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CME REVIEW ARTICLE 6

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Risk Factors for Birth Defects

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Importance: Major congenital abnormalities, or birth defects, carry significant medical, surgical, cosmetic, or lifestyle consequences. Such abnormalities may be syndromic, involving multiple organ systems, or can be isolated. Overall, 2% to 4% of live births involve congenital abnormalities. Risk factors for birth defects are categorized as modifiable and nonmodifiable. Modifiable risk factors require thorough patient education/counseling. The strongest risk factors, such as age, family history, and a previously affected child, are usually nonmodifiable.

Objective: This review focuses on risk factors for birth defects including alcohol consumption, illicit drug use, smoking, obesity, pregestational diabetes, maternal phenylketonuria, multiple gestation, advanced maternal age, advanced paternal age, family history/consanguinity, folic acid deficiency, medication exposure, and radiation exposure.

Evidence Acquisition: Literature review via PubMed.

Results: There is a strong link between alcohol use, folic acid deficiency, obesity, uncontrolled maternal diabetes mellitus, uncontrolled maternal phenylketonuria, and monozygotic twins and an increased risk of congenital anomalies. Advanced maternal age confers an increased risk of aneuploidy, as well as nonchromosomal abnormalities. Some medications, including angiotensin converting enzyme inhibitors, retinoic acid, folic acid antagonists, and certain anticonvulsants, are associated with various birth defects. However, there are few proven links between illicit drug use, smoking, advanced paternal age, radiation exposure, and statins with specific birth defects.

Conclusions and Relevance: Birth defects are associated with multiple modifiable and nonmodifiable risk factors. Obstetrics providers should work with patients to minimize their risk of birth defects if modifiable risk factors are present and to appropriately counsel patients when nonmodifiable risk factors are present.

Target Audience: Obstetrician and gynecologists, family physicians, maternal-fetal medicine physicians, and genetic counselors.

Learning Objectives: The learner should be better able to (1) outline the most common modifiable maternal risk factors that are associated with birth defects; (2) locate high-quality health information resources for patients; and (3) promote patient autonomy, responsibility, and motivation to pursue healthy lifestyle choices during pregnancy.

This review aims to describe the most common maternal risk factors for birth defects, discuss current guidelines and recommendations, and provide reliable patient resources for risk factors described. By providing evidence-based patient education/counseling and direction toward high-quality patient education materials, our aim is to minimize maternal risk factors for birth defects in the fetus.

Brent[1] estimated that 65% to 75% of birth defects are due to unknown causes with suspected polygenic and multifactorial etiologies. Single-gene disorders (15%–20%) and chromosomal abnormalities (5%) are the most common genetic etiologies. The remaining 10% of birth defects arise from environmental exposures including maternal medical conditions, substance abuse, infection,

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medications, radiation, hyperthermia, chemical exposure, and uterine abnormalities.

Alcohol

Alcohol-Related Birth Defects

Prenatal alcohol exposure continues to be the leading preventable cause of birth defects. It is estimated that 5% to 10% of pregnancies worldwide are currently at risk of alcohol-related birth defects.[2] The effects of alcohol include birth defects and severe developmental delay due to the fetal alcohol syndrome (FAS). Alcohol also contributes to preterm delivery, fetal death, and stillbirth.[3] Considering the potential to prevent or at least significantly decrease the likelihood of the aforementioned risks, increased knowledge across medical professionals and society on alcohol's risk to fetal development is critical.[4]

In fetal development, the frontal lobe and facial anatomy develop along a similar embryologic timeline and therefore are affected by alcohol at similar time points.[5] Cells in the nervous system are particularly sensitive to the effects of alcohol; thus, prenatal exposure may result in significant neurocognitive impairments including but not limited to attention, behavior, and intellectual problems. It is often these neurocognitive disruptions that have the most severe and devastating long-term consequences.[4] Facial development and physical manifestations of FAS can develop as a result of alcohol use during any state of pregnancy. The second half of the first trimester is the period during which fetal development is most susceptible to the impact of alcohol. Heavy alcohol use during this time is associated with facial findings including an increased risk of smooth philtrum, thin vermillion, microcephaly, and weight and height deficiencies.[5] Overall, there is a greater than 4-fold increase in birth defects associated with heavy prenatal alcohol exposure during the first trimester.[6]

The Prevalence of Alcohol Use Among Pregnant Women

Alcohol use is defined as a risky behavior when greater than 3 drinks are consumed in 1 sitting (binge drinking) or drinking on more than 7 occasions a week.[3] Among nonpregnant women of childbearing age, 53.6% reported drinking alcohol, and 18.2% noted binge drinking in the past month. These drinking behaviors extend to pregnant women as well, with 10.2% reporting regular drinking and 3.1% reporting binge drinking.[7,8] Considering that nearly half of pregnancies are unplanned, the likelihood that women are inadvertently consuming alcohol while pregnant is high.

Screening

Screening for alcohol use during pregnancy is underutilized.[3] Providers should routinely screen all females of childbearing age for alcohol use and provide materials detailing the risks of alcohol on fetal development. Current barriers to identifying in utero exposure include provider hesitance to initiate conversations, lack of provider education regarding alcohol-related birth defects, and current stigmas associated with drinking during pregnancy. While the teratogenic effects of alcohol may be known, clinicians may not be as familiar with screening and intervention opportunities.[4] Normalization of such questioning in every prenatal visit is expected to help women become more comfortable and honest with their healthcare providers. The T-ACE protocol was designed specifically for pregnant women and asks 4 questions[3]:

- How many drinks does it take for you to feel high (TOLERANCE)?
- Do you feel ANNOYED by people complaining about your drinking?
- Have you ever felt the need to CUT down on your drinking?
- Have you ever had a drink first thing in the morning to steady your nerves or to get rid of a hangover (EYE-OPENER)?

This standardized screening and documentation during prenatal visits for pregnant women will help identify at-risk individuals. In addition, proper documentation of maternal alcohol use is essential in early diagnosis of children with FAS. This is especially critical because some children will have mild facial dysmorphic characteristics and may not be acutely identified as having FAS. This delay in diagnosis may lead to a delay in appropriate treatment such as behavioral and cognitive therapy, special education classes, and various community support resources.[4]

Given the sensitivity of developing cells to alcohol, no safe threshold has been identified for maternal alcohol intake. According to the Centers for Disease Control, it is recommended that any woman of childbearing age who is sexually active without a reliable form of birth control should avoid the use of alcohol, given the risk of potential fetal alcohol exposure.[9]

Interventions

Once patients have been identified as engaging in unsafe behavior, physicians need to be equipped not only to speak of the risks, but also to provide pointed guidance to modify that behavior. One such form of guidance is motivational interviewing.

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Motivational interviewing provides physicians a framework to identify their patients' goals in improving their health. One key component of successful interviewing is determining the patient's readiness to change her behavior Specifically, it is important for clinicians to identify whether these patients recognize and understand the potential impact of their drinking habits. In some circumstances, basic education regarding the harmful effects of binge drinking and/or regular alcohol consumption may be enough to deter from future use. However, for other patients, continued discussions and counseling may be necessary before patients are prepared to make necessary changes. The importance of using the "stages of readiness" model is to create an environment for actionable change opportunities. It is well known that if patients do not feel that there is a problem they will not actively engage in correcting it.[3]

Illicit Drug Use in Pregnancy

Substance abuse in pregnancy is a multifaceted problem that has been linked to a variety of developmental defects and poor obstetric outcomes. Despite increasing evidence regarding these detrimental complications, prenatal exposure to illicit substances is increasing in the United States.[10] In 2004, the US National Household Survey found that 10% of women between the ages of 15 and 44 years reported drug use within the past month. The following rates of substance abuse were reported among women in this group: any illicit drug use (4.6%), cannabis use (3.6%), and cocaine use (0.3%).[11] The effects of commonly abused substances including opiates, benzodiazepines, stimulants, and cannabis are discussed in the following sections.

Opiates

The prevalence of opiate use in pregnancy has increased significantly in recent years. In an evaluation of greater than 1 million Medicaid patients, Desai et al[12] demonstrated that 1 (21.6%) in 5 pregnant women filled opiate prescriptions, and 2.5% received chronic opiate prescriptions (>30 days). Between 1992 and 2012, the proportion of pregnant women admitted for substance abuse treatment for prescription opiate abuse has increased from 2% to 28%.[13] As a result of increasing opiate use among pregnant women, there has been a substantial increase in neonatal abstinence syndrome (NAS), which had a rate of 5.8 per 1000 hospital births in 2012.[14] Between 2000 and 2012, the incidence of neonates affected by NAS has tripled, accounting for close to 50% of all neonatal intensive care unit hospital days. Although NAS is a growing problem, and opiate use in pregnancy is associated with numerous adverse obstetric outcomes, it has not been associated with any consistent pattern of birth defects.[10]

Benzodiazepines

Benzodiazepines are commonly prescribed for the management of anxiety and have been extensively studied for teratogenic effects.[10] Maternal use of benzodiazepines results in fetal exposure as they easily cross the placental barrier.

During the first trimester, benzodiazepine exposure has been linked to development of oral cleft palate.[15] However, there are no studies definitively associating benzodiazepines with causing specific anomalies.[10]

Stimulants

Stimulants, including cocaine and methamphetamines, block monoamine reuptake in the nervous system, increasing the levels of norepinephrine, dopamine, and serotonin. The vasoconstrictive effects of norepinephrine on uterine vessels result in fetal hypoxia and hypoperfusion of fetal tissues, which is associated with fetal growth restriction, low birth weight, and obstetric complications, including spontaneous abortion, placental abruption, and stillbirth. Regarding birth defects, amphetamine use during pregnancy has not been studied extensively, but case reports have suggested that heart defects, gastroschisis, small intestinal atresia, and cleft lip and palate may be associated with amphetamine abuse in pregnancy. However, other studies have shown no proven links between stimulants and birth defects, and they are not considered teratogens.[10]

Marijuana

The prevalence of marijuana use in pregnant women ranges from 3% to 16%. As with other illicit substances, THC, the active ingredient in marijuana, readily crosses the placental barrier.[10] There is a report of increased rate of anencephaly associated with cannabis use, especially during neural tube development in the first month after conception, although this finding has not been duplicated in all studies regarding marijuana.[11] Marijuana may be mixed with other illicit substances, so women may be unknowingly exposed to potentially more teratogenic substances.[2]

Screening for Illicit Drug Use

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. Not only are women wary of the social stigmas associated with drug use during pregnancy, but they may also be fearful of possible prosecution.

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Implementation of urine drug screens alongside bedside counseling provides significant benefits given the underreported nature of drug use among pregnant women. Obtaining an adequate history is vital in determining length and quantity of fetal drug exposure.[15]

Smoking

Prevalence

Smoking during pregnancy is associated with numerous adverse maternal, fetal, and neonatal outcomes. Cigarette smoking is arguably the most important modifiable risk factor during pregnancy.[16] According to 2014 US Birth Certificate Data, 10.9% of women reported smoking during the 3 months prior to pregnancy. Of those women, 75% continued smoking during pregnancy.[17]

According to Kmietowicz, cigarette smoking during pregnancy is most prevalent among women who are unmarried (15%), 20 to 24 years old (13%), non-Hispanic American Indian or Alaska Native (18%), or residents of West Virginia (27%).[18] Despite well-documented health risks associated with cigarette smoking during and outside pregnancy, the rate of smoking during pregnancy is declining very slowly at a rate of 0.1% annually.[18]

Associated Anomalies

Although difficult to isolate the pathophysiologic effect of fetal cigarette smoke exposure, there appears to be an increased risk of specific congenital malformations among infants born to smokers. Cigarette smoking during pregnancy is associated with development of cleft lip (with or without cleft palate), gastroschisis, anal atresia, transverse limb reduction defects, cardiac defects, digital anomalies, and bilateral renal hypoplasia or agenesis.[19–25]

The effects of cigarette smoking are multifactorial and are likely confounded by duration/amount, maternal age, genetic susceptibility, and gestational age at exposure. Sullivan et al[26] performed a case-control study of 14,000 infants born with congenital heart defects (CHDs) compared with 60,000 unaffected infants. They found that infants born to mothers exposed to cigarette smoke in the first trimester were at increased risk of pulmonary artery/valve anomalies and atrial septal defects. This effect was potentiated in patients with increased (ie, daily) exposure in the first trimester.[26]

Treatment

Routine screening for tobacco use should take place during preconception and prenatal visits.[27] Once identified, mothers who are exposed to cigarette smoke can be subject to targeted intervention through smoking cessation counseling, nicotine replacement, or pharmacotherapy.

The US Preventive Services Task Force (USPSTF) recommends screening all pregnant women for tobacco use and providing counseling and education for patients who use tobacco.[28] Nicotine replacement therapy (NRT) is considered first-line treatment for smoking cessation in pregnancy. According to the American College of Obstetricians and Gynecologists (ACOG), NRT is appropriate in pregnant patients if used under close supervision in individuals with a strong desire to quit smoking.[29]

There is conflicting evidence regarding NRT's ability to increase rates of abstinence among pregnant smokers. In addition, it does not appear to increase long-term abstinence.[30,31] There does not appear to be any strong evidence of adverse perinatal outcomes (eg, teratogenesis) in pregnant patients who use NRT when compared with those who do not use NRT.[32]

Alternatively, bupropion and varenicline are pharmacotherapies that can be utilized for smoking cessation in pregnancy. In a study by Chan et al,[33] smoking cessation among pregnant patients was higher among individuals receiving bupropion when compared with control subjects (45 vs 14%). Bupropion crosses the placenta, but a review by Briggs[34] suggests a low risk of birth defects in pregnant patients who use this medication as pharmacotherapy for smoke cessation. Varenicline functions through interaction with central nicotinic receptors. There is limited evidence regarding safety of this medication in pregnancy.[35]

Obesity

Prevalence

For the obese patient, pregnancy can be associated with a wide range of perinatal risks and/or complications. Minimizing these risks and managing potential complications are becoming increasingly challenging for women's health providers.[36] According to the 2009–20010 National Health and Nutrition Examination Survey, 31.9% of women of reproductive age (20–39 years old) were obese (body mass index [BMI], $\geq$30 kg/m^2). The prevalence of obesity was highest in non-Hispanic blacks (56.2%).[37]

Congenital Anomalies

Cai et al[38] performed a systematic review and meta-analysis of 14 case-control and cohort studies and found that obese women were at significantly higher

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risk of adverse fetal outcomes including CHDs, neural tube defects (NTDs), and orofacial clefts. Their data demonstrated a direct correlation between increasing maternal BMI and risk of CHDs. Pooled odds ratios (ORs) for all CHDs were as follows: 1.08 (95% confidence interval [CI], 1.02–1.15) for overweight (25–30 kg/m^2), 1.15 (95% CI, 1.11–1.20) for moderately obese (30.1–34.9 or 30.1–39.9 kg/m^2), and 1.39 (95% CI, 1.31–1.47) for severely obese (>35.0 or >40.0 kg/m^2).[38] These data included defects such as hypoplastic left heart, pulmonary valve stenosis, and tetralogy of Fallot (OR, 1.94; 95% CI, 1.49–2.51), which demonstrated the highest correlated risk with maternal obesity.[38]

In a 2008 meta-analysis of 12 case-control and cohort studies by Rasmussen et al,[39] the odds of having a child with a common NTD (eg, anencephaly, spina bifida) was significantly higher in obese versus mothers with normal BMI: overweight (OR, 1.22; 95% CI, 0.99–1.49), obese (OR, 1.70; 95% CI, 1.34–2.15), and severely obese (OR, 3.11; 95% CI, 1.75–5.46).[39]

In addition, a 2009 systematic review (39 studies) and meta-analysis (18 studies) of observational studies by Stothard et al[40] demonstrated increased odds of pregnancies affected by cardiac septal anomalies (OR, 1.20; 95% CI, 1.09–1.31), cleft lip and palate (OR, 1.20; 95% CI, 1.03–1.40), anorectal atresia (OR, 1.48; 95% CI, 1.12–1.97), hydrocephaly (OR, 1.68; 95% CI, 1.19–2.36), and limb reduction anomalies (OR, 1.34; 95% CI, 1.03–1.73).

Recommendations

For women who are overweight or obese, prepregnancy weight loss is strongly recommended given its overall health benefit and risk reduction. These patients should also be counseled about the appropriate levels of weight gain during pregnancy. The ACOG advises women who are overweight (BMI, 25–29.9 kg/m^2) to gain no more than 15 to 25 lb during pregnancy. An 11- to 20-lb weight gain is recommended for obese women with a BMI greater than 30 kg/m^2. Some physicians believe these allowances are too high and advocate for lower weight gain. The lower weight gain has not been shown to have a negative effect on fetal growth or neonatal outcomes.[41]

Diabetes Mellitus

Prevalence

Diabetes complicates approximately 3% to 10% of pregnancies, with 20% of women having pregestational diabetes (1% of all pregnant women) and the other 80% with gestational diabetes.[42] With the increasing rate of obesity, more women of childbearing age are likely to develop diabetes.[43]

Associated Anomalies

Pregestational diabetes (type 1 or 2) with poor maternal glycemic control has been associated with numerous congenital anomalies, including cardiac malformations (atrial septal defect, ventricular septal defect, transposition of the great vessels, coarctation of the aorta, hypoplastic left heart syndrome), caudal regression syndrome, central nervous system defects (NTDs), gastrointestinal malformations (duodenal and anorectal atresia, hypoplastic left colon), skeletal abnormalities, and genitourinary anomalies (renal agenesis, cystic kidneys, hydronephrosis).[43,44] Rates of central nervous system, cardiac, renal, gastrointestinal, and skeletal anomalies are increased as much as 4-fold in poorly controlled diabetics over the general population. In 1 study of congenital heart disease in infants of diabetic mothers, preexisting diabetes was associated with a 5-fold increased risk of congenital heart disease.[45] Maternal hemoglobin A_{1c} values correlate with the level of risk. Values of less than 7% carry a minimally increased risk of anomalies. Values between 7% and 8.5% confer a 5% risk, and values greater than 10% confer a 22% risk of congenital anomalies. At least 50% of anomalies affect the central nervous system or cardiovascular system.[43]

Management

Preconception counseling is absolutely necessary in patients with diabetes who are of childbearing age. Given the significant difference in risk of anomalies between well-controlled and poorly controlled diabetes, patients must be counseled to lower their hemoglobin A_{1c} prior to conception. When pregnancy is confirmed, patients need to maintain tight glucose control in order to improve neonatal morbidity and mortality.[43] In addition to a routine anatomy scan, fetal echocardiography is recommended at 22 weeks' gestation, given the significantly higher risk of cardiac anomalies in patients with poorly controlled pregestational diabetes.[42]

Phenylketonuria

Prevalence

Phenylketonuria (PKU) is an autosomal recessive disorder that, in most cases, is caused by deficiency of the hepatic enzyme phenylalanine hydroxylase (PAH).[46] The incidence of PKU is 1 in 13,500 to 1 in 19,000 in the United States.[47] In African Americans, the incidence

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is approximately 1 in 50,000.[48] Phenylketonuria is especially rare in Japanese and Finnish populations.[49,50]

The enzyme PAH is responsible for conversion of the essential amino acid phenylalanine to tyrosine. Almost all cases of PKU are caused by PAH gene mutations, which are mapped to chromosome 12q24.1.[51] Deficiency in PAH results in elevated serum phenylalanine and associated metabolites (ie, phenylacetate and phenyllactate). While the majority of cases of PKU originate from PAH deficiency, approximately 2% are caused by defects in the metabolism of tetrahydrobiopterin (BH4), an essential PAH cofactor.[52]

Associated Anomalies

In mothers affected by PKU, the presence of elevated serum phenylalanine concentrations during early pregnancy can result in teratogenicity. Uncontrolled maternal PKU can result in microcephaly, cardiac malformations, intrauterine growth restriction, and intellectual disability (ie, mental retardation). The risk and severity of fetal abnormalities are dependent on maternal serum phenylalanine levels.[53–55] Two studies analyzed the association between untreated maternal PKU and developmental complications. In pregnancies where maternal phenylalanine concentration was greater than 20 mg/dL, there was a significant increase in the incidence of microcephaly and intellectual disability (73% and 92%, respectively). Among this cohort, 12% of children were born with CHDs.[56,57] The development of fetal cardiac defects is dependent on maternal phenylalanine concentrations during the period of fetal cardiac development (4–10 weeks' gestation). In the Maternal PKU Collaborative Study,[57] CHD occurred in 34 of 235 infants of mothers with baseline phenylalanine levels greater than 15 mg/dL and persistent levels greater than 10 mg/dL by the eighth week of gestation. This was compared with 1 of 99 control pregnancies that were not affected by PKU. Two specific heart defects, coarctation of the aorta and hypoplastic left heart syndrome, were more common than in the general population (20% and 11%, respectively).[57]

Prevention

Fortunately, the teratogenic effects of untreated maternal PKU are preventable with dietary treatment. The maintenance of strict metabolic control of maternal phenylalanine levels before and throughout pregnancy can be achieved through a diet low in natural protein in combination with vitamin, mineral, and tyrosine-rich amino acid supplementation. According to the National Institutes of Health Consensus Development statement, it is recommended that phenylalanine levels should be maintained at levels less than 6 mg/dL 3 months prior to conception. During pregnancy, phenylalanine levels should be maintained between 2 and 6 mg/dL. Maternal phenylalanine levels should be measured weekly throughout pregnancy.[47]

The risk of adverse fetal outcomes is significantly reduced with maternal PKU treatment and resultant low phenylalanine concentrations prior to conception and/or 10 weeks' gestation. In the International Collaborative Study of Maternal Phenylketonuria,[58] a prospective evaluation of 572 pregnancies with maternal PKU and 99 control subjects, 16% and 18% of mothers achieved metabolic control with a phenylalanine-free diet prior to conception or by 10 weeks, respectively. In these patients, rates of microcephaly (3.6% and 5%, respectively) were significantly lower than those in patients with untreated PKU.[56]

In a retrospective study from the United Kingdom PKU Registry (1978–1997), it was demonstrated that infants born to mothers who underwent phenylalanine-restricted diets prior to conception showed significant improvement in neonatal outcomes compared with infants born to mothers who began this diet during pregnancy.[59] Regarding congenital anomalies, these infants had lower rates of CHD (2.4% vs 17%).[59]

It is important for all women with PKU to receive dietary education regarding good metabolic control of their phenylalanine levels prior to conception. Pregnancy planning and appropriate contraceptive counseling are essential to prevent unplanned pregnancy in this patient population.

Multiple Gestations

Prevalence

Multifetal pregnancies have increased throughout the years. Between 1980 and 2006, the number of twin pregnancies increased by 101%.[60] Twin pregnancy rates then stabilized at 32 per 1000 births between 2004 and 2006.[60] Two driving forces behind the increased incidence of twins and higher-order multiples include advanced maternal age (AMA) and the increased use of assisted reproductive technology (ART). With the increased use of ART, twin pregnancies have increased by 47%, and triplet pregnancies have grown by 37%.[61]

Associated Anomalies

Twins are at an increased risk of congenital anomalies, but this risk differs depending on zygosity and chorionicity. In 1 study of 73,264 deliveries, including 1688 twins, the frequency of malformations was greater

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in twins than in singletons, but in a subanalysis, rates in dizygotic twins were similar to those of singletons, whereas the rate in monozygotic twins was 5-fold higher than in singletons.[62] Another study of congenital anomalies in twins demonstrated a relative risk of anomalies of 1.8 (95% CI, 1.3–2.5) in monochorionic compared with dichorionic twins (Glinianaia et al[63]). Monozygotic twins are more likely to be affected by sirenomelia, holoprosencephaly, anencephaly, microcephaly, intestinal atresia, aplasia cutis, and limb amputation.[64]

Anomalies in multiple gestations have been reported in all organ systems, but the most common involve the cardiovascular and central nervous systems. In a systematic review by Bahtiyar et al,[65] the incidence of CHDs was found to be highest in monochorionic diamniotic twins than in the general population with a relative risk over the general population of 9.18 (95% CI, 5.51–15.29). Ventricular septal defects were the most common abnormality in multiple gestations.

High-order multiples are at increased risk of aneuploidy simply because of the combined risk of aneuploidy for each individual fetus.[60] In addition, chromosomal abnormalities become more common with age, and maternal age in multiple pregnancies is generally greater, so it follows that the incidence of chromosome abnormalities would be greater.[62]

Management

In response to the growing trend of multiples in ART, fewer embryos are now being transferred during IVF.[61] For those patients undergoing ART, counseling should include the risk of having multiples with the various modes of ART (natural cycle intrauterine insemination vs ovulation induction vs in vitro fertilization), as well as the maternal and fetal complications associated with multifetal gestations.

Once a multiple gestation occurs, there are few interventions that can improve outcomes, but multifetal pregnancy reduction should be offered to patients.[66] Patients should also be offered genetic screening, given the increased risk of aneuploidy. Monochorionic twins should be referred for fetal echocardiography, given their increased risk of cardiac defects.[42]

Advanced Maternal Age

Prevalence

Women are entering motherhood at increasingly later ages. Currently, approximately 10% of pregnancies in the United States are in women older than 35 years.[67] A number of factors are responsible for the increases in average maternal age. As the age of pregnancy has increased with time, medical advancements, including ART and more effective contraceptive measures, have supported women who have decided to pursue pregnancy options later in life.[68] Following successful conception, AMA pregnancies are associated with obstetric, fetal, and maternal complications.

Risks and Associated Anomalies

Weakened chromosomal cohesion in aging oocytes results in chromosomal segregation errors, serving as the presumed mechanism of aneuploidy. These chromosomal abnormalities result in increased likelihood of infertility, miscarriages, and birth defects.[69] At age 40 years, a chromosomal abnormality is found in every 50 births. The most common chromosomal abnormalities associated with AMA are trisomies 21, 18, and 13 and sex chromosome abnormalities.[70] Down syndrome occurs in 1 in 400 women at age 35 years, 1 in 105 at age 40 years, and 1 in 12 at age 45 years.[71]

Increasing maternal age is also associated with a rise in nonchromosomal malformations. A prospective study of maternal age and nonchromosomal abnormalities by Hollier et al[70] found that, compared with a reference group of women 20 to 24 years old, structural malformations increased significantly and progressively after age 25 years. The rate or malformations in the 20- to 24-year-old age group was 3.5% compared with 4.4% in women 35 to 39 years old and 5.0% in women older than 40 years. The OR for cardiac defects in women older than 40 years was 3.95 (95% CI, 1.70–9.17) compared with women 20 to 24 years old. Risk of clubfoot and diaphragmatic hernia increased with maternal age.[70] Gill et al,[72] as part of the National Birth Defects Prevention Study, examined rates of birth defects in 10 US states over a 10-year period and found that age older than 40 years was associated with cardiac defects, esophageal atresia, hypospadias, and craniosynostosis.

Management

Because of the increased prevalence of chromosomal abnormalities, women older than 35 years are offered diagnostic testing for chromosomal abnormalities. Accurate and early identification of these chromosomal abnormalities is important to provide management options for expectant mothers. Invasive diagnostic testing includes chorionic villus sampling or amniocentesis. Aneuploidy screening options also include noninvasive screening tests such as cell-free fetal DNA, first-trimester screening with pregnancy-associated plasma protein A, free β-human chorionic gonadotropin, and nuchal translucency, integrated screening, sequential

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screening, second-trimester screening including triple or quadruple marker screening, and diagnostic ultrasound.[71]

Advanced Paternal Age

Prevalence

Advanced paternal age is associated with an increase in sporadic gene mutations for autosomal dominant conditions including achondroplasia and Apert, Waardenburg, Crouzon, Pfeiffer, and Marfan syndromes. These mutations can potentially result in associated congenital anomalies.[73] According to Friedman,[74] the estimated frequency of autosomal dominant disease due to sporadic mutations in fathers older than 40 years was 0.3% to 0.5%.

Associated Birth Defects

In a large population-based retrospective cohort study by Yang et al,[75] the prevalence of birth defects was 1.5%. When compared with infants born to fathers aged 25 to 29 years, the adjusted ORs for any birth defects were 1.08 (1.04–1.12), 1.08 (1.02–1.14), and 1.15 (1.06–1.24) for fathers aged 40 to 44, 45 to 49, and older than 50 years, respectively. In this cohort, advanced paternal age was associated with a slightly increased risk of the following birth defects: CHDs, tracheoesophageal fistula/atresia, and trisomy 21.[75]

Interventions

Based on available data, advanced paternal age is associated with a slight increased risk of birth defects. Aside from ultrasonography, which can aid in detection of congenital malformations associated with autosomal dominant disorders, there are no specific screening tests specific to advanced paternal age.[76] According to the American College of Medical Genetics, pregnancies sired by a father with advance paternal age should be managed routinely according to the American College of Medical Genetics and ACOG guidelines, which include a prenatal counseling session and consideration of anatomic ultrasonography at 18 to 20 weeks' gestation.[77]

Family History

Obstetric providers should collect a thorough personal and family to assess for a history of heritable disorders, mental retardation, or psychiatric disorders. Specifically, a family history of birth defects could potentially increase the patient's risk of having an affected child depending on the affected relatives (eg, first-degree, second-degree) and the inheritance pattern (eg, autosomal recessive, autosomal dominant, X-linked). Evaluation for consanguinity is essential, given the associated increased risk of birth defects caused by rare recessive mutations in affected families. Positive family history of birth defects and/or genetic disorders should warrant referral to a genetic counselor or clinical geneticist for risk stratification and review of genetic testing options.[76]

Folic Acid Deficiency

Neural Tube Defects

Neural tube defects are potentially preventable birth defects, impacting 1 in 1000 pregnancies.[78] The 2 most common NTDs, anencephaly and spina bifida, are both the result of inappropriate neural development within the first 28 days after conception.[2] Anencephaly, which is fatal, is the inadequate closure of the anterior neural tube and results in an open skull. In contrast, children with spina bifida, the incomplete fusion of the posterior neural tube resulting in exposed spinal cord and nerves, can live well into adulthood.[79]

Although the exact etiology of NTDs remains unclear (at least 90% of NTDs occur without any prior history), both genetics and prenatal diet have been identified as contributing factors.[80] Studies have shown that folic acid supplementation prior to conception and during pregnancy decreased the prevalence of NTDs.[81]

Folate is a necessary coenzyme in DNA synthesis. During fetal development, cells are undergoing widespread and constant division to sustain the evolution of the growing embryo. Given the importance of folic acid in proper fetal development, the US Public Health Service issued a recommendation in 1992 that all women of childbearing age capable of becoming pregnant supplement their daily diet with 0.4 mg of folic acid. However, a 1998 study found that only 29% of women were following this guideline.[81] Therefore, the US Food and Drug Administration (FDA) mandated folic acid fortification of food. Since this FDA mandate, a 19% reduction in NTD birth prevalence has been observed in the United States.[82] Studies have also shown that by taking a daily multivitamin containing folic acid prior to conception and throughout pregnancy, women had a 25% to 50% decreased risk of having children with an orofacial cleft.[82]

Current Recommendations

In 1996, the USPSTF released an update on folic acid supplementation.[78] All women planning for pregnancy are recommended to take a daily supplement of 0.4 to 0.8 mg, which is the dose available in most multivitamin preparations. For women with a prior pregnancy

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with an NTD, 4 mg/d is the recommended dose.[78] This supplementation should be started 1 month prior to conception and continued during the first 2 to 3 months of pregnancy. In April 2016, the FDA approved folic acid fortification of corn masa flour, which is a staple ingredient in the diet of Latin Americans in the United States in an effort to decrease the incidence of NTDs in this population.

Given that nearly half of pregnancies are unplanned and NTDs develop in the first month after conception, the USPSTF additionally recommends that all women capable of becoming pregnant also consume 0.4 mg of daily folic acid.[78]

Although the evidence regarding the importance of folic acid during pregnancy is insurmountable, spina bifida and anencephaly continue to occur. Variability in access to folic acid supplementation, fortified foods, and education regarding the importance of folic acid in fetal development poses a barrier to prevention of NTD.[82]

Medication Exposures

There are a number of medications that should be avoided in pregnancy or that are absolutely contraindicated. While there are many medications that could potentially adversely affect a developing fetus, we briefly discuss the medications most commonly used in pregnancy and those most strongly associated with congenital anomalies.

ACE Inhibitors

Angiotensin converting enzyme (ACE) inhibitors have long been known to have adverse fetal effects. A systematic literature review by Hanssens et al[83] suggested that the ACE inhibitors captopril and enalapril caused severe neonatal dysfunction, leading to oligohydramnios, pulmonary hypoplasia, contractures, and long-lasting neonatal anuria. A more recent study from 2006 by Cooper et al[84] examined the association between first-trimester exposure to ACE inhibitors and major congenital malformations. Exposed infants had an increased risk of major congenital malformations (risk ratio, 2.71; 95% CI, 1.72–4.27) mostly due to defects of the cardiovascular, renal, and central nervous systems. Cardiac defects included atrial septal defect, patent ductus arteriosus, ventricular septal defect, and pulmonic stenosis.[84]

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. Pregnant women rarely eat large amounts of vitamin A, but they could take a large dose in a supplement or use a prescription drug containing retinoids. Retinoids are currently used for skin conditions, such as isotretinoin (Accutane) for acne and etretinate and acitretin for psoriasis. Central nervous system defects, including hydrocephalus, cerebellar hypoplasia, absent vermis, and structural malformations of the cerebral cortex, as well as craniofacial abnormalities (cleft palate), and heart and thymus defects have been observed in children exposed in utero to isotretinoin. Similar anomalies have been seen with etretinate exposure. Of note, Retin-A or tretinoin is a topical treatment for acne that has not been associated with anomalies, given that it achieves low concentrations in the maternal circulation (soprano). Regarding vitamin A supplements, 1 study showed that the ratio of birth defects associated with cranial-neural-crest tissue (craniofacial defects, CNS defects excluding NTD, thymic defects) in women taking more than 15,000 IU/d was 3.5 (95% CI, 1.7–7.3) compared with women taking less than 5000 IU/d.[85]

Folic Acid Antagonists

Folic acid supplementation has been shown to reduce the risk of NTDs, which have an incidence of 1 in 1000 births in the United States. Subsequently, folic acid antagonists have been implicated in increasing the risk of NTDs, as well as other congenital anomalies. They fall into 2 categories, dihydrofolate reductase inhibitors, and drugs that affect other aspects in folate metabolism (antiepileptics). Dihydrofolate reductase inhibitors include methotrexate, aminopterin, methotrexate, pyrimethamine, triamterene, and trimethoprim. The group of antiepileptics includes carbamazepine, phenobarbital, and phenytoin.[86]

In 2 retrospective case-control studies, folic acid antagonists were associated with an increased risk of NTDs (OR, 2.8; 95% CI, 1.7–4.6), cardiac defects (Relative Risk (RR), 3.4; 95% CI, 1.88–6.4), and oral clefts (RR, 2.6; 95% CI, 1.1–6.1). Specifically, the risk of NTDs increased 4-fold after trimethoprim exposure and 6-fold after carbamazepine exposure.[86,87]

Antiepileptics/Anticonvulsants

In addition to the folic acid antagonists, other antiepileptics have been linked to birth defects, including valproate sodium. More limited studies are available on the newer drugs topiramate and levetiracetam. The combination of major malformations, growth restriction, and hypoplasia of the midface and fingers is known as anticonvulsant embryopathy. This constellation of abnormalities is associated with anticonvulsant

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medications rather than epilepsy itself and is one of the common presentations seen in infants exposed to anticonvulsants in utero.[88] A multitude of specific malformations are described in the literature, but the major malformations observed in infants exposed to antiepileptics largely involve the central nervous and cardiovascular systems and also include oral clefting defects.

Many of the antiepileptics are used as single agents, but polytherapy is common and increases the risk of malformations. In 1 study of anticonvulsant polytherapy, among infants exposed to lamotrigine, the risk of malformations was 1.9%, whereas the risk was 9.1% for lamotrigine plus valproate sodium. The risk of malformations was 2.9% with single-agent carbamazepine but 15.4% for carbamazepine plus valproate sodium. The risk associated with lamotrigine or carbamazepine plus any other anticonvulsant was no different than lamotrigine or carbamazepine alone, suggesting that the risk of polytherapy is greatly increased when valproate sodium is included in the therapy regimen.[89] A more recent study examined polytherapy without valproate sodium to determine whether valproate sodium is increasing the risk of malformations, or if polytherapy in general confers a higher risk. Malformation rates were higher in pregnancies exposed to polytherapy compared with monotherapy, and they were higher in polytherapy involving topiramate but not levetiracetam.[90] It is therefore recommended that both valproate sodium and polytherapy in general be avoided in the first trimester of pregnancy to decrease the risk of major congenital malformations.[91]

Statins

As the prevalence of hypercholesterolemia, diabetes, hypertension, and obesity increases, HMG-CoA reductase inhibitors, or statins, are being prescribed more frequently to reproductive-age women. Statins are a category X medication in pregnancy based on animal data showing teratogenic effects. As a result, few studies have evaluated adverse fetal effects caused by these medications. Available data are from small cohort studies and case reports.[32]

Limb defects and central nervous system defects including holoprosencephaly were reported among a series of 52 cases of statin exposure in 2004.[92] A subsequent case series found 21 cases of CHDs, cleft lip with or without cleft palate, or NTDs in exposed infants, but no limb defects or holoprosencephaly. No consistent pattern of defects could be identified, and most patients were also obese and had diabetes, confounders that were not controlled for.[93]

In contrast, a review of pregnancy outcomes after exposure to simvastatin and lovastatin showed no difference in the rate of congenital anomalies (3.8% vs 3.2% in the background population).[94] These findings were further corroborated by a prospective cohort study that demonstrated no difference in the rate of malformations among exposed infants compared with unexposed control subjects.[95] Finally, in a recent cohort study from 2015 including 1152 women who used a statin during the first trimester of pregnancy, the rate of malformations was 6.34% compared with 3.55% in women who did not use a statin, a relative risk of 1.79 (95% CI, 1.43–2.23). However, when controlled for the confounder of diabetes, the RR was only 1.07 (95% CI, 0.85–1.37).[32]

Larger studies are needed before statins can be considered safe in pregnancy, and current recommendations are to discontinue use prior to conception. However, current data do not consistently support a significantly increased risk of congenital malformations associated with statins.

Radiation Exposure

Prevalence

Diagnostic imaging during pregnancy is becoming increasingly common.[96] Ultrasound remains the imaging modality of choice during pregnancy, given its accuracy and the absence of radiation exposure. Frequently, additional imaging modalities (eg, x-ray, computed tomography, nuclear studies) are required for evaluation.

Associated Birth Defects

There are no human studies regarding the effects of ionizing radiation on the developing fetus. Available data on the risk of ionizing radiation have been derived from case reports and extrapolation from studies of survivors from the atomic bomb in Japan and the Chernobyl accident. Based on available data, adverse fetal effects of ionizing radiation can be divided into 4 categories: pregnancy loss (miscarriage, stillbirth), malformation, disturbances in growth or development, and mutagenic or carcinogenic effects.[97,98]

Adverse fetal effects of ionizing radiation exposure are directly related to the gestational age at the time of exposure, the dose absorbed by the fetus, and fetal cellular repair mechanisms. During the first 14 days after conception, the developing embryo is most sensitive to the lethal effects of ionizing radiation. At this gestational age, the embryo generally is either resorbed or survives without damage (ie, “all or none”

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phenomenon).[99] During organogenesis (approximately 2–8 weeks after fertilization), the developing embryo can be subject to multiple sequelae of ionizing radiation including cell death, abnormalities of cell migration and proliferation, or mitotic delay.[100]

Congenital malformations of the central nervous system (eg, microcephaly, eye abnormalities) and fetal growth restriction are considered to be major sequelae of radiation damage during organogenesis. Specifically, microcephaly is the most commonly cited consequence of fetal exposure to ionizing radiation.[101] A study on radiation exposure among Hiroshima bomb survivors demonstrated that radiation exposure between 8 and 15 weeks was associated with the highest risk of mental retardation and microcephaly.[102]

Available Interventions

When pursuing diagnostic imaging modalities (eg, x-ray, computed tomography, nuclear studies), special consideration must be given to ionizing radiation exposure to a woman and her pregnancy. In making management decisions, risk of maternal-fetal exposure to ionizing radiation must be weighed against the risk of a missed or delayed diagnosis and any associated hazards to the mother or the fetus.[103] Where applicable, shielding can be used to prevent fetal exposure to ionizing radiation. Consultation with a radiologist or radiation physicist regarding dosing may be helpful when possible.

CONCLUSIONS

Through the provision of evidence-based patient and provider guidelines, the obstetric provider will be better able to promote patient autonomy, responsibility, and motivation to pursue healthy lifestyle choices during pregnancy. In doing so, patients can be empowered to minimize modifiable risk factors for birth defects in the fetus.

RESOURCES FOR PATIENTS AND PROVIDERS

National Organization on Fetal Alcohol Syndrome (NOFAS) (http://www.nofas.org/). NOFAS educates the public, practitioners, and policymakers about the risk of alcohol use during pregnancy and FASD.

National Institute on Alcohol Abuse and Alcoholism (http://www.niaaa.nih.gov/alcohol-health/fetal-alcohol-exposure). This page offers a brief description of, and risk factors for fetal alcohol spectrum disorders.

Centers for Disease Control and Prevention—Birth Defects (http://www.cdc.gov/ncbddd/birthdefects/index.html). The Centers for Disease Control's pages on Birth Defects provides facts, data and statistics, and information about various birth defects for health care providers, including free educational materials to give to patients. Included are steps that women can take to increase their chances of having a healthy baby by managing health conditions and adopting healthy behaviors.

MedlinePlus (https://www.nlm.nih.gov/medlineplus/). Produced by the National Library of Medicine, MedlinePlus is a Web site for patients and families and is the world's largest medical library. Its section on pregnancy and reproduction provides in-depth information to consumers to address many of the topics and concerns outlined in this article.

The American Congress of Obstetricians and Gynecologists (http://www.acog.org/Patients). The ACOG hosts a dedicated page for patients providing information, facts sheets, and videos on pregnancy and women's health.

March of Dimes (http://www.marchofdimes.org/index.aspx).

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