ORIGINAL ARTICLE

The recurrence of sonographic 'soft markers': ominous sign or 'just' genetics?

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ABSTRACT

Objectives 'Soft markers' (SMs) are nonspecific findings that might convey a higher risk for Down syndrome. We sought to determine the recurrence rate of the most common SM in subsequent pregnancies.

Methods This is a retrospective study of all women who underwent early or late fetal sonographic anatomical screening in our ultrasound unit. The examined SMs were pyelectasis, thickened nuchal fold (TNF) and echogenic intracardiac foci (EIF). Data on recurrence and pregnancy outcome were retrieved retrospectively.

Results The database included 20 672 singleton pregnancies; SMs were detected in 2347 (11.1%) of the fetuses and were isolated in 1739 (74%). Rates of solitary findings in the pregnancies were 6.5% (1360/20 672) EIF, 3% (624/18 850) TNF and 1.7% (363/20 672) pyelectasis. The recurrence rate of EIF, TNF and pyelectasis in subsequent consecutive pregnancies was 21%, 27% and 16%, respectively. Overall, 62 cases of Down syndrome were diagnosed in (1 : 333 pregnancies). No cases were diagnosed in patients with recurrent SMs.

Conclusion The high recurrence rate of solitary SM implies for genetic predisposition. These results might improve our counseling for pregnant women affected by the reappearance of solitary SM. Further studies are needed to assess the likelihood ratio for SM if recurrence occurs. © 2017 John Wiley & Sons, Ltd.

INTRODUCTION

Soft markers (SMs) are minor nonspecific and often transient structural findings, which are detected during fetal sonographic anatomical screening in approximately 10% of normal fetuses.[1] Findings such as thickened nuchal fold (TNF), short long bones, mild fetal pyelectasis and echogenic intracardiac focus (EIF), although not pathologic per se, were found to convey a statistically likelihood for fetal aneuploidies such as trisomies 21 [Down syndrome (DS)], 13 and 18.[2–6]

However, despite the large amount of data, there is still no consensus regarding the significance of SM and their implementation in clinical use. In 1998, Nyberg *et al.* suggested reassessing the initial risk of aneuploidies by developing likelihood ratios (LRs) for each marker as an isolated finding.[1] In a meta-analysis published by Agathokleous *et al.*, the pooled estimates of positive and negative LR were respectively: 5.83 and 0.80 for EIF, 23.30 and 0.80 for increased nuchal fold and 7.63 and 0.92 for mild hydronephrosis.[3] According to the American Congress of Obstetricians and Gynecologists practice bulletin concerning fetal aneuploidy screening,[7] the LR for TNF, EIF and pyelectasis were 11–18.6, 1.4–1.8 and 1.5–1.6, respectively.

The preliminary assumption regarding LR is that each sonographic marker has a similar distribution among women. Surprisingly, searches in the medical records revealed almost no data regarding the recurrence rate of either solitary or combined SM in subsequent pregnancies. A high prevalence of recurrence might imply a genetic inheritance and a decrease in the calculated risk for fetal aneuploidy with reappearance.

In this study, we aimed to determine the recurrence rate of the common SM in consecutive pregnancies and to estimate the effect of such on the risk for aneuploidy.

MATERIAL AND METHODS

This is a retrospective observational study of a low-risk population, consisting of all women who underwent an ultrasound screening between 14 + 0 and 17 + 0 weeks of gestation (early anatomical survey) or 22 + 0 and 24 + 0 weeks of gestation (late anatomical survey) in an ultrasound institution during 1995–2016. The study was approved by the Institutional Review Board on Human Experimentation in Rambam Medical Center (0210-10-RMB). All ultrasound screening examinations were performed by a single observer (M. B.) using an ELSCINT 3000 Machine with an annular probe 7.5 MHz, or a PHILIPS IU 22 ultrasound with a 5–9 MHz probe. The examinations were made transvaginally and transabdominally according to gestational age. The scheduled

examination time was 30 min, including time to discuss the results with the patients.

The SMs included: pyelectasis (renal pelvis ≥3 mm during 14–17 weeks or renal pelvis ≥6 between 20 and 29.6 weeks)[8]; TNF, which was defined only during early anatomical scan (≥5 mm in gestational weeks 14–18.6)[9–11] and EIF. Ultrasonographic markers were considered isolated when not associated with other markers or structural anomalies. Other possible SMs such as absent nasal bone and single umbilical artery were not included. Short femur and humerus were routinely measured but not analyzed because of variations in their definitions.[4] Ultrasound findings were registered, and cases with SMs were documented and compiled in a local database. Data on pregnancy outcome were retrieved retrospectively by contacting the parents via email or by phone.

RESULTS

The database included 20 672 singleton pregnancies; 18 850 were scanned at 13–17 weeks. The mean maternal age was 31.8 years: 20–25 years (656), 25–30 years (6801), 30–35 years (8616), 35–40 years (4062) and 40–45 years (537). All patients were Caucasian. From the 20 672 examined pregnancies, 62 fetuses were identified with DS (1 : 333).

Soft markers were detected in 2347 (11.3%) of the fetuses. Markers were found to be isolated in 74% (1739) of the cases. EIF was a solitary finding in 6.5% (1360/20 672) of the examined pregnancies, an occurrence rate of approximately one in every 15 examinations. Of the 283 pregnancies affected by EIF in their first pregnancy, 60 were diagnosed with repeated EIF (recurrence rate of 21.2%) in consecutive pregnancies, based on ultrasound anatomy screening. TNF was a solitary finding in 3.3% (624/20 672) of the examined pregnancies, an occurrence rate of approximately one in every 30 examinations. Of the 168 pregnancies affected by TNF, in which the ultrasound examination was repeated in sequential pregnancies, 47 presented an increased nuchal fold (recurrence rate of 27%). Pyelectasis was detected as a solitary finding in 1.7% of the cases (363/20 672), an occurrence of approximately one in every 58 examinations. The recurrence rate of pyelectasis in the sequential pregnancies was 16% (18/113), with a similar ratio between men and women (Table 1).

Different combinations of SM were found in 131 (0.06%) of the cases (Table 1). Although the prevalence of DS was significantly higher in this group than among those with solitary SM (16/131, 12% vs 12/1739, 0.6%), we emphasize that all of the former had additional malformations such as atrioventricular septal defect, hypoplastic left heart and brain anomalies. Although the numbers are small, the recurrence rate of combined SM was low (4.1–5.2%).

Neither T21 nor any other trisomies were detected in any of the sequential pregnancies affected by repeated solitary or combined markers, when presented with no other fetal malformations.

DISCUSSION

In this study of a population of 20 672 singleton pregnancies, SMs were detected in 11.3% of the fetuses. Recurrence rates of

Table 1 **The incidence and recurrent rate of 'SMs'**

		SMs				
		EIF	Pyelectasis	TNF	No. of cases	No. of T21
Overall SM		+			1360/20 672 (6.5%)	20
			+		363/20 672 (1.7%)	3
				+	624/20 672 (3.0%)	28
First episode	Isolated SM[b]	+			1040/20 672 (5.0%)	4 (all over 35 years old)
			+		293/20 672 (1.4%)	0
				+	406/20 672 (1.9%)	8
	Combined SM[c]	+	+		64/20 672 (0.31%)	9 (all had additional malformations)
		+		+	38/20 672 (0.18%)	3 (all had additional malformations)
			+	+	24/20 672 (<0.01%)	3 (all had additional malformations)
		+	+	+	5/20 672 (<0.01%)	1 (all had additional malformations)
Recurrence	Isolated SM[a]	+			60/283 (21%)	0
			+		47/168 (28%)	0
				+	18/113 (16%)	0
	Combined[c]	+	+		3/64 (4.6%)	0
		+		+	2/38 (5.2%)	0
			+	+	1/24 (4.1%)	0
		+	+	+	1/5 (<0.01%)	0

TNF, thickened nuchal fold; EIF, echogenic intracardiac foci; SM, soft marker.

[a]All SM including solitary SM, combined SM and SM accomplished by additional malformations.

[b]Solitary SM.

[c]Combined SM.

21%, 27% and 16% in sequential pregnancies were respectively demonstrated for solitary EIF, TNF and pyelectasis. The recurrence rate for combined SM was low (4.1–5.2%).

The overall incidence of DS in our study population was 1 : 333 pregnancies. Considering the gestational weeks in which the US examinations were performed and the mean age of the participants, our results are consistent with the common worldwide prevalence.[12]

Disclosure of solitary SM during routine ultrasound screening represents a clinical uncertainly and counseling dilemma. Although its overall sensitivity is low, solitary SMs have been found to confer a statistically increased risk for fetal aneuploidy.[7] Many studies[1,4,7] have recommended recalculating the risk by multiplying the original risk by specific LRs for each SM. However, for such calculation, each SM must have a similar distribution among all euploid women.

Searches in medical databases (PubMed and Medline) revealed limited data regarding reoccurrence rates of SMs. In 1997, Degani *et al.*[13] examined the recurrence rate of pyelectasis among 420 sequential pregnancies. According to their data, the recurrence rate of pyelectasis was 10.2%. No data were found regarding the recurrence rate of either EIF or TNF.

Surprisingly, in our retrospective study, consistency was evident between pregnancies for the presence of solitary EIF, TIF and pyelectasis. According to our analysis, the presence of these fetal SMs increases their risk for reappearance in subsequent pregnancies. Recurrence rates of EIF, TNF and pyelectasis were 21%, 27% and 16%, respectively. In contrast to the high recurrence rate of solitary SM, the recurrence rate of combined SM was low (5%). The incidence of DS, however, was higher among the combined SM group, although no cases of DS were observed in sequential pregnancies affected by either solitary or combined SM. These results support the assumption that although each SM may have a 'self' genetic disposition, there is no genetic correlation between different SM unless aneuploidy or a genetic problem exists.

The combination of serum marker and ultrasound nuchal translucency is still offered worldwide, as a primary screening test for fetal aneuploidies. However, the introduction of the noninvasive prenatal testing (NIPT) and the anticipation of lower costs in the future are changing the field of prenatal screening. Recently,[14] the Society for Maternal-Fetal Medicine published new recommendations regarding fetal ultrasound and NIPT. Accordingly, an isolated SM without other clinical implications (as EIF) should be described as a normal variant if NIPT or a second-trimester screening result are normal; and no diagnostic testing should be recommended for an isolated SM if NIPT is negative. Diagnostic testing with chromosomal microarray should be offered if structural abnormality is identified by ultrasound. Our current results, which imply a normal genetic predisposition of solitary SM, support these new recommendations, especially in SM recurrence. As so, if SM is detected and no previous screening was performed, NIPT might be offered in order to achieve reassurance. The only consideration should be in cases of combined SM, because of the high incidence of aneuploidy.

Our findings support the hypothesis that genetic factors may be at the basis of reappearance of EIF, TNF and pyelectasis. Using these results, an adjustment for the LR should be performed in cases of recurrence of SM if the outcomes of the previous affected pregnancy were non-affected fetus. Further studies are needed for validating the LR for each SM.

WHAT'S ALREADY KNOWN ABOUT THIS TOPIC?

- Soft markers are minor nonspecific and often transient structural findings, which are detected during fetal sonographic anatomical screening in approximately 10% of normal fetuses.
- Despite the large amount of data, there are no studies that evaluated the recurrence rate of SM and no consensus regarding their implementation into clinical use.
- In this study, we aim to determine the recurrence rate of common SM.

WHAT DOES THIS STUDY ADD?

- We found that the recurrence rate of pyelectasis, TNF and EIF in subsequent consecutive pregnancies was 21%, 27% and 16%, respectively.
- No cases of Down syndrome were diagnosed in patients with recurrent SMs.
- The high recurrence rate of solitary SM implies for genetic predisposition. These results might improve our counseling for pregnant women affected by the reappearance of solitary SM.

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