Amniotic Band Syndrome: Is There Anything We Can Do In The Underdeveloped Countries Of Sub-Saharan Africa? Report Of 3 Cases And Literature Review

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Citation

Abstract
Amniotic band syndrome or sequence (ABS) is a fetal congenital malformation, mainly affecting limbs and mostly characterized by digital amputations and constrictions rings due to fibrous amniotic bands (AB). It can also affect the craniofacial area and internal organs.

Two main pathological mechanisms have been proposed - amnion rupture (exogenous theory) leading to fibrous bands, which wrap up the fetal body; endogenous theory which is of vascular origin resulting in the failure of development of embryo. This second theory can explain the occurrence of disease when no amnion rupture is observed.

The outcome of the disease during pregnancy depends on the severity of the malformations. Termination of pregnancy is usually considered when severe abnormalities were diagnosed. In-utero lysis of bands, by laser application, is sometimes done before amputation, for isolated amniotic band with a constricted limb. Such treatment is not possible in the underdeveloped countries of sub-Saharan Africa in view of suboptimal antenatal diagnosis. The disease is often discovered only in newborn. Minor limb defects can be repaired with postnatal surgery. However overall prognosis of ABS in the underdeveloped countries of sub-Saharan Africa is often poorer. Our 3 cases illustrated these points.

INTRODUCTION
Amniotic Band Sequence or Syndrome (ABS) is a rare syndrome of congenital deformities (usually at limbs or digits), caused by entrapment of these parts in fibrous amniotic bands [1]. In this congenital condition, it is hypothesized that a fibrous band of amniotic tissue results in variable soft tissue derangement [2–6]. This condition is also known as the ‘Amniotic Deformity, Adhesion, and Mutilation’ (ADAM) sequence (acronym used by Hermann and Opitz in the 1974). It is a heterogeneous condition, with a broad spectrum of anomalies, where intrinsic causes such as defect of germplasm [7], vascular disruption (8) and disturbance of threshold boundaries of morphogens during early gastrulation, and extrinsic causes such as amnion rupture can account for this condition [9]. The clinical manifestations vary from extremity amputations to anencephaly or fetal death secondary to strangulation of umbilical cord [10].

This syndrome is a sporadic condition and is reported to occur in approximately 1 in 1,200 to 1 in 15,000 births. The patient may present with craniofacial, thoracic, abdominal, and/or limb involvement [11]. Antenatal diagnosis and in utero support by laser application are possible in developed countries but not in poor sub-Saharan countries where antenatal care is suboptimal.

The main objective of this work was to highlight the difficulties in an underdeveloped sub-Saharan country, in the diagnosis and management of ABS and their effects on the neonatal outcome. From our three clinical cases, we first looked at the epidemiology, clinical features and prognosis of disease. Then we discussed the etiological theories & pathogenesis, risks factors, natural course and therapeutic possibilities of ABS.

FIRST CASE REPORT
Mrs A, a 25-year-old woman, with no particular antecedent history, presented for her fourth pregnancy (G4P3). Ultrasound (US) scan performed at 13 weeks of gestation
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(WG) was unremarkable. At 22 WG, US scan showed anomalies of left hand fingers (syndactyly) except thumb (Fig. 1a), with voluminous edema of right foot (Fig. 1b) which was confirmed 3 weeks later by another operator (Fig. 2a and 2b). The patient and partner asked for medical interruption of pregnancy which was obtained with oral prostaglandin (Misoprostol). Fetal macroscopic analysis confirmed presence of huge amniotic string wrapping right foot, with huge downstream edema. There was upper limb disorders such syndactyly of right hand (fingers 2-3-4-5), with distal amputation and syndactyly of left hand fingers (2-3-4) and integrity of thumb (Fig. 3 and 4). Placental and amnion histological examination confirmed diagnosis of ABS.

**Figure 1a**
Ultrasound scan of 22 week of gestation. Left hand syndactyly

**Figure 1b**
Ultrasound scan of 22 week of gestation. Right foot downstream edema

**Figure 2a**
US scan of 25 week of gestation. Right foot downstream huge edema
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Figure 2b

Figure 4
Left hand syndactyly and amputations of fingers 2-3-4

Figure 3
Right foot large furrow striction and edema

SECOND CASE REPORT
Mrs. B, 35-year-old, with no medical history presented for her fifth pregnancy, having four living children (G5P4). She had a low level of education, similar to her husband. Both were evangelical Christian. She presented late for her systematic morphological US scan, near 30 WG. This showed fetal right leg amputation with downstream edema and club-foot of left limb (Fig. 5). There was normal and regular fetal heart activity and pregnancy was carried to term till childbirth with no incident. The newborn had good Apgar score, right leg amputation associated and left limb club-foot (Fig. 6). He was immediately transferred to a neonatal orthopedic surgery center where foot splint is made. Mother was discharge 12 hours after birth in view of the absence of postpartum complications.
emergency maternity for uterine contractions and leaking liquor at term. Poor antenatal care and monitoring of pregnancy with no antenatal diagnosis were noted. Examination on admission revealed imminent delivery. One hour later, she gave birth, with no difficulties, after episiotomy, of a newborn in apparent good health with Apgar score of 9 at first minute and 10 at 5 minutes. Placental delivery and perineum suture were done. Newborn examination in delivery room found many cutaneous constriction furrows of left foot, with large downstream edema (Fig. 7). The baby boy was then transferred to neonatal orthopedic surgery center for better support. Mother was discharged 12 hours after delivery. Pathological examination of placenta and amnion for diagnosis of ABS were not done.

**DISCUSSION**

The ABS is sporadic condition reported to occur approximately between 1:1200 to 1:15000 live births in developed countries [1,3,4,5,6,10]. The presence of amniotic band (AB) is associated with 1% to 2% of fetal malformations [12]. In literature, different prevalences of the disease were found in various populations. For Pietro et al. [9], a Latin American study, the birth prevalence rate of
rupture (after day 45 of gestation) in limb constrictions [18]. rupture results in multiple severe deformities while a late severity of deformities. According to this theory, an early occurrence is a result of premature rupture of amnion, followed by loss of amniotic fluid and extravasation of all or parts of fetus into the chorionic cavity [21]. Vascular compression and then necrosis ended the process [15]. This ‘amniotic band theory’ suggests that the occurrence is a result of premature rupture of amniotic sac, where AB is unelastic and produce ligature effects. The time of the amniotic sac rupture seemed to correlates with the severity of deformities. According to this theory, an early rupture results in multiple severe deformities while a late rupture (after day 45 of gestation) in limb constrictions [18].

Constriction ring syndrome is an uncommon deformity with multiple manifestations, mostly of the lower extremities [15]. There is currently no consensus about origin or etiological factors of ABS despite much etiological, embryological, pathological and experimental works [16]. Two main theories of pathogenesis are the “extrinsic model” and “intrinsic model” [9].

The intrinsic model, proposed by Streeter in 1930 [17], suggests that the anomalies and fibrous bands have a common origin, caused by a ‘perturbation’ of developing germinal disc of the early embryo. This is ‘failure of development theory’ suggests that limb ring constrictions are due to localized areas of imperfectly formed tissue caused by defective germplasm [18]. Proponents of this theory consider that the AB arise as an integral part of the same localized failure of development that gives rise to the limb constriction rings [15]. The endogenous mechanism is the more accepted theory today although it cannot satisfactorily explain the other types of defects associated such as imperforated anus, polydactyly, septo-optic dysplasia [19] and cleft lip with or without palate [20].

In 1965, Torpin proposed [22] the “extrinsic theory”, or “amniotic band theory”. He suggested that the birth defects are caused by the action of the fibrous AB as a consequence of rupture of amnion, followed by loss of amniotic fluid and extravasation of all or parts of fetus into the chorionic cavity [21]. Vascular compression and then necrosis ended the process [15]. This ‘amniotic band theory’ suggests that the occurrence is a result of premature rupture of amniotic sac, where AB is unelastic and produce ligature effects. The time of the amniotic sac rupture seemed to correlates with the severity of deformities. According to this theory, an early rupture results in multiple severe deformities while a late rupture (after day 45 of gestation) in limb constrictions [18].

Both two theories however still cannot explain certain changes and therefore some workers suggested a genetic basis [19,20] for its pathogenesis. Evidence was provided that vascular compromise could explain craniofacial and abdominal wall defects [9]. It is however, difficult to prove if AB is the primary cause or is secondary to vascular disruption. Vascular disruptive process during gestation may lead to a variety of congenital anomalies as terminal transverse limb reduction defects, clubfoot, small intestinal atresia, gastrochisis, renal agenesis and microtia [9]. A prospective study from South Africa conducted in 1992, supported the theory of vascular compromise as the main pathogenesis mechanism underlying ABS [10]. In this study, limbs affected by AB were observed in children born alive, using angiography techniques. Vessel abnormalities such as “bifurcation or trifurcation of the popliteal artery or a much attenuated segment with no discernable branches of the popliteal artery”, were found in the limbs affected. These abnormalities were however absent in the healthy contralateral limbs [10]. Other vascular abnormalities in the affected limbs included absent major vessels, atretic segments in the major limb arteries and also absent branches.

Another important clinical association is the presence of AB with limb reduction defects and cleft palate, due to mutations of genes. The genes involved in cleft lip and cleft palate (CLP) are well known and this perhaps could be the basis for a better understanding of the genes involved in the ABS. It is interesting to note that several of the recently identified CLP genes have oral or facial fibrous bands as one component finding and much has been inferred from murine breeding studies [22].

The mechanism underlying ABS are controversial and many possible risks factors have also been proposed. In a large and comprehensive literature review, Pietro et al [9] found many studies which suggested different risk factors. The role of the hypoxia mechanism of living at high altitude has been suggested in etiopathogenesis of some ADAM, in a Latin American study on congenital malformations in 1999 [23]. In a study in Bolivia, ethnicity was a factor [9]. Luciano et al. [24], found a familial occurrence for the risk of ADAM sequence was higher among first-degree relatives, and also higher among second degree relatives when compared to general population and these were statistically significant (p<0.001) [24]. Pietro et al in a review, found risk factors for ADAM, such as firstborn; medication drug use like misoprostol, and vaginal bleeding during first trimester [9].
The observed approximate twofold increases in risk of ARS-NL (amnion rupture sequence without limb lesion) and BWC (presence of body wall defects with evisceration of thoracic and/or abdominal organs, limb deficiency, and myelocystocele) for a first-born, suggest it may be important [9]. Data from the Boston study suggest risk factors that might increase risk of BWC in offspring included young maternal age, low maternal education, unplanned pregnancy, and non-white/non-Hispanic race/ethnicity. These are clearly the characteristics of the pregnant women in the poor sub-Saharan countries. In addition, a Hungarian study found that multiparous women had a greater risk association for maternal age [9], and also reported positive associations for low socioeconomic status, unplanned pregnancy, and smoking during pregnancy in relation to ARS-L. Cigarette smoking during early pregnancy is vasoconstrictive and has been related to gastrochisis, which is thought to arise from vascular disruption [25]. Cigarette smoking is however, not a common practice of women in our sub-Saharan African countries.

In a Californian study, young paternal age (i.e., less than 29 years), was associated with an increased risk of amniotic bands. In our three cases, two of them are young and less than 30 years old. The increase in risk observed among younger fathers could be attributable to an interaction of genetic factors with behavioral factors such as the use of alcohol and recreational drugs [26]. For a study conducted by the National Center on Birth Defects and Developmental Disabilities (CDC, Atlanta), maternal cigarette smoking and aspirin use each increased the risk of AB-L (Limb reduction deficiencies that are accompanied by AB) [27].

Amnioentesis role have been mentioned when several workers had been able to reproduce experimentally typical amputations (cranial malformations, and syndactylies), even in absence of band formation. They noted vascular changes, and hemorrhage or hematoma as the primary event. In some cases, secondary adhesions to the amnion could exist [9]. The incidence and risk factors for Pseudoamniotic Band Syndrome (PABS) after fetoscopy- guided laser have not also been documented [9].

The deformities due to constriction ring syndrome are multiple polymorphic and asymmetrical manifestations [28]. The severity of lesion is variable - can range from isolated skin furrow to craniofacial and visceral malformations which are often incompatible with life [17, 21]. The frequency of malformations is quite variable but 77% of cases would have at least two anomalies [29]. The most common change occurs at the lower extremities especially limb, in patients with a single anomaly [16] (as in our cases highlighted in Fig. 6 and 7). The constriction ring or band causes soft tissue depressions (Fig. 7), encircling digits, extremities or limbs (similar to our case in Fig. 3), sometimes neck, thorax or abdomen. Digital ring constrictions (Fig. 3 and 4), digital atrophy, congenital intrauterine amputations, acrosyndactyly, lymphoedema and club-feet can also be observed (Fig. 4, 5 & 6). Patterson (1961) cited by Siemers et al, described the extent of the constrictions [15] in several types as simple constriction rings without distal deformity and constriction rings with distal soft tissue deformities including or excluding downstream lymphedema; constriction rings with distal deformities including distal bony fusions from mild to severe acrosyndactyly and intrauterine amputations [15].

Prenatal diagnosis of constriction band syndrome involving the upper limbs has been reported as current in developed countries and are generally diagnosed at the end of first or the beginning of second trimester using two-dimensional ultrasonography (2D US) [30,31,32]. Furthermore, three-dimensional ultrasonography (3D US) in rendering mode allows spatial analysis of the fetus and AB, and makes diagnosis easier, that enables better counseling for the parents [30]. The 3D US made it possible to see the spatial relationship of these bands to the fetal body, thereby confirming their adherence to the limb. In the poor countries of sub-Saharan Africa, we do not have such high performance Ultrasound (US) devices and only use basic 2D US machines. The diagnosis of ABS with organ constriction was usually made at birth in our countries (Fig 7). The difficulties for diagnosis of ABS is also due to its rarity which makes sonographer training to diagnose this very challenging. In addition US machines are expensive. We agreed with Pietro et al that all these lesions can be diagnosed by trained sonographers using high-end performance device if the pregnant women avail themselves for US examination. Color and pulsed Doppler are also essential to confirm antenatal diagnosis as it is essential to demonstrate presence or absence of vascularization in color and pulsed Doppler in the strapped organs [16]. Most of the US scan machines used in our country do have not this technology. In our 3 reported cases, US examination reviews were not completed, due to its unavailability (case 1 and 2), or late diagnosis at birth (case 3).
Uterine Contents Radiography can show the skeletal abnormalities (vertebral and limb deformities) and search bone mineralization preservation in strangled limb. It can be an alternative to 3D US in resource-poor countries. In ABS, the karyotype examination is usually normal and thus not a good aid for diagnosis [16], but a normal karyotype can eliminate certain differential diagnosis. It is rarely done in our context because prenatal diagnostic karyotyping is mostly unavailable or its cost is too high. Histology examination of conception product remains indispensable in all cases and confirms diagnosis by showing presence of partially or all separated chorion of amnion in front of a lesion [16].

When craniofacial or limbs anomalies are accompanied AB, the diagnosis is quite certain [16]. The differential diagnoses we need to consider are: anencephaly due to primary defect closure of neural tube, facial clefts (lip and palate), Cantrell pentalogy [33], limb-body wall complex, and congenital tegumentary aplasia in the differentials. We must also consider sub-chorionic hemorrhage, lack of fusion of amnion, second twin evanescence, biamniotic twin pregnancy, bilobed placenta or circumvallata [33].

Natural evolution of ABS is unpredictable [34]. Two parameters not yet well evaluated, could have useful predictive value. They are the occurrence of distal lymphedema (reflecting constriction of neurovascular structures and lymphatics), and the study of vascular flow (color and pulsed Doppler) within the strangled limb. Using just regular basic US monitoring, it would be challenging to differentiate between constrictor rings leading to future in-utero amputation (fetal indication for surgery) and those responsible for isolated striction skin furrow (indication for non-intervention). In presence of craniofacial and visceral polymalformations, natural history is of little importance, prognosis is known and very poor. Situation is quite different in case of isolated and superficial constriction of limb, as in our reported cases 2 and 3.

Schematically, we can have 4 scenarios: firstly exceptional spontaneous regression without after constriction [16]; secondly limb constriction gets deeper, with strangulation of neurovascular structures, with risk of cutaneous or subcutaneous downstream necrosis; third ring constrictor causes in-utero amputation of limbs and finally, occurrence of downstream lymphedema with vascular compression of arterio-venous structures and lymphatic, significant decrease in vascular perfusion in distal segment, and in utero amputation [34].

The support and management of ABS can be achieved in both before (with fetoscopy-guided laser) and after birth in occidental countries, but only after birth in sub-Saharan African countries. This is because of less medicalisation, illiteracy and poverty which make the diagnosis late (only at birth) in sub-Saharan African countries (like in Fig. 6 & 7 of our case). Newborn treatment could be surgical or orthopedic treatment. It is however of use only in isolated or associated anomalies with possible improvement in functional outcome (furrow constrictions, pseudo-syndactyly, and club-feet). Severe craniofacial and visceral polymalformations are generally incompatible with life and thus not suitable for any therapeutic option. Without any in-utero treatment, skin creases and pinch pseudo-syndactyly are irreversible but do not worsen after birth [35]. In case of vascular lesion (venous stasis and lymphedema), excision with release of neurovascular bundle is urgently required and can be performed within first 48 hours of life. Microsurgical excision of constrictive circumferential furrows, gives better cosmetic result [16] and the edema does not regress. Very tight constricting furrow can reach up to skeleton with thinning of bones, or bone continuity solution [31]. Early neonatal period release of pseudo-syndactyly is recommended, to limit camptodactyly issues when end of two fingers is connected by single membrane. Roth et al. have suggested in-utero release of constricting ring to avoid in-utero amputation, and at birth secondary release of digital amputation to give maximum length to amputated fingers [31,32]. Orthopedic treatment of club-feet with knee furrow is an alternative. There is currently no indication for in-utero surgery in ABS for many authors, who dispute fact that in-utero amputation is linked to hypothetical process of constrictive AB [28]. In addition, surgical procedure in-utero is neither easy nor free of complications. Some infants with groove pinch skin surface have excellent functional prognosis, in contrast with neurovascular structures constriction [16]. Beyond 32 weeks, fetal delivery could be an interesting compromise between functional prognosis and prematurity, and alternative to in-utero surgery. Before considering in-utero treatment, it is essential to ensure that there are no other malformations.

CONCLUSION

ABS represents acquired embryo-fetopathy with asymmetric malformations, mainly affecting the limbs. Although its pathogenesis remains controversial, it is likely to have been the consequence of different pathological processes. Management and support are difficult in the underdeveloped
resource-poor countries. People are poor and illiterate as well. Ultrasonography are unavailable or too cost prohibitive. Management is thus suboptimal and ABS prognosis remains poor. Hopefully with improving economy, increasing proper antenatal care and closer monitoring of pregnancies and also earlier diagnosis & possibility of in-utero lysis surgery, the outcome of ABS can be improved in our countries in sub-Saharan Africa.

References
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