Taiwanese Journal of Obstetrics & Gynecology 56 (2017) 691–693

Contents lists available at ScienceDirect

Taiwanese Journal of Obstetrics & Gynecology

journal homepage: www.tjog-online.com

Case Report

Application of non-invasive prenatal testing in late gestation in a pregnancy associated with intrauterine growth restriction and trisomy 22 confined placental mosaicism

Chih-Ping Chen [a, b, c, d, e, f, *], Chris Tsai [g], Ming-Huei Lin [a], Schu-Rern Chern [b], Shin-Wen Chen [a], Shih-Ting Lai [a], Wen-Lin Chen [a], Chen-Wen Pan [a], Wayseen Wang [b, h]

[a] Department of Obstetrics and Gynecology, MacKay Memorial Hospital, Taipei, Taiwan
[b] Department of Medical Research, MacKay Memorial Hospital, Taipei, Taiwan
[c] Department of Biotechnology, Asia University, Taichung, Taiwan
[d] School of Chinese Medicine, College of Chinese Medicine, China Medical University, Taichung, Taiwan
[e] Institute of Clinical and Community Health Nursing, National Yang-Ming University, Taipei, Taiwan
[f] Department of Obstetrics and Gynecology, School of Medicine, National Yang-Ming University, Taipei, Taiwan
[g] Bionet Corp., Taipei, Taiwan
[h] Department of Bioengineering, Tatung University, Taipei, Taiwan

ARTICLE INFO

Article history:
Accepted 30 August 2017

Keywords:
Confined placental mosaicism
Intrauterine growth restriction
NIPT
Non-invasive prenatal testing
Trisomy 22

ABSTRACT

Objective: We present the application of non-invasive prenatal testing (NIPT) in late gestation in a pregnancy associated with intrauterine growth restriction (IUGR) and trisomy 22 confined placental mosaicism (CPM).

Case report: A 35-year-old pregnant woman underwent chorionic villus sampling (CVS) at 12 weeks of gestation. The pregnancy was conceived by *in vitro* fertilization and intracytoplasmic sperm injection. CVS revealed a karyotype of 47,XY,+22 in all of 15 cultured chorionic villi cells. Array comparative genomic hybridization analysis on uncultured chorionic villi revealed a result consistent with trisomy 22. The woman underwent amniocentesis at 17 weeks of gestation. Amniocentesis revealed a karyotype of 46,XY in all 20 colonies of cultured amniocytes. Additional polymorphic DNA marker analysis excluded uniparental disomy 22. The parental karyotypes were normal. Prenatal ultrasound at 23 weeks of gestation revealed fetal retrognathia, IUGR and a calcified placenta. NIPT at 27 weeks of gestation using maternal plasma cell-free DNA analysis showed a chromosome Z-score of 5.74 for chromosome 22 (the Z-score for each pair of chromosomes is defined as “increased” if >3), indicating an abnormal placenta with trisomy 22 CPM leading to IUGR in the fetus. At 36 weeks of gestation, a 1754-g male fetus was delivered with cleft palate and imperforate anus but no other phenotypic abnormalities. The cord blood had a karyotype of 46,XY (40/40 cells), the umbilical cord had a karyotype of 47,XY,+22[9]/46,XY[31], and the placental tissues had a karyotype of 47,XY,+22[15]/46,XY[25].

Conclusion: NIPT in late gestation is useful in detection of placental abnormality associated with CPM and IUGR but a normal karyotype at amniocentesis.

Introduction

Confined placental mosaicism (CPM) is related to mosaicism of extra-fetal origin that is confined to placenta. CPM is considered as the main cause of false-positive findings in chorionic villus sampling (CVS). Three types of CPM have been reported, *i.e.*, type I: abnormal cells in direct preparations of cytotrophoblasts only; type II: abnormal cells in cultured cells of extraembryonic mesoderm; and type III: abnormal cells in both cell lineages of cytotrophoblasts and extraembryonic mesoderm cells [1,2].

Trisomy 22, commonly found in spontaneous abortions, is second to trisomy 16 in the frequency of occurrence. Fetuses with full trisomy 22 is characterized by the phenotype of intrauterine growth restriction (IUGR), microcephaly, broad flat nasal bridge,

* Corresponding author. Department of Obstetrics and Gynecology, MacKay Memorial Hospital, 92, Section 2, Chung-Shan North Road, Taipei 10449, Taiwan. Fax: +886 2 25433642, +886 2 25232448.
E-mail address: cpc_mmh@yahoo.com (C.-P. Chen).

http://dx.doi.org/10.1016/j.tjog.2017.09.001

epicanthal folds, ocular hypertelorism, microtia, cleft palate and lip, webbed neck, cardiac anomalies, renal anomalies, hypoplastic distal phalanges, digitalized thumbs, anal atresia/stenosis and genital anomalies in males [3]. Here, we present our experience of trisomy 22 CPM with positive non-invasive prenatal testing (NIPT) in late gestation in a pregnancy conceived by assisted reproductive techniques (ART) and associated with IUGR.

Case report

A 35-year-old, primigravid woman was referred for genetic counseling because of an abnormal result of trisomy 22 obtained by CVS. This pregnancy was conceived by ART of *in vitro* fertilization (IVF) and intracytoplasmic sperm injection (ICSI). The woman underwent CVS at 12 weeks of gestation because of advanced maternal age and an abnormal first-trimester Down syndrome screening result with a Down syndrome risk of 1/4 calculated from 2.303 multiples of the median (MoM) of maternal serum free β-human chorionic gonadotropin (β-hCG), 0.402 MoM of maternal serum pregnancy-associated plasma protein A (PAPP-A) and a nuchal translucency of 64 mm. CVS revealed a karyotype of 47,XY,+22 in 15/15 cells of cultured chorionic villi, and array comparative genomic hybridization (aCGH) analysis on the DNA extracted from uncultured chorionic villi revealed a result of arr [GRCh37] (22) × 3, (X,Y) × 1. She underwent amniocentesis at 17 weeks of gestation which revealed a karyotype of 46,XY in 20/20 colonies of cultured amniocytes. The parental karyotypes were normal. Polymorphic DNA marker analysis using the DNAs extracted from the cultured amniocytes and parental bloods showed biparental inheritance and excluded uniparental disomy (UPD) 22. Prenatal ultrasound revealed retrognathia and IUGR in the fetus and calcification in the placenta. NIPT at 27 weeks of gestation using maternal plasma cell-free DNA sequencing performed by Bionet Corp. showed a chromosome Z-score of 5.74 for chromosome 22, indicating an abnormal calcified placenta with trisomy 22 CPM leading to IUGR in the fetus. The Z-score for each pair of chromosomes is defined as “increased” if >3 and “decreased” if <−3 [4,5]. At 36 weeks of gestation, a male fetus was delivered with a body weight of 1754 g, a body length of 44 cm, cleft palate and imperforate anus but no other phenotypic abnormalities. The cord blood revealed a karyotype of 46,XY in 40/40 cultured lymphocytes. The placental tissues revealed a karyotype of 47,XY,+22[15]/46,XY [25]. The umbilical cord revealed a karyotype of 47,XY,+22[9]/46,XY[31].

Discussion

The present case has the association of ART with congenital anomalies of facial cleft and imperforate anus. Children conceived by ART are at an increased risk of 15%–40% for congenital anomalies [6]. Zwink et al. [7] reported a significantly increased risk of anorectal malformations after IVF [odds ratio (OR): 10.9; 95% confidence interval (CI): 6.2–19] and after ICSI (OR: 7.5; 95% CI: 4.6–12.2). Zwink et al. [7] reported an OR of 4.9 for isolated anorectal malformations, an OR of 11.9 for anorectal malformations with associated anomalies and an OR of 7.9 for anorectal malformations with VATER/VACTERL association in children conceived by ART. Hutt et al. [8,9] reported cleft palate disorders in the offspring of mothers exposed to environmental toxicants during fetal life. Xiao et al. [10] reported multiple orofacial malformations in a child conceived by ICSI. Reefhuis et al. [11] reported an OR of 2.4 (95% CI: 1.2–5.1) for cleft lip with or without cleft palate, an OR of 3.7 (95% CI: 1.5–9.1) for anorectal atresia and an OR of 4.5 (95% CI: 1.9–10.5) for esophageal atresia in the singleton births of mothers who reported ART use (IVF or ICSI), and suggested that facial cleft, anorectal atresia and esophageal atresia occur more often among infants conceived by ART.

Bryan et al. [12] reported IUGR and hypospadias in a fetus with a normal male karyotype of 46,XY and CPM for trisomy 22. Choi et al. [13] reported false-positive NIPT associated with CPM for trisomy 22 and IUGR but without dysmorphic features in the fetus in a pregnancy. Trisomy 22 CPM may occur in cases with CVS. Wolstenholme [14] reported combined incidence of 9–20 per 100,000 samples for mosaic and non-mosaic trisomy 22 CPM in diagnostic CVS series. The peculiar aspect of the present case is the association of a false-positive result of NIPT in late gestation with CPM and IUGR. False-positive NIPT results can be caused by CPM or maternal mosaicism [15,16]. Taglauer et al. [17] suggested that cell-free fetal DNA in the maternal circulation can provide information about the placenta and potentially be used to predict placental health and disease. Our case provides evidence that application of NIPT is useful to confirm the association of CPM and IUGR in cases with normal karyotype at amniocentesis but IUGR and/or calcified placenta in late gestation.

Conflicts of interest

The authors have no conflicts of interest relevant to this article.

Acknowledgements

This work was supported by research grant MOST-105-2314-B-195-012 from the Ministry of Science and Technology and MMH-E-106-04 from MacKay Memorial Hospital, Taipei, Taiwan.

References

[1] Kalousek DK, Barrett IJ, Gartner AB. Spontaneous abortion and confined chromosomal mosaicism. Hum Genet 1992;88:642–6.
[2] Simoni G, Sirchia SM. Confined placental mosaicism. Prenat Diagn 1994;14:1185–9.
[3] Bacino CA, Schreck R, Fischel-Ghodsian N, Pepkowitz S, Prezant TR, Graham Jr JM. Clinical and molecular studies in full trisomy 22: further delineation of the phenotype and review of the literature. Am J Med Genet 1995;56:359–65.
[4] Liang D, Lv W, Wang H, Xu L, Liu J, Li H, et al. Non-invasive prenatal testing of fetal whole chromosome aneuploidy by massively parallel sequencing. Prenat Diagn 2013;33:409–15.
[5] Shaw S-WS, Hsiao C-H, Chen C-Y, Ren Y, Tian F, Tsai C, et al. Noninvasive prenatal testing for whole fetal chromosomal aneuploidies: a multicenter prospective cohort trial in Taiwan. Fetal Diagn Ther 2014;35:13–7.
[6] Pinborg A, Henningsen A-KA, Malchau SS, Loft A. Congenital anomalies after assisted reproductive technology. Fertil Steril 2013;99:327–32.
[7] Zwink N, Jenetzky E, Hirsch K, Reifferscheid P, Schmiedeke E, Schmidt D, et al. Assisted reproductive techniques and risk of exstrophy-epispadias complex: a German case-control study. J Urol 2013;189:1524–9.
[8] Hutt KJ, Shi Z, Albertini DF, Petroff BK. The environmental toxicant 2,3,7,8-tetrachlorodibenzo-p-dioxin disrupts morphogenesis of the rat preimplantation embryo. BMC Dev Biol 2008;8:1.
[9] Hutt KJ, Shi Z, Petroff BK, Albertini DF. The environmental toxicant 2,3,7,8-tetrachlorodibenzo-p-dioxin disturbs the establishment and maintenance of cell polarity in preimplantation rat embryos. Biol Reprod 2010;82:914–20.
[10] Xiao W-L, Zhang D-Z, Hou J-W, Sun J, Jia M-Y. Multiple orofacial malformations in a boy who was conceived by intracytoplasmic sperm injection. J Plast Reconstr Aesthet Surg 2009;62:e298–300.
[11] Reefhuis J, Honein MA, Schieve LA, Correa A, Hobbs CA, Rasmussen SA, et al. Assisted reproductive technology and major structural birth defects in the United States. Hum Reprod 2009;24:360–6.
[12] Bryan J, Peters M, Pritchard G, Healey S, Payton D. A second case of intrauterine growth retardation and primary hypospadias associated with a trisomy 22 placenta but with biparental inheritance of chromosome 22 in the fetus. Prenat Diagn 2002;22:137–40.
[13] Choi H, Lau TK, Jiang FM, Chan MK, Zhang HY, Lo PSS, et al. Fetal aneuploidy screening by maternal plasma DNA sequencing: 'false positive' due to confined placental mosaicism. Prenat Diagn 2013;33:198–200.
[14] Wolstenholme J. Confined placental mosaicism for trisomies 2, 3, 7, 8, 9, 16, and 22: their incidence, likely origins, and mechanisms for cell lineage compartmentalization. Prenat Diagn 1996;16:511–24.
[15] Lebo RV, Novak RW, Wolfe K, Michelson M, Robinson H, Mancuso MS. Discordant circulating fetal DNA and subsequent cytogenetics reveal false

negative, placental mosaic, and fetal mosaic cfDNA genotypes. J Transl Med 2015;13:260.

[16] Wang L, Meng Q, Tang X, Yin T, Zhang J, Yang S, et al. Maternal mosaicism of sex chromosome causes discordant sex chromosomal aneuploidies associated with noninvasive prenatal testing. Taiwan J Obstet Gynecol 2015;54:527–31.

[17] Taglauer ES, Wilkins-Haug L, Bianchi DW. Review: cell-free fetal DNA in the maternal circulation as an indication of placental health and disease. Placenta 2014;35(Suppl.):S64–8.