Review Article

Genetic Counseling of Fetal Microcephaly

CME Credits

Shu-Chin Chien[1], Chih-Ping Chen[2,3,4,5,6,7,8]*

[1]Kan-Ru Clinic, New Taipei, Taiwan, [2]Department of Obstetrics and Gynecology, MacKay Memorial Hospital, Taipei, Taiwan, [3]Department of Medical Research, MacKay Memorial Hospital, Taipei, Taiwan, [4]School of Chinese Medicine, College of Chinese Medicine, China Medical University, Taichung, Taiwan, [5]Department of Biotechnology, Asia University, Taichung, Taiwan, [6]Institute of Clinical and Community Health Nursing, National Yang Ming Chiao Tung University, Taipei, Taiwan, [7]Department of Obstetrics and Gynecology, School of Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan, [8]Department of Medical Laboratory Science and Biotechnology, College of Medical and Health Science, Asia University, Taichung, Taiwan

Abstract

Fetal microcephaly is a small head with various losses of cerebral cortical volume. The affected cases may suffer from a wide range in severity of impaired cerebral development from slight to severe mental retardation. It can be an isolated finding or with other anomalies depending on the heterogeneous causes including genetic mutations, chromosomal abnormalities, congenital infectious diseases, maternal alcohol consumption, and metabolic disorders during pregnancy. It is often a lifelong and incurable condition. Thus, early detection of fetal microcephaly and identification of the underlying causes are important for clinical staff to provide appropriate genetic counseling to the parents and accurate management.

Keywords: Congenital infections, fetal microcephaly, genetic counseling, genetic mutations, metabolic diseases

Introduction

Fetal microcephaly is defined as a fetal occipital-frontal head circumference (OFC) 2 or 3 standard deviations below the mean for gestational age.[1-4] The estimated risk is low but there was variation due to the different diagnostic criteria of microcephaly. The reported prevalence of microcephaly was 1.53–6 per 10,000 births.[5,6] The smaller OFC may relate to the greater risk of impaired neurodevelopment due to the various reduction of cerebral cortical volume. Children with microcephaly were observed to have many neurological problems such as mental retardation, delayed development, epilepsy, cerebral palsy, as well as audiology and ophthalmologic defects.[7] Thus, fetal microcephaly is an important predictor of impaired neurodevelopment in the future.

Microcephaly can be congenital and secondary. Fetal cerebral cortical development begins with the neural tube at 3 weeks of gestation, and the cerebral cortical neurons mostly generate at mid-gestation.[8] The disturbance or defects in neurogenesis resulting in deceased production of neurons can cause congenital microcephaly. Secondary microcephaly may be the defective maturation of neurons involving the reduced numbers of dendritic processes and synaptic connections after birth.[9]

Fetal microcephaly can be a solitary feature or combine with other anomalies based on the underlying causes. The causes are heterogeneous including genetic mutations, chromosomal abnormalities, congenital infectious diseases, maternal alcohol consumption, and metabolic disorders during pregnancy [Table 1].[4,9,10] The reported congenital infections causing microcephaly include *Cytomegalovirus* (CMV), herpes simplex virus (HSV), rubella virus, *Toxoplasma gondii*, varicella zoster virus (VZV), and Zika virus (ZIKV).[11,12] Prognosis of fetal microcephaly usually depends on the underlying etiologies and here we review the literature to summarize these causes. Prenatal diagnosis of microcephaly and identification of the etiologies are critical for clinical staff to manage accurately and provide appropriate genetic counseling about long-term prognosis and the recurrent risk to the parents.

Address for correspondence: Prof. Chih-Ping Chen, Department of Obstetrics and Gynecology, Mackay Memorial Hospital, No. 92, Section 2, Chung-Shan North Road, Taipei 10449, Taiwan.
E-mail: cpc_mmh@yahoo.com

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Table 1: The causes of fetal microcephaly

Genetic mutations
Autosomal recessive inheritance
Autosomal dominant inheritance (rare)
Chromosomal abnormalities
Congenital infectious diseases
CMV
HSV
Rubella virus
Toxoplasma gondii
VZV
ZIKV
Maternal alcohol consumption
Metabolic disorders during pregnancy
Maternal PKU
Fetal 3-PGDH
Fetal amish lethal microcephaly

CMV: *Cytomegalovirus*, HSV: Herpes simplex virus, VZV: Varicella zoster virus, ZIKV: Zika virus, PKU: Phenylketonuria, 3-PGDH: 3-Phosphoglycerate dehydrogenase deficiency

Genetic Mutations

Efficient and effective regulation of neural progenitor numbers and subtypes is critical for controlling the fetal cerebral size and morphology[11] The reported causative genetic mutations in cases with the inherited microcephaly have been found to be associated with impaired neurogenesis involving centriole duplication and the centrosomal cycles, mitotic checkpoint activation and regulation of mRNA translation.[13,14] To date, more novel microcephaly-causing mutations are discovered owing to the advent and improvement of whole-exome sequencing.

Monogenic hereditary microcephaly is mainly with an autosomal recessive pattern of inheritance including microcephaly primary hereditary (MCPH) and microcephalic primordial dwarfisms (MPDs). When the couple is consanguineous, the recurrence risk in siblings is high. The MCPH brain can have the reduced cerebral cortex with normal architecture.[15] The clinical features vary greatly in severity of impaired cerebral development from mild to severe mental retardation. The mutations involved genes include *MCPH 1* (OMIM 251200, on chromosome 8p23), *WDR62* (OMIM 613583, on chromosome 19q13), *CDK5RAP2* (OMIM 604804, on chromosome 9q33), *KNL1* (OMIM 604321, on chromosome 15q15), *ASPM* (OMIM 608716, on chromosome 1q31), *CENPJ* (OMIM 608393, on chromosome 13q12), *STIL* (OMIM 612703, on chromosome 1p33), *CEP135* (OMIM 614673, on chromosome 4p), *CEP152* (OMIM 614852, on chromosome 15q21), *ZNF335* (OMIM 615095, on chromosome 20q13), *PHC1* (OMIM 615414, on chromosome 12p13), *CDK6* (OMIM 603368, on chromosome 7q21), *CENPE* (OMIM 616051, on chromosome 4q24), *SASS6* (OMIM 661402, on chromosome 1P21), *ANKLE2* (OMIM 616681, on chromosome 12q24), *CIT* (OMIM 617090, on chromosome 12q24), *COPB2* (OMIM 617800, on chromosome 3q23), *KIF14* (OMIM 617914), *NLAPD2* (OMIM 617983), *NCAPD3* (OMIM 617984), *NCAPH* (OMIM 617985), *NUP37* (OMIM 618179), *TRAPPC14* (OMIM 618351), *RRP7A* (OMIM 619453), and *PDCD6IP* (OMIM 620047). *WDFY3* (OMIM 617520, on chromosome 4q21) in MCPH is an exception with autosomal dominant inheritance.[16] MPDs, a family of microcephaly accompanied by prenatal and postnatal growth restriction, include Seckel syndrome, Meier–Gorlin syndrome, and microcephalic osteodysplastic primordial dwarfism (MOPD) type II. Seckel syndrome, known as bird-headed dwarfism, is characterized by severe microcephaly with mental retardation, proportional short stature, low birth weight, and dysmorphic faces.[17] The syndrome is subdivided into several types based on the mutations involved genes including *ATR* (OMIM 601215, on chromosome 3q23), *RBBP8* (OMIM 604124, on chromosome 18q11), *CENPJ* (OMIM 609279, on chromosome 13q12), *CEP152* (OMIM 613529, on chromosome 15q21), *CEP63* (OMIM 614724, on chromosome 3q22), *NIN* (OMIM 608684, on chromosome 14q22), *DNA2* (OMIM 601810, on chromosome 10q21), *TRAIP* (OMIM 605958, on chromosome 3p21), and *NSMCE2* (OMIM 617246, on chromosome 8q24).[13,17] Meier–Gorlin syndrome is manifested by microcephaly, short stature, bilateral microtia, and absent or hypoplastic patella.[18] The mutations involved genes include *ORC1* (OMIM 224690), *ORC4* (OMIM 613800), *ORC6* (OMIM 613803), *CDT1* (OMIM 613804), and *CDC6* (OMIM 613805).[19,20] *GMNN* mutations in Meier–Gorlin syndrome are an exception with autosomal dominant inheritance.[21] MOPD type II is characterized by microcephaly, fetal and postnatal growth restriction, disproportionate face, abnormal skin pigmentation, insulin resistance, and an increased risk of cerebrovascular and hematologic disorders. It can be caused by mutations in *PCNT* (OMIM 210720).[22]

Autosomal dominant microcephaly is rare, including MLCRD syndrome (microcephaly, primary lymphedema, and chorioretinal dysplasia) (OMIM 152950), CDMMR syndrome (chorioretinal dysplasia, microcephaly, and mental retardation) (OMIM 156590), and *DYRK1A* syndrome (microcephaly, intellectual disability, autism spectrum disorder, and others). The reported mutations involved genes include *KIF11*, *TUBA1A, TUBB2B, TUBB3,* and *DYRK1A*.[23-25]

Chromosomal Abnormalities

Microcephaly can be associated with hundreds of syndromal congenital anomalies in the OMIM, including various types of chromosomal abnormalities.[26,27] The severity of phenotype is usually related to the numbers of genes involved. Only a few syndromes can be phenotypically recognizable, such as classical 4p16 deletion (Wolff − Hirshhorn syndrome, [WHS]). When symmetric intrauterine growth restriction together with microcephaly, hypoplastic nasal bone, and facial abnormalities are present on prenatal ultrasound, WHS should be considered.[28]

Congenital Infectious Diseases

Cytomegalovirus

CMV, a β-herpes DNA virus, is the most common congenital viral infection in the world with seroprevalence of 0.6%–0.7% in developed countries and 1%–5% in developing countries.[29-31] Most women of childbearing age are estimated to be infected and seroprevalence ranging from 45% to 100% tended to be higher in developing countries and lower in developed countries.[31] During pregnancy, primary infection is rare only about 0.7%–1.4% and nonprimary infection (viral reactivation) is more common in about 10% of seropositive women.[32] A higher risk of vertical transmission was reported in primary (32%) than in nonprimary (1.4%) maternal infection in pregnancy.[26] The transmission risk increases with advancing gestational age (30% in the first trimester vs. 65% in the third trimester) but infection at earlier gestation is related to more severe complications.[33] Almost all congenital CMV infections can be diagnosed by a polymerase chain reaction (PCR) test of viral DNA in the amniotic fluid at 20–21 weeks' gestation or 7 weeks after maternal infection and combined with culture.

Congenital CMV infection can result in spontaneous abortion, prematurity, and stillbirths[34] The reported abnormal prenatal features include brain anomalies, an echogenic bowel, intrauterine growth restriction, amniotic fluid anomalies, placentomegaly, hepatic calcifications or hydrops fetalis. Brain Magnetic resonance imaging (MRI) reveals the abnormal findings such as periventricular calcifications, ventriculomegaly, microcephaly, intraventricular septa, temporal pole lesions, and cortical anomalies. Several mechanisms of CMV-related brain abnormalities have been proposed. Odeberg *et al*.[35] in 2006 observed that aborted fetal brain cells are susceptible to CMV infection and then inhibit neuronal differentiation and induce apoptosis in human neural precursor cells. Rolland *et al*.[36] recently reported that the activation of nuclear Peroxisome proliferator-activated receptor gamma (PPARγ) which was detected in the congenitally CMV-infected brain can inhibit neurogenesis from human neural stem cells.

Many congenital CMV cases result from nonprimary maternal infection and most of them are mild or asymptomatic. About 10% of congenitally infected infants have symptoms and signs and most cases with clinical symptoms have neurological sequelae including sensorineural hearing loss, microcephaly, mental retardation, development delay, seizure, and cerebral palsy.[30,37] More than 30% of symptomatic infants have sensorineural hearing loss or neurologic problems during the first or early second-trimester infection.[32,38] Up to 13.5% of asymptomatic infected infants at birth could develop neurodevelopmental defects later in childhood and the most common defect is hearing loss.[39] Therefore, a fetus exposure to CMV infection should be followed for years after birth.[40]

It is a lack of benefit with CMV hyperimmune globulins to reduce the risk of vertical transmission. Valganciclovir administered to symptomatic neonates might improve hearing and neurological symptoms but the detailed treatment is still debated.[41] Screening is being considered for CMV in developed countries, but it is not recommended at present.

Herpes simplex virus

HSV type-1 and type-2 are a part of *Herpesviridae* family. HSV transmission occurs across epithelial mucosal cells and via skin breakdown. HSV can migrate to nerve tissues and remains latent within the central nervous system. HSV-1 is predominantly located in the trigeminal ganglia, whereas HSV-2 is in the lumbosacral ganglia. Genital HSV-2 is the leading sexually transmitted disease. HSV-1- or HSV-2-infected pregnant women can manifest tingling at the skin, or urogenital pain with blisters and ulcerations. Maternal HSV-1 encephalitis mostly occurs in the third trimester.[42] Perinatal HSV infection from vaginal delivery is more common than in-utero infection.[43] Thus, cesarean delivery is strongly recommended to decrease fetal exposure to virus despite antiviral therapy in pregnant women with genital lesions.

Congenital HSV infection may result in spontaneous abortion, prematurity, and stillbirths.[44] The abnormal prenatal features include intrauterine growth restriction and ventriculomegaly.[45] New-onset ventriculomegaly in a fetus of maternal HSV infection could be considered an indicator of antenatal central nervous system HSV infection.[45] A triad of cutaneous, ophthalmological, and neurological abnormalities (including microcephaly) can be found in prenatally HSV-infected cases. The activation of CD8 T-cells in HSV-infected brain cells limiting proliferation through the production of Interferon-γ might be the possible mechanism for brain abnormalities.[46]

At present, universal screening for HSV in pregnant women is not recommended.[47] The fast and sensitive diagnostic method is PCR testing of HSV-1 and HSV-2 in maternal serum.[48] Acute primary HSV can be diagnosed by the presence of Immunoglobulin M (IgM) antibody in symptomatic pregnant women but asymptomatic ones might miss this diagnosis. Antiviral suppressive therapy with acyclovir or valacyclovir in pregnant women with recurrent genital herpes at 36 weeks of gestation is recommended to reduce viral transmission to neonates.[49]

Rubella virus

Rubella is a single-stranded RNA virus in the genus *Rubivirus*, belonging to the *Matonaviridae* family. Rubella infection mostly occurs in childhood, known as German measles or three-day measles. No specific treatment is available now. The transmission can occur through respiratory droplets or transplacental route. Fortunately, rubella infection can be prevented by Mumps, Measles, Rubella vaccine which is a live-attenuated viral vaccine avoided in women being pregnant within 1 month of vaccine or during pregnancy.

Congenital rubella infection can end in miscarriage or stillbirth. The risk of congenital rubella infection reduces from 80% at the 1st 12 weeks of gestation, 54% at 13–14 weeks of gestation, to 25% at the second trimester respectively, and fetal abnormalities are rare if congenital rubella infection

occurs after 20 weeks of gestation.[50] Congenital rubella syndrome has the classical fetal Gregg's triad of congenital cataract, deafness, and cardiac defects.[51] The detected fetal or neonatal abnormalities include sensorineural hearing loss, ophthalmologic abnormalities (such as cataracts, microphthalmia, retinopathy, and glaucoma), cardiovascular abnormalities (patent ductus arteriosus, peripheral pulmonary artery stenosis, or coarctation of aorta), neurologic abnormalities (microcephaly, hydrocephalus, cerebral calcifications, intellectual disability, and meningoencephalitis) and intrauterine growth restriction.[52,53] It is still unknown the association between congenital rubella infection and brain abnormalities but the neurodegenerative mechanism involving degenerated brain vessels following rubella infection was observed.[11]

Despite routine vaccination, screening for the rubella virus with the detection of rubella-specific IgG in maternal serum is still recommended for all pregnant women now. Congenital rubella cases can be diagnosed with the detection of rubella virus by PCR or positive rubella-specific IgM antibody at birth.[54] Low avidity of IgG detected in pregnant women can help the diagnosis of a recent infection. The administration of Igs may be of benefit to prevent fetal rubella infection when the presence of maternal rubella infection.[55] Therefore, it is important to early identify rubella infection during pregnancy and to provide intensive prenatal and postnatal follow-up.

Toxoplasma gondii

Toxoplasmosis is caused by *T. gondii,* an obligate intracellular parasite. Most affected women (90%) are usually asymptomatic. The symptomatic women may only manifest a flu-like illness such as fever and malaise.[56] Congenital toxoplasmosis is caused by primary infection in pregnant women or reactivation of *T. gondii* in compromised pregnant women. Its prevalence is 0.1–0.3 per 1000 livebirths.[57]

The rate of vertical transmission increases with the advancing gestational age, ranging from 15% at 13 weeks, 44% at 26 weeks, to 71% at 36 weeks.[57,58] First-trimester infections can result in miscarriage or serious neurological disorders, but the severity of diseases often decreases with the advancing gestational age. Congenital toxoplasmosis has the classical triad of chorioretinitis, microcephaly or hydrocephaly, and widespread intracranial calcifications.[59] The incidence risk of brain defects was reported 30% at 5 weeks of gestation, 10% at 20 weeks of gestation, and <5% at 28 weeks of gestation.[57,58]

An acute infection can be diagnosed by the detection of low avidity *T. gondii* IgG antibodies and higher titers of *T. gondii* IgM antibodies. Fetal infection with *T. gondii* can be determined by analysis of amniotic fluid samples and guide therapy. Prenatal administration of spiramycin or pyrimethamine and sulfadiazine with folic acid can reduce the clinical manifestations in fetuses with congenital toxoplasmosis.[56,58] Prenatal and neonatal screening for toxoplasmosis is routinely done in some specific countries where fetal screening and treatment with spiramycin or pyrimethamine are offered if primary toxoplasma infection is detected in pregnant women. Thus, the occurrence of severe sequelae from congenital toxoplasmosis is rare now.

Varicella zoster virus

VZV, a double-stranded DNA virus, is a part of α-*herpesviridae* family. It is a highly contagious pathogen and varicella can be transmitted by contact with respiratory droplets or skin lesions, and transplacental route. Initial VZV infection causing varicella (chickenpox) mostly occurs in children with self-limiting manifestations, but it becomes usually severe in adults. Varicella can be prevented by Zostavax vaccine, a live-attenuated virus avoided in women being pregnant within 1 month of vaccine or during pregnancy. Primary infection usually can offer lifelong immunity.[60] Reactivation of prior latent VZV virus can cause herpes zoster (shingles) which is rarely seen in pregnancy because of the presence of antibodies against transplacental viral transmission and there is no adverse fetal effects observed in pregnant women with zoster.[61]

The risk of vertical VZV transmission is low about 0.5%–1.5% in the first and second trimesters.[62] The reported abnormalities associated with congenital varicella syndrome include limb deformities, growth restriction, ophthalmologic defects (cataracts and chorioretinitis), and neurologic defects (microcephaly, hydrocephaly, cerebellar hypoplasia, and mental retardation).[63,64]

VZV DNA can be detected by amniocentesis or cordocentesis to diagnose congenital varicella infection. Currently, no effective treatment is available to reduce the rate of vertical transmission. Prophylaxis with varicella zoster immune globulin and valacyclovir is suggested in immunocompromised pregnant women exposed to VZV or exposed newborns.[65,66]

Zika virus

ZIKV, an arthropod-borne *Flavivirus* (within the family of *Flaviviridae*), relates to the dengue virus, yellow fever virus, Japanese encephalitis virus, and West Nile virus. It is a single-stranded RNA virus. The virus can be transmitted by Aedes mosquitoes' bites, sexual activity, blood transfusions, and placental route. The symptoms in ZIKV-infected people include fever, rash, arthralgia, and conjunctivitis, but up to 80% of cases with ZIKV infection are asymptomatic.[67]

Sporadic ZIKV-infected cases have been documented for more than 60 years. Several outbreaks were documented in Yap Island (estimated 73% of the population infected) in 2007, in French Polynesia (up to 66% IgG positive) in 2013–2014, and in central and south America in 2014–2015. The relationship between ZIKV infection and fetal or neonatal microcephaly born to infected pregnant women was proposed during the 2015 outbreak.[11]

Congenital ZIKV infection can result in fetal loss. There are significant fetal neurological complications, especially infection in the first trimester. Brain abnormalities are the major features of congenital ZIKV, including microcephaly, cerebral calcifications, ventriculomegaly, malformations of cortical development, and

anomalies of the corpus callosum and the posterior fossa. The extra-brain abnormalities include arthrogryposis, ophthalmologic defects, and intrauterine growth restriction, placentomegaly, transient hepatitis, mild anemia.[68] The mechanisms between ZIKV and microcephaly have been studied.[69-71]

Neither effective treatment nor vaccine is available now. Early identification of ZIKV infection during pregnancy is important. In acute symptomatic maternal infection, ZIKV can be detected in serum, blood, oral fluid, or urine by PCR testing. Specific IgM can be detected in the mother as early as 4–5 days' postinfections and for up to 12 weeks.[72] PCR testing of amniotic fluid for ZIKV is available but the need is still debated.[73] Screening is being considered for ZIKV in countries with high rates of transmission but is still not recommended at present. To inform the appropriate protective methods are required by preventing mosquitoes' bites, avoiding pregnancy at least 2 months after a trip in high-risk ZIKV areas, and using condoms for 6 months when sexual contact.[74]

Maternal Alcohol Consumption

Maternal consumption of alcohol during pregnancy can result in fetal alcohol spectrum disorder, which can affect neuronal proliferation and apoptosis resulting in microcephaly. Blockade of N-methyl-D-aspartate (NMDA) receptors might be a role to impair fetal brain development.[75] Retinoid acid deficiency caused by alcohol exposure during embryogenesis was also reported to influence the normal craniofacial development.[76] Thus, to avoid alcohol consumption during pregnancy is strongly recommended.

Maternal and Fetal Metabolic Diseases

Maternal phenylketonuria

Phenylketonuria (PKU) is an inborn error of metabolism with a defect in the hepatic enzyme, phenylalanine hydroxylase, which converts phenylalanine into tyrosine. During pregnancy, untreated maternal PKU or hyperphenylalaninemia may result in neonatal microcephaly, low birth weight, intellectual or developmental disability, facial dysmorphisms, and congenital heart diseases. Fortunately, the sequelae can be prevented by dietary control of phenylalanine concentration, and the treatment is strongly suggested to start before conception.[77]

Fetal 3-Phosphoglycerate dehydrogenase deficiency

Three-Phosphoglycerate dehydrogenase (3-PGDH) deficiency is an autosomal recessive inherited disease and the manifestations include congenital microcephaly, epilepsy, and severe psychomotor retardation. 3-PGDH deficiency is caused by defects in the biosynthesis of L-serine, a precursor of nucleotides, phospholipids, and NMDA receptor agonists. L-serine deficiency can impair dentritogenesis and neuronal survival *in vitro*.[78] A genetic study of *3-PGDH* can confirm the diagnosis when the presence of decreased L-serine levels in plasma and cerebrospinal fluid. Prenatal administration with a combination of L-serine and glycine in the mother can treat a fetus with 3-PGDH deficiency effectively and successfully.[79] Therefore, prenatal diagnosis and genetic counseling are important to provide early management and prevent the recurrent siblings.

Fetal Amish lethal microcephaly (OMIM 607196)

Amish lethal microcephaly is an autosomal recessive disorder, manifested by severe congenital microcephaly and highly elevated 2-ketoglutarate or lactic acidosis.[80] The microcephaly is more severe than other genetically-defined microcephaly. *SLC25A19* mutations on chromosome 17q25.1 cause Amish lethal microcephaly.[81] Only supportive treatment is available for the disease and the average life span is usually months. Thus, it is required to prevent the recurrent cases by offering prenatal genetic testing or preimplantation genetic diagnosis for the pregnancies at risk.

Conclusion

Prenatal counseling of fetal microcephaly is a challenge to clinical staff because the prognosis of fetal microcephaly with impaired neurodevelopment depends on the severity of microcephaly and the underlying causes. Thus, it is important for clinicians to make early diagnoses and confirm the causes. A fetal OFC is easily measured by prenatal ultrasound; Initial detection of fetal microcephaly can tailor appropriate diagnostic evaluation and management.

Detailed history taking is the first and vital step to determine if the presence of maternal causes or congenital infections, such as maternal alcohol consumption during pregnancy, presence of febrile illness and travel history during or before pregnancy, and maternal PKU. If alcohol misuse is suspected, it is needed to offer support to reduce or stop maternal alcohol consumption. Subsequently, maternal blood can be drawn to screen for high suspicion of congenital infectious pathogens when presence of maternal illnesses, a trip to areas with a high prevalence of ZIKV during or before pregnancy, or even asymptomatic mothers during pregnancy. If suspicious results are shown on maternal blood, analysis of infectious pathogens by amniocentesis or cordocentesis may be considered for some congenital infections. Prenatal administration of prophylactic medication might be of benefit to reduce some congenital infections or side effects such as rubella virus, *T. gondii*, and VZV infections. Amniocentesis can also be offered to make a diagnosis of genetic or chromosomal abnormalities. Further investigation of fetal metabolic diseases is required when suspecting the possible genetic abnormalities.

When fetal microcephaly is an isolated feature on prenatal ultrasound, fetal brain MRI may be another valuable tool to provide more information about the brain development. In addition, serial prenatal sonographic scanning is required to monitor the fetal changes in the remaining pregnancy.

In summary, this article reviews the causes of fetal microcephaly. The information is helpful for clinical practitioners such as physicians, sonographers, and genetic counselors because of

its incurable condition. Prenatal diagnosis of microcephaly and confirmation of the causes can initiate accurate management and provide appropriate genetic counseling to the parents.

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