CASE REPORT

Importance of early complex evaluation in high-risk pregnancy associated to diabetes mellitus. Case presentation and review of the literature

LAVINIA GHEORMAN1), D. ILIESCU2), IULIANA CEAŞU3), DANIELA PAULESCU4), I. E. PLEŞEA5), V. GHEORMAN2)

1)Physician, PhD candidate in Obstetrics and Gynecology
2)Department of Obstetrics and Gynecology
University of Medicine and Pharmacy of Craiova, Romania
3)Department of Obstetrics and Gynecology, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania
4)Department of Obstetrics and Gynecology, Gaia Hospital, Athens, Greece
5)Department of Morphopathology, University of Medicine and Pharmacy of Craiova, Romania

Abstract
We report and analyze a case of pregnancy associated with pre-existent diabetes mellitus and fetal congenital anomalies involving neural tube defect (NTD) and congenital heart defect (CHD). We discuss the early antenatal management of such high-risk pregnancies. The clinical course, maternal paraclinic profile and morpho-sonographic investigation of the fetus are described. A 28-year-old pregnant woman with pre-existing diabetes and a pre-pregnancy BMI 31 kg/m², without preconception counseling for optimization of glycemic control was evaluated in our center for first trimester genetic screening at 12 weeks of gestation. Considering a high-risk pregnancy, careful fetal morphological assessment by ultrasound was performed; the extensive examination using high-resolution probes, both by transabdominal and transvaginal approach, found hypoplastic left heart syndrome (HLHS) and open spina bifida (OSB). Both anomalies present important difficulties regarding first trimester diagnostic. The couple was informed and chose termination of pregnancy (TOP). We consider that an anomaly scan at 12–13 + 6 gestational weeks by expert operators should be offered to high-risk pregnancies, because it provides the chance to detect the majority of fetal anomalies. This offer for couples the option of an early decision about the management of pregnancy in cases of severe fetal anomalies; postnatal treatment could be discussed as well as TOP and if the latter is chosen, the maternal risk and the potential psychological burden are lowered, as compared with TOP performed in the mid-second trimester.

Keywords: gestational diabetes, first trimester screening, spina bifida, congenital heart defects.

Introduction
The majority of congenital anomalies have unexplained causes, but about 10% of the structural defects can be attributed to environmental factors such as maternal medical illness [1, 2]. The most common anomalies associated with pre-existing diabetes involve the cardiovascular system (such as transposition of the great vessels, ventricular septal defect, situs inversus, single ventricle and hypoplastic left ventricle), the central nervous system (such as anencephaly, encephalocoele, meningomyelocele, spina bifida, and holoprosencephaly), and the face and extremities [3, 4]. Rates of fetal malformation appear to be similar for maternal type 1 and type 2 pre-existing diabetes [5], ranging from 4% to 10%, 1.9 to 10 times higher than in the total population, with incidence of CHD evaluated from 2 to 34 per 1000 births and CNS abnormalities in 5–10 per 1000 births [3, 6].

A dose-response effect was demonstrated, regarding relation between congenital anomalies and glycemic control: the poorer the glucose control periconceptionally or in early pregnancy, the greater the risk for congenital anomalies [3, 7]. Also, obesity is a well-known risk factor for diabetes and its association with congenital anomalies has been established in many studies [18], probably due to common metabolic disorders. Moreover, women as the one presented in this paper, with gestational diabetes or pre-existing diabetes and a pre-pregnancy BMI bigger than 28 kg/m², have shown a minimum multiplicative 3-fold increase in the risk of congenital abnormalities [22], and the risk increases proportionally with BMI [22–24].

The pathogenesis of diabetic embryopathy is multifactorial and teratogenicity was associated in animal models and human studies with hyperglycemia and disturbances of carbohydrate, fat, and protein metabolism [25, 26]; consecutive nutrient deficiencies or toxic metabolites associated with hyperglycemia, and glycosylation of proteins, hypoxia, ketone and amino acid abnormalities, have been reported to alter molecular
signaling pathways and adversely affect embryogenesis, interfering with normal cardiogenesis and neural tube closing [27].

**Patient, Methods and Results**

A 28-year-old pregnant woman gravida 3, para 1, was referred to our center at 12 weeks of gestation for the routine combined genetic screening. Giving the pre-existing diabetes type I, with a pre-pregnancy BMI 31 kg/m² and the lack of pre-conception counseling for optimization of glycemic control, the case was considered and investigated as a high-risk pregnancy at the first trimester genetic screening at 12 weeks of gestation. Careful morphological assessment by ultrasound was performed by an examiner who had obtained the Fetal Medicine Foundation Certificate of Competence in the 11 to 13 weeks scan; extensive examination of the fetus and the acquisition of images were realized transabdominally and transvaginally, using probes from GE Voluson 730 Pro, GE medical Systems, Kretztechnik, ZIPF, Austria.

For fetal morphological assessment, the following protocol was observed:

- **Skull and brain** – transverse planes of cranium at the level of choroid plexus and cerebral peduncules, sagittal view of the face with morphometry of posterior brain: fourth ventricle, brain stem antero-posterior diameter, brain stem diameter to brain stem-occipital bone distance ratio.
- **Face** – examination of the orbits and retronasal triangle, evaluation of the fetal profile with measurement of facial angle; evaluation of nasal bone.
- **Spine** – sagittal plane of spine and underlying on the sagittal section used for the measurement of crown-rump length (CRL).
- **Thorax** – examination of diaphragm and fetal hearth [28]:
  - situs evaluation;
  - area one quarter to one third of the chest and angle 45±15° from the midline;
  - four chambers view with the left atrium in front of the spine and the right ventricle just below the sternum; atrioventricular valve offsetting;
  - aorta arising centrally in the heart from the left ventricle and the pulmonary trunk arising from the anteriorly placed right ventricle and crossing to the fetal left side over the ascending aorta and being equal in size; color-flow mapping investigation of four-chamber, outflows emergence, arterial duct and aortic arch; visualization with color/power Doppler. ‘X’ sign (the crossing of the main pulmonary artery with the aorta); ‘V’ sign (the connection of the aorta and ductus arteriosus).
- **Abdomen** – presence of stomach in the left upper abdomen, abdominal wall and umbilical cord insertions (abdominal and placental), intestinal echogenicity.
- **Urinary tract** – evaluation of the kidneys or renal arteries, evaluation of bladder, paravesical presence of umbilical arteries.
- **Extremities** – examination of the symmetry of segments, fingers, toes posture and movement of joints.

Using transabdominal approach, hypoplastic left heart syndrome was suspected by non-visualizing the left ventricle on the four-chamber view, along the demonstration of a thin aorta in the three-vessel plane, presenting retrograde blood flow in the aortic arch. In order to perform a differential diagnosis with other “single” ventricle anomalies, transvaginally approach was recommended. A small left ventricle with poor contractility was identified (Figure 1).

Transabdominally open spina bifida (OSB) was suspected during the scan of the standard morphological sections used in our clinic for early neurosonogram. Thus, the fourth ventricle aspect and brain stem on brain stem to occipital bone ratio, considered important in detecting morpho-physiologic pattern of Arnold–Chiari malformation in the sagittal visualization of the fetal cranium, suggested caudal displacement of the brain stem and compression of the fourth ventricle–cisterna magna complex [29, 30], therefore indirect signs of OSB (Figure 2). The spine visualization transabdominally was considered unsatisfactory, therefore transvaginal
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an approach was proposed and performed; a cystic mass adjacent to sacral spine was evidentiated transvaginally (Figure 2).

Persistent exomphalos was identified (Figure 3) both in transabdominal and transvaginal approach.

Figure 2 – Open spina bifida suspected in 12 weeks fetus. A: Indirect markers present at transabdominal assessment with failure in visualizing and measure the fourth ventricle. B: Suspicion of cystic mass resembling to myelo-meningocele during transvaginally exam.

Both cardiac and neural anomalies present important difficulties regarding first trimester detection and differential diagnosis.

Off-line analysis with competent and experienced examiners of first trimester anomaly scan and cardiologist was performed, and the conclusions were similar.

A reassessment within a one week was recommended to confirm the suspicions of heart abnormality, neural tube defect and persistent exomphalos, but a later extensive exam was not performed, because the informed couple chose termination of pregnancy (TOP) at request as soon as possible.

Histological aspects

We can see that villi are congestive and more dense, separated by intervillous spaces larger but not so much as these at term (Figure 4).

Double cell layer present at villi in second pregnancy trimester is less represented and cytotrophoblast became very difficult to identify.

Syncitiotrophoblast villous layer became thinner making a syncitiotrophoblast membrane, which represents villous interface with intravillous maternal blood flow.

Start to be visible at villous syncitiotrophoblast level high density of syncitial cells called “knots”. Between villi we can observe fibrin stores (Figures 5 and 6).
Discussion

Prevention in high-risk pregnancies is of great importance in fetal medicine. Primary prevention strategies before conception are important because the pathogenesis of defects induced by maternal diabetes has origins in early stages of embryogenesis. With pre-existing diabetes, prospective studies and meta-analyses have demonstrated that pre-conception counseling with optimization of glycemic control before conception can significantly lower the prevalence of major congenital anomalies [11, 31–39]. The risks of congenital anomalies is reduced if optimal pre-conception and early pregnancy care with early referral for care with a multidisciplinary team are provided [11, 36, 40]. Diabetes and obstetrical international associations recommends that pregnant women with type 1 or type 2 diabetes should strive to attain a pre-conception glycosylated hemoglobin (HbA1c) <7% to decrease the risk of congenital malformations [6] and folic acid supplementation of 1 to 5 mg per day beginning before conception and continuing until 13 weeks’ gestation [6, 41]. Still, unplanned pregnancies occur in about one half to two thirds of women with diabetes and consecutively the majority of women do not seek their first prenatal visit until after the time of embryogenesis [33, 42] in studies conducted in well-developed societies. Women who do not present for pre-conception care are more likely to be low socioeconomic status [43], important issue in developing countries, or during economic difficulties periods.

Thus, we can accept that the diabetic pregnancy should be considered and investigated as a high-risk pregnancy and presently [44] efficient secondary prevention is needed, by fetal ultrasound scan, with morphologic and morphometric evaluation. First trimester ultrasound examination is necessary for dating purposes (useful for monitoring fetal growth later in pregnancy) and prenatal screening for chromosomal abnormalities; ultrasound morphological examination of the fetus is recommended with detailed assessment at 18 to 20 weeks, and consecutively morphology scanning with echocardiography in selected cases; in the third trimester, the fetal biometry and wellbeing are the main purposes of ultrasound scan.

The problem that we intend to highlight is that if we consider a priority to detect diseases prior to delivery, we have to accept that we inevitably diagnose conditions with a poor prognosis, as the case described before. In such situations the physiological and psychological impacts of TOP increase with increasing gestational age, leading to ethical dilemmas in the second half of pregnancy, especially in cases of severely handicapped but viable fetuses as OSB and HLHS. The solution should be efficient detection of severe fetal congenital anomalies by the end of the first trimester using morphological ultrasound examination. In consequence, for more than a decade studies have shown that fetal sonographic morphological assessment represents a useful diagnostic tool at 12–13 weeks [45–58]. It is accepted that presently the heart defects and OSB diagnosis associate important difficulties in detection and positive morphologic diagnosis, being usually missed at first trimester morphologic evaluation [59–64]. The direct evaluation of the fetal heart and spine transabdominally is particular difficult when local conditions associate increased thickness of the maternal abdomen and anterior position of placenta as in the case presented, even with the help of a high-resolution ultrasound machine. Recent research show that important progress have been made in both anomalies’ detection. Fetal echocardiography at the end of the first trimester performed by experienced examiners using high resolutions machines and combined transabdominal and transvaginal scan show a significant improvement in rates major CHD detection [28, 45, 55, 58, 65–67]. Also for OSB, early detection efficient indirect markers related to posterior brain morphology and morphometry are suggested by recent research and investigated in previous studies conducted in our department. Although the morphological protocols described above are not routinely studied in the first trimester because of technical and time limitations, we demonstrated their utility in the case presented and we consider important to perform detailed fetal morphological ultrasound evaluation in high-risk pregnancies, where it may prove cost-effective.

Conclusions

Pregnancy in women with diabetes should be planned and pre-pregnancy counseling is essential. Strategies are needed to offer to pregnant woman interventions associated with improved pregnancy outcomes, such as maintaining periconceptional euglycemia and folic acid use.

Implementation of modern protocols of first trimester fetal morphological assessment in high-risk pregnancies is an important tool given the right of a pregnant woman to decide against continuing a pregnancy with a severe anomaly; in such cases we should provide as much relevant morphological information as possible to the couple, as early as possible thus reducing the number of late abortions.

References

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**Corresponding author**
Dominic Iliесcu, Teaching Assistant, MD, PhD student, Department of Obstetrics and Gynecology, University of Medicine and Pharmacy of Craiova, 2–4 Petru Rareş Street, 200349 Craiova, Romania; Fax +40251–502 179, e-mail: dominic.iliescu@yahoo.com

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