CASE REPORT

Pregnancy in fibrodysplasia ossificans progressiva

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Summary: Fibrodysplasia ossificans progressiva (FOP) is a rare disabling genetic disorder characterized by progressive postnatal heterotopic ossification leading to cumulative disability. Heterotopic bone formation in FOP usually begins in early childhood following a series of painful, post-traumatic, inflammatory soft-tissue swellings known as flare-ups, which later undergo ossification resulting in the progressive immobilization of the chest wall, limbs and jaw by early adulthood. Pregnancy in FOP has occurred infrequently and reproductive decisions are a dilemma for an individual or couple with FOP. We present the clinical course, medical management and potential concerns of four cases of pregnancy in FOP.

Keywords: fibrodysplasia ossificans progressiva, heterotopic ossification, bone morphogenetic protein

INTRODUCTION

Fibrodysplasia ossificans progressiva (FOP) is a disabling genetic disorder of connective tissue characterized by congenital malformation of the great toes and progressive postnatal heterotopic ossification of soft tissue in specific anatomic patterns, with proximal to distal predilection.[1–3] FOP is an extremely rare disorder with a worldwide prevalence of approximately one in 2 million live births.[4] There is no racial, ethnic, gender or geographic predilection.[4]

Most cases of FOP arise as a result of a spontaneous new mutation in the gene encoding activin A receptor, type I/activin-like kinase-2 (ACVR1/ALK2), a bone morphogenetic protein type I receptor.[5,6] An identical mutation occurs in all classically affected individuals worldwide regardless of whether the disease occurs sporadically or is inherited.[5,6] Advanced paternal age has been associated with the occurrence of new mutations in FOP.[7] The disease is progressively disabling and reproductive fitness is low.[3] Fewer than 10 multigenerational families are known worldwide, and inheritance occurs by autosomal dominant transmission, most often from affected fathers.[5–8] Identical twins with this condition have been reported.[9]

In FOP, an ectopic skeleton develops postnatally due to genetic dysregulation of bone morphogenetic protein signalling in the presence of inflammatory triggers.[10–14] Heterotopic bone formation in FOP usually begins in early childhood following a series of painful, post-traumatic, inflammatory soft-tissue swellings known as flare-ups.[1–3] These flare-ups seize the body's skeletal muscles and replace them with heterotopic bone, eventually immobilizing almost all muscles and joints of the axial and appendicular skeleton.[1–3]

Heterotopic ossification occurs by an endochondral mechanism and follows a characteristic anatomic and temporal progression that closely mimics the formation of the normotopic skeleton *in utero*.[15] Several animal models presently recapitulate features of FOP.[13,14,16]

Most patients with FOP are misdiagnosed early in life before the appearance of heterotopic ossification and undergo diagnostic procedures that can exacerbate formation of heterotopic bone and accelerate the extensive and lifelong disability.[17,18] Disease progression is episodic, but disability is cumulative, resulting in the progressive immobilization of the chest wall, limbs and jaw by early adulthood.[1–3] Most patients are wheelchair-bound by the third decade of life.[1–3] Median life-expectancy is approximately 40 years, and patients usually die from complications of thoracic insufficiency syndrome.[19,20]

While patients with FOP can live fulfilling lives,[21] most patients do not marry, and even fewer have children.[4] Reproductive decisions are often a dilemma for an individual or couple with FOP and present formidable management challenges to the patient, family members and health-care providers.[22]

Here we present four cases of pregnancy in young women with advanced FOP, three of which have been reported from the USA while one was identified in the UK.

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CASE REPORTS

Case 1

A 24-year-old nulliparous woman with known classic FOP and limited movement of the cervical spine and shoulders presented

with a six-week history of amenorrhoea. An ultrasound examination confirmed a sac-like structure corresponding to a four-week gestation. A follow-up scan confirmed a viable intrauterine pregnancy of six weeks gestation. She was referred for antenatal care in tertiary unit. However, at 10 weeks of gestation, the patient presented with complaints of heavy vaginal bleeding. An ultrasound scan revealed an intrauterine gestational sac with no fetal heartbeat. A surgical evacuation was considered, but medical management of the miscarriage was selected in order to avoid musculoskeletal trauma and risks of general anaesthesia. The woman was given mifepristone 200 mg orally followed by two doses of misoprostol vaginally. Successful treatment of the miscarriage was confirmed by ultrasound scan. An infusion of hydrocortisone (100 mg) was administered immediately after medical management of the miscarriage to prevent a flare-up of FOP. She had mild vaginal bleeding for several days and recovered completely without any FOP flare-up.

Case 2

A 22-year-old nulliparous woman with known classic FOP had severe kyphoscolioisis and suffered complete ankylosis of the neck, shoulders, elbows and hips. She had a six-week history of amenorrhoea, and presented for a pregnancy evaluation. An ultrasound examination confirmed a viable six-week intrauterine pregnancy. The woman was referred to a tertiary care centre for antenatal care in view of fibrodyplasia, but soon suffered a spontaneous miscarriage at eight weeks of pregnancy. She had mild vaginal bleeding for several days, and recovered completely without any FOP flare-up.

Case 3

A 27-year-old married woman with classic FOP and complete fusion of the neck, shoulders, elbows, hips, knees and jaw became pregnant for the first time. She received antenatal care and had an uneventful intrauterine pregnancy without exacerbation of FOP. But she had emergency caesarean section at 30 weeks gestation under general anaesthesia and delivered a girl with FOP. (As this is one of the older cases and no records were available, the reason for emergency caesarean section and the details of the anaesthetic procedure are unknown.) The caesarean section induced an FOP flare-up and heterotopic bone formed at the operative site. Due to her rapidly progressive FOP following childbirth, the mother had difficulty caring for her child. The child inherited FOP from the mother and was diagnosed at birth following confirmation of the malformed great toes. The child was later transferred to a chronic care nursing facility at 15 years of age for care of severely progressive FOP, and died at 22 years of age from cardio-respiratory complications of FOP. At the time of the child's death, the mother was 49 years old, had complete ankylosis of all major joints of the axial and appendicular skeleton, was wheelchair restricted and required assistance with all activities of daily living.

Case 4

A 27-year-old employed data technician with severe, classic FOP and complete ankylosis of the neck, shoulders, elbows, wrists, back, hips and knees who had relatively uneventful pregnancy was admitted in premature labour with pathological cardiotocograph. An emergency caesarean section was performed at 34 weeks of gestation without administration of steroids for fetal lung maturity. The child did not have FOP, but as a result of possible intrapartum hypoxia developed cerebral palsy with mild motor deficits. The mother had no flare-ups of FOP during pregnancy, or any subsequent heterotopic ossification at the operative site after the caesarean section. However, heterotopic bone formation at other sites progressed thereafter, further impairing the mother's ability to care for the child.

DISCUSSION

Pregnancy is a rare event in FOP; however, it is possible for a woman with FOP to carry a child owing to the absence of smooth muscle involvement in this condition, and at least five known instances of childbirth have been reported in the medical literature, including two in this report.[5,23–25] However, pregnancy and childbirth have substantial life-threatening risks to both the mother and child.[22] This case series reflects varied outcomes of pregnancy in women with FOP, with each case presenting unique management challenges.

Individuals with FOP have markedly reduced reproductive fitness and the fertility potential of women with FOP is poorly understood.[4] Although hypogonadism may be associated with FOP and menstrual periods often stop prematurely, sterility should not be assumed.[4,22]

With advances in medical care women who are at high risk and have complicated medical disorders, including rare connective tissue disorders, embark on pregnancy. If pregnancy is contemplated in a woman with FOP, prepregnancy counselling is absolutely mandatory because FOP is an autosomal dominant disorder with complete penetrance.[5,6] If a parent is affected with FOP, the chances of an affected child are 50%.[4] Although preimplantation genetic testing is now possible following the FOP gene discovery, embryo selection in these patients would be an impractical procedure requiring these women to undergo *in vitro* fertilization. Prenatal genetic diagnosis could potentially be used to exclude FOP.[5,6,18]

A pregnancy, even with an unaffected fetus, poses substantial risks to a mother with FOP. Although data are scant, one of the initial risks of pregnancy associated with FOP is a general risk of miscarriage, which may be increased due to ossification of the abdominal wall.[22] But even if the pregnancy continues, there is substantial risk of premature birth. This can follow spontaneous preterm labour and may be secondary to fetal distress encountered during the later stages of pregnancy.[22]

The management of miscarriage, antenatal care and delivery poses substantial difficulties because of the specific risks associated with FOP. The potential outcome of a full-term gestation and problems associated with labour and delivery in a patient with FOP remains unknown, as no term pregnancy with FOP has been reported. Vaginal delivery is perilous in a woman with FOP due to severe pelvic deformity as well as fusion of the lumbar spine, hip joints and sacroiliac joints. The use of pelvimetry to specify the pelvic abnormalities may not be ideal because of possible inaccuracies and radiation exposure in conventional computed tomography. Therefore, delivery by caesarean section appears to be the only relatively safe mode of delivery after the age of viability is achieved.[22]

However, steroid administration for fetal lung maturity is imperative if delivery is anticipated before 36 weeks of gestation. There is also a genuine risk of heterotopic ossification at the surgical site, as occurred in one of our patients. Many reports describe exacerbation of FOP following surgical procedures.[1–3] However, in other cases (5 surgical operations including 2 hysterectomies), no heterotopic ossification formed in the abdominal wall.[23–25] The use of prednisolone or intravenous equivalent at the time of elective surgery and three days following surgery is recommended if there are no other contraindications. The rational use of corticosteroids early in the course of an FOP flare-up is based primarily on its potent anti-inflammatory effects[26] and on emerging knowledge of the importance of inflammatory triggers in FOP flare-ups.[10,27]

In addition to the physical problems associated with delivery, the choice of anaesthesia becomes a challenge due to technical difficulties with both regional and general anaesthesia.[22,28] Regional anaesthesia is technically difficult due to pre-existing heterotopic bone and the danger of precipitating new episodes of heterotopic ossification following an epidural block.[22] Similar problems, including ossification in tracheal rings and the danger of overstretching the jaw, may cause difficult intubation during general anaesthesia.[22] Also, it is impossible to extend the neck in young adults with FOP due to orthotopic ankylosis of the cervical paravertebral joints that ossify in childhood, even before the appearance of heterotopic ossification.[29] The use of fibreoptic nasal intubation when the patient is awake was found to be the only safe option.[22]

FOP results in breathing difficulties during the later part of pregnancy because of reduced lung capacity and severe limitation of expansion of the chest wall due to developmental anomalies in the costovertebral joints.[19,30] Breathing problems can be further aggravated by bone formation in the chest muscles or heterotopic bone in the abdominal wall.[19] Careful monitoring including respiratory function tests may be required during the antepartum and intrapartum course to establish any requirement for respiratory support.[22]

Another substantial risk is thromboembolism, which is exacerbated by severe immobility of FOP in addition to the hyper-coagulable state of pregnancy. This life-threatening complication warrants the use of prophylactic low-molecular-weight heparin throughout the duration of pregnancy.[22]

In addition to substantial risk to the mother with FOP, pregnancy also poses substantially increased risks to the unborn child including the risk of FOP (50%), prematurity, fetal distress and the risk of complications from general anaesthesia.[22] One of the specific risks to the mother associated with FOP is a flare-up during pregnancy. The chronic use of high-dose glucocorticoids and non-steroidal anti-inflammatory medications has potential embryonic and fetal toxicity and their use should be avoided, when possible.[22]

The recent discovery of the FOP gene mutation has changed the treatment horizon for the condition.[5,6] The availability of effective preventions and treatments might substantially reduce the risks associated with pregnancy in FOP or could paradoxically complicate the pregnancy if such therapies posed substantial embryonic or fetal toxicity. In summary, although pregnancy in women with FOP is possible, FOP is a progressive and life-limiting condition, and pregnancy may accelerate the progression of the disease. FOP poses major life-threatening risks to mother and child as well as life altering consequences to the entire family if a child is born with this condition. Moreover, the limitation of the mother's ability to care for the child is a real issue that must be carefully considered and balanced before pregnancy is contemplated.

DECLARATIONS

Disclosure of interest: The authors have no interest to disclose.
Contribution to authorship: JM, ES and FK initial concept, literature review and wrote the review article. FK provided critical revision of paper. AG, TP, DU and MJD did the literature search and revised the paper. All authors approved the final version of the manuscript.

REFERENCES

1 Connor JM, Evans DAP. Fibrodysplasia ossificans progressiva: the clinical features and natural history of 34 patients. *J Bone Joint Surg Br* 1982;**64**:76–83
2 Kaplan FS, Glaser DL, Shore EM, *et al.* The phenotype of fibrodysplasia ossificans progressiva. *Clin Rev Bone Miner Metab* 2005;**3**:183–8
3 Kaplan FS, Le Merrer M, Glaser DL, *et al.* Fibrodysplasia ossificans progressiva. *Best Pract Res Clin Rheumatol* 2008;**22**:191–205
4 Shore EM, Feldman GJ, Xu M, Kaplan FS. The genetics of fibrodysplasia ossificans progressiva. *Clin Rev Bone Min Metab* 2005;**3**:201–4
5 Shore EM, Xu M, Feldman GJ, *et al.* A recurrent mutation in the BMP type I receptor ACVR1 causes inherited and sporadic fibrodysplasia ossificans progressive. *Nat Genet* 2006;**38**:525–7
6 Kaplan FS, Xu M, Seemann P, *et al.* Classic and atypical fibrodysplasia ossificans progressiva (FOP) phenotypes are caused by mutations in the bone morphogenetic protein (BMP) type I receptor ACVR1. *Hum Mutat* 2009;**30**:379–90
7 Rogers JG, Chase GA. Paternal age effect in fibrodysplasia ossificans progressiva. *J Med Genet* 1979;**16**:147–8
8 Kaplan FS, McCluskey W, Hahn G, Tabas J, Muenke M, Zasloff MA. Genetic transmission of fibrodysplasia ossificans progressiva. *J Bone Joint Surg* 1993;**75-A**:1214–20
9 Hebela N, Shore EM, Kaplan FS. Three pairs of monozygotic twins with fibrodysplasia ossificans progressiva: the role of environment in the progression of heterotopic ossification. *Clin Rev BoneMiner Metab* 2005;**3**:205–8
10 Kaplan FS, Glaser DL, Shore EM, *et al.* Hematopoietic stem-cell contribution to ectopic skeletogenesis. *J Bone Joint Surg Am* 2007;**89**:347–57
11 Kaplan FS, Groppe J, Pignolo RJ, Shore EM. Morphogen receptor genes and metamorphogenes: skeleton keys to metamorphosis. *Ann NY Acad Sci* 2007;**1116**:113–33
12 Kaplan FS, Shen Q, Lounev V, *et al.* Skeletal metamorphosis in fibrodysplasia ossificans progressiva. *J Bone Miner Metab* 2008;**26**:521–30
13 Lounev V, Ramachandran R, Wosczyna MN, *et al.*. Identification of progenitor cells that contribute to heterotopic skeletogenesis. *J Bone Joint Surg (Am)* 2009;**91**:652–63
14 Kan L, Liu Y, McGuire TL, *et al.* Dysregulation of local stem/progenitor cells as a common cellular mechanism for heterotopic ossification. *Stem Cells* 2009;**27**:150–6
15 Pignolo RJ, Suda RK, Kaplan FS. The fibrodysplasia ossificans progressiva lesion. *Clin Rev Bone Miner Metab* 2005;**3**:195–200
16 Yu PB, Deng DY, Lai CS, *et al.* BMP type I receptor inhibition prevents ectopic ossification in mouse model of fibrodysplasia ossificans progressiva (FOP). *Nat Med* 2008;**14**:1363–9
17 Kitterman JA, Kantanie S, Rocke DM, Kaplan FS. Iatrogenic harm caused by diagnostic errors in fibrodysplasia ossificans progressiva. *Pediatrics* 2005;**116**:654–61
18 Kaplan FS, Xu M, Glaser DL, *et al.* Early diagnosis of fibrodysplasia ossificans progressiva. *Pediatrics* 2008;**121**:e1295–300
19 Kaplan FS, Glaser DL. Thoracic insufficiency syndrome in patients with fibrodysplasia ossificans progressiva. *Clin Rev Bone Miner Metab* 2005;**3**:213–6
20 Kussmaul WG, Esmail AN, Sagar Y, Ross J, Gregory S, Kaplan FS. Pulmonary and cardiac function in advanced fibrodysplasia ossificans progressiva. *Clin Orthop Rel Res* 1998;**346**:104–9
21 Hair MS, Peeper JL. The international fibrodysplasia ossificans progressiva association. *Clin Rev Bone Miner Metab* 2005;**3**:267–9

22 Kaplan FS, and The International Clinical Consortium on Fibrodysplasia Ossificans Progressiva. The medical management of fibrodysplasia ossificans progressiva: current treatment considerations. *Clin Proc Intl Clin Consort FOP* 2008;**3**:1–82
23 Davidson BN, Bowerman RA, LaFerla JJ. Myositis ossificans progressiva and pregnancy: a therapeutic dilemma. *J Reprod Med* 1985;**30**:945–7
24 Fox S, Khoury A, Mootabar H, Greenwald EF. Myositis ossificans progressiva and pregnancy. *Obstet Gynecol Mar* 1987;**69**:453–5
25 Thornton YS, Birnbaum SJ, Lebowitz N. A viable pregnancy in a patient with myositis ossificans progressive. *Am J Obstet Gynecol* 1987;**156**: 577–8
26 Rhen T, Cidlowski JA. Anti-inflammatory action of glucocorticoids- new mechanisms for old drugs. *N Engl J Med* 2005;**353**:1711–23
27 Lounev VY, Ramachandaran R, Wosczyna MN, *et al.* Identification of progenitor cells that contribute to heterotropic skeletogenesis. *J Bone Joint Surg Am* 2009;**91**:652–63
28 Meier R, Bolliger KP. Anaesthesiologic problems in patients with fibrodysplasia ossificans progressive. *Anaesthesist* 1996;**45**:631–4
29 Schaffer AA, Kaplan FS, Tracy MR, *et al.* Developmental anomalies of the cervical spine in patients with fibrodysplasia ossificans progressiva are distinctly different from those in patients with Klippel-Feil syndrome. *Spine* 2005;**30**:1379–85
30 Mahboubi S, Glaser DL, Shore EM, Kaplan FS. Fibrodysplasia ossificans progressiva. *Pediatr Radiol* 2001;**31**:307–14

(Accepted 2 August 2011)