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Review Article

Binder Phenotype—Prenatal Diagnosis, Management, and Postnatal Outcome: Insights from a Case Series and Updated Review of the Literature

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Abstract

Binder phenotype (BP) or maxillonasal dysplasia is a developmental disorder of the anterior part of the maxilla and nasal complex and is characterized by a short nose with a flat nasal bridge, short columella, acute nasolabial angle, perialar flatness, convex upper lip, and tendency to a class III malocclusion. The etiology of BP is heterogeneous with diverse features and outcomes. The ultrasound features of BP are midfacial hypoplasia with verticalized nasal bones, short columella with flattened tip and alar wings, and the nasofrontal angle measuring >140 degrees. In this case series, we present seven cases of BP detected antenatally, their varied etiology, management, and outcomes with a 2-year follow-up. We conclude that the diagnosis of facial dysmorphisms, such as BP, brings a lot of apprehension and agony in the parents amounting to multiple tests and counseling sessions. Physiognomy which is the normal familial appearance should be considered before concluding whether the observed feature is normal or pathological. Accurate diagnosis, adequate testing, and personalized counseling will help in the prevention of needless termination of pregnancies and ensure an optimal perinatal outcome.

Keywords

- Binder phenotype
- Binder syndrome
- maxillonasal hypoplasia
- midfacial hypoplasia
- nasofrontal angle
- facial dysmorphism

Introduction

Zuckerkandl described the Binder phenotype (BP) in 1882 as an anomaly of the anterior nasal floor, where the normal crest that separates the nasal floor from the anterior surface of the maxilla was absent.[1] Noyes described the entity in his first case report in 1939.[2] However, it was Von Binder in 1962[3] who described the six features of this phenotype namely short nose with a flat bridge, short columella, acute nasolabial angle, perialar flatness, convex upper lip, and a tendency to class III malocclusion of teeth. The ultrasound (US) features of BP are midfacial hypoplasia with verticalized nasal bones, short columella with flattened tip and alar wings, and the nasofrontal angle (NFA) measuring >140 degrees.[4]

Materials and Methods

Prenatal diagnosis of BP was based on the US detection of an abnormal profile in the sagittal view of the face in which a flat nasal bridge was identified. In all these patients, the NFA was measured between the nasal bone and the frontal bone in the midsagittal plane when the fetal neck was in mild flexion and the three echogenic lines denoting the nasal tip, skin on the nasal bone, and the nasal bone were imaged. The 5th and 95th percentile values of NFA are 117 and 140 degrees, respectively, and the mean is 128 degrees.[5] Coronal views of the lips and nose were imaged to demonstrate the short columella with flattened tip and alar wings. Three-dimensional (3D) images of the face were taken to

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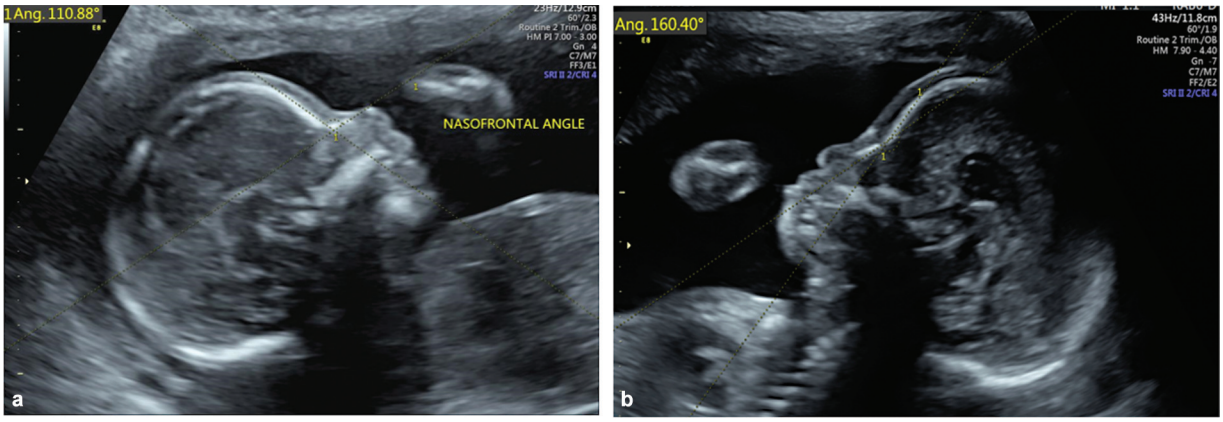

Fig. 1 Facial profile images showing normal (**a**) and abnormal frontonasal angle (**b**).

complement the two-dimensional (2D) image findings. The normal and abnormal NFAs in the profile views and columella and the alar wings in the coronal views of the nose and mouth are shown in ►**Figs. 1a, b** and **2a, b** respectively.

After confirming the BP, detailed targeted imaging for other fetal anomalies was done with a meticulous search for markers of chromosomal abnormalities (trisomy 21/18), skeletal dysplasia, epiphyseal stippling, and spinal/limb deformities. Associations of chondrodysplasia punctata (CDP) (asymmetrically short limbs, epiphyseal stippling, hemivertebrae, scoliosis), Crouzon's syndrome (craniosynostosis, brachycephaly, short occipital–frontal diameter), Stickler's syndrome (features of osteochondrodysplasia, congenital talipes), Rudiger's syndrome (short digits), Robinow's syndrome (short forearms, clinodactyly, and macrocephaly), Aarskog's syndrome (brachycephaly, clinodactyly of the fifth finger), Apert's syndrome (irregular craniosynostosis, short occipital–frontal diameter, flat occiput, ventriculomegaly, syndactyly), Rudiger's syndrome (short digits, talipes), Keutel's syndrome (hypoplasia of the distal phalanges, diffuse calcification of ears, nose, trachea), and achondroplasia (frontal bossing, macrocephaly, rhizomelia) were also specifically looked for.

Maternal history of connective tissue/autoimmune disorders, chronic malabsorption syndromes, hepatic diseases, intractable vomiting in the present pregnancy, and intake of teratogens such as phenytoin, alcohol, or warfarin intake was checked. Physiognomy, which is the normal familial appearance was also looked for in the parents before concluding whether the observed feature was normal or pathological.[4]

Genetic counseling and invasive testing by amniocentesis to check for chromosomal/genetic abnormalities were offered. Multidisciplinary input was also obtained about the possible implications and outcomes.

In this second-largest reported case series, we discuss seven cases of antenatally detected BP, their varied etiology, management, and outcomes.

Case Reports

Case 1

A 28 year old third gravida with two previous normal deliveries was referred at 26 weeks of gestational age (GA) for a second opinion for the fetal face. Her obstetric and medical history was unremarkable except for intractable vomiting in the first trimester, for which she was treated

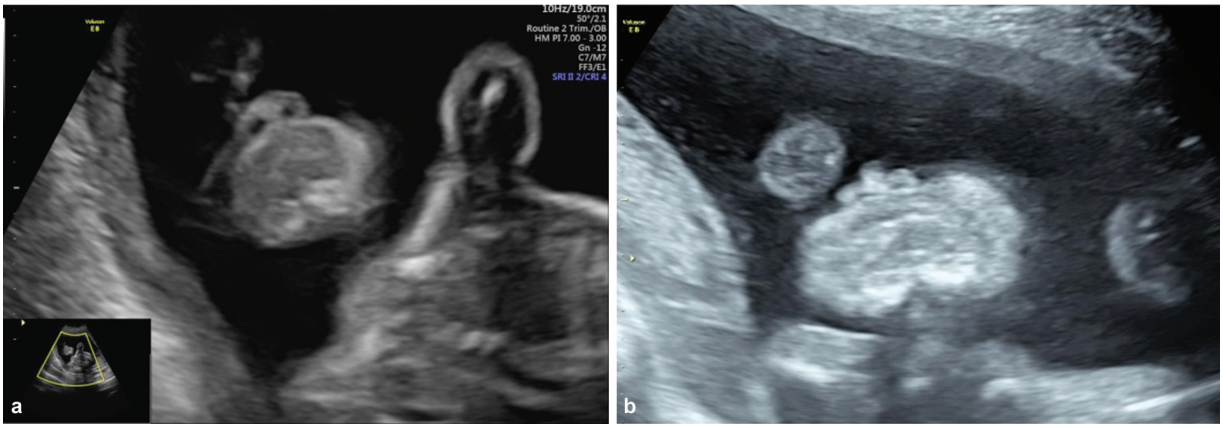

Fig. 2 Coronal view of the face showing normal columella and rounded alar wings (**a**) and abnormal appearance of the columella and flat alar wings (**b**).

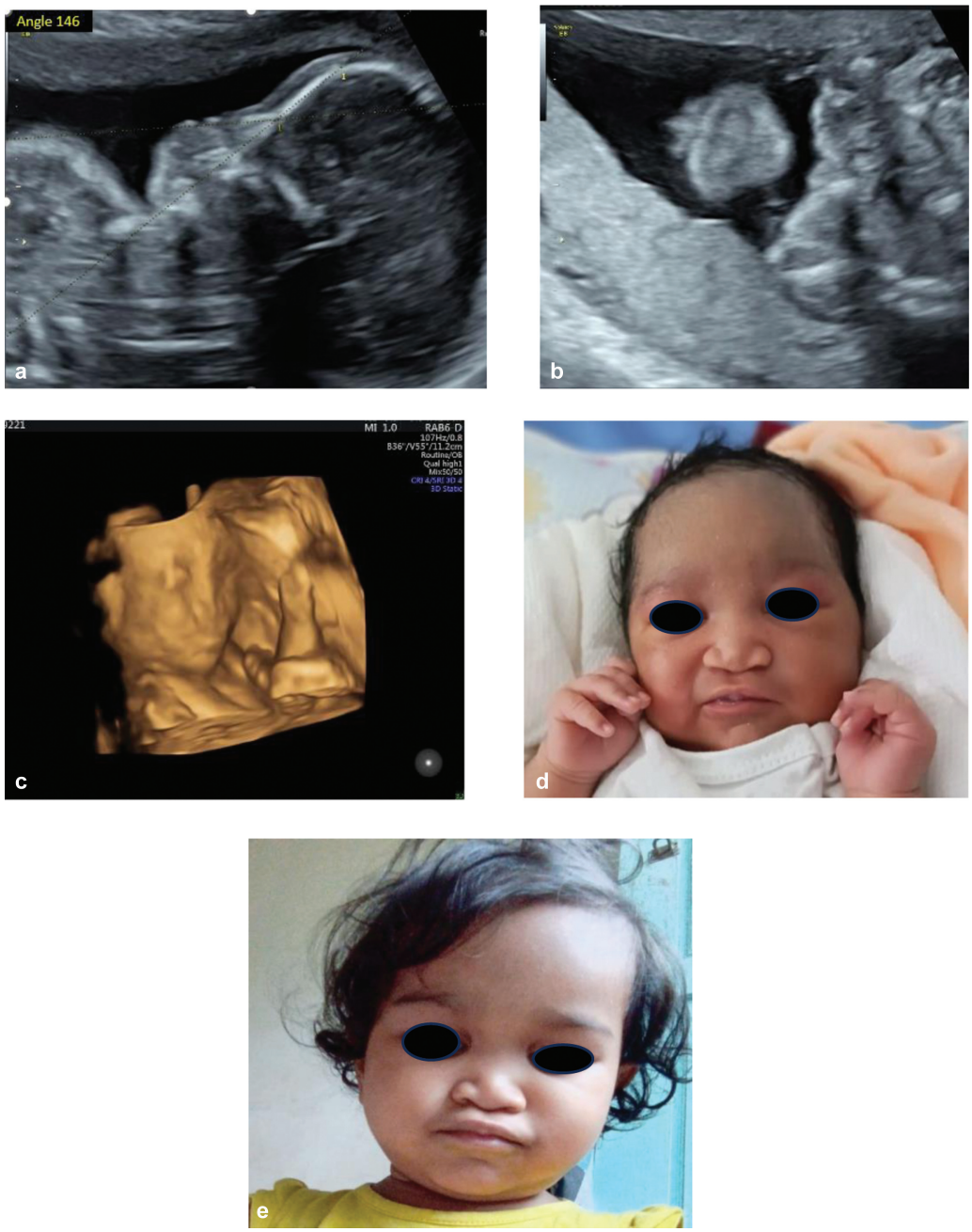

Fig. 3 Case 1—Antenatal ultrasound (US) and postnatal images. Two-dimensional US showing antenatal images of flattened midfacial profile with increased nasofrontal angle (146 degrees) (**a**), short columella, flat nasal tip, and alar wings (**b**), and three-dimensional US showing flat facies (**c**). Immediate neonatal appearance (**d**) and postnatal appearance at 1.5 years of age (**e**).

with intravenous fluids. No aneuploidy screen was done. US features were abnormal facial profile with verticalization of the nasal bone and increased NFA (146 degrees) with short columella, flat nasal tip, and alar wings, suggestive of BP. She also had polyhydramnios. Genetic counseling was done and amniocentesis for chromosomal microarray (CMA)/DNA store was suggested which was declined by the family. There were no features suggestive of skeletal dysplasia/CDP. Follow-up scans were done at 30 and 34 weeks to look for any evolving pathology. Her pregnancy progressed uneventfully and a female neonate weighing 2,600 g with good Apgar scores was delivered by cesarean section. No neonatal respiratory issues were encountered. Currently, the infant is 1.5 years old and has normal neurodevelopment for age as assessed by her pediatrician. US findings including 2D and 3D images, the immediate postnatal, and the current photographs are shown in ►**Fig. 3a** to **e**.

Case 2

A 27 year old second gravida with a previous uncomplicated vaginal delivery and an unremarkable obstetric and history was booked with us from early pregnancy. Her first-trimester screening for fetal aneuploidies was a low risk with low human chorionic gonadotropin (HCG), and she was on oral

Fig. 4 Case 2—Antenatal ultrasound (US) and postnatal images. Two-dimensional US showing antenatal images of flattened midfacial profile (**a**), short columella, flat nasal tip, and alar wings (**b**) and three-dimensional US showing flat facies (**c**). Immediate neonatal appearance (**d**) and postnatal appearance at 1 year of age (**e**).

hypoglycemics for gestational diabetes. Her anomaly scan at 19 weeks revealed verticalization of nasal bone with NFA measuring 145 degrees, with short columella, flat nasal tip, and alar wings, suggestive of BP. The mother's facial physiognomy was similar to the fetal facial profile. However, she was advised to do amniocentesis (CMA) to rule out chromosomal anomalies/genetic syndromes which was declined by the family. She was closely followed up with serial scans and induced at 38 weeks when she delivered vaginally a female neonate of weight 2,710 g with good Apgar scores. Postnatal examination confirmed a BP with no other associated anomalies. The infant is 1 year old now, has achieved all developmental milestones for her age, and is asymptomatic. US features including 2D and 3D images, the immediate postnatal, and the current photographs are shown in ►**Fig. 4a** to **e**.

Case 3

A 24 year old primigravida, a known case of overlap syndrome, antinuclear antibody positive, antiribonucleoprotein, and smooth muscle antibody strong positive, antiphospholipid antibody negative, on regular rheumatology follow-up and on tacrolimus while conception, was referred to our fetomaternal unit at 18 weeks. She had not done first-trimester screening. An anomaly scan revealed an abnormal facial profile with a depressed nasal bridge, verticalized nasal bone with increased NFA (162 degrees), short columella, flat nasal tip, and alar wings, suggestive of BP. The fetus also had an echogenic cardiac focus in the left ventricle. Given the periconceptional intake of tacrolimus, an immunosuppressant, and BP in the fetus, the family decided on medical termination of pregnancy. She expelled a male fetus of 413 g and a fetal autopsy revealed facial dysmorphism suggestive

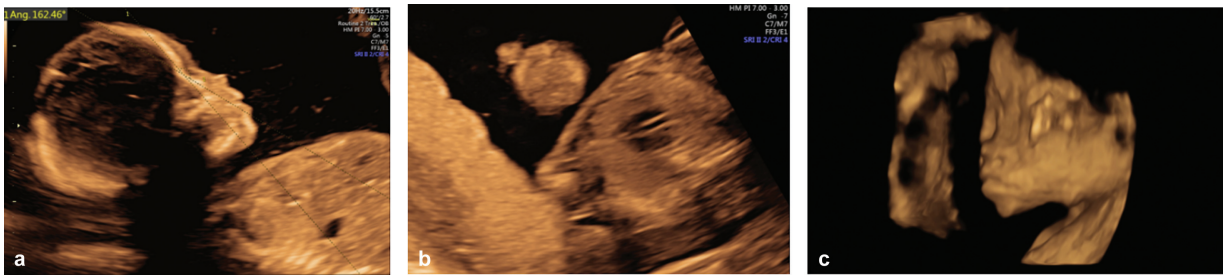

Fig. 5 Case 3—Antenatal ultrasound (US) images. Two-dimensional US showing antenatal images of flattened midfacial profile (**a**), short columella, flat nasal tip, and alar wings (**b**), and three-dimensional US showing flat facies (**c**).

of BP and generalized hydrops with no other anomalies. The genetic analysis of the expelled fetus assessed by CMA was normal. US features including 2D and 3D images are given in ►**Fig. 5a** to **c**.

Case 4

The above-mentioned patient with overlap syndrome conceived again in a year. Her first-trimester aneuploidy screening was normal, but a targeted anomaly scan at 19 weeks

Fig. 6 Case 4—Antenatal ultrasound (US) and postnatal images. Two-dimensional US showing antenatal images of flattened midfacial profile (**a**), short columella, flat nasal tip, and alar wings (**b**), and three-dimensional US showing flat facies (**c**). Immediate neonatal appearance (**d**) and postnatal appearance at 1 year of age (**e**).

revealed a dysmorphic face with verticalization of nasal bone with short columella, flat nasal tip, and alar wings and increased NFA measuring 143 degrees suggestive of BP. After detailed counseling, she decided against any genetic testing and wished to continue the pregnancy. She was closely monitored for any evolving features of skeletal dysplasia. Her pregnancy progressed uncomplicated, and she delivered a preterm female neonate of weight 2,310 g. Postnatally, the infant had subtle features of BP with no other abnormality, is currently 1 year old, and has achieved normal developmental milestones for the age. US features including 2D and 3D images, the immediate postnatal, and the current photographs are shown in ►**Fig. 6a** to **e**.

Case 5

A 32 year old second gravida with previous normal delivery, with a history of subclinical hypothyroidism on thyroxine, booked with us from early gestation. First-trimester aneuploidy screening was low risk. She had low HCG and her targeted anomaly scan at 21 weeks revealed dysmorphic facies with verticalized nasal bone, increased NFA measuring 146 degrees, short columella, flat nasal tip, and alar wings suggestive of BP. Mild hypertelorism was also noted. There was an echogenic cardiac focus in the left ventricle and polyhydramnios with a single deep pocket of 8.2 cm. There were no features of skeletal dysplasia. Serial US scans revealed no other evolving abnormalities and the pregnancy continued to term with no complications. She delivered a male neonate of weight 2,890 g by cesarean section and postnatal examination of the neonate confirmed BP. The infant had noisy breathing with recurrent respiratory tract infections and one episode of acute otitis media. The infant is currently well with normal neurodevelopment and is 2 years old now. US features including 2D and 3D images, the

Fig. 7 Case 5—Antenatal ultrasound (US) and postnatal images. Two-dimensional US showing antenatal images of flattened midfacial profile (**a**), short columella, flat nasal tip, and alar wings (**b**), and three-dimensional US showing flat facies (**c**). Postnatal images at 2 months (**d**) and 1 and 1/2 years of age (**e**).

immediate postnatal, and the current photographs are shown in ►**Fig. 7a** to **e**.

Case 6

A 26 year old primigravida with no other comorbidities, first-trimester screening showing low risk for aneuploidies, and high HCG was referred at 21 weeks for a second opinion for short, long bones. A targeted anomaly scan revealed flat facies with unilateral hypoplastic nasal bone with verticalization of the contralateral nasal bone with increased NFA (156 degrees) and short columella suggestive of BP. Biometry was at the 10th centile suggestive of early-onset small for GA. Associated features were polyhydramnios, echogenic cardiac focus in the left ventricle, echogenic bowel, and umbilical artery showing high resistance flow. There were no features suggestive of skeletal dysplasia. Genetic counseling followed by amniocentesis was done which confirmed trisomy 21. The couple opted for medical termination of pregnancy. US features including 2D and 3D images are given in ►**Fig. 8a** to **d**.

Case 7

A 26 year old primigravida with no other comorbidities, first-trimester screening showing low risk for aneuploidies, and low HCG was referred at 21 weeks for a second opinion for abnormal facial profile. A targeted anomaly scan revealed flat facies with verticalization of the nasal bone and increased NFA (160 degrees), short columella, and flat alar wings suggestive of the BP, with an echogenic cardiac focus in both ventricles. The mother also had a similar flat facial phenotype. Genetic counseling followed by amniocentesis was done which confirmed a normal CMA. Currently, her GA is 24 weeks and is on regular follow-up. US features including 2D and 3D images are given in ►**Fig. 9a** to **d**.

The summary of US features of the fetuses with BP, their associations, outcome, and the possible etiology is given in ►**Table 1**.

Discussion

BP is considered a rare condition with a population-based survey reporting the incidence to be 1 in 18,000 with equal distribution between males and females.[5] The etiology of BP can be categorized into three groups: (1) isolated (2) associated with fetal chromosomal/metabolic abnormality/abnormal vitamin K metabolism/maternal conditions, and (3) syndromic.

Fetal conditions associated with BP are chromosomal abnormalities such as trisomies 21, 18, and mosaic trisomy 18, metabolic abnormalities such as Zellweger's syndrome, and cholesterol abnormalities. Studies show that maxillonasal hypoplasia and BP are caused by the reduced growth of the embryonic nasal septum because of vitamin K deficiency and the resulting abnormal formation of the vitamin K-dependent matrix gamma-carboxyglutamic protein.[6,7] Maternal malabsorption syndromes due to celiac disease

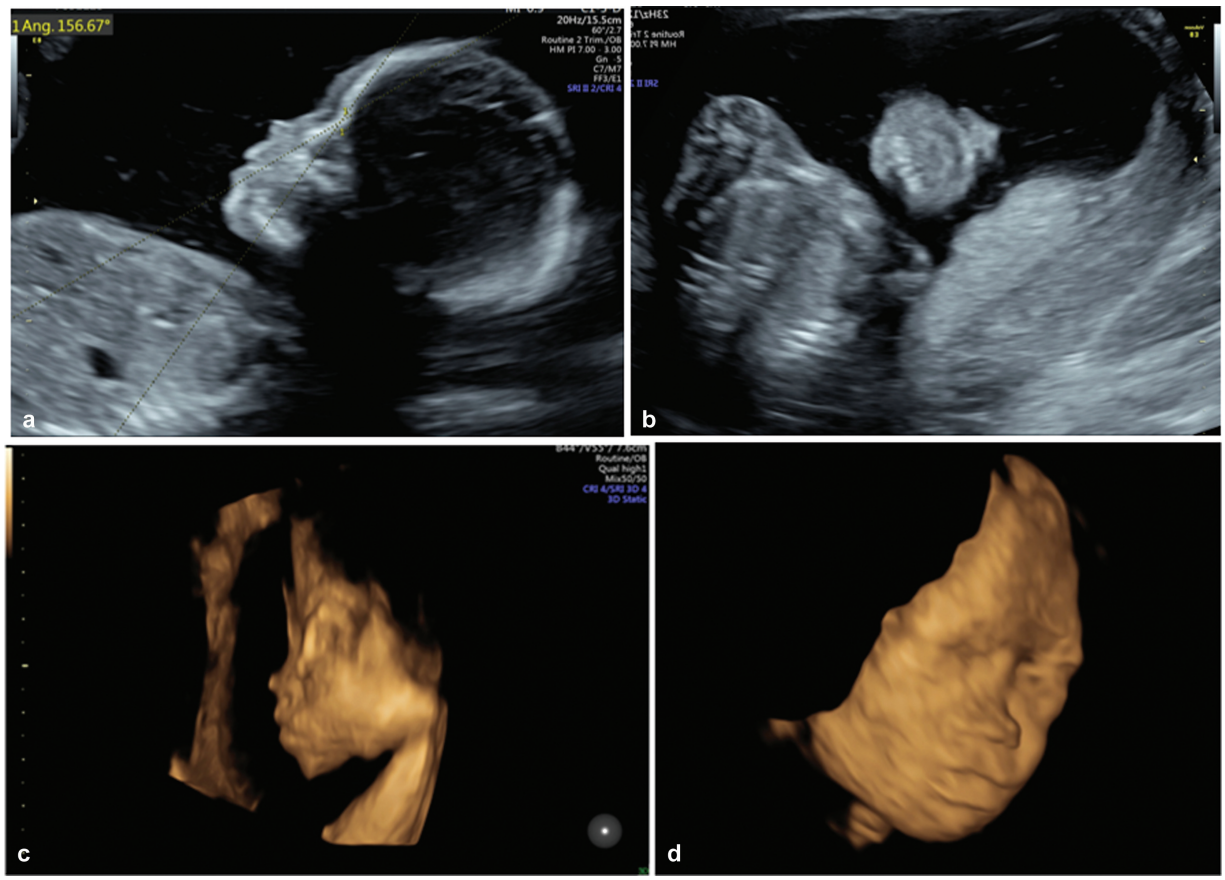

Fig. 8 Case 6—Antenatal ultrasound (US) images. Two-dimensional US showing antenatal images of flattened midfacial profile (**a**), short columella, flat nasal tip, and alar wings (**b**) and three-dimensional US showing flat facies (**c, d**).

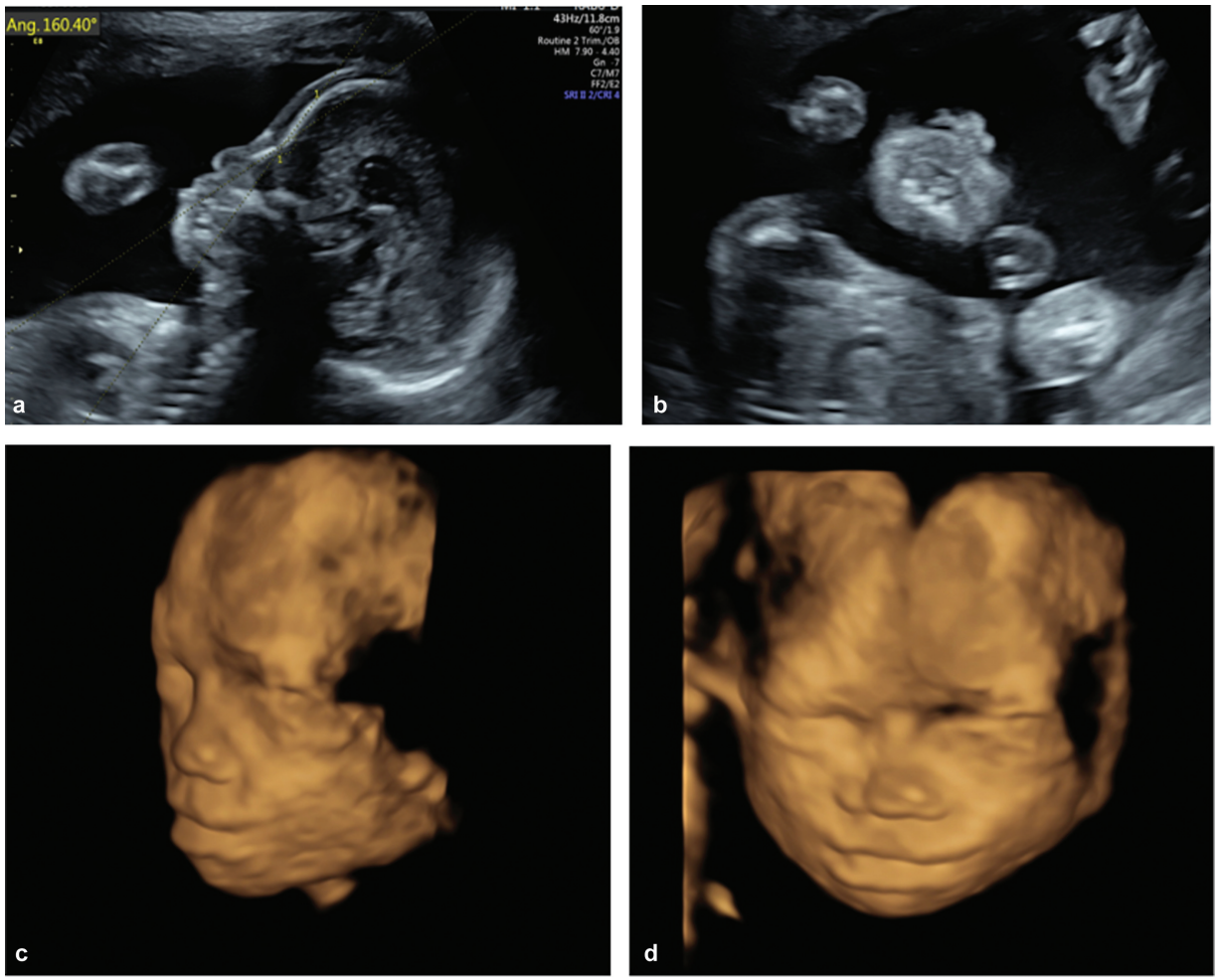

Fig. 9 Case 7—Antenatal ultrasound (US) images. Two-dimensional US showing antenatal images of flattened midfacial profile (**a**), short columella, flat nasal tip, and alar wings (**b**) and three-dimensional US showing flat facies (**c, d**).

Table 1 Summary of US features of the fetuses and their outcomes

Cases	POG	NFA	Columella and alar wings	NBL	Other associations	Pregnancy outcome and neurodevelopment	Probable final diagnosis
1	26	146	Short/flat	9.2	Polyhydramnios	Well 1.6 y	Intractable vomiting
2	19	145	Short/flat	6.5	None	Well 1 y	Physiognomy
3	18	162	Short/flat	6.1	ECFLV/hydrops	MTP	Connective tissue disorder
4	19	143	Short/flat	6.8	None	Well 1 y	Connective tissue disorder/drug-induced
5	21	146	Short/flat	7.8	ECFLV/polyhydramnios	Well 2 y	Sporadic
6	21	156	Short/flat	7.2	Polyhydramnios Unossified nasal bone, hypoechoic liver, echogenic bowel, umbilical artery high resistance flow	MTP	Trisomy 21
7	28	160	Short/flat	6	ECFLV	CMA-normal Ongoing	Probable physiognomy

Abbreviations: CMA, chromosomal microarray; ECFLV, echogenic cardiac focus in the left ventricle; MTP, medical termination of pregnancy; NBL, nasal bone length; NFA, nasofrontal angle; US, ultrasound; POG, Period of Gestation.

or short bowel syndrome, intractable vomiting in early pregnancy, and intake of coumarin-based anticoagulants during pregnancy have all been associated with infants having severe nasal hypoplasia with epiphyseal and vertebral stippling where these findings are linked with vitamin K deficiency. Genetic disorders associated with vitamin K deficiency include autosomal recessive vitamin K epoxide reductase deficiency, X-linked recessive form of CDP, and Xp22.3 deletion.[8–12] Sheffield et al[13] suggested that the BP represents a mild form of CDP and reported 103 cases of CDP in a 20-year examination period. However, in our case series, we could not identify any CDP cases. Recent studies have pointed out that women affected with autoimmune conditions such as systemic lupus erythematosus are associated with a BP characterized by stippled epiphyses, mimicking fetal warfarin syndrome. Many authors also have related vitamin K deficiency to the presence of circulating anticoagulant or antiphospholipid antibodies.[14] Our case series had one pregnant woman with overlap syndrome which could be the contributing factor for BP. More than 50 neonatal syndromes are associated with BP namely Stickler, Rudiger, Aarksog, Crouzon, Robinow, Apert, and Keutel to specify a few.[6]

The etiology of BP is listed in ►**Table 2** and the distinguishing features of the common syndromes are tabulated in ►**Table 3**.

According to the literature, most cases of BP occur sporadically with likely multifactorial inheritance. However, Olow-Nordenram and Rådberg[15,16] reported a positive family history in 36% of cases with various other reports suggesting autosomal-dominant inheritance with reduced penetrance, autosomal-recessive inheritance, or multifactorial inheritance pointing to the heterogenous etiology of BP.[17,18]

Isolated BP carries an excellent prognosis with favorable long-term outcomes. Sense of smell is not affected and intelligence is most often normal. Gorlin et al suggested that there is a 5% risk of hearing defects and a 5% risk of nonspecific congenital cardiac defects.[19] Studies have shown that with the growth of the child, the face develops into a normal profile. However, in severe BP, the facial defect can lead to functional as well as psychological issues. Minor malocclusions can be corrected by orthodontic implants. Surgical reconstruction with inlay of costal cartilage grafts has been used in children as well as adults with promising results.[20,21]

Levaillant et al in their largest case series analyzed the clinical and etiological heterogeneity in eight fetuses prenatally identified as BP by comparing the prenatal and postnatal phenotypes. All cases had CDP with verticalized nasal bones and abnormal convexity of the maxilla, consistent with the Binder profile appearance. The postnatal diagnosis was unclassified for five cases: one fetal warfarin syndrome, one infantile sialic acid storage, and one probable Keutel's syndrome, reiterating the clinical diversity.[22,23]

Our study is the second largest reported one in literature so far with seven cases. In our case series, the probable etiology in Case 1 is intractable vomiting leading to vitamin K deficiency which is an established cause for BP. In Case 2, the mother had a similar physiognomy and hence they accepted the findings and were unwilling to further genetic testing as there were no other associated anomalies. In Cases 3 and 4, connective tissue disorder with tacrolimus intake could be the probable reason as she had done the genetic testing in her first pregnancy when her fetus was diagnosed with similar features which turned out to be normal. In Case 5, there was no causal association identified and hence could be sporadic as the boy is doing neurodevelopmentally well as assessed by his pediatrician at 3 years of age. Case 6 revealed trisomy 21, while Case 7 was chromosomally normal both of which were confirmed by amniocentesis. Case 7 is on regular follow-up with her pregnancy ongoing. Out of our seven cases, two were due to connective tissue disorders, one due to probable vitamin K deficiency, one with trisomy 21, two were due to physiognomy, and one was considered as unclassified cause.

Implications in Clinical Practice

Once the diagnosis of BP is confirmed in the midsagittal and coronal views of the fetal face, a detailed and meticulous evaluation of the fetus is done with a special focus on the heart and the skeletal system. 3D imaging complements 2D imaging findings. Magnetic resonance imaging can provide added information if skeletal defects are suspected. A comprehensive review of antenatal and preconception history such as comorbidities like hepatic disease, chronic malabsorption syndromes and connective tissue disorders, intractable vomiting, intake of teratogens like alcohol, warfarin, etc. should be embarked. Invasive testing (amniocentesis for CMA) is advised as it identifies common chromosomal

Table 2 Etiology of Binder phenotype

A. Isolated
B. Associated
1. Chromosomal—trisomy 21, trisomy 18, mosaic trisomy 18
2. Metabolic conditions—Zellweger's syndrome, cholesterol disorders
3. Maternal autoimmune disorder—systemic lupus erythematosus, antiphospholipid antibody syndrome
4. Abnormal vitamin K metabolism
• Inherited: Autosomal recessive vitamin K epoxide reductase deficiency, X-linked recessive form of chondrodysplasia punctata, and Xp22.3 deletion
• Acquired: Prenatal exposure to phenytoin, alcohol, coumarin derivative, untreated celiac disease, short bowel syndrome, intractable vomiting in early pregnancy
C. Syndromic
Stickler, Rudiger, Aarksog, Crouzon, Robinow, Apert, Keutel, etc.

Source: Adapted and modified from Levaillant et al.[22]

Table 3 Common genetic syndromes with Binder phenotype and their differentiating features

Syndromes	US features	Associated features	Mode of inheritance
Binder	Flat facies/midfacial hypoplasia	Nil	AD/AR
Rudiger	Flat facies	Short digits	AR
Stickler	Flat facies Micrognathia Facial cleft	Features of osteochondrodysplasia Congenital talipes equinovarus	AD
Crouzon	Flat facies with a beaked nose Hypertelorism	Craniosynostosis Brachycephaly	AD
Aarksog	Flat facies Hypertelorism	Brachydactyly/clinodactyly	X-linked recessive
Robinow	Flat facies Hypertelorism	Macrocephaly Clinodactyly	AD
Keutel	Flat facies	Brachytelephalangic (hypoplasia of the distal phalanges) Diffuse calcification of ears, nose, trachea	AR
Chondrodysplasia punctata	Flat facies with nasal hypoplasia	Epiphyseal stippling, asymmetrically short limbs Hemivertebrae/scoliosis	X-linked dominant
Apert	Flat facies	Craniosynostosis Acrocephaly Syndactyly	AD
Warfarin syndrome	Flat facies	Epiphyseal stippling Brachydactyly Scoliosis	Teratogen induced
Achondroplasia	Flat bossing Frontal bossing	Macrocephaly Short long bones—Rhizomelia	AD
Wolf–Hirschhorn	Flat facies Sloped forehead/Greek warrior helmet facies	Fetal growth restriction Cleft lip/palate Cardiac abnormalities	Partial deletion of the p arm of chromosome 4(4p-)

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; US, ultrasound.
Source: Adapted and modified from Cook et al.[4]

abnormalities and microdeletions. A skeletal dysplasia panel can be opted for if dysplasia of the skeletal system is suspected. Physiognomy, which is the normal familial appearance should be considered before concluding whether the observed feature is normal or pathological.

Additional blood tests for hepatic conditions, vitamin K deficiency, and drug assays for chronic conditions are recommended as a normal result gives solace to the parents. Counseling by a multidisciplinary team consisting of the primary obstetrician, perinatologist, fetal medicine specialist, and neonatologist is pertinent and may need multiple sessions to reduce the anxiety of the parents and family. Serial US evaluation to monitor, growth/liquor, and any evolving pathologies should be done. Delivery should be planned in a tertiary care center as the neonate may experience immediate respiratory compromise. The mode of delivery is based on obstetric indication. A detailed postnatal evaluation and liaison with an orthodontist/oromaxillary surgeon is advised.

Conclusion

BP is a type of facial dysmorphism with a heterogeneous phenotype, varied etiology, and outcomes. Physiognomy, which is the normal familial appearance should be considered before concluding whether the observed feature is normal or pathological. Preconceptional counseling and optimization of the chronic disease status and modifying the medication (warfarin to unfractionated/low-molecular-weight heparin) will reduce the incidence of BP. Isolated BP carries a favorable outcome. The diagnosis of such facial dysmorphism brings a lot of apprehension and agony in the parents amounting to multiple tests and counseling sessions. However, accurate diagnosis, adequate testing, and dedicated counseling will help in the prevention of needless termination of pregnancies.

Conflict of Interest
None declared.

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