A case of dyssegmental dysplasia
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Objective
To describe a case of dyssegmental dysplasia, a rare autosomal recessive skeletal dysplasia recently diagnosed in our fetal medicine unit at Tygerberg Hospital and review the literature surrounding the subject.

Methods
A patient of Xhosa heritage was referred to the fetal medicine unit at Tygerberg Hospital because of unusually short limbs at 25 weeks’ gestation. At our centre additional ultrasound findings were: bowing of the femurs, irregular vertebral bodies containing double ossification centres, narrow and pear shaped chest, a midline defect of the occipital bone without herniation of intracranial structures, vermian hypoplasia and micrognathia. The patient was counselled about the suspected diagnosis of dyssegmental dysplasia and poor prognosis and opted for termination of pregnancy. Postnatal examination revealed poor mobility of the femurs, fixed flexion of the elbows, talipes, brachycephaly, flattened nasal tip, low set and posteriorly rotated right ear and proptosis. On skeletal survey the vertebrae were irregular in size with sagittal clefting, very short broad long bones with bowed femurs, splayed metaphyses and abnormal iliac bones. In absence of further genetic testing and as the mother opted for termination of pregnancy we are unsure of which subtype of dyssegmental dysplasia was present. A postmortem was requested and results are awaited. This case is the fourth known case of dyssegmental dysplasia in South Africa in the past 20 years. Two previous cases were also found Xhosa patients and the other in a patient of Zulu heritage.

Results
The main findings in dyssegmental dysplasia described in the literature include bowed long bones with flaring of the metaphyses, micromelia, narrowing of the chest with flared anterior rib margins, decreased joint mobility, clubfeet, short neck, anisospondyly and vertebral clefting. Other findings include abnormal facies with flattened profile, micrognathia, cleft palate, occipital encephalocele, inguinal hernias, cryptorchidism, hirsutism, midline cerebellar hypoplasia and occasionally other brain and cardiac abnormalities. Pathognomonic ultrasound features are an irregular appearance of the spine with varying size and shape of vertebral bodies and ossification centres (anisospondyly) with camptomelia and micromelia. The literature suggests 2 distinct types, a more severe Silverman-Handmaker (SH) type and a milder Rolland-Desbuquois (RD) type. The overlap in clinical and radiological findings is significant with the main differences being the length in survival, severity of micromelia and bowing, presence of encephalocele (although occipital defects have been documented in both) and abnormality of the iliac bones and scapulae. The pathological differences however are prominent, with near normal growth plate morphology, normal size calciospherites in the bone and large bands of collagen fibres in the resting cartilage in RD and disorganisation of the growth plate with large non-merging calciospherites in the bone and almost no bands of collagen fibres detectable in resting cartilage in SH. SH is caused by mutations in the HSPG2 (Heparin Sulphate ProteoGlycan) gene (chr 1p36. 1-35) which codes for Perlecan which is present in basement membranes, on certain cell surfaces, in cartilage and stroma of connective tissue, has Fibroblast Growth Factor 2 as binding partner and in mice has been shown to localise AChE to neuromuscular junctions. Absence of Perlecan therefore contributes to the destabilized matrix structure, growth defects and respiratory failure with early demise in SH. The exact genetic cause of RD is unknown but is also suspected to be allelic mutations in the HSPG2 gene but may also be related to low levels of Matrix Metalloproteinase-2 and Tissue Inhibitor of Metalloproteinase-1, disrupting blood vessel invasion into the calcified cartilage.

Conclusion
Parents of children with dyssegmental dysplasia need genetic counselling regarding the recurrence risk and very limited survival. Distinction between the two subtypes could be improved by identifying the gene mutation in RD type and ascertaining if there are differences in AChE levels at neuromuscular junctions in the two types which may account for the difference in duration of survival.