

# LIMB–BODY WALL COMPLEX WITH CRANIOFACIAL DEFECTS AFTER OVARIAN STIMULATION

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A primigravid woman aged 34 years was referred for genetic counseling at 23 weeks' gestation because of fetal abdominal wall defects, cranioplacental attachment, craniofacial (CF) abnormalities, and an upper limb abnormality. The father was aged 36 years. The mother reported no illnesses or recent infections. She had no history of prenatal exposure to teratogenic agents, nor any family history of congenital malformations. The woman had a 4-year history of primary infertility. She conceived after ovarian stimulation with clomiphene citrate and human menopausal gonadotropin. Level II ultrasound examinations demonstrated a live fetus with cranioplacental attachment, an occipital encephalocele, facial cleft, hypoplasia of the right humerus, absence of the right forearm and right hand, absence of the right hemithorax, extracorporeal right lungs, abdominal wall defects with eviscerated liver, stomach and bowel, a normal amount of amniotic fluid, a fetal biometry equivalent to 20 weeks' gestation, and scoliosis. The pregnancy was subsequently terminated. A female fetus was delivered with a body weight of 394 g. Cytogenetic analysis of fetal tissues revealed a 46,XX karyotype. Postnatal examinations confirmed limb–body wall complex (LBWC) with CF defects (Figure). The female external genitalia, anus, lower extremities and umbilical cord were normal.

LBWC describes a heterogenic group of fetal malformations, including lateral body-wall defects and limb reduction anomalies [1–8]. Cases of LBWC with CF defects frequently show severe anomalies of the upper limbs, CF defects, constrictive amniotic bands, and cranioplacental attachment, whereas cases of LBWC



**Figure.** The fetus at birth with limb–body wall complex and craniofacial defects.

without CF defects usually present with major anomalies of the lower limbs, abnormal genitalia, anal atresia, renal defects, abdominoplacental attachment, and umbilical cord abnormalities [6,9]. The difference in the incidence of births between these two groups may be in part because of their different pathogenesis, or due to lethality resulting in early pregnancy loss in cases of LBWC with CF defects [6]. The possible pathogenetic mechanisms for LBWC include early amnion rupture [10], vascular disruption [7,8], and early embryonic maldevelopment [11,12]. Russo et al [9] suggested that LBWC with CF defects is caused by an early vascular disruption, whereas LBWC without CF defects is related to defective lateral and caudal folding of the embryonic disk.

Recent reports have suggested that infants conceived by assisted reproductive technology have an increased risk of congenital malformations, compared



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Accepted: October 31, 2008

with naturally conceived infants [13]. Litwin et al [14] reported iniencephaly, craniorachischisis, complete absence of external genitalia and LBWC in a fetus after *in vitro* fertilization (IVF). Hirokawa et al [15] reported a case of a body stalk anomaly arising in the second baby of a triplet pregnancy after IVF. Shanske et al [16] reported omphalocele-exstrophy-imperforate anorectal defects in a triplet pregnancy after IVF and chorionic villus sampling. Pre-ovulatory administration of clomiphene citrate to mice has been shown to impair uterine functions and cause fetal growth retardation and neural tube defects in post-implantation embryos [17]. Ovarian stimulation may also increase the risk of imprinting disorders [18–20]. This report raises the possibility that the etiologic factors in cases of LBWC with CF defects may include ovulation stimulation in addition to IVF, multiple pregnancies, and exposure to CVS, as demonstrated by other reports of LBWC and neural tube defects in association with assisted reproductive techniques.

## Acknowledgment

This work was supported by a research grant MMH-E-97004 from Mackay Memorial Hospital, Taipei, Taiwan.

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