Scientific Research Publishing

Open Journal of Endocrine and Metabolic Diseases, 2025, 15(5), 79-89
https://www.scirp.org/journal/ojemd
ISSN Online: 2165-7432
ISSN Print: 2165-7424

Poorly Controlled Maternal Diabetes and Pregnancy Associated with Fetal Dandy Walker Malformation and Subtotal Amelia: A Case Report and Review of the Literature

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How to cite this paper: Elilie Mawa Ongoth, F., Potokoue Mpia, N.S.B., Buambo, J.R.G., Ngakéni, Y.N., Andzouana Mbanognoua, N., Okoumou-Moko, A., Dinghat, O.M.Y., Ekoundzola, J.R., Moyikoua, R., Bouenizabila, E. and Itoua, C. (2025) Poorly Controlled Maternal Diabetes and Pregnancy Associated with Fetal Dandy Walker Malformation and Subtotal Amelia: A Case Report and Review of the Literature. *Open Journal of Endocrine and Metabolic Diseases*, **15**, 79-89.
https://doi.org/10.4236/ojemd.2025.155008

Received: March 8, 2025
Accepted: May 27, 2025
Published: May 30, 2025

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Abstract

Diabetes mellitus is a metabolic condition characterized by chronic hyperglycemia. Its association with pregnancy constitutes a very high-risk situation responsible for embryofetopathy. This diabetic embryofetopathy can be the cause of the occurrence of fetal congenital malformations during the first trimester of pregnancy. These are generally cardiac, digestive, skeletal, and genitourinary malformations. The role of hyperglycemia in the occurrence of congenital anomalies has been clearly established. The specific malformation of dandy walker affecting the central nervous system, grouping a Cyst of the posterior cerebral fossa in communication with the 4th ventricle and agenesis or hypoplasia of the cerebellar varnish, however, is rarely described in pregnant women with pre-existing diabetes. In this article, without confirming the direct link with diabetes mellitus, we report a rare case of Dandy-Walker malformation associated with amelia sub-total in a pregnant diabetic woman. The pregnancy occurred in the context of poor glycemic control and the absence of pre-conception diabetological preparation.

Keywords

Dandy-Walker Malformation, Diabetes Mellitus, Pregnancy, Brazzaville

1. Introduction

The association of maternal diabetes with pregnancy constitutes a high-risk metabolic situation for the mother and the fetus. This risk is dominated by diabetic embryofetopathy, responsible for fetal congenital malformations. The incidence of these malformations varies according to the studies [1] [2]. They are nevertheless a real cause of perinatal mortality and can, depending on the case, lead to termination of pregnancy or require surgical management and special care during the first years of life. These congenital anomalies affect many organs and systems of the developing fetus, in particular, the central nervous system, the heart, and the skeletal system. Several mechanisms appear to be involved in the teratogenicity of pre-conception maternal diabetes, but the major role of chronic hyperglycemia is established [3]-[5].

Dandy-Walker malformation (DWM) is a complex fetal malformation involving the posterior fossa and cerebellum. It is a rare anomaly with an estimated incidence of 1 in 10,000 to 30,000 births. It involves a posterior fossa cyst communicating with the fourth ventricle and agenesis or hypoplasia of the cerebellar varnish. It is frequently associated with other disorders of the central nervous system and other organs and has rarely been described in diabetic subjects [6] [7].

In this article, we report a case of antenatal diagnosis of Dandy-Walker malformation associated with Amelie subtotal observed in a 34-year-old pregnant woman with poorly controlled maternal diabetes who had not benefited from pre-conception diabetological preparation.

2. Clinical Observation

This is a 34-year-old primigravida patient admitted to our center for polyuria and polydipsia at the end of a 20-week pregnancy. She has type 2 diabetes mellitus that has been developing for a year, without specialized monitoring, treated with oral antidiabetic drugs (Metformin cp 1000 mg in two daily doses orally, with lack of adherence to treatment and without known degenerative complications.

The anamnesis revealed an absence of other known chronic diseases and symptoms evolving over a week marked by diurnal and nocturnal polyuria associated with polydipsia, physical asthenia, and repeated vomiting of food in a context of amenorrhea, without pre-conceptional diabetological preparation and without initiated obstetric monitoring.

The examination revealed an asthenic patient with a good state of consciousness, normotensive, apyretic, without respiratory problems, and weighing 90 kg. Eucorticism and clinical euthyroidism without goiter were also noted.

The metabolic assessment showed hyperglycemia at 14.63 mmol/l with ketosis, without ionic disorders, and an absence of biological inflammatory syndrome.

The diagnosis of diabetic ketosis was made, leading to the implementation of Intensive intravenous insulin therapy, which allowed resolution of the ketosis episode, followed by intensified basal-bolus insulin therapy for better glycemic

control.

Self-monitoring of blood glucose and individualized dietary prescription were associated with insulin therapy with biweekly diabetological monitoring.

The additional endocrinological assessment did not find any retinopathy, nephropathy, or dysthyroidism. The obstetrical assessment made it possible to link amenorrhea to a gravid origin and to confirm the existence of an evolving singleton pregnancy, motivating the establishment of obstetrical monitoring. This began late, at 27 weeks of amenorrhea, according to the ultrasound. This revealed a cystic dilatation of the posterior fossa with short thoracic and pelvic limbs and absent femurs (Figure 1). These fetal malformation lesions were linked to the Dandy-Walker malformation associated with a subtotal Amelie.

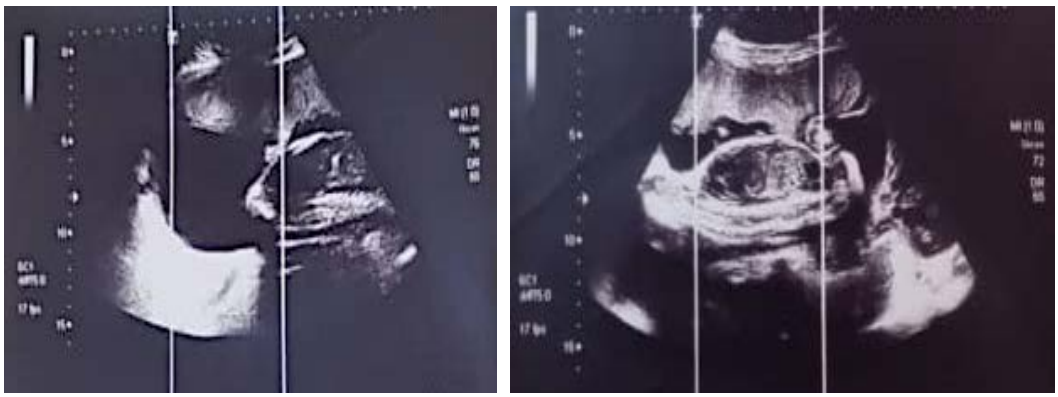

Figure 1. Ante-natal ultrasound shows a cystic dilatation of the posterior fossa with short thoracic and pelvic limbs and absent femurs.

Figure 2. Polymalformed fetus after expulsion.

The prenatal assessment, more specifically the toxoplasmosis and rubella serologies, were negative. Cytomegalovirus and parvovirus B9 serologies are not car-

ried out in our laboratories due to insufficient technical facilities.

Faced with this polymalformative syndrome, the indication for a eugenic termination of the pregnancy was raised in a multidisciplinary consultation meeting and accepted by the pregnant woman. It led to the expulsion of a polymalformed fetus (**Figure 2**), presenting a macrocrania with dolichocephaly, microtia, upward slanting or "Mongoloid" palpebral fissures, abnormal insertion of the limbs which are agenetic and hypoplasia of the toes (four instead of five).

The patient received supportive psychotherapy. A consultation and psychological follow-up were offered to the patient and her partner.

3. Discussion

Diabetes mellitus is a metabolic disease characterized by chronic hyperglycemia. It is a real public health problem on a global scale. The International Diabetes Federation (IDF) estimates that there are approximately 536.6 million people with diabetes mellitus worldwide and 24 million in Africa [8]. The increasing prevalence of diabetes mellitus in women of childbearing age explains the occurrence of pregnancies in the context of pre-gestational maternal diabetes mellitus, which is associated with maternal, fetal, and perinatal complications [9].

Liu *et al.* [3] in Canada reported that pre-pregnancy diabetes has nearly doubled among Canadian women aged 35 and over, from 6.4 per 1000 live births in 2002 to 12.3 per 1000 live births in 2012; they also noted that the proportion of congenital anomalies attributable to maternal pre-pregnancy diabetes has also increased over the past 10 years.

The occurrence of pregnancy on the grounds of maternal diabetes constitutes a metabolic situation with maternal-fetal risk, which is characterized by a risk of embryofetopathy generating congenital anomalies during the first trimester of pregnancy [10] [11].

Maternal diabetes prior to pregnancy is thus a major and modifiable risk factor for congenital anomalies. This risk is increased two to five times more in the presence of maternal diabetes than in its absence [2] [5].

Several authors show that the fetal prognosis in the context of maternal diabetes pre-existing during pregnancy is all the worse when the diabetes is old, the glycemic imbalance is major, and the degenerative complications are present [5] [11] [12].

In our observation, the pregnancy occurred in the context of maternal diabetes evolving for a year, without follow-up, and unbalanced. The patient was admitted to the hospital with a picture of major hyperglycemia with ketosis.

The mechanisms explaining the occurrence of diabetic embryofetopathy are not clearly described. However, the key role of pre-conception maternal hyperglycemia in the occurrence of congenital malformations is clearly established. Indeed, maternal hyperglycemia leads to a major disruption of the carbohydrate metabolism of the developing embryo resulting in an alteration of metabolic pathways, such as the polyol pathway, the metabolism of prostaglandins and arachidonic

acid. The resulting excess production of reactive oxygen species generates oxidative stress that is deleterious for the proper development of the embryo and the fetus [2] [11] [13].

In studying the effect of maternal diabetes on the risk of congenital malformations, Chung *et al*. [14] found that the risk of major and minor congenital malformations was twice that of newborns of white mothers with manifest diabetes compared with newborns of non-diabetic mothers. These malformations involved multiple organ systems.

Normalization of blood glucose levels in the pre-conception period is essential. It reduces the risk of congenital malformations, perinatal death, and preterm delivery [11] [15].

Nielsen *et al*. [2] in Denmark showed that newborns of mothers with type 1 and 2 diabetes before pregnancy were 2 to 10 times more likely to be affected by congenital malformations than newborns of non-diabetic mothers, particularly congenital heart disease and central nervous system abnormalities. Embryopathy can affect any developing organ, but neural tube and cardiovascular defects are the most serious and can be associated with prematurity and high perinatal mortality [3] [4] [12].

In our case, the fetus presented malformations of the skeletal system and a specific anomaly of the central nervous system, namely the Dandy-Walker malformation.

Dandy-Walker syndrome is a rare complex malformation involving the cerebellum and posterior fossa. It was first described in 1914 by Dandy and Blackfan. Its description was then completed in 1942 by Taggart and Walker in 1942. It was in 1954 that Bender reported the current description of this malformation. The Dandy-Walker malformation is characterized by the presence of a cyst in the posterior fossa communicating with the 4th ventricle and agenesis or hypoplasia of the cerebellar varnish causing hydrocephalus [6] [7].

This malformation generally appears around the 4th week of gestation, and the phenomena explaining the occurrence of this syndrome seem to involve a complex anomaly of the cerebellar vermis with an absence of closure of the fourth ventricle, leading to a persistence of Blake's pouch. The enlargement of the 4th ventricle leads to an upward displacement of the cerebellar vermis. All of these mechanisms result in an enlarged posterior fossa with a shifted position of the lateral sinus, tentorium, and torcula Herophili [6] [7] [16].

The performance of a morphological ultrasound in the second trimester of gestation, as part of an obstetrical evaluation, was the method of discovering the malformation anomaly in our observation. As in several studies, morphological ultrasound generally contributes to the identification of congenital anomalies in prenatal [7] [17] [18].

Indeed, the diagnosis of Dandy-Walker malformation is generally made antenatally by ultrasound examination in the second trimester, showing an enlargement of the large cistern (>10 mm), separated cerebellar hemispheres, and an absence or

hypoplasia of the vermis. A variable degree of ventriculomegaly (>10 mm) concerning the lateral ventricles can also be observed. This ventriculomegaly would be dependent on dynamic disorders in the cerebrospinal fluid generated by the mass effect induced by the malformation [6] [7].

Advances in medical imaging have made it possible to detect more cases of Dandy-Walker syndrome before birth using ultrasound or fetal magnetic resonance imaging (MRI). In particular, fetal MRI allows detailed anatomical assessment of the posterior fossa and supratentorial structure, facilitating the investigation of the cerebral anomalies present in Dandy-Walker syndrome [7].

Habi *et al*. [18] reported that Dandy-Walker syndrome is a rare malformation presented on MRI by an upward displacement of the sinus tent, torcular and lateral sinuses, as well as an anteroposterior widening of the posterior fossa.

In this multicenter study re-evaluating retrospective MRI findings of fetuses and children previously diagnosed with Dandy-Walker malformation or vermian hypoplasia, authors in the USA showed that modern phenotype of Dandy-Walker malformation is best defined on MRI by predominant inferior vermian hypoplasia, widened tegmento-vermian angle, inferolateral displacement of the choroid plexus, obtuse fastigial recessus and odd caudal lobule [19].

Several authors describe the association of Dandy-Walker malformation with other anomalies or malformations in the fetus or newborn. They specify a frequent association of chromosomal anomalies or not association and malformations of the central nervous system or not malformations, with a Dandy-Walker syndrome [6] [16] [19].

Postnatal studies show that Dandy-Walker syndrome is associated with other malformations in 50% to 70% of cases. Central nervous system abnormalities frequently associated with Dandy-Walker syndrome are agenesis of the corpus callosum, ventriculomegaly, encephalocele, and holoprosencephaly [7].

Non-central nervous system abnormalities commonly associated with Dandy-Walker syndrome include congenital cardiac, renal, cleft facial, genitourinary, skeletal, and gastrointestinal system disorders [7] [16].

Some authors have also reported associations of Dandy-Walker syndrome with chromosomal abnormalities such as trisomies 9, 13, 18, and 21, 6p and 3q22-q24 deletion, and triploidy. Associations with nonchromosomal syndromes, such as Meckel and Walker-Warburg syndromes, have been described in case studies. The variable association of Dandy-Walker malformation with other types of congenital anomalies leads to varied clinical presentations and prognoses in individuals with this condition [6] [7].

Coban *et al*. [16] in Türkiye stated that Dandy-Walker syndrome usually appears around the 4th week of gestation and is often associated with abnormalities involving the cardiac, skeletal, genitourinary, and gastrointestinal systems. They also reported a rare case of a live male infant with Dandy-Walker malformation associated with ventricular and atrial septal defect, unilateral renal agenesis, and hypoparathyroidism.

Habi *et al*. [20] in Casablanca, Morocco, reported in an 8-month-old infant with psychomotor delay and ataxia the association of a Dandy-Walker malformation and Joubert syndrome, which is a ciliopathy. Rare recessive characterized on MRI by the presence of thick and straight superior cerebellar peduncles, a deep interpeduncular fossa, and a hypoplastic/dysplastic vermis Tsirikos *et al*. [21] in the United Kingdom reported the association of Dandy-Walker syndrome with skeletal abnormality including thoracic scoliosis and increased lumbar lordosis.

Literature data also show rare associations of Dandy-Walker syndrome with environmental exposures such as alcohol, infections (rubella, cytomegalovirus), and maternal diabetes, as the case in our observation [7] [21] [22].

As long ago as 1980, a team of American researchers reported a clinical observation similar to our own. They noted a poly malformation fetal syndrome, including Dandy-walker malformation in a diabetic woman [22].

These authors described the poly-malformed fetus of a diabetic woman, treated with insulin, who had already had a non-malformed stillborn male child and a normal female child.

This fetus presented an unusual combination of malformations not often described in diabetic embryopathy. These anomalies included upper limb amelia, "caudal regression" with bilateral absence of fibulae, unilateral absence of femur and ipsilateral oligodactyly; undescended testes; atrial septal defect; multiple vertebral and costal anomalies with cervical scoliosis and palmar neck on the right; cleft lip and cleft palate on the left; severe micrognathia; left microtia with ear canal atresia. This polymalformative syndrome was associated with abnormalities of the central nervous system, including hydrocephalus with Dandy-Walker malformation, asymmetry of the lateral ventricles, abnormal formation of the frontal gyri and ependymal and ganglionic heterotopies of the spinal cord [22].

The particularity of our clinical case is the association of the Dandy-Walker malformation with a malformation affecting the locomotor system marked by amelia sub-total, all occurring on a background of poorly controlled maternal diabetes in the absence of pre-conceptional diabetological preparation and without the context of rubella, cytomegalovirus infection or other teratogenic pathologies or therapies. The direct involvement of hyperglycemia in the occurrence of this specific malformation is not clearly established. However, fetal exposure to an environment of hyperglycemia related to unbalanced maternal diabetes during the first trimester of pregnancy considerably increases the contribution of maternal hyperglycemia pre-existing to pregnancy in the occurrence of fetal malformations or congenital anomalies that may explain the appearance of a fetal polymalformative syndrome.

Obstetric management in a woman in whom a Dandy-Walker malformation has been observed during morphological ultrasound takes into account the characteristics of the anomalies observed and the associated malformations. Medical termination of pregnancy may be a possible option proposed to the pregnant woman when a major malformation is detected on imaging [7] [23] [24].

The early discovery of lethal congenital anomalies in the case of our observation had led the care team to propose, as part of a multidisciplinary consultation, a medical termination of pregnancy. The involvement of the pregnant woman and her partner in the therapeutic choice by explicitly presenting the situation led to obtaining informed consent from the latter in the decision to terminate the pregnancy. The continuation of the pregnancy by the patient, when a Dandywalker malformation is suspected, requires the establishment of rigorous monitoring of fetal growth through repeated ultrasound evaluation and continuous assessment of the degree of ventriculomegaly or hydrocephalus allowing a reassessment of the medical decision and the choice of cesarean section during delivery in the event of macrocephaly [7] [25].

Fetal prognosis in the context of Dandy-Walker malformation depends on the existence of associated malformations, the presence of genetic anomalies, and the degree of hydrocephalus [7] [25]-[27].

Dandy-Walker malformation is responsible for neurodevelopmental damage that is manifested in early infancy if a pregnancy has been carried to term with a live birth. A favorable outcome in the case of Dandy-Walker malformation has been reported in 30% to 42% of infants without genetic abnormalities [7] [27].

4. Conclusions

The occurrence of pregnancy in a diabetic woman remains a metabolic risk situation responsible for diabetic embryofetopathy. The specific Dandy-Walker malformation is rarely described in pregnant women with pre-existing diabetes. This observation of Dandy-Walker malformation is the first description in our center. It recalls the interest of pre-conception diabetological preparation, which involves an optimal balance of maternal diabetes at least 3 months before conception, the search for and multidisciplinary management of complications of diabetes mellitus, and the identification of prognostic elements for pregnancy or its contraindication. Early prenatal determination of congenital malformations such as Dandy-Walker malformation generally leads to termination of pregnancies.

The association of this syndrome with maternal diabetes is poorly described. The association in our patient of unbalanced diabetes mellitus with Dandy-Walker syndrome appears sporadic.

The role of hyperglycemia in the occurrence of congenital malformations is well established to date. However, the specific relationship between pre-existing maternal diabetes and Dandy-Walker malformation is unclear. Further scientific studies involving solid epidemiological data and rigorous genetic analysis will be required to clarify the relationship between maternal diabetes mellitus and Dandy-Walker syndrome.

This clinical case highlights the importance of careful obstetrical assessment and monitoring and the importance of maintaining optimal glycemic control to minimize the risk of fetal malformation in the relationship between diabetes and pregnancy.

Consent

Informed consent was obtained from the patient for the publication of this report and any accompanying images.

Acknowledgements

The authors want to sincerely thank the patient for her participation in the research study.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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