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Inherited Treacher-Collins Syndrome in Twins After Artificial Insemination

Hermann F. Sailer, MD, DMD
Renato Josca, MD, DMD

Zurich, Switzerland

We present two cases of the Treacher-Collins syndrome and one case of plagiocephalus in a trigeminus childbirth resulting from artificial insemination. The mother, although affected with the Treacher-Collins syndrome, was not diagnosed before the birth of her children. Genetic counseling did not occur. Medical and forensic problems resulting from modern techniques of reproduction are briefly discussed.

Key Words: Fertilization procedures, craniofacial anomalies, Treacher-Collins syndrome

Mandibulofacial dysostosis is a rare congenital malformation involving structures derived from the first and second pharyngeal arch. The syndrome was first observed by Berry [1], and was later described in detail by Collins [2] and by Franceschetti and Klein [3]. It is transmitted by autosomal dominant inheritance with variable characteristics. It may occur by either spontaneous or induced mutation. In its complete form, patients display the following typical traits. The face is narrow with a receding chin. There are tongue-shaped processes of hair that grow toward the cheeks. The palpebral fissures appear antimongoloid, and in 75% of patients, there is a coloboma of the outer one third of the lower eyelids. The lower lacrimal puncta are absent; the malar bone may be totally absent or hypoplastic. The lateral pterygoid plates of the sphenoid bone and the pterygoid muscles are hypoplastic. The external, middle, and inner ear are malformed, and the mastoid bones are not pneumatized. The paranasal sinuses may be absent or underdeveloped. In the mouth, macrostomia, cleft palate, and velopharyngeal incompetence may be observed.

We report on a pair of twins with Treacher-Collins syndrome, born as triplets with a third infant with plagiocephaly conceived by artificial insemination.

Department of Cranio-Maxillofacial Surgery, University Hospital, Zurich, Switzerland.

Address correspondence to Dr Sailer, Department of Cranio-Maxillofacial Surgery, University Hospital, Zurich, Switzerland.

Family History

A 33-year-old woman, unknowingly a carrier of Treacher-Collins syndrome, visited her obstetrician because of inability to conceive. Gynecologic, hysterographic, and ultrasound examinations revealed a slight infantilism of the ovaries, closure of the right fallopian tube, and the presence of a uterine leiomyoma. A decision was made to surgically remove the leiomyoma and to artificially inseminate the woman as a combined procedure.

To facilitate the ovulation process, the woman was treated with clomifene for a period of 4 menstrual cycles. On the 18th day of the fourth cycle, the leiomyoma, which measured 8 cm by 2 cm, was removed laparoscopically. At the same time, two ovules were taken and the artificial insemination process was performed. During the resulting pregnancy, the woman was observed with regular sonograms and chromosomal diagrams.

The course of the pregnancy was difficult and ended prematurely with eutocic delivery of triplets at the end of the seventh month. Two of the newborns showed clear signs of Treacher-Collins syndrome; the third had plagiocephalia (Fig 1).

Mother's Symptoms

There were clear manifestations of Treacher-Collins syndrome, such as antimongoloid lid axes and bilateral hypoplasia of the zygomatic bones with zygomatic arches present. Both lower eyelids had colobomas in the area between the lateral and medial third of the lid. Exophthalmus was present but mild. Evaluation of the mother's hearing was normal (Fig 2). Both ears had normal size but showed disfigurations.

Symptoms of Trigeminus No. 1, Male

The cranial circumference was 44 cm, and the zygomatic bones were markedly hypoplastic bilaterally. The eyes showed antimongoloid lid axes (especially on the left side) plus a small coloboma of the left lower lid between the middle and lateral third. Both external ears were rudimentary, with no visible external auditory canals. There were no signs of micromandibulism, macrostoma, or cleft palate

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Fig 1 Two of the triplets with Treacher-Collins syndrome (middle and right) and the third with plagiocephalia (left).



Fig 2 The mother shows all signs of Treacher-Collins syndrome, especially the hypoplastic zygomatic complexes and disfigurement of the auricles, which have otherwise normal size.

(Fig 3). At 2 months, acoustic tests revealed cochlea response to bone conduction bilaterally. Computed tomographic (CT) scans demonstrated middle ear aplasia bilaterally, although the semicircular canals, the vestibule, and the cochleas were visible on the CT scan. A diagnosis of Treacher-Collins syndrome was made.

Treatment Plan

A hearing aid is necessary, and the child should be sent to a school for hearing-impaired individuals. Artificial auricles



Fig 3 This child presented with a severe form of Treacher-Collins syndrome with hypoplastic cheek bones, coloboma of the lower left eyelid, and rudimentary auricles on both sides.

supported by osteointegrated implants could be inserted at the age of 8 or 10 years. Prior to attending school, the hypoplastic zygomatic complex should be corrected by lyophilized cartilage onlays [4–6]. Mandibular growth should be observed; if growth impairment occurs, functional orthodontic treatment and possibly mandibular advancement may be indicated.

Symptoms of Trigeminus No. 2, Female

Symptoms were less pronounced than in trigeminus no. 1. The cranial circumference was 44 cm. A hemangioma was present on the left side of the neck. Antimongoloid lid axes were obvious, as was a coloboma of both lower eyelids. Bilateral hypoplasia of the auricular helix exists, and there is a pronounced microgenia. The CT scan demonstrates normal middle ear structures (Fig 4). A diagnosis of Treacher-Collins syndrome plus a hemangioma of the left side of the neck was made.

Treatment Plan

Audiological examinations should be performed at frequent intervals. The hemangioma should not be treated but observed because spontaneous regression most often occurs. The hypoplastic zygomatic complex can be treated



A B

Fig 4 This child shows a milder degree of the syndrome, with hypoplastic zygomatic bones and colobomas of the lower eyelids (A) and ear deformities (B); in addition, there is a cavernous hemangioma present on the left submandibular area (B).

by lyophilized cartilage onlay grafts prior to school admission. Mandibular growth should be stimulated by functional orthodontic treatment during mixed dentition.

Symptoms of Trigeminus No. 3, Female

The cranial circumference was 41.8 cm. The right frontal region was slightly flat; the left showed some bassing. The fontanelles were open, and the eyelids were normal with a normal lid axis.

After birth, this infant suffered from coxofemoral arthritis caused by a *Klebsiella* and *Proteus* infection, which, according to her parents, was treated by local application of antibiotics and immobilization with a cast. The precise origin of the infection was never established. A diagnosis of plagiocephalus was made.

Discussion

Artificial insemination, ovular transfer, and similar procedures are currently routine when conception problems exist. In a literature survey, we found another situation describing a fetal abnormality (Goldenhar syndrome) in one triplet after in vitro fertilization [7]. There is worldwide agreement that these fetal abnormalities are uncommon: less than 1% [8]. Sonographic diagnosis of mandibulofacial dysostosis is possible during midtrimester [9].

Our patients are unique in 2 ways. It is the first time that siblings with Treacher-Collins syndrome were born after artificial insemination. Also, this technique was performed in a parent with typical signs of Treacher-Collins unrecognized by the carrier of the syndrome and by the gynecologist performing the procedure. This oversight compromises the value and necessity of reproduction medicine. Genetic counseling in addition to a close family history are advisable to avoid depending only on the clinical experience of one specialist. Also, forensic problems can be involved: The mother of the siblings insists that she would have never agreed to the fertilization procedure if she had been aware of being a carrier of the syndrome. During pregnancy, the mother was under observation with regular sonograms and chromosomal diagrams. The malformation was obviously not recognized despite the fact that one of the siblings had severe external ear hypoplasia. According to Crane and Beaver [8], Treacher-Collins syndrome can be diagnosed sonographically at midtrimester.

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