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CASE REPORT

Partial trisomy 9: prenatal diagnosis and recurrence within same family

Jana López-Félix[1,†], Leticia Flores-Gallegos[1,†], Luz Garduño-Zarazúa[2], Teresa Leis-Márquez[1], Luz Juárez-García[1], Ricardo Meléndez-Hernández[2], Ernesto Castelazo-Morales[3] & Dora Mayén-Molina[2]

[1]Clínica Materno-Fetal, Hospital Angeles Lomas, Huixquilucan, México
[2]Genetics Clinic, Hospital Angeles Lomas, Huixquilucan, México
[3]Centro Especializado para la Atención de la Mujer, Hospital Angeles Lomas, Huixquilucan, Mexico

Correspondence
Dora Mayén-Molina
Genetics Clinic, Hospital Ángeles Lomas
Av. Vialidad de la Barranca s/n, PB, Col. Valle de las Palmas
Huixquilucan, Estado de México 52787. MEXICO
Tel/fax: +52 55 5246 9610
E-mail: dgmayen32@gmail.com

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[†]Both authors contributed equally to the article.

Key Clinical Message

Trisomy 9 can be suspected and confirmed in the prenatal period since the 11–13.6 weeks of screening. In cases of partial trisomy 9, the diagnosis is important especially to counseling the couple due to the increased likelihood of recurrence in subsequent pregnancies.

Keywords

Partial trisomy 9 first-trimester diagnosis.

What is already known about this topic?

Prenatal diagnosis of complete and partial trisomy 9 is rare and is usually made after second trimester of pregnancy due to severe malformations, especially in the central nervous system.

What does this study add?

Trisomy 9 can be suspected and confirmed since the 11–13.6 weeks of pregnancy through the first-trimester scan screening, providing the parents with complete information, and an early genetic counseling.

Introduction

Trisomy 9 (T9) is a rare chromosomic anomaly with multiple malformations [1]. Sonographic suspicion during the first and second trimesters is uncommon due to high lethality rate of the disease.

Clinical reports mention multiple and severe malformations primarily occurring in the central nervous system, heart, kidneys, and limbs (Table 1). Prenatal growth restriction, postnatal mental retardation, and early mortality are also reported [1–6].

Cytogenetically, all trisomies can be classified either as *full* (complete) or *partial* [7, 8]. A full trisomy is when an extra chromosome in all cells is found. A partial trisomy is the presence of an additional chromosomic

Table 1. Sonographic findings in trisomy 9.

Organ/system	Alteration
Skull/head	Abnormal morphology ("strawberry shape"), brachycephaly, dolichocephaly.
Central nervous system	Ventriculomegaly Vermis hypoplasia Megacisterna magna
Face	Dismorphic Hypotelorism Microphthalmia Micrognathia
Neck	Edema
Thorax	Thoracic narrowing Pleural effusion Pericardial effusion Diaphragmatic hernia
Heart	Septal defects Hypoplasia Thickened muscle wall
Abdomen	Ascites Echogenic bowel
Kidneys	Policystic kidneys Dysplasia Hydronephrosis
Limbs	Bilateral clubfoot Clenched hands Overlaying fingers
Other findings	Single umbilical artery Reversed ductus venous Short femur Oligohydramnios

fragment (usually as the result of gamete segregation patterns from a balanced carrier but could also be de novo) [8]. If there are two or more cellular lines in one individual (usually one with normal number of chromosomes), *somatic mosaicism* is present and the expression of the phenotype relies on the different chromosomic complement and the number of cellular lines that are affected [9, 10.]

The majority of full and partial T9 end in spontaneous abortion. Clinical reports of partial T9 that show second- and third-trimester survival and postnatal outcomes have usually a variable amount of extra genetic material that correlates with the severity of the malformations or the phenotype [11–17]. We present the familiar case of a couple with two subsequent pregnancies affected by partial T9.

Case Report

A 28-year-old woman arrived to the maternal fetal clinic in order to perform a first-trimester combined screening

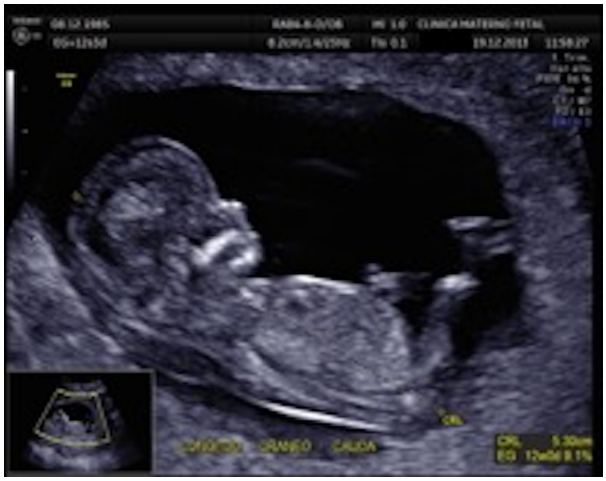

Figure 1. Crown-rump length (CRL).

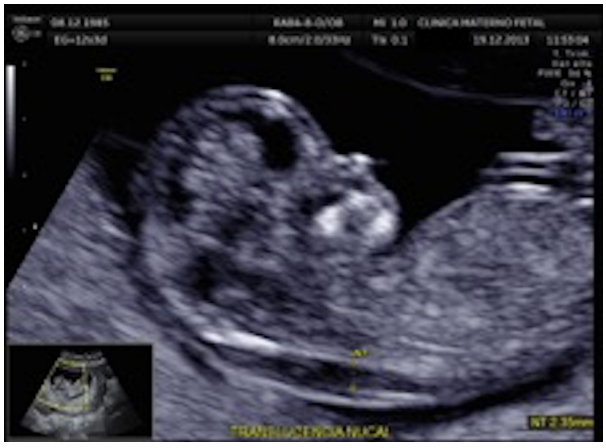

Figure 2. Nuchal translucency.

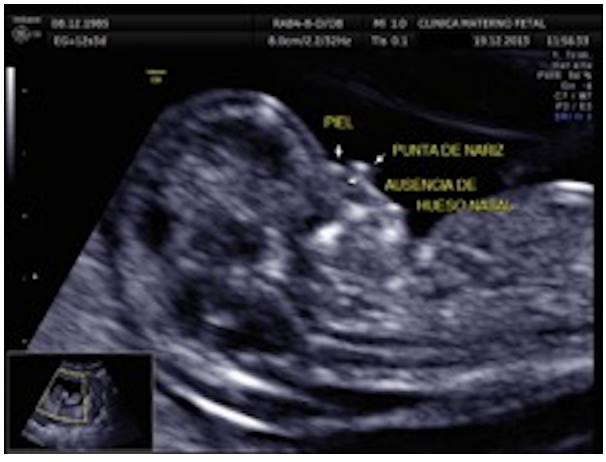

Figure 3. Absence of nasal bone.

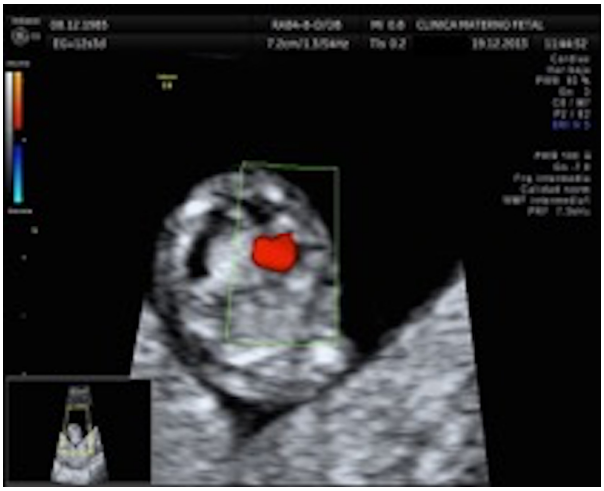

Figure 4. Axial thoracic section with pleural effusion.

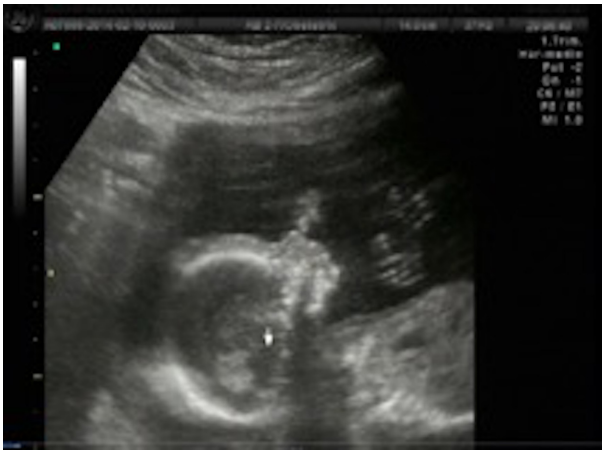

Figure 6. Fetal profile at 20 weeks with absent nasal bone.

at 12.3 weeks. Sonographic findings were as follows: crown-rump length (CRL) of 53 mm according with gestational age (Fig. 1), nuchal translucency of 2.35 mm (Fig. 2), normal ductus venosus, absent nasal bone (Fig. 3), and left pleural effusion (Fig. 4). The biochemical markers showed PAPP-A 2.97 mIU/mL (1.07 MoM) and free β hCG 15.3 ng/mL (0.36 MoM). The first-trimester risk calculation program Fetal Test® (Dr. Domingo J. Ramos-Corpas, Spain) showed a high risk for trisomy 18 with a 1 in 234 risk (established cutoff is 1/250).

A second ultrasound was performed at 15.1 weeks of gestation with sonographic findings of CRL of 77.6 mm, (which accorded to 13.6 gestational weeks) and no pleural effusion. Amniocentesis was performed at 17.4 weeks by last menstrual period (LMP) with a *GTG banding conventional karyotype* result of 47,XX,+der(9)(pter→?q32) in 25 cells from four primary cultures (Fig. 5). A third ultrasound at 20 gestational weeks by LPM showed a fetus of 18 weeks with absent nasal bone (Fig. 6), thickness and dilatation of right cardiac walls (Fig. 7), echogenic focus in left ventricle, and "claw-like" hands (Fig. 8). After the karyotype results, pregnancy termination was decided by the couple and they refused pathological anatomy analysis.

The family's past medical history only revealed childhood seizures of the mother and maternal uncle with

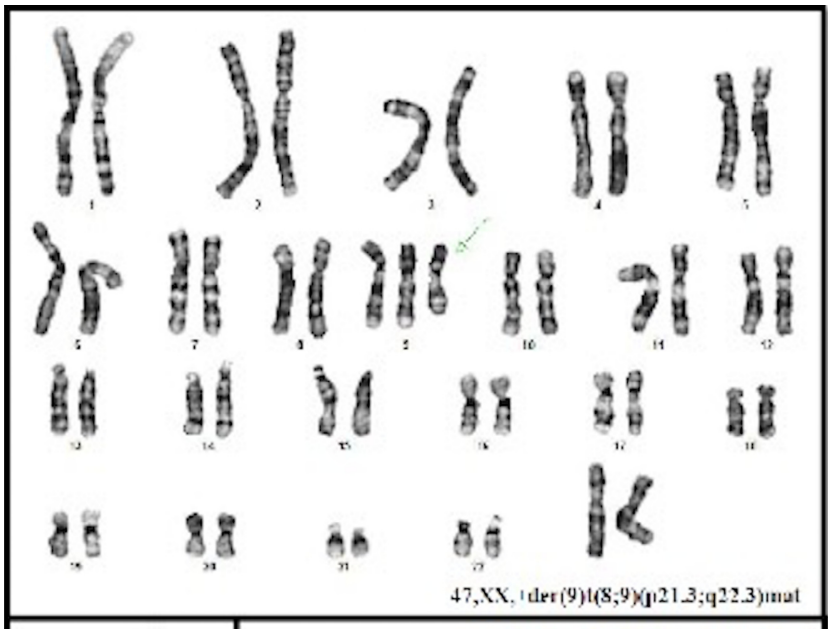

Figure 5. GTG banding conventional karyotype result of 47,XX,+der(9)(pter→?q32) in 25 cells from four primary cultures.

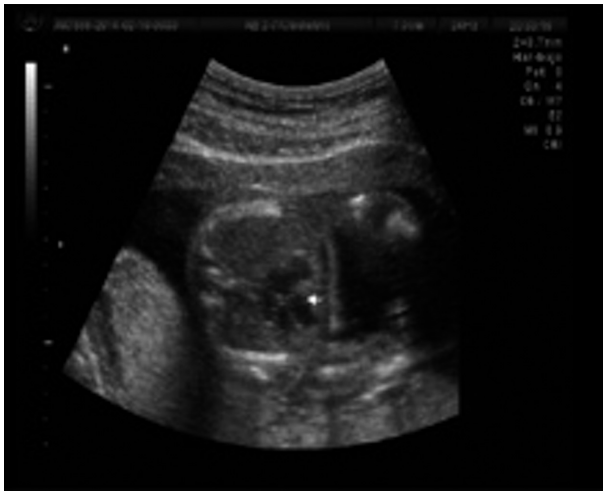

Figure 7. Thoracic axial view with right ventriculum wall thickening and dilation.

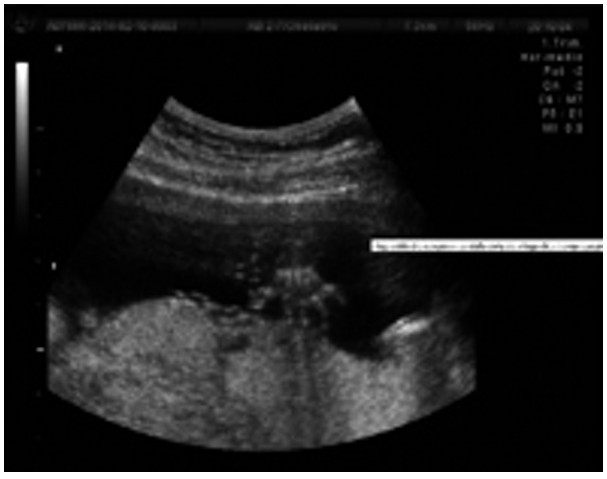

Figure 8. Hand "claw-like".

successful oral treatment. Parents received genetic counseling during the follow-up period. A karyotype analysis in the blood sample from both parents was performed:

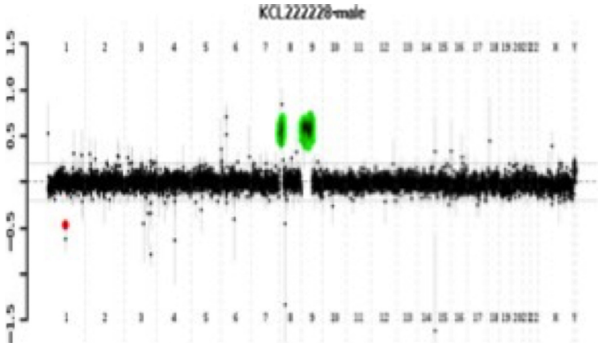

Figure 10. Whole genome summary. Green dots represent copy number gains in chromosomes 8 and 9. Red dot represents copy number losses that in this specific case was a polymorphism.

father's karyotype resulted 46,XY, and the mother's karyotype revealed a reciprocal balanced translocation 46,XX, t(8;9) (p21.3;q22.3) (Fig. 9A and B).

During their second pregnancy, chromosomal microarray analysis (CMA) was performed in chorionic villus sample (CVS) at the eleventh week of pregnancy (Fig. 10). The result revealed multiple copy number gains including approximately 25.837 Mb of the distal short arm of chromosome 8 (8p), and approximately 88.745 Mb of chromosome 9, from 9pter to 9q21.33. No increased blocks of region of heterozygosity (ROH) suggestive of uniparental disomy (UPD) were detected. Termination of pregnancy was decided.

Case Review

The literature search in major databases was performed looking for articles reporting on prenatal diagnosis of trisomy 9 (either complete or partial). Few case reports as well as a recompilation of nine cases within a 12-year period were found [7].

According to these reports, partial trisomy 9 was only found in five cases [15, 18–21], all of them during second and third trimesters (Table 2).

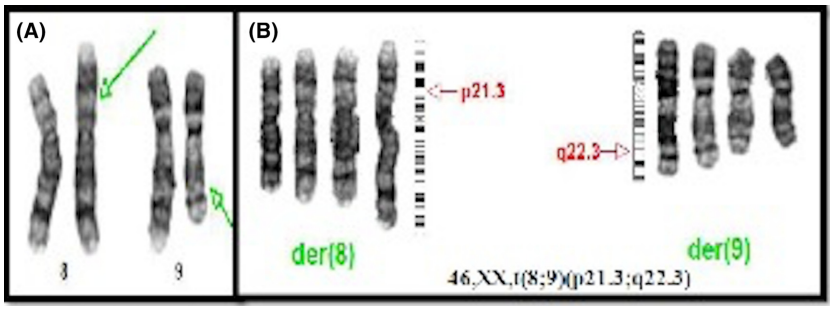

Figure 9. (A and B) Mother karyotype with balanced translocation between chromosomes 8 and 9.

Table 2. Prenatal diagnosis of partial trisomy 9 in the literature research.

Author/Year	Karyotype	Fetal scan (weeks)	Prenatal findings	Postnatal findings
Sherer (1993) [18]	47,XX+i(9p)	23	Twin pregnancy: One fetus with abnormal cerebellum, echogenic kidneys, bilateral clubfoot, cleft palate.	Corpus callosum and cerebellar vermis agenesis. Died 1 week after.
Chen (1999) [19]	Trisomy 9p with Trisomy 21p (Amniocentesis at 17 weeks by amniocentesis for familial chromosomal translocation)	24	Bilateral ventriculomegaly, wide cisterna magna, intrauterine growth restriction.	Pregnancy termination. Microcephaly, short stature, hypertelorism and low-set ears.
Von Kaisenberg (2000) [15]	47,XX,+der(9)t(7;9) (q35;q22.2)	23	Cerebellar vermis hypoplasia, wide cisterna magna, bilateral ventriculomegaly	Pregnancy termination Mother Translocation (7;9)(q35;q22.2).
Hengstschläger (2002) [20]	Trisomy 9p with trisomy 10p	18	Facial cleft, clubfoot, abnormal cerebellum, kidney cysts.	Pregnancy termination at 18th week of gestation Postmortem examination: nose anomalies (snout-like), bilateral cleft lip palate, low set ears, club feet, lung anomalies, cystic kidney and aplasia of the uterus
Chen (2002) [21]	Trisomy 9p with distal deletion of 12p (Amniocentesis at 17 weeks for a 5-year-old daughter with trisomy 9p)	20	Bilateral ventriculomegaly, brachycephaly, Dandy Walker malformation with enlarged cisterna magna and absence of the cerebellar vermis.	Pregnancy termination Mother balanced translocation
López (Present case)	47,XX+der(9)t(8;9)(p21.3;q22.3)mat (Amniocentesis at 17 weeks by ultrasound findings)	12.3	Nuchal translucency 2.35 mm, absent nasal bone, pleural effusion, early growth restriction, "claw-like" hands, heart malformations	Pregnancy interruption. Mother balanced translocation 46,XXt(8;9)(p21.3;q22.3)

Discussion

Partial or full trisomy 9 (T9) is a rare chromosomal alteration. Its high lethality and very low prevalence make prenatal and postnatal diagnosis difficult. Few medical reports can be found in the literature and its suspicion usually raises during second and third trimesters when the severe malformations (detected by ultrasound) precede diagnostic procedures. Technology advances in fetal ultrasound allow an earlier diagnosis of severe structural malformations and suspicion of chromosomal aberrations during the first trimester with combined screening. Findings in previous reports of full trisomy 9 during the first trimester are only nuchal translucency over 3 mm and abnormal reverse ductus venosus wave, which are not really specific of trisomy 9 [7, 22]. Second- and third-trimester findings are malformations in different organs with particular attention to central nervous system, heart, and limbs [23].

Our case was detected at the 12th week of gestational age, with altered sonographic findings as absent nasal bone, abnormal reverse ductus venosus wave, pleural effusion, and nuchal translucency of 2.35 mm (above 95 percentile for CRL). Three weeks after initial appearance, pleural effusion was not visualized, but early growth restriction could be documented. Combined first-trimester screening aims for physical and biochemical search for the most common aneuploidies (T21, T18, and T13). Rare chromosomal alterations such as trisomy 9 are not usually part of the screening program. There are some clinical reports where biochemical abnormal values result positive for trisomy 18 (T18) due to very low quantity of PAPP-A and free β-hCG, suggesting the suspicion not only for trisomy 18, but also for trisomy 9 when these values are decreased [24–26]. In our case, even though the values of PAPP-A were normal, free β-hCG was decreased and the global calculation result was *high risk* for trisomy 18, as reported in the literature.

There are few case reports in medical literature of partial trisomy 9. And only five reports were made in prenatal period (Table 1). All of them are reported in the second and third trimesters of pregnancy, and the earlier gestational age reported was 17 weeks. Our case had similar malformations as those reported in the literature, but they were detected in the first trimester (12th week) by sonographic and biochemical findings in the first

pregnancy, and the second pregnancy was affected by the same chromosomic alteration due to the same 3:1 segregation pattern.

The breaking point in 9q21.3 represents a big amount of genes/material in chromosome 9 (64.12%), and sonographic findings showed a similar phenotype as complete trisomy 9. Only two other articles with similar breaking points were found in newborn babies. In both reports, maternal translocations between chromosomes 1 and 9 with 3:1 segregation patterns were found. The karyotypes were t(1,9)(p36;q22)mat and t(1;9)(q41;q21.32)mat. These phenotypes were similar to partial trisomy 9 with few different characteristics due to the presence of chromosome 1 material. Five additional cases of carrier mothers of chromosomal rearrangements in 9q21-22 with an estimate of 23% risk of unbalanced products by a 3:1 segregation pattern exist. This risk and segregation pattern can be applied to our case because the second pregnancy was also affected by partial trisomy 9 [27–29].

Conclusions

Complete and partial trisomy 9 are a rare chromosomal alteration with high lethality rates. Uncommon pathologies can be now detected in earlier stages of pregnancy due to technologic advances in prenatal care allowing us to understand natural history of rare and lethal diseases.

There are no specific sonographic findings for trisomy 9 in the first trimester, but the suspicion of a chromosomic alteration by abnormal nuchal translucency, absent nasal bone, altered reverse ductus venosus wave, and pleural effusion, along with low values of PAPP-A and β-hCG, can be considered suspects not only for trisomy 18, but also for trisomy 9. Trisomy 9 can also be suspected in the second trimester, primarily when sonographic findings consist of malformations of the central nervous system and abnormal limbs' postures. Parents' karyotype is mandatory for a precise genetic counseling.

Conflict of Interest

All authors declare that they have no conflict of interest in relation to this work.

Authorship

JLF: took part in maternal–fetal medicine, bibliographic research, and first-trimester ultrasound scan detecting anomaly. LFG: participated in bibliographic research and first-trimester ultrasound scan detecting anomaly. LGZ: performed cytogenetic analysis of the couple and both pregnancies. LJG: involved in second ultrasound scan and maternal–fetal medicine. RMH: performed cytogenetic analysis of the couple and both pregnancies. ECM: took part in Ob-gyn management in both pregnancies. DMM: Head of Genetic laboratory and Genetic Conuseling of the couple.

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