RESEARCH PAPER

Recurrent Severe Polyhydramnios as an Antenatal Clue to Bartter Syndrome: A Case Series with Postnatal and Genetic Correlation

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ABSTRACT

Background: Antenatal Bartter syndrome is a rare inherited renal tubular disorder characterized by defective electrolyte transport in the thick ascending limb of the loop of Henle, resulting in fetal polyuria, severe polyhydramnios, prematurity, and neonatal electrolyte imbalance. Prenatal diagnosis remains challenging because affected fetuses commonly demonstrate structurally normal anatomy despite progressive and recurrent polyhydramnios. Early recognition is essential for antenatal surveillance, neonatal preparedness, and genetic counseling.

Case Presentation This case series describes three pregnancies complicated by severe recurrent polyhydramnios subsequently diagnosed as antenatal Bartter syndrome.

Case 1 involved a gravida 3 woman with recurrent adverse pregnancy outcomes associated with severe polyhydramnios. Indomethacin therapy was administered for four weeks during pregnancy. The neonate was delivered preterm at 30 weeks gestation, required prolonged neonatal intensive care, and died on the 31st day of life. Genetic analysis demonstrated a homozygous pathogenic BSND gene variant confirming antenatal Bartter syndrome.

Case 2 involved recurrent severe polyhydramnios with structurally normal fetus and previous mid-trimester pregnancy losses. Amniotic fluid biochemical analysis demonstrated elevated sodium and chloride concentrations suggestive of fetal renal salt wasting. Molecular analysis identified a homozygous KCNJ1 gene deletion consistent with antenatal Bartter syndrome type 2.

Case 3 involved severe recurrent polyhydramnios in a consanguineous pregnancy with previous neonatal loss. Indomethacin therapy was administered for two weeks with serial fetal surveillance. Genetic testing identified a homozygous pathogenic SLC12A1 mutation diagnostic of antenatal Bartter syndrome type 1. The neonate required neonatal intensive care management for prematurity and electrolyte imbalance but survived and is presently clinically stable and doing well on follow-up.

Conclusion Persistent severe polyhydramnios with structurally normal fetal anatomy, particularly in the presence of recurrent adverse obstetric history or consanguinity, should raise suspicion for antenatal Bartter syndrome. Amniotic fluid biochemical analysis and molecular genetic testing play important roles in establishing prenatal diagnosis. Early recognition and multidisciplinary management may improve neonatal preparedness, optimize postnatal care, and contribute to better clinical outcomes.

Keywords: *Antenatal Bartter syndrome; Polyhydramnios; Fetal polyuria; BSND mutation; KCNJ1 mutation; SLC12A1 mutation; Indomethacin therapy; Prematurity; Neonatal electrolyte imbalance; Case series.*
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INTRODUCTION

Antenatal Bartter syndrome is a rare autosomal recessive renal tubular disorder characterized by defective sodium, potassium, and chloride transport within the thick ascending limb of the loop of Henle [1,2]. The disorder results in excessive fetal urinary electrolyte loss, severe fetal polyuria, progressive polyhydramnios, prematurity, and significant neonatal electrolyte imbalance [3]. Antenatal Bartter syndrome represents the severe prenatal variant of Bartter syndrome and is commonly associated with mutations involving genes encoding renal tubular transport proteins, including SLC12A1, KCNJ1, CLCNKB, BSND, and CASR [4,5]. Delayed diagnosis may result in adverse perinatal outcomes including extreme prematurity, dehydration, nephrocalcinosis, growth failure, and neonatal mortality [6]. Polyhydramnios is one of the earliest and most consistent antenatal manifestations of Bartter syndrome [7]. Excessive fetal urine production secondary to impaired tubular electrolyte reabsorption leads to progressive accumulation of amniotic fluid, usually during the second or early third trimester [8]. However, prenatal diagnosis remains challenging because detailed fetal anatomical surveys are often structurally normal despite severe and recurrent hydramnios [9]. Consequently, many pregnancies are initially categorized as idiopathic polyhydramnios until recurrent disease pattern, biochemical abnormalities, or postnatal manifestations become apparent [10]. The diagnosis of antenatal Bartter syndrome requires high clinical suspicion, particularly in pregnancies complicated by recurrent unexplained polyhydramnios, consanguinity, previous neonatal deaths, recurrent pregnancy losses, or structurally normal fetuses with severe hydramnios [11]. Amniotic fluid biochemical analysis may demonstrate elevated chloride and sodium concentrations suggestive of fetal renal salt wasting [12]. Molecular genetic testing has substantially improved prenatal diagnostic accuracy by enabling identification of pathogenic variants responsible for different molecular subtypes of Bartter syndrome [13]. Prenatal recognition is clinically significant because early diagnosis permits closer fetal surveillance, therapeutic interventions such as indomethacin administration for severe polyhydramnios, timely neonatal intensive care preparedness, and appropriate parental counseling regarding recurrence risk and prognosis [14]. Neonatal manifestations commonly include prematurity, polyuria, dehydration, hypokalemia, metabolic alkalosis, and failure to thrive, often requiring prolonged neonatal intensive care management [15]. The present case series describes three pregnancies complicated by severe recurrent polyhydramnios subsequently diagnosed as antenatal Bartter syndrome with distinct molecular subtypes involving BSND, KCNJ1, and SLC12A1 gene mutations. The series highlights the importance of integrating antenatal ultrasonography, amniotic fluid biochemical analysis, obstetric history, neonatal manifestations, and molecular genetic evaluation for early recognition and management of this rare fetal renal tubular disorder.

CASE SERIES

CASE 1

A 22-year-old pregnant woman, gravida 3 para 2 living 0, presented at 23 weeks of gestation with complaints of progressive abdominal distension and discomfort. She was born of a second-degree consanguineous marriage. Her obstetric history was significant for two previous adverse pregnancy outcomes associated with severe polyhydramnios. During her first pregnancy, she developed severe polyhydramnios in the third trimester and subsequently experienced intrauterine fetal demise at approximately 8 months of gestation. Indomethacin therapy had been administered from 28 weeks gestation for a duration of four weeks because of progressive polyhydramnios. In her second pregnancy, ultrasonography at 22 weeks revealed severe polyhydramnios without detectable congenital anomalies. The pregnancy was complicated by preterm premature rupture of membranes, following which an emergency lower segment cesarean section was performed at 30 weeks gestation. The neonate required admission to the neonatal intensive care unit and survived for 31 days after birth before succumbing to complications associated with prematurity and severe neonatal illness.

In the current pregnancy, the patient was referred for further evaluation of severe hydramnios detected during routine antenatal ultrasonography. Targeted imaging for fetal anomalies (TIFFA scan) demonstrated severe polyhydramnios with no identifiable structural malformations. Fetal growth parameters were appropriate for gestational age.

Because of the recurrent history of unexplained severe polyhydramnios and poor perinatal outcomes, antenatal Bartter syndrome was strongly suspected.

Investigations

Amniotic fluid analysis was performed to evaluate biochemical abnormalities associated with fetal renal tubular disorders. The following findings were obtained:

- Alpha-fetoprotein: 2138 ng/mL
- Sodium: 137 mEq/L
- Potassium: 3.78 mEq/L
- Chloride: 117 mEq/L

Markedly elevated chloride concentration in the amniotic fluid strongly supported the diagnosis of antenatal Bartter syndrome.

Molecular genetic analysis demonstrated a homozygous pathogenic BSND gene variant:

- Gene: BSND (NM_057176.3)
- Variant: c.450delC (p.Pro151fs*27)
- Zygosity: Homozygous
- Inheritance: Autosomal recessive

- Variant classification: Pathogenic

Ultrasonography consistently demonstrated:

- Severe polyhydramnios
- Structurally normal fetus
- Absence of congenital malformations

Routine antenatal investigations were otherwise within normal limits.

FINDINGS RELATED TO PHENOTYPE

Gene&Transcript	Variant	Location	Zygosity	In silico Parameters**	Disorder(OMIM)	Inheritance	Variant Classification
BSND NM_057176.3	c.450delC p.Pro151fs*27	Exon 3	Homozygous	NA	BARTTER SYNDROME, TYPE 4A, NEONATAL, WITH SENSORINEURAL DEAFNESS; BART4A 602522	Autosomal Recessive	Pathogenic

Figure 1: Molecular genetic analysis demonstrating homozygous pathogenic BSND gene mutation associated with antenatal Bartter syndrome type 4A

Figure 1 demonstrates molecular genetic findings confirming antenatal Bartter syndrome type 4A. Genetic analysis identified a homozygous pathogenic BSND gene variant, c.450delC (p.Pro151fs*27), located in exon 3 of transcript NM_057176.3. The mutation exhibited an autosomal recessive inheritance pattern and was classified as pathogenic. The identified BSND mutation showed strong clinicopathological correlation with the antenatal presentation of severe recurrent polyhydramnios, fetal renal salt wasting, prematurity, and adverse neonatal outcome observed in the present case.

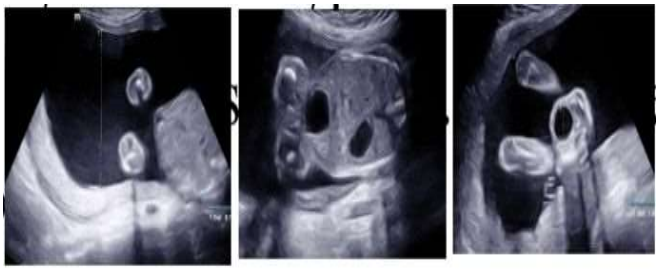


Figure 2: Antenatal ultrasonographic images demonstrating severe polyhydramnios with structurally normal fetal anatomy in antenatal Bartter syndrome

Figure 2 demonstrates targeted fetal ultrasonographic evaluation showing marked polyhydramnios with structurally normal fetal anatomy. The images reveal excessive amniotic fluid accumulation surrounding the fetus without evidence of congenital malformations, gastrointestinal obstruction, hydrops fetalis, or skeletal abnormalities. Detailed anomaly assessment demonstrated preserved fetal anatomical structures despite severe hydramnios, thereby raising suspicion for functional fetal disorders such as antenatal Bartter syndrome. The persistent severe polyhydramnios observed in the presence of normal fetal anatomy strongly supported the diagnosis of fetal renal tubular salt-wasting disorder associated with excessive fetal polyuria.

Case 2

A 24-year-old G3P0A2 woman was referred to the fetal medicine unit during the second trimester for evaluation of severe recurrent polyhydramnios. Her obstetric history was significant for two previous mid-trimester pregnancy losses associated with unexplained polyhydramnios, raising suspicion for an underlying recurrent fetal disorder. Detailed obstetric ultrasonography demonstrated a single live intrauterine fetus with severe polyhydramnios. Fetal biometry corresponded appropriately with gestational age. Detailed anomaly scan revealed normal intracranial anatomy, spine, thorax, heart, abdominal organs, kidneys, urinary bladder, and extremities with no detectable congenital malformation. No evidence of fetal hydrops, gastrointestinal obstruction, skeletal dysplasia, or fetal growth restriction was identified. Maternal evaluation for gestational diabetes mellitus and TORCH infections was unremarkable. Persistent severe hydramnios in the presence of structurally normal fetal anatomy strongly raised suspicion for antenatal Bartter syndrome. (Figures 1–4)

Because of progressive maternal discomfort and rapidly increasing amniotic fluid volume, therapeutic amnioreduction was performed. Approximately 800 mL of amniotic fluid was drained for symptomatic relief and biochemical evaluation.

Amniotic fluid biochemical analysis demonstrated:

- Sodium: 194 mmol/L
- Chloride: 209 mmol/L

- Potassium: 5.2 mmol/L
- Total protein: 0.2 g/dL
- Alpha-fetoprotein: >1000 IU/mL

Marked elevation of sodium and chloride concentrations with low protein levels strongly suggested fetal renal tubular salt wasting secondary to excessive fetal polyuria, thereby supporting the diagnosis of antenatal Bartter syndrome.

In view of recurrent adverse obstetric history, severe recurrent polyhydramnios, and characteristic biochemical abnormalities, rapid clinical exome sequencing was performed using amniotic fluid samples. Molecular genetic analysis identified a homozygous 50-base pair deletion in exon 2 of the KCNJ1 gene (NM_153766.3), consistent with antenatal Bartter syndrome type 2. The molecular findings showed strong clinicopathological correlation with the prenatal phenotype and biochemical profile.

The patient and family received genetic counseling regarding the autosomal recessive inheritance pattern, recurrence risk in future pregnancies, and possible neonatal complications including prematurity, dehydration, electrolyte imbalance, and prolonged neonatal intensive care requirement. Close antenatal surveillance and neonatal preparedness planning were subsequently continued.

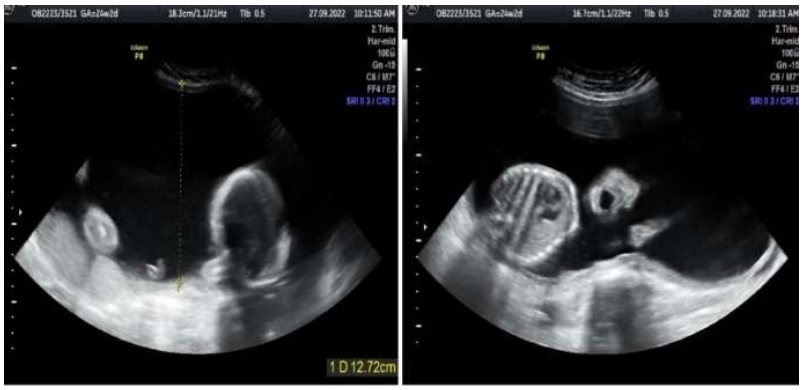


Figure 3: Obstetric ultrasonography demonstrating severe polyhydramnios with preserved fetal anatomical structures in antenatal Bartter syndrome

Figure 3 demonstrates antenatal ultrasonographic findings of marked polyhydramnios characterized by excessive amniotic fluid accumulation surrounding a structurally normal fetus. The left image shows significantly increased deepest vertical pocket measurement suggestive of severe hydramnios, while the right image demonstrates preserved fetal thoracic and abdominal anatomy without detectable congenital malformations. Absence of structural abnormalities despite severe and persistent polyhydramnios supported the clinical suspicion of antenatal Bartter syndrome secondary to fetal renal tubular salt-wasting disorder and excessive fetal polyuria.

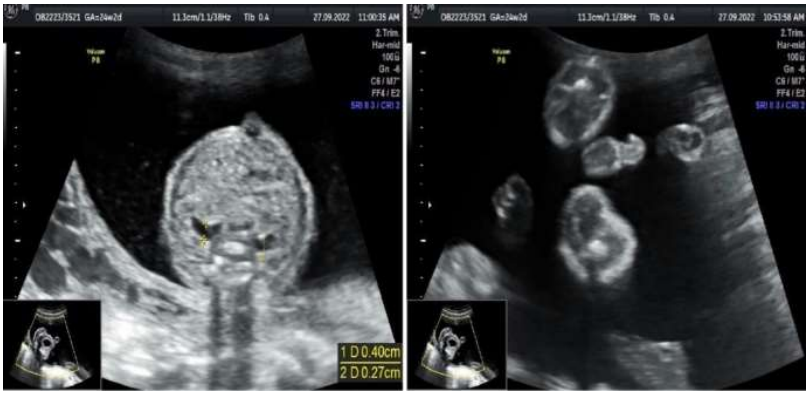


Figure 4: Targeted fetal anomaly scan demonstrating normal fetal cranial and facial anatomy in the presence of severe polyhydramnios

Figure 4 demonstrates detailed fetal anatomical assessment during targeted anomaly scan in a pregnancy complicated by severe polyhydramnios. The left image shows preserved intracranial anatomy with normal visualization of cerebral structures, while the right image demonstrates normal fetal facial profile and orbital

anatomy without evidence of craniofacial malformation. Despite marked excess amniotic fluid, no detectable congenital anomalies were identified on detailed fetal imaging. The presence of structurally normal fetal anatomy in association with persistent severe polyhydramnios further supported the diagnosis of antenatal Bartter syndrome related to fetal renal tubular dysfunction and excessive fetal polyuria.

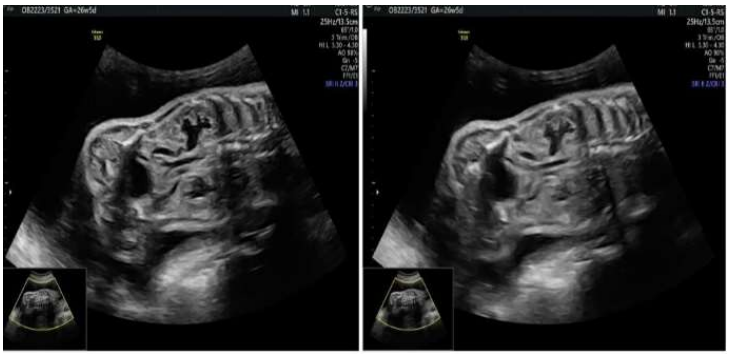


Figure 5: Fetal ultrasonographic images demonstrating severe polyhydramnios with preserved thoracoabdominal anatomy in antenatal Bartter syndrome

Figure 5 demonstrates antenatal ultrasonographic evaluation of the fetus in the presence of severe polyhydramnios. The images show preserved fetal thoracic cage, abdominal viscera, and diaphragmatic contours without evidence of congenital structural malformations, hydrops fetalis, or gastrointestinal obstruction. Despite excessive amniotic fluid accumulation, fetal anatomical structures remained grossly normal on detailed imaging. The persistence of marked hydramnios with structurally normal fetal anatomy supported the suspicion of antenatal Bartter syndrome associated with fetal renal tubular salt wasting and excessive fetal polyuria.

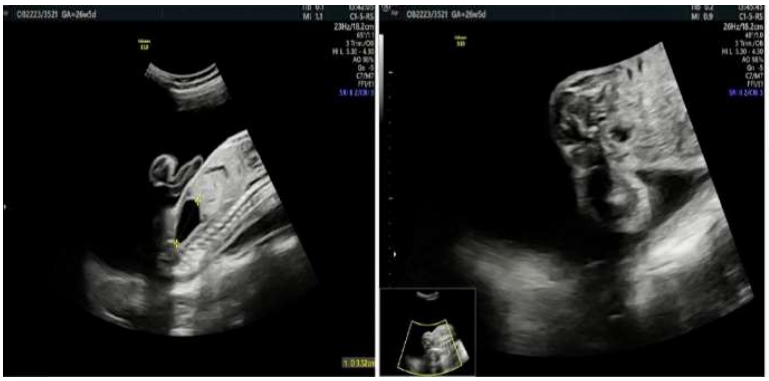


Figure 6: Targeted fetal ultrasonography demonstrating severe hydramnios with structurally normal fetal profile and preserved anatomical architecture

Figure 6 demonstrates targeted fetal ultrasonographic assessment in a pregnancy complicated by severe polyhydramnios. The left image shows markedly increased amniotic fluid volume with elevated deepest vertical pocket measurement suggestive of severe hydramnios, while the right image demonstrates preserved fetal facial profile and anatomical contours without evidence of craniofacial or structural abnormalities. Detailed fetal imaging failed to identify congenital malformations despite progressive and persistent polyhydramnios. These findings strongly supported the diagnosis of antenatal Bartter syndrome associated with fetal renal tubular dysfunction and excessive fetal urine production.

NDINGS RELATED TO PHENOTYPE

Gene & Transcript	Variant	Location	Zygosity	Disorder (OMIM)	Inheritance	Classification
KCNJ1 NM_153766.3	Deletion (50 bp)	Exon 2	Homozygous	Bartter syndrome, type 2 (241200)	Autosomal Recessive	Uncertain Significance

orrelation with clinical profile and family history is required

Figure 7: Molecular genetic analysis demonstrating homozygous KCNJ1 gene deletion associated with antenatal Bartter syndrome type 2

Figure 7 demonstrates molecular genetic findings supportive of antenatal Bartter syndrome type 2. Genetic analysis identified a homozygous 50-base pair deletion involving exon 2 of the KCNJ1 gene (NM_153766.3), inherited in an autosomal recessive pattern. The detected molecular abnormality showed strong clinicopathological correlation with the antenatal presentation of recurrent severe polyhydramnios, fetal renal salt wasting, and characteristic biochemical abnormalities observed in the present case. The genetic findings supported the diagnosis of antenatal Bartter syndrome type 2 in correlation with clinical phenotype and family history.

CASE 3

A 30-year-old G3P1D1A1 woman born of a third-degree consanguineous marriage was referred during the second trimester for evaluation of severe polyhydramnios. Her obstetric history was significant for one previous neonatal death at three months of age due to suspected renal disease and one prior stillbirth at approximately six months gestation associated with severe polyhydramnios. The recurrent adverse pregnancy outcomes and consanguinity strongly suggested the possibility of an inherited fetal disorder.

Targeted anomaly scan performed during the second trimester demonstrated severe polyhydramnios with markedly elevated amniotic fluid measurements. Detailed fetal anatomical survey revealed structurally normal intracranial anatomy, thoracic cavity, abdominal organs, kidneys, urinary bladder, spine, and extremities without evidence of congenital malformation. No sonographic features of hydrops fetalis, gastrointestinal obstruction, skeletal dysplasia, or fetal growth restriction were identified. Persistent severe polyhydramnios in the presence of structurally normal fetal anatomy raised strong antenatal suspicion for fetal renal tubular pathology, particularly antenatal Bartter syndrome. (Figures 5 and 6) Because of progressive maternal discomfort and rapidly worsening polyhydramnios, indomethacin therapy was initiated and continued for two weeks under close fetal surveillance. Serial ultrasonographic monitoring was performed to assess amniotic fluid volume, fetal well-being, and ductus arteriosus status during therapy. Despite temporary symptomatic improvement, progressive hydramnios persisted during the antenatal period. The patient subsequently developed spontaneous preterm labor and delivered a preterm female neonate weighing 1.68 kg at 32 weeks gestation. The neonate required admission to the neonatal intensive care unit because of prematurity, dehydration, polyuria, and electrolyte imbalance. Laboratory investigations during the neonatal period demonstrated elevated blood urea nitrogen, increased serum creatinine, mild hyponatremia, and persistent urinary salt wasting consistent with renal tubular dysfunction. Aggressive fluid replacement therapy, electrolyte correction, and intensive neonatal supportive care were initiated promptly. Molecular genetic evaluation using whole exome sequencing identified a homozygous missense mutation in exon 12 of the SLC12A1 gene, c.1465G>A (p.Gly489Arg), classified as likely pathogenic and diagnostic of antenatal Bartter syndrome type 1.

Ophthalmological screening for retinopathy of prematurity demonstrated immature retinae without plus disease. Following stabilization of hydration status and electrolyte abnormalities, the neonate was discharged on oral sodium and potassium supplementation with advice for long-term pediatric nephrology follow-up.

At follow-up, the child was alive, clinically stable, and doing well with ongoing medical management and monitoring.

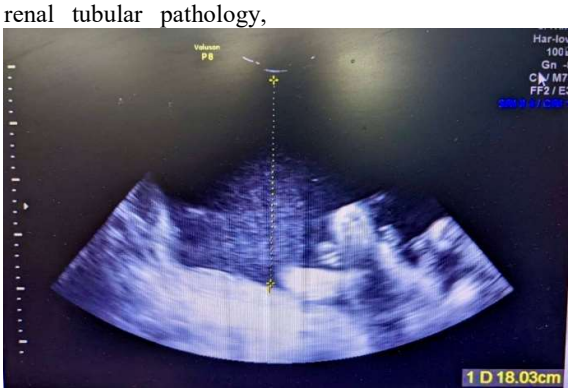


Figure 8: Obstetric ultrasonography demonstrating markedly increased deepest vertical pocket measurement suggestive of severe polyhydramnios

Figure 8 demonstrates antenatal ultrasonographic assessment showing severe polyhydramnios with markedly elevated deepest vertical pocket (DVP) measurement of 18.03 cm. Excessive amniotic fluid accumulation surrounding the fetus is evident without associated structural fetal abnormalities. The persistent and severe hydramnios observed on ultrasonography strongly supported the diagnosis of antenatal Bartter syndrome secondary to excessive fetal polyuria caused by fetal renal tubular salt-wasting disorder.

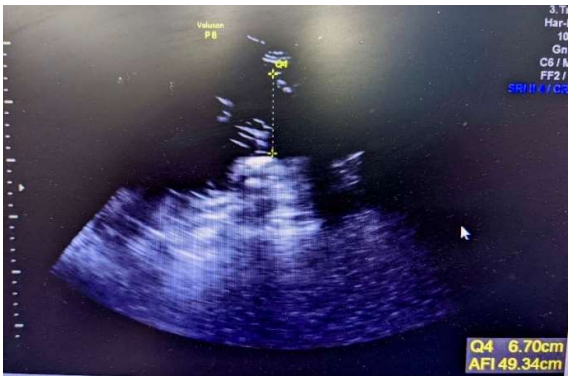
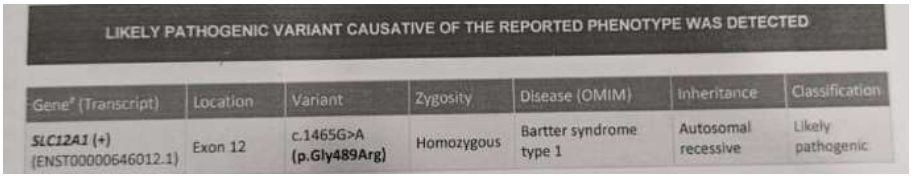


Figure 9: Ultrasonographic image demonstrating markedly elevated amniotic fluid index consistent with severe polyhydramnios

Figure 9 demonstrates antenatal ultrasonographic evaluation showing severe polyhydramnios with markedly elevated amniotic fluid index (AFI) measuring 49.34 cm. The image also demonstrates increased quadrant fluid pocket measurement of 6.70 cm, indicating excessive amniotic fluid accumulation. No associated structural fetal abnormalities were identified on detailed imaging. The pronounced elevation in AFI strongly supported the diagnosis of antenatal Bartter syndrome associated with fetal renal tubular dysfunction, excessive fetal urine production, and persistent fetal polyuria.



LIKELY PATHOGENIC VARIANT CAUSATIVE OF THE REPORTED PHENOTYPE WAS DETECTED

Gene# (Transcript)	Location	Variant	Zygosity	Disease (OMIM)	Inheritance	Classification
SLC12A1 (+) (ENST00000646012.1)	Exon 12	c.1465G>A (p.Gly489Arg)	Homozygous	Bartter syndrome type 1	Autosomal recessive	Likely pathogenic

Figure 10: Molecular genetic analysis demonstrating homozygous likely pathogenic SLC12A1 gene mutation associated with antenatal Bartter syndrome type 1

Figure 10 demonstrates molecular genetic findings confirming antenatal Bartter syndrome type 1. Genetic evaluation identified a homozygous missense mutation involving exon 12 of the SLC12A1 gene, c.1465G>A (p.Gly489Arg), inherited in an autosomal recessive pattern and classified as likely pathogenic. The identified SLC12A1 mutation showed strong correlation with the antenatal presentation of severe recurrent polyhydramnios, fetal renal tubular salt wasting, prematurity, neonatal electrolyte imbalance, and requirement for neonatal intensive care management observed in the present case.

FIGURES INTERPRETATION

The present case series illustrates the characteristic antenatal, ultrasonographic, biochemical, and molecular genetic findings associated with antenatal Bartter syndrome across three clinically distinct pregnancies complicated by severe recurrent polyhydramnios.

Figure 1 demonstrates molecular genetic confirmation of antenatal Bartter syndrome type 4A through identification of a homozygous pathogenic BSND gene mutation, c.450delC (p.Pro151fs*27). The identified autosomal recessive mutation strongly correlated with severe recurrent polyhydramnios, fetal renal tubular salt wasting, prematurity, and adverse neonatal outcome observed in Case 1. **Figure 2** demonstrates targeted fetal ultrasonographic assessment showing marked polyhydramnios with structurally preserved fetal anatomy. Despite severe excess amniotic fluid accumulation, no congenital malformations, gastrointestinal obstruction, skeletal abnormalities, or hydrops fetalis were identified, thereby supporting suspicion for a functional fetal renal tubular disorder rather than structural anomaly. **Figure 3** further demonstrates severe polyhydramnios with markedly increased deepest vertical pocket measurement in association with preserved fetal thoracoabdominal anatomy. The persistent hydramnios in the absence of detectable fetal malformations strongly supported antenatal Bartter syndrome secondary to excessive fetal polyuria. **Figure 4** demonstrates normal fetal cranial, facial, and intracranial anatomy during targeted anomaly scanning despite severe hydramnios. Absence of detectable congenital anomalies on detailed imaging further strengthened the clinical suspicion of antenatal Bartter syndrome related to fetal renal tubular dysfunction. **Figure 5** demonstrates preserved fetal thoracic and abdominal anatomical structures despite severe polyhydramnios in Case 3. No evidence of hydrops fetalis, gastrointestinal obstruction, or major congenital anomalies was identified, emphasizing the characteristic presentation of structurally normal fetuses with severe hydramnios in antenatal Bartter syndrome. **Figure 6** demonstrates markedly increased amniotic fluid volume with preserved fetal facial profile and anatomical contours. Persistent severe hydramnios without associated structural abnormalities further supported fetal renal tubular salt-

wasting disorder associated with excessive fetal urine production. **Figure 7** demonstrates molecular genetic findings supportive of antenatal Bartter syndrome type 2 through identification of a homozygous 50-base pair deletion involving exon 2 of the KCNJ1 gene. The genetic abnormality showed strong clinicopathological correlation with recurrent severe polyhydramnios and biochemical evidence of fetal renal salt wasting observed in Case 2. **Figure 8** demonstrates severe polyhydramnios with markedly elevated deepest vertical pocket measurement of 18.03 cm. The pronounced excess amniotic fluid accumulation strongly supported excessive fetal polyuria secondary to fetal renal tubular dysfunction characteristic of antenatal Bartter syndrome. **Figure 9** demonstrates markedly elevated amniotic fluid index measuring 49.34 cm, confirming severe polyhydramnios. The excessive amniotic fluid accumulation without associated structural abnormalities strongly supported persistent fetal renal salt wasting and excessive fetal urine production. **Figure 10** demonstrates molecular genetic confirmation of antenatal Bartter syndrome type 1 through identification of a homozygous likely pathogenic SLC12A1 gene mutation, c.1465G>A (p.Gly489Arg). The identified mutation correlated strongly with severe recurrent polyhydramnios, prematurity, neonatal electrolyte imbalance, and requirement for prolonged neonatal intensive care management observed in Case 3.

Overall, the figures collectively highlight the importance of integrating antenatal ultrasonography, amniotic fluid assessment, biochemical evaluation, and molecular genetic testing for accurate prenatal diagnosis of antenatal Bartter syndrome. The images emphasize the classical presentation of severe recurrent polyhydramnios with structurally normal fetal anatomy and demonstrate the diagnostic significance of molecular confirmation in differentiating various genetic subtypes of antenatal Bartter syndrome.

DISCUSSION

Antenatal Bartter syndrome is a rare but important cause of severe recurrent polyhydramnios in structurally normal fetuses [1,2]. The disorder results from defective electrolyte transport within the thick ascending limb of the loop of Henle, leading to excessive fetal urinary salt wasting and profound fetal polyuria [3]. Progressive fetal urine production subsequently causes marked accumulation of amniotic fluid, maternal discomfort, recurrent hydramnios, preterm labor, and significant neonatal metabolic complications [4].

The present case series highlights the characteristic antenatal presentation of Bartter syndrome, namely severe recurrent polyhydramnios with absence of major fetal structural abnormalities. In all three pregnancies, detailed fetal anatomical surveys remained essentially normal despite progressive and marked hydramnios. This observation is clinically important because many such pregnancies are initially labeled as idiopathic polyhydramnios until recurrent disease pattern, biochemical abnormalities, or neonatal manifestations become evident [5].

An important clinical feature observed in the present series was recurrent adverse obstetric history. Case 1 demonstrated repeated severe polyhydramnios with previous intrauterine fetal demise and neonatal loss, while Case 2 involved recurrent mid-trimester pregnancy losses associated with unexplained hydramnios. Case 3 additionally demonstrated consanguinity with previous neonatal death and stillbirth. Such recurrent patterns significantly strengthen suspicion for inherited fetal renal tubular disorders and should prompt early biochemical and molecular evaluation [6].

Ultrasonography played a central role in prenatal suspicion of antenatal Bartter syndrome in the present series. Persistent severe polyhydramnios with structurally normal fetal anatomy was consistently observed in all cases. Absence of congenital malformations, gastrointestinal obstruction, hydrops fetalis, or skeletal dysplasia helped exclude more common causes of severe hydramnios [7]. The findings emphasize that structurally normal fetuses with recurrent or rapidly progressive polyhydramnios require careful evaluation for functional fetal disorders including renal tubular pathologies [8].

Amniotic fluid biochemical analysis provided important supportive diagnostic evidence in the present study. Elevated sodium and chloride concentrations observed in Cases 1 and 2 strongly suggested fetal renal salt wasting secondary to defective tubular electrolyte transport [9]. Excessive fetal electrolyte loss and associated fetal polyuria represent important pathophysiological hallmarks of antenatal Bartter syndrome [10]. Biochemical evaluation therefore serves as a valuable adjunctive prenatal diagnostic tool, particularly when severe hydramnios occurs in the absence of structural fetal abnormalities.

Molecular genetic analysis substantially strengthened diagnostic confirmation in all three pregnancies. Distinct pathogenic variants involving BSND, KCNJ1, and SLC12A1 genes were identified, representing different molecular subtypes of antenatal Bartter syndrome [11,12]. Identification of these mutations not only confirmed the diagnosis but also facilitated accurate genetic counseling regarding autosomal recessive inheritance and recurrence risk in future pregnancies [13]. The present series therefore highlights the growing importance of prenatal molecular diagnostics in evaluation of recurrent unexplained polyhydramnios.

Neonatal manifestations in the present series were consistent with severe renal tubular dysfunction associated with antenatal Bartter syndrome. Prematurity, dehydration, polyuria, electrolyte imbalance, and prolonged neonatal intensive care requirement were major postnatal findings [14]. However, neonatal outcomes varied considerably among the cases. Case 1 resulted in neonatal death despite prolonged intensive care support, whereas Case 3 demonstrated favorable survival outcome following early neonatal recognition, aggressive electrolyte correction, and

intensive supportive management. These contrasting outcomes emphasize that early prenatal suspicion and timely neonatal preparedness may significantly influence postnatal survival and long-term prognosis [15].

Indomethacin therapy was administered antenatally in Cases 1 and 3 for management of severe symptomatic polyhydramnios. Reduction of fetal urine production through prostaglandin inhibition may temporarily improve hydramnios and reduce maternal symptoms [16]. However, therapy requires close fetal surveillance because of potential complications including constriction of the fetal ductus arteriosus and oligohydramnios [17]. In the present series, indomethacin provided temporary symptomatic improvement but did not completely prevent recurrence of severe hydramnios or prematurity.

The present case series highlights the importance of integrating antenatal ultrasonography, obstetric history, amniotic fluid biochemical analysis, neonatal manifestations, and molecular genetic evaluation for early recognition of antenatal Bartter syndrome [18]. Persistent severe polyhydramnios with structurally normal fetal anatomy, especially in the presence of recurrent pregnancy loss, consanguinity, or previous neonatal death, should strongly raise suspicion for fetal renal tubular disorders [19].

Although antenatal Bartter syndrome remains rare, increasing availability of molecular genetic testing has substantially improved diagnostic accuracy and understanding of genotype-phenotype correlation [20]. Early diagnosis and multidisciplinary management involving fetal medicine specialists, neonatologists, geneticists, and pediatric nephrologists are essential for optimizing antenatal counseling, neonatal preparedness, and long-term outcomes.

LIMITATIONS

The present case series is limited by the small number of cases and incomplete availability of antenatal imaging documentation for all pregnancies, particularly Case 1. Long-term neonatal follow-up and detailed functional renal outcome data were also unavailable. Nevertheless, the study provides important clinical, biochemical, imaging, and molecular insights into the antenatal presentation of Bartter syndrome and highlights the importance of maintaining high clinical suspicion in recurrent severe polyhydramnios.

CONCLUSION

Antenatal Bartter syndrome is a rare but clinically significant fetal renal tubular disorder that should be strongly considered in pregnancies complicated by severe recurrent polyhydramnios with structurally normal fetal anatomy. Recurrent adverse obstetric history, consanguinity, unexplained hydramnios, and absence of major congenital anomalies are important clinical indicators that may aid early prenatal suspicion.

The present case series demonstrates the important diagnostic role of antenatal ultrasonography, amniotic fluid biochemical analysis, and molecular genetic testing in establishing prenatal diagnosis of different molecular subtypes of antenatal Bartter syndrome. Identification of pathogenic BSND, KCNJ1, and SLC12A1 variants enabled accurate diagnostic confirmation and facilitated appropriate genetic counseling regarding recurrence risk and neonatal prognosis.

The series also highlights variable neonatal outcomes associated with antenatal Bartter syndrome, ranging from severe prematurity with neonatal mortality to successful survival following timely neonatal intensive care and electrolyte management. Early antenatal recognition combined with multidisciplinary fetal and neonatal management may significantly improve neonatal preparedness, postnatal stabilization, and long-term clinical outcomes.

Increased awareness among obstetricians, fetal medicine specialists, neonatologists, and pediatric nephrologists is essential for prompt diagnosis and optimal management of pregnancies complicated by recurrent unexplained polyhydramnios suggestive of fetal renal tubular disorders.

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