Pregnancy in a woman with proportionate (primordial) dwarfism: a case report and literature review

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Summary: Primordial dwarfism is a rare form of severe proportionate dwarfism which poses significant challenges in pregnancy. A 27-year-old with primordial dwarfism (height 97 cm, weight 22 kg) and coexisting morbidities of familial hypercholesterolaemia and hypertension presented to our unit. Early pregnancy was complicated by difficult blood pressure control, sinus tachycardia, biochemical hyperthyroidism and insulin-requiring gestational diabetes. Delivery was indicated at 24 weeks with uncontrollable hypertension, progressive renal impairment and intrauterine growth restriction. A caesarean section was performed under general anaesthesia, resulting in the delivery of a 486 g male infant. This case highlights the difficulties of managing pregnancy in a woman with primordial dwarfism. Her limited capacity to respond to the physiological demands of pregnancy created a life-threatening situation, culminating in profound preterm birth.

Keywords: pregnancy, dwarfism, primordial, dwarf, proportionate, short stature, skeletal dysplasia

INTRODUCTION

Dwarfism is defined as the failure to achieve a height of 148 cm at maturity.¹ There are over 300 different types of genetic disorders of the skeleton classified currently,² but these can be broadly divided into two groups: those with proportionate growth (short-trunk and short limbs) and those with disproportionate development (short limbs). Most women with skeletal dysplasia have a normal life-expectancy and fertility, and so may seek advice regarding pregnancy. Although in the past 50 years there have been many case reports of successful pregnancies in these conditions, these have been mainly in women with disproportionate dwarfism who have relatively well preserved trunk height and organ proportions, and therefore a more favourable prognosis for pregnancy. There are fewer cases of pregnancy in women with proportionate dwarfism,^{3–5} and as such, there is a paucity of data on pregnancy, labour and delivery in these conditions. Our case highlights the problems of managing a pregnancy in a woman with severe proportionate dwarfism and multiple medical co-morbidities.

CASE REPORT

A 27-year-old G0P0 presented for pre-pregnancy counselling. She was of proportionate short stature; her height was 97 cm

(approximately the height of a 3-year-old child) and pre-pregnancy weight was 22 kg (average weight for 6-year-old child) (see Figure 1). Her brother was similarly affected, with a height of 100 cm. However, neither of their parents were affected, suggesting an autosomal recessive pattern of inheritance. She had been seen by a geneticist with a special interest in skeletal dysplasia who considered her and her brother to have a rare, proportionate 'primordial' bone developmental dysplasia or 'primordial dwarfism'. She had a significant history of early onset, severe hypertension, requiring hospitalization during her mid teens, where multiple investigations failed to reveal an underlying renal arterial, endocrine or auto-immune cause. When compliant with medications, her blood pressure was mostly stable on lisinopril 10 mg daily. Familial hypercholesterolaemia was also confirmed at approximately age 12, requiring treatment with 20 mg atorvastatin (1 mg/kg/day). Pre-pregnancy, her cholesterol was 8.3 mmol/L (normal range <5.5 mmol/L), triglycerides 2 mmol/L (normal range <2 mmol/L), HDL 1.03 (normal range >1 mmol/L) and LDL 6.4 mmol/L (normal range <3 mmol/L). Other relevant history included jaw-lengthening surgery under general anaesthetic at a paediatric centre without complication. Menarche had occurred at age 13 and she had irregular cycles prior to the insertion of a subdermal etonogestrel implant (Implanon) for contraception. She had a significant family history of ischaemic heart disease with her mother requiring a coronary stent at age 43 years.

As part of pre-pregnancy evaluation, she had an echocardiogram performed, which showed left and right ventricular

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Figure 1 Photo of patient taken at 21 weeks gestation

function appropriate for body size and mild aortic regurgitation. Her cardiac output was 2.4 L/minute (compared with an average adult female cardiac output of 4.5 litres/minute) and her resting heart rate was 100 beats/minute. Respiratory function tests showed ventilatory function within normal limits. She had normal renal and hepatic function, although her serum creatinine was reduced at 24 $\mu\text{mol/L}$ (normal range 30–97 $\mu\text{mol/L}$), presumed due to relative sarcopaenia. Twenty-four hour urine collection revealed a low creatinine excretion of 4 mmol/day (normal range 5–13 mmol/day) with protein excretion 0.07 g/day (within the normal adult range of <0.15 g/day) and a normal protein-creatinine ratio of 0.02 g/mmol (normal range <0.03 g/mmol). Cerebral magnetic resonance imaging/angiography was recommended in view of the association of some forms of primordial dwarfism with Moyamoya disease,⁶ but the patient declined this investigation.

She was counselled regarding the significant risks in pregnancy posed by her proportionate dwarfism, in particular those of limited abdominal size and cardio-respiratory reserve. As her husband is of above average male height (185 cm – see Figure 2) and is not a blood relative, it was expected that the fetus would be unaffected. She was counselled regarding the increased likelihood of problematic hypertension and superimposed preeclampsia in pregnancy. With regard to fetal outlook, she was advised of the high likelihood of extreme prematurity and impaired growth, given her diminished cardiac capacity to perfuse the demands of the uteroplacental bed. The option of surrogacy was discussed but there

Figure 2 Photo of patient prior to pregnancy with her husband

was no clear candidate, given that she had no sister and her mother had significant ischaemic heart disease.

She conceived spontaneously within five months of having the etonogestrel implant removed and had her first antenatal visit at five weeks gestation. At this time, her blood pressure, now managed with methyldopa, 500 mg once daily (maximum recommended paediatric dose 65 mg/kg), was 150/90 mmHg at booking and she was commenced on aspirin 100 mg daily. Early pregnancy was complicated by labile blood pressure and the methyldopa dose was increased to 500 mg twice daily. She also developed a resting sinus tachycardia of 120 beats per minute. Thyroid function demonstrated prolonged suppression of her thyroid-stimulating hormone (TSH) into the mid-trimester: TSH 0.05 (normal range 0.35–5.6 mU/L), T3 8.4 (normal range 3.8–6 pmol/L) T4 19.5 (normal range 7.5–21.1 pmol/L), requiring brief treatment with propylthiouracil 12.5 mg twice daily. Thyroid autoantibodies were negative and thyroid function normalized after treatment was ceased at 20 weeks. The multidisciplinary team assembled for her pregnancy and delivery care included an anaesthetist, cardiologist, renal physician, paediatric endocrinologist, intensive unit care (ICU) physician, midwife and dietician.

First trimester combined screening returned a low risk for aneuploidy. A 20-week morphology scan revealed a fundal

placenta, normal biometry and anatomy. At 21 weeks' gestation a repeat maternal echocardiogram was performed which showed normal left and right ventricular function with chamber enlargement consistent with pregnancy. Gestational diabetes was diagnosed on a 75 g oral glucose tolerance test at 22 weeks. Insulin was subsequently required to achieve acceptable glycaemic control.

Despite increasing her antihypertensive medication, she required admission into the high dependency unit at 22 + 3 weeks with severe hypertension (blood pressure 170/100 mmHg) and proteinuria. Methyldopa was increased to maximal weight-based dose (1250 mg in three divided doses). Oral nifedipine and intravenous hydralazine were added to achieve blood pressure control. Her tachycardia continued to worsen to 140 beats per minute and metoprolol 12.5 mg twice daily was added, recognizing the potential risks to fetal growth. After seven days, her hypertension again worsened and prazosin 0.5 mg mane and 1 mg nocte was commenced. At 22 weeks' gestation, fetal size was estimated to be 459 g with normal liquor volume and normal umbilical artery Doppler findings on sonographic evaluation. The patient and her partner were extensively counselled about the high risk of perinatal mortality and morbidity at this fetal size and gestation. Both requested full resuscitation from 24 weeks' gestation, on the basis that this might be her only pregnancy. Dose-adjusted betamethasone (reduced to account for maternal body size and to minimize any adverse impact on blood pressure and glycaemic control) was therefore administered at 23+ weeks gestation.

Despite maximal medical therapy, at 24 + 0 the patient's blood pressure increased to 205/115, with a concomitant decline in renal function. Ultrasound revealed absent end diastolic flow in the umbilical artery, and a decision was made for delivery following maternal stabilization.

The patient was anaesthetized with a general anaesthetic after first establishing invasive blood pressure monitoring. Drug doses were weight adjusted and no difficulties were experienced with airway management. A central venous catheter was inserted in the right internal jugular vein with ultrasound guidance. A midline abdominal incision was performed, and a lower segment caesarean section was performed through a surprisingly well-developed lower segment. The estimated blood loss was 300 mL and there was very little haemodynamic disturbance intraoperatively. The patient was electively transferred to ICU postdelivery and extubated later that evening. She returned to the general maternity ward on the third postpartum day, and was discharged home on day 6. During her admission, metoprolol was ceased and lisinopril was re-commenced on the fourth postpartum day. The doses of other antihypertensive medications were reduced and her renal function improved. She had an etonorgestrel implant (Implanon) inserted early in the postpartum period. Following discharge she was seen for follow-up in our obstetric clinic. She was gradually weaned off prazosin and aldomet, which were ceased by four weeks postpartum. She was also seen at six weeks postnatally by a physician with special interest in hypertension to optimize blood pressure control. Atorvastatin was planned to be re-commenced after cessation of breastfeeding. She was referred back to her long-term physician for ongoing management of her co-morbidities.

The male baby was delivered in satisfactory condition with a birthweight of 486 g. After elective intubation and surfactant administration, he was transferred to neonatal intensive care.

He suffered a unilateral grade 4 intraventricular haemorrhage, with secondary hydrocephalus requiring neurosurgical intervention with a fenestration which was successful. He has moderate bronchopulmonary dysplasia. At the time of writing (7 months corrected age) he is happy, sociable, interacting and very vocal. He has evolving right-sided hemiparesis, with increased tone in his right arm but not in his legs, indicating a degree of evolving cerebral palsy. He uses the left hand more than the right hand. He has been in an early intervention programme since five months corrected age and has ongoing follow-up with a paediatric developmental medicine team.

COMMENT

We report on the management of a pregnant woman with proportionate dwarfism and a range of multisystem medical complications. Primordial dwarfism is a categorical term referring to a heterogeneous group of dwarfism disorders which includes Seckel Syndrome, Osteodysplastic Primordial Dwarfism Type I (ODPDI), IMAGE Syndrome, Osteodysplastic Primordial Dwarfism Type II (ODPDII), Meier-Gorlin Syndrome and Russell-Silver Syndrome. It is likely that many women with Russell-Silver Syndrome have had successful pregnancies as their final height can approach the range of those with normal stature. There is considerable literature detailing the obstetric management of women with the more common forms of disproportionate dwarfism, predominately achondroplasia and osteogenesis imperfecta, as well as the less common forms due to cartilage-hair hypoplasia and vitamin D resistant rickets. These women face specific management issues related to the individual conditions but generally do not experience the same threats to cardiorespiratory function due to their relatively well-preserved trunk height. The various forms of dwarfism in which pregnancy has been reported are outlined in Table 1.

To our knowledge, this is the first case of pregnancy in a woman with primordial dwarfism. Proportionate dwarfism due to other causes is also reported less frequently than disproportionate dwarfism. The obstetric outcomes from published cases are summarized in Table 2, but most of these patients were significantly taller than our patient. In one of the largest series published, involving 150 women with mixed forms of dwarfism, Allanson and Hall commented that it was impossible to compare obstetric and gynaecological problems in disproportionate short stature to those of proportionate short stature because of the smaller numbers in the latter group.⁴

It has been suggested that, whatever the cause of dwarfism, antenatal care for these women should include early onset of prenatal care in a centre capable of managing high-risk pregnancies, early pulmonary function testing and early involvement of a respiratory physician as well as an anaesthetist.⁵ Varying degrees of respiratory deterioration have been reported in patients with dwarfism; while there are several reports of patients asymptomatic to the third trimester,⁴ other authors report patients 'propped up in rocking chairs for the last 50 days of gestation because of respiratory embarrassment'³ and one report of a pregnancy termination as a life-saving measure in a mother with osteogenesis imperfecta who was 78 cm tall and developed respiratory failure at 16 weeks.⁷ Particularly in a woman with proportionate dwarfism, a reduced symphysis to xiphoid measurement results in the gravid uterus becoming an abdominal organ from the early weeks of gestation. Diaphragmatic impingement subsequently

Table 1 Specific considerations for pregnancy in various forms of dwarfism

Condition	Type of dwarfism	Inheritance	Features	Specific considerations for pregnancy
Spondyloepiphyseal dysplasia	Proportionate	Autosomal dominant or spontaneous mutation	Develops from infancy. Abnormal spine with central anterior pointing of vertebral bodies and odontoid hypoplasia. Ligamentous laxity. Thoracic dysplasia with respiratory failure possible. Association with myopia, retinal detachment, pectus cavatum, cleft palate and talipes equinovarus	Platypellic pelvis, atlanto-occipito instability, laryngotracheal stenosis and short trunk
Pituitary/ateliotic dwarfism	Proportionate	Autosomal recessive or autosomal dominant	Normally proportioned and therefore short trunk. May have other pituitary hormone deficiencies, i.e. hypopituitary amenorrhea requiring ovulation induction	None reported above that of short stature and short trunk
Primordial dwarfism	Proportionate	Varied	Severe proportionate dwarfism beginning <i>in utero</i> . Normally proportioned and therefore short trunk	None reported above that of short stature and short trunk
Achondroplasia	Disproportionate	Autosomal dominant	Average adult female height of 123 cm, short limbs and relatively normal sized trunk	Reduced size of upper cervical spine canal, accentuation of hyperlordosis leading to spinal claudication
Osteogenesis imperfecta	Disproportionate	Type 2 – autosomal recessive or types 1, 3 and 4 – autosomal dominant	Heterogeneous group of collagen disorders characterized by bone fragility, blue sclera and dentinogenesis imperfecta	Kyphoscoliosis, possible collagen defect increasing risk of uterine rupture, CPD due to pelvic fractures, short neck, potential for fracture of mandible and cervical spine, malignant hyperthermia, fractured ribs, breastfeeding may further increase risk of osteoporosis
Cartilage-hair hypoplasia	Disproportionate	Autosomal recessive	The limbs and ribs are most affected, with sparing of the spine and skull	Nil reported
Rachitic dwarfism (vitamin D resistant rickets)	Disproportionate	N/A	High forehead with prominent bosses, bent long bones, and Harrison's groove	Nil reported

N/A, not applicable

contributes to reduced respiratory function at an early stage in pregnancy.

Reduced cardiac output also means there is a diminished capacity to respond to the increasing circulatory demands of the expanding uteroplacental bed. Our patient's progressive tachycardia may have represented the physiological response of a small heart trying to maximize cardiac output. The reduced maternal blood volume has implications for delivery, with a relatively small intraoperative or intrapartum blood loss representing a much larger proportion of the patients circulating blood volume.

Our patient developed severe early onset preeclampsia in the setting of significant preexisting hypertension; it is plausible that her dwarfism may have been an exacerbating factor. In 1970 Gardiner postulated that preeclampsia may be more common in patients with dwarfism.³ Although Tyson did not report any cases in his series, Lattanzi and Harger⁸ reviewed the literature of maternal achondroplasia and found four cases out of 16 patients had preeclampsia (all occurring in the 8 primigravid patients) and one case was complicated by eclampsia at 28 weeks necessitating delivery with subsequent fetal death. In addition to this patient's preexisting hypertension, it is plausible that an exaggerated placental and hormonal stimulus (relative to uterine size and maternal blood volume) may play a contributory role in these patients.⁹ A similar mechanism may have been responsible for our patient's early onset of insulin-requiring gestational diabetes, and the exaggerated hyperthyroidism in early pregnancy (excessive beta human chorionic gonadotropin effect).

Although indicated on fetal grounds in our case, caesarean section appears to be the most common mode of delivery for

women with dwarfism.^{3–5} Tyson *et al.*³ reported that, while vaginal delivery may be possible in patients with proportionate dwarfism, the combination of an engaged head and favourable cervix are usually accompanied by such severe respiratory difficulty as to preclude vaginal delivery. There has been speculation that uterine rupture may be more likely to occur in women with dwarfism due to the proportionately greater stretching of the uterus in pregnancy, labour and delivery.³ However, the two cases of ruptured uterus reported in the literature were both in patients with osteogenesis imperfecta and may relate to associated collagen defects.^{10,11}

Most of the anaesthetic literature regarding dwarfism and caesarean section is case reports regarding achondroplastic patients. What little is published about proportionate dwarfism suggests that they can be managed as a paediatric patient of corresponding size;^{5,12} in many obstetric facilities this means ensuring there is appropriate equipment and expertise available for its use. In most parturients for caesarean delivery, regional anaesthesia has been perceived as having less risk to mother and fetus, mainly by avoiding the risk of failed intubation. While this may be generally true, the shorter spinal cord length of dwarfism presents the additional risk of a regional block ascending to a high spinal segmental level with concomitant respiratory compromise and haemodynamic instability. There are no studies to define an appropriate spinal anaesthetic dose, although a titrated epidural has been recommended by some authors.¹³ The decision around anaesthetic choice in our patient was also informed by her two previous anaesthetics as an adult. In both episodes no airway difficulties had been encountered. In our case we

Table 2 Summary of obstetric outcomes in patients with proportionate dwarfism

Reference	Type of dwarfism	Height and weight	Partner	Pregnancy outcomes		
				Antenatal complications	Labour/delivery	Neonatal outcomes
Tyson <i>et al.</i> (1970) ³	Spondyloepiphyseal dysplasia	Not reported	Dwarfism	No specific complications reported	Caesarean section, term	Normal infant
Tyson <i>et al.</i> (1970) ³	Spondyloepiphyseal dysplasia	Not reported	Cartilage hair hypoplasia dwarfism	No specific complications reported	Spontaneous vaginal delivery	2183 g infant, XO karyotype
Tyson <i>et al.</i> (1970) ³	Pituitary dwarfism	Not reported	Pituitary dwarfism	No specific complications reported	Caesarean sections × 3 at 38 weeks	3090 g (pituitary dwarfism), 2778 g (unaffected), 3232 g (pituitary dwarfism)
Tyson <i>et al.</i> (1970) ³	Pituitary dwarfism	Not reported	Normal stature	No specific complications reported	Vaginal delivery × 6	3 infants with pituitary dwarfism, 3 infants unaffected (10 previous pregnancy losses)
Tyson <i>et al.</i> (1970) ³	Pituitary dwarfism	Not reported	193 cm tall	No specific complications reported	Caesarean sections × 2 at 37 weeks	1 × neonatal death due to respiratory distress, 1 × normal male 3090 g
Tyson <i>et al.</i> (1970) ³	Pituitary dwarfism	135 cm, 51 kg	Normal stature	Not reported	37 weeks	474 g stillborn infant (3 previous mid-trimester fetal losses and 2 early miscarriages)
Tyson <i>et al.</i> (1970) ³	Same patient as above	“ “	“ “	Developed respiratory distress at 30 weeks which progressed to respiratory failure necessitating delivery	Caesarean section at 35 + 4 weeks	2860 g infant
Cassar <i>et al.</i> (1980) ¹⁴	Pituitary dwarfism	140 cm	Not reported	Ovulation induction. Twin pregnancy with abdominal discomfort requiring admission at 35 weeks	Lower segment caesarean section at 37 weeks	2180 g and 2340 g female infants with good apgar scores
Batrinos <i>et al.</i> (1981) ¹⁵	Pituitary dwarfism	131 cm, 39 kg	Not reported	Ovulation induction complicated by severe ovarian hyperstimulation requiring 31-day hospital admission	Caesarean section at 37 weeks	3000 g female with right renal agenesis and supralevator anal agenesis with rectovestibular fistula
Merimee <i>et al.</i> (1982) ¹⁶	Pituitary dwarfism	110 cm	Normal stature	Not reported	Caesarean section at 37 weeks	Normal male (2 previous spontaneous miscarriages)
Allanson and Hall (1986) ⁴	Spondyloepiphyseal dysplasia	Not reported	Not reported	Developed respiratory difficulty in the last two months of pregnancy	Not reported	Not reported
Rodney <i>et al.</i> (1991) ¹⁷	Spondyloepiphyseal dysplasia	100 cm, 40 kg	Not reported	Initially planned caesarean section at 32 weeks but this was delayed as there was no deterioration in maternal lung function	Caesarean section under epidural at 36 weeks	1970 g male with good apgar scores
Ratner and Hamilton (1998) ¹²	Pituitary dwarfism	124 cm, 35 kg	Not reported	No specific complications reported	Caesarean section at 39 weeks with epidural anaesthesia	2580 g male
Narahara <i>et al.</i> (2000) ¹⁸	Pituitary dwarfism	133 cm, 27.5 kg	Not reported	Hospitalized at 31 weeks with threatened preterm labour and severe iron deficiency anaemia	Caesarean section at 37 weeks	2341 g male (healthy)
deBoer <i>et al.</i> (2001) ¹⁹	Spondyloepiphyseal dysplasia	134 cm, 75 kg	Not reported	Twin pregnancy with no specific complications reported	Caesarean section at 37 weeks	2700 g and 2800 g
Fukami <i>et al.</i> (2006) ²⁰	Pituitary dwarfism	138 cm	Not reported	Diabetes insipidus	Caesarean section at 37 weeks	2302 g female
Vance <i>et al.</i> (2011)	Primordial dwarfism	97 cm, 22 kg	Normal stature (185 cm)	Unstable hypertension, severe preeclampsia, IUGR	Lower segment caesarean section at 24 weeks	486 g male, grade 4 intraventricular haemorrhage

IUGR, intrauterine growth restriction

had the additional problems of severe hypertension, and a contracted blood volume, with a significant risk of haemodynamic instability.

Few adult intensive care physicians have training or experience in the management of paediatric-sized patients. Careful planning in the context of a multidisciplinary team was extremely useful to

consider all possible contingencies such as a need for prolonged mechanical ventilation, invasive monitoring or renal replacement therapy. This planning process provided the opportunity to ensure that the necessary expertise and equipment was available to manage a paediatric-sized patient in an adult intensive care unit that did not ordinarily manage children.

The case reported highlights the difficulties of managing a pregnancy affected by primordial dwarfism. This patient's limited capacity to respond to the usual physiological demands of pregnancy, together with her pre-existing morbidities, created a potentially life-threatening situation in the mid-trimester, culminating in extreme preterm birth. The involvement of a multidisciplinary team with the appropriate skill-mix, resources and equipment throughout pregnancy, delivery and the postpartum period in these patients is essential to optimize maternal and fetal outcome.

DECLARATIONS

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