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The Variation of Fetal Cephalic Index of the Second Trimester Possibly Associates with Fetal Sonographic Soft Markers: A Retrospective Study

*Yao F, Jing L, Zhen Z, Xin Y, Yuan W and Xiaoyan X**

Sonographic Department of Gynecology and Obstetrics, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, China

Abstract

Background and Object: Antenatal ultrasonographic screening is the most important examination for fetal screening. Abnormal fetal skull shape is a soft marker which indicates a higher risk of fetal aneuploidy. But evaluation of skull shape relies more on sonographer's subjective judgement. Cephalic Index (CI) is used to evaluate fetal skull shape variations and is a reliable indicator of dolichocephaly and brachycephaly. But the association between CI and adverse fetal outcomes is still controversial.

Method: Four hundred twenty-five women with single pregnancy were included in our retrospective study in Tongji Hospital of Wuhan from January 1st, 2021 to December 31st, 2021. All the fetuses' growth parameters and CI were recorded and analyzed. The fetuses were distributed in group 1 to 6 according to their CIs of the second-trimester. The women's demographic characteristics and fetal sonographic soft markers of each study group were analyzed.

Results: The demographic characteristics of each study group did not show statistical difference. Ultrasonographic gestational age increased with increasing fetal CI (p=0.0001) while the difference between clinical gestational age and ultrasonographic gestational age reduced with increasing fetal CI (p=0.0006). Fetal sonographic soft markers (p=0.09) and maternal gestational complications (p=0.09) did not show statistical difference among study groups. But statistical differences of fetal sonographic soft-markers were found between group 2 and 5 (p=0.002), 3 and 5 (p=0.02), 4 and 5 (p=0.03). Five fetuses with CI lower than 72.0 were induced in this study due to serious fetal abnormalities. Group 3 had the highest incidence of induced labor (2.6%).

Conclusion: The fetus has the lowest incidence of fetal sonographic soft marker if the CI between 76.0 and 79.9. The fetal CI seems to have no statistical associations with fetal abnormalities. Dolichocephalic fetus is more likely to be small for clinical gestational age. Maternal pregnancy complications would not affect fetal head shape as our results demonstrated.

Keywords: Fetus; Cephalic index; Antenatal diagnosis; Fetal sonographic soft marker

***Correspondence:**
Xu Xiaoyan, Sonographic Department of Gynecology and Obstetrics, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Jiefang Road No 1095, Wuhan, Hubei Province, China, Tel: +86-027-83663680;
E-mail: 375934714@qq.com

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Introduction

Antenatal ultrasonography screening of the second trimester is the most comprehensive fetal assessment throughout pregnancy. The main object of this screening is to detect fetal abnormalities. The assessment of fetal head size is the most basic measurement of every antenatal ultrasonography, which includes Biparietal Diameter (BPD) and Head Circumference (HC). According to some former literature, abnormal skull shape associates with fetal trisomy 21 because of a smaller frontal lobe would lead to a shorter frontal occipital brain length [1]. Moreover, fetal brain morphology, volume and growth had strong associations with skull shape [2]. Anomalies which may affect cerebral development could also lead to skull malformations [3].

But in sonographic clinical practice, evaluating fetal skull morphology relies more on the sonographers' subjective judgements, which might lead to higher incidence of misdiagnose. Some scholastics suggested the Cephalic Index (CI) as a method to evaluate the variations of fetal skull shape. The definition of CI is the ratio of BPD to Occipitofrontal Diameters (OFD), and multiplies by 100. According to former research, CI is gestational age-independent which remains 78.3 ± 4.4 between 14 to 40 weeks' gestation [4,5]. In a clinical practice, CI is used as a reliable indicator of dolichocephaly and brachycephaly [6]. The association between CI and adverse fetal outcomes is still controversial. Recently, Kenneth et al. studied 597 fetuses retrospectively, a trend of CI towards significance was seen in 21-trisomy fetuses, but no statistical difference was detected between study and control group [7]. However, Kenneth Lim presented that there might be interethnic differences in CI between fetuses. Another recent study stated that a progress reduction in CI from the second trimester sonographic screening into the third trimester should be a hint of a thorough scanning of fetal cranial morphology [8].

Our research aims to investigate if the fetal head CI has any association with fetal sonographic soft markers. This research mainly studied the relevance between fetal head CI and the fetal sonographic soft markers. The secondary outcomes include the associations between fetal head CI and fetal structural abnormalities, fetal karyotype anomalies and/or Copy Number Variation (CNV) anomalies.

Materials and Methods

Participants

This retrospective study was approved by the ethical committee of Wuhan Tongji hospital (No.TJ-IRB20211147). This study analyzed pregnant women who came to Wuhan Tongji hospital for prenatal counselling from January 1st, 2021to December 31st, 2021. One thousand eighteen pregnant women had their second trimester screening ultrasonography in our hospital were eligible for this study. Women were excluded because of multiple gestation (n=51), taking Nuchal Translucency (NT) screening in other hospitals (n=576), delivering in other medical institutions (n=587) or losing to follow-up. 425 women were included and analyzed in our study (Figure 1).

All the fetuses were examined by pediatricians and obstetricians after birth, and followed up from the first trimester to 42 days after birth. All UEs were done using Voluson E10 and Voluson E8 ultrasound machines (GE Healthcare, Kretz Ultrasound, Zipf, Austria) with a 4 MHz to 8 MHz transabdominal transducer as default and a 5 MHz to 9 MHz or 6 MHz to 12 MHz transvaginal transducer for cases in which transvaginal brain evaluation was needed. Clinical Gestational Age (CGA) was adjusted using the Crump-Rump Length (CRL) during 11+0 weeks' and 13+6 weeks' gestation [9]. Fetal growth parameters were measured in each antenatal UE, which includes CRL, BPD, HC, abdominal circumference, femur length. The Ultrasonographic Gestational Age (UGA) was determined according to the growth parameters, and compared to CGA to assess whether the fetus has intrauterine growth restriction. The fetal CI was calculated using the formula described by Hadlock et al. [4] BPD/Occipito Frontal Diameter (OFD) × 100. BPD and OFD were measured at the level of the thalamus and cavum septi pellucidi plane, from the outer edge of the parietal skull (outer to inner) at the widest or longest part. BPD, OFD, HC, HC deviation of each fetus were recorded.

Grouping and analyze

All the women included in our study were grouped according to the CI of the second trimester screening ultrasonography. The woman was assigned into group 1 to 6 if the CI was less than 64.0, between 64.1 and 67.9, between 68.0 and 71.9, between 72.0 and 75.9, between 76.0 and 79.9 or more than 80.0. All the research data were compared between 6 groups (Figure 1). To get comparable group size of each study group, we set group intervals of 4.0 according to the maximum (91.6) and minimum (57.7) CI of our study. The demographic characteristics were compared between groups, which include women's age, gravidity and parity history, and pregnancy complications.

Continuous variables were presented using means ± standard deviations, median and range. Categorical variables were presented with frequencies and percent's. Correlations of continuous variables between each two study groups were examined using a t-test. For categorical variables, Chi-square was used. The relative risks along with 95% confidence intervals were presented. Statistical analysis and data management were performed using GraphPad Prism 5 (La Jolla, CA).

Results and Discussion

Demographic characteristics

From January 1st, 2021 to December 31st, 2021, a total of 425 pregnant women were retrospectively analyzed in our study. Table 1 presented the overall demographic characteristics. And the demographic characteristics of each study group were listed in Table 2. The maternal age, gravidity and parity history, CGA did not show statistical significance among groups. Statistical differences were found in UGA among 6 groups ($p<0.05$), which increases with increasing CI. The value of (CGA-UGA) reduced with increasing fetal CI and were statistically different among groups ($p=0.0006$).

Fetal and maternal outcomes of each group

Table 3 presented the main results of our study. We compared BPD among the six study groups. Fetal BPD and OFD seems to increase with CI and statistical differences were detected in fetal BPD and OFD among groups. Fetal Sonographic Soft Markers (SSM) in our study include thickened nuchal fold, echogenic bowel, mild ventriculomegaly, echogenic focus in the heart, choroid plexus cyst, single umbilical artery, enlarged cisterna magna, and pyelectasis. Fetal SSM and maternal gestational complications did not show statistical difference. Group 5 has the lowest fetal SSM rate (8.2%). Maternal complications did not show any statistical differences among 6 study groups or each two study groups.

Of all the women in our study, 38 had amniocentesis for fetal chromosomal/gene screening. And no serious chromosomal/gene defect was found in chromosomal/gene screening. Five women in this study chose induced labor due to serious fetal abnormalities which include fetal kidney malformation, hydrocephaly, hypospadias or multi-malformation. The CIs of the 5 induced fetuses were below 71.9. The ratio of fetal gender in each study group did not show statistical differences. All the live birth fetuses complain of no serious congenital anomalies or other defects during the period of follow-up.

Table 1: Demographic characteristics of all the participants in our study.

Maternal age (years)	31.1 ± 4.1
Gravidity history	2.1 ± 1.4
Parity history	0.4 ± 0.6
CGA* of second-trimester screening UE& (days)	162.3 ± 5.8
UGA# of second-trimester screening UE& (days)	160.6 ± 1.0
CGA*-UGA# (days)	1.8 ± 4.1
BPD[a] (cm)	5.5 ± 0.3
OFD[b] (cm)	7.7 ± 0.4
HC[c] (cm)	20.7 ± 1.1
CI[d]	71.9 ± 3.7

*: Clinical gestational age; #: Ultrasonographic gestational age; &: Ultrasonographic examination; a: biparietal diameter; b: occipitofrontal diameters; c: head circumference; d: cephalic index

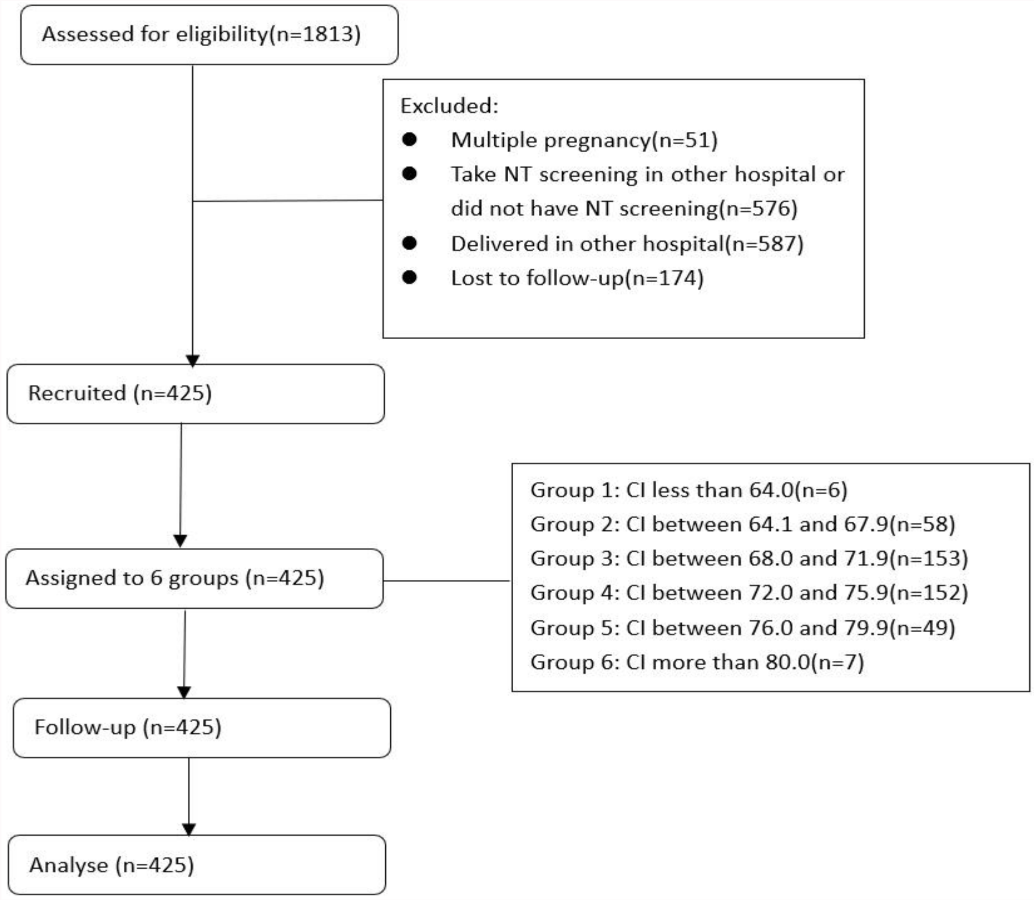

Figure 1: Flowchart.

Results of the fetal SSM between each two study groups

Table 4 presented the results of the fetal SSM between each of two study groups. Statistical differences were found between group 2 and 5 (p=0.002), 3 and 5 (p=0.02), 4 and 5 (p=0.03). Fetal abnormality risk seems to be obvious when fetal CI is below 76.0, and the risk increases significantly if CI is less than 68.0.

Discussion

Many sonographers had impressions of abnormal fetal head shapes that might indicate of higher incidence of fetal aneuploid or other abnormalities. Those abnormal head shapes were described as “strawberry” shaped or “lemon” shaped cranium. The judgement of fetal cranial shape relies more on sonographers’ subjective perception. Hadlock et al. proposed CI for evaluation of variations of skull shape [4]. During clinical practice recently, CI was used to assess craniosynostosis [10] and fetal head shape [1]. But the limited former researchers of CI drew different conclusions of the predictive value of CI during pregnancy. A study presented a case of rapidly decreased CI during 16 days and stated that CI could be a predictor of fetal demise [11]. Kenneth et al. [7] Retrospectively analyzed 46 fetuses with 18-trisomy or 21-trisomy and compared to 551 normal controls. The CIs of 18-trisomy/21-trisomy fetuses and controls did not show statistical difference in their study. But their research found a trend towards statistical differences in Caucasian and Oriental ethnic fetuses. Similarly, another literature found no statistical association between fetal CI and Down syndrome [12].

In recent studies, CI was used to evaluate cranial shape and antenatal diagnosis of craniosynostosis. The cranium is diagnosed as brachycephaly if the CI is more than 85.0 and dolichocephaly if less than 75.0 [13]. Those anomalies can possibly lead to cranium deformations, which could increase intracranial pressure and cause neurodevelopmental constrain and cognitive deficiency [14]. The morphology of cranial vault depends on the development of brain volume, morphology and growth [2]. Abnormal cranial morphology is usually a clinical manifestation of genetic or chromosomal disorders, infection, exposure to toxins, metabolic errors or intrauterine growth restriction [15], and could possibly lead to adverse gestational outcomes. An article of last year stated that the mean CI of fetal with sagittal craniosynostosis was 74.5 in the third-trimester, statistically different from the mean CI of normal controls [16]. A Japanese article studied fetal brain volume by Magnetic Resonance (MR) imaging as a method of antenatal evaluation [17]. Fetal CI was calculated using BPD and OFD measured in MR images, and a statistical correlation was detected between CI and total brain volume. Therefore, CI could be an evaluation method of not only variations of cranial shape, but also fetal brain growth.

The generally accepted fetal normal CI is 78.3 ± 4.4, which was reported by Hadlock et al. [4] and remains constantly from 14 to 40 weeks’ gestation [4]. However, some scholars held different opinions. Diana et al. [18] studied 1,361 normal fetuses and found a variation in CI with advancing gestational age [18]. They found fetuses of 14-weeks’ gestation has the highest value for CI (81.5), and the lowest value appears at 28 weeks’ gestational age (78.0). Their research also

Table 2: Demographic characteristics of each study group.

	1 (n=6)	2 (n=58)	3(n=153)	4 (n=152)	5 (n=49)	6 (n=7)	p
Maternal age(years)	32.5 ± 2.2	31.3 ± 4.3	31.3 ± 4.0	30.8 ± 4.2	31.1 ± 4.0	30.9 ± 5.3	0.87
Gravidity history	2.5 ± 1.0	2.4 ± 1.5	2.2 ± 1.4	2.0 ± 1.3	1.9 ± 1.2	2.6 ± 2.8	0.35
Parity history	0.7 ± 0.5	0.5 ± 0.6	0.3 ± 0.5	0.3 ± 0.6	0.2 ± 0.5	0.4 ± 0.8	0.16
CGA* of second-trimester screening UE& (days)	162.8 ± 4.5	160.9 ± 5.0	161.8 ± 4.8	163.0 ± 7.2	162.9 ± 4.3	162.1 ± 3.8	0.09
UGA# of second-trimester screening UE& (days)	157.2 ± 4.5	158.3 ± 6.0	159.4 ± 5.6	162.0 ± 7.8	162.5 ± 6.4	161.3 ± 5.6	0.0001
CGA*-UGA# (days)	5.7 ± 4.2	2.5 ± 5.6	2.4 ± 3.6	1.1 ± 3.7	0.4 ± 3.6	0.9 ± 1.9	0.0006

*: Clinical gestational age; #: Ultrasonographic gestational age: &: ultrasonographic examination

Table 3: Fetal and maternal outcomes of each group.

	1 (n=6)	2 (n=58)	3 (n=153)	4 (n=152)	5 (n=49)	6 (n=7)	P (t-test)	P (Chi-square)
BPD[a] (cm)	5.1 ± 0.3	5.3 ± 0.3	5.5 ± 0.3	5.7 ± 0.3	5.8 ± 0.3	5.8 ± 0.3	<0.0001	
HC[b] (cm)	20.7 ± 0.9	20.6 ± 1.1	20.6 ± 1.0	20.9 ± 1.2	20.7 ± 1.2	20.2 ± 1.2	0.34	
OFD[c] (cm)	8.2 ± 0.3	7.9 ± 0.4	7.8 ± 0.4	7.7 ± 0.4	7.5 ± 0.4	7.1 ± 0.6	<0.0001	
CI[d]	61.8 ± 2.3	66.8 ± 1.0	70.2 ± 1.1	73.7 ± 1.2	77.4 ± 1.1	82.2 ± 4.2	<0.0001	
Fetal abnormalities	2 (33.3%)	19 (32.8%)	37 (24.2%)	33 (21.7%)	4 (8.2%)	1 (14.3%)		0.09
Induced labor	1 (16.7%)	1 (1.7%)	4 (2.6%)	0	0	0		
Maternal complications	2 (33.3%)	22 (37.9%)	30 (19.6%)	43 (28.3%)	17 (34.7%)	2 (28.6%)		0.09
Fetal gender (Male/Female)	3/4	32/17	89/63	77/76	30/28	3/3		0.42

a: biparietal diameter; b: occipitofrontal diameters; c: head circumference; d: cephalic index

Table 4: Results of the fetal abnormality between each two study groups.

	1	2	3	4	5	6
1						
2	1.00					
3	0.61	0.21				
4	0.50	0.10	0.61			
5	0.06	0.002*	0.02*	0.03*		
6	0.66	0.32	0.55	0.64	0.50	

*: Statistical difference

revealed that the normal range of CI was broad and might be affecting by other factors which might influence cranial shape. Ethnicity, gender, heredity and geography are the main factors causing the differentiation of CI [19]. According to recent Korean research, the cranial shape of Koreans had changed rapidly from mesocephalic to brachycephalic in the last century until early twenty-first century [20]. However, the changing pattern has reversed to debrachycephalization in recent decades due to improvements in nutrition and health. A similar changing pattern was also detected in other countries or ethnicities, such as Japan, Mexico, Croatia, Hungary and American [20-23]. A Nepal study reported that the common cranial shape of Tharu population was dolichocephaly [24]. The mean CI of the Nepal population was 75.99 ± 4.97, different from the mean value reported by Hadlock et al. In our study, the mean CI of the 324 normal fetuses was 71.9 ± 3.7, which is lower than the value reported by Hadlock. Moreover, 253 (78.1%) of the normal fetuses were dolichocephaly because their CIs were below 75.0. And none of the normal fetuses were brachycephaly. It appears that dolichocephaly was more popular in the second-trimester of gestation. The reason for disparity of mean CI value might be ethnicity or gestational age. Large-scale research is required to verify the hypothesis.

In our 6 study groups, we found that the fetuses in group 5 have the lowest incidence (8.2%) of fetal SSM, the differences have statistical significances compared with group 2 (32.8%, p=0.002), 3 (24.2%, p=0.02) and 4 (21.7%, p=0.03). Six women in our study chose to have induced labor because of serious fetal malformations. The CIs of the 6 induced-labor fetuses were all below 71.9. It seems like that fetus with a lower CI was more likely to have serious fetal structural abnormalities, which might lead to an induction of labor. The rest of fetuses in our study did not develop other abnormalities till births, and no serious neonatal complication was detected after birth. Thirty-eight women in our study had amniocentesis for fetal chromosomal/gene screening, and nonpathogenic DNA copy number variations were found in chromosomal/gene screening. However, the limited proportion of amniocentesis in this study might not be enough to analyze the statistical association between fetal CI and chromosomal/gene abnormality.

The UGA of brachycephalic fetuses are more likely to conform with CGA. We suppose that dolichocephalic fetuses of second-trimester have a higher risk of developing intrauterine growth restriction (IUGR). However, recent research by Dana [25] studied the fetal head shapes of 65 preterm infants and deduced that dolichocephaly of the third-trimester is not associated with low birth weight of infants [25]. Further study is required to discover the association between fetal CI and IUGR.

Our study was conducted in Wuhan Tongji Hospital. Overall, fetal CI in our study was less than the value reported by Hadlock. The fetal CI seems to have no statistical associations with fetal abnormalities. However, the fetus with a CI ranges between 76.0 and 79.9 has the lowest incidence of fetal abnormalities when compared to fetus whose CI ranges between 64.0 and 75.9. Dolichocephalic fetuses are more likely to be small for CGA. Maternal pregnancy complication would not affect fetal head shape as our results demonstrated. Because of the limited data of amniocentesis in our study, no statistical associations were detected between fetal CI and chromosomal/gene abnormality.

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