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ORIGINAL ARTICLE

Sensitivity of Nasal Bone as Aneuploidy Marker—First Trimester *versus* Second Trimester Assessment

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Abstract
Objective To assess the reliability of nasal bone (NB) as an aneuploidy marker in the first trimester *vs.* second trimester and to highlight the technical difficulties in evaluating the nasal bone at 11–14 week scan.
Methods Nasal bone was examined in 4478 women who enrolled for nuchal translucency (NT) scan and NB was assessed in both midsagittal and coronal planes. Risk assessment was done based on serum biochemistry and NT without including the NB status. Absence of NB was confirmed at 17 week and aneuploidy risk was modified from the obtained first trimester risk. The midsagittal images from the cases with absent NB were randomly assorted among 81 normal ones and were peer reviewed.
Results Nineteen fetuses had absent NB in the first trimester, of which five had NT above the 90th percentile. In the remaining 14 cases followed up at second trimester, nasal bone was present in 3 cases in the subsequent scan. Five of 11 cases were screen positive after modifying the risk and were counseled appropriately. In retrospective evaluation of the 100 images, concordance was obtained only in 76%, reflecting the observer variability. Down's syndrome was confirmed in 4 cases of which three also had an increased NT.
Conclusions Routine inclusion of NB in first trimester risk assessment with conventional midsagittal view alone in all cases may lead to an increased number of false positives. Inclusion in the second trimester would still have the same detection rate but would eliminate technical difficulties of imaging NB in the first trimester.

Keywords Nasal bone · Aneuploidy · Retronasal triangle · Midsagittal plane · Equal sign · First trimester screening · Nuchal translucency · Non-invasive prenatal testing

Abbreviations

NT	Nuchal translucency
β-HCG	Beta human chorionic gonadotropin
PAPP-A	Pregnancy associated plasma protein—A
TR	Tricuspid regurgitation
DV	Ductus venosus
FPR	False positive rate
FMF	Fetal medicine foundation
RNT	Retronasal triangle
NIPT	Non-invasive prenatal testing
FTS	First trimester screening
2D	Two dimensional
3D	Three dimensional

Introduction

Ultrasound evaluation of the nasal bone has evolved as a powerful marker for aneuploidy screening as there is a high association between trisomy 21 and absent nasal bone [1–4]. As early as 1866 John Langdon Down described Down's syndrome with its distinctive facial features of flat facial profile with small nose and skin deficient in elasticity. Nasal bone abnormalities were first observed on radiography postnatally in babies with Down syndrome. It was only in 2001 the striking nasal bone abnormalities were recognised with prenatal

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ultrasonography and in about 73% of fetuses with trisomy 21, the nasal bone was not visible in the first trimester [1, 5].

A combination of fetal nuchal translucency (NT) along with measurement of maternal serum free beta human chorionic gonadotropin (β-HCG) and pregnancy associated plasma protein—A (PAPP-A) and assessment of the presence or absence of the fetal nasal bone (NB) has improved the potential performance of screening for trisomy 21 [6, 7]. Inclusion of NB in the first trimester along with other soft markers like tricuspid regurgitation (TR) and ductus venosus (DV) has been reported to reduce false positive rate (FPR) to about 2–3% [8–10]. Unfortunately, the technical expertise required to evaluate the fetal nasal bone at this early gestational age might limit the widespread application of this approach. Nasal bone varies in structure based on the race, and crown–rump length (CRL) measurement and hence in the calculation of likelihood ratios for trisomy 21, adjustments must be made for these confounding factors [11, 12]. To arrive at the appropriate risk assessment in the first trimester and to avoid unnecessary invasive procedure, it is necessary to standardise nasal bone evaluation. In a recent meta-analysis by Agathokleous et al. absent NB was the most sensitive marker in second trimester and had the highest likelihood ratio of 6.58 [13]. The reproducibility of NB assessment is better in the second than in the first trimester. In the present study authors have attempted to check the reliability of nasal bone as an aneuploidy marker in first *vs.* second trimester and also have assessed the interobserver variability in imaging the NB in first trimester [14]. They have discussed the pitfalls associated with imaging NB in midsagittal plane alone in first trimester and the potential advantages of its evaluation in midtrimester.

Material and Methods

This prospective study was performed from September 2012 through September 2015. NB assessment was done in 4478 antenatal women referred for first trimester aneuploidy scan with a CRL of 45–84 mm by a single fetal medicine foundation (FMF) certified operator. Informed consent was obtained from all the cases included in the study. Only those who followed up for anomaly scan and whose postnatal outcome was available were included. All fetuses with structural anomalies were excluded. Postnatal information was obtained from the referring clinician and the parents.

NB was assessed in two planes—the midsagittal plane and in coronal plane by visualising the retronasal triangle (RNT). Under appropriate magnification, in the midsagittal view the three distinct lines were assessed as per the FMF guidelines [12]. The first two lines, which are proximal to the forehead, are horizontal and parallel to each other, resembling an "equal sign". The top line represents the skin and the bottom one, which is thicker and more echogenic than the overlying skin, represents the nasal bone. A third line, almost in continuity with the skin, but at a higher level, represents the tip of the nose. NB was considered present when echogenicity of the second line was greater than that of the first line as in Fig. 1a.

In the coronal plane, the nasal bones were identified at the upper tip of the RNT as two paired small echogenic structures completing the apex of the triangle (Fig. 1b). The primary palate forms the base of RNT and the frontal processes of the maxilla forms its two lateral sides. The nasal bones were classified as both present and only one present depending on its visualisation. When the nasal bone line appears as a thin line less echogenic than the overlying skin or the second line is not visualised in midsagittal view

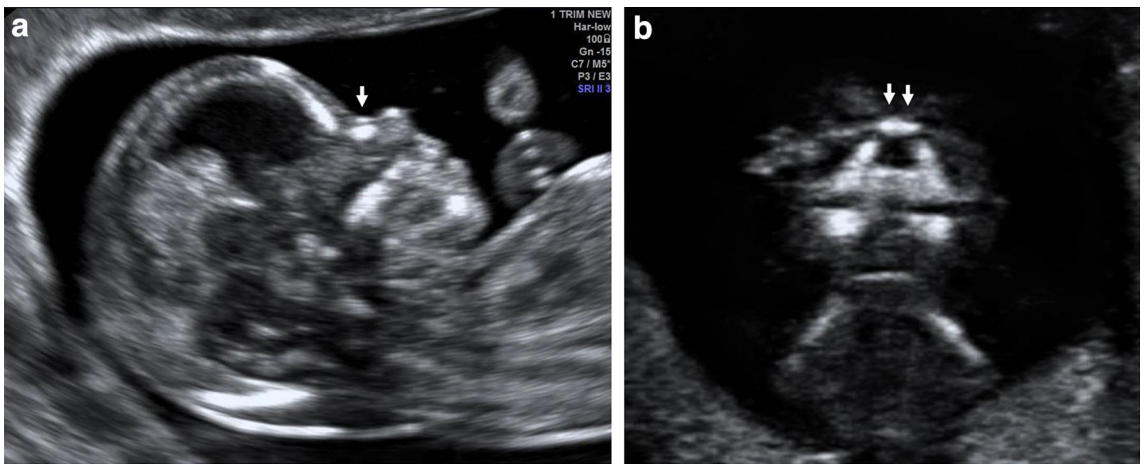

Fig. 1 Nasal bone in **a** midsagittal and **b** coronal view. **a** Midsagittal view depicting the nasal bone, the second line is more echogenic than the skin line (*arrow*) **b** retronasal triangle illustrating the two nasal bones forming the apex of triangle (*arrows*)

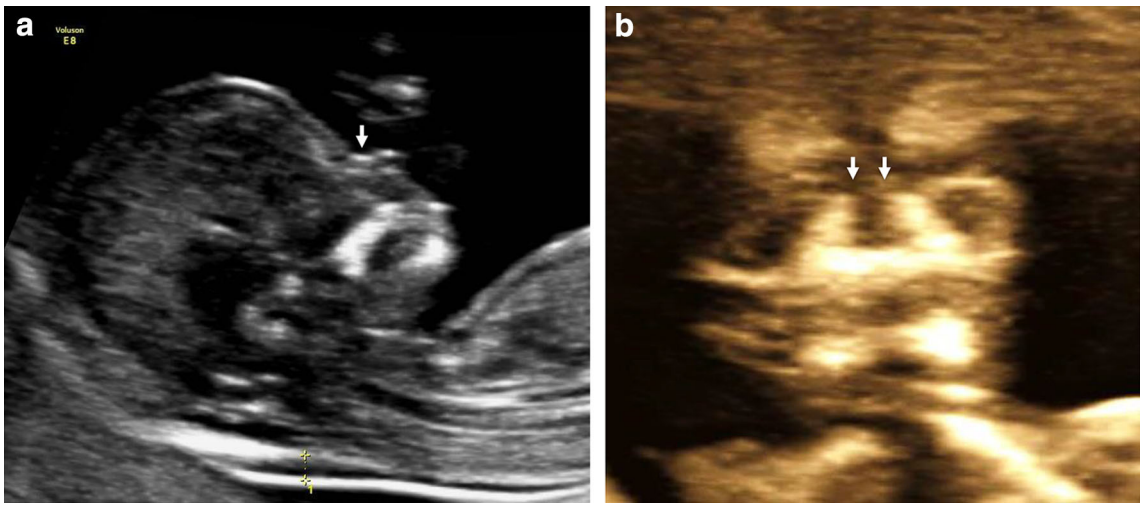

Fig. 2 Absent nasal bone in **a** midsagittal and **b** coronal view. **a** The second line is not echogenic (*arrow*) **b** apex of RNT is open (*arrows*)

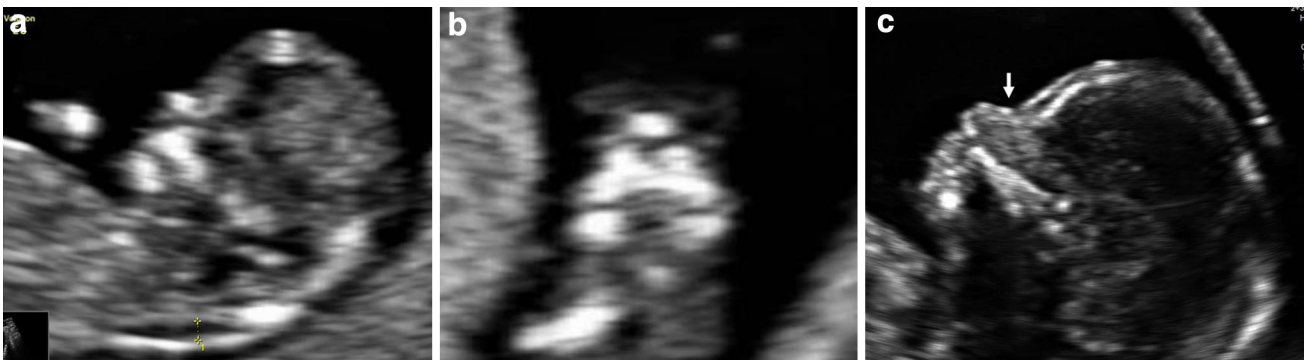

Fig. 3 Presence of nasal bone (NB) in **a** sagittal and **b** coronal view **c** at NT scan: unnossified nasal bone at 20 week scan (*arrow*)

(Fig. 2a) and when the apex of RNT is deficient, it was classified as being absent (Fig. 2b).

Risk assessment was done based on serum biochemistry and NT without including the status of NB. The cutoff for screen positive cases was 1: 250. The other soft markers like DV and TR were not used for risk prediction in the first trimester. Absence of NB was confirmed at 17 week scan and aneuploidy risk was modified from the obtained first trimester risk. At 17 week the authors looked for the presence or absence of the nasal bone in midsagittal view and the nasal bone length was also assessed. Invasive testing or NIPT was offered based on this modified risk. Absent NB images were randomly assorted among 81 normal ones and an opinion was obtained from another operator.

Results

Of the 4478 patients screened in the first trimester, 19 fetuses had absent nasal bone of which five had NT above the 90th percentile. In the remaining 14 patients followed up in second trimester, 3 patients had nasal bone present in the subsequent scan. Six cases were screen positive after modifying the risk and they were counseled appropriately. In retrospective evaluation of 100 images, concordance was obtained only in 79% reflecting the observer variability. Four fetuses were found to have Down's syndrome and one had Turner's syndrome. The rest 14 cases were found to be normal postnatally. However one case which was reported as present NB in the first trimester, turned out to have absent NB during routine anomaly scan (Fig. 3). No other cases of Down's syndrome were additionally detected at postnatal followup.

Discussion

Fetuses with Down's syndrome tend to have delayed maturation of the nasal bones and it is a possible explanation for the increased prevalence of absent or hypoplastic nasal bone in them [15]. Only 0.5% of euploid fetuses were found to have absent nasal bone and among the

aneuploidies other than Down's syndrome, nasal bone abnormalities were also found in trisomy 18 (57%), followed by trisomy 13 (31.8%) and Turner's syndrome (8.8%). Absence of nasal bone is higher in the normal Afro-Caribbean and Asian fetuses which reduces the contribution of this finding in assessing the risk of Down's syndrome in these populations [16]. Though incorporation of NB in first trimester screening improved the detection rate of trisomy 21 there are some pitfalls that need to be addressed. These are, poor echogenicity of nasal bone at an earlier gestation, delayed maturation in euploid fetus and the technical difficulty associated with visualising the nasal bone in midsagittal view in a small sized fetus.

The nasal bones develop from paired independent ossification centers located in a membrane which covers the cartilaginous nasal capsule [15]. Nasal bones were observed to increase both in length as well as in width and fuse in midline with advancing gestational age. Due to gestational age dependent differences in the onset of ossification, the incidence of absent NB in normal fetuses is considerably higher at 11 than at 13 week [12, 17]. In Sonek's opinion, the nasal bone evaluation in first trimester is to be done when the fetal CRL is in the range of 65–74 mm to avoid false positives [17].

According to standard guidelines, NB assessment is done by identifying the "equal" sign in midsagittal view. The nasal bone actually consists of two bones whereas the midsagittal view can identify only one bone at a time, both the nasal bones can be evaluated simultaneously in coronal plane. Since there is a gap between two nasal bones, a true midsagittal plane may falsely show an absent NB status (Fig. 4). In 11–14 week of gestation, a gap exists between the nasal bones in about 20% of fetuses, and in about 40% of these cases the nasal bone may erroneously be considered to be absent in the perfect midsagittal plane [18] (Fig. 4).

The ossification pattern of nasal bone may be the presence of only one nasal bone or hypoplastic nasal bones or complete absence of nasal bone. Unilateral nasal bone often presents as absent nasal bone in midsagittal view [19]. This differentiation can easily be found in RNT view; where the nasal bones appear as two echogenic dots at the apex of triangle [15, 19]. In the present series authors had three cases where the nasal bone was absent in the first trimester but appeared normal in the second trimester and hence the obtained FTS risk was not modified in these three cases. Measurement of NB length also was within the normal limits in second trimester in these cases (Fig. 5). Delayed ossification is associated with a lower risk of Down's syndrome than absent nasal bone [15]. Hypoplastic nasal bones and unilateral nasal bones may be indistinguishable from complete absence of nasal bones in a true midsagittal view in the first trimester (Fig. 6). Hypoplastic nasal bones in Down's syndrome generally do not fuse in midline and appear divergent in coronal plane whereas in the euploid fetus there is fusion in midline [20]. Hence persistent absence of nasal bone in second trimester is a more effective marker as both the concept of unilateral nasal bones and delayed ossification would be taken care of. Genetic counseling based on a sagittal profile view alone in first trimester may be associated with an artificially increased FPR and could result in an elevated number of unwarranted invasive procedures as opined by Gonçalves et al. [15].

The concern over the operator dependency and observer variability in interpreting the nasal bone in first trimester do exists and there was about 20% discordance in the index study [14]. The ability to differentiate the equal sign and to appreciate the echogenic second line is highly dependent on image resolution which is much compromised in maternal obesity. Often the second line appears to exist but may not be echogenic leading to an indeterminate nasal bone status which can then be evaluated in coronal planes (Fig. 7). Using RNT view in addition, avoids the difficulties such as imaging the gap between the nasal bones or visualising the frontal process of maxilla instead of nasal bones.

Considering the inclusion of NB status for assessment of aneuploidy risk in first trimester the advantages claimed are

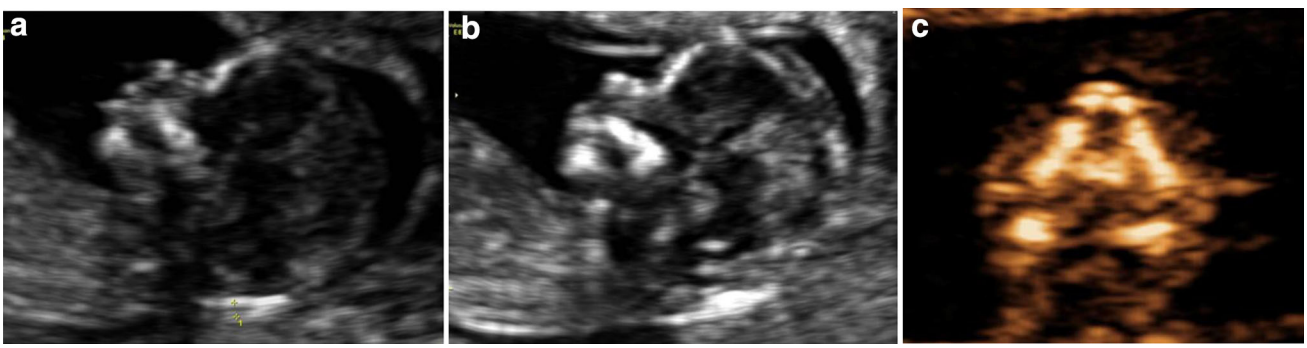

Fig. 4 **a** and **b** A true midsagittal plane showing falsely absent nasal bone status due to a gap between two nasal bones, **c** RNT view confirming the presence of nasal bone

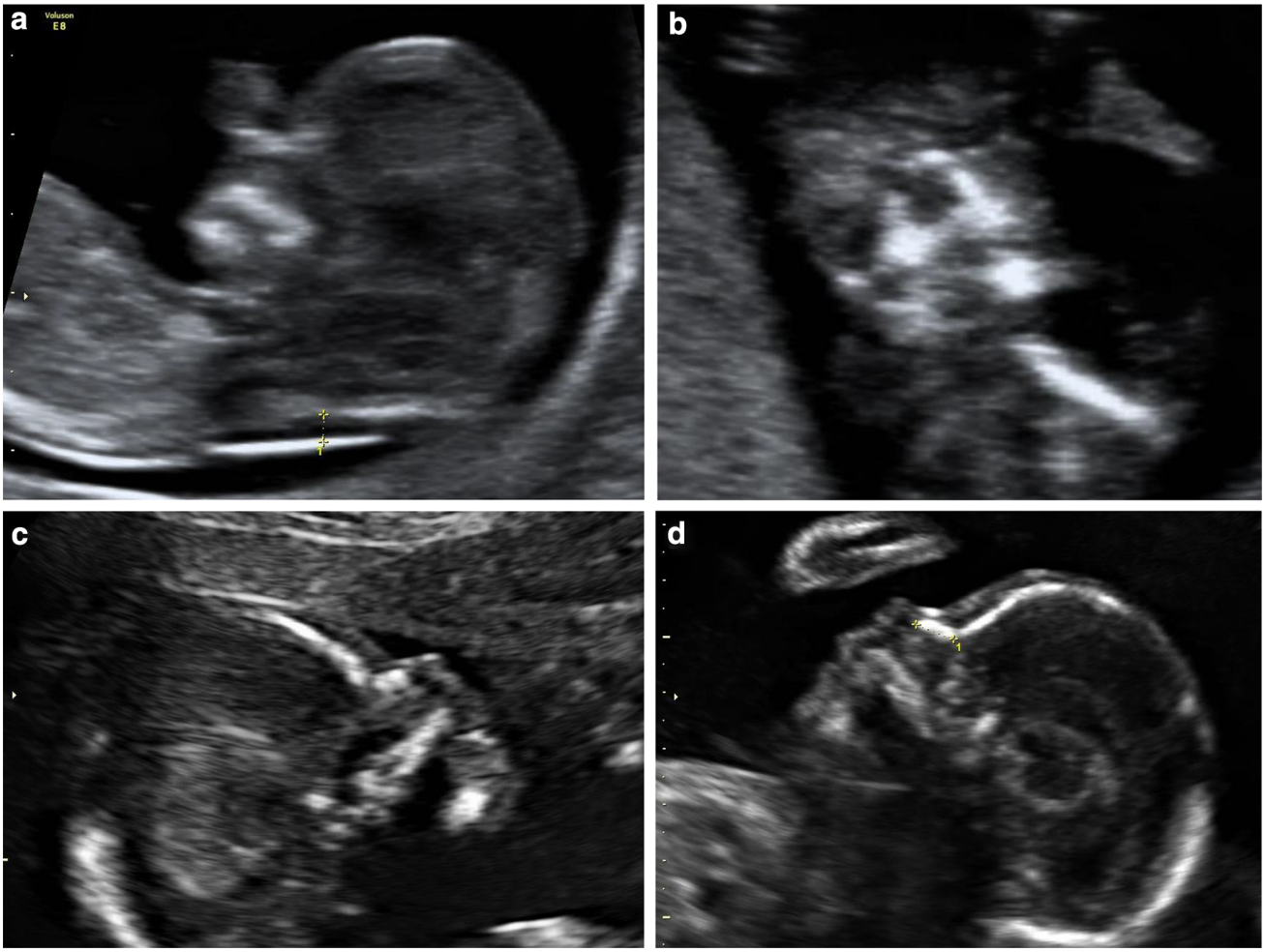

Fig. 5 **a** Nasal bone not imaged in sagittal view at 12 week **b** presence of unilateral nasal bone in RNT view **c** nasal bone imaged at 17 week **d** normal nasal bone length at 21 week (7 mm)

to increase the detection rate and to decrease FPR. The authors present two case scenarios to illustrate the influence of absent NB in first trimester risk prediction. The risk for Down's syndrome in a 22 year old primi with a CRL of 68 mm and NT of 1.9 mm is 1: 51,536 after combined testing with NT and serum biochemistry. Including absent nasal bone status in first trimester raises her risk to 1 in 809, changing the low risk status to an intermediate one. However when she was evaluated in the second trimester and absent NB status included, the risk modified on 1: 51,536 changes to 1 in 7832 which is in the low risk group. The same marker when included in the first trimester yields a risk of 1: 809, whereas when included in the second trimester, yields a risk of 1: 7832. Addressing the question of whether including the presence of NB in risk prediction decreases the need for NIPT or invasive testing always, in a case scenario with a CRL of 71 mm and NT of 2.3 mm, the risk of Down's syndrome with inclusion of NT and serum biochemistry is 1: 193. When nasal bone present status is added then the risk changes to 1:409 which is still in the intermediate risk group. Hence, inclusion of nasal bone status in this case did not modify the counseling options.

In the present study involving 4478 antenatal women the nasal bone was assessed in first trimester as a part of anatomical evaluation of face. Moreover, the inclusion of RNT view also helped the authors to identify the indeterminate ones and to confirm absence of nasal bones. They did not include the NB status in risk prediction as a routine protocol in first trimester. This avoided the need to call fetuses with a CRL between 45 and 55 mm a week later to assess the nasal bone alone and hence the risk prediction was not delayed. Counseling based on the modified risk in midtrimester helped the authors to minimise the cases to whom further invasive testing was offered. Analysis of outcomes revealed no compromise in the detection rates for Down's syndrome when NB was used for risk prediction in

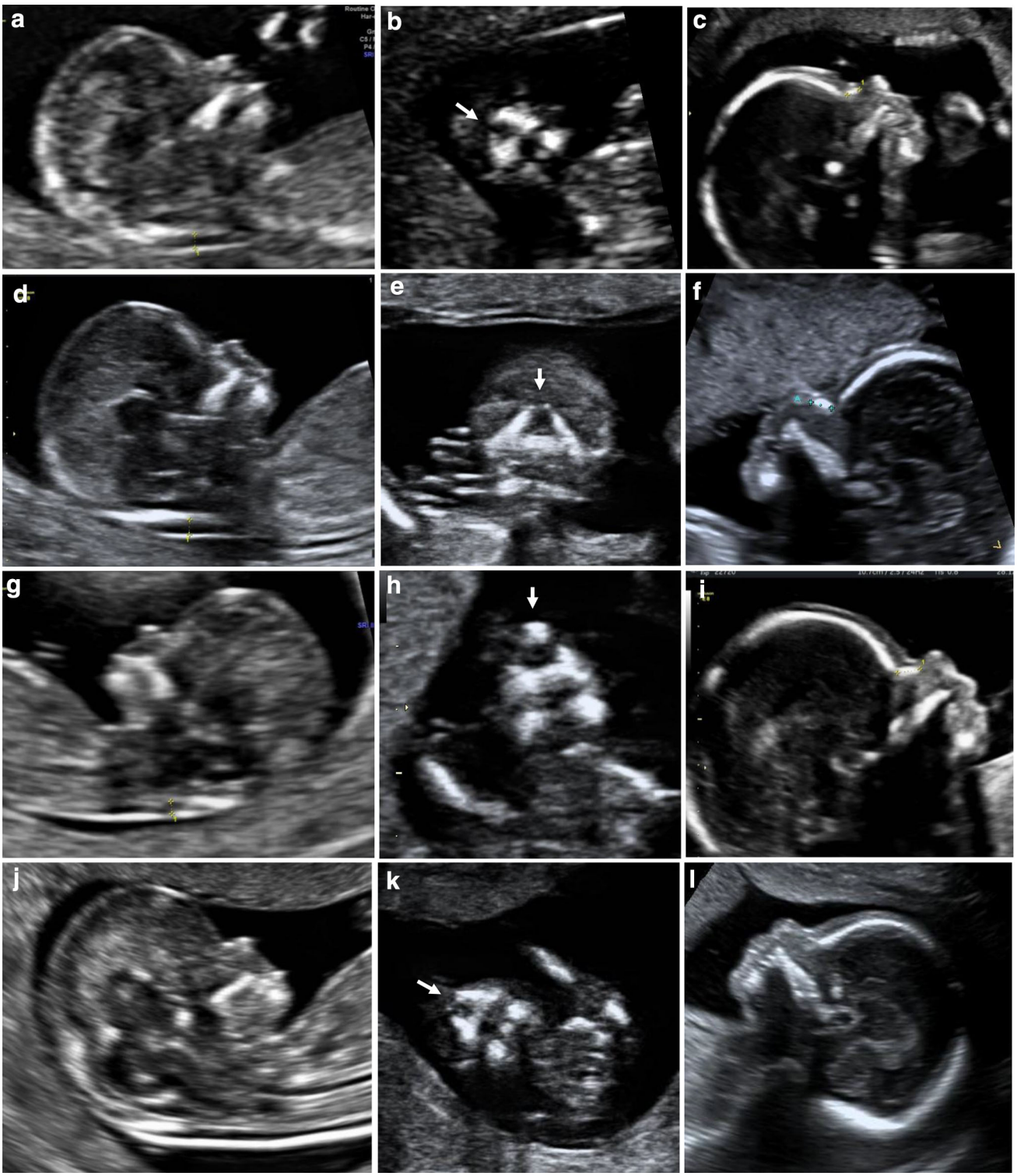

Fig. 6 Illustration of hypoplastic, normal and absent nasal bones in midsagittal and coronal view at NT scan with corresponding scan done in mid trimester *Case 1*: **a**, **b**, **c**: **a** CRL—68 mm, NB in midsagittal view **b** RNT view (*arrow* points to NB). **c** Hypoplastic NB measuring 4 mm at 22 week (<5th centile as per ref 35). *Case 2*: **d, e, f**: **d** CRL—66 mm, NB in midsagittal view **e** RNT view (*arrow* points to NB). **f** NB measuring 5 mm at 20 week (>5th centile as per ref 35). *Case 3*: **g, h, i**: **g** CRL—53 mm, NB in midsagittal view **h** RNT view. **i** NB measuring 5 mm at 20 week (>5th centile as per ref 35). *Case 4*: **j, k, l: j** CRL—67 mm, NB in midsagittal view **k** RNT view. **l** Absent NB at 22 week. *CRL* Crown-rump length; *NB* Nasal bone

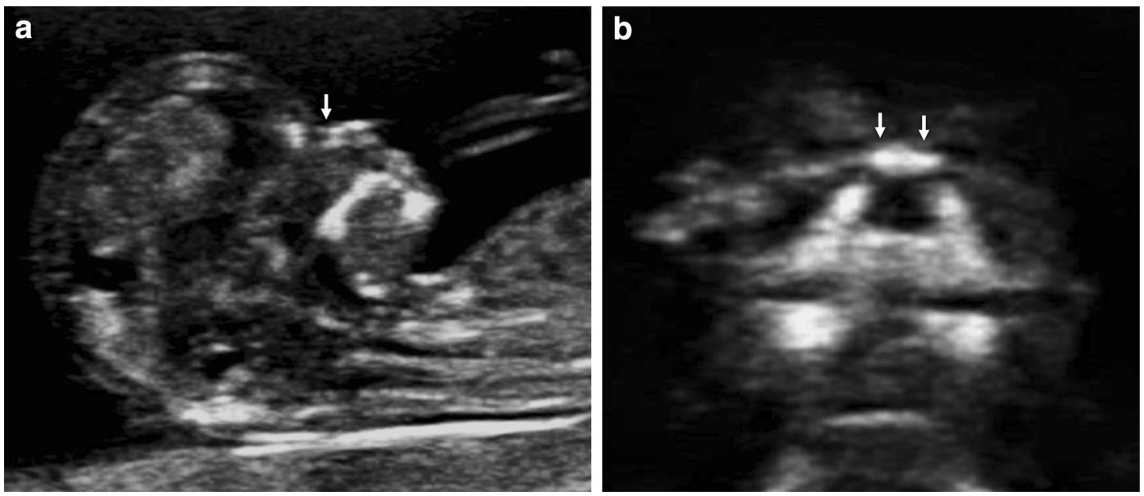

Fig. 7 Indeterminate NB status (second line equal in echogenicity to first line) (**a**) in midsagittal view (*arrow*) (**b**) but clearly evident in RNT view (*arrows*)

the second trimester by modifying the obtained first trimester risk.

The nuchal translucency serves as the most efficient marker in first trimester [21]. The incidence of absent NB increases with NT, and hence the likelihood ratio for trisomy 21 with absent nasal bone is considerably higher [12]. Other markers do exist in first trimester like wide frontomaxillary angle, TR and reversed 'a' wave in DV which can improve the performance of screening in first trimester [8, 10]. Hence even without inclusion of NB status in first trimester, reasonably good detection rates can be achieved. Ramos Corpas et al. concluded that evaluation of the presence/absence of NB in Down's syndrome screening during the first trimester has a low sensitivity in a low risk population [22]. It plays a lesser role in the re-evaluation of already high risk pregnancies in first trimester assessment. NB assessment in first trimester is limited in sensitivity and is also challenging to assess in multiple pregnancies [23].

Prevalence of soft markers have been evaluated in midtrimester and absence of NB has a 6–7 fold increase in risk for trisomy 21 [13]. The option of measuring the nasal bone length is also available in the second trimester and can be used to increase the sensitivity of this parameter as illustrated in Table 1 [24–27]. Various normograms have been plotted for NB length in second trimester according to ethnicity [35, 36]. Though 2D and 3D assessments of NB length have been done in the first trimester [37, 38], acceptable NB imaging could be obtained in almost all cases in the second trimester when compared to the first trimester [3, 33, 34]. When the concept of assessing the presence or absence of nasal bone itself is very tedious and the nasal bone status is indeterminate in many cases assessed in first trimester with conventional midsagittal view, then the reproducibility of nasal bone length assessment in first trimester becomes questionable [39, 40].

Conclusions

Prenatal nasal bone evaluation with ultrasound is proving to be an exceptionally powerful marker for Down's syndrome but the question of when should the NB status be included in risk prediction has to be addressed. The idea of inclusion of multiple markers in a screening protocol is to increase the detection rate and to decrease the FPR. However, the technique used for identification of these markers must be standardised to achieve this goal and there should be no ambiguity in determining the marker status due to technical limitation or operator expertise. Evaluation of nasal bone in coronal view in addition to midsagittal view in first trimester minimised the false positives in the present study. Though this had been observed earlier [41], RNT view is yet to be incorporated in routine imaging. Inclusion of NB to risk assessment in all cases in first trimester might falsely increase the number of screen positive cases. Its inclusion in intermediate risk group alone after doing NT and serum testing might be beneficial. If nasal bone has to be included in risk prediction for wide spread screening purpose which involves less technical expertise, then ideally NB assessment for risk prediction should be taken up in second trimester.

Table 1 Summary of previous studies in first and second trimester using nasal bone for risk prediction

Author	No. of cases	Acceptable NB imaging	GA in weeks	Markers included for risk prediction	Detection rate	FPR	Sensitivity	LR
Cicero et al. [1]	701	701	11–14	NT, NB		1%	85%	
Bunduki et al. [33]	1631	–	16–24	NBL <5th %ile		5.1%	59%	11.6 [Hy]
Cicero et al. [30]	1046	1046	15–22	NBL < 2.5 mm				50.5 [Hy]
								0.38 [Pr]
Malone et al. [28]	6324	4801	10^{+3}–13^{+7}	NB		0.3%	7.7%	
Prefumo et al. [29]	628	572	11–14	DV, NB				6.42 [Ab]
Gamez et al. [34]	7054	6972	18–22	NBL <2.5th %ile			43%	
Orlandi et al. [6]	2411	–	11–14	NT, SB, NB	90%	2.5%		
Ramos Corpas et al. [22]	1800	1682	11–14	NB		1.13%	33.3%	
Nicolaides [10]	100,000	–	11–14	NT, NB, SB, FMF angle, TR, DV	95%			
Vos et al. [31]	159	–	15–33	1) PT/NBL	1) 86.2%	1) 5%		
				2) NBL	2) 61.9%	2) 5%		
Abele et al. [8]	1916	–	11–14	NT, NB, TR, DV	80% [1 marker]	3%		
					87% [2 markers]			
					94% [3 markers]			
Tournemire et al. [32]	91—Normal 26—T21	–	15–36	PT/NBL—0.98			88.5%	

Ab Absent; *DV* Ductus venosus; *FMF angle* Frontomaxillary facial angle; *FPR* False positive rate; *GA* Gestational age; *Hy* Hypoplastic; *LR* Likelihood ratio; *NB* Nasal bone; *NBL* Nasal bone length; *NT* Nuchal translucency; *Pr* Present; *PT* Prenasal thickness; *SB* Serum biochemistry; *Se* Sensitivity; *TR* Tricuspid regurgitation

Compliance with Ethical Standards

Conflict of Interest None.

Source of Funding None.

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