Elmer Press

Case Report

J Clin Gynecol Obstet. 2015;4(1):184-187

Maternal Genetic Skeletal Disorders: Lessons Learned From Cases of Maternal Osteogenesis Imperfecta and Fibrodysplasia Ossificans Progressiva

Rachel Shulman[a, d], Jane Ellis[a], Eileen Shore[b], Frederick S. Kaplan[c], Martina Badell[a]

Abstract

Due to advances in neonatal care, prenatal diagnostics, and artificial reproductive techniques, women affected by skeletal disorders now survive into their reproductive years, desire fertility, and become pregnant. Osteogenesis imperfecta (OI) is a disease of brittle bones prone to fracture and is one of the most common of the skeletal dysplasias. Fibrodysplasia ossificans progressiva (FOP) is a rare debilitating genetic condition characterized by congenital malformations of the great toes and progressive, disabling heterotopic ossification (HO) in which bone forms outside of the skeleton. Here we report two cases of viable pregnancies with severe maternal skeletal disorders. This is only the fourth reported case of a viable pregnancy in a woman with FOP. These cases highlight the complexity of caring for women during pregnancy affected by severe skeletal disorders, the formidable risks when these women become pregnancy, and how these high-risk pregnancies can be successfully managed by a collaborative multidisciplinary care team.

Keywords: Fibrodysplasia ossificans progressiva; Osteogenesis imperfecta; Skeletal dysplasia; Genetic skeletal disorders; Pregnancy

Introduction

There are 456 genetic skeletal disorders, which vary widely in their inheritance, severity, and underlying genetic, molecular, and biochemical basis [1]. Advances in medicine have led to improvements in neonatal care, prenatal diagnostics, and artificial reproductive techniques. With these advances, more women affected by skeletal disorders survive into their reproductive years, desire fertility, and become pregnant. These disorders often affect multiple organ systems, and thus have implications on pregnancy that must be recognized. Additionally, caring for these women requires a multidisciplinary approach with collaboration between perinatologists, obstetricians, pediatricians, anesthesiologists, orthopedists, geneticists and additional subspecialists such as intensive care physicians.

Osteogenesis imperfect (OI) is a disease of brittle bones prone to fracture and is the most common of the skeletal dysplasias. Manifestations of the disease include skeletal deformity, poor dentition, blue sclera, and hearing impairment. The overall prevalence is 6 - 7/100,000, and it affects 1/20,000 - 1/30,000 pregnant women [2, 3]. There are eight subtypes of OI, but types I - IV are the best defined. Most cases of OI have an autosomal dominant pattern of inheritance and more than 90% are attributable to defects in type I collagen structure as a result of mutations of the genes COL1A1 or COL1A2 [3].

Fibrodysplasia ossificans progressiva (FOP) is the most catastrophic disorder of heterotopic ossification (HO) in which bone forms outside of the skeleton causing extensive and lifelong disability. FOP has a prevalence of approximately 1/2 million births [4]. Most cases result from a spontaneous activating mutation of activin receptor 1A (ACVR1), a bone morphogenetic protein type I receptor [5-7]. However, autosomal dominant inheritance has been reported [8].

Here we report two cases: one case of maternal OI type III with severe disease and the rare case of a viable pregnancy in FOP.

Case Reports

Case 1: OI type III

A 28-year-old G2P0010 woman with OI type III was transferred to our care at 17 weeks 5 days gestation. Her obstetric history includes a termination due to findings on ultrasound highly suspicious for OI in the fetus. An ultrasound done at the time of her transfer revealed no evidence of fetal OI. She was counseled about her options by maternal fetal medicine

Manuscript accepted for publication February 02, 2015

[a]Department of Gynecology and Obstetrics, Emory University School of Medicine, 69 Jesse Hill Jr. Drive, S.E., Atlanta, GA 30303, USA
[b]Department of Orthopaedic Surgery and Genetics, The Perelman School of Medicine, University of Pennsylvania, 426A Stemmler Hall, 3450 Hamilton Walk, Philadelphia, PA 19104-6081, USA
[c]Department of Orthopaedic Surgery and Medicine, The Perelman School of Medicine, University of Pennsylvania, Penn Musculoskeletal Center Suite 600, 3737 Market Street, Philadelphia, PA 19104, USA
[d]Corresponding Author: Rachel Shulman, Department of Gynecology and Obstetrics, Emory University School of Medicine, 69 Jesse Hill Jr. Drive, S.E., Atlanta, GA 30303, USA. Email: Rachel.Shulman@emory.edu

doi: http://dx.doi.org/10.14740/jcgo306w

Articles © The authors | Journal compilation © J Clin Gynecol Obstet and Elmer Press Inc™ | www.jcgo.elmerpress.com
This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited

and decided to continue the pregnancy. The patient declined amniocentesis and had a normal serum screen for aneuploidy.

She measured 2 feet tall, weighed 27 kg, and was wheelchair bound with multiple lower extremity contractures, a history of multiple back surgeries, and restrictive lung disease. Consultations by neonatology, maternal fetal medicine, genetics, and anesthesia were completed. The plan of care was to follow the patient weekly and deliver via cesarean under general anesthesia due to her severe skeletal, vertebral, and pelvic deformities.

At 27 weeks gestation, she completed pulmonary function testing, which revealed obstructive lung disease as well as a component of restrictive lung disease. Repeat ultrasound was performed at that time and again revealed no evidence of fetal OI. At 34 weeks gestation, she presented to labor and delivery with severe shortness of breath and hypoxia. Bedside ultrasound revealed an infant in transverse, backup presentation. She underwent a low transverse cesarean delivery and tubal ligation following an awake endotracheal intubation secondary to respiratory compromise. Total blood loss was 450 mL. She delivered a 2,270 g female infant with Apgar scores of 8 and 9 at 1 and 5 min respectively. The patient was taken to recovery on the ventilator due to poor respiratory effort and low tidal volumes and was extubated later that afternoon. She was transferred to the postpartum unit in stable condition, and she and the infant were discharged home 4 days later. She was using oxygen by nasal cannula upon discharge.

The patient was readmitted on postoperative day 9 with respiratory distress and hypertension. She was intubated and started on a heparin drip and magnesium sulfate due to concerns for pulmonary embolism and pre-eclampsia respectively. A chest CT scan revealed right lower lobe pneumonia but was inconclusive for diagnosis of pulmonary embolism. An echocardiogram was normal, with an ejection fraction of 60% but with findings consistent with a pulmonary embolism. Blood and respiratory cultures were positive. Antibiotics were initiated, magnesium sulfate was discontinued when pre-eclampsia was excluded, and she was transitioned from a heparin drip to enoxaparin. She was extubated on hospital day 8 and discharged home on hospital day 13. She was doing well at her routine 6-week postpartum clinic visit.

Case 2: FOP

A 24-year-old G2P0010 woman with FOP was referred for prenatal management at 22 weeks gestation. She became pregnant despite preconception counseling of the possible serious risks to herself and her child, including a 50% risk of inheritance [9]. Her obstetric history includes a missed abortion treated with misoprostol.

She measured 5 feet tall and weighed 58 kg. She inherited FOP from her father and suffered multiple flare-ups during childhood leaving her with complete ankylosis of the neck, jaw, elbows, hips, and one wrist. Her ability to ambulate was limited due to severe kyphoscoliosis, and she required assistance with most activities of daily living. Ultrasound revealed normal fetal anatomy including normal toes. She was offered an amniocentesis for prenatal FOP testing; however, she declined. Alpha-fetal protein was elevated on a serum screen. She had prenatal consultations with anesthesiology and neonatology. An orthopedic surgeon from an outside institution with specific interest in and knowledge of FOP was contacted and consulted on the case.

At 25 weeks 4 days gestation, she presented in preterm labor. She was given tocolysis, a course of oral corticosteroids, and was monitored for 3 days. However, she continued to dilate and began bleeding. The decision was made to proceed with cesarean delivery for preterm labor with severe maternal skeletal dysplasia. She underwent awake fiberoptic nasotracheal intubation with precautions for emergent tracheostomy due to jaw deformities related to her underlying disease process. The cesarean and a bilateral tubal ligation were performed with a total blood loss of 2,800 mL. Her disease process had caused significant abnormalities in the tissue, making the surgery technically challenging. She received four units of packed red blood cells and two units of fresh frozen plasma for resuscitation and 3 days of intravenous solumedrol to prevent a flare-up of FOP [9]. She delivered a male infant weighing 760 g with Apgar scores of 1 and 8 at 1 and 5 min respectively who tested negative for FOP. His neonatal course was complicated by a bowel obstruction at 1 week of life requiring an ileostomy and subsequent takedown. He was discharged at approximately 5 months in good condition, but his mother's FOP significantly impaired her ability to care for him. At the 6-week postpartum clinic visit, she had no bone formation at her incision site.

Discussion

OI

OI is a disease characterized by brittle bones and frequent fractures with minimal trauma leading to skeletal deformities. Type I is the most common subtype, accounting for 60% of OI cases. It is also the mildest form. Type II, accounting for 20% of OI cases, is the most severe and is lethal. Type III is severe and progressive and accounts for 20% of OI cases. It can be a result of germ cell mosaicism in 6% of cases. Type IV is the least common and is intermediate in its severity [2]. Severe OI can lead to significant limb and spinal deformities, leading many of those affected by OI type III to be wheelchair bound by the time they reach adulthood. Only a third of those with OI type III will survive into their adult years [10].

Pregnancy in women with OI is complicated by the many associated conditions seen in those with this disease. Abnormal coagulation increases the risks of blood loss and hemorrhage during delivery. Heart muscle is made of type I collagen leading to an increased prevalence of cardiac abnormalities and congenital heart disease in individuals with OI. Collagen is imperative to wound healing, and this process can be impaired in individuals with OI [11]. Kyphoscoliosis and severe chest wall deformities may lead to cardiorespiratory complications as was the case in our patient [10]. Up to 35% of those with OI will have hypertension, and a small case series found a 20% rate of pre-eclampsia in pregnant women with OI. Due to immobility, women with OI are more likely to develop venous

thrombosis during the hyper-coagulable state of pregnancy. This complication occurred in our described case during the postpartum period. Severe back and musculoskeletal pain is common in pregnancies affected by maternal OI, with 13% having pain severe enough to disrupt their daily lives. Pregnancy does not increase the risk of fractures for individuals with OI [12].

Management of pregnancies affected by maternal OI poses several challenges to providers as well as to the mother and child. Primarily, it is important to determine if the fetus has the disease. Most forms of OI are inherited in an autosomal dominant pattern, and each child of an affected parent has a 50% risk of inheritance [13]. Diagnosis of fetal OI was historically performed using radiographs. Advances in ultrasonography now allow for severe fetal OI to be diagnosed prior to 20 weeks gestation on ultrasound. Ultrasound findings associated with fetal OI include increased nuchal translucency, decreased acoustic shadowing, bowing and shortening of long bones, and multiple fractures. Less severe forms of the disease, however, may go undetected on ultrasound [14]. Women with OI should be offered invasive fetal diagnostic testing for OI such as chorionic villi sampling or amniocentesis with analysis for mutations of COL1A1 on chromosome 16 or COL1A2 on chromosome seven [13]. Invasive diagnostic techniques have the highest yield when there is known to be a dominant inheritance pattern of OI in the family [14]. Our patient had a low risk ultrasound and refused invasive testing. She did receive a genetics, maternal-fetal-medicine, and neonatal consultation to assess and discuss the fetal risk of OI, implications of OI on the pregnancy and delivery, as well as risks to the fetus if he/she were to be affected. Antenatal care for women with OI includes serial growth scans, during which the fetus should be reassessed for development of fetal fractures [15].

Close collaboration for delivery planning with anesthesia is imperative. Spinal deformities can make obtaining regional anesthesia difficult if not impossible. Endotracheal anesthesia is complicated by risk of fracture to the jaw, cervical spine, and ribs [15]. Many women will require delayed extubation due to respiratory muscle weakness in the late phase of surgical anesthesia [11]. Additionally, malignant hyperthermia is more common in individuals with OI [12]. We obtained anesthesia consult early during our patient's antenatal care. This allowed the team to plan for an awake endotracheal intubation technique. The patient and family were also counseled on the risk of delayed extubation during this consult and therefore had appropriate expectations for her postoperative course.

Review of the literature suggests that cesarean delivery in cases of maternal OI should be reserved for usual maternal or fetal indications, though there are two reported cases of spontaneous uterine rupture complicating vaginal deliveries in women with OI [15]. Our decision to deliver via planned cesarean was made based on this woman's severe skeletal deformities and concerns for cephalopelvic disproportion given her stature, pelvic deformities, and body habitus. At the time of this patient's delivery, fetal malpresentation also impacted the decision to proceed via cesarean.

Other delivery complications in cases of maternal OI may include postpartum hemorrhage due to uterine atony and coagulation disorders, and oxytocin should be administered after the third stage of labor [10, 12]. There is also a reported increased risk of hernia formation after cesarean delivery in these women [12].

Postpartum, a radiograph should be performed to evaluate for new maternal fractures. Due to the increased risk of fractures from pregnancy-associated osteoporosis, breast feeding is relatively contraindicated in cases of maternal OI [15].

FOP

Individuals with FOP appear normal at birth except for characteristic malformations of the great toes. In childhood, painful, inflammatory swellings (flare-ups) transform soft connective tissues into heterotopic bone. Minor trauma, muscle fatigue, intramuscular immunizations, or influenza-like illnesses trigger painful flare-ups that lead to progressive HO in characteristic anatomic and temporal patterns. Most patients are wheelchair bound by their third decade and require lifelong assistance. Severe disability results in low reproductive fitness [4, 16]. The median survival is 41 years [17].

Pregnancy is perilous in FOP and poses a substantial life-threatening risk to mother and child [18]. Considering advances in medical care, it is likely that additional FOP patients will become pregnant. Major risks to the mother include the need for cesarean delivery due to pelvic deformities, joint fusion and decreased plasticity of the birth canal, breathing difficulties due to malformed costovertebral joints, and the inability to have regional anesthesia. Thepro-thrombotic state of pregnancy in combination with severe immobility in women with FOP may increase the risk of thromboembolic events in women with FOP during pregnancy. Therefore, it has been suggested to use low molecular weight heparin throughout pregnancy for prophylaxis in this population [18]. Major risks to the infant include preterm delivery, fetal distress, complications from general anesthesia, and 50% risk of inheritance [9, 18]. No full term pregnancy in a woman with FOP has ever been reported. In a recent case report of four pregnancies in women with FOP, two resulted in first trimester miscarriage, and the other two resulted in spontaneous preterm births [18]. Limited data suggest that women with FOP are at an increased risk for early spontaneous abortion due to ossification of the abdominal wall [18].

Premature birth has been reported in all documented cases of viable pregnancies affected by maternal FOP both due to spontaneous preterm and fetal distress necessitating iatrogenic preterm delivery. The cause of our patient's preterm delivery was premature labor for which the cause is unknown, but may be related to the underlying disease process [18, 19]. Traditionally, intramuscular steroids are given to patients in premature labor. Despite the lack of data supporting an oral regimen, we opted for this as FOP precluded intramuscular injections due to the risk of bone formation at the site of injection [9, 20]. More data are required to determine if oral corticosteroids are effective.

The case we describe illustrates a number of challenges associated with FOP during pregnancy, specifically related to delivery. The need for cesarean delivery and inability to give regional anesthesia poses a clinical dilemma particularly if the jaw is affected prohibiting routine oral intubation. This was

 Articles © The authors | Journal compilation © J Clin Gynecol Obstet and Elmer Press Inc™ | www.jcgo.elmerpress.com

managed by having the anesthesiologist perform awake fiberoptic nasal intubation with a surgeon available to perform an emergency tracheotomy, if needed [21]. This method is recommended for all women with FOP requiring intubation [9].

The operative risks for patients with FOP cannot be understated and include muscle damage during positioning for delivery, difficult surgical technique secondary to abnormal tissue and anatomy, hemorrhage, postoperative complications, and subsequent HO at the sites of surgery. Because this patient had ankylosed joints, positioning for surgery was challenging. Her anatomy and early gestational age necessitated that we use a vertical skin incision and classical uterine incision. Secondary to difficultly obtaining hemostasis of the uterine incision, she had a postpartum hemorrhage requiring transfusion. The cesarean delivery was challenging due to her abnormal tissue from FOP. Postoperative oxygenation was difficult given fluid shifts, limitations of chest wall expansion, and pre-existing HO in the chest muscles.

Conclusion

Pregnancy in FOP and OI should not be undertaken without serious consideration and preconception counseling. Undesired pregnancies should be avoided entirely. In summary, pregnancy in FOP and OI poses major life-threatening risks to both mother and child, and therefore, its consequences should be cautiously considered. The successful outcomes of these two high-risk pregnancies and deliveries can be attributed to collaboration between different specialty teams and planning for the known complications that may affect pregnancy and delivery in women with these genetic skeletal disorders.

Conflict of Interest

None of the authors have a conflict of interest.

References

1. Warman ML, Cormier-Daire V, Hall C, Krakow D, Lachman R, LeMerrer M, Mortier G, et al. Nosology and classification of genetic skeletal disorders: 2010 revision. Am J Med Genet A. 2011;155A(5):943-968.
2. McCarthy EF. Genetic diseases of bones and joints. Semin Diagn Pathol. 2011;28(1):26-36.
3. Chetty SP, Shaffer BL, Norton ME. Management of pregnancy in women with genetic disorders, Part 1: Disorders of the connective tissue, muscle, vascular, and skeletal systems. Obstet Gynecol Surv. 2011;66(11):699-709.
4. Shore E, Feldman G, Xu M, Kaplan F. The genetics of fibrodysplasia ossificans progressiva. Clin Rev Bone Miner Metab. 2005;3(34):201-104.
5. Couzin J. Biomedical research. Bone disease gene finally found. Science. 2006;312(5773):514-515.
6. Shore EM, Xu M, Feldman GJ, Fenstermacher DA, Cho TJ, Choi IH, Connor JM, et al. A recurrent mutation in the BMP type I receptor ACVR1 causes inherited and sporadic fibrodysplasia ossificans progressiva. Nat Genet. 2006;38(5):525-527.
7. Kaplan F. The key to the closet is the key to the kingdom: a common lesion of rare disease. Orphan Dis Update. 2006;24(3):1-9.
8. Kaplan FS, McCluskey W, Hahn G, Tabas JA, Muenke M, Zasloff MA. Genetic transmission of fibrodysplasia ossificans progressiva. Report of a family. J Bone Joint Surg Am. 1993;75(8):1214-1220.
9. Kaplan F, Shore E, Pignolo R (eds). The International Clinical Consortium on FOP. The medical management of fibrodysplasia ossificans progressiva: current treatment considerations. Clin Proc Intl Clin Consort FOP 4. 2011.
10. Parasuraman R, Taylor MJ, Liversedge H, Gilg J. Pregnancy management in type III maternal osteogenesis imperfecta. J Obstet Gynaecol. 2007;27(6):619-621.
11. Zhao X, Yan SG. Recent progress in osteogenesis imperfecta. Orthop Surg. 2011;3(2):127-130.
12. Litos M, Michala S, Brown R. Osteogenesis imperfecta and pregnancy. Eur J Obstet Gynecol Reprod Biol. 2008;136(1):126-127.
13. Sharma A, George L, Erskin K. Osteogenesis imperfecta in pregnancy: two case reports and review of literature. Obstet Gynecol Surv. 2001;56(9):563-566.
14. Thompson EM. Non-invasive prenatal diagnosis of osteogenesis imperfecta. Am J Med Genet. 1993;45(2):201-206.
15. Krishnamoorthy U, Vausse S, Donnai P. Management of pregnancy complicated by maternal osteogenesis imperfecta. Report of a case with uterine rupture. J Obstet Gynaecol. 2002;22(3):316.
16. Rocke DM, Zasloff M, Peeper J, Cohen RB, Kaplan FS. Age- and joint-specific risk of initial heterotopic ossification in patients who have fibrodysplasia ossificans progressiva. Clin Orthop Relat Res. 1994;(301):243-248.
17. Kaplan FS, Zasloff MA, Kitterman JA, Shore EM, Hong CC, Rocke DM. Early mortality and cardiorespiratory failure in patients with fibrodysplasia ossificans progressiva. J Bone Joint Surg Am. 2010;92(3):686-691.
18. Muglu JA, Garg A, Pandiarajan T, Shore EM, Kaplan FS, Uchil D, et al. Pregnancy in fibrodysplasia ossificans progressiva. Obstet Med. 2012 Mar 1;5(1):35-38.
19. Thornton YS, Birnbaum SJ, Lebowitz N. A viable pregnancy in a patient with myositis ossificans progressiva. Am J Obstet Gynecol. 1987;156(3):577-578.
20. Brownfoot FC, Crowther CA, Middleton P. Different corticosteroids and regimens for accelerating fetal lung maturation for women at risk of preterm birth. Cochrane Database Syst Rev. 2008;(4):CD006764.
21. Lynde G, Guffey R, Gershon R. Cesarean Section of a 25 3/7 Week Parturient with Fibrodysplasia Ossificans Progressiva: A Case Report. Internet J Anesthesiol. 2013;31(1).