

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

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 ; $P = 0.32$). Gravity and other factors had no significant differences between the mothers of two groups [Table 1].

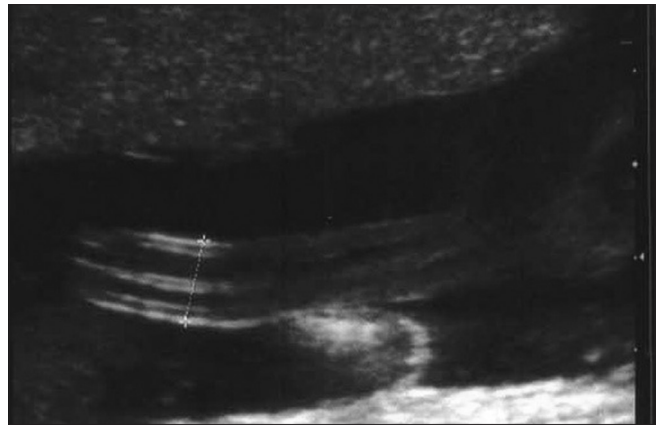


Figure 1: Umbilical cord diameter measurement at 18 weeks

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]

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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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