An update on amniotic bands sequence

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ABSTRACT
Amniotic bands sequence is a congenital disorder characterized by craniofacial, body wall, and limb anomalies that may be associated with fetal-placental fibrous bands. Its prevalence has been reported to range from 0.19 to 8.1 per 10 000 births. Different theories have attempted to explain the etiology of amniotic band sequence; however, none has individually been able to support each and every defect observed, so it has been considered to be a multifactorial condition. The (pre- and post-natal) identification of anomalies suggestive of amniotic band sequence is useful for the diagnostic approach and implementation of timely therapeutic interventions favoring the release of the amniotic bands using fetoscopy with recovery of the involved distal limb perfusion, or else the possibility of performing a post-natal surgical repair. It is also helpful to provide genetic counseling. This article offers an update on the epidemiological aspects, etiological theories, risk factors, clinical characteristics, diagnosis (including antenatal diagnosis), genetic counseling, therapeutic approach, and prognosis of amniotic bands sequence.

Key words: amniotic bands, constriction ring.

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INTRODUCTION
Amniotic bands sequence (ABS) (OMIM #217100)1-3 is a congenital disorder presenting with fetal anomalies associated with fetal-placental fibrous bands that may cause disruptions, deformations or malformations4 without a consistent anatomical pattern.5,6 Anomalies are limited to external structures with or without body wall disruption or internal malformations that vary in severity and location.7,9 Some authors consider ABS separately from the limb-body wall complex (LBWC), body wall defects (BWD) or the body wall complex (BWC),10-12 whereas others believe these are all part of the same disease.13-16

Classification
Although different classifications have been proposed (Table 1), the European Surveillance of Congenital Anomalies (EUROCAT) suggests using the terms “congenital constriction bands” or “amniotic bands” together with the specific description of each identified congenital anomaly.22,23

Epidemiology
The prevalence of ABS with or without LBWC or BWD is variable and has been reported to range from 0.1924 to 8.125 per 10 000 births. Such variability lies in the different definitions, terminology, classification, and study population (Table 2).

The prevalence is higher among fetuses of 9-20 weeks of gestational age (178.5 per 10 000 cases)2 and stillbirths (191 per 10 000 deaths).31 Assuming that approximately 20% of identified pregnancies are lost before 20 weeks of gestational age and 1% after 20 weeks, a study estimated that per every 100 ABS cases, approximately 90 underwent a miscarriage, 5 were stillbirths, and 5 were born alive, indicating that the frequency of ABS had been underestimated.31

Etiology
Theory of embryonic (endogenous) dysplasia and derived theories
Streeter32 suggested that amniotic bands appeared early during development and were not the primary cause of defects but a consequence of an imperfect histogenesis that caused necrosis, scarring, constrictions, and fusions, and that the deficiency in one or two cells resulted in a larger anomaly of the final structure.32,33 McKenzie34 supported this theory and suggested that tissue alterations were an example of an abnormal distribution of cell death areas.22,23
Hartwig et al.\textsuperscript{37} suggested that limb and lateral body wall anomalies were caused by defects in ectodermal placodes, which resulted in mesodermal deficiency and, therefore, abdominal wall deficiency, that was substituted by the amnion and, in the case of rupture, it allowed the abdominal content to fill the extraembryonic celom.\textsuperscript{36,37} Facial and limb anomalies were attributed to a defect in the craniofacial placodes, whereas internal anomalies were explained by the alteration in lateral abdominal placodes that caused an intermediate mesoderm deficiency.\textsuperscript{33,37}

Table 1. \textit{Classifications proposed for amniotic bands sequence}

| Reference | Bases for classification | Groups |
|-----------|-------------------------|--------|
| Pagon et al., 1979\textsuperscript{17} | Location and extent of the body wall defect and associated characteristics | Thoracoschisis and/or abdominoschisis (congenital cleft of the thoracic and/or abdominal wall with a visceral protrusion) with major cranial malformation, facial clefts, and amniotic bands Midline defects with an absent/rudimentary right lower limb, right renal aplasia/hypoplasia, and genital anomalies Lateral abdominal wall defects with central nervous system anomalies, external genitalia, imperforate anus, and short umbilical cord |
| Seeds et al., 1982\textsuperscript{5} | Anatomical region where the defect is located | In the limbs In the craniofacial region In the viscera, including omphalocele and gastroschisis |
| Van Allen et al., 1987\textsuperscript{18} | Type of limb anomaly | Secondary to vascular and underlying tissue disruption Secondary to amniotic bands or adhesions Secondary to deformations versus hemorrhages |
| Moerman et al., 1992\textsuperscript{19} | Presence of constriction bands and associated defects | Constriction bands Constriction bands and craniofacial defects Complex defects, including body wall defects with thoracic or abdominal organ evisceration (BWD or BWC) |
| Russo et al., 1993\textsuperscript{20} | LBWC and associated anomalies | LBWC with exencephaly/encephalocele, facial clefts and amniotic bands or adhesion between the cranial defect and the placenta LBWC without craniofacial defects but with urogenital anomalies, anal atresia, lumbosacral meningocele, short umbilical cord or persistent extraembryonic celom |
| Martínez-Frías, 1997\textsuperscript{11} y Martínez–Frías, 2000\textsuperscript{12} | Presence or absence of BWD | ABS with limb or craniofacial defect or digital constriction BWD of any cause (except omphalocele and gastroschisis), including amniotic bands Severe clefts of the abdominal wall, short/absent umbilical cord or a cord that extends into the placenta |
| Jamsheer et al., 2009\textsuperscript{10} | Presence or absence of BWD | ABS with BWD ABS without BWD |
| Guzmán et al., 2013\textsuperscript{11} | Defect location | Craniofacial and limb defects Craniofacial and limb defects with BWD Limb defects with BWD Isolated craniofacial or limb defects or BWD in the presence of amniotic bands |
| Lowry et al., 2017\textsuperscript{16} | Presence of amniotic bands and defect location | Amniotic bands/constriction rings with or without limb defect BWD with or without limb defect, with or without amniotic bands/constriction rings Amniotic bands/constriction rings with craniofacial defects Amniotic bands/constriction rings with limb and craniofacial defects Amniotic bands/constriction rings, craniofacial defects and BWD |

ABS: amniotic band sequence; BWD: body wall defects; BWC: body wall complex; LBWC: limb-body wall complex.
The objections to this theory are that the mesoderm and the endoderm are established as the epiblasts migrate internally through the primitive streak and are not induced by the ectoderm,33,38 limbs originate from the mesoderm with the secondary formation of the apical ectodermal ridge, and internal organs originate in the internal migration of epiblasts through the primitive streak (mesoderm progenitor cells).33,39 Hartwig et al.37 also suggested the possibility of familial recurrence, which was considered in other case reports.6,19,28,40-44 Kruszka et al.13 even reported the case of a patient with clinical characteristics of LBWC for whom a heterozygous de novo and nonsynonymous mutation was identified in the IQCK gene (IQ Motif containing K) (c.667C>G;p.Q223E).

**Theory of amnion disruption**

Torpin7 proposed the amnion rupture or detachment with temporal loss of the amniotic fluid (initial resorption through the chorion) and partial or total emergence of the fetus towards the extraembryonic celom, forming mesodermal fibrous bands between the outer side of the chorion and the amnion, which may cause developmental alterations (constrictions and/or amputations, as well as secondary facial clefts) when coming into contact with the fetus.7,35 Higginbottom et al.1 supported

| Reference | Source of information | Study period | Reported rate | Other findings |
|-----------|-----------------------|--------------|---------------|----------------|
| Garza et al., 1988 | Metropolitan Atlanta Congenital Defects Program, United States of America | 1968-1982 | 1.16 per 10 000 LBs | Ratio 1:1.5 (female/male). |
| Bower et al., 1993 | Western Australia Birth Defects Registry, Australia South Australia Birth Defects Registry, Australia | 1986-1989 | 2.03 per 10 000 LBs | Both males and females equally affected. |
| Czeizel et al., 1987 | Hungarian Congenital Abnormality Registry, Hungary | 1975-1984 | 1.31 per 10 000 LBs | Both males and females equally affected. |
| Froster et al., 1993 | British Columbia Health Surveillance Registry, Canada | 1952-1984 | 0.19 per 10 000 LBs (limb defect cases were excluded, even if they occurred in the presence of constriction rings) | 3 reported cases were considered familial. |
| Martínez-Frías, 1997 | Spanish Collaborative Study of Congenital Malformations (Estudio Colaborativo Español de Malformaciones Congénitas), Spain | 1976-1996 | 0.59 per 10 000 LBs | Higher frequency of amniotic bands isolated among females and of other anomalies or BWD among males. |
| Luehr et al., 2002 | Tertiary care referral facility Australia | 1996-2001 | 3.3 per 10 000 LBs and miscarriages/abortions | Cases who met LBWC criteria. 1 reported case was considered familial. The prevalence was not calculated based on a population registry. |
| Orioli et al., 2003 | Latin-American Collaborative Study of Congenital Malformations (Estudio Colaborativo Latino-Americano de Malformaciones Congénitas), South America | 1982-1998 | 0.97 per 10 000 LBs and deaths | 8 reported cases were considered familial. |
| Jamsheer et al., 2009 | Polish Registry of Congenital Malformations (PRCM), Poland | 1998-2006 | 0.29 per 10 000 LBs and deaths | Higher severity and frequency of anomalies among patients with BWD. |
| Koskimies et al., 2015 | Finnish population registries, Finland | 1993-2005 | 0.9 per 10 000 LBs and stillbirths | Ratio 1:1.46 (female/male). |
| Lowry et al., 2017 | Alberta Congenital Anomalies Surveillance System, Canada | 1980-2012 | 1.08 per 10 000 LBs, stillbirths and abortions (< 20 weeks of gestation) | Ratio 1:1.15 (female/male). Higher severity of limb defects among patients with BWD. |
| Guzmán et al., 2013 | Registry of the Maternal-Fetal Medicine of the Instituto Nacional de Perinatología Isidro Espinosa de los Reyes, Mexico | 1993-2010 | 5 per 10 000 LBs | The prevalence is not estimated based on a population registry. |

ABS: amniotic band sequence; LBs: live births; BWD: body wall defects; LBWC: limb-body wall complex.
this theory and proposed that an early damage (before 45 days of gestation) caused craniofacial clefts and severe cranial and brain anomalies frequently but not always with constriction rings and amputations, whereas late damage (after 45 days of gestation) affected the limbs more. They suggested that neural tube defects and facial clefts were caused by band disruption and/or compression, whereas BWD were considered a primary malformation.1,35,45,46 Davies et al.47 reported an association between fetal amniotic adhesions and multiple malformations, which predominately occurred in the same area and on the same side, thus supporting the theory of amniotic adhesions as the initial factor.

Romero et al.48 maintained that ABS was generated by the early rupture of amniotic and chorionic membranes and also proposed that the epithelial-mesenchymal transition was a factor that could contribute to ABS pathogenesis.49-51 The objections to the theory of amnion disruption are that there is no evidence of the initial resorption of amniotic fluid through the chorion or of the abrasive nature of the chorion on the fetal skin and the presence of anomalies without evidence of amnion rupture or amniotic bands, so damage should occur very early during gestation to account for some associated anomalies, and the presence of internal malformations (in the kidneys and the heart) cannot be explained by such mechanical phenomenon.33,35,52-54

Theory of vascular disruption
Van Allen et al.18 proposed that internal or external events caused vascular accidents or had a negative impact on blood flow to the embryo because they interrupted the morphogenesis or destructed structures, whereas amniotic bands were a form of superficial necrosis. This theory was supported by some experiments in animal models that resulted in anomalies following an amniotic puncture55,56 and the demonstration of vascular alterations proximal to the band or the amputation.57 The objections to this theory are that humans do not undergo such immediate loss of amniotic fluid following the rupture of the amniotic membrane during early pregnancy, so that such vascular changes are not expected to occur that account for the alterations observed in ABS.27 Another objection is that, compared to other cases of ABS, acardiac twins (considered the clearest example of vascular disruption) show a pattern of different anomalies, so the probability of the same causal mechanism is low.58

Theory of disorganization
The mouse mutant disorganization (Ds) gene was initially described by Hummel;59 however, this gene has not been identified in humans.60 It has been proposed that limb anomalies in humans may be equivalent to those reported in Ds61-69 although some characteristics observed in ABS are not part of the phenotype described.33,70

Hypothesis of primary ectodermal failure in the early embryonic disc
Hunter et al.33 proposed that the anomalies observed in LBWC were caused by a primary defect/ectodermal deficiency of the embryonic disc. The affected area and severity may depend on the defect size and location in the ectoderm.

In general, none of the theories individually accounts for each and every anomaly observed in ABS, so it has been proposed that it is a multifactorial pathology with involvement of different processes.35

Risk factors (Table 3)
The increased risk for ABS among young parents has been attributed to the interaction of genetic factors and age-related environmental factors (greater exposure to tobacco, alcohol, and drugs).72 Tobacco has a vasoconstrictor effect94,95 and carbon monoxide has been associated with fetal hypoxia, the same that causes vascular disruption.96,97 Cocaine is a potent vasoconstrictor and may damage the uteroplacental blood flow during the critical periods of development.28,76

Cignini et al.9 suggested that even though acetaminophen has been associated with a small increase in the risk for gastroschisis,9,94,98 the risk observed for ABS should consider the confounding effect of this drug in the case of fever because it has been associated with vascular disruption, neural tube defects, and oral clefts.99,100 In relation to the increased frequency of ABS in populations living at high altitude, hypoxia has been proposed as a mechanism, although the genetic variants typical of these populations cannot be ruled out.9

Clinical description (Table 4)

Limb anomalies
Amniotic bands may or may not be attached to the fetus abnormal portions and be associated with deep constriction rings. Some bands are not connected to the amnion but join two abnormal portions of the fetus; other bands stem from the fetus or the amnion and remain loose without
a distal anchor point. Patterson classified limb congenital anomalies into agenesis and constriction rings, whereas Hennigan and Kuo classified constriction bands of the lower limbs by dividing their location into 4 areas and graded their severity. Homer et al. classified constriction bands of the upper limbs based on Hennigan and Kuo’s proposal.

Craniofacial defects
Craniofacial clefts are usually asymmetric and do not follow the anatomy of facial clefts; they extend from the lip and/or palate towards the skull and may or may not be connected to the brain malformation caused by the amniotic bands, although “normal” cleft lip and palate cases have also been reported. Tessier classified facial clefts focusing on the orbit and assigning a number to each cleft counterclockwise. David et al. broadened the description of craniofacial clefts described by Tessier supported by two- and three-dimensional reconstruction studies by high-resolution computed tomography.

Body wall defects and other anomalies
Anterior abdominal wall defects (excluding gastroschisis, omphalocele, and umbilical hernia) are uncommon, large, and complex injuries, although some bands do not affect the body wall.

DIAGNOSIS
A histopathological analysis may show the absence of the amniotic membrane on the fetal surface of the chorionic sac (including the placenta), the remaining amnion on the umbilical cord base, and cell detritus or amniotic lamellae embedded on the chorionic surface.

Imaging studies help to establish the location, type, and extent of the anomaly. Magnetic resonance imaging tests study the depth of constrictions, the extent of lymphedema, and muscular integrity, and define vascular anatomy (which may be anomalous) to propose a surgical approach and prevent vascular damage during surgery.

Cytogenetic and molecular tools, in addition to being useful to rule out chromosomal numerical or structural alterations (fluorescence in situ hybridization, FISH) and genomic imbalances (comparative genomic hybridization, CGH) and to analyze the single-nucleotide polymorphism by chromosomal microarray, allow to identify common, rare or new variants in deoxyribonucleic acid (DNA) with a high risk for ABS. This is the case of exome sequencing; however, it has successfully identified mutations in predominantly Mendelian phenotypes with high penetration alleles, whereas ABS may be caused by a combination of DNA variants, so it is necessary to perform a family-wide analysis and assess functional pathways that may be involved in ABS development to select the variants that should be validated by Sanger sequencing and, therefore, replicate the sequencing method in the family or the control population.
ANTENATAL DIAGNOSIS

A two-dimensional ultrasound allows to detect the LBWC in the second trimester of gestation; however, unlike a three-dimensional ultrasound, it has certain limitations to obtain orthogonal multi-planar images of the cavity and the surface, which help to see the defect and the adjacent structures.131-134 A prenatal ultrasound marker suggestive of ABS is the presence of amnion loose in the cavity,135-137 so a fetal structural assessment should be done to rule out other anomalies.18,19,33,131,134,138

If an ultrasound image is indicative of amniotic band sequence, a differential diagnosis of the following is required:

- Succenturiate lobed placenta: a separate mass of chorionic villi connected to the main part of the placenta by blood vessels inside the membranes. Blood flow is observed in the Doppler ultrasound.139
- Intrauterine adhesions: the amnion and chorion layers are doubled. A Doppler ultrasound shows vascularity with arterial pulse consistent with the maternal heart rate.140-142
- Uterine septum: remaining from the middle septum secondary to curettage or surgery.
- Amniotic sheet: adhesion not related to the uterine lateral walls and completely surrounded by the chorion and the amniotic sac (in the incomplete presentation, there is a free-floating oval edge or “sperm sign”).140,143
- Adhesions: intrauterine scarring secondary to curettage or surgery.
- Amniotic sheet: adhesion not related to the uterine lateral walls and completely surrounded by the chorion and the amniotic sac (in the incomplete presentation, there is a free-floating oval edge or “sperm sign”).

Table 4. Anomalies identified in amniotic bands sequence

| Body System | Anomalies |
|-------------|-----------|
| **Limbs**   | Deformation: Hip dislocation, talipes equinovarus, talipes valgus  
              Defects: Complete  
              Digital: Syndactyly, pseudo-syndactyly, camptodactyly, polydactyly, brachydactyly, nail hypoplasia, altered dermatoglyphics |
| **Head and neck** | Head and central nervous system: Encephalocele, exencefalia, aphaecephaly, anencephaly / acrania, holoprosencephaly, microcephalus, ventriculomegaly and / or hydrocephalus, septo-optic dysplasia, periventricular nodular heterotopia, polymicrogyria, cortical dysplasia with pachygyria, hypoplasia of the corpus callosum, craniostenosis, myeloschisis, meningoecele, myelocele |
| **Face** | Asymmetry, agnathia, clefts |
| **Eyes** | Orbital hypertelorism, eyelid coloboma, anophthalmia / microphthalmia, ectropion |
| **Nose** | Choanal atresia |
| **Mouth** | Microstomia, high-arched palate, aglossia / microglossia, cleft lip and / or palate |
| **Ears** | Low ear implantation or rotation, poorly-differentiated pinna, melotia |
| **Cardiovascular** | Heart anomalies |
| **Respiratory** | Lung anomalies |
| **Skin** | Skin appendages, hamartomatous pedicles, pterygium, sacrococcygeal appendage |
| **Chest** | Thoracochisis, supernumerary nipples |
| **Abdominal and gastrointestinal** | Abdominoschisis, tracheoesophageal fistula, diaphragmatic defect, hepatomegaly, intestinal malrotation, single umbilical artery, short or ectopic umbilical cord, imperforate anus |
| **Genitourinary** | Epispadias, bladder extrophy, cloacal extrophy |
| **Skeletal** | Cervical ribs, segmentation defects of the vertebrae, kyphoscoliosis, arthrogryposis |
Management

ABS requires a multidisciplinary approach. An ultrasound control should be done to determine whether amniotic bands (if present) show spontaneous lysis,\(^{144,145}\) whether the process is causing fetal deformation or if it is necessary to release band constriction in utero by fetoscopy.\(^{146-150}\)

Based on the post-natal classification suggested by Weinzweig,\(^{151}\) Hüsler et al.\(^{150}\) proposed the prenatal staging of ABS in the limbs by Doppler velocimetry and artery pulsatility index (Table 5).\(^{150}\) Fetuses that may benefit from amniotic band release by fetoscopy are those with an abnormal flow (compared to the opposite limb or available reference values) in the distal portion of the limb.\(^{150,152,153}\) The objective of this procedure is to prevent irreversible injuries and have a potentially reconstructible limb post-natally.\(^{153}\)

If diagnosis is made post-natally, the classification proposed by Hennigan and Kuo\(^{155}\) is used to select the surgery, i.e., an elective and cosmetic surgery for patients with superficial bands that do not affect the lymphatic or circulatory drainage or an emerging treatment for patients with deep bands affecting the anatomical and functional integrity of the site involved.\(^{106}\) Craniofacial and body wall anomalies should be approached by surgery based on clinical practice guidelines individually for each case.\(^{154}\)

Prognosis

Prognosis depends on the time of diagnosis (most cases are diagnosed post-natally), type and location of anomalies, and may vary from cosmetic to life-threatening consequences.\(^{21}\) The antenatal diagnosis of amniotic adhesions has been associated with an adverse prognosis. Most craniofacial and body wall defects are incompatible with extrauterine life.\(^{127}\) In relation to amniotic bands, the most important fetal prognostic factor is perfusion of the distal portion of the affected limb.\(^{150}\) There have been reports of fetal death caused by umbilical cord strangulation by an amniotic band,\(^{2,155,156}\) although spontaneous resolution of constriction bands has also been reported.\(^{145,150}\)

In the case of post-natal diagnosis of anomalies in the limbs, prognosis is good following surgical repair.

Genetic counseling

To date, ABS is considered a sporadic, probably multifactorial event with a risk of recurrence similar to that of the general population (< 1%), although familial cases have been reported for which the risk should be estimated for each family in particular.\(^{6,28,40-44}\)

DISCUSSION

The higher prevalence of ABS among fetuses < 20 weeks of gestation and stillbirths implies that this disease has been under-diagnosed. Different risk factors and a great variability of clinical manifestations and prognoses have been reported. At present, ABS may be diagnosed antenatally, which means potential benefits, specifically in the presence of amniotic bands that could be released by fetoscopy to prevent irreversible injuries and have the possibility of reconstructing the affected limb.\(^{155}\)

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| Stage | Description |
|-------|-------------|
| 1     | Amniotic bands without signs of constriction. |
| 2     | Constriction without vascular involvement (normal Doppler ultrasound compared to the opposite limb); may present distal deformity with: A. Mild or no lymphedema. B. Severe lymphedema. |
| 3     | Severe constriction with progressive arterial involvement. Flow should be measured proximally and distally to the constriction band. A. Normal distal Doppler ultrasound compared to the opposite limb. B. Without vascular flow to the limb. |
| 4     | Long bone curvature or fracture at the constriction site. |
| 5     | Intrauterine amputation. |

During stages 2-5, amniotic bands may or may be seen by ultrasound.
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