

Brittle Bone Disease: Optimising Perinatal Outcome through Multidisciplinary Collaboration

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Obstetrics — Genetic Disorders

Case Report | ISUOG World Congress



Cambridge
University Hospitals
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Background

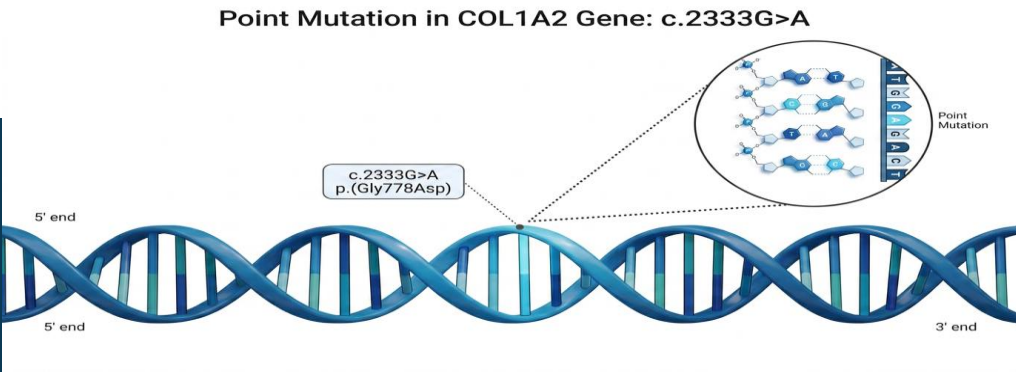
Osteogenesis imperfecta (OI) is a heterogeneous group of heritable skeletal dysplasias causing bone fragility, fractures with minimal or absent trauma, dentinogenesis imperfecta, post-pubertal hearing loss, joint hypermobility and short stature.

At least 7 recognised OI types exist; most are autosomal dominant (COL1A1/COL1A2), but a substantial proportion of severe or lethal cases arise as de novo variants.

Key Molecular Finding

COL1A2 c.2333G>A p.(Gly778Asp)

Heterozygous, de novo, likely pathogenic – consistent with COL1A2-related skeletal dysplasia (OI types II–IV, MIM 166210/259420/166220; combined OI/Ehlers–Danlos syndrome 2, MIM 619120). Parent gene MIM 120160.



Case Summary

31-year-old woman, G4P1+2: previous spontaneous vaginal delivery. Late booker at ~19/40.

20-week anomaly scan identified shortened, bowed fetal long bones .

Amniocentesis performed: negative QF-PCR; rapid prenatal exome sequencing (R21) identified the COL1A2 variant above, confirming a molecular diagnosis of severe OI.

→ referred to a tertiary fetal medicine unit at 27+5 weeks due to the fetal skeletal difference and genetic diagnosis for specialist counselling and multidisciplinary birth planning.

Couple counselled in detail by the fetal medicine team, clinical genetics and neonatal teams; after independent reading, they were committed to the pregnancy.

Genetic Counselling

De novo variant explained – first occurrence in the family; autosomal dominant OI carries a 50:50 transmission risk should the individual survive to reproduce.

Given the prenatal-onset of the findings, a severe phenotype (e.g. progressively-deforming type III OI) was anticipated – neonatal fractures with routine handling, possible respiratory compromise from rib fractures, need for mobility support, short adult stature, normal intelligence, and later risk of basilar invagination and hearing loss.

Moreover, referral was arranged to Paediatrics Endocrinology and Brittle Bone Society information leaflets were provided on diagnosis and infant care.

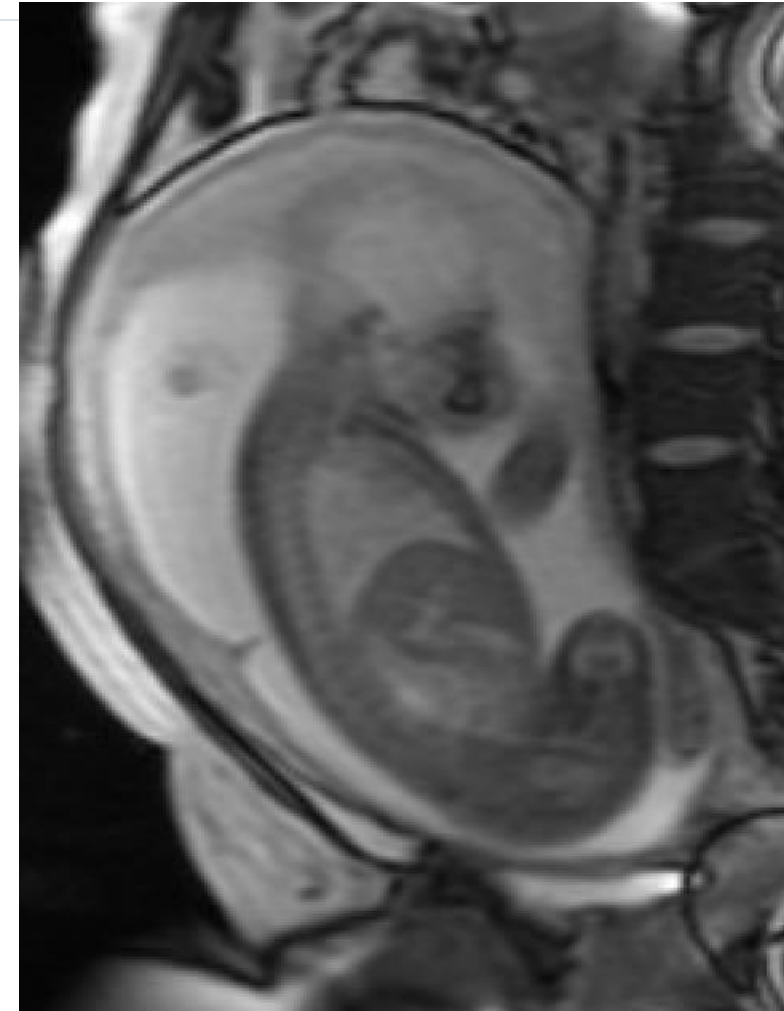
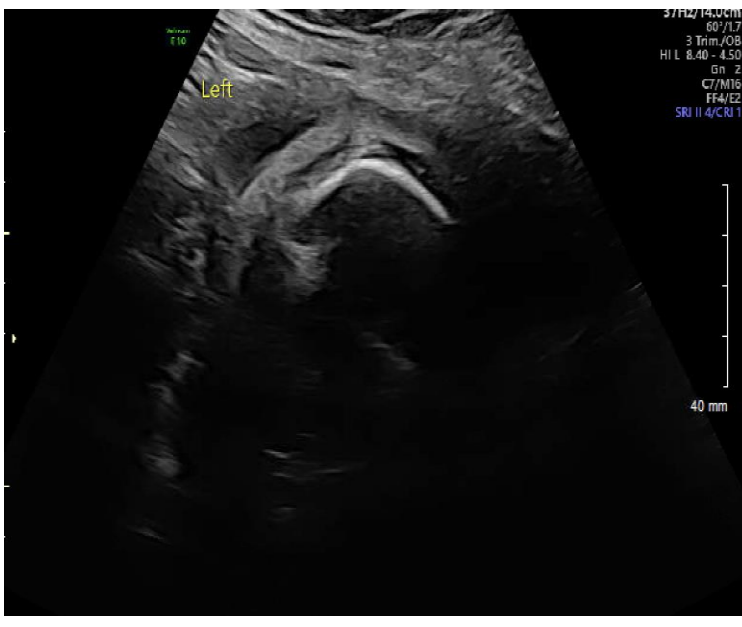
Evidence Informing Prognosis

The same COL1A2 variant has previously been reported in association with progressively-deforming (type III) OI in the published literature. A lethal outcome has also been reported in one patient carrying this variant, underlining the wide phenotypic variability possible with this genotype.

Regional MDT genetic review identified 2 further reported cases of this de novo variant, with no accompanying clinical follow-up data – supporting the decision to anticipate and plan for a severe phenotype.

Serial Prenatal Imaging

Gestation	Key Findings
27+5 wks	Normal head; ribs short, reduced curvature, straight toward the tip; long bones short and bowed. FL/AC ratio 0.105. Normal fluid & good fetal movements.
30+6 wks	Chest/abdomen ratio 0.86; cardiothoracic ratio 0.509 (both normal). Femur angulated ~90° mid-shaft – fracture not excluded.
Fetal MRI	Normal lung volume (~50ml, expected ~40ml) and structurally normal viscera. Bilateral prominent renal pelvises, no dilated ureters, normal DWI function. Proximal long bones short; distal long bones poorly seen; spine and brain grossly normal.
34+6 wks	Breech presentation; fetal brain unusually easy to visualise through the skull on US – suspected poor cranial ossification.



Ultrasound and MRI images during the course of the pregnancy showing shortened and bowed long bones and straight deformed rib cage bones.

Regional MDT & Birth Planning

Joint virtual MDT: Cambridge (CUH) fetal medicine, genetics, neonatology and endocrinology with the Birmingham Women's & Children's specialist OI team, informed by prior Nottingham experience of severe-OI delivery.

Consensus: severe OI with major implications for safe handling; classical caesarean incision favoured over lower-segment for atraumatic breech extraction.

Elective admission from 36 weeks to avoid unplanned local delivery; caesarean timed close to 39 weeks to maximise lung maturity and minimise the need for neonatal intubation and neck extension.

Detailed handling protocol pictogrammed in the notes: baby kept flat at all times, spine straight, no swaddling, palms supporting spine, two senior consultant operators.

Antenatal steroid use, analgesia strategy and neonatal bisphosphonate (pamidronate) dosing pre-agreed with Birmingham ahead of delivery.

Core Multidisciplinary Teams

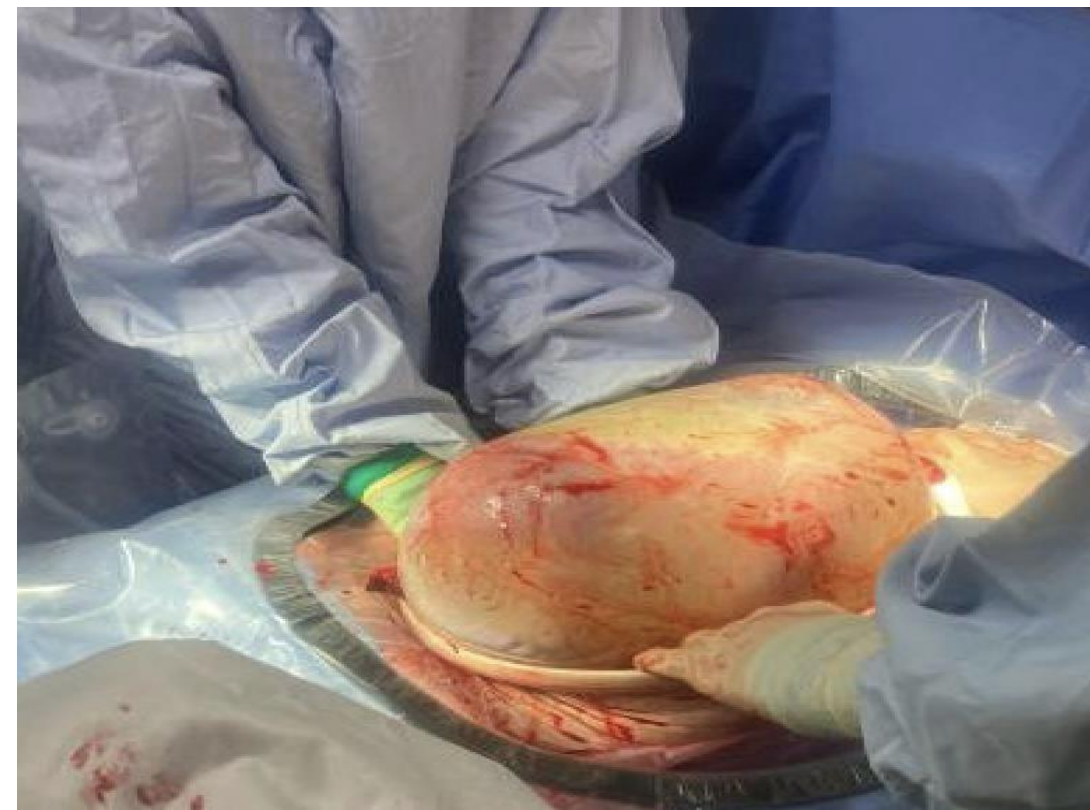
Fetal Medicine	Clinical Genetics	Neonatology	Endocrinology (CUH)	Obstetric Anaesthesia
Regional OI / Metabolic Bone Service (Birmingham)			Community OT & Physiotherapy	

Delivery & Maternal Course

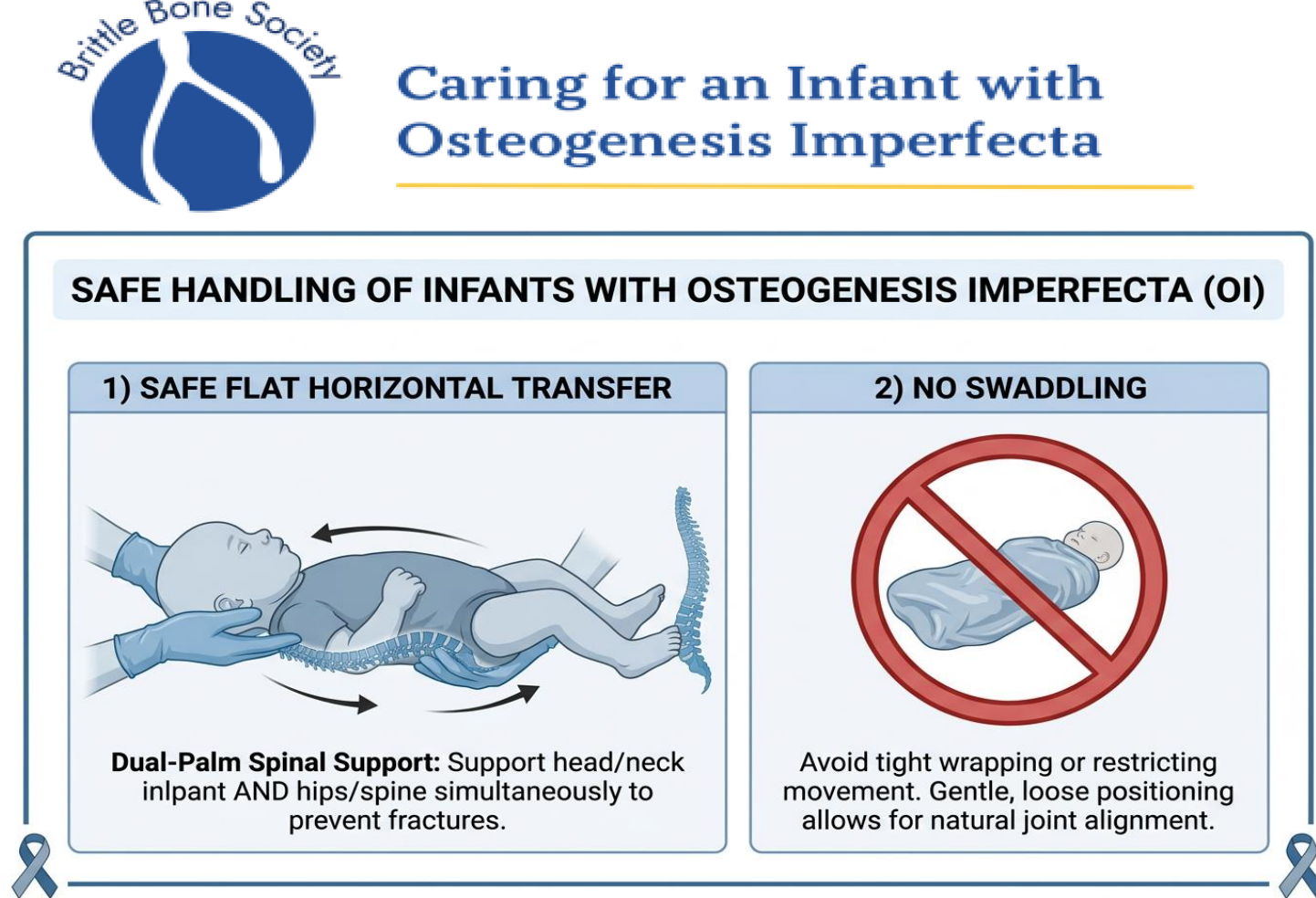
Elective classical caesarean, two fetal medicine consultants; breech confirmed on table, back posterior. Generous classical uterine incision; the baby delivered en caul atraumatically, then membranes ruptured, and the baby moved flat directly to the resuscitation platform.

Birthweight 3220g. EBL 1500ml, managed with uterotonics (Syntocinon, Ergometrine, Misoprostol).

Day 3: transient pyrexia (38°C) treated with IV co-amoxiclav, and discharged home on postnatal day 4.



Classical CS with en caul delivery



Neonatal Course & Outcome

APGAR 7/9/10 at 1/5/10 min. Facial CPAP for respiratory support; admitted to NICU, clinical assessment was consistent moderate–severe OI, with likely joint hypermobility.

Full skeletal survey, cranial MRI, echocardiogram and hip ultrasound as per pre-agreed protocol; no routine BP-cuff readings or hip manoeuvres given fracture risk.

Analgesia (paracetamol/opioids), cholecalciferol for vitamin D deficiency, and pamidronate infusion protocols (2 consecutive days, calcium cover for 7 days, 8-weekly cycles planned to age 2) were initiated with Birmingham guidance. Discharged to local hospital day 13.

Left humeral fracture happened on the day of discharge and was managed conservatively – recognised as typical of OI, not a marker of inadequate handling.

By 9 months: no further fractures, good emerging head control, alert and socially responsive infant and growth tracked proportionate to stature (moderate–severe OI infants fall outside standard WHO centiles).

Ongoing wraparound MDT support – community OT/physiotherapy (bathing, tummy time, side-lying progression), metabolic-bone CNS home visits, housing needs assessment, and psychology input for the family.

Conclusion

Early, coordinated multidisciplinary collaboration – spanning fetal medicine, clinical genetics, neonatology and a specialist regional OI service – enabled comprehensive parental counselling and meticulous birth planning, optimising neonatal outcome in this case of severe, prenatally-diagnosed Osteogenesis Imperfecta.