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Major craniofacial defects: case series and prenatal diagnosis at the Instituto Nacional de Perinatología, Mexico

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ABSTRACT

Objective. To describe the prenatal diagnosis, characteristics, development, perinatal outcome, and final diagnosis of pregnancies complicated by fetuses with major craniofacial defects, at the Instituto Nacional de Perinatología, México, 1997-2008. **Material and methods.** A retrospective, descriptive study from January of 1997 to January 2008, analyzed 152 pregnancies complicated by fetuses with major craniofacial defects, diagnosed at the Department of Fetal Medicine of the National Institute of Perinatology. Data were obtained from patients clinical records. **Results.** The mean age was 28 ± 8 years, with the largest number of cases between 20 and 24. The mean gestational age at diagnosis was 27.5 ± 6.4 gestational weeks. The average termination of pregnancy was at 35 ± 5 gestational weeks. In 43.4% of cases there were no major structural defects associated with the facial defect. The most commonly associated structural alterations were cerebral, cardiac, and limb abnormalities. Karyotyping was performed in only 57 cases, and was abnormal in 25. **Conclusions.** Structural ultrasound should be performed on all pregnant women between weeks 18 and 24 for detection of major craniofacial defects. Where defects are found, a thorough review of other structures should be carried out to determine whether the defects are syndromic. A systematic and multidisciplinary approach is essential to providing the best care and appropriate advice to parents.

Key words. Fetal. Craniofacial. Lip. Palate. Defects.

Defectos craneofaciales mayores: serie de casos y diagnóstico prenatal en el Instituto Nacional de Perinatología

RESUMEN

Objetivo. *Describir el diagnóstico prenatal, características, evolución, resultado perinatal y diagnóstico final de embarazos complicados con fetos con defectos craneofaciales mayores, atendidos en el Instituto Nacional de Perinatología en el periodo 1997-2008.* ***Material y métodos.*** *Estudio retrospectivo descriptivo, de enero de 1997 a enero 2008, en el cual se analizaron 152 embarazos complicados con fetos con defectos craneofaciales mayores que llevaron su seguimiento en el Departamento de Medicina Materno-Fetal del Instituto Nacional de Perinatología. Los datos se obtuvieron de los expedientes clínicos de las pacientes.* ***Resultados.*** *El promedio de edad fue de 28 ± 8 años, con el mayor número de casos entre los 20 y 24 años. La edad promedio al diagnóstico de hendiduras faciales fue de 27.5 semanas ± 6.4. La interrupción del embarazo fue en promedio a la semana 35 ± 5. En 43.4% de los casos no se encontraron otros defectos estructurales mayores asociados al defecto facial. Las alteraciones estructurales con mayor frecuencia asociadas fueron las cerebrales y cardiacas y alteraciones de las extremidades. Sólo en 57 casos se realizó cariotipo y de éstos en 25 fue anormal.* ***Conclusiones.*** *El ultrasonido estructural debe realizarse a todas las embarazadas entre las semanas 18 a 24 para la detección de defectos craneofaciales mayores; en los casos que lo presenten se deberá realizar la revisión minuciosa del resto de las estructuras, ante la posibilidad de que se trate de un caso sindromático. El abordaje sistemático y multidisciplinario es fundamental para brindar la mejor atención y proporcionar la adecuada asesoría a la pareja.*

Palabras clave. *Fetal. Craneofacial. Labio. Paladar. Defectos.*

INTRODUCTION

In Mexico, facial defects are in many cases discovered only at birth, which heightens the emotional impact on parents who expect a healthy newborn. In this country, where prenatal diagnosis is still not available to the entire population, there is an incidence of 1.39 defects for every 1,000 live births.[1]

Facial defects are the most frequent birth defects, and among these the most common are cleft lip and palate.[1,2] These have a significant impact on morbidity and mortality, quality of life, and the family economy, as there is still a lack of specialized, multidisciplinary perinatal attention in Mexico.

The craniofacial region is very complex, considering all types of specialized tissues and structures including, neural, sensory, respiratory, masticatory system, and in general the vascular, skeletal, muscular, endocrine and integumentary systems, and therefore it is possible to find a wide range of developmental abnormalities, these may be classified as malformations, disruptions and deformations.[3]

Craniofacial malformations constitute a comparatively rare combination of conditions occurring with varying degrees of severity in a multitude of patterns.[3, 27-29]

A craniofacial cleft is a partial or total defect of any part of the cranial area or of the face. It can occur in unilateral or bilateral form, and frequently causes serious alterations in physical appearance and structural function. The degree of severity runs from a small hollow in the skin, hair loss, or almond-shaped eyes, to clefts of the nose, lip, and palate, to absence of the nose or face.[4] The type and severity of the clefts are also related to the stage of development when the disruption occurred.[5, 29]

In 1984, Benacerraf, *et al*. recommended routine facial examination as part of the prenatal structural ultrasound, particularly in patients with risk factors such as family history of facial clefts, or exposure to teratogens or infections.[5,6]

The majority of congenital facial defects are established during the first 12 weeks of gestation.[2,6-8] The face is formed from the paraxial mesoderm, deriving from the frontonasal, maxillary, and mandibular prominences. These form the primary palate, which will develop into the lip and anterior palate. The palatal plates form the secondary palate, which will form the hard and soft palates, and these are fused with the primary palate in the ninth week.[2,9,11] The complex embryology of the face allows for a wide variety of potential disruptions to these vulnerable tissues during embryonic development, and a flaw in fusion during any of the processes involved can lead to facial clefts. The exact mechanism of development of facial clefts is unknown, but they are believed to have a multifactorial etiology involving a combination of environmental and genetic causes in a critical period of embryonic development. A number of genes involved in the development of cleft lip and palate have been identified, including TBX22, IRF6, and PVRL1,[5,9,10] as have teratogens including radiation, infections including toxoplasmosis, and deficiencies in folic acid and vitamin A.[10]

Although from the embryological perspective facial clefts are of distinct types, it is useful to study them in a global manner, owing to their anatomical location and their low frequency. In 1981, the American Cleft Palate-Craniofacial Association grouped them into 5 categories in order to facilitate a general overview and understand the etiology, evaluation, and treatment of the majority of craniofacial defects. Facial clefts form part of type I, and include encephaloceles and dysostosis.[7-9] In 1976, Tessier proposed an anatomical classification, assigning a number to each malformation according to its position in relation to the median plane.[4,5,12] Van der Meulen, *et al*. devised a classification of facial clefts, using the term "focal dysplasia", based on embryological events in the formation of the face.[7] In 1995, Nyberg, *et al.*, also classified them into 5 types, taking the lip and palate as a reference. Other classifications of facial clefts are based on the surgical approach to repair of facial defects.[13]

Cleft lip can be unilateral or bilateral, and also be accompanied by unilateral or bilateral cleft palate, and cleft palate can occur with the lip intact. Facial clefts are also classified as syndromic, when associated with other facial defects, and non-syndromic, when they occur in isolation. More than 350 syndromes associated with facial clefts have been described, among which the most frequently reported are disruptive processes like amniotic band syndrome, malformations like holoprosencephaly, and chromosomal and monogenic alterations, like trisomies 13, 18, and 21 and Van der Woude syndrome, among others. Other anomalies most frequently associated with major craniofacial clefts are alterations in the extremities, cardiac anomalies, and central nervous system anomalies.[2,17-19,22]

Structural ultrasound in the second trimester has significantly increased the prenatal diagnosis of major craniofacial defects and associated defects, with highly variable detection rates that range from 5% for isolated cleft palate to 91% for cleft lip and palate with associated anomalies. Although ultrasound

has the disadvantage of low sensitivity, it has a very high specificity.[7,16,20]

MATERIAL AND METHODS

A descriptive study was carried out from January 1998 to January 2008 in the Research Unit of the Department of Fetal Medicine at the Instituto Nacional de Perinatología in Mexico City. The study included all pregnancies with a diagnosis of craniofacial defects in the fetus, with prenatal diagnosis, with or without associated anomalies (in accordance with Nyberg's classification),[14] and which were established as syndromic or non-syndromic.

The study describes demographic characteristics, risk factors, first- or second-level ultrasound diagnoses, associated anomalies, complementary prenatal studies, and postnatal diagnoses; also grouped according to the Tessier classification.

It uses descriptive statistics, with appropriate measurements of central tendency and dispersion for each variable.

RESULTS

One hundred fifty-two pregnancies with fetal and neonatal diagnosis of major craniofacial defects, specified either isolated or with associated structural defects, were analyzed from among the clinical records of patients during the period, January 1998 to January 2008 at the Instituto Nacional de Perinatología "Isidro Espinosa de los Reyes" in Mexico City.

The average age of the patients at the time of pregnancy was 28 ± 8 years, most cases were between 20 and 24 years, and an average of 2 previous pregnancies. Ninety percent of the patients had no family history of structural defects, and only 4.6% had a history of cleft lip and palate without providing more details. There were cases of exposure to teratogens, 2.7% had a history of anticonvulsant use, and one patient presented with a history of inhalant substance abuse during the first trimester of pregnancy.

Eleven patients had pregnancy-related pathologies: four were diagnosed with pregestational diabetes mellitus, another four with gestational diabetes mellitus, two with epilepsy with intake of anticonvulsants, and one with thyroid disease.

The mean gestational age at diagnosis was 27.5 ± 6.4 gestational weeks, ranging from 13.5 to 39 weeks at ultrasound diagnosis (Figure 1).

A single case was diagnosed by ultrasound in first trimester of pregnancy (0.7%), 45.3% (69/152) in the second trimester, and 54% (82/152) in the third trimester. Karyotyping was performed on only 57 patients. In 19 cases it was abnormal, with numerical as well as structural alterations; the remaining cases were normal (Table 1).

In 43.4% (66/152) of the cases no major structural defects associated with the facial clefts were found, whereas 56.6% (86/152) had one or more associated defects. The associated structural alterations were cerebral (41.4%), cardiac (13.8%), limb abnormalities (27.6%), and other abnormalities (17.2%). Large facial clefts at the level of the nose and eyes always occurred with cleft lip and/or

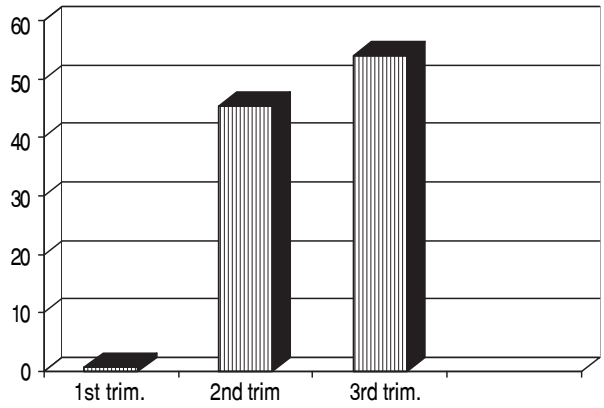

Figure 1. Time of prenatal diagnosis of craniofacial defect.

Table 1. Karyotypes in fetuses and/or neonates with facial cleft.

Karyotype	Number	Percent (%)
45, XX, der (18;21)(q10;q10)	1	0.7
46, XX t:13:14	1	0.7
46, XX izq +	1	0.7
46, XX, t 13; 13 der	1	0.7
46, XX, 9qh+	1	0.7
46, XX normal	21	13.8
46, XY T13:14 inv9+13	1	0.7
46, XY 1qh	1	0.7
46, XY 22p+	1	0.7
46, XY, add(9)(p24)	1	0.7
46, XY +13	1	0.7
46, XY normal	11	7.2
46, XY qh+	1	0.7
47, XX +13	4	2.6
47, XX +18	3	2.0
47, XY +13	2	1.3
47, XY +18	3	2.0
69, XXY	1	0.7
Trisomy 11/Monosomy 18	1	0.7
Not performed	95	62.5
Total	152	100

palate. No isolated nasal or ocular clefts were reported.

The average gestational age at birth was 35 ± 5 gestational weeks, ranging from 17 to 41.5 gestational weeks. Births occurred before week 28 in 12.5% (19/152) of the cases, in weeks 28-31.6 in 9.2% (14/152), in weeks 32-36 in 20.4% (31/152), and after 36 weeks in the remaining 57.9% (88/152) of the cases.

Pregnancy was resolved by cesarean section in 53.9% (82/152) of the cases, by normal delivery in 40.1% (61/152), by complicated delivery in 5.3% (8/152), and by induced abortion in 0.7% (1/152). The most frequent indication for interruption of pregnancy was onset of labor, in 26.1%.

The children born were 51.3% (78/152) female and 48.7% (74/152) male. Birth weight was 1,000-1,999 g in 22.4% (34/152) of the cases, 2,000-2,999 g in 38.8% (59/152), and 3,000-3,999 g in 22.4% (34/152). The remaining 16.4% were less than 1,000 g or more than 4,000 g.

Live births occurred in 54.6% (83/152) of the cases, while 25.7% (39/152) were stillborn and 19.7% (30/152) were early neonatal deaths (Figure 2). The average hospital stay was 9.2 days, and all of the newborns were sent upon birth to pediatric hospitals for evaluation and scheduling of corrective surgery.

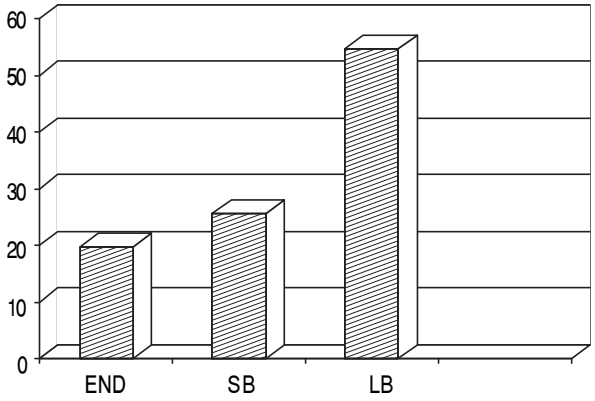

Figure 2. Mortality of fetus and newborns with facial clefts. END: early neonatal deaths. SB: stillbirths. LB: live births.

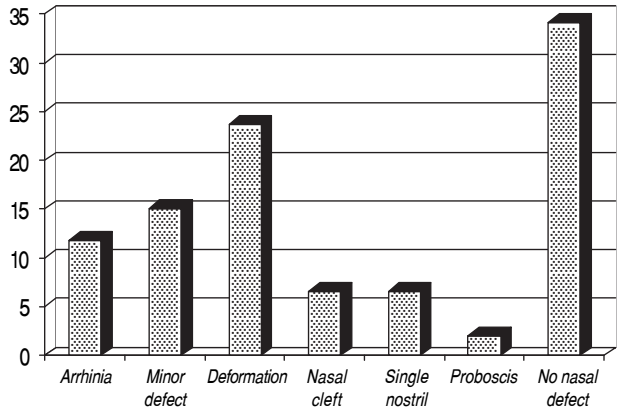

Figure 3. Nasal defects in craniofacial clefts.

Among the craniofacial defects found in eyes and orbits, 55.2% (84/152) of newborns had no ocular defects, 21.1% (32/152) had a major defect (cyclopia, anophthalmia, microphthalmia, agenesis of orbits), 21.1% (32/152) had a minor defect (hypotelorism, hypertelorism, oblique palpebral fissures, telecanthus), and only 2.6% (4/152) presented orbital clefts, all of them by amniotic bands.

Among nasal defects, 11.8% (18/152) of the cases presented with arrhinia, 2% (3/152) with the presence of a proboscis, 6.6% (10/152) with a single nostril, 6.6% (10/152) with nasal clefts, 23.7% (36/152) with nasal deformity caused by cleft lip and/or palate, 15.1% (23/152) with minor nasal defects (flat nasal bridge, wide base, anteverted nostrils, etc.), and 34.2% (52/152) with no nasal defects. The premaxilla was absent in 26.3% of the cases (40/152), deformed in 2% (3/152), and present without alteration in 71.7% (109/152) (Figure 3).

An intact lip was found in 15.8% of the cases (24/152), bilateral cleft lip in 15.8% (24/152), central cleft lip in 21.1% (32/152), left cleft lip in 19.1% (29/152), right cleft lip in 16.4% (25/152), and cleft lip with unspecified location in 11.8% (18/152). Cases with palate defects included 23.6% with central cleft palate (36/152), 21.7% with bilateral cleft palate (33/152), 13.2% with right cleft palate (20/152), 12.5% with left cleft palate (19/152), and 21.1% with cleft palate with unspecified location (32/152). There were no palate defects in 7.9% (12/152) of the cases (Figure 4). Retrognathia was reported in 13.2% (20/152), retromicrognathia in 4.6% (7/152), micrognathia in 1.97% (3/152), and normal in 80.2% of the cases. No mandibular clefts were reported (Figures 4-6).[5,6]

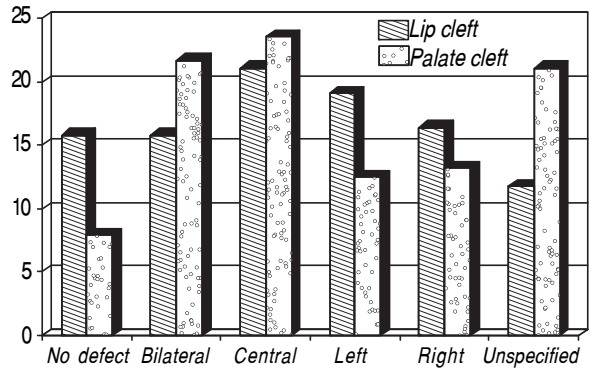

***Figure 4.** Frequency of cleft lip and/or palate (phenotype).*

The final diagnoses (Table 1) were as follows: isolated cleft lip and palate, 40.1% (61/152); not found any central defect in isolated cases. Amniotic band syndrome, 16.4% (25/152); holoprosencephaly, 9.9% (15/152) of these cases, 4 were semilobar form and facial defects found were bilateral cleft lip and palate in two cases and central in the other two. Eleven were alobar form with central facial defects in three cases; with premaxillary agenesis, three cases with central cleft palate and five cases with central cleft lip and palate; chromosome abnormalities 12.5% (19/152) suspected chromosome abnormalities where no karyotyping was performed, 3.3% (5/152); and diabetic embryopathy diagnosed by exclusion, 5.3% (8/152). The remaining cases were genetic syndromes, associations, and other non-specified aggregated defects (Table 2). A total of 23% (35/152) gave permission for autopsies; none of these resulted in findings distinct from the final diagnosis.

Because the information was obtained from medical records, we have no detailed description of facial clefts to establish Tessier's classification in each case, however the most of cases are unilateral or bilateral Tessier 1-3, in cases of orbital/ocular clefts by amniotic bands are rated Tessier 1,4, 5,11.

Table 2. Final diagnoses in neonates with major craniofacial defect.

Postnatal diagnosis	Number	Percent
Acrania	1	0.7
Vaterh association	2	1.3
Diabetic embryopathy	8	5.3
Disruptive event resulting from substance abuse	1	0.7
Holoprosencephaly	15	9.9
Isolated cleft lip and palate	61	40.1
Partial monosomy c9/partial trisomy c6 resulting from unbalanced translocation	1	0.7
Omphalocele	2	1.3
Charge syndrome	1	0.7
PB chromosome abnormality	5	3.3
Sx cardiofacial	3	2
Hydrolethalus	2	1.3
Sx Stickler	1	0.7
Amniotic band sequence	25	16.4
Pierre robin sequence	1	0.7
Sx Bixler	1	0.7
Sx short rib-polydactyly	1	0.7
Sx van der woude	1	0.7
Sx Walker warburg	1	0.7
Triploid syndrome	1	0.7
Trisomy 13 resulting from unbalanced translocation	4	2.6
Regular trisomy 13	6	3.9
Trisomy 18 resulting from unbalanced translocation	2	1.3
Regular trisomy 18	5	3.3
Trisomy 21 resulting from unbalanced translocation	1	0.7
Total	152	100

DISCUSSION

The Instituto Nacional de Perinatología is a national referral center, so the prevalence of facial defects found there does not reflect their prevalence in

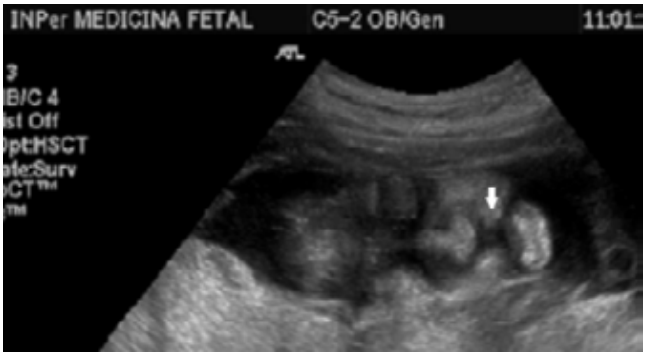

Figure 5. Central lip and palate defect (arrow) face coronal view.

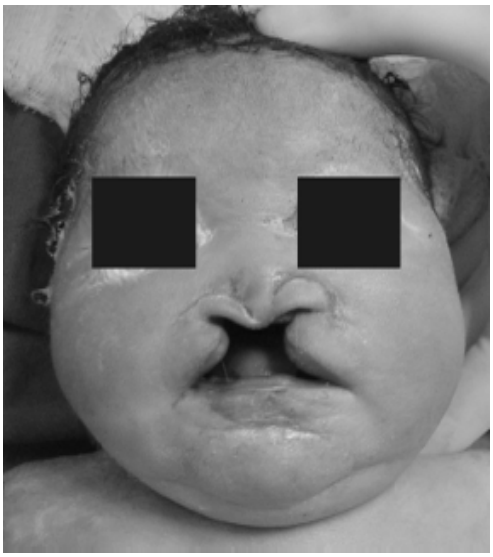

Figure 6. Central lip and palate defect. Postnatal view.

the general population. Because facial clefts are a multifactorial congenital defect, their incidence and prevalence undergo minimal modification with the passage of time.[3] Maternal age at birth is not a risk factor for facial clefts. In this study, the average was 27.74 ± 7.52 years, with the largest number of observed cases between 20 and 24 years. These data concur with previous reports; in spite of an increased risk in patients younger than 20 or older than 39 years, the greatest incidence is found in those between 20 and 30 years of age, given the greater frequency of pregnancy in this age range. The number of prior pregnancies has not been observed to be a risk factor for facial clefts, and this study has a high incidence of first-time pregnancies. Among the cases in this study, 4.6% had a first-degree relative with cleft lip and palate. Only two cases were found of patients with cleft lip and palate, and one with cleft uvula, the most minor defect in the wide spectrum of facial clefts. A total of 84.2% reported using no drugs or medications during the first trimester. Anticonvulsant medications that affect the metabolism of folic acid may interfere with normal development of the face. Although a clear association has been established between folic acid deficiency and neural tube defects, it has been shown that a mutation in the methylenetetrahydrofolate reductase (MTHFR) gene can increase the risk of having a child with cleft lip and palate by a factor of up to 4.6.[1-4,6,9] Five cases were reported of patients with a history of anticonvulsant use. Nonsteroidal anti-inflammatory drugs (NSAIDs) have a significant association with disruptive vascular processes, suggesting the possibility of a pathophysiological relationship between the use of these drugs and the incidence of facial clefts. In this group of patients there were none who reported use of NSAIDs or of vitamin A or its derivatives, which have also been implicated in the formation of these defects.

The most frequently observed concomitant maternal pathology was pregestational or gestational diabetes mellitus, observed in 5.9% of the cases. The embryotoxicity of hyperglycemia in the early embryonic period has been amply demonstrated, which explains the large incidence of facial and cranial alterations in the children of diabetic mothers. The relation between facial clefts and environmental factors like alcohol and tobacco use has not been fully demonstrated. Some studies have found a relative risk between 1.3 and 1.5 for cleft lip and palate, but the toxic effect depends directly on the quantity of tobacco inhaled, as well as the factor of concomitant heavy alcohol use. Relative risks ranging from 1.5 to 4.7 have been reported for cleft lip and palate, depending on the quantity of alcohol consumed. Low levels of alcohol consumption have not successfully been related to facial clefts. In this study, only two patients reported tobacco addiction, one of whom was also an alcoholic who used antidepressive medications during the first trimester.[2,9,13]

A slightly higher frequency of facial clefts was observed in female fetuses than in males. This point, however, remains controversial: several studies report a higher incidence of cleft lip in females and cleft palate in males, but cleft lip and palate is generally more common than isolated cleft palate. Our findings are therefore similar to what has been reported in the literature.

The average gestational age at diagnosis was 27.5 ± 6.4 weeks, somewhat later than that specified in the international literature, where the majority of cases were diagnosed prior to week 24 of the second trimester. This could be perhaps be explained by the fact that not all of our patients seek prenatal care in the earliest stages of pregnancy, and also that some who were screened for structural defects in their communities experienced a delay in referral.

The timing and mode of birth was related to fetal prognosis, based principally on the structural defects presented, as well as related genetic and chromosomal abnormalities. Facial clefts in themselves do not contraindicate vaginal birth. However, associated anomalies, including macrocrania, some encephaloceles, and cardiopathy with hydrops, may require cesarean section.

Weight at birth showed no differences from that of the general population. Newborns with isolated cleft lip and palate showed no increased restriction of intrauterine growth. Differences in birth weight of patients with chromosomal abnormalities were the result of the genetic defect as such and not a secondary effect of the facial cleft. The mean weight observed in this study was 2303 ± 725 g, although if we consider solely cases of isolated facial defect the average weight was 3,050 ± 115 g.

There was significant mortality of newborns with facial clefts in this study, owing to the presence of many cases with major associated defects. The prognosis depends primarily on the presence and type of associated defects, which points to the diagnosis of chromosomal abnormalities or genetic syndromes,[27] as well as the seriousness of the defect itself.

The most common facial defect in this study was unilateral cleft lip and palate, found in 28.2% of the cases, which accords with the report of Perrotin, *et al.* The next most common was central cleft lip and

palate, in 19.1% of the cases, which was more often related to genetic syndromes and diabetic embryopathy.[7,13]

Facial clefts of the nose and orbits were extremely rare, in accordance with the international literature. In this study, all such defects were concomitant with cleft lip and palate; 6.6% of the cases presented a nasal cleft and 2.4% an oro-ocular cleft.

Karyotyping was performed on 57 patients with two or more major structural defects to rule out numerical or structural chromosomal abnormalities. In this study only 12.5% of cases were found to be chromosomal abnormalities associated with facial defects, a figure that represents less than half of that reported by Perrontin, *et al.* and Offerdal, *et al.*; these authors report frequencies of up to 37%. It is important to point out that cytogenetic analysis could not be carried out on 5 patients with postnatal diagnosis of probable chromosomal disorders; ideally, karyotyping would have been performed in these cases, since the phenotypic alterations that suggest chromosomal abnormalities may not be present.[7,15]

The frequency of associated defects, that is, of syndromic cleft lip and palate, has been reported at 37-45%. In this study the frequency of isolated cleft lip and palate was 44.1%, and that of syndromic facial clefts was 55.9%. This difference can be explained by the greater frequency with which cases with major structural defects are referred to the Institute,

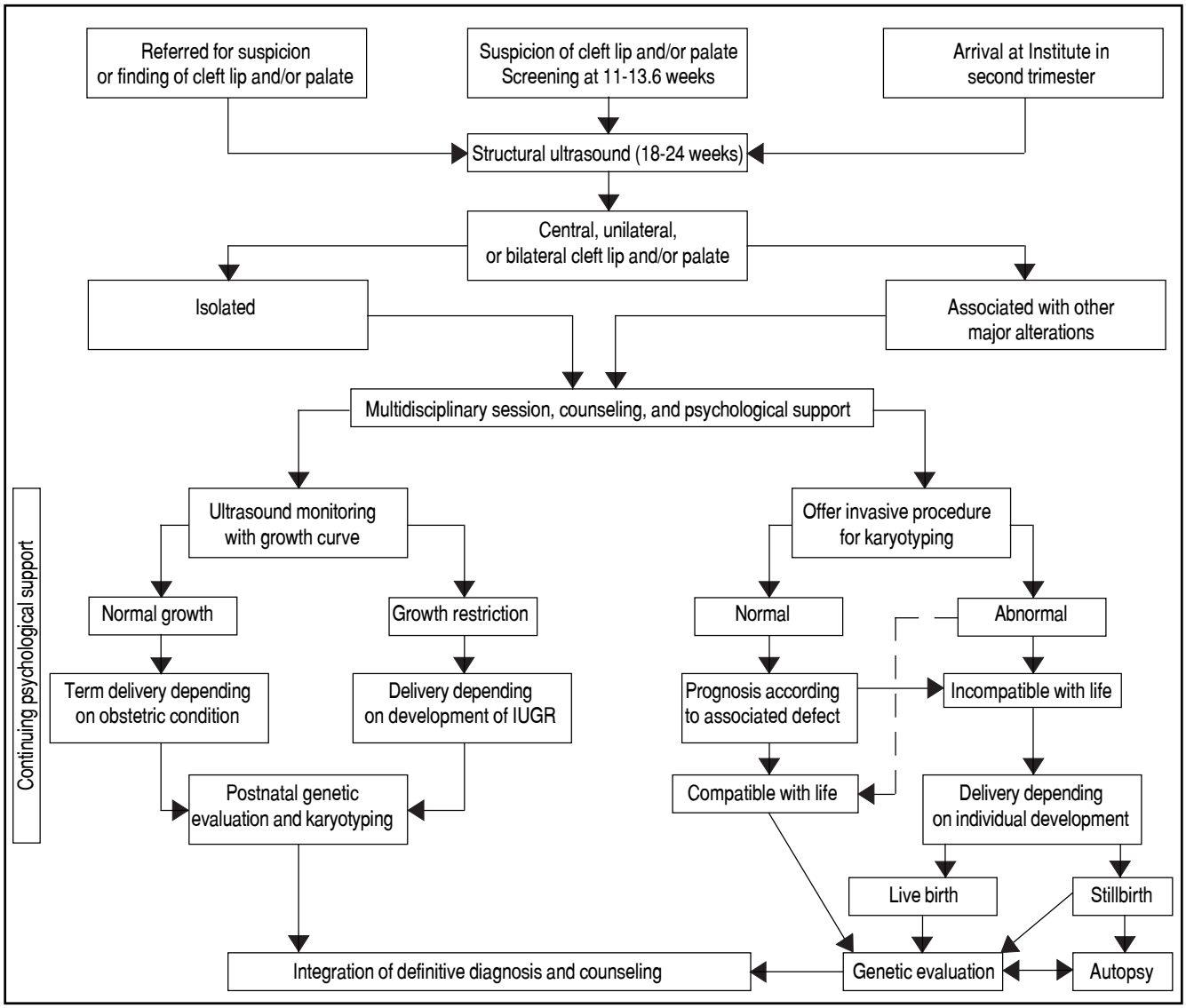

Figure 7. Diagnostic flowchart for cleft lip and/or palate (Fetal Medicine Department).

in comparison with those with isolated facial defects.[15,16]

CONCLUSIONS

Facial defects continue to present a public health problem in our country, owing to deficiencies in prenatal diagnosis, postnatal management, and surgical treatments. A child born with a facial defect needs an average of at least 4 surgeries in order to establish functionality. In Mexico there is insufficient interdisciplinary attention to address the needs of all of those with facial defects.[1] The great majority of our population has no access to prenatal ultrasound evaluation that permits fetal diagnosis and early prenatal treatment.

There are specific risk factors that can help with diagnosis, among them uncontrolled diabetes mellitus and medications that interfere with the metabolism of folic acid. It is important to emphasize that environmental factors that are increasingly common among women, like smoking, alcoholism, and drug addiction, have been associated with the presence of facial defects at birth.[9,26,28]

As there are more than 350 known syndromes associated with different patterns of facial clefts, it is always advisable to perform tests like karyotyping on patients with associated structural defects, as well as an examination by a geneticist at birth.[22,23,25] In the case of isolated facial clefts, mortality is comparable to that of the general population, since the defect poses no specific risk to the life of the newborn, but in the case of syndromic craniofacial defects, mortality depends on the structural or chromosomal abnormalities involved. The most common of these are cardiac and central nervous system defects and their specific diagnosis will determine the prognosis. The presence of chromosomal abnormalities is a determining factor; apart from the structural defects they cause, the most commonly associated ones, like trisomies 13 and 18, are fatal.[3,4,12,15]

Postnatal genetic counseling is of vital importance for these patients, as the risk of recurrence can be up to 6% in those with isolated defects and higher in cases associated with unbalanced chromosomal rearrangements and genetic syndromes. Identification of these factors permits counseling regarding the specific risks in future pregnancies, according to the type of inheritance (autosomal dominant or recessive, X-linked). Genetic evaluation at birth, as well as complementary testing such as karyotyping, molecular studies, and autopsy, need to be made available; we must use all available diagnostic tools to obtain the maximum information possible and provide better care for both current and future pregnancies.

Structural ultrasound should be routinely performed on all mothers in the second trimester of pregnancy with the aim of increasing not only the detection of craniofacial defects, but also the entire range of structural defects detectable at this gestational age. Once a diagnosis has been made, subsequent tests should be carried out to establish the prognosis, to decide on the advisability of invasive complementary tests, to determine the timing and the appropriate mode of birth and to establish the possible postnatal management. In our country there are specialist centers for the care of these babies (Figure 7).[30]

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