

Normal Range of Fetal Nasal Bone Length during the Second Trimester in an Afro-Caribbean Population and Likelihood Ratio for Trisomy 21 of Absent or Hypoplastic Nasal Bone

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ABSTRACT

Objective To establish the normal reference range of fetal nasal bone length (NBL) during the second trimester in an Afro-Caribbean population and the likelihood ratio for fetal trisomy 21.

Methods Prenatal records of euploid, non-malformed singleton fetuses who underwent second-trimester ultrasonographic scans at 20 to 24 weeks of gestation were retrospectively analyzed for NBL and gestational age (GA). Only Afro-Caribbean couples were selected. The relation between fetal NBL and GA was determined. Data on all fetuses with Down syndrome were provided by REMALAN.

Results There was a significant linear association between fetal NBL and GA ($R^2 = 0.354$). The 50th percentile for NBL increased from 5.0 mm to 7.0 mm from week 20 to 24 of gestation. The nasal bone (NB) was absent or hypoplastic in 8.6% of the euploid fetuses and in 69.2% of the trisomy 21 fetuses. The likelihood ratio for trisomy 21 of absent or hypoplastic NB in an Afro-Caribbean population was 8.02 but only 2.32 when this sign was isolated.

Conclusion The reference range for fetal NBL at 20 to 24 weeks of gestation in an Afro-Caribbean population and the likelihood ratio for trisomy 21 of absent or hypoplastic NB differed from the other populations.

Key words: Ultrasound · Normal range · Second trimester · Fetal nasal bone · Afro-Caribbean population · Trisomy 21 · Down syndrome · Likelihood ratio

Introduction

In his original description in 1866, Langdon Down reported that the face of a patient with trisomy 21 was flat and the nose small [1]. As long ago as 1893, Manouvrier reported that ethnic variations in the nasal bone (NB) are related to interorbital distance, the width of the nasal notch, and the height of the face [2]. Guis et al. were the first to present a reference range for the growth of the nasal bone (NB) from 14 to 34 weeks [3]. In 2001, Cicero et al. published their results on NB abnormalities in fetuses with Down syndrome [3]. Since then,

numerous studies have since investigated the association between absence or hypoplasia of NB and this aneuploidy, with contradictory results [4-8]. Many biases in these studies appeared: definition of hypoplasia, angle between the ultrasound beam and the axis of the nasal bone, presence or not of other ultrasound abnormalities, method of measurement that includes both the hyperechoic central part of the NB and the echogenic extensions at each end or only the hyperechoic center and especially the race and ethnicity of the patient [9]. Cicero et al. reported a higher incidence of NB hypoplasia or absence in Afro-Caribbean fetuses (8.8%) compared with Caucasian fetuses (0.5%) [10]. Chen et al. detected shorter fetal nasal bones in the Chinese population [11]. Several studies have since shown the impact of race and ethnicity on the NBL in second-trimester fetuses: Chinese [11-12], Korean [13], Iranian [14], Turkish [15-16], Indian [17], Japanese [18], Brazilian [19], and Australian [20]. However, no data have been published about the reference range of NBL of normal fetuses in a large Afro-Caribbean population. The aim of this study was to determine the distribution of fetal NB length between 20 and 24 weeks of gestation in an Afro-Caribbean population and to establish the likelihood ratio for fetal trisomy 21 of absent or hypoplastic nasal bone (NB).

Materials and methods

Study design and participants

This was a retrospective study conducted from January 2013 to August 2015 at the Multidisciplinary Center of Prenatal Diagnosis of Martinique, University Hospital of Martinique, French West Indies and at the French West Indies Register of Congenital Malformations (REMALAN). All Afro-Caribbean women with singleton pregnancies attending the routine ultrasound scan at 20-24 weeks of gestation were included in the study. Before the routine morphology scan, all women were asked to define their own and their partner's ethnic origin. Non-Afro-Caribbean couples were excluded.

In Martinique, 86% of pregnant women undergo screening for Down syndrome. The false-positive rate is 5.4%. Of these women, 61% undergo first-trimester screening (fetal nuchal translucency thickness combined with first-trimester serum biochemistry) and 25% second-trimester screening (second-trimester serum biochemistry alone or combined with fetal nuchal translucency thickness).

Pregnancy outcomes were ascertained by searching the ViewPoint database (ViewPoint 5.6.8.428; ViewPoint Bildverarbeitung GmbH, Wessling, Germany). Those women with a confirmed normal outcome were included. All women with structural or chromosomal abnormalities (including Down syndrome), intrauterine growth restriction, or intrauterine fetal death were excluded from the analysis. REMALAN provided data on fetuses with Down syndrome, live births, fetal deaths, and terminations of pregnancy.

Procedure

All scans were performed by four experienced operators (holders of Certificate of Competence from the Fetal Medicine Foundation) using GE Healthcare VE730/E8 machines (GE Healthcare, Cincinnati, OH, USA). Measurements were obtained with an abdominal probe (RA4B). Images were digitally archived in a ViewPoint obstetric imaging database (ViewPoint 5.6.8.428; ViewPoint Bildverarbeitung GmbH, Wessling, Germany) used for all routine scans.

The NB was measured once, according to the methodology described by Sonek and Nicolaides [21], using a strict mid-sagittal section of the facial profile, identifying lips, tip of nose, maxilla and mandible, showing the NB perpendicular to the angle of insonation of the ultrasound beam (around 45°), and by placing the calipers on the outer margins of the NB whilst taking care to include only the bony part, at the level of the synostosis. The correct plane for the measurement of fetal NBL is illustrated in Fig. 1.

Demographic characteristics, ultrasound findings, images and 3D facial data were recorded in the database at the time of the examination.

Two authors (MaG, BS) together reviewed every digital image in the ViewPoint database to ensure appropriate methodology had been used and repeated the measurement if it was unsatisfactory. The stored three-dimensional volumes of the fetal profile were used (Fig. 2). Data values that appeared aberrant were checked against original records and corrected or confirmed. Interobserver variability was not studied, because this was a retrospective study. GA was determined by ultrasound measurement of the first-trimester crown-rump length. In accordance with French law, all women before the routine scan, gave their consent to ultrasound scans and to the use of the data collected for further research.

The NB was considered to be hypoplastic if it was less than the 5th percentile of the curves.

Statistical analysis

Statistical analysis was performed with SPSS Version 19 IBM. Continuous variables were presented as mean +/- standard deviation. A p-value < 0.05 was considered as significant. Simple linear regression was performed to define the relation between NBL and GA. NBL median and percentiles for each gestational week were determined.

The incidence of absent and hypoplastic NB in the chromosomally normal and trisomy 21 fetuses was determined. The likelihood ratio was calculated when the absent or hypoplastic NB was isolated and associated with another marker.

Results

Between January 2013 and August 2015, routine scans were performed in our center for 1846 singleton pregnancies, 356 of which were excluded: 198 were not Afro-Caribbean, 34 had no first-trimester dating, 1 was lost to follow-up, 42 had congenital anomalies or intrauterine

growth restriction or intrauterine fetal death, 13 had trisomy 21 and 68 had no nasal bone. The remaining 1490 pregnant women were eligible to participate and successfully recruited for the study. In 59 cases (4%) we measured the NBL again using stored three-dimensional volumes of the fetal face, because the first measurement was unsatisfactory or the image was not recorded according to the correct methodology. 114 of the 1490 cases were excluded because GA was less than 20 or more than 24 weeks. Data analysis was based on the remaining 1376 cases. Median maternal age was 28 years (range 13-47). The distribution of fetal NBL according to GA was established and the 50th, 5th and 2.5th percentiles were calculated between 20 and 24 weeks of gestation (Table 1). The 50th percentile of fetal NBL ranged from 5.0 mm to 7.0 mm between 20 and 24 weeks of gestation.

A significant positive correlation was observed between fetal NBL and GA. NBL increased linearly with GA, with linear regression producing the equation: $NBL = 0.467 GA - 3.380$ ($R^2 = 0.354 - p < 0.001$) (Fig. 3).

During the study period, 13 trisomy 21-affected infants were born in our center: 5 live births, 8 terminations of pregnancy. Eleven cases were diagnosed prenatally (85%).

Among the 13 trisomy 21 fetuses, 9 had no NB or hypoplastic NB (69.2%) and 4 had NB.

The NB was absent or hypoplastic in 9/13 (69.2%) fetuses with trisomy 21 and in 141/1634 (8.6%) chromosomally normal fetuses.

In the trisomy 21 group, 1/13 (7.7%) had no abnormal ultrasound findings, 3/13 (23.1%) had at least one major defect (atrioventricular septal defect), and 9/13 (69%) had at least one chromosomal marker (short femur or humerus, sandal gap, clinodactyly, echogenic intracardiac foci, tongue thrusting, polyhydramnios).

In the absent or hypoplastic NB group with trisomy 21, the incidence of major defect, one more chromosomal marker and no abnormal ultrasound findings was 3/9 (33.3%), 5/9 (55.6%), 1/9 (11.1%), respectively.

The likelihood ratio for trisomy 21 was 8.02 [95% CI 5.40 – 11.91] for absent or hypoplastic NB and 0.34 [95% CI 0.15 – 0.76] for presence of the NB. The sensitivity for absent or hypoplastic NB was 69.2% with a 95% CI [38.57 – 90.91] and the specificity was 91.4% with a 95% CI [89.90 – 92.69].

The likelihood ratio for trisomy 21 for absent or hypoplastic NB was 2.32 [95% CI 0.40-13.47] when it was isolated. When the absent or hypoplastic NB was isolated, the sensitivity decreased to 20% with a 95% CI [0.51 – 71.64] and the specificity was 91.4% with a 95% CI [89.90 – 92.69].

Discussion

Guis et al. [3] reported the normal range of fetal NBL in a Caucasian population (376 cases) at 14-34 weeks of gestation.

Previous studies investigating the impact of race and ethnicity on the second-trimester fetal NBL have produced conflicting results. Cicero et al. were the first to report a higher prevalence of nasal hypoplasia (< 2.5 mm) in the Afro-Caribbean population compared with the Caucasian population: 8.8% vs. 0.5% [10]. This cut-off of 2.5 mm defines a very hypoplastic nasal bone during gestation and increases the predictive value. However, the Afro-Caribbean population in this study was small (72 patients). Conversely, Sonek et al. concluded in a cross-sectional study of fetal NBL that different normal ranges for Afro-American and Caucasian women are not required [21]. Perhaps the Afro-Caribbean population is different from the Afro-American population.

Many investigators have since reported second-trimester NBL values for ethnic groups including Caucasian [23], Afro-American [22], Chinese [11-12], Korean [13], Iranian [14], Turkish [15-16], Indian [17], Japanese [18], South American [19] and Australian [20] (Table 2). However, ethnicity-related variations in NBL during gestation are likely to have an impact

on the efficacy of NBL-based screening for trisomy 21. Reference ranges of fetal NBL according to race and ethnicity are therefore needed [9-11-12-18], and normal NBL values must be defined for the target population.

To the best of our knowledge, ours is the first study to define a normal range of second-trimester NBL measurements in an Afro-Caribbean population. In line with previous studies, we found that NBL measured between 20 and 24 weeks of gestation was linearly associated with GA in an Afro-Caribbean population. The nasal bones in our Afro-Caribbean population were shorter than the values reported for South Americans, Caucasians, Iranians and Chinese, but the same as or smaller than the values reported for Japanese, Indian and Turkish populations (Fig. 4). The reason for this difference may be phenotypical differences in the Afro-Caribbean population itself and may reflect racial effects on nasal bone growth. As long ago as 1893, Manouvrier reported that ethnic variations in the nasal bone are related to interorbital distance, the width of the nasal notch, and the height of the face [2]. Another reason could be the differences in our patient population and inclusion criteria. The efficacy of NBL measurement in non-selective population would probably be quite different from that in high-risk pregnancies that require karyotyping [10-19-24].

Many reports suggest that fetal NBL during the second trimester of pregnancy is a highly sensitive and specific marker of trisomy 21 [4-8], with a likelihood ratio of 50 if the NB is absent or hypoplastic [10].

Twelve studies have compared the length of the NB during the second trimester, in trisomy 21 and normal fetuses [7-8-10-19-23-24-25-26-27-28-29-30]. The studies essentially used 1 of 3 methods to define NB hypoplasia: first, a measurement below the 5th percentile of the normal range for gestation [19]; second, a measurement below a fixed cut-off of 2.5 mm [10-23-27] or 3 mm [11]; third, a ratio above specific cut-offs in the ratio of the biparietal diameter to NBL [7-24-26-28-29-30]; and below 0.75 multiples of the median [8].

The likelihood ratio for absent or short NB was 115.83 to 6.16 and 0.70 to 0.15 for the normal NB (Table 3). In a meta-analysis, Agathokeous et al. considered that the NB was short or absent in 59.8% of trisomy 21 fetuses and in 2.8% of normal fetuses [31]. The overall likelihood ratio was 23.27 for absent or short NB and 0.46 for presence of the NB [31]. Most of these studies concern a high-risk population, with a high prevalence of Down syndrome (7 to 20%), which increases the likelihood ratio because the group of euploid fetuses with normal NB was reduced. In our study, 69,2% of fetuses with trisomy 21 and 8.6% of chromosomally normal fetuses had absent or hypoplastic NB, because absence of the NB is more common in the Afro-Caribbean population. We found that the likelihood ratio was 8.02 for absent or hypoplastic NB and 0.33 for presence of the NB. Therefore, the likelihood ratio for absent or hypoplastic NB is lower in the Afro-Caribbean population. These data suggest that using NBL as an isolated screening test for trisomy 21 is probably less effective in Afro-Caribbeans than in Caucasians. The incorporation of NBL measurement into screening strategies for trisomy 21 needs to take into account ethnicity. The shorter NBL values in the Afro-Caribbean population, compared with Caucasians, are an important observation as the number of invasive tests would decrease for absent or hypoplastic nasal bone, thereby averting a significant number of unnecessary interventions and miscarriages, as well as unnecessary parental anxiety. However, our study is limited by its retrospective nature.

Conclusion

We provide a normal range of fetal NBL values measured in normal singleton fetuses between 20 and 24 weeks of gestation in an Afro-Caribbean population. The range of fetal NBL values between 20 and 24 weeks of gestation differed from values in other populations. The likelihood ratio for trisomy 21 of absent or hypoplastic NB during the second trimester in an Afro-Caribbean population was lower than in most ethnicities. These data are applicable

not only to Afro-Caribbeans, but also to all those of African origin, ie, more than 16% of the world population.

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Conflicts of interest: None declared

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Figure legends

Fig. 1. Measurement of the length of the fetal nasal bone

Fig. 2. The multiplanar mode used to define the mid-sagittal plane and to measure nasal bone length

Table 1. Nasal bone length percentiles from 20 to 24 weeks of gestation (in mm)

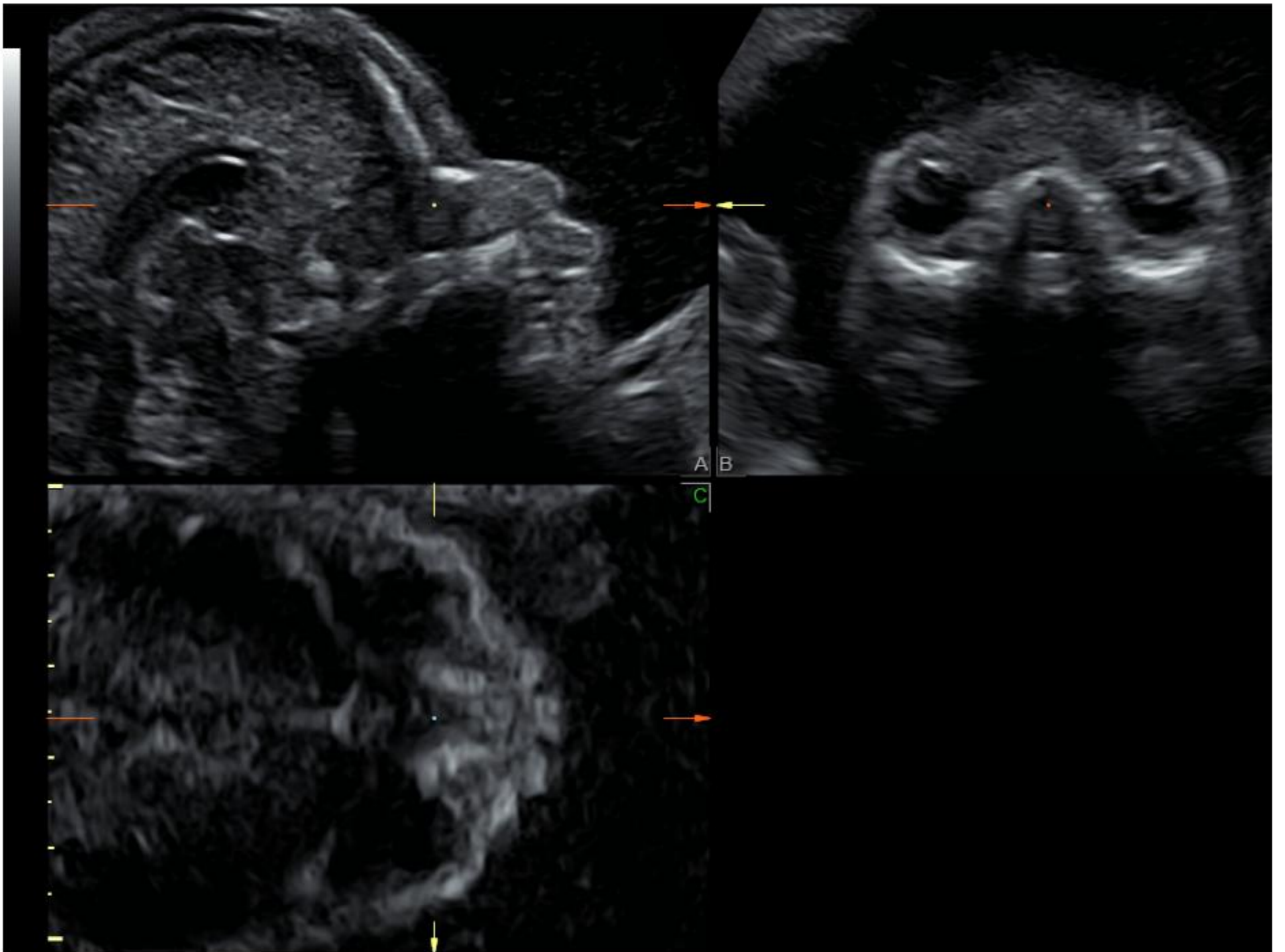
Fig. 3. Linear regression line of NBL in mm and the GA in week

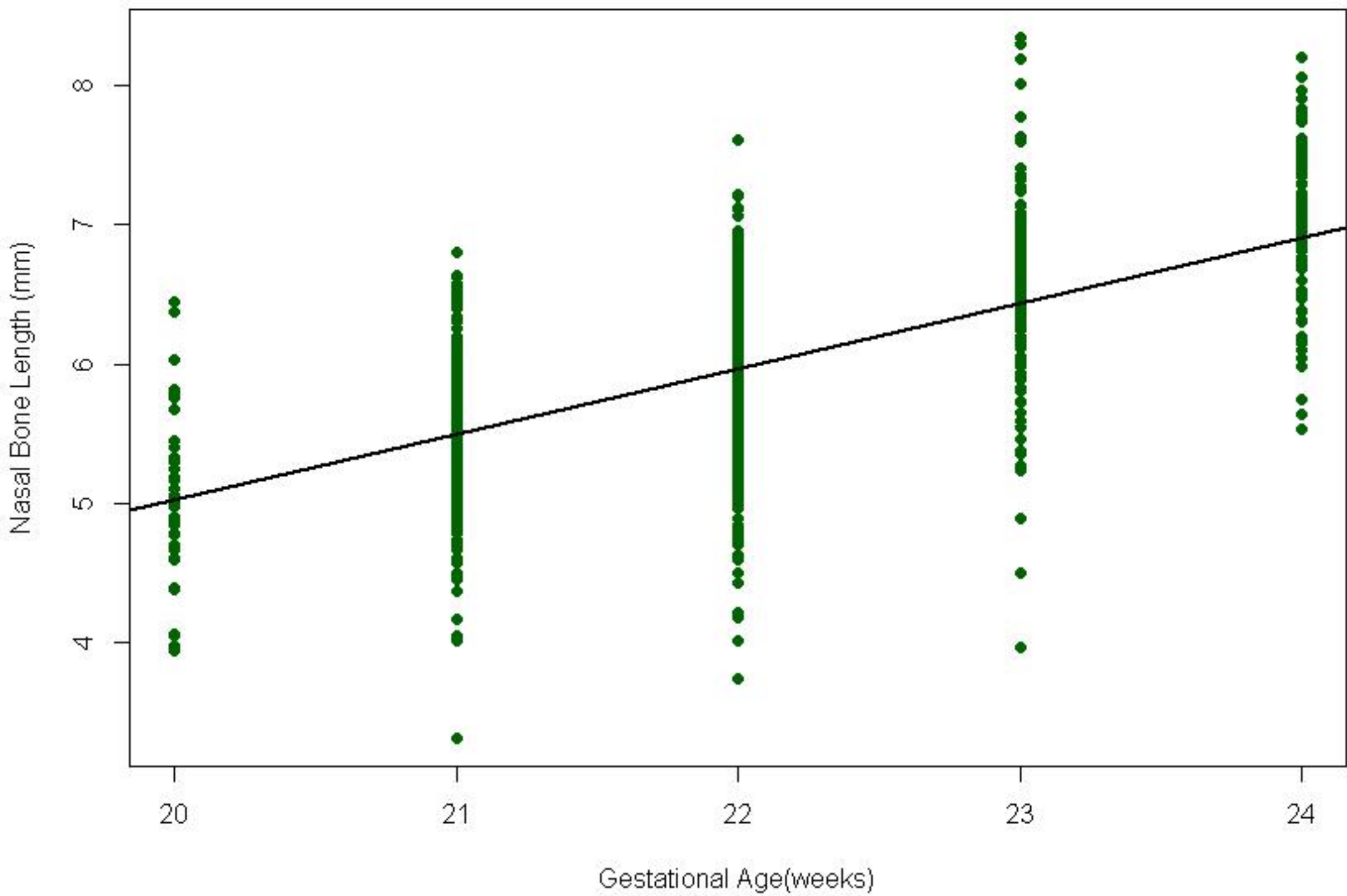
Table 2. Literature values of nasal bone length from 20 to 24 weeks of gestation (in mm)

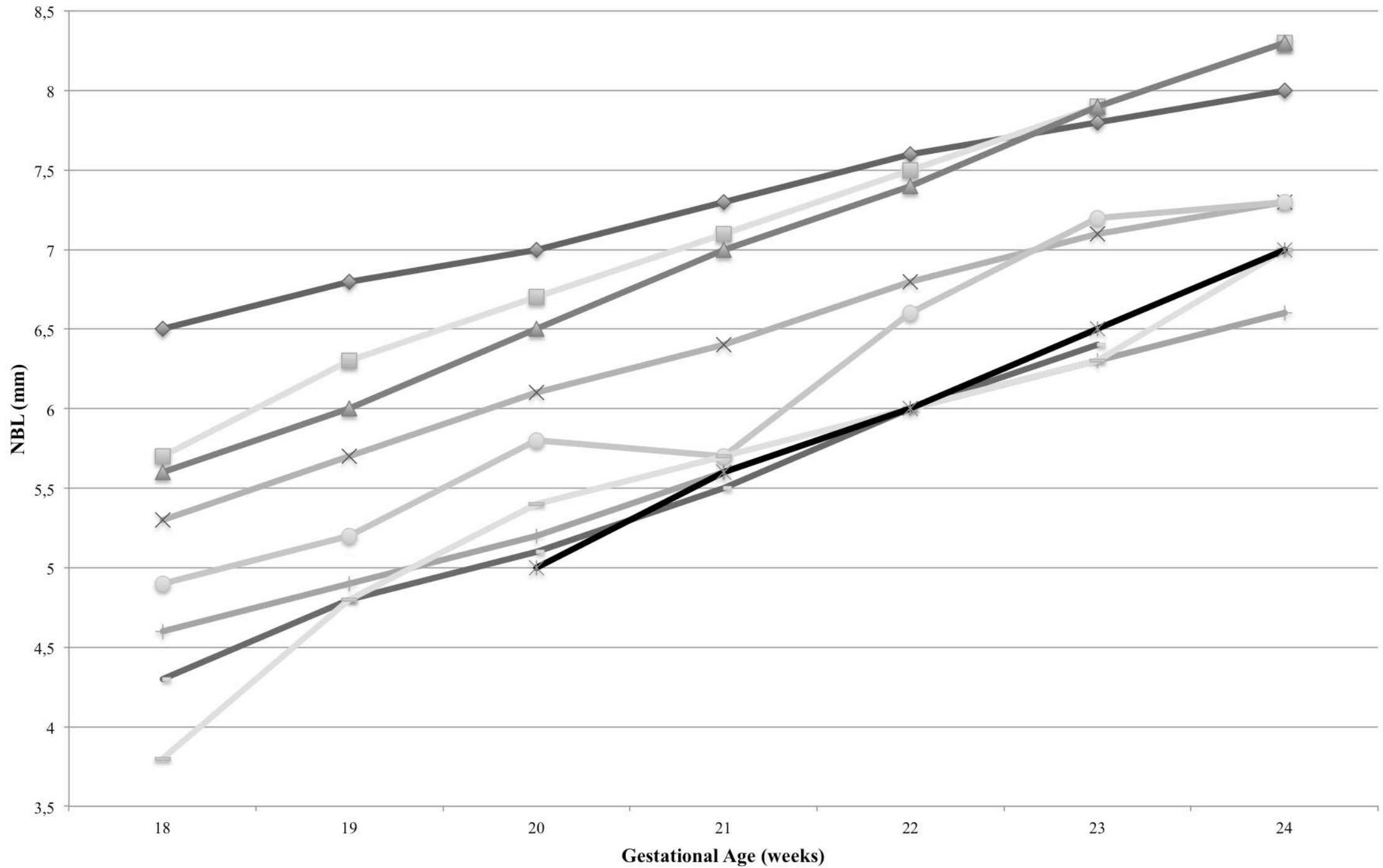
Fig. 4. Comparaison of fetal NBL in different ethnic population

Table 3. Effectiveness of absent or hypoplastic nasal bone in screening for trisomy 21 (12 studies and our study)









- ◆ Bunduki et al (2003) South Am
- × Hung et al (2008) Chinese
- ◆ Yanik et al (2011) Turkish
- Sonek et al (2003) Caucasian
- Kanagawa et al (2006) Japanese
- Jung et al (2007) Korean
- ▲ Rahimi et al (2011) Iranian
- Sharma et al (2013) Indian
- ◆ Schaub et al (2015) Afro-Caribbean

Table 1. Nasal bone length percentiles from 20 to 24 weeks of gestation (in mm)

Gestational age (weeks)	Subjects	2.5 percentile	5 percentile	50 percentile
20 (20-20+6)	43	3.9	4.0	5.0
21 (21-21+6)	323	4.4	4.7	5.6
22 (22-22+6)	774	4.7	5.0	6.0
23 (23-23+6)	151	5.2	5.4	6.5
24 (24-24+6)	85	5.6	5.8	7.0

Table 2. Literature values of nasal bone length from 20 to 24 weeks of gestation (in mm)

Authors	n	Population	Gestational age (weeks)				
			20	21	22	23	24
Guis et al (1995) ^a	376	Caucasian	6.31	N/A	7.62	N/A	8.24
Bunduki et al (2003) ^b	1631	South American	6.50	6.80	7.00	7.30	7.60
Sonek et al (2003) ^b	1610	Caucasian	5.7	6.3	6.7	7.1	7.5
Chen et al (2004) ^b	198	Chinese	5	5.60	5.80	6.20	6.70
Gamez et al (2004) ^a	2035	Caucasian	N/A	6.19	6.41	6.54	6.77
Hung et al (2008) ^b	342	Chinese	5.29	5.71	6.09	6.44	6.77
Jung et al (2006) ^a	2885	Korean	4.00	4.70	5.40	5.70	6.00
Kanagawa et al (2006) ^b	359	Japanese	4.90	5.20	5.80	5.70	6.60
Rahimi et al (2011) ^a	3201	Iranian	5.50	6.00	6.40	6.90	7.30
Yanik et al (2001) ^b	1467	Turkish	4.30	4.80	5.10	5.50	6.00
Sharma et al (2013) ^b	6436	Indian	4.60	4.90	5.20	5.60	6.00
Our study (2016) ^b	1376	Afro-Caribbean	5.00	5.65	5.97	6.55	6.96

a Mean value

b Median value

Table 3. Effectiveness of absent or hypoplastic nasal bone in screening for trisomy 21 (12 studies and our study)

Study	Definition	Type	Trisomy 21 n/N – (%)	Normal n/N – (%)	LHR + [95% CI]	LHR – [95% CI]
Bromley ⁷	BPD/NBL \geq 11	HR	11/16 (68.8)	11/223 (4.9)	13.94 [7.17-27.08]	0.33 [0.16-0.68]
Gianferrari ⁸	NBL <0.75 MoM	HR	18/21 (85.7)	74/2515 (2.9)	29.13 [21.92-38.71]	0.15 [0.05-0.42]
Cicero ¹⁰	NBL < 2.5 mm	HR	21/34 (61.8)	12/982 (1.2)	50.50 [27.15-94.09]	0.38 [0.25-0.59]
Bunduki ¹⁹	NBL < 5 th perc	HR	13/22 (59.1)	82/1600 (5.1)	11.53 [7.68-17.32]	0.43 [0.26-0.71]
Gamez ²³	NBL < 2.5 mm	HR	5/5 (100.0)	34/1899 (1.8)	55.85 [40.03-77.93]	0.00
Obido ²⁴	BPD/NBL \geq 12	HR	6/16 (37.5)	19/508 (3.7)	10.03 [4.64-21.68]	0.65 [0.44-0.95]
Cusick ²⁵	NBL < 3 mm	HR	4/4 (100.0)	0/422 (0.0)	–	0.00
Tran ²⁶	BPD/NBL \geq 18	HR	15/31 (48.4)	5/136 (3.7)	13.16 [5.17-33.49]	0.54 [0.38-0.76]
Viora ²⁷	NBL < 2.5 mm	HR	10/18 (55.6)	2/417 (0.5)	115.83 [27.36-490.37]	0.45 [0.27-0.75]
Cusik ²⁸	BPD/NBL \geq 11	HR	7/11 (63.6)	16/371 (4.3)	14.76 [7.66-28.41]	0.38 [0.17-0.83]
Sooklim ²⁹	BPD/NBL \geq 12	HR	3/10 (30.0)	2/386 (0.5)	57.90 [10.84-309.25]	0.70 [0.47-1.06]
Obido ³⁰	BPD/NBL \geq 12	Sc	9/22 (40.9)	161/2423 (6.6)	6.16 [3.65-10.40]	0.63 [0.45-0.90]
Schaub	NBL < 5 th perc	Sc	9/13 (69.2)	141/1634 (8.6)	8.02 [5.40-11.91]	0.34 [0.15-0.76]

NBL: Nasal bone length – BPD: biparietal diameter – perc: percentile – MoM: multiple of the median - HR: high-risk population –

Sc: screening – n: absence or hypoplastic nasal bone – N: presence of nasal bone - LHR: likelihood ratio - CI: confidence interval