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REVIEW

Genetic considerations in the prenatal diagnosis of overgrowth syndromes

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Large (>90%) for gestational age (LGA) fetuses are usually identified incidentally. Detection of the LGA fetus should first prompt the provider to rule out incorrect dates and maternal diabetes. Once this is done, consideration should be given to certain overgrowth syndromes, especially if anomalies are present. The overgrowth syndromes have significant clinical and molecular overlap, and are associated with developmental delay, tumors, and other anomalies. Although genetic causes of overgrowth are considered postnatally, they are infrequently diagnosed prenatally. Here, we review prenatal sonographic findings in fetal overgrowth syndromes, including Pallister-Killian, Beckwith-Wiedemann, Sotos, Perlman, and Simpson-Golabi-Behmel. We also discuss prenatal diagnosis options and recurrence risks. Copyright © 2009 John Wiley & Sons, Ltd.
KEY WORDS: overgrowth; genetic syndrome; prenatal diagnosis; Beckwith-Wiedemann syndrome; Pallister-Killian syndrome; Simpson-Golabi-Behmel syndrome; Sotos syndrome; Weaver syndrome

INTRODUCTION

Large (>90%) for gestational age (LGA) fetuses are usually identified during a routine office visit when fundal height is measured, or during an ultrasound examination performed for other reasons. The most common reason for an LGA fetus is maternal diabetes mellitus or incorrect dates. When these two causes are ruled out, attention should be given to other etiologies of fetal overgrowth. Generally, macrosomia is not detectable at the 16–20-week anatomy survey. Many fetuses with overgrowth syndromes will fall into the normal weight range until later in gestation. This makes early diagnosis of overgrowth syndromes difficult. However, many fetuses with overgrowth syndromes will have other anomalies detectable in the second trimester. The overgrowth syndromes have significant clinical and molecular overlap, and are associated with developmental delay, tumors, and other anomalies (Baujat *et al*., 2005). It is our impression that although genetic conditions are considered in the postnatal differential diagnosis of overgrowth, they are relatively infrequently diagnosed prenatally. Genetic causes of overgrowth include chromosomal abnormalities, as well as syndromes such as Sotos, Beckwith-Wiedemann, Perlman, and Simpson-Golabi-Behmel. When an overgrowth syndrome is suspected prenatally, it is essential that a clinical geneticist be involved to assist in the differential diagnosis and selection of appropriate tests. In the majority of these cases, a prenatal diagnosis will not be made. However, increased awareness of the differential diagnosis of overgrowth syndromes can prepare the neonatologist for potential neonatal problems associated with these syndromes. Many overgrowth syndromes exist, but in this review, we will focus on the overgrowth syndromes that have been described with a prenatal presentation and that have clinically available molecular testing.

CONSIDERATIONS IN THE DIFFERENTIAL DIAGNOSIS

Many of the overgrowth syndromes have overlapping clinical and molecular features. A suggested approach to the prenatal diagnosis of overgrowth syndromes is given in Figure 1.

Chromosomal abnormalities

Several chromosomal abnormalities are associated with fetal overgrowth, including trisomy 12p, mosaic tetrasomy 12p (also known as Pallister-Killian syndrome), trisomy 4p16.3, trisomy 5p, trisomy 15q25, mosaic trisomy 8 and monosomy 22q13 (Segel *et al*., 2006; Cohen *et al*., 2005). With the introduction of chromosome microarrays into clinical medicine, chromosome abnormalities associated with overgrowth will be more commonly found. For example, a case report described two unrelated patients with trigonocephaly, overgrowth, and macrocephaly with a *de novo* microdeletion in 9q22.32-q22.33 found by array comparative genomic hybridization (Redon *et al*., 2006). Prenatal microarrays are currently available that can diagnose microdeletions in the

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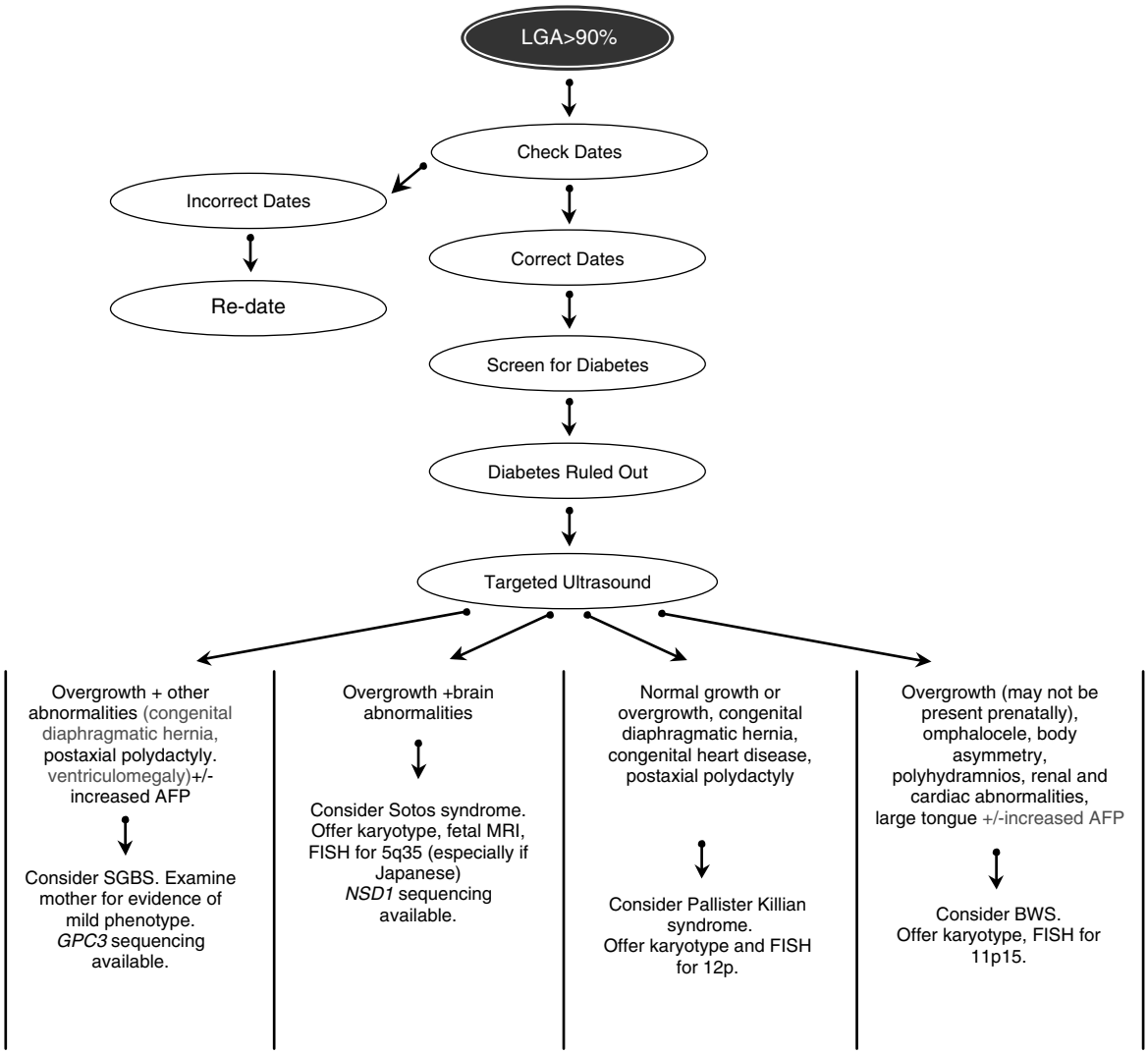

Figure 1—Suggested algorithm for the diagnostic workup of the fetus with overgrowth and other anomalies

following genomic regions; Sotos (5q35), Beckwith-Wiedemann (11p15), and 22q13. A prenatal microarray study may be useful if there is evidence of overgrowth with other abnormalities. Clinical trials are in progress to determine the clinical utility of prenatal micorarrays.

Pallister-Killian syndrome

Pallister-Killian syndrome (Online Mendelian Inheritance in Man [OMIM] #601 803) is caused by mosaicism for tetrasomy of chromosome 12p. Clinical features include severe mental retardation, hypo- or hyperpigmentation, seizures, postaxial polydactyly, and facial dysmorphism, including prominent forehead with sparse anterior scalp hair, hypertelorism, flat occiput, short, anteverted nose, and short neck. Skeletal anomalies, congenital heart defects, and congenital diaphragmatic hernia are also seen in this condition. Pallister-Killian syndrome is associated with advanced maternal age, and is thought to be caused by nondisjunction, followed by an abnormal centromere division in meiosis I or II (Struthers *et al*., 1999). This results in an isochromosome 12p. Tetrasomy 12p can be detected by amniocentesis and confirmed with FISH studies using specific probes for 12p. The detection of tetrasomy 12p is affected by the tissue type. It is more readily detected in amniocytes and skin because it is thought that peripheral blood lympocytes lose the extra chromosome due to their more frequent cell division. In an affected infant, if the peripheral blood karyotype is normal, then skin biopsy or karyotype of other tissue sources should be considered. Recurrence risk is low because this is a sporadic condition.

The most common prenatal sonographic findings seen in Pallister-Killian syndrome and other conditions are listed in Table 1 (Doray *et al*., 2002; Bresson *et al*., 1991; Paladini *et al*., 2000; Liberati *et al*., 2008). It is important to distinguish this syndrome, which occurs sporadically, from Fryns syndrome, an autosomal recessive condition, which is also associated with skeletal anomalies and diaphragmatic hernia. Patients with Fryns syndrome, however, typically have intrauterine growth restriction and die more often in the newborn period.

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Table 1—Differential diagnosis of genetic overgrowth syndromes

Syndrome	Gene location	Inheritance	Possible sonographic findings	Other aids to diagnosis
Beckwith-Wiedemann	11p15	Variable; sporadic in 85% of cases but can be autosomal dominant; also can be caused by uniparental disomy and imprinting defects	Macrosomia, polyhydramnios, omphalocele, enlarged tongue, placentomegaly, long umbilical cord, enlarged echogenic kidneys, pancreatic cystic dysplasia	Karyotype but <1% of BWS have cytogenetically detectable abnormalities; examination of parents by clinical geneticist
Pallister-Killian	Tetrasomy 12p	Sporadic	Polyhydramnios, rhizomelic micromelia, congenital heart disease, diaphragmatic hernia (Figure 3), increased nuchal translucency, facial abnormalities	Karyotype; confirm diagnosis with FISH probes for 12p
Sotos	*NSD1* on 5q35	Sporadic in 95% of cases	Brain abnormalities, macrocephaly	Fetal MRI; Karyotype, FISH for 5q35, *NSD1* sequencing
Perlman	Unknown	Autosomal recessive	Polyhydramnios, macrosomia, visceromegaly, enlarged echogenic kidneys, cystic hygroma	
Simpson-Golabi-Behmel	*GPC3* on Xp26	X-linked recessive	Polyhydramnios, omphalocele, cystic hygroma, diaphragmatic hernia, enlarged or cystic kidneys, agenesis of the corpus callosum, Dandy Walker malformation, and macrosomia, placentomegaly	Elevated MSAFP level; examination of mother by clinical geneticist; determine fetal gender; *GPC3* sequencing

Significantly, intrauterine growth restriction has never been reported in Pallister-Killian syndrome.

Beckwith-Wiedemann syndrome

Beckwith-Wiedemann syndrome (BWS) has an incidence of 1/13,700 and is the most common overgrowth syndrome. Under-reporting of minor cases may underestimate its true incidence (Carlin *et al*., 1990). BWS (OMIM catalog #130 650) is characterized by macrosomia, macroglossia, visceromegaly, neonatal hypoglycemia, omphalocele, embryonal tumors, ear creases and pits, renal abnormalities, and adrenocortical cytomegaly (Elliott *et al*., 1994). Patients with BWS have an increased risk of Wilms' tumor, hepatoblastoma, neuroblastoma, rhabdomyosarcoma, and adrenocortical carcinoma (Wiedemann, 1983). It is important for affected children to have abdominal sonographic screening for tumors every three months until age eight, after which tumor development is uncommon. Serum alphafetoprotein (AFP) levels should also be checked in the first few years of life so that hepatoblastoma can be detected early.

Approximately twenty cases of prenatally diagnosed BWS have been reported in the literature (Williams *et al*., 2005). The most commonly described sonographic findings are included in Table 1. (Williams *et al*., 2005; Cohen, 2005; Le Caignec *et al*., 2004; Fremond *et al*., 1997). A targeted ultrasound examination is recommended to evaluate for body asymmetry, abdominal wall defects, renal and cardiac anomalies, macroglossia, adrenomegaly, and an enlarged pancreas (Figure 2) (Williams *et al*., 2005).

An antenatal diagnosis can prepare neonatologists for problems specific to BWS, such as airway compromise due to macroglossia, and severe hypoglycemia (Williams *et al*., 2005; Pettenati *et al*., 1986). Many neonatal intensive care units regularly check blood sugars on LGA infants because of the risk of undiagnosed maternal gestational diabetes. This kind of protocol will also prevent complications in neonates with BWS or other genetic syndromes. The reported perinatal mortality rate in BWS from prematurity, macroglossia, and cardiomyopathy is as high as 20% (Williams *et al*., 2005). Also, the diagnosis may affect mode of delivery, depending on the degree of macrosomia.

The genetics of BWS are quite complex and the diagnosis relies primarily on clinical findings. This complexity can cause difficulty in obtaining a molecular diagnosis. Ten to twenty percent of patients with BWS have paternal uniparental disomy (UPD) (Cytrynbaum *et al*., 2005). The majority of these patients have segmental paternal UPD for 11p15, suggesting that there was a postzygotic recombination that caused the mosaicism. UPD may be difficult to detect because of low-level mosaicism. Examination of other tissues, such as skin, may be needed.

BWS is also caused by changes in genes involved in growth regulation on chromosome 11p15, which are also susceptible to imprinting. Imprinting, or methylation defects affecting several different genes, have also been reported to cause BWS. The imprinting defects in BWS have been well described by other authors and

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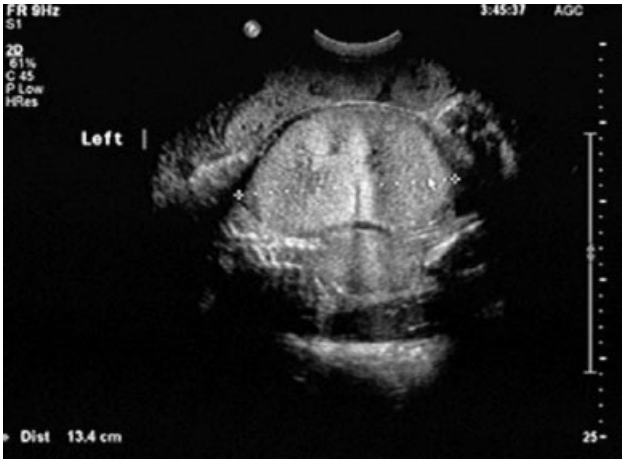

Figure 2—Prenatal sonographic image from a fetus at 32 weeks' gestation showing renal enlargement and hyperechogenicity. This kidney measures 13 cm in the transverse view. The normal value at this gestational age is 3.8 cm. Image courtesy of the Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, Tufts Medical Center. Reproduced with permission

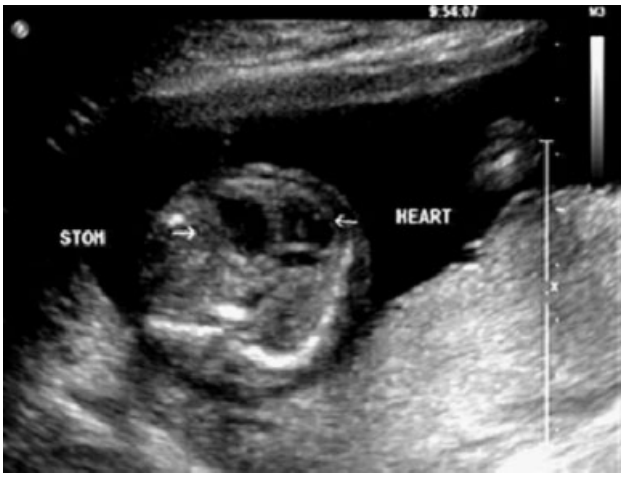

Figure 3—Prenatal sonographic image from a fetus at eighteen weeks' gestation with congenital diaphragmatic hernia (CDH). When CDH and overgrowth are seen in combination, a karyotype should be performed to look for Pallister-Killian syndrome. SGBS should also be considered. Image courtesy of the Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, Tufts Medical Center. Reproduced with permission

will not be discussed in detail here. (Cooper *et al*., 2005; Bliek *et al*., 2001; Weksberg *et al*., 2001; Cytrynbaum *et al*., 2005; Debaun *et al*., 2003; Lam *et al*., 1999).

There is obvious difficulty in making an antenatal diagnosis of UPD or imprinting defects. However, if macrosomia and other features of BWS are noted prenatally, FISH analysis and karyotype can be performed to detect translocations or inversions that affect genes in the 11p15 region (Reish *et al*., 2002). Less than 1–2% of cases of BWS have cytogenetically detectable abnormalities in 11p15 (Slavotinek *et al*., 1997). Translocations and inversions are usually maternally inherited but can arise *de novo*; thus, parental samples should always be submitted with prenatal samples because of the possibility of familial chromosomal rearrangements, deletions, or duplications. The fastest and most accurate method of detecting BWS is methlyation-specific multiplex ligation-dependent probe amplication (MS-MLPA), but use of this method prenatally is limited and has not been well described prenatally (Priolo *et al*., 2008).

Although most cases of BWS are sporadic (up to 85%), 10–15% have autosomal dominant inheritance with preferential maternal transmission (Cohen, 2005). Because there is variable penetrance, a thorough family history and physical examination of both parents for hemihypertrophy, earlobe grooves, and posterior helical pits is recommended. Pregnant women carrying fetuses with sonographic findings suspicious for BWS should be counseled about all aspects of BWS, including the risk of embryonal tumors. With UPD, the recurrence risk is very low (<1%), because the UPD is thought to arise from a postzygotic somatic recombination. If no genetic etiology is identified, the risk to future offspring is low, but there should be a discussion with the parents about the possibility of gonadal mosaicism and the limitations of currently available testing.

Sotos syndrome

Sotos syndrome (OMIM #117550), also known as cerebral gigantism, was first described in 1964 (Sotos *et al*., 1964). Sotos syndrome is characterized by pre- and postnatal overgrowth, developmental delay, and a typical facial appearance that includes macrocephaly, dolichocephaly, a prominent forehead, large hands and feet, advanced bone age, prominent jaw, and variable psychomotor developmental delay (Sotos *et al*., 1964). Most cases of Sotos syndrome are sporadic, although familial cases have been reported. When inherited, it is thought to be an autosomal dominant disorder with variable penetrance.

Case reports of prenatal findings of Sotos syndrome have been published (Chen *et al*., 2002; Lemire *et al*., 2008), and are summarized in Table 1. Sotos syndrome is associated with certain brain abnormalities. One author found that all patients with Sotos syndrome had abnormal MRI scans (Gusmao Melo *et al*., 2000). The postnatal neuroimaging abnormalities include enlargement of the lateral ventricles, the trigones, and the occipital horns, midline defects, including abnormalities of the corpus callosum with complete or partial agenesis of hypoplasia, as well as other abnormalities (Schaefer *et al*., 1997; Gusmao Melo *et al*., 2000). However, brain abnormalities in Sotos syndrome are nonspecific (Tatton-Brown *et al*., 2005) and many fetuses with Sotos syndrome will not be large for gestational age at the time of level II sonographic examination (16–20 weeks), making it very difficult to diagnose this condition prenatally. If brain abnormalities with or without overgrowth are noted by prenatal sonography, fetal MRI should be obtained.

Sotos syndrome is caused by haploinsufficiency of the *NSD1* (nuclear receptor SET domain containing gene 1) gene on chromosome 5q35. To date, more than 100 mutations have been identified in *NSD1*. Most of

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the mutations have a truncating effect on the protein (Faravelli *et al*., 2005).

Many reports have indicated that up to 80–90% of patients with Sotos syndrome have an intragenic mutation or a submicroscopic microdeletion that impairs the function of *NSD1* (Kurotaki *et al*., 2002; Douglas *et al*., 2003; Kamimura *et al*., 2003; Rio *et al*., 2003; Visser *et al*., 2003). Routine karyotype analysis usually shows normal results. Non-Japanese patients have an intragenic mutation in 27–93% of cases. The variability in detection rates is the result of the level of expertise of the clinicians who referred the patients for testing. In contrast, only 12% of Japanese patients have intragenic mutations in the *NSD1* gene. Fifty percent of Japanese patients have microdeletions in 5q35 that can be detected by FISH, whereas only 10% of non-Japanese patients have this microdeletion (Kurotaki *et al*., 2003; Tatton-Brown *et al*., 2005). It has been noted that the microdeletions occur more often in the paternally inherited chromosome (Miyake *et al*., 2003; Faravelli *et al*., 2005).

In summary, when Sotos syndrome is suspected prenatally, a metaphase karyotype should be performed to determine whether there is a translocation. *NSD1* sequencing and FISH for 5q35 microdeletion are available clinically. If there is an affected member of the family, a mutation in a proband should be identified before prenatal diagnosis is performed. However, more than 95% of cases of Sotos syndrome are secondary to a *de novo* mutation, so this is only possible in a very small percentage of cases. If neither parent has Sotos syndrome, the risk to future offspring is low (<1%). However, the patient should receive counseling regarding the possibility of germline mosaicism. Offspring of an affected parent have a 50% risk of Sotos syndrome.

Perlman syndrome

Perlman syndrome is a rare autosomal recessive fetal overgrowth syndrome associated with a high fetal and neonatal mortality rate (64%). Survivors have a high incidence of Wilms' tumor and mental retardation (Perlman *et al*., 1973). Perlman syndrome is characterized by dysmorphic facial features, including small mouth, and small upturned nose with a deep crease over the nasal bridge. Other features include bilateral renal enlargement with fetal macrosomia, renal hamartomas, hydronephrosis, hydroureter, developmental delay, and cryptorchidism.

There have been a few reports of abnormal prenatal sonographic findings in Perlman syndrome (Table 1) (Chitty *et al*., 1998; DeRoche *et al*., 2004; van der Stege *et al*., 1998; Henneveld *et al*., 1999). Significant overlap between Perlman, Simpson-Golabi-Behmel, and Beckwith Wiedemann syndromes exists. All three should be considered in the differential diagnosis of overgrowth with visceromegaly. Distinction between the three can be made postnatally by a medical geneticist.

Parents should be counseled about the 25% recurrence risk if a postnatal diagnosis of Perlman syndrome is made. The etiology of Perlman syndrome is unknown at present and no diagnostic testing is available.

Simpson-Golabi-Behmel syndrome

Simpson-Golabi-Behmel syndrome (SGBS) is an X-linked recessive condition associated with prenatal and postnatal overgrowth, macrocephaly, congenital diaphragmatic hernia, coarse facies, supernumerary nipples, palatal abnormalities, congenital heart defects, and generalized hypotonia (Xuan *et al*., 1999). There are also variable visceral, skeletal, and neurological abnormalities present, including ventriculomegaly. Hypoglycemia can manifest in the newborn period. Although normal intelligence has been described, mild to severe mental retardation is common. There is variable expressivity, ranging from mild forms in carrier females to infantile lethal forms. As many as 50% of affected males die in the neonatal period (Neri *et al*., 1998). Because these patients are at increased risk of tumor development in early childhood, they should have regular sonographic surveillance (Neri *et al*., 1998). Five types of tumors have been described: Wilms tumor, hepatoblastoma, adrenal neuroblastoma, gonadoblastoma, and hepatocellular carcinoma. There is significant clinical overlap with other overgrowth syndromes, especially BWS and Perlman syndrome.

Only a few case reports of prenatal findings in SGBS are available (Table 1) (Hughes-Benzie *et al*., 1994; Yamashita *et al*., 1995). There have been three reports of elevated MSAFP levels in SGBS (none of which had an abdominal wall or spine defect) (Chen *et al*., 1993; Hughes-Benzie *et al*., 1994). Hughes-Benzie *et al.* presented a case report of SGBS, and suggested that fetal macrosomia with a low head-to-abdominal circumference ratio (4 SD below the mean) and elevated MSAFP level may be antenatal markers for SGBS.

SGBS is an X-linked recessive disorder with variable expression in males caused by mutations in the *GPC3* gene on Xp26. DNA analysis is available on a clinical basis. The sensitivity of detection of an abnormality ranges from 37% (Li *et al*., 2001) to 70% (Lin *et al*., 1999; Veugelers *et al*., 2000). All males with a mutation in *GPC* 3 will have clinical findings of SGBS. Carrier females may have certain manifestations of SGBS including accessory nipples, narrow palpebral fissures, extra lumbar and thoracic vertebrae, prominent chin, hypoplastic fingernails, upturned nose, coccygeal skin tags and bony appendages (Golabi *et al*., 1984). If the mother of an affected child has a mutation, the chance of transmitting the disease-causing mutation is 50%. Thus, 50% of male children will be affected and 50% of female children will be carriers. Prenatal testing is also available if there is a known mutation in the family.

In the setting of a positive family history, prenatal testing should first determine the fetal sex by noninvasive testing using cell-free fetal DNA to determine whether markers for the Y chromosome are present in maternal blood. CVS or amniocentesis can also be performed to determine fetal sex if noninvasive prenatal diagnosis is not clinically available. If the karyotype is 46, XY, then DNA from fetal cells can be analyzed for the known familial mutation. Preimplantation genetic diagnosis (PGD) is also available in families that have been molecularly characterized.

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Other syndromes

Costello syndrome (OMIM #218040) is an autosomal dominant condition associated with multiple congenital anomalies, mental retardation, and prenatal overgrowth. There is a characteristic facial appearance that includes macrocephaly, full lips, large mouth, epicanthal folds, and full cheeks. The face becomes 'coarse' over time postnatally. Other typical features include deep palmar and plantar creases, nasal papillomata, and loose skin over the back of the hands. There is beginning to be an appreciation of the fetal phenotype in Costello syndrome (Lin *et al*., 2009; Smith *et al*., 2009), which includes overgrowth, polyhydramnios, macrocephaly, large for gestational age, shortened long bones, ventriculomegaly, and cardiac arrhythmias. If the above abnormalities are seen antenatally, prenatal DNA diagnosis for *HRAS* mutations should be considered. Missense mutations in exon 2 of the *HRAS* gene are found in 80–90% of affected individuals. If no mutation is found in exon 2, then full sequencing of the gene should be performed.

Weaver syndrome (OMIM #277590) is characterized by prenatal overgrowth, developmental delay, macrocephaly, camptodactyly, distinctive facial features, broad thumbs, loose skin, a small chin with a deep skin crease, metaphyseal widening, and advanced bone age (Weaver *et al*., 1974). There is phenotypic overlap between Sotos syndrome and Weaver syndrome, especially during infancy, but experienced dysmorphologists can appreciate the differences. Some authors have suggested that Sotos syndrome and Weaver syndrome are allelic (Opitz *et al*., 1998).

Although Weaver and Sotos syndromes are phenotypically similar, the brain abnormalities noted in Sotos syndrome are specific to Sotos syndrome. To date, there are no reports of prenatal findings in Weaver syndrome, but macrocephaly and overgrowth would also be expected.

NSD1 mutations have been demonstrated in patients with the diagnosis of Weaver syndrome. Over time, the phenotype of the Weaver syndrome patients with the *NSD1* mutations strongly resembles the phenotype of Sotos syndrome. However, patients considered to have 'classic' Weaver syndrome did not have mutations in the *NSD1* gene, suggesting that a separate gene may be involved in this condition (Douglas *et al*., 2003; Tatton-Brown *et al*., 2005).

Another overgrowth syndrome called Macrocephaly Cutis Marmorata Telangiectasia Congenita (M-CMTC) is associated with macrocephaly, neurologic abnormalities (Chiari malformations, ventriculomegaly, hemimegalencephaly), asymmetry, and polydactyly/syndactyly (Moore *et al*., 1997). This should be considered in the differential diagnosis when the above abnormalities are noted.

Summary and recommendations

If the fetus is noted to be LGA, dating of the pregnancy should be confirmed, and maternal diabetes mellitus should be excluded. Once these two issues are ruled out, consideration should then be given to other etiologies. Constitutional overgrowth is possible, especially in obese mothers. However, genetic overgrowth syndromes should be included in the differential diagnosis, especially when other abnormalities are noted on sonography or serum screen.

Because these syndromes are rare, we recommend that a medical geneticist be involved in any suspected case of overgrowth to assist in selection and interpretation of molecular testing. Even if a definitive diagnosis is not made prenatally, the neonatal team will be prepared to deal with problems such as hypoglycemia if the obstetrician communicates to the neonatologist that an overgrowth syndrome is suspected. Also, it should be noted that the turnaround time for many of the molecular tests may be several weeks. Thus, the definitive diagnosis may not be available until after birth.

We have developed an algorithm for providers who identify overgrowth and other anomalies on prenatal ultrasound examination. An increased awareness of these syndromes among obstetricians will improve their prenatal detection rates and allow pregnant patients to make more informed choices.

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