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Taiwanese Journal of Obstetrics & Gynecology 51 (2012) 271–275

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Case Report

Osteogenesis imperfecta type IV: Prenatal molecular diagnosis and genetic counseling in a pregnancy carried to full term with favorable outcome

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Accepted 17 February 2012

Abstract

Objective: To present molecular diagnosis and genetic counseling for osteogenesis imperfecta (OI) type IV in a pregnancy carried to term with favorable outcome.

Case Report: A 34-year-old, primigravid woman was referred for genetic counseling in the second trimester because of advanced maternal age and a positive family history of OI type IV. Her husband had a weight of 40 kg and a height of 145 cm. Her husband had normal sclerae, moderate short stature and osteopenia, and had sustained multiple fractures with minimal trauma since childhood. The husband and his relatives including his mother, aunt, uncle, sister and nephew had suffered from OI type IV. Molecular analysis of the affected individuals in the family revealed a G to T change at position c.2197 (c.2197G>T, GGT>TGT) of the exon 37 in the *COL1A2* gene leading to a change of glycine at codon 733 to cysteine (G733C). Cytogenetic analysis of cultured amniocytes revealed a karyotype of 46,XY. Molecular analysis of uncultured amniocytes revealed a missense mutation of G733C in *COL1A2*. Level II ultrasound at 23 weeks of gestation revealed significant shortness of the limbs. Small stature for gestation age was obvious in the third trimester. At 37 weeks of gestation, a fetal ultrasound showed curvature of the femurs. A cesarean section was performed at 38 weeks of gestation, and a male baby was delivered uneventfully. The baby had normal sclerae, a body weight of 2190 g (< 5th centile) and a body length of 46 cm (< 5th centile). X-rays showed thin clavicles and short curved femurs but no bony fractures. No fractures were noted at the age of 1 month.

Conclusion: The present case adds to previous examples of favorable outcome in pregnancies with non-lethal forms of OI.

Keywords: COL1A2; osteogenesis imperfecta type IV; pregnancy outcome; prenatal diagnosis

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1028-4559/$ - see front matter
doi:10.1016/j.tjog.2012.04.019

Introduction

Osteogenesis imperfecta (OI) is a genetic disorder of bone development caused by defective collagen synthesis that results in increased bone fragility, osteopenia and other connective-tissue manifestations such as blue sclerae, dentinogenesis imperfecta, hyperlaxity of ligaments and skin, and hearing loss [1,2]. The incidence of OI varies between 1:20,000 and 1:60,000 births, and maternal OI has been estimated to occur once in every 25,000–30,000 pregnancies [3,4].

Most patients with autosomal dominant OI have mutation in either *COL1A1* (OMIM 120150) or *COL1A2* (OMIM 120160). However, mutations in other genes such as *FKBP10* (OMIM 607063), *CRTAP* (OMIM 605497), *LEPRE1* (OMIM 610339), *PPIB* (OMIM 123841), *SERPINH2* (OMIM 600943), *SP7* (OMIM 606633) and *SERPINF1* (OMIM 172860) can also cause autosomal recessive OI.

OI type I to type IV have been inherited in an autosomal dominant pattern. OI type I (OMIM 166200) is caused by heterozygous mutation in *COL1A1*. OI type II (OMIM 166210), type III (OMIM 259420) and type IV (OMIM 166220) are caused by heterozygous mutation in either *COL1A1* or *COL1A2*. OI type V (OMIM 610967) is inherited in an autosomal dominant pattern, but the causative gene is unknown.

OI type VI to type XII have been inherited in an autosomal recessive pattern. OI type VI (OMIM 610968) can be caused by homozygous mutations in *FKBP10*, OI type VII (OMIM 610682) is caused by homozygous or compound heterozygous mutations in *CRTAP*, OI type VIII (OMIM 610915) is caused by homozygous or compound heterozygous mutations in *LEPRE1*, OI type IX (OMIM 259440) can be caused by homozygous mutations in *PPIB*, OI type X (OMIM 613848) can be caused by homozygous mutations in *SERPINH2*, OI type XI (OMIM 613849) can be caused by homozygous mutations in *SP7*, and OI type XII (OMIM 613982) can be caused by homozygous mutations in *SERPINF1*.

Currently, early prenatal diagnosis of OI in at-risk pregnancies is possible by preimplantation genetic diagnosis, chorionic villus sampling (CVS) or amniocentesis using molecular genetic techniques if the mutated gene has been identified in affected individuals in the family. Here, we report our experience of application of prenatal molecular genetic testing on uncultured amniocytes in the second trimester for prenatal diagnosis of OI type IV in a Taiwanese family. The parents elected to carry the pregnancy to term, and a male baby was delivered with mild OI and favorable outcome.

Case report

A 34-year-old, primigravid woman was referred for genetic counseling in the second trimester because of advanced maternal age and a positive family history of OI type IV. The woman had a body weight of 62 kg and a height of 162 cm, whereas, her husband had a weight of 40 kg and a height of 145 cm. Her husband had normal sclerae, moderate short stature and osteopenia, and had sustained multiple fractures with minimal trauma since childhood. The husband and his relatives including his mother (135 cm in height), aunt (130 cm), uncle (150 cm), sister (135 cm) and nephew had suffered from OI type IV. All had moderate short stature and white sclerae. Molecular analysis of the husband in the family revealed a G to T change at position c.2197 (c.2197G>T, GGT>TGT) of the exon 37 in the *COL1A2* gene leading to a change of glycine at codon 733 to cysteine (G733C) (Fig. 1). Prenatal ultrasound examination at 19 weeks of gestation revealed a fetus with no skeletal abnormalities and a biparietal diameter (BPD), an abdominal circumference (AC) and a femur length (FL) equivalent to 19 weeks. The woman underwent amniocentesis at 19 weeks of gestation. Cytogenetic analysis revealed a karyotype of 46,XY. Molecular analysis of uncultured amniocytes revealed a missense mutation of G733C in *COL1A2* (Fig. 1). Level II ultrasound at 23 weeks of gestation revealed significant shortness of the limbs with the measurements of the humerus of 3.67 cm (22 weeks),

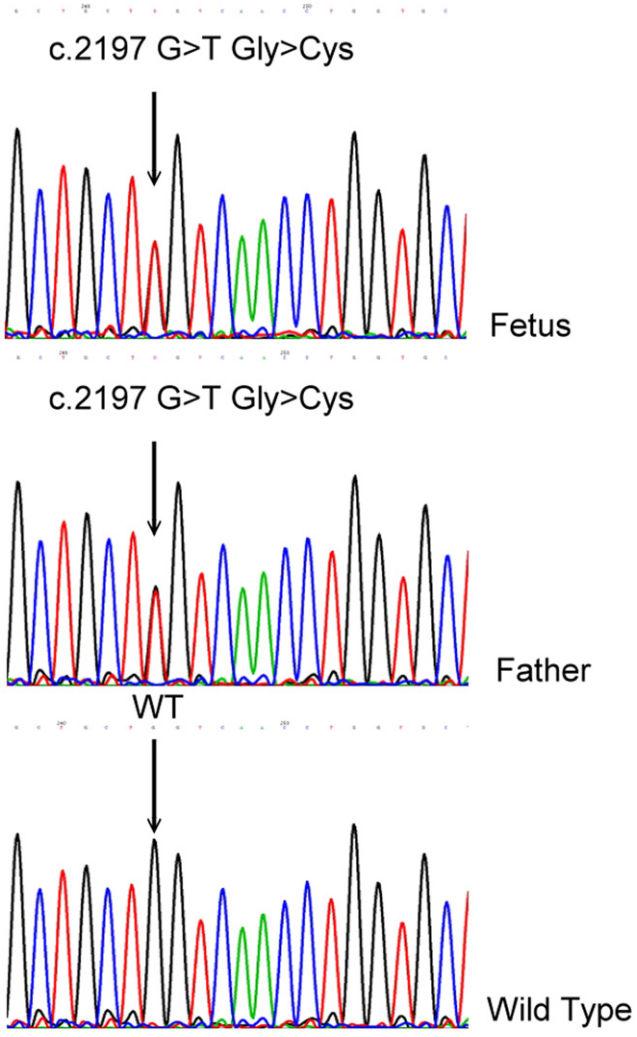

Fig. 1. Molecular analysis of the father and the fetus shows a G to T change at position c.2197 (c.2197G>T, GGT→TGT) of the exon 37 in the *COL1A2* gene leading to a change of glycine at codon 733 to cysteine (G733C).

radius of 3.0 cm (21 weeks), ulna of 3.08 cm (21 weeks), femur of 3.5 cm (21 weeks), tibia of 3.24 cm (21 weeks) and fibula of 3.13 cm (21 weeks). After genetic counseling of possible phenotypic variability in OI with the parents, the parents elected to carry the pregnancy to term. Small stature for gestation age was obvious in the third trimester. At 37 weeks of gestation, the fetal ultrasound showed a BPD of 8.6 cm (34 weeks), an AC of 29.7 cm (35 weeks), an FL of 5.8 cm (31 weeks), and curvature of the femurs (Fig. 2). A cesarean section was performed at 38 weeks of gestation, and a male baby was delivered uneventfully. The baby had normal sclerae, a body weight of 2190 g ($< 5^{th}$ centile), a body length of 46 cm ($< 5^{th}$ centile), a head circumference of 32.5 cm (5^{th} centile), and a chest circumference of 29.5 cm ($< 5^{th}$ centile). X-rays showed thin clavicles and short curved femurs but no bony fractures (Fig. 3). The baby was doing well, and no fractures were noted at the age of 1 month.

Discussion

OI is clinically and genetically heterogeneous with variable clinical features in different types ranging from nearly asymptomatic manifestations with normal stature and mild fractures to symptomatic manifestations with very short stature, severe skeletal deformities, multiple fractures and mobility impairment or worse, perinatal lethality. OI types I and IV are mild forms of OI caused by mutation in either *COL1A1* or *COL1A2*. OI type I is characterized by blue sclerae, normal height or mild short stature and a premature stop codon in *COL1A1*, whereas, OI type IV is characterized by moderately short stature, grayish or white sclerae, dentinogenesis imperfecta, adult-onset hearing loss and glycine substitutions in *COL1A1* or *COL1A2* [1,2]. In the present case the fetus and father had white sclerae, moderate short stature, a glycine substitution in *COL1A2* and OI type IV.

In the second trimester, only the severe and lethal forms of OI can be detected by ultrasound before 20 weeks of gestation. The mild forms of OI are usually detected in late gestation when skeletal deformities occur. The diagnosis of OI type I by ultrasound is difficult and is only rarely apparent due to femoral bowing [5]. The diagnosis of OI type IV is usually not apparent by ultrasound until after 20 weeks of gestation when femoral bowing and short limbs become obvious [5]. In cases of mild forms of familial OI, early prenatal diagnosis is possible only through prenatal genetic testing by CVS or amniocentesis.

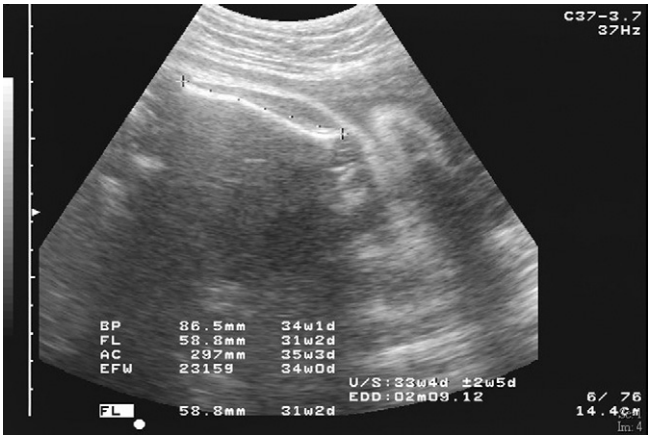

Fig. 2. Prenatal ultrasound at 37 weeks of gestation shows curvature of the femur.

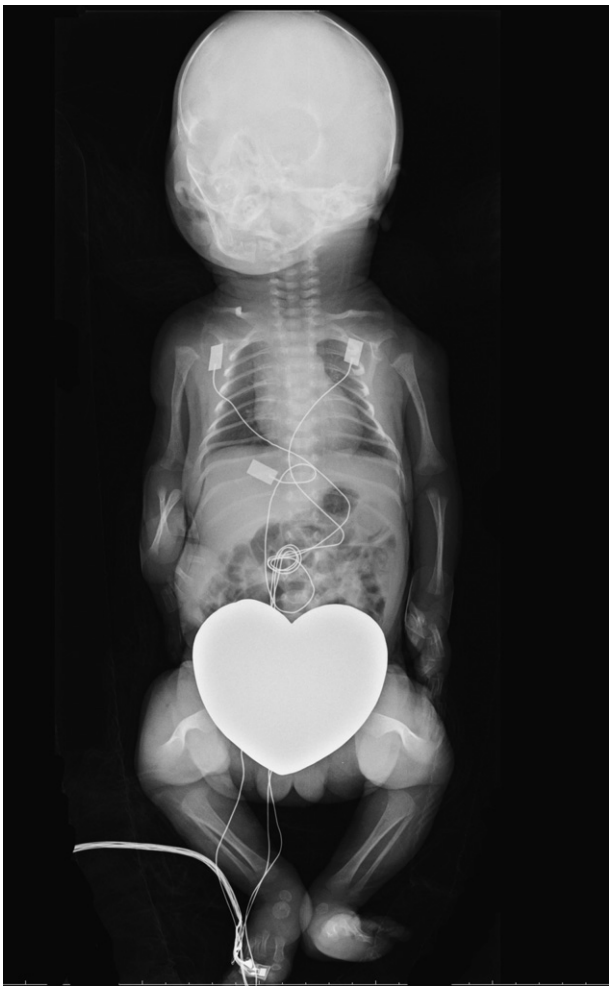

Fig. 3. Postnatal radiograph shows short curved femurs and thin clavicles but no bony fractures.

Clinical cases of prenatally detected OI carried to term have been reported. Phillips et al [6] reported the first prenatal diagnosis of OI type III with abnormal ultrasound findings suggestive of OI at 14.8 weeks of gestation and definitive ultrasound findings of OI at 17 weeks in a pregnancy with OI type III in the mother. The mother was 106 cm tall and had severe scoliosis, gray sclerae and severe bowing and shortening of the lower extremities. After genetic counseling, the parents elected to continue the pregnancy, and a baby was delivered at 34 weeks of gestation by cesarean section with a body weight of 1685 g ($35–50^{th}$ centile), a length of 37.5 cm (10^{th} centile), a head circumference of 30.5 cm ($25–50^{th}$ centile), a broad forehead, blue sclerae, a soft skull and bilaterally bowed extremities but no obvious fractures. Zolezzi et al [7] reported prenatal ultrasound diagnosis of short limbs and multiple fractures in a fetus at 25 weeks of gestation in

a pregnancy with familial OI type IV in the father and paternal grandmother. Termination of pregnancy was proposed by the obstetrician, but the parents elected to continue the pregnancy after genetic counseling and awareness of familial OI type IV. A splicing site mutation of IVS26+3 A>G was found in the *COL1A2* gene in the father and the paternal grandmother. The baby was delivered at term by cesarean section with a weight of 2240 g, a length of 39 cm, a head circumference of 32.4 cm, bowing lower limbs and talipes varus but no bony fractures. At the age of 6 months, the affected neonate was of short stature with brachycephaly, round face, and shortening and bowing limbs, but normal psychomotor development. In this case, there was intrafamilial clinical variability. The father was 156 cm tall, the paternal mother was 155 cm tall, and both presented only subtle clinical and radiological signs of OI. Ries et al [8] reported prenatal molecular diagnosis of a nonsense mutation of R848X in the *COL1A1* gene by CVS in a pregnancy because of familial OI type I and the previous aneuploidy of trisomy 18. The fetus was found to carry the same mutation as the affected father. After genetic counseling of possible phenotypic variability in OI with the parents, the parents elected to carry the pregnancy to term. A male baby was born at term in an uncomplicated delivery with a fractured clavicle, bowed right tibia and blue sclerae. No additional fractures were noted at 12 months of age. The father was 163 cm tall and manifested blue sclerae and shortening of the right leg due to poorly healed fracture and osteopenia. Chen et al [9] reported prenatal ultrasound diagnosis of shortening femurs at 28 weeks of gestation in a pregnancy with maternal OI type I. The mother was 148 cm tall and had blue sclerae, shortening of the legs as a result of old fractures, and a missense mutation of G844D in the *COL1A2* gene. The parents refused any prenatal molecular genetic diagnosis for OI and decided to carry the pregnancy to term. A cesarean section was performed at 37 weeks of gestation, and a 2358 g female baby was delivered uneventfully with a length of 47 cm, short curved femurs, blue sclerae, but no bony fractures. Molecular analysis showed that the baby had the same mutation as the mother. Coors and Townsend [10] reported prenatal ultrasound diagnosis of a fetus with multiple congenital fractures at 21 weeks of gestation consistent with the diagnosis of OI type II. Despite of genetic counseling of the lethality of OI type II and a recommendation of vaginal delivery for the fetus, the woman elected to carry the pregnancy to term and chose cesarean delivery. The baby survived for only several days, and X-rays confirmed the severity of OI. The mother felt that she had done everything appropriate for her infant. Robyr et al [11] reported prenatal ultrasound diagnosis of moderate bowing of the long bones in a pregnancy with paternal genu varum and kyphscoliosis. The pregnancy was carried to term with a baby having bowed femur and tibia. Parasuraman et al [4] reported prenatal ultrasound diagnosis of bowed right femur at 22 weeks of gestation and bowed left tibia at 23 weeks of gestation in a pregnancy with maternal OI type III. The mother decided to continue the pregnancy, and a 1708 g affected baby was delivered by elective cesarean section at 34 weeks of gestation.

Current practice of prenatal diagnosis and genetic counseling of familial OI should include more information based on genotype, phenotype, previous reports, prenatal ultrasound findings, intrafamilial variability, detailed family history and perspectives of treatment [9,12]. Mutation analysis of the family is important for genetic counseling of OI. In familial autosomal dominant OI, the recurrence risk for OI is estimated to be 50%. However, severe and lethal forms of OI may result from parental mosaicism for dominant mutations in *COL1A1* or *COL1A2* with intrafamilial variability and mild or no symptom in the parent [13,14]. Therefore, in cases of parental mosaicism, the recurrence risk for autosomal dominant OI is variable and may not be as high as 50%. In cases of lethal forms of OI, Pyott et al [15] suggested that in the absence of parental somatic mosaicism or recessive inheritance, the risk of recurrence is below 0.1%; in the presence of parental mosaicism, the risk of recurrence can be up to 50%; and in the presence of carriers of a recessive mutation in both parents, the risk of recurrence is 25%. In cases of unaffected parents with parental gonadal mosaicism, an empirical risk of recurrence risk ranges from 1% to 3% [12,16]. Recent advances in therapies with bisphosphonates, injection of human growth hormone and bone marrow transplantation have shed light on effective treatment of OI [2,17]. On the other hand, cesarean delivery may not protect against fractures in infants with OI, and obstetricians should reserve cesarean section for usual obstetric indications [18].

In summary, we present molecular diagnosis and genetic counseling of OI type IV in a pregnancy carried to term with favorable outcome. Our case adds to the examples of favorable outcome in pregnancies with non-lethal forms of OI.

Acknowledgments

This work was supported by research grants NSC-97-2314-B-195-006-MY3 and NSC-99-2628-B-195-001-MY3 from the National Science Council, and MMH-E-100-04 from Mackay Memorial Hospital, Taipei, Taiwan.

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