

Prenatal to Postnatal Outcomes in a Whole Maternal Isodisomy 6: A Case Report with Favorable Prognosis and Literature review

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Case Report

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Abstract

Introduction

Whole maternal isodisomic uniparental disomy of chromosome 6 (UPiD6) is extremely rare, associated with various clinical manifestations and few favorable outcomes have been reported. We investigated a prenatally diagnosed fetal case with whole maternal UPiD6 and reviewed literature of maternal UPD6.

Case report

A female fetus with microdeletion and microduplication of chromosome 6 by non-invasive prenatal test (NIPT) subsequently diagnosed with whole maternal UPiD(6) was selected as the study subject. The amniotic fluid karyotype was normal. Except whole maternal UPiD6, no pathogenic copy number variations (CNVs) and pathogenic sequence variants was found by chromosomal microarray analysis (CMA) and trio whole-exome sequencing (WES), respectively. After genetic counseling, the parents opted to continue the pregnancy. Except intrauterine growth restriction (IUGR) from 26 weeks in gestation period and catch-up growth at postnatal stages, no major anomalies were found at her 27-month age. CMA of multiple placental samplings demonstrated mosaicism of large-segment deleterious deletions or duplications of chromosome 6p which was consistent with NIPT results while CMA of umbilical cord showed UPD6. Additionally, placental pathology showed dysplasia and infarctions. Previously reported maternal UPD6 cases were reviewed for prenatal and postnatal features. Literature review of 26 maternal UPD6 cases identified IUGR in 23 (88.5%), which often with single-gene disorders and poor prognosis.

Conclusions

Confined placental mosaicism (CPM) of large-segment deleterious deletions or duplications of 6p likely explains IUGR and placental dysfunction in our case. Importantly, when pathogenic CNVs/SNVs are prenatally excluded by CMA/WES in whole maternal UPiD6 fetuses, a favorable postnatal outcome may be achievable with close management.

Introduction

Uniparental disomy (UPD) is a rare genetic phenomenon, first described in 1980, in which an individual inherits both copies of a specific chromosome, or a segment of a chromosome, from a single parent [1]. Its estimated incidence ranges from 1 in 3,500 to 1 in 5,000 live births [2]. UPD is categorized into two main types: uniparental isodisomy (UPiD) and uniparental heterodisomy (UPhD)[3]. UPiD occurs when two identical copies of the chromosome are inherited from one parent, typically resulting from non-disjunction of sister chromatids during meiosis II, followed by trisomy or monosomy rescue[4]. In contrast, UPhD arises from non-disjunction between homologous chromosomes during meiosis I, also corrected by trisomy rescue [4]. Additionally, other rare mechanisms leading to UPD have also been reported and include chromosomal rearrangements involving acrocentric chromosome, mitotic crossing over, a post-fertilization error, gamete complementation, somatic replacement of a derivative chromosome, correction of interchange monosomy, and the correction of a trisomy that results in a small supernumerary marker chromosome[5, 6]. The clinical consequences of UPD are primarily determined by the specific chromosomal regions and genes involved. Potential outcomes include the manifestation of autosomal recessive (AR) disorders, imprinting disorders, X-linked recessive disorders in females (or father-to-son transmission of X-linked disorders), and fetal or placental mosaicism for trisomy [5, 7].

Maternal uniparental disomy of chromosome 6 (UPD6) is a rare event, with only approximately 26 cases previously reported, exhibiting diverse phenotype[8, 9]. The clinical presentation associated with maternal UPD6 is highly variable and depends on several factors, including whether the disomy involves the entire chromosome or a segment, whether it is

UPiD, UPhD, or a combination of both, the presence of recessive pathogenic variants within the disomic region, and the involvement of imprinted regions regulated by epigenetic mechanisms such as DNA methylation. Among these, whole maternal UPiD6 is exceptionally rare, with only 10 cases documented to date. The clinical spectrum of whole maternal UPD6 is also variable. Based on prior reports, intrauterine growth retardation (IUGR) and preterm delivery are the most common manifestation; however, most cases have also presented with various congenital malformations and/or pathogenic gene variants [8, 10–17]. Although IUGR has been partially associated with maternal UPD6, the underlying mechanisms remain incompletely understood. Among the 7 reported cases that underwent comprehensive genetic testing, pathogenic variants in autosomal recessive genes on chromosome 6 were identified in 5 cases[11, 12, 16–18], while the other 2 cases were associated with X-linked disorders originating from chromosomes other than 6[8, 13]. The remaining cases, which lacked comprehensive genetic testing, presented primarily with malformations or developmental delay[10, 14, 15]. Notably, none of the previously reported cases had an entirely favorable prognosis. Herein, we report a novel case of entire maternal UPiD6 presenting with isolated IUGR prenatally and low birth weight postnally, without structural malformations or other significant comorbidities, and with an apparently favorable outcome upon follow-up. Furthermore, we conducted a comprehensive literature review to summarize the characteristics of all reported cases of maternal UPD6.

Case report

A 27-year-old woman, who claimed no family history of genetic abnormalities and previously had one induced abortion, was referred to our center. She underwent selective amniocentesis at 19 weeks of gestation due to a non-invasive prenatal test (NIPT) result suggesting a potential abnormality involving chromosome 6 (average Z-score: pter-6p25.1: -4; 6p25.1-p22.3: +4, while the rest part of 6p: 0.39, and 6q was 0) (Fig. 1). The karyotype of cultured amniocytes was 46,XX and CMA analysis of DNA extracted from uncultured amniocytes showed UPD6. After comparison of CMA from the spouse's peripheral blood, whole maternal UPiD(6) was identified in the fetus. The pregnancy progressed uneventfully until 26 weeks' gestation, when ultrasound surveillance revealed the development of IUGR characterized by the abdominal circumference (AC) falling below the 10th percentile for gestational age (based on the Asian population standards from the National Institute of Child Health and Human Development, NICHD), while other biometric parameters (biparietal diameter, head circumference, femur length) remained relatively preserved. The prenatal growth curves are shown in Fig. 2. Then, trio-WES and fetal infection etiologies were further conducted. Also, maternal etiologies for fetal growth restriction were studied. A multidisciplinary team (including perinatology, clinical genetics, and neonatology) provided comprehensive counseling regarding potential fetal and postnatal clinical phenotypes, after which the patient opted to continue the pregnancy. Serial ultrasound monitoring was conducted throughout the pregnancy. Due to the onset of oligohydramnios which was without evidence of rupture of the membranes, an elective cesarean section was performed at 37 weeks' gestation. The newborn achieved Apgar scores of 10 at 1, 5, and 10 minutes. Anthropometric measurements at birth, standardized according to the age- and weight-corrected standards for girls (World Health Organization, WHO), were as follows: weight 1640 g (< -3 SD), and length 41 cm (< -3 SD). Comprehensive follow-up monitoring, including pediatric healthcare, was provided after birth.

Materials and Methods

Karyotype analysis

Prenatal cytogenetic analysis was performed on cultured amniocytes. A standard G-banded karyotype analysis with a resolution of approximately 400 bands was conducted on amniotic fluid samples to assess for chromosomal structural abnormalities.

Chromosomal microarray analysis (CMA)

Genomic DNA was extracted from amniotic fluid, parental peripheral blood samples, umbilical cord, and placenta samples from multiple sites (maternal surface and fetal surface). The placenta samples from uncultured villi, containing cytotrophoblast cells and the mesenchymal core, were used for CMA. And then, genomic DNA was digested, attached to adapters, amplified, purified, fragmented, and then hybridized with an Affymetrix® Cytoscan TM 750K array (Affymetrix, Santa Clara, CA, USA) that contained SNP probes. The CMA was carried out to identify chromosomal copy number variation according to standard protocol, as previously described[19].

Trio-Based Whole-Exome Sequencing (trio-WES)

Prenatal trio-WES was performed to investigate genetic etiologies of IUGR using genomic DNA extracted from amniotic fluid cells (proband) and parental peripheral blood leukocytes. Libraries were prepared with the NanoWES Human Exome V1 kit (Berry Genomics) and sequenced on an Illumina NovaSeq 6000 platform with minimum 100×coverage, followed by bioinformatic analysis involving alignment to the GRCh38/hg38 reference genome, variant calling using GATK v4.[X], and annotation through ANNOVAR integrating population frequency (gnomAD v[X]), clinical significance (ClinVar), and in silico prediction databases. Variant interpretation adhered to the American College of Medical Genetics and Genomics (ACMG) guidelines[20, 21].

Fetal infection etiologies and maternal etiologies studies

Potential fetal infections [22] (cytomegalovirus, toxoplasmosis, herpes simplex) were analyzed via PCR of amniotic fluid, while maternal contributors to IUGR were evaluated through autoimmune serology (antinuclear antibodies, anti-double-stranded DNA, anti-Smith antibody), antiphospholipid syndrome markers (anticardiolipin antibody, anti-β2 glycoprotein type I antibody [GPI], lupus anticoagulant [LA] 1 and 2), and thrombophilia assessment (protein C/S activity, platelet aggregation rates, homocysteine, plasma D-dimer) in maternal plasma.

Placental histopathology

Placental histopathological examination was assessed by microscopy through fixation of the placental disc and umbilical cord in 10% buffered formalin, paraffin embedding, and hematoxylin-eosin (H&E) staining according to standard institutional protocols.

Literature search

A literature search was conducted in databases including Pubmed, Ovid Embase, and Ovid Medline from inception to July 12, 2026 with the search query: (“uniparental disomy”[MeSH] OR “uniparental disomy” OR “UPD”) AND (“maternal” OR “maternal origin” OR “UPD(6)mat”) AND (“chromosome 6”). Ovid Medline was searched by limiting the search terms to include human, English language, abstracts, and full text. Two investigators(YPQ and HW) independently conducted the initial search and study selection, including removing duplicated studies, irrelevant publications, animal studies, and UPD(6)pat, screening the titles and abstracts, and identifying studies for full-text review.

Results

Cytogenetic studies, CMA and WES

Cytogenetic analysis revealed a normal G-banded karyotype (400-band resolution) on cultured amniocytes. Chromosomal microarray identified a whole-chromosome 6 region of homozygosity (ROH) (Fig. 3a) without pathogenic copy-number variants, with parental confirmation establishing maternal uniparental disomy 6 in amniotic fluid. The CMA results

obtained from the umbilical cord and from multiple placental sites—including the inner and lateral sides of the fetal counterpart and the inner and lateral sides of the maternal counterpart—are summarized in Table 1 and illustrated in Figs. 3b–3f. Trio whole-exome sequencing corroborated complete maternal isodisomy of chromosome 6 while excluding clinically significant copy-number variations, pathogenic variants associated with fetal growth restriction, and recessive disorders within chromosome 6 homozygous regions.

Table 1
The CMA results of different samples of placenta and umbilical cord.

Sample	CMA results(ISCN Nomenclature)	Region of chromosomal abnormality	Types of CNVs	Size (bp)	% of total tested cells
umbilical cord	arr[GRCh37] (6)x2 hmz	chr6:203878-170896644	ROH	170692767	100
Inner side of the placenta fetal counterpart	arr[GRCh37] 6p25.3p24.3(156,975_9,583,993)x1 ~ 2	chr6:156975-9583993	LossMosaic	9427019	81
	arr[GRCh37] 6p24.3q27(9,933,492_170,896,644)x2 hmz [0.2]	chr6:9933492-170896644	ROH	160963153	20
Lateral side of the placenta fetal counterpart	arr[GRCh37] 6p25.3p24.3(156,975_7,450,801)x1 ~ 2	chr6:156975-7450801	LossMosaic	7293827	low-proportion
	arr[GRCh37] 6p24.3p21.1(7,452,350_45,990,584)x2 ~ 3	chr6:7452350-45990584	GainMosaic	38538235	60
	arr[GRCh37] 6p21.1q27(45,994,063_170,896,644)x2 mos hmz	chr6:45994063-170896644	ROH	124902582	low-proportion
Inner sides of the placenta maternal counterpart	arr[GRCh37] 6p25.3p24.3(156,975_7,481,166)x1 ~ 2	chr6:156975-7481166	LossMosaic	7324192	58
	arr[GRCh37] 6p24.3p22.3(7,494,202_19,467,927)x2 ~ 3	chr6:7494202-19467927	GainMosaic	11973726	60
	arr[GRCh37] 6p22.3(19,470,297_22,988,080)x3	chr6:19470297-22988080	Gain	3517784	100
	arr[GRCh37] 6p22.3q27(23,309,545_170,896,644)x2 hmz [0.5]	chr6:23309545-170896644	ROH	147587100	50
Lateral side of the placenta maternal counterpart	arr[GRCh37] 6p25.3p24.3(156,975_7,494,202)x1 ~ 2	chr6:156975-7494202	LossMosaic	7337228	47
	arr[GRCh37] 6p24.3p22.3(7,495,756_19,525,832)x2 ~ 3	chr6:7495756-19525832	GainMosaic	12030077	52
	arr[GRCh37] 6p22.3(19,558,580_22,988,080)x3	chr6:19558580-22988080	Gain	3429501	100
	arr[GRCh37] 6p22.3q27(23,202,962_170,896,644)x2 hmz [0.55]	chr6:23202962-170896644	ROH	147693683	55

CMA: chromosomal microarray analysis; ISCN: international system for human cytogenetic nomenclature; ROH: regions of homozygosity; CNV: copy-number variants

Fetal infection etiologies and maternal etiologies studies

Maternal evaluation revealed an isolated elevation in plasma D-dimer (2.53 mg/L; non-pregnant reference < 0.55 mg/L). All immunological and thrombotic parameters tested were negative, including antinuclear antibodies, anti-dsDNA, anti-Smith,

anticardiolipin, anti- β 2GPI, lupus anticoagulants (LA1/LA2), protein C/S activity, platelet aggregation, and homocysteine. Furthermore, amniotic fluid PCR screening excluded cytomegalovirus, toxoplasmosis, and herpes simplex infections.

Placental Histopathology

Macroscopic examination revealed a small placenta (230 g, <3rd percentile; normal 500–600 g) measuring 13×12×2 cm with intact membranes and a normocoiled 40-cm trivascular umbilical cord, while histology demonstrated villous immaturity (Fig. 4a) for gestational age, distal villous dysplasia with intervillous space expansion, multifocal infarctions with syncytial knots, and evidence of a mild-to-moderate chronic villitis (Fig. 4b).

(a) The placenta maturity is less mature than that of the gestational week. The villi show localized distal villus dysplasia changes with uneven maturity, presenting as relatively mature villus (red rectangular box) and immature villus (blue rectangular box) morphology. (b) Mild-to-moderate chronic villitis was apparent (red rectangular box).

Clinical follow-up

Elevated umbilical artery systolic/diastolic ratio (S/D) ratios were first observed at 31⁺₄ weeks of gestation (3.88; 96.6th percentile) and subsequently fluctuated within a relatively normal range (2.67 ~ 3.26; 58th ~ 89th percentile). Other Doppler indices including umbilical artery pulsatility index, resistance index and middle cerebral artery peak systolic velocity remained relatively normal before 36 weeks. In response, low molecular weight heparin (LMWH) therapy was initiated daily until 36 weeks. Between 35 and 36 weeks, fetal growth plateaued. Subsequently, amniotic fluid volume rapidly declined following the 36-week assessment.

Following delivery, the newborn required a 10-day hospitalization for management of low birth weight and neonatal pathological jaundice, with blood cultures positive for *Staphylococcus epidermidis*. Post-discharge, the infant exhibited significant catch-up growth despite severe prenatal intrauterine growth restriction. Serial anthropometric measurements demonstrated progressive improvement: at 1 month, weight was 2.20 kg (<-3 SD) and length 46.2 cm (<-3 SD); by 4 months, these parameters improved to 4.90 kg (-2 to -2.5 SD) and 57.4 cm (-2 to -2.5 SD), subsequently stabilizing between -2SD and 0SD. Concurrently, occipitofrontal circumference normalized from 34.0 cm (-2 SD) at birth to 40.0 cm (mean for age) at 4 months, maintaining age-appropriate percentiles thereafter (Fig. 5). During longitudinal follow-up to 2 years 3 months of age, neurodevelopment has progressed appropriately for age, evidenced by a normal Denver Developmental Screening Test at 12 months. Physical examinations remain unremarkable except for subclinical hypothyroidism managed with levothyroxine 12.5 μ g every other day. There was resolution of hypothyroidism by 25 months of age, and the girl has since remained off medication with normal thyroid function.

Literature review

The search yielded 10203 articles up to now (Pubmed: 380; Ovid Embase: 4852; Ovid Medline: 4971). We identified 26 cases of maternal UPD6 from 21 articles[8, 10–18, 23–33] and extracted the following clinical information (including our case): method for UPD detection, NIPT results, additional genetic information, reason for ascertainment, prenatal and postnatal phenotypic features, placental genetical and (or) pathological manifestations. The detailed information is shown in Supplementary 1, listing first whole isodisomies, followed by partial isodisomies, then heterodisomies, and finally isodisomy & heterodisomy UPD6.

Discussion

Whole maternal UPiD6 remains exceptionally rare, with only ten documented cases worldwide since 1996[8, 10–18]. However, with the only short tandem repeat (STR) locus technique used, one case[26] remained ambiguous as to whether it represented complete or partial maternal UPiD6. Prenatal IUGR was reported in all of the cases (10/10). However, among the 10 cases that underwent molecular testing, more than half (N = 7) had abnormal phenotypes caused by the

unmasking of different autosomal recessive diseases due to UPiD. Additionally, the majority presented with neurodevelopmental delay or structural anomalies (Supplementary 1). Notably our case, with no identified pathogenic variants for single gene disorders, demonstrates isolated fetal growth restriction and low birth weight with favorable neurodevelopmental outcomes during longitudinal follow-up, representing the first report of near-normal development in whole isodisomic UPD(6)mat.

Fetal growth restriction (FGR), previously referred to as IUGR[34], along with low birth weight, constitutes the hallmark phenotype associated with complete UPD(6)mat [28], though the precise etiology remains elusive. While FGR pathogenesis typically involves multifactorial mechanisms—including fetal, placental, and maternal contributors [22]—confined placental mosaicism (CPM) is a well-recognized cause of UPD-related FGR [35]. CPM refers to chromosomally abnormal cell lines restricted to the placenta while the fetal karyotype is normal [36], and it has been associated with adverse outcomes including low birth weight and placental dysfunction [37, 38]. CPM can be classified into three types based on the affected cell lineages: type I is confined to the cytotrophoblast (CTB), type II involves the mesenchymal core (MC), and type III affects both cell lineages [39]. CTB derived from trophoblast will develop into placenta, while MC derived from inner cell mass will develop into hypoblast [40]. Since NIPT investigates the CTB, only types 1 and 3 can be detected [41]. Based on the UPD forming theory of trisomy or monosomy rescue, the NIPT could be presented as high risk of trisomy or monosomy of chr6. NIPT findings were not documented in the majority of cases. However, high risk of trisomy 6 was reported in 3 cases[18, 30], and low risk of chromosome aneuploidy NIPT result was observed in one case[33]. In our case, NIPT results did not show high risk of trisomy 6 instead of presenting a similar trend as CMA results in placental maternal sides (Fig. 3e and 3f). And, placental CMA results showed mosaicism gain and/or loss of CNVs in 6p and mosaicism of bi-copy number of 6q (Fig. 3c ~ 3f), while whole maternal UPiD6 was found in amniotic fluid and umbilical cord in our case (Fig. 3a and 3b). Combined the fetal, umbilical, and placental CMA results, the formation of whole maternal UPiD6 in amniotic fluid and umbilical cord may be suggested into mitotic origin rather than meiosis origin. A plausible mechanism is that an early post-zygotic chromosomal imbalance involving chromosome 6 (e.g., a mosaic deletion or an isodicentric chromosome) occurred in trophoblast/embryonic precursor cells, followed by a somatic recombination using the normal homologous chromosome as a template. This process would progressively restore a balanced chromosomal complement in the lineage giving rise to the fetus, while leaving segmental imbalances confined to the placenta. Such a model of “post-zygotic rescue” leading to uniparental disomy has been described in the context of CPM [42]. Notably, a gradient of mosaicism was observed from the placental maternal side (highest complexity) to the umbilical cord and amniotic fluid (pure UPiD6), consistent with gradual resolution of the imbalance during embryonic development. However, uncultured villi of mixed both cell lineages of CTB and MC, and limited placental samplings makes the precise origin mechanism complicated and still unclear. Comprehensive genotyping of additional placental sections is warranted.

Placental dysfunction is also documented in UPD. Cajas et al. described placental dysfunction in paternal UPD6, featuring cytogenetic trisomy 6 mosaicism alongside pathological findings of immature chorionic villi, dilated vessels, and myxoid changes [43]. While one case reported normal functional placenta[11], one normal placental CNV-seq results [18], and one noted dysfunction without detailed placental genetics [14], most lack reported placental function data (Supplementary 1). Severe placental dysfunction, including large infarcts and abnormal villous development, has been linked to high-level CPM on chromosome 2 despite normal amniotic fluid karyotype [44]; however, a study of 69 prenatally diagnosed CPM cases found no specific histopathology [45]. Placental dysfunction in our case was evident from histopathology: a small placenta (230 g, <3rd percentile), villous immaturity, distal villous dysplasia with intervillous space expansion, and multifocal infarctions (Fig. 4). These findings are similar to previously reported cases where high-level CPM on other chromosomes led to severe placental insufficiency [44, 46]. Although the level of mosaicism in our placental samples was not uniformly high, even moderate or localized mosaicism of deleterious segmental CNVs on chromosome 6p may be sufficient to impair villous development and placental function, ultimately contributing to FGR.

Additionally, isodisomy UPD elevates risks for autosomal recessive disorders due to loss of heterozygosity. For instance, recessive *CUL7* mutation resulting in 3M syndrome was implicated in one case with low birthweight and segmental maternal isodisomy (*CUL7* being located at 6p21.1) [31], whereas another case with segmental 6p UPD (and autosomal recessive molybdenum deficiency due to a maternal *MOCS1* mutation, *MOCS1* being located at 6p21.2) exhibited normal intrauterine growth [23]. Critically, our trio-WES excluded pathogenic variants in growth-related genes—particularly chromosome 6 recessive loci—effectively eliminating autosomal recessive disorders as the FGR etiology in this case.

Imprinted genes on chromosome 6 of maternal UPD6 are also implicated in fetal growth regulation. In a fetus with IUGR of whole maternal UPdD, increased methylation of *PLAGL1*(6q24) and *IGF2R*(6q25) was found by multilocus quantitative methylation-sensitive single-nucleotide primer extension (MS-SNuPE) test, however, the maternal UPdD was detected by STR of chr6 while not by SNP array typing or trio-WES[29]. In the reported cases [32] of partial maternal isodisomy& heterodisomy UPD6, one fetus with IUGR showed hypermethylation of the *PLAGL1* and *IGF2R* differentially methylated regions by methylation-specific multiplex ligation probe-dependent amplification (MS-MLPA) and MS-SNuPE, the other fetus with IUGR showed hypermethylation of *PLAGL1* by MS-MLPA. Seemingly, abnormal methylation of imprinted genes in maternal UPD6 were reported in hypermethylation of imprinted *PLAGL1* gene presented in heterodisomy or isodisomy& heterodisomy maternal UPD6, while no reports have described in whole UPiD6. Previous studies in humans and mice with IUGR had identified *PLAGL1* gene as a key regulator in various imprinted and non-imprinted gene networks governing cell growth and metabolism [47, 48]. Based on the limited evidences, it cannot be definitively established whether imprinting defects serve as the genetic mechanism underlying FGR in cases of whole maternal UPiD6. Further transcriptomic analyses or third-generation sequencing, especially focusing on imprinted gene expression, may provide valuable insights into the clinical phenotype observed in our case of whole maternal UPiD6.

Except for IUGR in prenatal stage or low birth weight after birth, most of these reported whole isodisomic UPD(6)mat cases [8, 11–13, 16–18] had abnormal phenotypes in combination with pathogenic gene mutations. Some of these have been attributed to AR[11, 12, 16, 17], while one case[33] cannot be accounted for by single-gene disorders. The case [33]showed negative genetic diseases by WES but with other abnormalities (e.g. fetal abdominal cyst) in a female fetus with hetero/isodisomy partial UPD(6)mat who presented with IUGR in prenatal stages. The fetus was aborted, and no further clinical information was available. Another case [25]also showed negative genetics by WES but with postnatal abnormalities (e.g. growth retardation, feeding difficulties, and strange appearance ar) in a male fetus with partial hetero/isodisomy UPD(6)mat who presented with only IUGR in prenatal stages. Therefore, whether autosomal recessive disorders are the sole cause of the other fetal abnormalities in UPD(6)mat remains unclear. In our case, except for mild hypothyroidism and growth delay before 7months (catch-up growth after birth), no other phenotypic abnormalities were found. Due to the limited number of UPD(6)mat, the mechanism by which it leads to differing phenotypes is unclear. Further studies should be conducted to explore the specific phenotypes and the mechanisms that can lead to whole isodisomic upd(6)mat.

Conclusions

This study documents a case of whole maternal UPiD6 with a favorable prenatal and postnatal prognosis based on comprehensive follow-up to 2 years and 3 months. Our findings suggest that in UPD(6)mat without pathogenic CNVs/SNVs excluded by prenatal CMA/WES, a favorable outcome is achievable under close clinical management. The prenatal diagnosis of UPD6 also enabled a valuable placental study, providing insights into the origin of UPD and the impact of CPM on fetal development. In this case, the observed FGR was most likely attributable to placental dysfunction resulting from complex mosaicism involving large-segment deletions and/or duplications of chromosome 6p, coupled with placental immaturity and infarction.

Declarations

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Author Contributions

Yanping Qian: drafted the manuscript, searched the literature and data extraction, analyzed and interpreted the data. Hao Wang: searched the literature and data extraction, analyzed and interpreted the data, and participated in revising the manuscript. Qingsong Liu and Bocheng Xu: performed the experiments, analyzed and interpreted the data and participated in revising the manuscript. Jie Ruan: revised the manuscript. Shumin Zhao: conceived and edited the manuscript. Zhu Zhang: conceived and designed the study, revised the manuscript, and approved the final version.

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Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval

This study received approval from the Institutional Review Board (IRB) of West China Second University Hospital of Sichuan University (Protocol Number 2024-228). Clinical and laboratory examinations were performed on the fetus after obtaining written informed consent from the parents. Written informed consent was also obtained from the legal guardians of the baby after birth. All procedures were conducted in accordance with the ethical principles of the Declaration of Helsinki (2013 revision).

Competing Interests

The authors declare that they have no competing interests.

Generative AI statement

The author(s) declare that no Generative AI was used in the creation of this manuscript.

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Figures

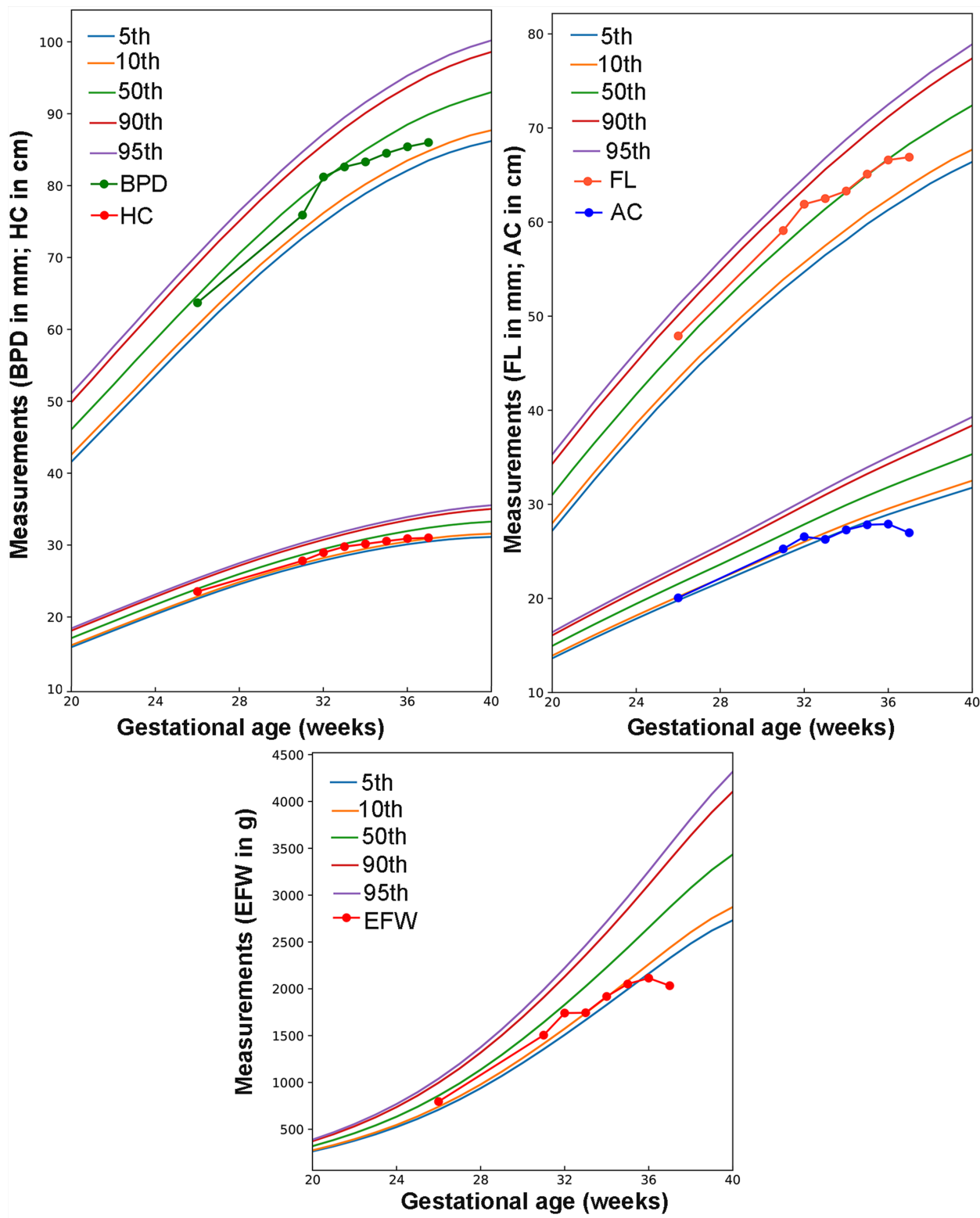


Figure 2

Graphic diagrams of fetal biometric data at different gestational weeks. Standard growth curves (mean and different percentile) are indicated on the same chart. The parameters are corrected by standard of NICHD. BPD, biparietal diameter; HC, head circumference; AC, abdominal circumference; FL, femoral length; EFW, estimated fetal weight.

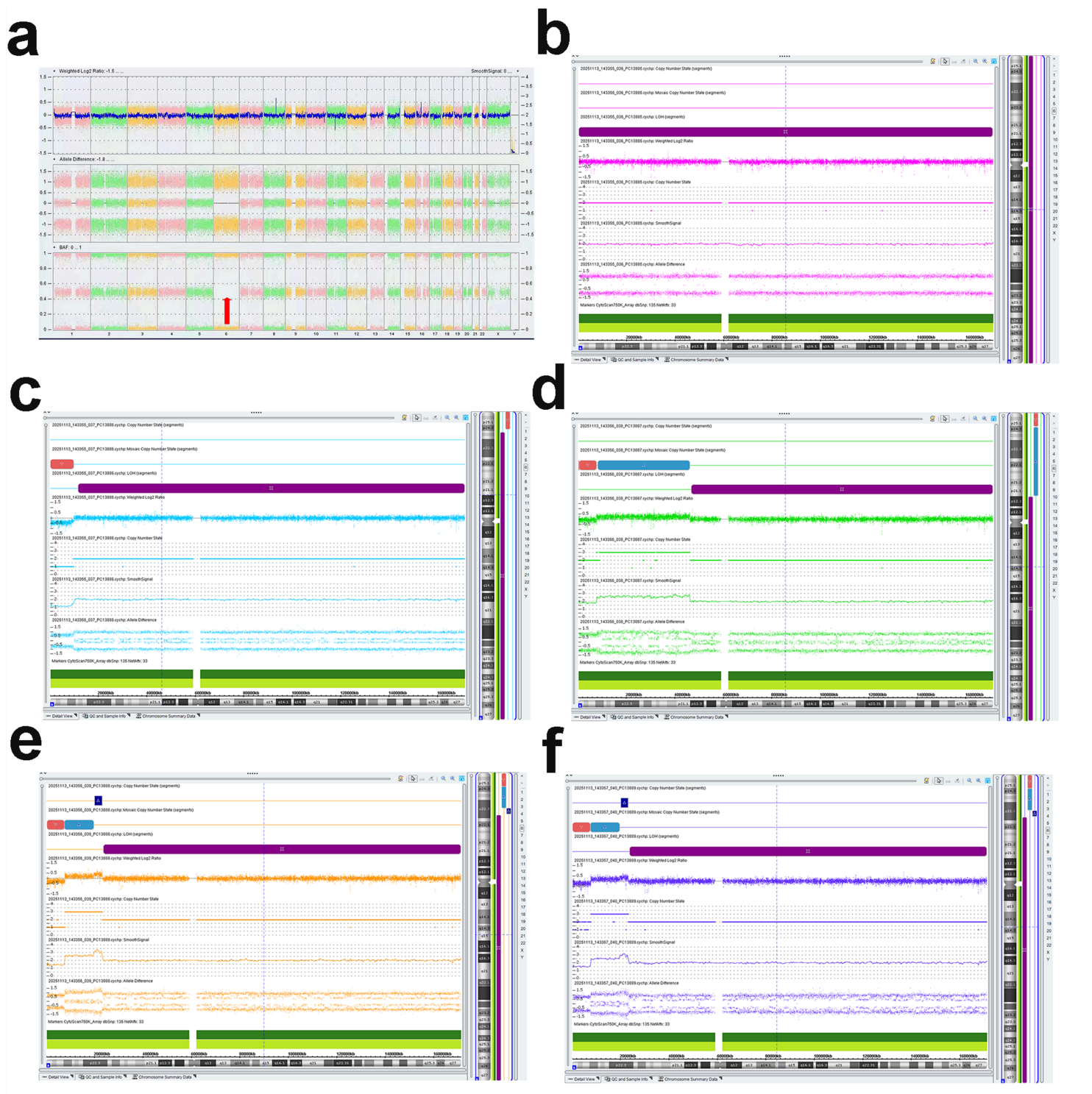


Figure 3

CMA results of different samples. (a) UPD for chromosome 6 in the DNA derived from the amniotic fluid cells. Red arrow showing region of homozygosity spanning the entire chromosome 6. CMA results of UPD6 in umbilical cord (b), inner side of the placenta fetal counterpart(c), lateral side of the placenta fetal counterpart (d), inner side of the placenta maternal counterpart (e), and lateral side of the placenta maternal counterpart (f). CMA: chromosomal microarray analysis

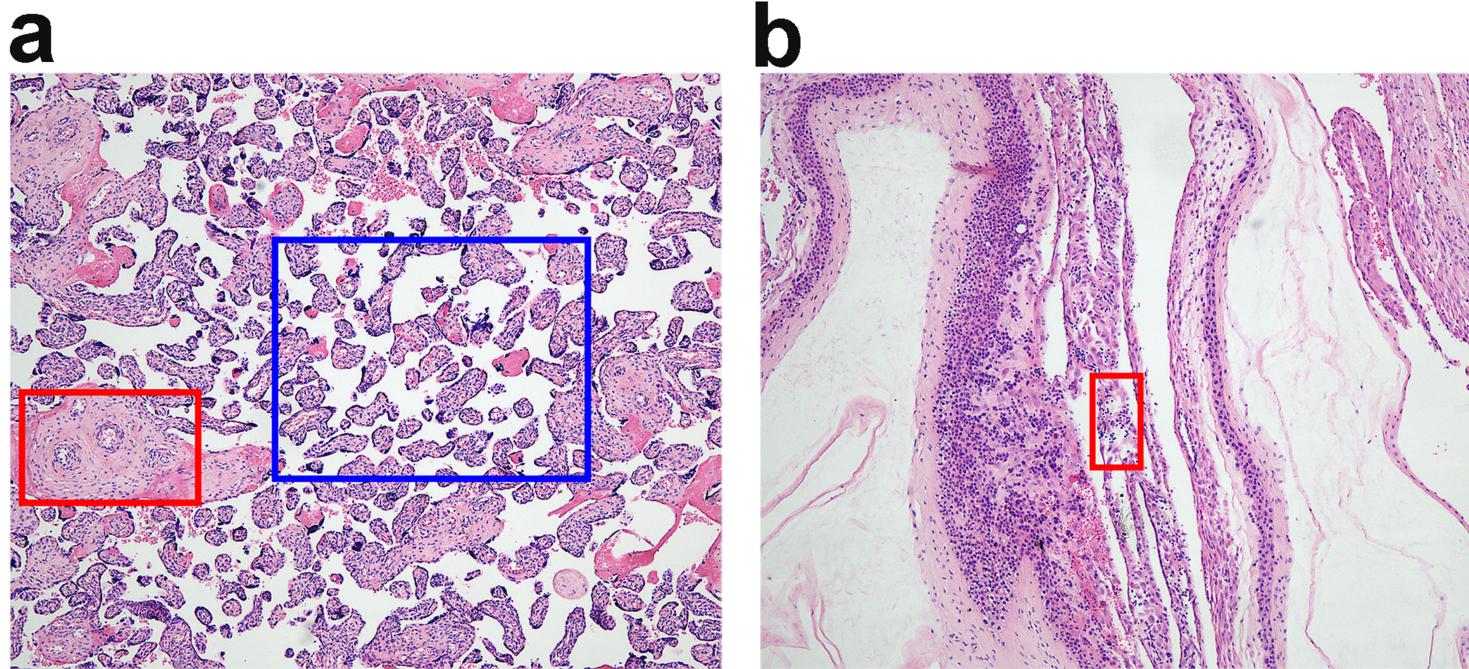


Figure 4

Histopathology with HE staining of placenta (4a) and fetal membranes (4b) (40 ×).

(a) The placenta maturity is less mature than that of the gestational week. The villi show localized distal villus dysplasia changes with uneven maturity, presenting as relatively mature villus (red rectangular box) and immature villus (blue rectangular box) morphology. (b) Mild-to-moderate chronic villitis was apparent (red rectangular box).

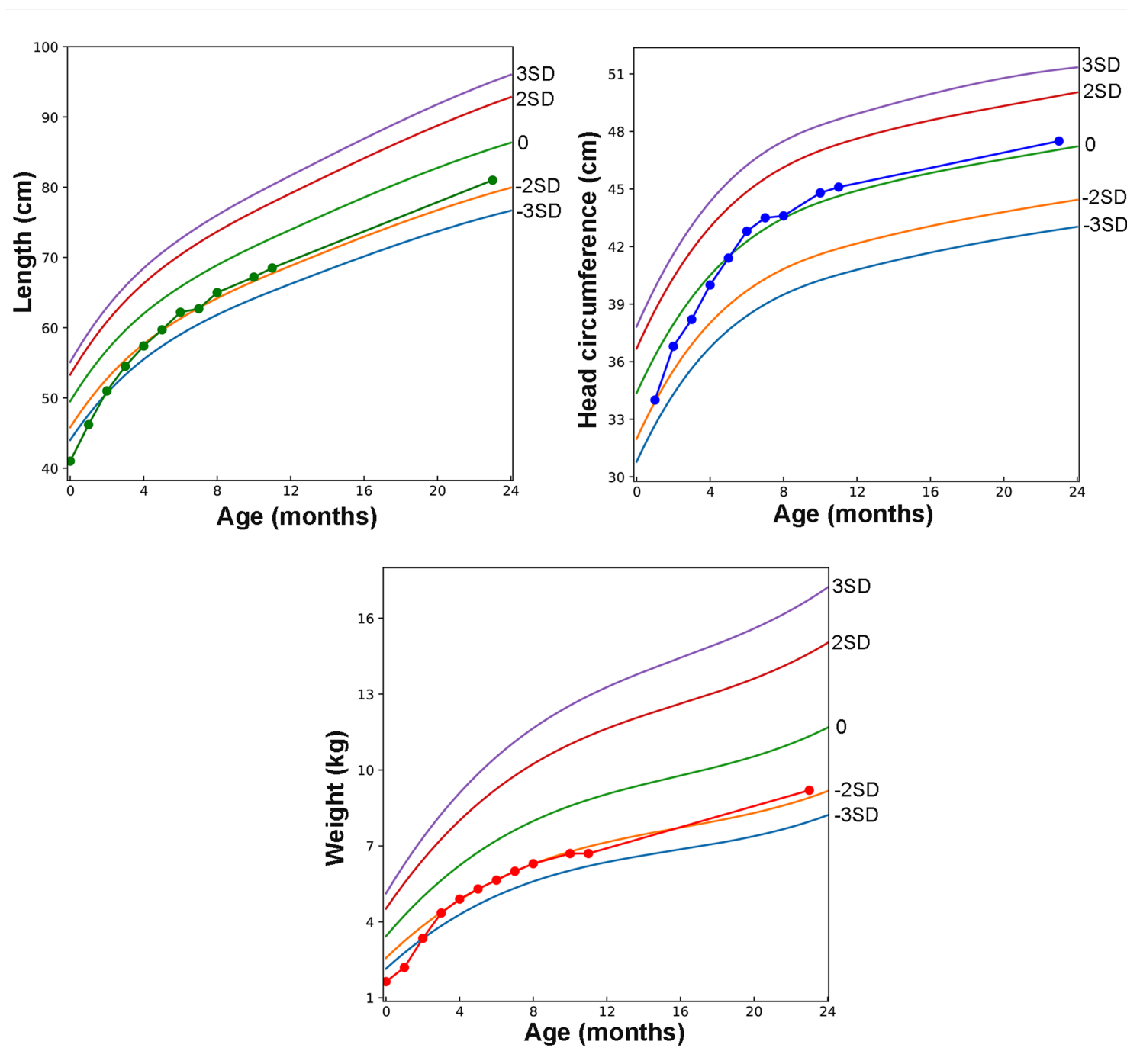


Figure 5

The physical growth parameters of the baby after birth at different months of age according to the age- and weight-corrected standards for girls (WHO).

Supplementary Files

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- [Supplementary1.xlsx](#)