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REVIEW

First trimester detection of fetal open spina bifida using BS/BSOB ratio

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Abstract

Background Despite the well-known second trimester ultrasound signs, current possibilities of in utero surgical repair of open spina bifida require a timely detection of the spine defect.

Objective To evaluate the diagnostic accuracy of the ratio between brain stem (BS) diameter and its distance to the occipital bone (BSOB) (BS/BSOB ratio) in the detection of fetuses with open spina bifida at first trimester ultrasound.

Methods A systematic review and meta-analysis of diagnostic accuracy was performed by searching seven electronic databases from their inception to February 2019 for all studies assessing the association between BS/BSOB ratio and diagnosis of spine bifida. Diagnostic accuracy of BS/BSOB ratio in prenatal diagnosis of spine bifida was assessed as sensitivity, specificity, positive and negative likelihood ratios (LR + and LR−), and area under the curve (AUC) on SROC curves.

Results Four studies, including 17,598 fetuses with 23 cases of open spina bifida, were included in the meta-analysis. BS/BSOB ratio showed pooled sensitivity of 0.70 (95% CI 0.47–0.87; $I^2 = 78.3\%$), specificity of 1.00 (95% CI 0.99–1.0; $I^2 = 99.2\%$), LR + and LR− of 51.44 (95% CI 9.53–277.64; $I^2 = 85.5\%$) and 0.23 (95% CI 0.04–1.17; $I^2 = 64.8\%$), respectively, and an AUC of 0.9649.

Conclusion First trimester BS/BSOB ratio has a high diagnostic accuracy in detecting fetuses with open spina bifida.

Keywords Spina bifida · Myelomeningocele · BS/BSOB · First trimester · Ultrasound · Tailored medicine

Introduction

Spina bifida is a congenital malformation in which the spinal column is split (bifid) as a result of failed closure of the embryonic neural tube, during the fourth week post-fertilization. In its commonest and most severe form, open spina bifida (also termed myelomeningocele, or spina bifida aperta), spinal cord is open dorsally, forming a placode on the back of the fetus or newborn baby that frequently rests on a meningeal sac. The vertebrae at the level of the lesion lack neural arches, and so are incomplete dorsally [1]. The prevalence of spina bifida in the USA and many European countries is estimated at 0.5–0.8/1000 births [2] whereas prevalence in some regions of China has been reported to be more than 20 times higher [3].

The prenatal diagnosis of spina bifida has been of main interest throughout the last decades. First studies on the prenatal diagnosis were published in the 1970s, with the finding of an elevated concentration of alpha-fetoprotein in amniotic fluid samples from pregnancies with anencephaly or open spina bifida [4]. Furthermore, the finding of elevated alpha-fetoprotein concentrations in maternal serum samples in open spina bifida greatly enhanced the utility of alpha-fetoprotein measurements as screening for open spina bifida [5].

Open spina bifida is associated with the Arnold-Chiari II malformation which is thought to be the consequence of leakage of cerebrospinal fluid into the amniotic cavity and hypotension in the subarachnoid spaces, leading to caudal

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displacement of the brain stem and obliteration of the cisterna magna. Prenatal diagnosis of open spina bifida by ultrasound examination during the second trimester of pregnancy was greatly improved in the mid-1980s by the description of the lemon and banana signs [6]. The banana sign is the consequence of the Arnold–Chiari malformation and results in obliteration of the cisterna magna by the posterocaudal displacement of the brainstem and the cerebellum. In the last decade, improvements in ultrasound technology, in particular in spatial resolution, have made it possible to identify many fetal defects during the first trimester. Acrania, alobar holoprosencephaly, and cephaloceles can confidently be diagnosed at that stage and should actively be looked for in every fetus undergoing first-trimester ultrasound [7]. Chaoui et al. found the intracranial translucency, the ultrasound presentation of the fourth ventricle, absent in 4 cases with open spina bifida and compared it with the intracranial translucency in 200 normal cases without anomalies [8]. This absence was proposed as an early sign of spina bifida at first trimester screening. Intracranial translucency changes are associated with the displacement of the brain stem (BS) in fetuses with neural tube defects. In particular, in a mid-sagittal view of the posterior brain, the examiner can identify three structures: the posterior border of the sphenoid bone, the middle of the line produced by the posterior border of the brain stem and the anterior border of the fourth ventricle, and, third, the anterior border of the occipital bone. The distance between the first two structures is the vertical thickness of the brain stem, and the distance between the second and the third structure is the vertical distance between the brain stem anteriorly and the occipital bone posteriorly (BSOB) (Fig. 1). In the case of open spina bifida, a shift of BS is assumed with an increase of its diameter, so that the BS appears to be thicker and the distance to the occipital bone (BSOB) to be smaller (Fig. 2). As a result, the ratio of these two parameters (BS/BSOB) is increased [9]. However, the role of BS/BSOB ratio as standard first trimester marker of open spina bifida is still a subject of debate.

The aim of this systematic review and meta-analysis of diagnostic accuracy was to evaluate the performance of first trimester BS/BSOB ratio in the detection of fetuses with open spina bifida.

Materials and methods

Study protocol

Methods for electronic search, study selection, risk of bias assessment, and extraction and analysis of data were defined a priori. Two authors (AS, AR) independently performed all steps. Disagreements were resolved by discussion with a third author (GMM). The study was reported following the Preferred Reporting Item for Systematic Reviews and Meta-analyses (PRISMA) statement [10] and the Synthesizing Evidence from Diagnostic Accuracy Tests (SEDATE) guidelines [11].

Search strategy

MEDLINE, Web of Sciences, Scopus, Google Scholar, ClinicalTrial.gov, Cochrane Library, and EMBASE were searched from their inception to February 2019, using a combination of the following text words and all their synonyms found on Medical SubHeading (MeSH) vocabulary: "BS/BSOB"; "brain stem" "brain stem occipital bone"; "first

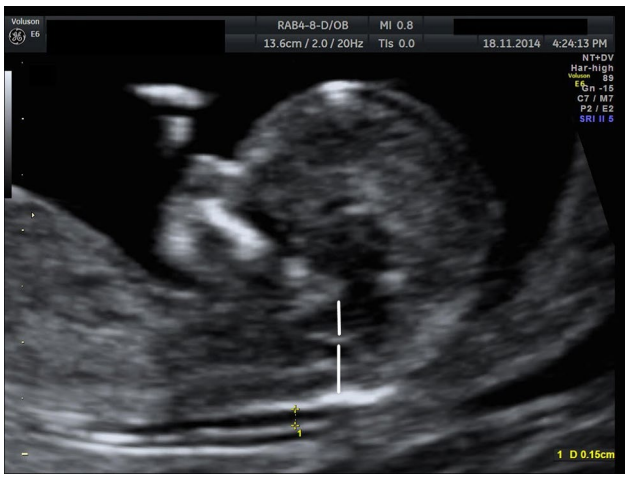

Fig. 1 Normal appearance of first trimester fetal posterior brain in a mid-sagittal view. Brain stem (BS) and the distance between BS and the occipital bone (OB) are identifiable. Normally, BS/BSOB ratio is < 1

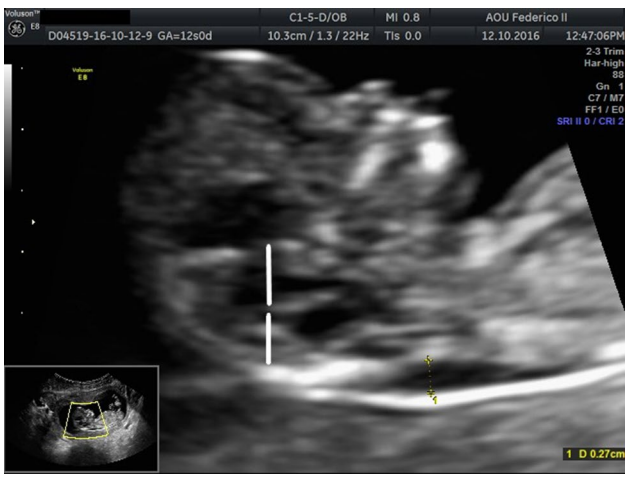

Fig. 2 First trimester fetal posterior brain in a case of spina bifida with the displacement of brain stem (BS), which appears thicker and the reduction of the distance between BS and the occipital bone (BSOB). Consequently, BS/BSOB ratio is increased

trimester"; "intracranial"; "spina bifida". All relevant references from each selected study were also evaluated.

Study selection

All peer-reviewed, retrospective, or prospective studies assessing the association between increased BS/BSOB ratio and fetal spine bifida were included in the systematic review. Exclusion criteria were: reviews; case reports; sample size < 5 cases. In case of overlapping data between several studies (i.e., same institution and period of enrollment, similar methods and results), the study with the higher sample size was considered.

Data extraction

Data from included studies were extracted without modification to create 2 × 2 contingency tables for each study, reporting two qualitative variables:

- BS/BSOB ratio (index test), alternatively dichotomized as "increased" or "normal";
- diagnosis of fetal spine bifida (reference standard), dichotomized as "present" or "absent".

BS/BSOB ratio was assessed during fetal ultrasound scan at 11–14 gestation weeks. Diagnosis of open spina bifida was considered "present" when subsequently confirmed during the second half of pregnancy at ultrasound scan, or at delivery by perinatal autopsy.

Assessment of risk of bias within studies

The risk of bias within studies was evaluated following the revised Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) [12]. Each study was assessed for four domains related to the risk of bias: (1) patient selection (i.e., if the selection was performed including consecutive or randomly selected patients); (2) index test (i.e., if BS/BSOB ratio was unbiased evaluated, e.g., if it was evaluated by the same operators and/or expert operators for all patients; if it was assessed using the same ultrasound machine for all patients; if criteria of ultrasound evaluation were clearly and correctly stated); (3) reference standard (i.e., if the diagnosis of fetal spine bifida was unbiased); (4) flow and Timing (i.e., if all patients were evaluated with both index and reference standard; if all patients were assessed with the same tests; if the latency time between index and reference standard did not affect the results).

Each domain was categorized as "low risk", "high risk", or "unclear risk" of bias if data regarding the domain were "reported and adequate", "reported but inadequate", and "not reported" respectively.

Data synthesis and analysis

Fetuses with increased BS/BSOB ratio and present diagnosis of spine bifida at birth were considered as true positive; fetuses with normal BS/BSOB ratio and absent diagnosis of spine bifida at birth as true negative; fetuses with increased BS/BSOB ratio and absent diagnosis of spine bifida at birth as false positive; fetuses with normal BS/BSOB ratio and present diagnosis of spine bifida at birth as false negative.

Sensitivity, specificity, and positive and negative likelihood ratios (LR + and LR−) were calculated for each study and as pooled estimate. Results were graphically reported on forest plots with 95% confidence interval (CI). The random effect model of DerSimonian and Laird was used.

Area under the curve (AUC) was calculated on summary receiver-operating characteristic (SROC) curves. The diagnostic usefulness was considered as absent for AUC ≤ 0.5,

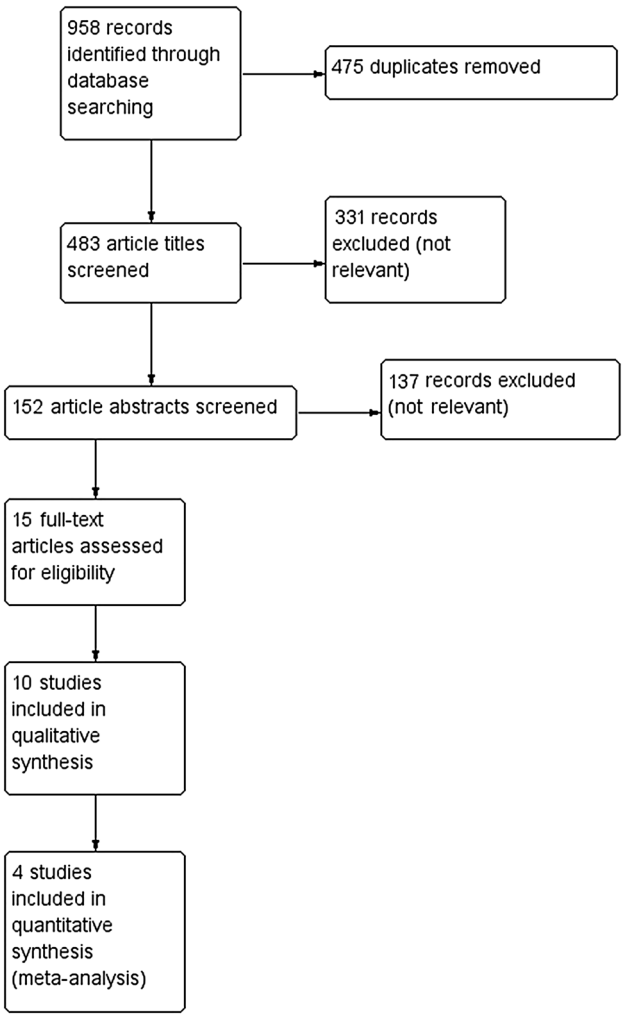

Fig. 3 Flow diagram of studies identified in the systematic review [Prisma template (Preferred Reporting Item for Systematic Reviews and Meta-analyses)]

low for $0.5 < AUC \leq 0.75$, moderate for $0.75 < AUC \leq 0.9$, high for $0.9 < AUC < 0.97$, and very high for $AUC \geq 0.97$.

The post-test probabilities of present and absent spine bifida were calculated and graphically reported using a Fagan's nomogram with 95% CI. The pre-test probability of spine bifida was 0.008, and was calculated as the mean of prevalence of spine bifida in the studies included in the meta-analysis, resulting in accordance with epidemiologic data reported in the literature [2].

Statistical heterogeneity amongst the included studies was evaluated using the Higgins I^2 statistic. Heterogeneity was considered as null for $I^2 = 0\%$, minimal for $0\% < I^2 \leq 25\%$, low for $25 < I^2 \leq 50\%$, moderate for $50 < I^2 \leq 75\%$, and high for $I^2 > 75\%$.

The data analysis was performed using Review Manager 5.3 (Copenhagen: The Nordic Cochrane Centre, Cochrane Collaboration, 2014) and Meta-DiSc version 1.4 (Clinical Biostatistics Unit, Ramon y Cajal Hospital, Madrid, Spain).

Results

Study selection

Figure 3 shows the flow diagram of the study selection. Ten observational studies, including 17,661 fetuses with 86 cases of open spina bifida, were included in the systematic review [13–22]. Of them, four studies, including 17,598 fetuses with 23 cases of open spina bifida, were included in the meta-analysis for the pooled data [15, 16, 21, 22].

Study characteristics

Gestational age at ultrasound BS/BSOB ratio evaluation ranged between 11 and 14 weeks of gestation in all studies. An increased BS/BSOB ratio was defined as a ratio > 95th centile in five studies [14, 16, 18, 20, 22], > 0.87 in one study [13], > 99th centile in one study [21], as a value of + 2.5 *Z*-scores in one study [15]; ≥ 1 in one study [19]; in one study, a clearly stated definition of increased BS/BSOB ratio was not provided [17].

Diagnosis of open spina bifida was confirmed at subsequent ultrasound or autopsy in one study [13], at subsequent ultrasound in five studies [14, 15, 19, 21, 22], and at autopsy or at birth in one study [20]. Three studies did not report the mode of confirmation for the diagnosis of open spina bifida [16–18].

Characteristics of the included studies are shown in detail in Table 1.

Risk of bias within studies

In the "patient selection" domain, three studies were classified as unclear risk given that two of them did not report data on healthy fetuses [14, 17], and the other one included only fetuses with trisomy 13 or 18 [16]. Four studies were considered at high risk of bias in the "patient selection" domain, because they included only fetuses with open spina bifida [13, 18–20]. The remaining three studies were considered at low risk of bias.

In the "index test" domain, two studies were categorized at unclear risk of bias, since they reported neither whether

Table 1 Characteristics of the included studies

Study	Study location	Study design	Included fetuses	Fetuses with spina bifida	Gestational age at ultrasound scan (weeks)	Definition of increased BS/BSOB ratio	Diagnosis confirmation of spina bifida
Chaoui et al. [11]	Germany	Case series	6	6	11–13	> 0.87	Ultrasound, autopsy
Lachmann et al. [12]	UK, Germany	Retrospective	1030	30	11–13	> 95th centile	Ultrasound
Scheier et al. [13]	Austria, Germany, Czech Republic, UK	Prospective	13	3	11–13	+ 2.5 *Z*-scores	Ultrasound
Ferreira et al. [14]	UK	Retrospective	81	7	11–13	> 95th centile	–
Kavalakis et al. [15]	Greece	Prospective	1330	2	11–14	–	–
Garcia-Posada et al. [16]	Spain	Retrospective	5	5	11–13	> 95th centile	–
Iuculano et al. [17]	Italy	Retrospective	17	17	11–14	≥ 1	Ultrasound
Orlandi et al. [18]	Italy	Prospective	3	3	11–14	> 95th centile	Autopsy, birth
Chen et al. [19]	Germany	Prospective	16,164	11	11–14	> 99th centile	Ultrasound
Kose et al. [20]	Turkey	Prospective	1340	2	11–13	≥ 95th centile	Ultrasound

BS/BSOB ratio was assessed by expert operators for all patients nor criteria of ultrasound evaluation clearly and correctly stated [13, 17]. The remaining eight studies were considered at low risk of bias.

In the "reference standard" and "flow and timing" domain, all studies were categorized at low risk of bias.

Results of risk of bias assessment are shown in Fig. 4.

Diagnostic accuracy assessment

Of the ten studies included in the systematic review, six studies at high risk of bias in the "patient selection" domain were excluded from meta-analysis of diagnostic accuracy: four reported only true positive [13, 14, 18–20], and one did not report positive cases [17]. Finally, 4 studies (3 prospective and 1 retrospective) with a total of 17,598 fetuses and 23 cases were included in the meta-analysis [15, 16, 21, 22].

In diagnostic accuracy assessment, BS/BSOB ratio showed a pooled sensitivity of 0.70 (95% CI 0.47–0.87), with high heterogeneity among studies ($I^2 = 78.3\%$); a pooled specificity of 1.00 (95% CI 0.99–1.0) with high heterogeneity ($I^2 = 99.2\%$); pooled positive and negative likelihood ratios of 51.44 (95% CI 9.53–277.64) and 0.23 (95% CI 0.04–1.17) with high and moderate heterogeneity, respectively ($I^2 = 85.5\%$ and 64.8%) (Fig. 5). The overall diagnostic accuracy was high, with an AUC of 0.9649 (Fig. 6).

In the case of a positive test (present BS/BSOB ratio), the probability of spine bifida increased from 0.008 (pre-test probability) to 0.29 (post-test probability) (95% CI 0.26–0.33), while in the case of a negative test (normal BS/BSOB ratio), the post-test probability was 0 (95% CI 0–0) (Fig. 7).

Discussion

This systematic review aimed to evaluate the performance of the BS/BSOB ratio in the detection of fetuses with open spina bifida at first trimester ultrasound. The meta-analysis included four studies, assessing 17,598 fetuses with 23 cases of open spina bifida. Pooled results showed that first trimester BS/BSOB ratio has a high accuracy in detecting fetuses with open spina bifida.

Currently, fetuses with spina bifida are usually referred for fetal surgery at 18–22 weeks, after being identified with the well-known second trimester ultrasound markers. Recently, in a large cohort of 627 fetuses with spina bifida, Bahlmann et al. demonstrated that, at 18–23 gestation weeks, the detection rate for spina bifida was 97.1% for banana sign, 88.6% for lemon sign, and 96.7% for cisterna magna obliteration [23]. However, a first trimester detection of spina bifida may be extremely useful to provide a better counseling to the couple and to offer them the chance to be referred to a center for fetal surgery in time.

According to our results, BS/BSOB ratio may be the best first trimester identifier of fetuses with spina bifida. In fact, a recent systematic review with meta-analysis showed that intracranial translucency has a sensitivity of 53.5% (95% CI 42.4–64.3) and a specificity of 99.7% (95% CI 99.6–99.8) in detecting spina bifida, lower than the BS/BSOB ratio [24].

Several other markers for early detection of fetuses with spina bifida have also been proposed. Authors reported that the biparietal diameter (BPD) of fetuses with spina bifida was significantly smaller compared with that in normal fetuses [25–27]. However, in a series of 34,951 unselected consecutive pregnancies, Bernard et al. found that only 50% of cases with spina bifida had a BPD < 5th percentile [25]. Other authors have suggested that non-visualization of the cisterna magna could be a valuable first trimester sign for early spina bifida detection [15, 28]. Kose et al. found in their study that cisterna magna non-visibility was

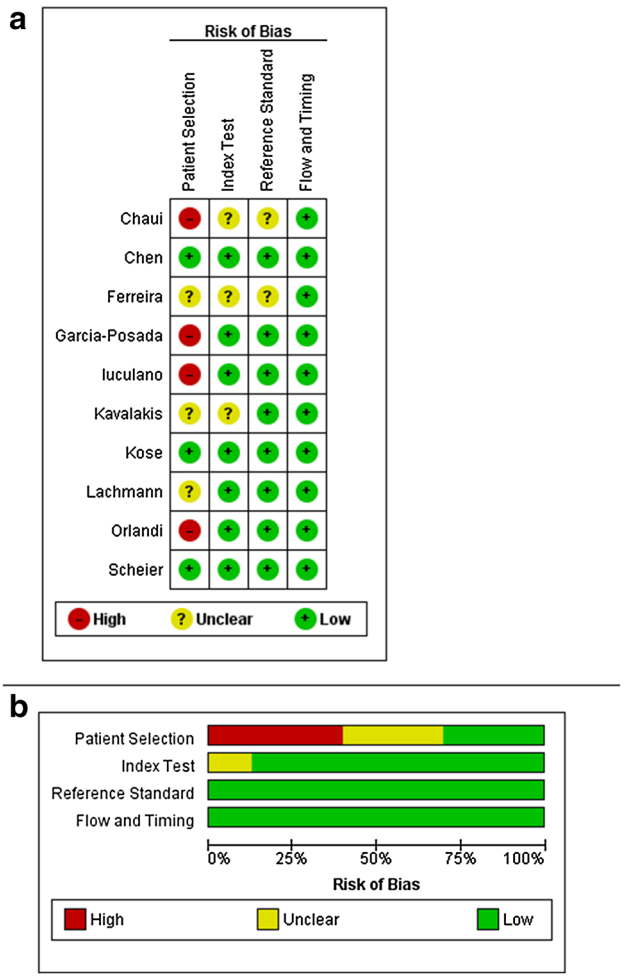

Fig. 4 **a** Assessment of risk of bias. Summary of risk of bias for each study; plus sign: low risk of bias; minus sign: high risk of bias; question mark: unclear risk of bias. **b** Risk of bias graph about each risk of bias item presented as percentages across all included studies

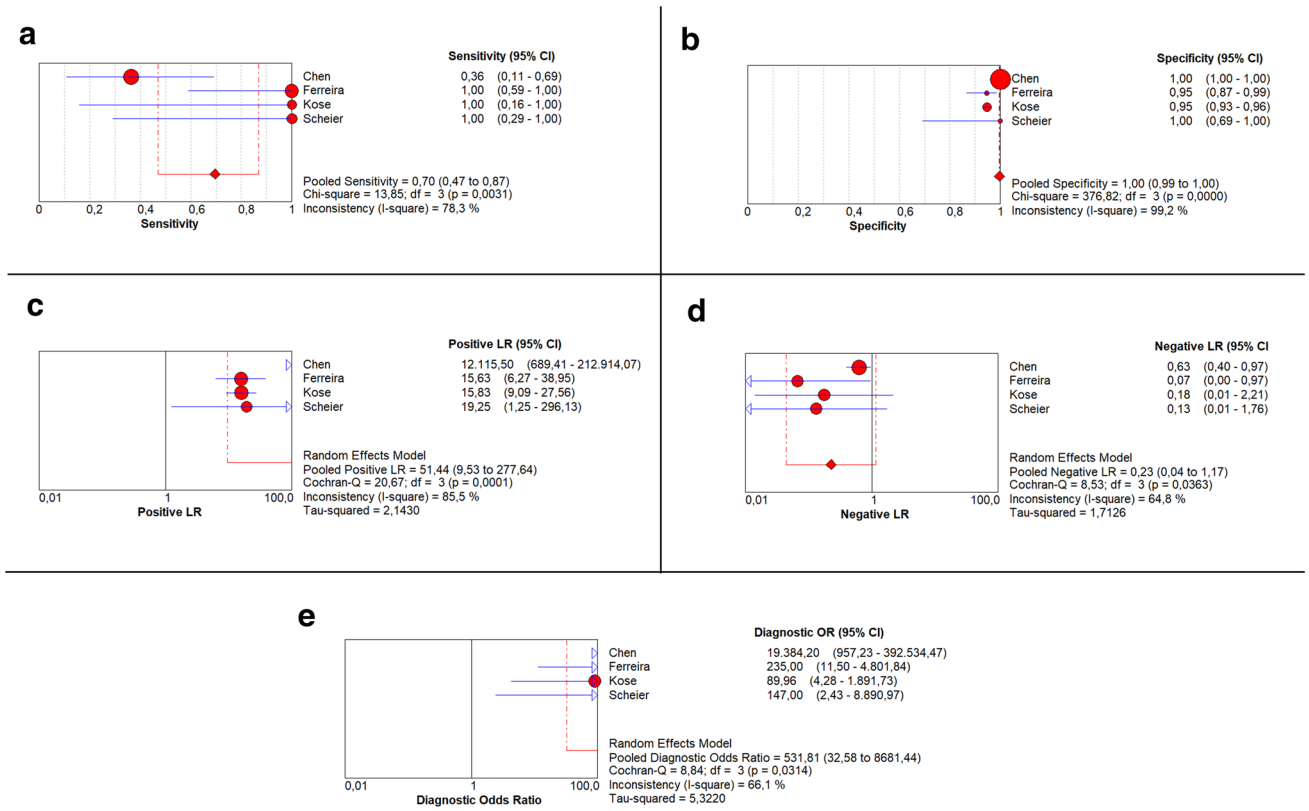

Fig. 5 Forest plots of individual studies and pooled sensitivity (**a**), specificity (**b**), positive and negative likelihood ratios (**c**, **d**), and diagnostic odds ratio (**e**) of BS/BSOB in prenatally diagnosing spine bifida at first trimester fetal ultrasound scan

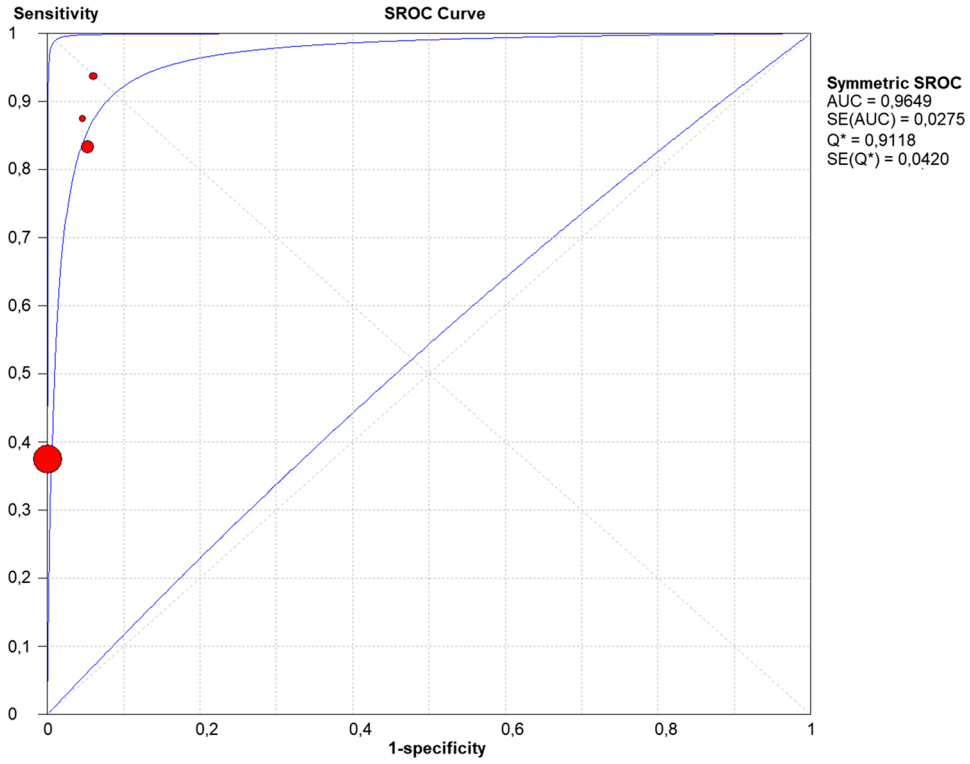

Fig. 6 Area under the curve (AUC) on summary receiver-operating characteristic (SROC) curves of BS/BSOB in prenatally diagnosing spine bifida at first trimester fetal ultrasound scan

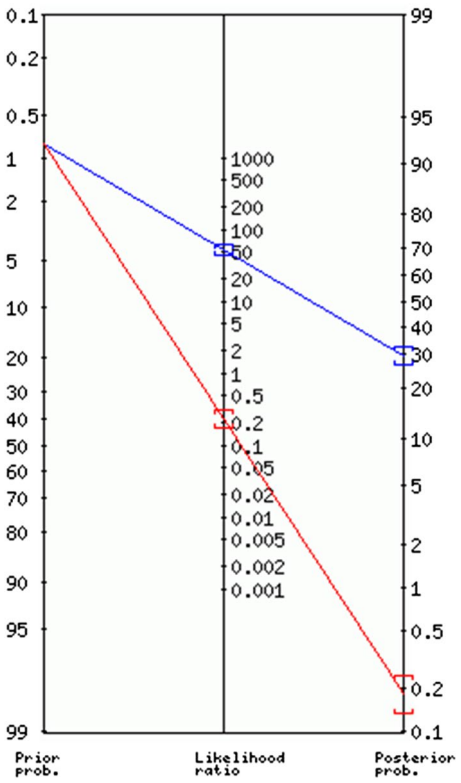

Fig. 7 Fagan's nomogram reporting pre-test and post-test probability of open spina bifida in the case of increased BS/BSOB ratio (red line) or normal BS/BSOB ratio (blue line)

the best identifier for open spina bifida (sensitivity 100%, specificity 99.9%), even if they evaluated this marker in a cohort with only two fetuses with open spina bifida [22]. Furthermore, the evaluation of cisterna magna needs an axial view of the posterior brain, which is better visualized using transvaginal ultrasound and requires dedicated training. On the other hand, one of the main advantages of evaluating BS/BSOB ratio in the first trimester is that the examiner can use the same mid-sagittal view of the fetal face used to assess fetal NT and nasal bone in screening for aneuploidies. Therefore, it would not be difficult or time-consuming to routinely record the measurements of the brain stem and BSOB diameters. However, the sonographic evaluation of BS/BSOB ratio needs a detailed knowledge of the first trimester brain structures, which is not always common among sonographers who perform the first trimester ultrasound scans. In addition, as some authors suggest, a combined approach with the evaluation of BS/BSOB ratio, cisterna magna width, and intracranial translucency may offer an even better identification of fetuses with open spina bifida [5].

To the best of our knowledge, this may be the first systematic review and meta-analysis aimed to evaluate the diagnostic accuracy of first trimester BS/BSOB ratio for the diagnosis of open spina bifida. The most important strength of our study was the high number of women included. All the included studies have open spina bifida as main outcome. Moreover, the exclusion of studies at high risk of bias from the meta-analysis further strengthens our results. Although meta-analytical techniques pool all available data, limitations include those of the original articles, with particular regard to the retrospective design.

Conclusion

In summary, first trimester BS/BSOB ratio has a high accuracy in detecting fetuses with open spina bifida and its assessment may be performed in the routine first trimester screening to provide an early detection of this defect.

Author contribution AS: study conception, search strategy, data extraction and analysis, and risk of bias assessment. AR: study design, search strategy, data extraction and analysis, and risk of bias assessment. GS: study design, disagreements resolution, and manuscript preparation. AL: data collection and manuscript preparation. AT: data collection and manuscript preparation. LS: study design, manuscript preparation, and whole-study supervision. GR: search strategy, data extraction and analysis, and risk of bias assessment. GMM: study design, methods supervision, and manuscript preparation. FZ: study design, methods supervision, and whole-study supervision.

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Compliance with ethical standards

Conflict of interest The authors report no conflict of interest.

Ethical approval Not applicable.

Informed consent Not applicable.

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