Review Article

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Investigation of Some Modifiable Risk Factors That Lead to Congenital Anomalies: A Review Article

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ABSTRACT

Congenital anomalies are inborn errors of development. Genetic and environmental factors are known causes of congenital anomalies. Environmental factors are modifiable risk factors. This review focuses on modifiable risk factors for birth defects. There is a strong link between alcohol use and an increased risk of congenital anomalies. Marijuana can be expected to cause fetal growth restriction; smoking before conception, even with cessation in the first trimester, may also pose a risk for gastroschisis. Benzodiazepines during the first trimester were associated with Dandy–Walker malformation, anophthalmia or microphthalmia and esophageal atresia. While oral retinoids are absolutely contraindicated, topical retinoids, should conservatively be avoided during pregnancy but if were used by accident, the existing data can reduce the anxiety of happening adverse pregnancy outcomes. Antihypertensives such as labetalol, methyldopa and extended release nifedipine are relatively safe choices. Antiemetics such as doxylamine-pyridoxine and metoclopramide may have potential teratogenicity in first trimester. Ondansetron use was not significantly associated with major congenital anomalies but recent meta-analysis suggested more concern. An antiepileptic such as valproate poses the highest risk among antiepileptic drugs, whereas the prevalence of congenital anomalies is the lowest with lamotrigine, levetiracetam, and oxcarbazepine. Education and counseling to women who are planning to become pregnant can lower the risk of congenital anolamies.

Introduction

Congenital anomalies are inborn errors of development.[1] Every year 6% of all newborns worldwide are born with a serious birth defect, 94% of them occur in low- and middle income countries (LMICs). Higher birth rates, less accessibility to prenatal diagnosis, and lower rates of pregnancy termination following prenatal diagnosis of congenital anomalies (CAs) all contribute to an increased frequency of birth defects in LMICs.[2]

Studies performed in Iran between 2000 and 2016 reported the incidence rate of 18/1000 live births for congenital anomalies which 55.8% of them were males.[3] The etiology of nearly 50% of the congenital anomalies were known, which 30% -40% were related to genetic while 5%-10% were environmental and modifiable.[4]

Congenital anomalies are classified to majors versus minors as follows:

Anomalies which affect an infant's life expectancy, health status, physical or social functioning are described as "major" anomalies. Anomalies with little or no impact on health or function are called minor.[1]

This review describes some common maternal modifiable risk factors for congenital anomalies. Mothers should be informed about these environmental factors to reduce the birth incidence rate of congenital anomalies.

Alcohol exposure

Alcohol exposure is the most common cause of human birth defects related to environmental factors. The ethanol exposure can cause a wide range of birth defects, called fetal alcohol spectrum disorders (FASD).[5]

Although alcohol exposure leads to FASD, not all people exposed to alcohol would have FASD indicating that other risk factors were present. The study of monozygotic and dizygotic twins suggested that genetic loci regulating susceptibility to FASD might exist in the human population.[5]

FASD is a 100% preventable disorder because alcohol can be prevented during pregnancy. Therefore, FASD is one of the most important preventable forms of non-genetic birth defects associated with mental retardation.[6]

Alcohol consumption in the first trimester can cause usually gross structural anomalies. These structural defects may be associated with functional changes. Moreover there may be functional impairment with no obvious structural anomalies following alcohol exposure in the first trimester. Alcohol consumption in the second and third trimesters usually causes functional defects more frequently.[7]

FAS Anomalies: Structural defects associated with prenatal alcohol exposure include: prenatal and postnatal growth deficiencies, microcephaly, short palpebral fissures, maxillary hypoplasia, epicanthal folds, joint limitations, altered palmar creases, and septal or ductal defects of the heart.[8]

FASD Genetics: Ethanol is first cleared by converting into a highly reactive and toxic acetaldehyde, which then converts to acetate. The predominant enzyme involved in the conversion of alcohol to acetaldehyde is alcohol dehydrogenase (ADH), while CYP2E1 and catalase play minor roles. Acetaldehyde converts to acetate via aldehyde dehydrogenase (ALDH). Studies in mice have shown that inhibition of ADH activity but not ALDH increases the teratogenic effect of ethanol.[5]

Some candidate genes associated with ethanol and facial clefts anomalies are members of the Transforming growth factor (TGF) pathway, such as the Bmp target, MSX1, and the retinoic acid receptor, RAR-α. In addition SNPs in MLLT3 and SMC2 are significantly associated with ethanol usage and facial clefts. Some members of SHH pathway such as CDON, GLI2, and SHH does genetically interact with ethanol and result to holoprosencephaly in human.

Nitric oxide can be pro- apoptotic, which has been shown to protect nerve cells from apoptosis, making it a candidate to protect against ethanol-induced neuronal cell death.

PI3K/AKT/mTOR pathway can be inhibited by ethanol at multiple levels. Other

growth factor pathways, such as Insulin, that use the PI3K/AKT/mTOR pathway are likely to be ethanol-sensitive loci.[5]

Prevalence: The prevalence of FAS is estimated 13/1,000 live births. It is generally difficult to estimate the prevalence of prenatal alcohol exposure, as most of the exposed children are never diagnosed. Median age of diagnosis was 3.3 years, 6.5% were diagnosed at birth and 63% at age of 5-year- old.[9]

Prevention: There is no consensus on the safe amount of alcohol that could be ingested during pregnancy. Nevertheless, low levels of prenatal exposure may negatively affect embryo-fetal development. Considering this, the national health services in various countries suggest women to abstain completely from using alcohol during their pregnancy.[9]

Illicit Drug Use in Pregnancy

Marijuana: Marijuana's main psychoactive ingredient — tetrahydrocannabinol (THC) — can pass the placenta to reach the fetus and potentially harm brain development, cognition and birth weight.[10]

Marijuana and Anomalies: Marijuana is usually smoked and inhaled, which leads to high percentage of carbon monoxide leading to increased carboxyhemoglobin levels, and thus a decreased oxygen supply to the fetus. Therefore, Marijuana could be expected to cause fetal growth restriction.[11]

Prevalence: The prevalence of marijuana use in pregnant women ranges from 3% to 16%.[12]

Prevention: Mothers should aware of this risk factor and prevent using it.

Benzodiazepines: Benzodiazepines (BZD) are commonly prescribed for the management of anxiety and have been extensively studied for teratogenic effects. Maternal use of benzodiazepines results in fetal exposure as they easily cross the placental barrier.[12]

Benzodiazepines and Anomalies: BZD during the first trimester was associated with an elevated risk for Dandy–Walker malformation, anophthalmia or microphthalmia and esophageal atresia or stenosis.[13]

Some studies observed that BZD exposure during the first trimester of pregnancy seems not to be associated with an increasing risk of major malformations (MMs). However, during the second and third trimester of pregnancy, BZD exposure may be associated with some neonatal adverse reactions, such as a withdrawal syndrome and an infant floppy syndrome. No increase in the risk of neurobehavioral or cognitive disorders in infants exposed during pregnancy have been observed in the few studies focusing on this issue.[14]

Prevalence: The worldwide prevalence of benzodiazepine use or prescriptions during pregnancy was 1.9%. Highest prevalence was found in the third trimester. Lorazepam was the most frequently used benzodiazepine.[13]

Prevention: Mothers should aware of this risk factor and prevent using it.

Stimulants: Stimulants, including cocaine and methamphetamines, block monoamine reuptake in the nervous system, increasing the levels of norepinephrine, dopamine, and serotonin.[12]

Methamphetamine and Anomalies: According to the meta-analysis, the use of methamphetamine during pregnancy decreased birth weight, height, head circumference, and gestational age at birth. More studies are needed to extract safe conclusions about maternal complications.[15]

Recent work from prenatal models of exposure suggested enhanced developmental oxidative stress and impaired DNA repair as important components of its embryonic effects.[16]

Cocaine and Anomalies: Cocaine is available in natural and synthetic forms depending upon the source. It has direct effects on the central nervous system (CNS) through passing the blood brain barrier of both mother and fetus. Cocaine has vasoconstrictive effects on the maternal blood vessels including the placenta, often leading to intrauterine fetal growth restriction, hypoxia, preterm delivery and small for gestational age neonates.[17]

Prevalence: The prevalence of abuse during pregnancy in women seeking treatment is 5.8% for methamphetamine and 4.1% for cocaine.

Prevention: Given the detrimental effects of illicit substances, all women of childbearing age should be screened and counseled on illicit drug use as part of all health maintenance visits.[12]

Smoking

Approximately 10.9% of women reported smoking during the 3 months prior to pregnancy. Of those women, 75% continued smoking during pregnancy.[12]

Anomalies: Maternal tobacco use during pregnancy has been linked to a host of negative infant and child outcomes, including low birthweight, preterm birth, and various birth defects. Smoking during the few months before conception, even with cessation in the first trimester, may also pose a risk for fetal malformation such as gastroschisis.[18]

Ebstein anomaly is a rare congenital heart defects (CHDs) that may requires corrective surgery in the first year of life. Maternal exposure to second-hand cigarette smoke at home and a family history of CHD were associated with elevated odds of Ebstein anomaly.[19]

Prevalence: The prevalence of smoking during pregnancy decreased with rising education among women with a completed high school education or higher.[18]

Prevention: These findings highlight the importance of preconception women's health education efforts.

Medication Exposures

Retinoic Acid/Vitamin A: Vitamin A is a necessary nutrient for growth, tissue differentiation, reproduction, and vision, but excessive intake by pregnant women results in teratogenesis.[12] It belongs to a class of drugs known as retinoids.

Isotretinoin: Acne is the most common adverse event of skin from increased sebum production. Acne is very important for young adults because of risk of permanent scars. Acne can result in poor self-image, depression and anxiety, so affected women search for high effective treatments.[20] Isotretinoin or Accutane is a synthetic vitamin A medicine used to treat acne conditions that hasn't responded to other traditional treatments.[21] Data showed the use of isotretinoin is more than before because it is very successful in the treatment of the severe acne.[12,20]

Isotretinoin and Anomalies: Main side effects of isotretinoin are skin dryness, cracked lips, xerosis, blepharitis, itching, high triglycerides and hypervitaminosis. Isotretinoin may rarely cause serious problems like musculoskeletal adverse reactions, inflammation of liver or pancreas, cataracts, other vision changes and psychiatric disorders.[21]

Isotretinoin: must not be used during pregnancy or by those who may become pregnant during treatment, because isotretinoin contains a known teratogenic effect at any time with any dose during pregnancy and can causes congenital malformation in fetus.[20,22]

Isotretinoin in first trimester can cause cleft palate, heart defects, hydrocephaly, microcephaly, limb and sensory organ defects, facial dysmorphism, hypertelorism, intellectual disabilities, miscarriage, premature birth and central nervous system malformation.[23] The theory proposes that some kind of interaction between side effects of using isotretinoin in fetus are related to *Hox* genes.[20] *Hox* genes expression and function are essential during embryogenesis.[24]

Topical retinoids: Topical retinoids have good therapeutic activities but less adverse effects. A meta-analysis of pregnant women exposed to topical retinoids showed no clear increase in the risk of major congenital anomalies.[25]

MacDonald et al. also reported no significant difference in birth defects in pregnant women used topical retinoid.[26]

Prevalence: Taking isotretinoin among married females was 2.8%, the majority of whom were instructed by their physicians to use only one method of contraception. One

respondent got pregnant while using the medicine.[27]

Prevention:

Isotretinoin: Women who are candidate to use isotretinoin should read and sign a patient informed consent form to be aware of side effects and relapses of acne after using this medicine before its prescription.[28] They also should take a pregnancy test before starting isotretinoin.[22,29,30] They should also use an effective form of birth control, plus a backup method. They must have a monthly pregnancy test during treatment with isotretinoin.[22,30,31]

Topical retinoids: Topical retinoids, resulted in small changes in the serum concentrations of retinoids. Animal data indicated the relative safety of topical retinoids in pregnancy but the epidemiologic data supported this hypothesis were little. So the conservative recommendation would be retinoid avoidance during pregnancy but if topical retinoids were used by accident, the existing data can reduce the anxiety of happening adverse pregnancy outcomes.[32]

Antihypertensives

Both maternal hypertension and maternal antihypertensive use during pregnancy have been reported to be associated with increased risk of congenital heart defects (CHDs).[33]

However, further research that can adequately adjust for confounding by indication will provide much-needed clarity on the relative risks and benefits of different antihypertensive medications during pregnancy.[34]

ACEi, ARBs and Anomalies: ACEi and ARBs were associated with an increased risk of preterm delivery and miscarriage.[35]

First-trimester exposure to ACE inhibitors had an increased risk of major congenital malformations usually defects of the cardiovascular, renal, and central nervous system. The ACE inhibitors such as captopril and enalapril caused severe neonatal dysfunction, leading to oligohydramnios, pulmonary hypoplasia, contractures, and long-lasting neonatal anuria.[31]

Beta-blockers and Anomalies: exposure to the beta blockers in the setting of hypertension, was associated with an increased risk of preterm birth, being small for gestational age, increased perinatal mortality and low birth weight.[35]

The most compelling evidence was for associations between early pregnancy β-blocker use and CHDs.[33]

Calcium channel blockers and Anomalies: The results of the calcium channel blockers studies are mixed, with evidence of increased perinatal mortality, odds of preterm birth and malformations.[35]

Methyldopa and Anomalies: Methyldopa exposure was associated with an increased risk of preterm birth, perinatal mortality, and low birth weight.[35] Also There is evidence of the safety of methyldopa during pregnancy. Further studies are needed to clarify the influence of hypertension and treatment with antihypertensives on preterm birth and intrauterine growth.[36]

Diuretics and Anomalies: A cohort study from Denmark and Scotland identified increased odds of preterm delivery associated with prenatal exposure to diuretics among Danish offspring but not Scottish offspring. There was also an increased risk of low birth weight associated with diuretic use in the Danish offspring but not the Scottish offspring.[35]

Hydrochlorothiazide, triamterene, and amiloride are not teratogenic according to a small number of case reports. Some older studies raise concerns that thiazide diuretics might cause neonatal thrombocytopenia, but subsequent studies have shown that there was no increase in these events among neonates who were exposed to diuretics in uterus.[37]

Prevalence: Approximately 5-10% of pregnancies are complicated by hypertension in the US, The proportion of pregnant women in the US using antihypertensive medications increased over the past decade to approximately 3-5% of pregnancies.[34]

Prevention: The practitioner must carefully consider the risks versus the benefits of antihypertensive use in pregnancy, and clinical trials are needed to compare treatment of hypertension in pregnancy with and without antihypertensive drugs.

Antiemetics for Nausea and vomiting

Nausea and vomiting of pregnancy (NVP), is the most frequent medical condition in pregnancy, affecting up to 85% of pregnant women.[38]

Pyridoxine or doxylamine-pyridoxine combination are first-line pharmacologic treatments for NPV. Other antiemetics such as metoclopramide and ondansetron may be prescribed for the management of severe NVP.[39]

Ondansetron and Anomalies: For the majority of specific birth defects investigated, there was no increased risk associated with first-trimester use of ondansetron for treatment of nausea and vomiting of pregnancy compared with no treatment, although modest associations with cleft palate and renal agenesis–dysgenesis warrant further study.[40] Ondansetron use was not significantly associated with major congenital anomalies in the recent meta-analysis but diaphragmatic hernia, hypoplastic left heart and "respiratory system anomalies." Were increased.[41]

Moreover, ondansetron use was associated with less miscarriages and pregnancy terminations. These somewhat contradictory results suggest that more data are needed before the fetal safety of ondansetron can be assumed.[38]

H1 antihistamine and Anomalies: Studies provides reassuring information to both pregnant women and their health care providers regarding the safe use of h1 histamine during this sensitive time.[38]

Other drugs and Anomalies: Quebec Pregnancy Cohort (1998-2015) using 17 years-follow-up data reported the potential teratogenicity of doxylamine-pyridoxine and metoclopramide exposure in first trimester. Doxylamine-pyridoxine and metoclopramide use were associated with an increased risk of overall MCM. Doxylamine-pyridoxine exposure was associated with increased risks of spina bifida, nervous system and musculoskeletal system defects. Metoclopramide exposure was associated with an increased risk of genital organ defects.[39]

Prevalence: Within 17 years of follow-up, the prevalence of antiemetic use during pregnancy increased by 76%.[39]

Prevention: All guidelines recommend starting with dietary and lifestyle changes: avoiding triggers, fatty or spicy foods, avoiding an empty stomach, taking frequent small meals, fluids between meals, and/or keep crackers at bedside. Women with mild symptoms of NVP often find lifestyle and dietary modifications to sufficiently manage their NVP symptoms.[42]

Using antiemetics for mild or severe NVP, during pregnancy needs more studies.[38]

Antiepileptic drugs (AED)

AEDs used mainly for seizures, but also for neuropathic pain, migraines, and psychiatric disorders. AEDs can cause cognitive defects in low doses, but structural malformations in higher doses.[43]

Evidence related to the teratogenic risk of antiepileptic drugs is insufficient, particularly in relation to the dosage used.[44]

Prospective registries and meta-analyses have better defined the risk of major congenital malformations (MCMs) in offspring exposed to AEDs maternally at different dose levels. Valproate is the medicine with the highest risk, whereas the prevalence of MCMs is the lowest with lamotrigine, levetiracetam, and oxcarbazepine. For valproate, phenobarbital, phenytoin, carbamazepine, and lamotrigine, the risk of MCMs is dose-dependent.[45]

AED and Anomalies: Phenobarbital causes impaired growth and fetal mortality. Valproate can lead to cardiac anomalies, neural tube defects, dominantly spina bifida,

fetal valproate syndrome and developmental delay. Carbamazepine use can be associated with craniofacial defects, abnormal IQ, and growth retardation. Phenytoin exposure increases the risk of developing fetal phenytoin syndrome (FHS). Topiramate has been linked with hypospadias and oral clefts. Lamotrigine -although the safest mood stabilizer during pregnancy- carries an increased risk for facial cleft.[43]

Prevalence: One study estimated that 4.3 million AED were prescribed for the women of childbearing age in the USA in a year.[45]

Prevention: It is essential to inform women treated with AED that pregnancy planning is necessary. The problems related to antiepileptic therapy and the possibility of prenatal diagnosis should be accurately discussed with the patient before pregnancy: individual circumstances, desire to have children, severity of epilepsy, risks of seizures, family history of congenital malformations and all other potential risk factors must be considered, involving the patient in shared clinical decision-making.[46]

Conclusion

Physicians should provide mothers with the necessary information about risk factors of congenital anomalies, especially those which are modifiable. This can reduce the birth rate of babies with congenital anomalies.

Conflict of Interests

Authors have no conflict of interests.

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