonatal lupus syndromes (newborn with dermatologic, cardiac and hepatic abnormalities) is due to passive transfer of anti-Ro/SSA and/or anti-La/SSB antibodies (anti-nuclear autoantibodies) in some babies of mothers with autoimmune disease. The cardiac manifestations include conduction abnormalities (first-, second-, and third-degree atrio-ventricular block), endocardial fibroelastosis and cardiomyopathy. (32,33)

MYASTHENIA GRAVIS

Myasthenia gravis is an immune-mediated disorders caused by serum antibodies binding to the nicotinic acetylcholine receptor (anti-AchR antibodies), essential for neuromuscular transmission, resulting in progressive weakness and fatigue of voluntary muscles. Some studies showed that placental transfer of maternal anti-AChR antibodies to the fetus can cause increased risk of spontaneous abortions or premature births or, in about 10% of newborns, a transient neonatal myasthenia gravis with hypotonia, respiratory distress and feeding difficulties which commonly resolve in 4-6 weeks. In some cases was reported congenital multiple contractures in newborns, craniofacial dysmorphisms, cutaneous edema, kyphosis/scoliosis, multiple pterygia and low-set ears. (34,35)

PHENYLKETONURIA

Phenylketonuria is a rare disorder affecting phenylalanine metabolism, transmitted in an autosomal recessive manner, associated with plasma phenilalanine concentrations greater than 1,000 μmol/L. Phenylalanine has a teratogenic effect during pregnancy causing intrauterine and postnatal growth retardation, microcephaly, intellectual disability, cardiovascular defects (double-chambered right ventricle, tetralogy of Fallot, and ventricular septal defects). (36,37) Optimal phenylalanine maternal concentrations should be strictly maintained throughout pregnancy to reduce the risk of congenital abnormalities. (38)

MATERNAL FIRST TRIMESTER FEVER

Neural tube defects (anencephaly, spina bifida, encephalocele) have a complex etiology, involving both genetic and environmental factors. (39,40) Some studies have indicated that the reduced folate carrier gene (*SLC19A1*) is associated with an increased risk of neural tube defects (NTDs). The risk for NTDs was influenced by the interactions between the *SLC19A1* (rs1051266 GG/GA) variant and maternal first trimester fever. (41)

CONCLUSION

In conclusion, recognition of human teratogens offers the opportunity to prevent certain types of congenital malformations. This literature study demonstrates the continued need to evaluate the maternal health status when we are dealing with a children with congenital anomalies. Identifying mothers and pregnancies at risk as well as providing a teratogenic risk discussion and appropriate documentation is aimed at reducing potential teratogenic effects of maternal diseases.

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