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EDITORIAL

Obstetric Ultrasound for Diabetes-related Congenital Anomalies

[1]Karim D Kalache, [2]Farhat Gothey, [3]Daniel Kamil

ABSTRACT

Major structural fetal anomalies occur in approximately 3% of births and are the main cause of infant mortality in developed countries. Pregestational diabetes is well recognized as the main cause, with up to a significant increase (ninefold) in structural defects when compared with the rates observed in nondiabetic pregnancies. In this Editorial, we will discuss the association between diabetes and the risk of congenital anomalies and the type of defects seen in diabetics. We will focus this Editorial on the Ultrasound Semiology of the Diabetes-related Congenital Anomalies.

Keywords: Congenital anomalies, Diabetic embryopathy, Gestational diabetes, Pregestational diabetes, Ultrasonography.

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INTRODUCTION

Diabetes is the most common medical complication in pregnancy. Women with diabetes in pregnancy can be divided into two groups: Pregestational diabetes that complicates less than 1% of all pregnancies, and gestational diabetes, which is observed in about 2% of pregnancies in which the glucose intolerance is first diagnosed during pregnancy. Gestational diabetes is further subdivided according to the degree of severity of the glycemic control disturbance. Women with a normal fasting plasma glucose are referred to as class I and those with abnormal fasting plasma glucose are categorized as class II. The latter type might in reality represent undiagnosed pregestational diabetes type II.

[1]Professor, [2]Senior Sonographer, [3]Section Head

[1]Department Obstetrics and Gynecology, Weill Cornell Medical College Qatar; Maternal-Fetal Medicine, Sidra Medical and Research Center, Doha, Qatar

[2]Sidra Medical and Research Center, Doha, Qatar

[3]Department of Antepartum and Clinics, Maternal Fetal Medicine division at Sidra Medical and Research Center, Doha, Qatar

Corresponding Author: Karim D Kalache, Professor, Department Obstetrics and Gynecology, Weill Cornell Medical College Qatar Maternal-Fetal Medicine, Sidra Medical and Research Center Doha, Qatar, e-mail: kakalache@sidra.org

The risk of major congenital malformations is significantly higher in women with pregestational diabetes mellitus,[1] especially when glycemia is not well controlled during the periconceptional period.[2] Whether the risk of major congenital anomalies is also higher in gestational diabetes mellitus is still the subject of a debate. Some authors[3,4] have reported that there is an increased risk of congenital anomalies in the offspring of a diabetic mother, while others[2,5] have reported a risk, i.e., similar to the reference group except for women with class II gestational diabetes.[2]

INCIDENCE AND RANGE OF DEFECTS

It is reported that in the offspring of women with pregestational diabetes, the risk of congenital anomalies is increased by five when compared with the general population.[6] The two fetal organs that are most frequently affected are the fetal heart with the incidence of cardiovascular abnormalities ranging from 0.2 to 3% and the central nervous system with the incidence of abnormalities ranging from 0.1 to 5%.[2] Other organ systems that are frequently affected are the musculoskeletal (abnormalities from 0.2 to 2%) and the genitourinary (abnormalities from 0.2 to 3%) systems.[2]

Caudal regression syndrome (also frequently referred to as sacral dys- or agenesis, caudal dysplasia, or phocomelic diabetic embryopathy) is characterized by abnormal formation of the distal spine and pelvis. It is the only abnormality, i.e., known to be specifically associated and typical for diabetes in pregnancy. Given the interdependency of neighboring structures on the caudal elements, an entire range of congenital malformations (Table 1) affecting the caudal region of the fetus can also be seen

Table 1: Characteristic elements of caudal regression syndrome

Anomalies of the lower extremities	Bilateral femoral hypoplasia
	Unilateral femoral hypoplasia
Vertebral anomalies	Sacral agenesis
	Spina bifida
Gastrointestinal tract	Anal atresia
Urinary tract	Renal agenesis
	Urethral agenesis
	Bilateral pelvic kidneys
Genital anomalies	Cloacal anomaly
	Hydrometrocolpos
	Cryptorchidism
	Hypospadia

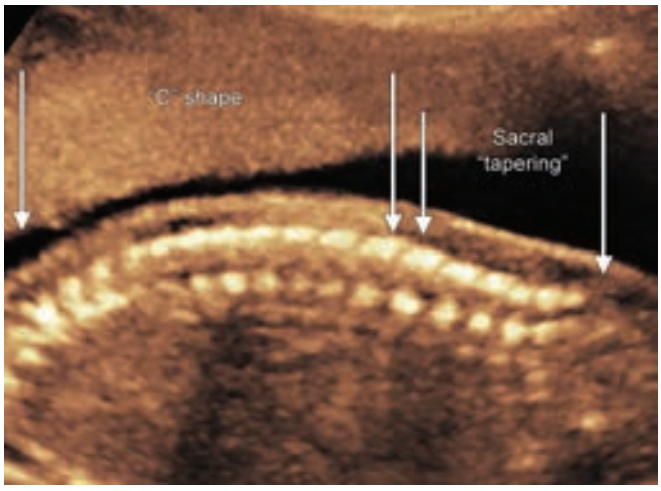

Fig. 1: Normal fetal spine at 22 weeks gestation with "c" shaped curvature with sacral "tapering"

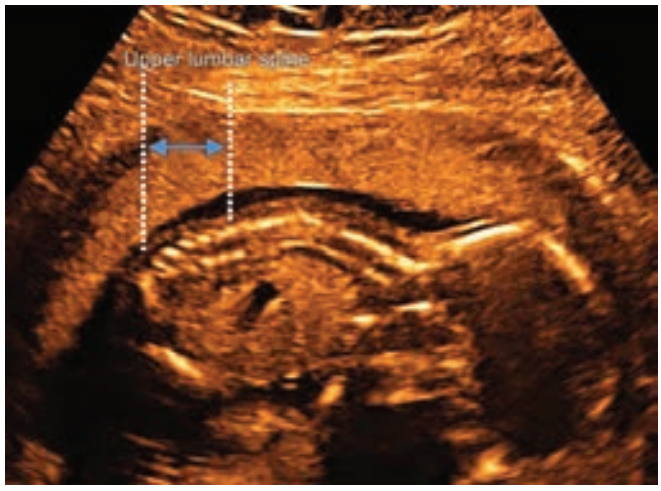

Fig. 2: Caudal regression syndrome at 16 weeks gesational age. There is a shortened spine with absence of sacral "tapering"

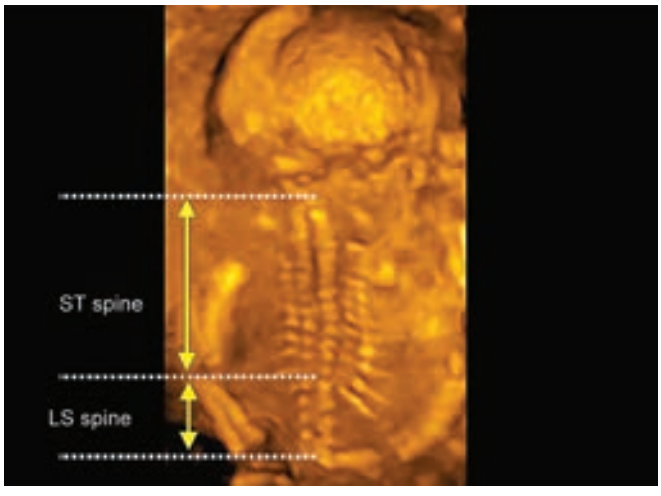

Fig. 3: Caudal regerssion syndrome at 16 weeks gesational age on 3D maximum rendering mode. Note the shortened lumbusacral (LS) spine when compared with cervicothoracal (CT) spine.

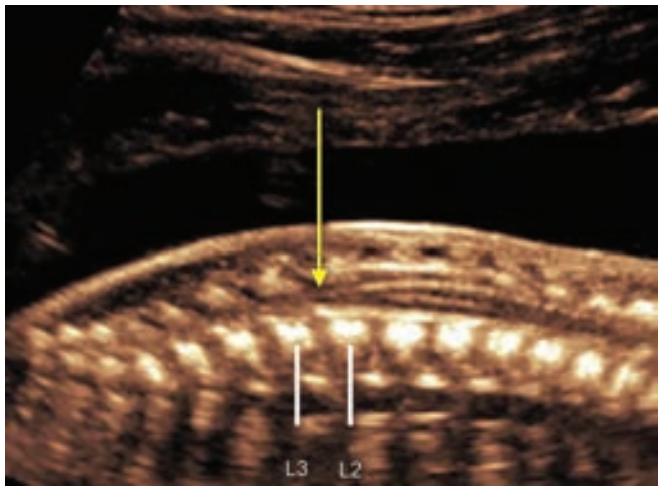

Fig. 4: Normal fetal spine at 22 weeks gestation with the level of the conus medullaris (arrow) between L3 and L2

as part of this condition. The incidence of this congenital anomaly in the normal population is about 1 per 25,000 live births and is about 150–200 times more common in infants of diabetic mothers.[7-10]

Imaging of the spine is usually easily achieved when the fetus is in a dorsoanterior position with enough amniotic fluid above it (Fig. 1). The fetal thoracolumbar spine curvature has a "c" shape with sacral "tapering," which should be seen in all fetuses after 22 weeks of gestation. Prenatal diagnosis of caudal regression syndrome by ultrasound is possible by showing a sudden interruption of the spine with absent "tapering" due to absence of lower vertebrae (Figs 2 and 3).

The position of the conus medullaris in relation to the spine changes with advancing gestational age as the spine develops and grows faster than the spinal cord. Its position is most frequently between L2 and L3 between 19 and 24 weeks' gestation (Fig. 4). Then, it undergoes its progressive relative ascent to be located above L2–L3 at term. The conus medullaris in caudal regression syndrome is abnormally high. Absent pelvic bones can be challenging to demonstrate.

Congenital heart defects are among the most important causes of perinatal mortality in offspring of diabetic mothers.[11-18] The commonest cardiac anomalies associated with diabetes in pregnancy are transposition of the great vessels, common arterial trunk, ventricular septal defects, visceral heterotaxia, and coarctation of the aorta.[19,20] Transposition of the great arteries is a conotruncal abnormality in which the right heart receiving blood from the body ejects blood directly into the aorta and the left heart receiving blood from the lungs ejects blood directly into the pulmonary artery. It is a common form of cyanotic congenital heart disease and one in which prenatal diagnosis has an important impact on neonatal outcomes. The outflow tract assessment is important for the diagnosis of transposition of the great arteries. Characteristic ultrasound images in D-transposition of

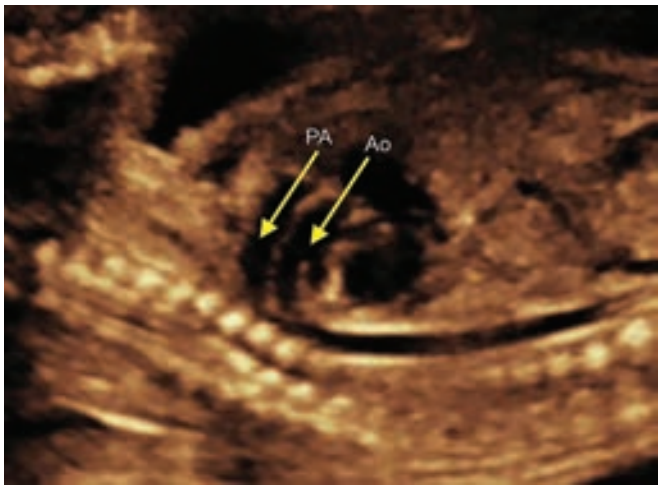

Fig. 5: Sagittal view in transposition of the great arteries showing the presence of parallel, rather than crossing, great arteries arising from the ventricles (PA: Pulmonary artery; Ao: Aorta)

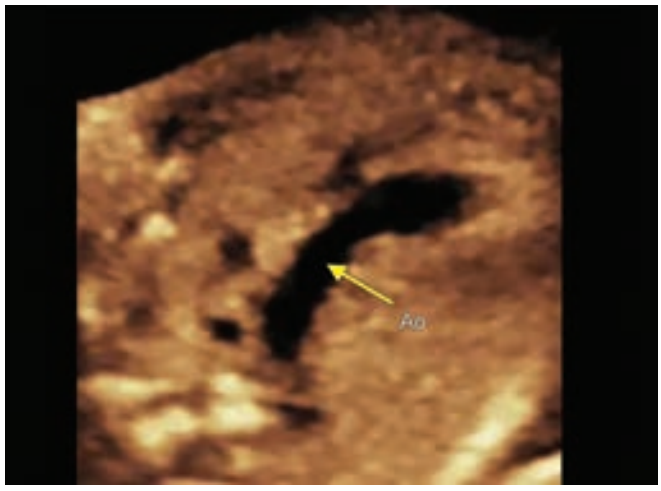

Fig. 6: Three vessel view in transposition of the great arteries showing the absence of the pulmonary artery as running below and parallel to the aorta (Ao: Aorta)

the great arteries demonstrate that the great vessels are arising from the "wrong" ventricle. The aorta runs anterior and to the right of the pulmonary artery. Additionally, the great vessels have a parallel course instead of crossing each other (Fig. 5). Another feature is an abnormal three-vessel trachea view in which only the aortic arch on the left side and the superior vena cava on the right side can be identified (Fig. 6). The pulmonary artery is positioned inferior to the aorta and, thus, not visible in the three-vessel view in transposition of the great arteries. Examination of the great arteries is important to diagnose the common arterial trunk. Inclining the transducer cranially will reveal a large, single great vessel that overrides a ventricular septal defect. Further anterior angulation of the transducer confirms that there is only a single great vessel with branches to the pulmonary, systemic, and coronary circulations arising from the heart (Fig. 7). A large, malaligned outlet ventricular septal defect is a common association.

In poor maternal glycemic control-related fetal hyperglycemia, glycogen can accumulate in the cardiac muscle and growth will be stimulated by the hyperinsulinism due to fetal pancreas hyperstimulation. This hypertrophy can obstruct the cardiac blood flow and even cause cardiac failure. Hypertrophic subaortic stenosis has been reported in very severe cases.[21,22] One of the common explanations for the unexplained death in late pregnancy of fetuses of diabetic patients is this phenomena.[23] However, the absolute prenatal risk of a hypertrophic myocardiopathy in pregnant women with diabetes and the adequate management and interventions are still poorly understood.

Hypertrophic myocardiopathy is characterized by hypertrophy of the interventricular septum and the ventricular walls. The interventricular septum should be measured in its midway part in the four-chamber view

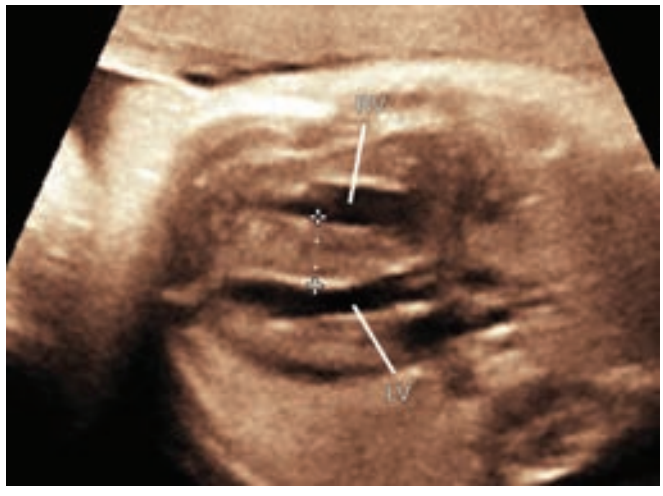

Fig. 7: Hypertrophic myocardiopathy with hypertrophy of the interventricular septum measuring more than 5 mm (RV: right ventricle, LV: left ventricle)

with the ultrasound beam perpendicular to the interventricular septum preferably in the end-diastolic phase. Hypertrophic myocardiopathy can be suspected if the interventricular septum measures more than 5 mm (Fig. 7).

The incidence of neural tube defect in the diabetic obstetric population is increased when compared with the nondiabetic one (approximately 20/1,000 *vs* 1–2/1,000). Myelomeningoceles account for more than 98% of open spina bifida while myeloceles are rather rare. The main difference between a myelomeningocele and myelocele is the position of the neural placode relative to the spinal canal. The neural placode is outside the spinal canal and protrudes above the skin surface with a myelomeningocele (Fig. 8) and is inside the spinal canal and flush with the skin surface with a myelocele (Fig. 9).

Accurate diagnosis of open spina bifida requires a thorough examination of spine and intactness of the overlying skin. However, the latter is difficult to demonstrate

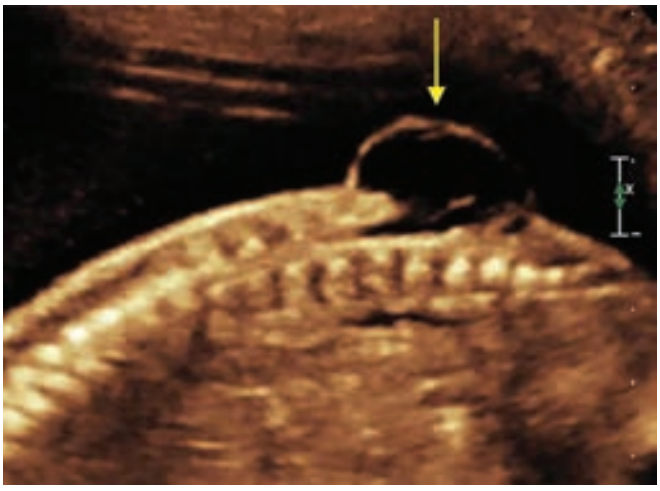

Fig. 8: Lumbosacaral myelomeningoceles with the neural placode protruding above the skin surface (arrow)

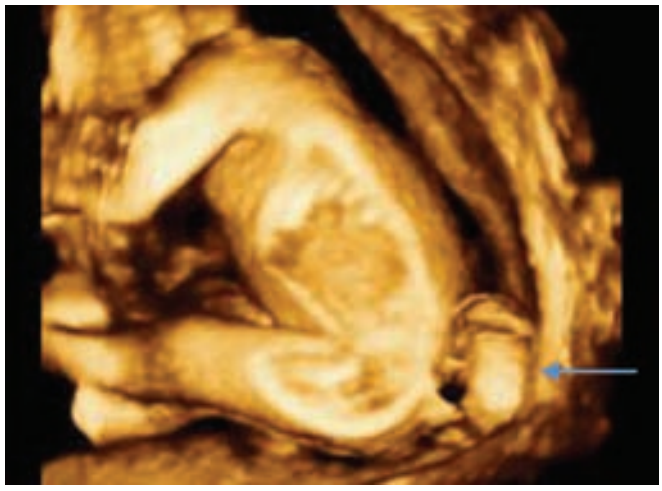

Fig. 9: 3D-rendering of a lumbosacaral myelomeningocele protruding above the skin.

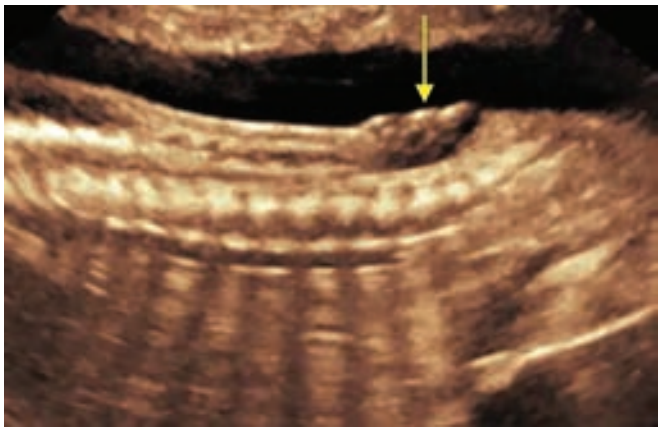

Fig. 10: Myelocele with the neural placode flush with the skin surface

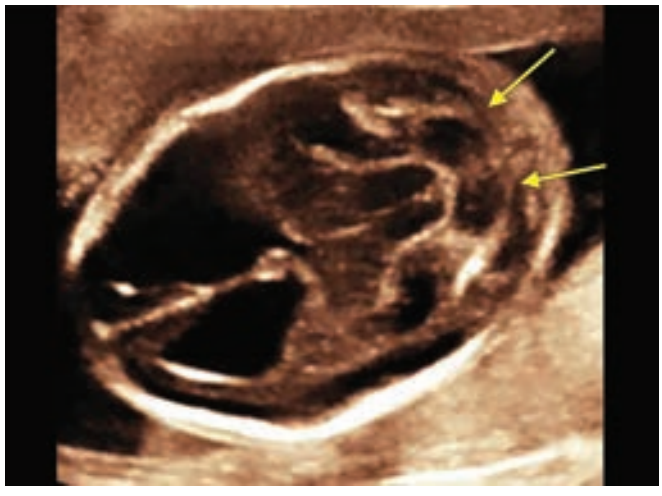

Fig. 11: Posterior fossa in open spina bifida. Not the absence of the cisterna magna and the abnormal shape of the cerbellum (so called banana sign)

in myelocele in which there is no cystic structure above the skin defect (Fig. 9). The only reliable way to diagnose open spina bifida is, thus, through a thorough examination of the posterior fossa. The typical abnormal shape of the cerebellum due to its dorsocaudal displacement into the spinal canal (so-called banana sign) with obliteration of the cisterna magna (Chiari II malformation) (Fig. 10) is pathognomonic for open spina bifida and will lead to the diagnosis.[24]

Recent first trimester ultrasound studies have shown that signs of caudal displacement of the posterior brainstem are present in fetuses with open spina bifida as early as 11–14 weeks gestation. This displacement causes enlargement of the fourth ventricle by compression of the cisterna magna (Figs 11 and 12). As a consequence, the so-called intracranial translucency will be absent.[25]

Anencephaly is with a rate of 1/200 diabetic pregnancies, a common complication of diabetic pregnancies. It is easily diagnosed as characterized by absent bony calvarium and prominent bulging eyes. Microcephaly is another central nervous system malformation associated with diabetes in pregnancy.

Imperforate anus is one of the most common gastrointestinal malformations associated with diabetes. An imperforate anus had been thought to be difficult to diagnose prenatally. However, prenatal diagnosis by direct visualization of the fetal perineum has been reported.[26-29] The fetal anal structures are best visualized on tangential views of the fetal perineum. The normal fetal anus appears as a hypoechogenic ring surrounding the hyperechogenic anal mucosa (so-called "target sign") (Fig. 13). Characteristic images of anal atresia are the nonvisualization of the anal sphincter muscles and anal mucosa and only a hyperechoic linear line across the perineum (Figs 14 and 15).

The association of the so-called femoral hypoplasia – unusual facies syndrome with maternal insulin-dependent diabetes – is well recognized.[30,31] Patients suffering from femoral hypoplasia–unusual facies

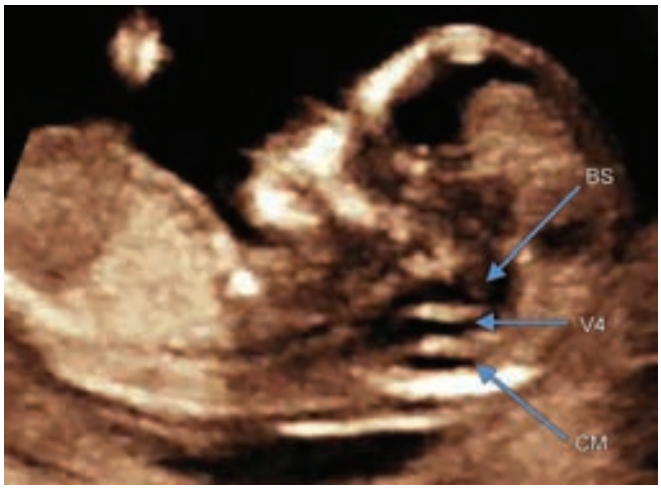

Fig. 12: Normal mid-sagittal plane of the fetal brain in the first trimester showing brain stem (BS), fourth ventricle (V4) and cisterna magna (CM)

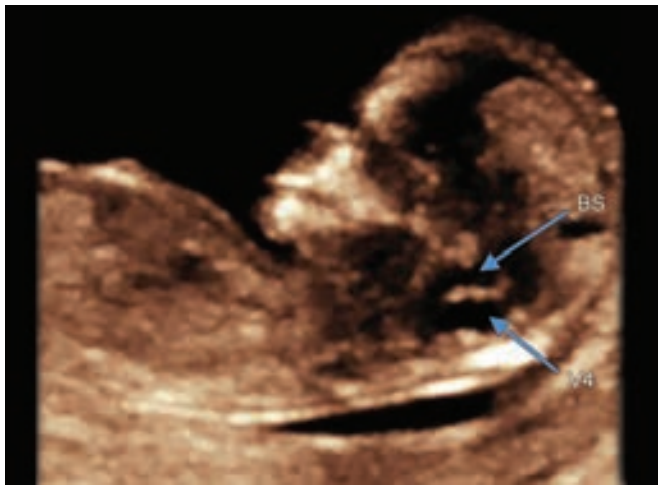

Fig. 13: Abnormal mid-sagittal plane of the fetal brain in the first trimester. The fourth ventricle (V4) appears enlarged and the cisterna magna is not visible

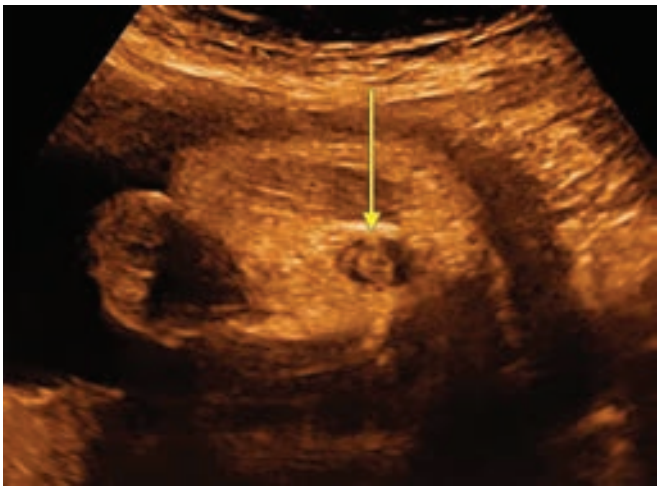

Fig. 14: Normal anal sphincter muscles appears as hypoechogenic ring surrounding the hoperchogenic anal mucosa (So called "target" "sign")

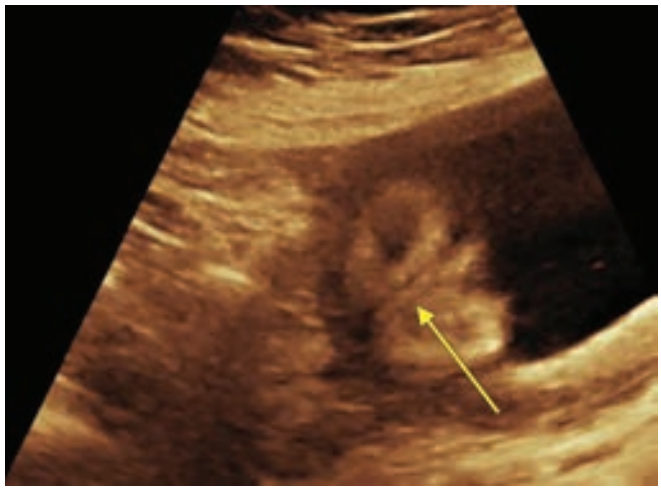

Fig. 15: Non-visualization of the anal sphincter muscles and anal mucosa and only a hyperechoic linear line across the perineum in anal atresia

syndrome are characterized by a variable degree of unilateral or bilateral femoral hypoplasia associated with facial clefting and occasionally other minor anomalies.

CONCLUSION

While the risk for major congenital defects has been well established in women with pregestational and gestational diabetes, their detection remains a challenge. One should bear in mind that ultrasound examination of obese diabetic pregnancies showed up to suboptimal image quality in up to 37% of the cases and incomplete examinations with repeat examinations in up to 17% of the cases. The malformation detection rate was markedly reduced in diabetic women when compared with the low-risk population (30 *vs* 73%).[32] Knowledge about the spectrum of anomalies and their ultrasound semiologies is important for their accurate prenatal diagnosis.

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