

Amniotic band sequence: prenatal diagnosis, phenotype descriptions, and a proposal of a new classification based on morphologic findings

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ABSTRACT

Objective. The aim of this study is to describe the phenotype of fetuses affected by amniotic band sequence (ABS) that were diagnosed at the Instituto Nacional de Perinatología Isidro Espinosa de los Reyes and to propose a new classification based on morphologic findings. **Material and methods.** Cases with a final diagnosis of amniotic band sequence, diagnosed between January 1993 and July 2010 in the Department of Maternal Fetal Medicine, were reviewed. Demographic, clinical, and periconceptional data were collected, and the defects were described and classified. The association frequencies of the defects were also determined. **Results.** We included 50 cases with prenatal diagnosis of amniotic band sequence. The mean maternal age was 25.7 ± 6.9 years. Of these patients, 54% (27/50) were primiparous compared to 22% (11/50) who had three or more previous pregnancies. Craniofacial defects were seen in 78% (39/50) of the cases, followed by defects of the extremities 70% (35/50), abdominal wall, spine, and/or thorax 52% (26/50). The most frequent defects were the following: a) Encephalocele and facial clefts in the craniofacial group. b) Shortening at any level in the limb defects group, and c) Alterations of the spinal column curvature in the group of "other" defects. **Conclusions.** The amniotic band sequence shows a tendency to affect women who are in their earlier years of reproduction. We observed an inverse relationship between the number of pregnancies and the frequency of presentation of this pathology. The majority of affected fetuses showed a phenotype that fit into one of many groups. Therefore, we propose classifying the amniotic band sequence phenotypes into the following groups: I. Craniofacial defect + limb defect. II. Craniofacial defect + limb defect + abdominal wall, spinal column, and/or thoracic defects. III. Limb defect + abdominal wall, spinal column, and/or thoracic defects; and IV. Isolated defect (craniofacial, limb, or thoraco-abdominal wall). This

Secuencia de banda amniótica: diagnóstico prenatal, descripciones fenotípicas y propuesta de una nueva clasificación basada en hallazgos morfológicos

RESUMEN

Objetivo. Describir el fenotipo de los fetos afectados por secuencia de bandas amnióticas que fueron diagnosticados en el Instituto Nacional de Perinatología Isidro Espinosa de los Reyes, y proponer una nueva clasificación basada en los hallazgos morfológicos. **Material y métodos.** Se revisaron los casos con diagnóstico final de secuencia de bandas amnióticas que se diagnosticaron desde enero de 1993 hasta julio 2010 en el Departamento de Medicina-Fetal. Se recabaron variables demográficas, clínicas, periconcepcionales y se describieron y clasificaron los defectos, así como la frecuencia de asociación entre ellos. **Resultados.** Se incluyeron 50 casos con diagnóstico prenatal de secuencia de bandas amnióticas. El promedio de edad materna fue de 25.7 ± 6.9 años. El 54% (27/50) de las pacientes eran primigestas en comparación con 22% (11/50) que tenían tres o más embarazos. Los defectos craneofaciales fueron los más frecuentes, presentes en 78% de los casos (39/50), seguidos por las anomalías en extremidades 70% (35/50) y en pared abdominal, columna vertebral y/o tórax observados en 52% (26/50). Los defectos más frecuentes por grupo fueron: a) Craneofaciales: encefalocele y hendiduras faciales. b) Extremidades: acortamiento a cualquier nivel, y c) La alteración en la curvatura de la columna para el grupo de otros defectos. **Conclusiones.** La secuencia de bandas amnióticas muestra cierta tendencia en afectar a un grupo de pacientes que se ubica en el extremo inferior del periodo reproductivo de la mujer. Se observó una relación inversa entre el número de embarazos y la frecuencia de presentación de esta patología. La gran mayoría de los fetos afectados por esta patología tuvo un fenotipo que puede

classification system will be helpful in diagnosing amniotic band sequence. Based on future research studies, we hope that we can use this classification system as a prognosis fetal factor to establish a more accurate fetal prognosis and recurrence probability. Finally, we created a flowchart describing all of the steps that were followed by our Department from the moment an amniotic band was found by ultrasound until the definitive diagnosis was made and the follow up according to the fetal findings.

Key words. Amniotic bands. Phenotype. Classification. Craniofacial defects. Limb defects.

INTRODUCTION

The amniotic band sequence (ABS) includes a group of congenital defects that are characterized by their asymmetry and polymorphism. The reported frequency of this pathology is 1:1,200 to 1:15,000 live births.¹ We have an incidence of 1:2,000 live births according to the database of the Maternal Fetal Medicine Department considering a total of 90,000 live births in the period of the data recollection. It is thought that the ABS occurs in a sporadic manner, although there have been reports of cases where a familial tendency has been observed.²

There are two classical theories regarding the pathogenesis of amniotic band sequence: the extrinsic and intrinsic models. The first model was proposed by Torpin,³ who considers that defects are disruptions caused by fibrotic amniotic bands, which are produced as a result of amnion rupture. In contrast, the intrinsic model, proposed by Streeter,⁴ suggests that the malformations and fibrotic bands have a common origin, which is caused by altering the germinal disc development during the early embryonic stage. This suggests that at least one subgroup of ABS cases, such as those presenting with associated malformations, have a genetic basis.⁵ A hypothesis has been proposed for the ABS that involves primary vascular disruption, it sustains that the interruption of vascular flow to the extremities during development leads to necrosis of the terminal portion, which adheres to and tears the amnion bands, and produces mechanical damage to the fetus.^{6,7} This mechanical damage includes constriction rings and facial clefts.⁸ Most of the defects related to amniotic bands are readily visible, mainly those anomalies of the limbs and craniofacial structures. Limb anomalies comprise a

incluirse en uno de los siguientes grupos, por lo cual, se propone una clasificación del fenotipo de la secuencia de bandas amnióticas: I. Defecto craneofacial + defecto en extremidades. II. Defecto craneofacial + defecto en extremidades + defecto en pared abdominal, columna y/o torácico. III. Defecto en extremidades + defecto en pared abdominal, columna y/o torácico. IV. Defecto aislado (craneofacial, en extremidad o en pared corporal). Esta clasificación será útil en el diagnóstico de secuencias de bandas amnióticas, pronóstico y probabilidades de recurrencia. Finalmente, se creó un flujograma que describe todos los pasos seguidos en nuestro Departamento desde el momento en que se encuentra por ultrasonido prenatal la presencia de una banda amniótica hasta que se integra el diagnóstico definitivo y el seguimiento sugerido de acuerdo con los hallazgos fetales.

Palabras clave. Bandas amnióticas. Fenotipo. Clasificación. Defectos craneofaciales. Defectos en extremidades.

spectrum from mild deformations to major positional anomalies, hypoplasia of all or part of one or more limbs, intercalary or terminal deficiency defects, amelia or syndactylies. Frequently we can found other anomalies such as anterior craniofacial defects containing not recognizable cerebral normal architecture and that may be connected by bands of amnion to the placenta. Other related findings can be ventral abdominal wall defects. Terms for this association have included Amniotic Band Dysruption Complex and Amnion Rupture Sequence.⁹

Some of the risk factors that have been identified for amniotic band sequences include the following: black race, primiparity, maternal age younger than 25 years, hemorrhage and febrile episode during the first trimester of gestation, tobacco use, and aspirin and paracetamol use during the periconceptual period.^{8,10-14}

The range of defects in ABS has been divided into three groups according to the body area affected:¹¹

- Limbs.
- Craniofacial.
- Other body areas.

The prognosis depends on the type and location of the defects, and may vary from a cosmetic repercussion to a defect incompatible with life. The ABS may be diagnosed prenatally by ultrasound. It has been shown that the intrauterine release of constriction bands by fetoscopy prevents the amputation and restores the morphological and functional parameters of the affected structure. Therefore, a detailed ultrasound scan is currently considered an indicator for fetoscopy in all cases of umbilical cord constriction and in stages 3 and 4 of the Weinzwieg prenatal classification.^{15,16}

OBJECTIVE

The aim of this study is to describe the phenotypes of fetuses affected by ABS that were diagnosed at the Instituto Nacional de Perinatología, and to propose a new classification based on morphologic findings.

MATERIAL AND METHODS

Patients were selected based on prenatal diagnosis of ABS by a detailed morphologic ultrasound scan. This data was collected in a database from the Department of Maternal Fetal Medicine at the Instituto Nacional de Perinatología Isidro Espinosa de los Reyes. From these cases, we identified those with diagnosis confirmed at birth, either by an autopsy report or by the newborn evaluation conducted by the Genetics and/or Neonatology Services.

We obtained the following data from the selected cases: maternal age, paternal age, education level, tobacco use, number of pregnancies, gestational age at the time of diagnosis, gestational age at birth, birth weight, and band findings at the time of birth. The defects identified at the ultrasound and birth evaluations were classified into three groups:

- Limb defects: shortening of extremities, amputations, constrictions, syndactyly, pseudo-syndactyly, hypoplasia, distal lymphedema, foot deformities, and hip luxation.
- Craniofacial defects: acrania, facial distortion, cleft lip and palate, eye, ear, and/or nose defects, encephalocele, facial cleft, choanal atresia, craniosynostosis, ventriculomegaly and/or hydrocephalus, and holoprosencephaly.
- Other defects: adhesion of fetal parts to amniotic bands or to the placenta, abdominal or thoracic wall defects, ectopia cordis, evisceration, gastros-

Table 1. Demographic characteristics of mothers with a fetus affected by ABS.

Characteristic	Result (n = 50)
Maternal age	25.7 ± 6.9 years
Paternal age	29.2 ± 7.5 years
Educational years	10.7 ± 3.6 years
Maternal tobacco use	11 / 50
First pregnancy	27 / 50
Gestational age at diagnosis	25 ± 5 years
Female fetuses	22 / 50
Gestational age at termination	30.5 ± 6.6
Live at birth	13 / 50

chisis, omphalocele, short umbilical cord, and spinal column alterations.

We excluded cases where we could not obtain all of the information needed and deliveries that were not conducted at this institution. In addition, we excluded cases with short umbilical cords regardless of the presence of amniotic bands because that pathology is considered to be of a different nosologic entity.

Statistical analysis was conducted using the Statistical Package for the Social Sciences (SPSS 14.0, SPSS Inc., Chicago, Ill., USA) and MedCalc 8.0 (MedCalc Software, Broekstraat, Belgium). The data were reported as percentages or as measures of central tendencies and dispersion measures based on the type of variable.

RESULTS

We identified 69 patients from the database with final diagnosis of ABS between January 1993 and July 2010. Of these patients, only 50 met all of the inclusion criteria and were considered for this study.

The average (\pm SD) maternal age was 25.7 ± 6.9 years (Table 1). The average education level (\pm SD) was 10.7 years ± 3.6 , and there were no illiterate patients. A history of tobacco use during the preconception period was positive in 22% (11/50) of the mothers of the affected fetuses. This was the first pregnancy for 54% (27/50) of the patients, and there was a tendency for the frequency of amniotic band sequence occurrence to decrease as the number of pregnancies increased (Figure 1).

Of the affected fetuses, 44% were females, 38% males and we were not able to determine the gender

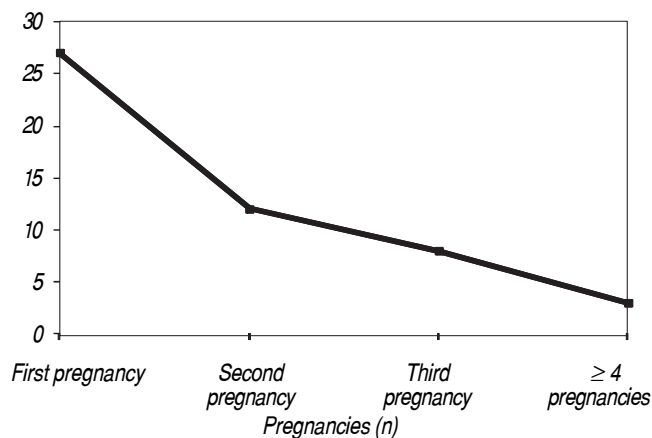


Figure 1. Relationship between the number of pregnancies and the occurrence of amniotic band sequence.

due to lesions caused by the amniotic bands in 18% of the cases (9/50). Karyotype was obtained in 5 cases in which the characteristics of the defects forced to rule out a chromosomal anomaly (fetuses with amniotic bands but also with defects considered sonographic markers for chromosomal anomalies). All cases (5/5) had a normal karyotype. Only 26% (13/50) of the fetuses were alive at birth. We confirmed the presence of fibrotic amniotic bands at the time of birth and/or during autopsy in 86% of the cases (43/50).

We used the Garza and Cordero classification (1988)¹¹ to classify the defects from the ABS. The most common group of defects in our study was craniofacial [78% (39/50)], followed by the group of limbs defects [70% (35/50)] and the group of other alterations [52% (26/50)], which most commonly includes defects of the abdominal wall, thorax, and spine.

Regarding the relationships between the different types of defects, we found that 34% (17/50) of the fetuses had at least one craniofacial alteration and at least one extremity defect. Defects belonging to the three groups were present in 22% (11/50) of the cases. Six fetuses had alterations of extremities, spinal column, thorax, and/or abdominal wall defect (other defect group). Of these cases, 10% (5/50) had a craniofacial defect and a defect from the other group (Figure 2).

We next analyzed the phenotype by defect group. We found that the craniofacial defects such as facial clefts and encephalocele were the most frequently observed in the 50 cases of amniotic band sequence. Both of these defects occurred in 51% (20/39) of the fetuses with a defect in this group and in 40% (20/

50) of the overall cases. When we evaluated limb defects, 58% (29/50) of the total cases and 82% (29/35) of those presenting with some defect in this group showed a limb reduction. Lastly, in the other defect group, 32% (16/50) of the cases showed an abdominal wall defect, and the most common defects were gastroschisis, omphalocele, and thoracic + abdominal wall defects. Only one case had a defect in the anterior abdominal wall that extended towards the pelvis. The most common spinal column defect was a curvature alteration, and it was observed in 30% (15/50) of the total cases. Eight thoracic defect cases were reported, 63% (5/8) as thoracoschisis (two cases associated with an abdominal wall defect) and 37% (3/8) as thoracic hypoplasia.

DISCUSSION

Our results show that 32% of patients with pregnancies complicated by ABS are younger than 20 years of age. Therefore, a greater presentation of this pathology is observed during the earlier years of the reproductive period as opposed to the latter portion (12% in patients 35 years of age or older). This differs from what has been previously reported by Werler, *et al.*,⁸ who found that only 19.4% of 139 patients with amniotic band sequences were younger than 20 years of age and 25.4% were 30 years of age or older. There is no clear biological mechanism for the association between younger maternal age and birth defects. The increase in risk observed among younger people could be attributable to an interaction of genetic factors with behavioral factors such as the use of alcohol and recreational drugs.¹⁷ In our study 11/50 (22%) mothers used tobacco. It is difficult to draw conclusions about why maternal age is younger in this case series because it is not an epidemiological study.

Previous reports have found an association between paternal age and amniotic band sequence. Orioli, *et al.*, found that 8.9% of the cases had a father who was 40 years of age or older, which coincides with the 9.0% found in our study. However, the odds-ratio (OR) found by Orioli was 1.08 (CI 95%: 0.49-2.37), which was not significant.¹²

Werler, *et al.*,⁸ reported the average education level as a risk factor for ABS, the average education level found in our study was 10 years, however, this could not be considered as a low education level because our national average number of education years in Mexico is 8.6 years according to the data in the INEGI's web page (Instituto Nacional de Estadística y Geografía).

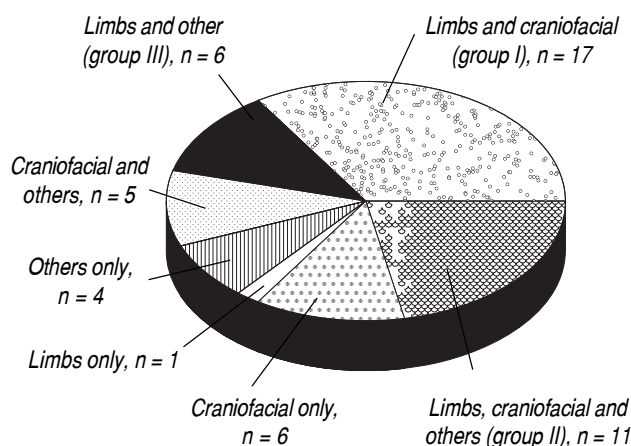


Figure 2. Amniotic band sequence phenotype and frequency of presentation.

Tobacco use has been proposed as a risk factor for ABS, Werler found an OR of 2.4 (CI 95%: 1.3-4.4) with the consumption of 15 or more cigarettes per day.⁸ In our study, only a fifth of the patients with affected fetuses reported a history of tobacco use. In addition, we do not have the quantity of cigarettes smoked per day to determine if this represents a risk factor, which is due to the retrospective nature of this study.

Previous studies have found that up to 60% of patients with ABS are primiparous, Werler, *et al.* establish an OR of 2.1 (CI 95%: 1.4-3.0).¹³ In the present study, we also found a higher occurrence of this pathology in primiparous patients (54%). Whether parity is a risk factor with regards to age or vice-versa is controversial; however, in the two studies conducted by Werler, *et al.*, an increase in the secondary risk to either of these factors is independent of the effect on the other.^{8,13} We believe that the occurrence of this defect in primiparous patients can be related to the fact that they are younger and can be exposed to drugs or a combination of environmental and genetic factors.

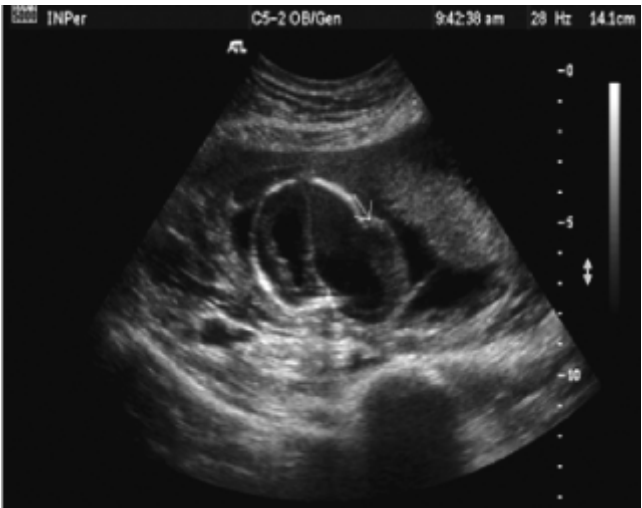


Figure 3. Skull defect in relation to amniotic band in a 20 weeks gestation fetus.

None of the previous published studies specify the gestational age at which the diagnosis was made. Therefore, it is impossible to determine if our institute is detecting ABS in a timely manner. Twenty-five weeks is generally considered late for detecting these anomalies, especially because the majority of defects (including those found in this study) may be diagnosed during the first trimester evaluation. The advantages of making an early diagnosis include the following: providing the parents with vital information related to the health status of their fetus and establishing a prognosis for life and function. In specific cases, fetoscopy and lysis of the amniotic bands could also be proposed as an alternative in the event that all the necessary criteria exist to perform this procedure.¹⁶

We found a higher presentation frequency of ABS in females (44 *vs.* 38%), which is in accordance to previous findings by Garza, *et al.*,¹¹ the majority of our patients (74%) were stillborn or died at birth, this percentage shows the severity of the defects caused by this pathology.

We excluded cases with short umbilical cords regardless of the presence of amniotic bands because that pathology is considered to be part of a different

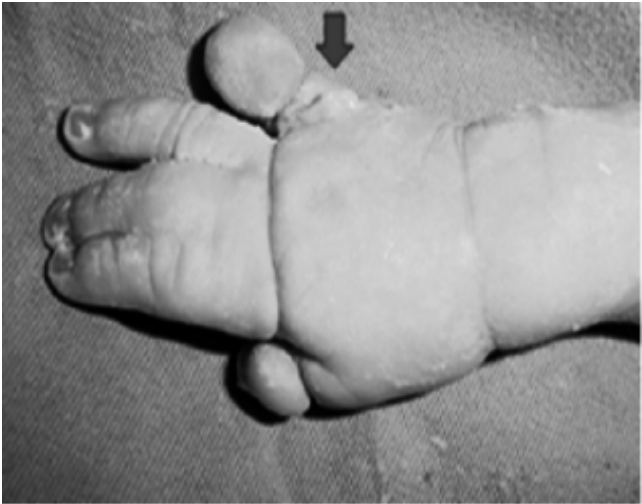


Figure 4. Constriction ring secondary to amniotic band in a newborn patient.

Table 2. Classification system proposed for amniotic band sequence.

Phenotype	Finding
I	Craniofacial defect + limb defects
II	Craniofacial defect + limb defects + abdominal wall, spinal column, and/or thoracic defects
III	Limb defects + abdominal wall, spine, and/or thoracic defects
IV	Isolated defect (craniofacial, limbs, or body wall)

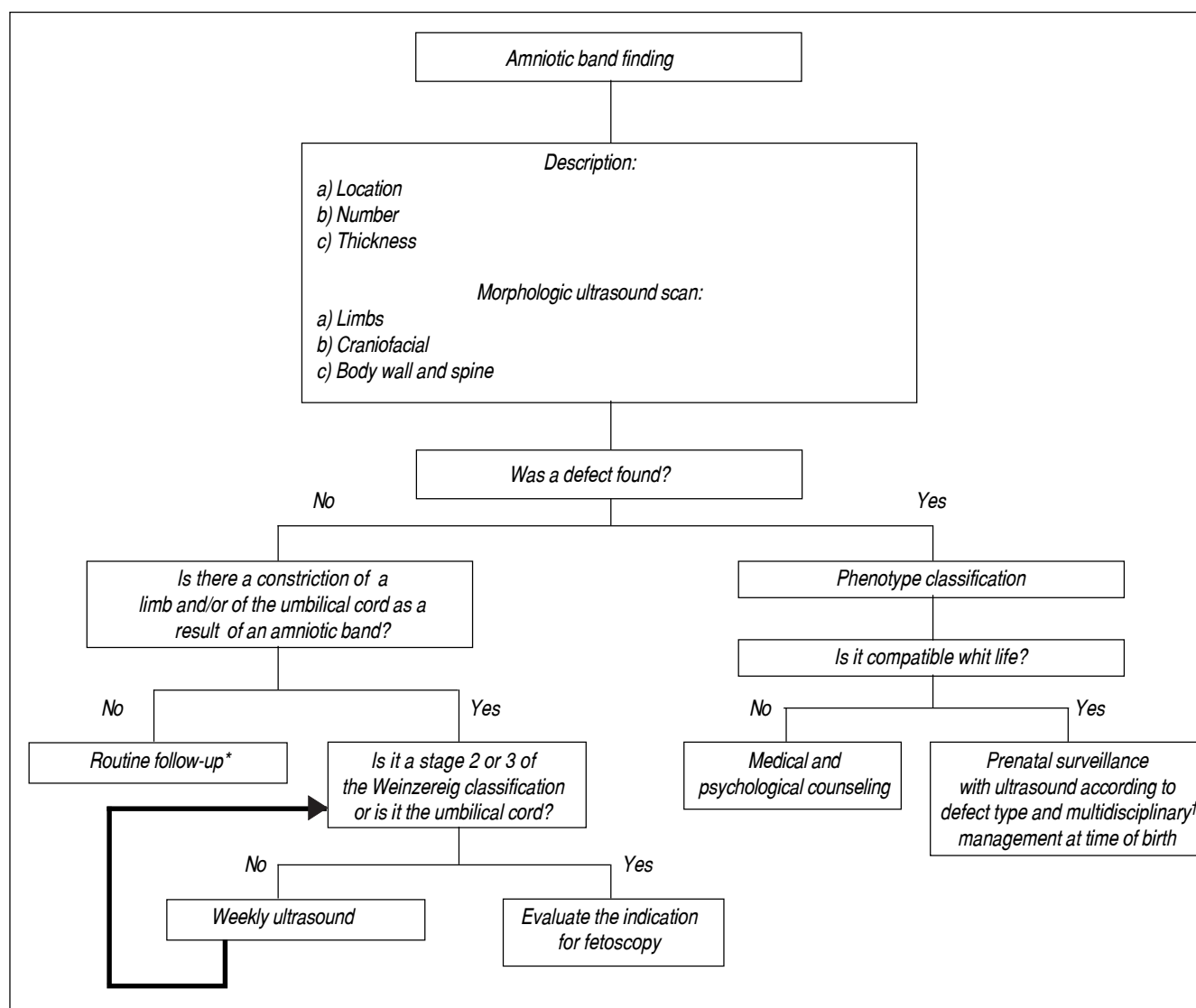


Figure 5. Follow-up scheme at prenatal diagnosis of amniotic band sequence. *Growth curve and pre-and postnatal follow-ups. †Prenatal and postnatal evaluations and follow-ups by maternal fetal medicine, perinatal genetics, fetal surgery, pediatric surgery, and neonatology.

nosologic entity (short umbilical cord syndrome group 1), despite this, 32% (16/50) of the cases showed an abdominal wall defect, and the most common defects were gastroschisis, omphalocele, and thoracic plus abdominal wall defects. Jamsheer, *et al.*,¹⁹ reported a comparative study of fetuses with amniotic rupture sequence with and without abdominal wall defect, finding a major frequency of internal organ anomalies in the second group, concluding that amniotic band sequence with abdominal wall defect could take place at an earlier developmental stage.

Our results show that craniofacial defects are an important phenotype of the amniotic band sequence

because they were found in 78% of the reported cases. This finding is different from previous findings that showed craniofacial defects in 24% of their reported cases.¹² This difference may be related to the fact that our study included holoprosencephaly and ventriculomegaly - hydrocephaly as craniofacial defects, in addition to the typical findings of acrania, encephalocele, facial clefts, and cleft lip and palate. The majority of studies only included the latter manifestations as craniofacial defects. According to the intrinsic theory,⁴ a fetus diagnosed with amniotic band sequence can also show different internal organ anomalies not related to disruptive events. We diagnosed important intracranial defects that were

present in fetuses with ABS^{18,20} and we consider that they need to be included as part of the classification as they modify the prognosis.

Limb defects were present in 70% of the cases in our study, which coincides with results determined by Orioli, *et al.*, (71.9%).¹² However, in contrast to this study, we did not find this to be the most common group of defects. It was found to be second to craniofacial defects. This can be because most of our cases were referred from other hospitals, and it is more probably they refer a fetus with a craniofacial defect (Figure 3), for further evaluation than a fetus with a limb defect (Figure 4).

With respect to the frequency of the combinations found in the defect groups, we propose a classification system according to the amniotic band sequence phenotype, which is shown in table 2. This classification system will help to diagnose amniotic band sequence, especially in cases where the bands are not evidenced at the time of ultrasound evaluation but the fetus has different defects not related between them but with disruptive characteristics that can be considered inside the proposed classification even if the amniotic band is not present anymore. Based on future research studies, we hope that we may use this classification system as a prognosis fetal factor. In future studies we are planning to analyze the presence of microarrays in each group and establish a more accurate fetal prognosis and recurrence probability.

Finally, we created a flowchart (Figure 5) describing all the steps that were followed by our Department since the moment an amniotic band was found until the definitive diagnosis was made. The phenotype classification of the amniotic band sequence has been added, which represents a contribution for the care of affected fetuses.

REFERENCES

1. Seeds JW, Cefalo RC, Herbert WNP. Amniotic Band Syndrome. *Am J Obstet Gynecol* 1982; 144: 243.
2. Hüsler M, Wilson R, Horri S, et al. When is fetoscopic release of amniotic bands indicated? Review of outcome of cases treated in utero and selection criteria for fetal surgery. *Prenat Diagn* 2009; 29(5): 457-63.
3. Torpin R. Amniochorionic mesoblastic fibrous strings and amniotic bands: associated constricting fetal malformations or fetal death. *Am J Obstet Gynecol* 1965; 91: 65-75.
4. Streeter GL. Focal deficiencies in fetal tissues and their relation to intrauterine amputation. *Contrib Embriol Carnegie Ins* 1930; 22: 1.
5. Robin N, Franklin J, Prucka S, et al. Clefting, amniotic bands, and polydactyly: a distinct phenotype that supports an intrinsic

- mechanism for amniotic band sequence. *Am J Med Genet* 2005; 137A(3): 298-301.
6. Kino Y. Clinical and experimental studies of the congenital constriction band syndrome, with an emphasis on its etiology. *J Bone Joint surg* 1975; 57A: 636-42.
7. Daya M, Makakole M. Congenital vascular anomalies in amniotic band syndrome of the limbs. *J of Pediatr Surg* 2011; 46: 507-13.
8. Werler M, Bosco J, Shapira S. Maternal vasoactive exposure, amniotic bands, and terminal transverse limb defects. *Birth Defects Res A Clin Mol Teratol* 2009; 85(1): 52-7.
9. Hunter AG, Seaver LH, Stevenson RE. Limb-body wall defect. Is there a defensible hypothesis and can it explain all the associated anomalies? *Am J Med Genet Part A* 2011; 155: 2045-59.
10. Seidman JD, Abbondanzo SL, Watkin, et al. Amniotic band syndrome. *Arch Path Lab Med* 1989; 113: 891-7.
11. Garza A, Cordero JF, Mulinare J. Epidemiology of the early amnion rupture spectrum of defects. *Am J Dis Child* 1988; 142(5): 541-4.
12. Orioli I, Ribeiro M, Castilla E. Clinical and epidemiological studies of amniotic deformity, adhesion, and mutilation (ADAM) sequence in a South American (ECLAMC) population. *Am J Med Genet* 2003; 118A(2): 135-45.
13. Werler M, Louik C, Mitchell A. Epidemiologic analysis of maternal factors and amniotic band defects. *Birth Defects Res A Clin Mol Teratol* 2003; 67(1): 68-72.
14. Martínez-Frías ML. Epidemiological characteristics of amniotic band sequence and body Wall complex: are two different entities? *Am J Med Genet* 1997; 73(2): 176-9.
15. Davies B, Giménez-Scherer JA, Hernández-Sierra JF. Fetal amniotic adhesions. Their topographic concordance with regionally clustered malformations. *Arch of Med Res* 2001; 32(1): 48-61.
16. Soldado F, Aguirre M, Peiró JL, et al. Fetoscopic release of extremity amniotic bands with risk of amputation. *J Pediatr Orthop* 2009; 29(3): 290-3.
17. Grewal J, Carmichael JL, Yang W, et al. Paternal Age and Congenital Malformation in Offspring in California 1989-2002. *Matern Child Health J* 2012; 16: 385-92.
18. INEGI. Estadísticas de educación. 2001.
19. Jamsheer A, Materna-kiryluk A, Badura-Stronka M, et al. Comparative study of clinical characteristics of amniotic rupture sequence with and without body wall defect: further evidence for separation. *Birth Defects Res A Clin Mol Teratol* 2009; 85: 211-5.
20. Chen Ch. Syndromes, disorders and maternal risk factors associated with neural tube defects (III). *Taiwan J Obstet Gynecol* 2008; 47(2): 131-40.

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