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Abstract

Background: Caudal Regression Syndrome is an infrequent congenital malformation of the vertebral spine's lower segments characterized by a truncated medullar cone and aplasia or hypoplasia of the sacrum. Specifically, sacral agenesis represents an incidence of 0.01 to 0.05 of every 1,000 newborn. Among the main risk factors are elevated glycosylated hemoglobin, hormonal imbalance, and lipid protein metabolic disorder. A correlation has been established between anomalous pregnancies and congenital malformations in newborns, with a prevalence of 5 to 10% in children of diabetic mothers, with an incidence of 1 per 350 cases, representing a 200% rise over the general population. **Objective:** To report an extremely uncommon epidemiologically rare case of Caudal Regression Syndrome, characterized by caudal musculoskeletal involvement. **Clinical case:** a 27-year-old female in her 34th week of gestation during her second pregnancy presented to the high specialty, high-risk pregnancy consultation with a background of glycemia of 205mg/dl, glycosylated hemoglobin percentage (%HbA1c) of 10.1%, and estimated average glucose levels of 243mg/dl. The patient arrived at the emergency room during active labor with premature membrane rupture, both deciding factors for pregnancy termination. The outcome was a sole female live product with a vertebral spine interrupted approximately by T10, non-palpable iliac crests, sacrum, and coccyx, and shortening of hypotrophied inferior extremities. Conclusion: successful prevention in the early diagnosis of malformations during pregnancy requires strict prenatal control for any pregnant woman with metabolic risk factors. The first prenatal consultation presents an opportunity to perform diabetic screening. If diagnosed, follow-up procedures such as ultrasounds at a second level of medical care should be performed for the timely detection of congenital malformations associated with high levels of glycemia.

Keywords: Caudal Regression Syndrome, Caudal Agensis, Sacral Regression.

Resumen

Antecedentes: el Síndrome de Regresión Caudal es una malformación congénita poco frecuente que afecta los segmentos inferiores de la columna vertebral, caracterizada por un cono medular truncado y aplasia o hipoplasia del sacro. Específicamente, la agenesia sacra presenta una incidencia de 0,01 a 0,05 por cada 1.000 recién nacidos. Entre los principales factores de riesgo se encuentran la hemoglobina glucosilada elevada, el desequilibrio hormonal y el trastorno metabólico de las proteínas lipídicas. Se ha establecido una correlación entre embarazos anómalos y malformaciones congénitas en recién nacidos, con una prevalencia del 5 al 10% en hijos de madres diabéticas, con una incidencia de 1 por cada 350 casos, lo que representa un aumento del 200% en comparación con la población general. **Objetivo:** Reportar un caso extremadamente raro desde el punto de vista epidemiológico de Síndrome de Regresión Caudal, caracterizado por afectación musculoesquelética caudal. **Caso clínico:** Mujer de 27 años en su semana 34 de gestación, durante su segundo embarazo, se presenta en la consulta de embarazos de alto riesgo y alta especialidad, con antecedentes de glucemia de 205 mg/dl, un porcentaje de hemoglobina glucosilada (%HbA1c) de 10,1% y niveles de glucosa media estimada de 243 mg/dl. La paciente ingresó a urgencias en trabajo de parto activo con ruptura prematura de membranas, ambos factores determinantes para la interrupción del embarazo. El resultado fue un único producto femenino vivo con interrupción de la columna vertebral aproximadamente a nivel de T10, crestas ilíacas, sacro y cóccix no palpables, y acortamiento de las extremidades inferiores hipotróficas. **Conclusión:** La prevención exitosa en el diagnóstico temprano de malformaciones durante el embarazo requiere un estricto control prenatal en cualquier mujer embarazada con factores de riesgo metabólico. La primera consulta prenatal es una oportunidad para realizar un tamizaje de diabetes. Si se diagnostica, deben realizarse procedimientos de seguimiento como ecografías en un segundo nivel de atención médica para la detección oportuna de malformaciones congénitas asociadas a niveles elevados de glucemia.

Palabras clave: Síndrome de regresión caudal, agenesia caudal, regresión sacra.

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Introduction

The term “Caudal Regression Syndrome (CRS)” first coined by Bernard Duhamel, 1961, and later on by Renshaw, 1978, naming it Caudal Regression Secuency or Caudal Agenesis (1). Different terms have been associated, amongst which: caudal dysplasia, dysgenesis or sacral regression, congenital sacral agenesis, sacral defect with anterior meningocele, sacrococcygeal dysgenesis and caudal dysplasia sequence, can be found thus, it can be defined as an infrequent congenital malformation of the vertebral spine’s lower segments characterized by a truncated medular cone and aplasia or hipoplasia of the sacrum, with variable involvement of the gastrointestinal, genitourinary, skeletal and nervous systems (2, 3). The neural tube defects vary between 1-10 of each 1,000 newborn, Specifically sacral agenesis manifests within 0.01 and 0.05 of every 1,000 newborn; in Latin America, in Costa Rica specifically an incidence between 2010 and 2014 of 0.07 for every 1,000 newborn (4). Multiple factors have been linked to the manifestation of this syndrome, highlighting: Diabetes Mellitus, being the most relevant factor, and the most correlated to the aforementioned syndrome, numerous reports indicate the correlation between gestational diabetes and the presence of fetal anomalies (5).

The mechanism of the malformation is yet to be found, but situations that can be associated have been identified, amongst which stand out:

-High levels of glycosylated hemoglobin (6) as well as hormonal imbalance and lipid protein metabolic disorder (7), which have been corelated to anomalous pregnancies leading to congenital malformations in newborns in up to 5 to 10%, of children of diabetic mothers (8), with an incidence of 1 case per 350 cases, and a rise of 200% over the general population (9).

The predisposing factors of Caudal Regression Syndrome are:

- Hematic depletion: In these patients, an aberrant vessel derived from the yolk artery has been observed, which redirects blood from the abdominal aorta to the placenta through the umbilical cord. This vessel finally acts as a single umbilical artery that steals the flow that should reach the caudal end of the fetus, conditioning ischemia and hypoperfusion (3).
- Genetic: 2 main genes become relevant:
 - Homeobox HLXB9 gene: A mutation in the homeobox HLXB9 gene, with an autosomal dominant inheritance pattern, in the 7q36 region of chromosome 7 is associated with sacral agenesis as an isolated finding or as part of Currarino syndrome (2,10).
 - TBX4 gene: Monoallelic variants of this gene have been found to be associated with skeletal defects of the pelvis and lower limbs (6), acinar dysplasia, pulmonary hypoplasia, and left-sided cardiac hypoplasia with congestive heart failure. Additionally, in a fetus with a new syndrome of multiple malformations, including sacrococcygeal

agenesis, bilateral aplasia of the lower limbs, left-sided hypoplasia, bilateral pulmonary hypoplasia, hydroureteronephrosis, and non-immune hydrops fetalis, a homozygous nonsense variant in the TBX4 gene was found. That is, biallelic variants in the TBX4 gene are associated with a severe syndromic phenotype of sacrococcygeal agenesis and lower limb reduction defects (11).

- Microdeletion of chromosome 22q13.31: This is a very rare condition described in a patient with neurodevelopmental disorders, dysmorphic features, and multiple congenital anomalies. Peripheral nervous system array analysis revealed a de novo interstitial microdeletion of 3.15 Mb in the 22q13.31 region, encompassing 21 RefSeq genes and seven non-coding microRNAs (12).
- VANGL1 and VANGL2 genes: Xing *et al.* (13), in 2024, discussed the role of these genes in vertebral development and found that their deletion causes vertebral anomalies resembling congenital vertebral malformations in humans.
- Environmental factors: alterations in notochord development have been linked to lithium salts, trypan blue, sulfides, cysteine, and retinoic acid (6).

CRS alterations range from partial or complete agenesis at the sacrococcygeal level with associations of urogenital and gastrointestinal malformations, respiratory diseases and a possible cardiac alteration such as ventricular septal defect (5).

Different classifications have been made, with antecedents dating back to 1924 (4). Currently, one of the most common is that of Renshaw, who in 1978 grouped patients with CRS into 4 categories or types, based on the anatomical characteristics detected by radiological studies (1,14):

- Type I: unilateral partial or total agenesis of the sacrum.
- Type II: bilateral and symmetrical partial agenesis of the sacrum.
- Type III: total agenesis of the sacrum associated with variable anomalies in the last lumbar vertebrae and iliac bones.
- Type IV: total agenesis of the sacrum with anomalies of the lumbar and iliac half fused behind the last vertebrae if present.

Another commonly used classification, which allows detailing the malformations and characteristics of CRS, is that of Pang (6,10,15), who in 1993 modified Renshaw's classification, grouping them into 5 types, with a spectrum ranging from subtotal coccygeal agenesis to total sacral agenesis with the absence of some lumbar vertebra.

More recent classifications have been reported in the literature, such as that made by Guille and his collaborators in 2002 and that of Baloğlu in 2016 (4, 6, 10). The first of these divides patients into 2 groups, each with three types; this classification system correlates the vertebral deformity with the walking potential of the affected patients. The Baloğlu classification proposes 2 groups: Group A, with the presence of myelomeningocele and Group B, without myelomeningocele (6).

To make a timely diagnosis, each case should be analyzed individually, and specific hospital infrastructure must be available to obtain ultrasonographic images capable of performing prenatal or postnatal diagnoses. Between 60% to 90% of the detected anomalies involve the spinal cord, anorectal, genitourinary, abdominal wall, and lower limb defects (6)

Performing a prenatal ultrasounography in the first trimester of pregnancy, proves difficult, due to the incomplete ossification of the sacrum making it difficult to make a timely diagnosis (8). The first signs that allow one to suspect a caudal regression syndrome in this first trimester is the decrease in craniocaudal length (16).

In the second and third trimester, an ossification of the sacrum has already occurred, finding manifestations of it or even its absence. Reassessment by a maternal-fetal specialist is recommended after 22 weeks (17). Using ultrasound, it is possible to identify characteristic patterns of the syndrome such as immobile lower extremities, in a "frog" or "Buddha" position, and appreciable muscular-cutaneous hypotrophy (16). Performing a prenatal ultrasound in the first trimester of pregnancy is challenging due to the incomplete ossification of the sacrum, which complicates making a timely diagnosis (8). The first signs that may suggest a Currarino Syndrome (SRC) in the first trimester are a reduction in crown-rump length (16). In the second and third trimesters, by this time, sacral ossification has occurred, revealing its presence or even its absence.

A reevaluation by a maternal-fetal specialist is recommended from 22 weeks onwards (17). Through ultrasound, it is possible to identify characteristic patterns of the syndrome such as immobile lower limbs in a 'frog-leg' or 'Buddha-like' position and visible muscle-skin hypotrophy (16). Magnetic resonance imaging (MRI) is an imaging study with greater sensitivity and specificity, improving the characterization of associated anomalies; it is the confirmatory study for the identification of associated spinal anomalies, such as a high medullary cone in cases of dysplasia (18).

In cases where a prenatal diagnosis cannot be made for some reason, the diagnosis should be established as soon as possible, with the support of a physical examination, where findings may include lumbar region deformity, narrow hips, gluteal hypoplasia, imperforate anus, flattening of the intergluteal fold, isolated or complex lower limb deformities, as well as imaging studies such as lumbosacral X-rays and MRI, which can be used to assess associated anomalies within the spinal canal or spinal and vertebral features (6).

The prognosis for fetuses with SRC depends on the severity of the lesion and the coexistence of other anomalies (1). In addition to the degree of vertebral abnormality, another important factor is the presence of associated malformations, with a worse prognosis for those related to the genitourinary system, such as bladder exstrophy or renal agenesis (6), and gastrointestinal anomalies, such as duodenal atresia, imperforate anus, intestinal malrotation, incontinence, and encopresis (10).

Signs of neurological deficit such as inability to mobilize the lower extremities considerably obscure the prognosis. This will depend on the severity of vertebral malformations and the presence of associated anomalies, being different for each case. It is important to distinguish the type of sacral agenesis, since each one is more often associated with specific deficits, mainly related to urological and cardiac malformations. Early neonatal death in severe forms occurs due to complications; Infants who survive usually have normal cognitive function (6).

The purpose and justification for reporting this case is to contribute to the development of knowledge about this pathology, considering that globally it is a low-incidence disease and, therefore, very rare and infrequent, even at the National Institute of Social Security of the State of Tabasco, Mexico. Additionally, the case highlights the importance of conducting prenatal consultations with targeted screening through ultrasound studies starting at the 22nd week of gestation, facilitating the early detection of potential malformations. A literature review was conducted over the past five years using Scopus, Web of Science, Clarivate, among others, to support the described topic, making comparisons and finding the similarities described by other authors worldwide.

Clinical Case Report

A 27-year-old female patient in her second pregnancy, currently at 34 weeks of gestation (WG) based on her last menstrual period (LMP) and confirmed at 32 WG by obstetric ultrasound. As part of her medical history, she reports that birth control was monitored monthly for six instances by a private physician with various ultrasounds. She attends her first prenatal consultation at the "Dr. Juan Puig Palacios" University Hospital of the Social Security Institute of the State of Tabasco (ISSET) at 28.5 WG, with private obstetric ultrasounds that reported no abnormalities. Her personal pathological history includes grade II obesity, gestational diabetes without nutritional or pharmacological control, a history of vaginal and urinary infections, and gestational hypertension.

After care and evaluation at the Family Medicine Unit, the patient was referred to the "Dr. Julián A. Manzur Ocaña" University Hospital of the Social Security Institute of the State of Tabasco (ISSET) for a high-risk obstetric consultation. She was seen by a specialist, who reported a pregnancy of 34 weeks according to the last menstrual period (LMP), with a blood pressure of 150/90 mmHg, blood glucose of 205 mg/dL, urea of 21.4 mg/dL, creatinine of 0.5 mg/dL, uric

acid of 3.4 mg/dL, cholesterol of 119 mg/dL, triglycerides of 113 mg/dL, glycated hemoglobin percentage (HbA1c) of 10.1%, and an estimated average glucose of 243 mg/dL. An obstetric ultrasound was requested, and a follow-up appointment was scheduled for results.

The institutional obstetric ultrasound reported a pregnancy of 32.4 weeks of gestational age in breech presentation, with no structural abnormalities detected. Seventy-two hours after the ultrasound, the patient was admitted to the hospital for vaginal bleeding, active labor, and premature rupture of membranes of less than 12 hours' evolution, with umbilical cord prolapse, which led to the decision to terminate the pregnancy. An emergency cesarean section was performed, with the fetus in a transverse presentation and shoulder impaction, which complicated the extraction and caused tears in the uterine artery. A single live female newborn (NB) was delivered, and resuscitation measures were initiated. Secondary apnea was observed, requiring mechanical ventilation to secure the airway, and the newborn was transferred to the Neonatal Intensive Care Unit (NICU) due to respiratory distress type 1, presenting as hypoactive with generalized cyanosis. On physical examination, primitive reflexes were absent. The newborn had a short neck, rhythmic heart sounds of good intensity, a grade II/V murmur, a soft abdomen with 2 cm hepatomegaly, an interrupted spine at approximately the T10 level, non-palpable iliac crests, sacrum, or coccyx, shortened and hypotrophic lower limbs, a fracture of the upper tibial epiphysis of the right leg, genitalia consistent with age and sex, and the following anthropometric measurements: weight: 3050 g, length: 39 cm, head circumference: 31 cm, chest circumference: 33 cm, abdominal circumference: 32 cm, foot length: 6 cm, APGAR: 3-5/8, SILVERMAN: 00; vital signs: heart rate: 146 beats per minute, respiratory rate: 0, temperature: 36.9°C, Capurro: 34 weeks of gestational age. An echocardiogram was performed, reporting hypertrophic obstructive cardiomyopathy, dysplastic pulmonary valve with dome-shaped opening causing mild pulmonary stenosis, and a ventricular septal defect (figures 1 and 2).



Figure 1. A portable anteroposterior (ap) full-body x-ray reveals interruption of the continuity of the vertebral bodies at the level of the lumbar vertebrae. The pelvic bones are not clearly defined, sacral aplasia and a fracture of the right tibia in the lower extremity are observed.

Source: Clinical archive of the Department of Radiology at ISSET.



Figure 2. Physical examination reveals hypoplastic lower segment with significant reduction in circulation and edema of the lower limbs.

Source: Clinical archive of the Neonatal Intensive Care Unit of ISSET.

At 72 hours of life and stay in the Neonatal Intensive Care Unit (NICU), the newborn developed jaundice classified as Kramer III, associated with moderate edema in the lower limbs, as well as bruising in the hypogastric region, with the presence of clubfoot and absence of pedal pulses, with capillary refill time of 3 to 4 seconds.

On the fourth day of life, borderline hyperbilirubinemia was observed, leading to the initiation of phototherapy. Subsequently, signs of pulmonary congestion appeared, prompting the initiation of diuretic therapy.

It was decided to begin Continuous Positive Airway Pressure (CPAP) due to improvement in the respiratory pattern, without desaturation, with the following ventilatory parameters: Peak Inspiratory Pressure (PIP) of 11, Positive End-Expiratory Pressure (PEEP) of 5, and Fraction of Inspired Oxygen (FiO₂) of 30.

On the 6th day, the respiratory pattern deteriorated, requiring reintubation. A chest X-ray showed complete atelectasis of the right lung. The patient was later evaluated by pediatric neurology, and a neuroaxis CT scan reported agenesis of L2, L3, L4, L5, and caudal regression of the sacrum (Figures 3 and 4).

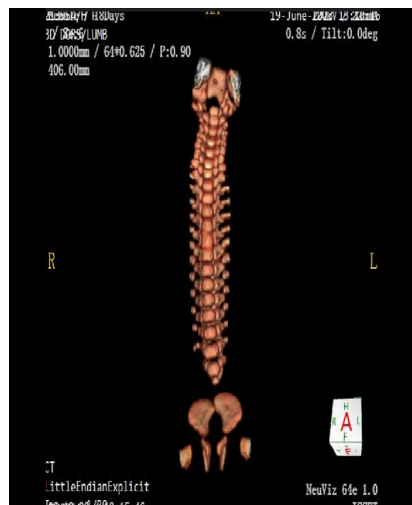


Figure 3. Spine CT scan: presence of cervical, thoracic, and lumbar vertebrae. Disruption at L3, L4-L5, sacrum not observed, iliac crests with a distance of 13 mm.

Source: Clinical file of the newborn from the Department of Imaging of ISSET.



Figure 4. Spine CT scan: intervertebral discs with homogeneous density, preserved spinal canal up to L3, no identification of the spinal cord.

Source: Clinical file of the newborn from the Department of Imaging of ISSET.

On the 8th day, leukocytosis was observed with a count of $14,000/\mu\text{L}$, as well as a decrease in hemoglobin levels to 11.3 g/dL , an elevated D-dimer of greater than 10 mg/L , and a negative blood culture.

At 15 days of life, leukocytosis persisted ($27,180/\mu\text{L}$), prompting a second bronchial culture, which led to the diagnosis of late-onset neonatal sepsis, and antibiotic treatment was initiated.

On the 19th day, metabolic, digestive, and hemodynamic deterioration was observed, leading to the initiation of fasting. Additionally, renal deterioration was noted, with hypertension and progressive reduction in urine output. Bradycardia persisted along with pulmonary patterns of wheezing and crackles. Due to ongoing hematological and hemodynamic alterations, a red blood cell transfusion was performed.

At 28 days of life, the infant was extubated to begin CPAP management. Forty-eight hours later (30 days of life), there was good improvement in the pulmonary pattern, so it was decided to progress to nasal cannula. However, reintubation was necessary following reevaluation, which showed poor secretion management.

At 32 days of life, digestive and hemodynamic deterioration persisted, with oral intolerance, severe abdominal distension, absence of bowel movements, and intestinal loop dilation on abdominal X-ray. Criteria for Systemic Inflammatory Response Syndrome (SIRS) and septic shock were met. Twenty-four hours later (33 days), positive culture results revealed moderate growth of *Stenotrophomonas maltophilia*, sensitive to trimethoprim/sulfamethoxazole.

At 36 days of age, the patient was noted to have pale skin and mucous membranes, with decreased alertness, absence of spontaneous eye opening, and respiratory difficulty, which worsened with sudden bradycardia and desaturation. Resuscitation maneuvers were initiated, including the administration of epinephrine, but there was no recovery of heart rate. Resuscitation efforts were discontinued, and the diagnosis of death was made.

Discussion

This is the first documented case, in at least the last three decades, of Caudal Regression Syndrome (CRS) at the “Dr. Julián A. Manzur Ocaña” Hospital of the ISSET; this makes it an epidemiologically relevant issue for the institution. Additionally, it underscores the importance of thorough prenatal care, emphasizing the indispensable practice of screening during prenatal consultations, particularly for women with metabolic disorders, and conducting ultrasound examinations. These should include a proactive search for potential malformations in pregnant women with risk factors. Globally, CRS has an incidence of 0.01-0.05% per 1,000 newborns, as described by Méndez-Salazar *et al.* in 2020 (4).

Gestational diabetes mellitus is the most common metabolic complication during pregnancy. Worldwide, its prevalence ranges from 1 to 14%, with Latin America being particularly susceptible. This condition has a high impact, with advanced age, obesity, and personal pathological history being the most commonly associated risk factors, increasing the likelihood of developing gestational diabetes by 1.2 times. The most frequently recorded risk factor in confirmed cases of CRS is gestational diabetes, with a prevalence of 4% (19); it is a pathological entity that predisposes the fetus to congenital malformations due to hyperglycemia during the first trimester of pregnancy. Among diabetic pregnancies, 11% are associated with congenital heart disease, the most common anomaly linked to caudal regression and diabetes (20, 21).

In the presented case, the patient attended her Family Medicine Unit for the first time at 28.5 weeks of gestation, with a history of uncontrolled gestational diabetes, neither through diet nor pharmacological management. Considering the 2022 prevalence of diagnosed and undiagnosed diabetes, which was 12.6%, and a total diabetes prevalence of 18.3% (22), these are alarming and suggestive data, urging healthcare personnel at the primary care level, both in public and private institutions, to ensure proper prenatal care with risk factor screenings, especially for gestational diabetes, and early detection of any malformations in the fetus. If there is even the slightest suspicion, early referral to secondary or tertiary care should be made.

CRS can be diagnosed through obstetric ultrasonography starting in the second trimester of pregnancy (17), conducted by a maternal-fetal subspecialist. If the necessary infrastructure is unavailable, the study should be outsourced or the patient referred to a tertiary care center. To confirm the structural damage in the newborn, magnetic resonance imaging (MRI) is the most sensitive and specific study, as it details the level at which the vertebral column and its corresponding spinal cord are interrupted (6). Cardiac anomalies are present in 50% of cases, with the most common being cardiomyopathy (23), as seen in this case, where the echocardiogram revealed asymmetric septal hypertrophic cardiomyopathy, mild tricuspid insufficiency, and a grade IV/VI mid-systolic murmur.

This malformation is associated with hyperglycemia, which disruptively promotes neural tube closure, reduces mitosis, and induces premature maturation (these findings have been observed in experimental models). Clinically, a range of malformations can be observed, from coccygeal absence to lumbar and sacral agenesis, and even spinal cord cyst formation (syringomyelia) (9).

CRS is linked to visceral malformations in various systems, including the gastrointestinal, genital, urinary, neurological, and cardiac systems. Musculoskeletal malformations can include narrow hips, flattening of the intergluteal fold, or gluteal hypoplasia, accompanied by various malformations such as flexion contractures, muscle atrophy, and femoral hypoplasia (3). In this clinical case, the newborn presented an interrupted spine at the T10 level, shortened and hypotrophic lower limbs, agenesis of the pelvis, and fractures of the right tibia and fibula. CT findings reported disruption of the spine from L3, incomplete obstruction of the spinal canal, fusion of the iliac crest, pubic bones separated by 13 mm from the intervertebral discs, and a preserved spinal canal up to L3, with no spinal cord identified through this method. The case presented in this report is interesting to evaluate and discuss in terms of its progression, as it constitutes a CRS case involving the lumbosacral region, which, according to global epidemiological statistics, has a low incidence rate. The literature documents several CRS cases where vertebral agenesis extends to the sacral and lumbosacral regions, similar to what is reported in this study; however, dorsolumbosacral agenesis remains the rarest (3).

The prognosis for fetuses diagnosed with CRS is directly related to the severity of the lesion and the simultaneous presence of other anomalies. Early prenatal diagnosis gives parents the opportunity to make informed decisions regarding potential neonatal complications. Multidisciplinary medical support (pediatrics, neonatology, cardiology, orthopedics, radiology, and neurology) is essential for the care and treatment of this syndrome, should the baby survive birth.

Conclusions

To achieve successful prevention in the early diagnosis of malformations during pregnancy, strict prenatal control is essential for every pregnant woman with metabolic risk factors. The first prenatal visit is an opportunity to screen for diabetes. If diagnosed, follow-up procedures such as ultrasounds at a secondary care level should be performed to ensure timely detection of congenital malformations associated with elevated blood glucose levels. Emphasis should be placed at the primary care level on educating both the patient and immediate family members about the potential complications of diabetes in pregnancy to ensure proper metabolic control and prevention. In most published cases, detection occurs during the second trimester of pregnancy, making it critical to conduct structural ultrasounds (between weeks 18 and 20) with a focus on verifying the integrity of the lumbar spine, especially in patients with Diabetes Mellitus.

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Ethical considerations

Consent was requested from the mother for the publication of the images.

Conflict of interest

There is no conflict of interest to carry out this study.

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