Original Article

Umbilical Cord Diameter at Early Second Trimester: Relation to Trisomy 21

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Abstract

Background: To compare the umbilical cord diameter (UCD) at early second trimester (at 17–19 weeks of gestation) in trisomy 21 and normal fetuses and determined value of measuring UCD in screening trisomy 21. **Methods:** This was a case–control study. The UCD was measured in 39 fetuses with trisomy 21 (documented by chorionic villus sampling or amniocentesis) and 39 fetuses in control group at 17–19 weeks of gestation. The control groups were low-risk fetuses for aneuploidy in routine screening and were shown not to have aneuploidy after birth. **Results:** Mean of UCD in fetuses with trisomy 21 was lower than normal fetuses, but there were no significant differences between them (7.48 ± 0.99 mm vs. 7.66 ± 0.91 mm; $P = 0.41$). Mean of UCD had no significant difference between other maternal variable, for example, body mass index and obstetric history. Mean of UCD among mothers who had previous cesarean section was significantly lower than without it (7.21 ± 0.97 vs. 7.71 ± 0.97; $P = 0.03$). **Conclusions:** At 17–19 weeks of gestation, the UCD of fetuses with trisomy 21 is thinner than normal, but the importance of this difference is too small for using this measurement in screening.

Keywords: *Aneuploidy, fetal screening, second trimester, trisomy 21, umbilical cord diameter*

Introduction

Early identification of high-risk fetuses for chromosomal abnormalities is one of the most important challenges.[1] Investigations continue to obtain better methods for screening trisomy 21 and reduce unnecessary invasive tests. Down syndrome is the most common nonlethal trisomy and its prevalence is approximately one per 500 recognized pregnancies.[2,3] Detectable intrauterine anomalies with sonography in Down syndrome include cardiovascular and gastrointestinal systems anomalies, esophageal atresia, duodenal atresia, exomphalos, atrioventricular septal defect with balanced ventricles, and ventricular septal defect.[4] Although prenatal ultrasound techniques had been known as powerful method for screening fetal abnormalities due to trisomy, 50% of fetuses with Down syndrome do not show any major or minor detectable anomaly. Physical characteristics that are not themselves anomalies but that occur more commonly in fetuses with Down syndrome are called soft markers.[5] Some of the most common ultrasonographic markers in the second trimester include nuchal fold thickening, echogenic intracardiac focus, shortened long bones, hyperechoic bowel, renal pyelectasis, choroid plexus cysts, clinodactyly, and hypoplastic or absent nasal bone.[6] Ghezzi *et al*. reported that umbilical cord diameter (UCD) at first trimester correlated with the growth of embryo and may be a marker for identifying the risk of chromosomal abnormalities.[7] In their future study, they concluded that with UCD above 95th centile, chromosomal abnormalities in the fetus or placenta were significantly higher than other fetuses. They suggested UCD as novel marker of fetal aneuploidy.[8] Rembouskos *et al*. reported UCD in the first trimester in fetuses with trisomy 21 was significantly smaller than normal fetuses.[9] Axt-flinder *et al*. showed that fetuses with chromosomal abnormalities are more likely to have an UCD above the 95th centile.[10]

There was no study on the difference between the diameter of the umbilical cord in embryos with trisomy 21 and normal embryos in early second trimester. We wanted to do this study and investigated further above value of measuring UCD at that time interval in screening for trisomy 21.

Methods

This was case–control study. Inclusion criteria for case group were singleton

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fetuses with trisomy 21 and gestational age at 17–19 3/7 weeks. Chorionic villus sampling or amniocentesis confirmed trisomy 21 previously. The control group was low-risk fetuses for aneuploidy in routine screening and gestational age 17–19 3/7 weeks and singleton. Their follow-up after birth shows normal infants. Exclusion criteria were maternal medical diseases, for example, diabetes, hypertension, and pregnancy complications, for example, preterm delivery and fetal growth restriction. The UCD was measured in 39 fetuses with trisomy 21 and 39 fetuses in control group. Our study was carried out in family health institute, maternal, fetal, and neonatal research center, Tehran University of medical sciences, Tehran, Iran, during a 16-month period (February 2014 to May 2015).

Measurement of the UCD was performed in long-axis view of free loops. Caliper was placed outer to outer border of the maximal magnification [Figure 1]. Three different images were obtained, and the mean of three measurements was recorded. The scan was performed by using 12MHz transducer with ultrasound machine SIMENC Antares model, Germany. All of the measurements were performed by single operator. Mean of UCD and gestational age and mother's information (age, body mass index, and past medical history including abortion, normal vaginal delivery/cesarean section, gestational diabetes, preeclampsia, and infertility) were recorded. All of the pregnancies in our study were singleton and mothers had not any significant medical disorders. Protocol of this study was approved in research ethical committee of Tehran University of medical sciences, and informed consent was obtained from all participants.

Statistical analysis

Statistical analysis was performed by using IBM SPSS Statistics 22.0 (New York, United States of America). Quantitative variables were presented by Student's *t*-test, and qualitative variables were presented with frequency and percentage. Quantitative variables such as maternal age, body mass index (BMI), gestational age, and UCD were compared between two groups of study by ANOVA test. Qualitative variables were compared between two groups by Chi-square. All $P < 0.05$ were assumed as significant results.

Results

Mean of maternal age in trisomy 21 group was 35.63 (23–44) years, and in control group, it was 31.03 (20–43). Maternal age in trisomy 21 group was significantly higher than control group (35.63 ± 5.66 vs. 31.03 ± 6.46; $P = 0.001$). Mean of maternal BMI in cases and controls had no significant differences (25.56 ± 3.99 vs. 26.39 ± 4.03; $P = 0.37$). Mean of gestational age in both groups was similar. In cases was 18 and in control group was 17.9 weeks (18.07 ± 0.70 vs. 17.91 ± 0.70; $P = 0.32$). Gravidity and other factors had no significant differences between the mothers of two groups [Table 1].

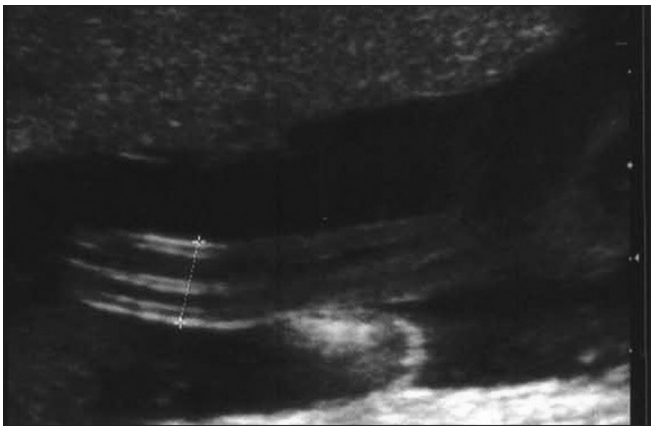

Figure 1: Umbilical cord diameter measurement at 18 weeks

Table 1: Comparing demographic and pregnancy-related factors between women of case and control group

Variables	Study groups		*P*
	Case	Control	
Maternal age (mean±SD)	35.63±5.66	31.03±6.46	0.001*
Body mass index (mean±SD)	25.56±3.99	26.39±4.03	0.37*
Gestational age (mean±SD)	18.07±0.70	17.91±0.70	0.32*
Frequency of abortion, *n* (%)	24 (31.58)	52 (68.42)	0.55**
Frequency of cesarean section, *n* (%)	21 (27.63)	55 (72.37)	0.79**
Preterm birth, *n* (%)	5 (6.58)	71 (93.42)	0.65**
Gestational diabetes, *n* (%)	1 (1.32)	75 (98.68)	0.31**
Infertility, *n* (%)	5 (6.58)	71 (93.42)	0.65**

*Calculated with independent sample *t*-test, **Calculated with Chi-square. SD=Standard deviation

The UCD was successfully measured in all fetuses. Mean of UCD in fetuses with trisomy 21 was lower than normal fetuses but had no significant differences between them (7.48 ± 0.99 vs. 7.66 ± 0.91; $P = 0.41$). Mean of UCD among mothers who had previous cesarean section (C/S) was significantly lower than without C/S (7.21 ± 0.97 vs. 7.71 ± 0.97; $P = 0.03$). Mean of UCD had no significant difference between the other variables of this study.

Discussion

The role of umbilical cord in normal or abnormal fetal growth is important.[11] Several studies demonstrated that UCD is linked to fetal metabolism (i.e., thick cord in diabetes and thin cord in adverse pregnancy outcome).[12-14]

Raio *et al*. reported a significant relationship between fetal anthropometric parameters and UCD. They founded that UCD increase as a function of gestational age and direct participate in fetal nutrition and size of fetus.[15] Cromi *et al*. studied diabetic pregnant women and founded that macrosomic infants had a large umbilical cord.[16] Raio *et al*. demonstrated a significant correlation between the crown–rump length and both the umbilical coiling index and the umbilical coiling angle and no correlation between UCD and them.[17] Their biochemical results reported a

higher concentration of hyaluronan in umbilical cords of Down syndrome compared with normal fetuses. It was consistent with previous studies on the skin of Down syndrome fetuses.[18-20]

There was no correlation between UCD and them.[15] Their biochemical results reported a higher concentration of hyaluronan in umbilical cords of Down syndrome compared with normal fetuses. It was consistent with previous studies on the skin of Down syndrome fetuses.[16-18]

Rembouskos *et al*. on their study at England reported that in first trimester, mean of UCD in fetus with trisomy 21 was significantly lower than normal values but noted this difference was not sufficient for using in screening tests and there was no significant differences between other chromosomal defects and normal fetuses.[21] In trisomy 18 was a tendency for increased UCD.[20] More than 2/3 of fetuses with trisomy 18 have a single umbilical artery.[21] Sepulveda *et al*. founded the umbilical artery diameter in a two vessel cord is significantly higher than in a three-vessel cord.[22] Sepulveda *et al*. founded the umbilical artery diameter in a two vessel cord is significantly higher than in a three-vessel cord.[22]

Previous study had been done at first trimester. Our study has done at early second trimester and confirmed mothers of fetuses with trisomy 21 are older than mothers of normal fetuses, and maternal age is the most important risk factor for trisomy 21. In our study, other demographic and pregnancy-related characters had no significant differences between two groups. In this study, mean of UCD in early second trimester in fetuses with trisomy 21 is lower than normal but is not significant.

There are physiological changes in umbilical cord structures throughout normal gestation. In first and early second trimester, the amount of Wharton's jelly is lower than that of third trimester. Causes of increased UCD might be increasing of amount of Wharton's jelly or increasing the cross-sectional area of cord vessels or both.

Some factors such as cardiac dysfunction, altered composition of the extracellular matrix, and abnormality in developing of the lymphatic system are reported as possible causes of the increased nuchal translucency (NT) among fetuses with trisomy 21.[21,23] Subcutaneous edema due to heart failure is secondary to extravasation of extracellular fluid through the capillaries but cord vessels are large and there are no capillaries in umbilical cord.

Baergan *et al*., by histopathological study of umbilical cord, described that increasing of water in Wharton's jelly might be responsible for increasing in UCD.[24] Proctor *et al*. reported that increased postdelivery, fresh-tissue UCD was due to increase in vessel area, specifically in umbilical artery wall area, and decreased Wharton's jelly volume might lead to decreased in UCD.[25]

In fetuses with trisomy 21, fibroblasts overexpress collagen type VI and there is inverse correlation between collagen synthesis and hyaluronan degradation. Collagen network reduces mobility of hyaluronic acid in tissue.[26]

Duran *et al*. reported that cord thickness measurement at umbilicus had a strong correlation with plasma protein A and not with free loop diameter in the first trimester. They founded that a mild correlation between UCD and NT while any correlation between cord thickness measurement at umbilicus and NT.[27] The absence of capillary in umbilical cord and extravasation from them may be explained there is no correlation between umbilicus cord diameter and NT. Alterations of composition and distribution of hyaluronan and collagens may influence the function and morphology of the umbilical cord. Moreover, neovascularization in tissue can be affected by the metabolic state of Hyaluronan. Native hyaluronan inhibits angiogenesis through direct action on endothelial cells.[28] Therefore, decreased turnover of hyaluronan can have an effect on the growth of the umbilical cord vessels.

In this study, we showed that the measurement of UCD in fetuses with trisomy 21 is lower than normal fetuses. However, this difference is not significant to use it for screening. Larger prospective studies should be performed to further investigate the potential role of UCD evaluation for all chromosomal abnormalities. In our study, mean of UCD among mothers who had previous cesarean section was significantly lower than without it. Adverse pregnancy outcome in women with previous C/S (i.e., increased intrauterine fetal death in subsequent pregnancy) may be correlated with thin umbilical cord.

Conclusions

At 17–19 weeks of gestation, the UCD of fetuses with trisomy 21 is thinner than normal, but the importance of this difference is too small for using this marker in screening. Novel ultrasonographic marker in Down syndrome such as prenasal fold could be investigated and may be helpful to screen and reduce unnecessary amniocentesis.

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Conflicts of interest

There are no conflicts of interest.

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References

1. Pandya PP, Brizot ML, Kuhn P, Snijders RJ, Nicolaides KH. First-trimester fetal nuchal translucency thickness and risk for trisomies. Obstet Gynecol 1994;84:420-3.
2. Cunningham F, Leveno K, Bloom S, Spong CY, Dashe J. Williams Obstetrics. 24E Mcgraw-hill. Vol. 13. 2014. p. 261.
3. Dolk H, Loane M, Garne E. The Prevalence of Congenital

Anomalies in Europe. Rare Diseases Epidemiology. Adv Exp Med Biol 2010;686:349-64.
4. Paladini D, Volpe P. Ultrasound of Congenital Fetal Anomalies: Differential Diagnosis and Prognostic Indicators. Vol. 10. CRC Press; 2014. p. 301-3.
5. Creasy R, Resnik R. Creasy and Resnik's Maternal-Fetal Medicine. Philadelphia: Elsevier; 2014.
6. Norton M, Scoutt L, Feldstein V. Callen's ultrasonography in Obstetrics and Gynecology. 6th ed. Vol. 3. Philadelphia: Elsevier; 2017. p. 57-77.
7. Ghezzi F, Raio L, Di Naro E, Franchi M, Brühwiler H, D'Addario V, *et al.* First-trimester sonographic umbilical cord diameter and the growth of the human embryo. Ultrasound Obstet Gynecol 2001;18:348-51.
8. Ghezzi F, Raio L, Di Naro E, Franchi M, Buttarelli M, Schneider H, *et al.* First-trimester umbilical cord diameter: A novel marker of fetal aneuploidy. Ultrasound Obstet Gynecol 2002;19:235-9.
9. Rembouskos G, Cicero S, Papadopoulos V, Tripsanas C, Nicolaides KH. Umbilical cord diameter at 11-14 weeks of gestation: Relation to chromosomal defects. Ultrasound Obstet Gynecol 2004;23:237-9.
10. Axt-Fliedner R, Schwarze A, Kreiselmaier P, Krapp M, Smrcek J, Diedrich K, *et al.* Umbilical cord diameter at 11-14 weeks of gestation: Relationship to nuchal translucency, ductus venous blood flow and chromosomal defects. Fetal Diagn Ther 2006;21:390-5.
11. Weissman A, Jakobi P. Sonographic measurements of the umbilical cord in pregnancies complicated by gestational diabetes. J Ultrasound Med 1997;16:691-4.
12. Todros T, Adamson SL, Guiot C, Bankowski E, Raio L, Di Naro E, *et al.* Umbilical cord and fetal growth – A workshop report. Placenta 2002;23 Suppl A: S130-2.
13. Weissman A, Jakobi P, Bronshtein M, Goldstein I. Sonographic measurements of the umbilical cord and vessels during normal pregnancies. J Ultrasound Med 1994;13:11-4.
14. Sun Y, Arbuckle S, Hocking G, Billson V. Umbilical cord stricture and intrauterine fetal death. Pediatr Pathol Lab Med 1995;15:723-32.
15. Raio L, Ghezzi F, Di Naro E, Gomez R, Franchi M, Mazor M, *et al.* Sonographic measurement of the umbilical cord and fetal anthropometric parameters. Eur J Obstet Gynecol Reprod Biol 1999;83:131-5.
16. Cromi A, Ghezzi F, Di Naro E, Siesto G, Bergamini V, Raio L, *et al.* Large cross-sectional area of the umbilical cord as a predictor of fetal macrosomia. Ultrasound Obstet Gynecol 2007;30:861-6.
17. Raio L, Ghezzi F, Cromi A, Cereda E, Passi A. Sonographic morphology and hyaluronan content of umbilical cords of healthy and down syndrome fetuses in early gestation. Early Hum Dev 2004;77:1-2.
18. Brand-Saberi B, Epperlein HH, Romanos GE, Christ B. Distribution of extracellular matrix components in nuchal skin from fetuses carrying trisomy 18 and trisomy 21. Cell Tissue Res 1994;277:465-75.
19. von Kaisenberg CS, Krenn V, Ludwig M, Nicolaides KH, Brand-Saberi B. Morphological classification of nuchal skin in human fetuses with trisomy 21, 18, and 13 at 12-18 weeks and in a trisomy 16 mouse. Anat Embryol (Berl) 1998;197:105-24.
20. Böhlandt S, von Kaisenberg CS, Wewetzer K, Christ B, Nicolaides KH, Brand-Saberi B, *et al.* Hyaluronan in the nuchal skin of chromosomally abnormal fetuses. Hum Reprod 2000;15:1155-8.
21. Rembouskos G, Cicero S, Longo D, Sacchini C, Nicolaides KH. Single umbilical artery at 11-14 weeks' gestation: Relation to chromosomal defects. Ultrasound Obstet Gynecol 2003;22:567-70.
22. Sepulveda W, Peek MJ, Hassan J, Hollingsworth J. Umbilical vein to artery ratio in fetuses with single umbilical artery. Ultrasound Obstet Gynecol 1996;8:23-6.
23. Von Kaisenberg C, Hyett J. Pathophysiology of increased nuchal translucency. In: Nicolaides KH, Sebire NJ, Snijders RJ, editors. In the 11–14 Week Scan: The Diagnosis of Fetal Abnormalities. London, UK: Parthenon Publishing Group; 1999. p. 95-113.
24. Baergen RN. Manual of Pathology of the Human Placenta. New York: Springer Science & Business Media; 2011.
25. Proctor LK, Fitzgerald B, Whittle WL, Mokhtari N, Lee E, Machin G, *et al.* Umbilical cord diameter percentile curves and their correlation to birth weight and placental pathology. Placenta 2013;34:62-6.
26. Klein J, Meyer FA. Tissue structure and macromolecular diffusion in umbilical cord. Immobilization of endogenous hyaluronic acid. Biochim Biophys Acta 1983;755:400-11.
27. Duran M, Köşüş A, Köşüş N, Turhan NÖ. Relation between serum PAPP-A level and umbilical cord thickness during first trimester of pregnancy. J Matern Fetal Neonatal Med 2014;27:385-7.
28. West DC, Kumar S. Hyaluronan and angiogenesis. Ciba Found Symp 1989;143:187-201.