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AOGS SYSTEMATIC REVIEW

Small fetal thymus and adverse obstetrical outcome: a systematic review and a meta-analysis

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Key words
Chorioamnionitis, fetal thymus, intrauterine growth restriction, neonatal sepsis, preeclampsia, prenatal diagnosis, preterm birth, ultrasound

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Conflict of interest
The authors have declared explicitly that there are no conflicts of interest in connection with this article.

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Abstract

Introduction. The aim of this study was to explore the association between small fetal thymus on ultrasound and adverse obstetrical outcome. *Material and methods.* Medline, Embase, Cochrane and Web of Science databases were searched. Primary outcome was the risk of preterm birth before 37 and 34 weeks of gestation in fetuses with, compared to those without, a small thymus on ultrasound. Secondary outcomes: occurrence of chorioamnionitis, intrauterine growth restriction, neonatal sepsis, gestational age at birth, birthweight, neonatal morbidity and preeclampsia. *Results.* Twelve studies including 1744 fetuses who had ultrasound assessment of thymus during pregnancy were included. Women with preterm premature rupture of the membranes or with preterm labor were at higher risk of preterm birth before 37 weeks ($p = 0.01$), or before 34 weeks ($p < 0.001$) for fetuses with a small fetal thymus compared to those without a small thymus, and the risk of chorioamnionitis was higher when the thymus was small ($p < 0.001$). Fetuses with small thymus were not at higher risk of intrauterine growth restriction ($p = 0.3$). A small thymus increased the risk of neonatal sepsis ($p = 0.007$) and morbidity ($p = 0.003$), but not the risk of preeclampsia ($p = 0.9$). *Conclusions.* A small fetal thymus is associated with a higher risk of preterm birth, chorioamnionitis, neonatal sepsis and morbidity, but not with intrauterine growth restriction and preeclampsia.

Abbreviations: DOR, diagnostic odds ratio; IUGR, intra-uterine growth restriction; LR+, positive likelihood ratio; LR−, negative likelihood ratio; OR, odds ratio; PPROM, preterm premature rupture of the membranes; PTB, preterm birth.

Key Message

Despite the association between a small fetal thymus and preterm birth, chorioamnionitis and neonatal morbidities, we still do not support the practice of ultrasound assessment of thymus to predict perinatal outcome in pregnancies at risk, such as those affected by preterm premature rupture of the membranes.

Introduction

The thymus is one of the main organs involved in the development of the fetal immune system (1). It is a symmetric, bi-lobulated organ, located in the anterior mediastinum, and is responsible for the development of

T lymphocytes. Its development begins early in pregnancy and it is usually complete at around 16–20 weeks of gestation (2,3).

Fetal thymus can be easily identified on ultrasound in a three-vessel and trachea view of the fetal heart as a round hypoechoic structure anterior to the great vessels and posterior to the sternum (4–6). Visualization of internal mammary arteries on color Doppler may help in identifying the thymus on ultrasound (7).

Fetal thymus plays a major role in the immune response against infection and inflammation. Postnatal studies have shown that chorioamnionitis is associated with a significant decrease in thymus size at birth in preterm infants as the result of as a nonspecific, steroid-mediated response to the increased production of pro-inflammatory mediators at the maternal–fetal interface (8).

Furthermore, a small fetal thymus on ultrasound has been associated with an increased risk of chromosomal anomalies, intrauterine growth restriction (IUGR) and pregnancy-related complications such as preeclampsia and IUGR (9,10). Finally, assessment of fetal thymus on ultrasound has been recently suggested to improve the detection rate of DiGeorge Syndrome in fetuses at risk for this anomaly such as those with cono-truncal anomalies (11). Despite this, it has still to be ascertained whether ultrasound assessment of fetal thymus may help to predict perinatal outcome in women at risk such as those with signs of preterm labor or chorioamnionitis (12).

The aim of this systematic review was to explore the association between a small fetal thymus on ultrasound and adverse obstetrical outcomes.

Material and methods

Protocol, eligibility criteria, information sources and search

This review was performed according to an a priori designed protocol and recommended for systematic reviews and meta-analysis (13). Medline, Embase, Cochrane and Web of Science databases were searched electronically on the 19 May 2017 using combinations of the relevant medical subject heading (MeSH) terms, key words, and word variants for “fetal thymus”, “chorioamnionitis”, “pregnancies” and “outcome” (see Supplementary material, Table S1). The search and selection criteria were restricted to English language. Reference lists of relevant articles and reviews were hand searched for additional reports. Prisma guidelines were followed (14). The study was registered with the PROSPERO database (Registration number: CRD42017060195).

Study selection, data collection and data items

Two authors (CC, FD) reviewed all abstracts independently. Agreement regarding potential relevance was reached by consensus; full text copies of those papers were obtained and the same two reviewers independently extracted relevant data regarding study characteristics and pregnancy outcome. Inconsistencies were discussed by the reviewers and consensus was reached or by discussion with a third author. If more than one study was published for the same cohort with identical endpoints, the report containing the most comprehensive information on the population was included to avoid overlapping populations. For those articles in which information was not reported but the methodology was such that this information would have been recorded initially, the authors were contacted. Quality assessment of the included studies was performed using the Newcastle–Ottawa Scale (NOS); according to NOS, each study is judged on three broad perspectives: the selection of the study groups; the comparability of the groups; and the ascertainment outcome of interest. Assessment of the selection of a study includes the evaluation of the representativeness of the exposed cohort, selection of the non-exposed cohort, ascertainment of exposure and the demonstration that outcome of interest was not present at start of study. Assessment of the comparability of the study includes the evaluation of the comparability of cohorts on the basis of the design or analysis. Finally, the ascertainment of the outcome of interest includes the evaluation of the type of the assessment of the outcome of interest, length and adequacy of follow up. According to NOS a study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability (15).

The primary outcome observed was the risk of spontaneous preterm birth (PTB) before 37 and 34 weeks of gestation in fetuses with a small thymus compared to those without a small thymus at ultrasound.

Secondary outcomes were:

(1) IUGR, defined as newborn with a birthweight <10th and <5th centiles respectively
(2) Birthweight
(3) Chorioamnionitis, confirmed by histological examinations of placenta and membranes
(4) Neonatal sepsis: defined as the presence of clinical signs (For example pallor, lethargy, irritability, apnea, respiratory distress, bradycardia, tachycardia, hypotension, vomitus, fever) and a positive blood culture
(5) Length of in-hospital stay of the mother

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(6) Composite neonatal morbidity including respiratory and neurological morbidity
(7) Preeclampsia, defined as the occurrence of de novo hypertension (systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg) and proteinuria (≥0.3 g/24 h or spot urine protein/creatinine ratio ≥30 mg/mmol) after 20 weeks of gestation, in accordance with the recommendations of the International Society for the Study of Hypertension in Pregnancy (16).

Fetal thymus was defined as small when its perimeter, surface, volume or diameter was below the 5th centile for the gestational age at assessment. Furthermore, we also included studies using the thymic–thoracic ratio as a proxy to define a thymus as small. We planned a sensitivity analysis according to the type of definition of small thymus, gestational age at assessment and population analyzed. Only case–control studies comparing the occurrence of the different explored outcomes in fetuses with, compared to those without, small thymus on ultrasound were considered eligible for the inclusion in the present systematic review. Postnatal or autopsy-based studies were excluded. Studies published before 2000 were excluded because advances in prenatal imaging make them less relevant. Only full text articles were considered eligible for the inclusion. Case reports, conference abstracts and case series with fewer than three cases, were also excluded to avoid publication bias.

Statistical analyses

We compared nine clinical outcomes in fetuses with small thymus vs. fetuses with normal thymus, using random-effect head-to-head meta-analyses. Of the nine outcomes, three were continuous (birthweight, gestational age at birth and length of hospital stay), and six were categorical (PTB, IUGR, preeclampsia, chorioamnionitis, neonatal sepsis and neonatal morbidity). In addition, two different thresholds were selected for two categorical outcomes (PTB: before 37 or 34 weeks of gestation; IUGR: below 10th or 5th centile), hence a total of 11 separate meta-analyses were performed.

For each continuous outcome, we computed a summary mean difference and its 95% CI; for each categorical outcome, results were expressed as summary odds ratio (OR) and 95% CI. In all meta-analyses, the statistical heterogeneity was quantified using the I^2 metric (17).

We also explored the diagnostic performance of the categorical outcomes to detect a small thymus size computing the summary estimates of sensitivity, specificity, positive and negative likelihood ratios (LR+, LR−) and diagnostic odds ratio (DOR). Depending on the number of studies that could be included in a meta-analysis, computations were based upon the hierarchical summary receiver operating characteristic model or the DerSimonian–Laird random-effect model (18). Rutter and Gatsonis hierarchical summary receiver operating characteristic parameterization was used because its hierarchical modeling strategy can be used when there is variability in threshold between studies (19). However, when fewer than four studies are included, the uncertainty associated with the estimation of the shape parameter could be very high, and models may fail to converge. RevMan 5.3 (The Cochrane Collaboration, 2014), Stata command metandi (Stata Corp., College Station, TX: 2013) and Meta-Disc 1.4 (Clinical Biostatistics Unit, Ramón y Cajal Hospital, Madrid, Spain) were used to analyze the data.

Results

General characteristics

In all, 258 articles were identified, 25 were assessed with respect to their eligibility for inclusion (see Supplementary material, Table S2) and 12 studies were included in the systematic review (Table 1, Figure 1) (9,10,20–29). These 12 studies included 1744 fetuses who had ultrasound assessment of thymus size. Eleven studies were prospective (9,10,20,21,23–29), only one was a retrospective study (22). Inclusion criteria differed among the included studies; six studies included women at risk of infectious-related complications, such as those presenting with preterm premature rupture of the membranes (PPROM) or signs of preterm labor (22–24,27–29), whereas the remaining studies included women with no apparent risk factors (Table 1) (9,10,20,21,25,26).

In nine studies, pregnancies with fetuses with anomalies were excluded (9,20–25,27,29). Gestational age at first ultrasound examination ranged between 18th and 40th weeks of gestation. We could not find information about antenatal management of included patients, except for the timing of ultrasound during the observational period. Regarding the definition of a small thymus on ultrasound, the large majority of the included studies used a diameter or perimeter below the 5th centile to define a thymus as small, whereas others used thymus area, volume or its ratio with the fetal thorax.

Results of quality assessment of the included studies using NOS for cohort studies are presented in Table 2. Most of the included studies showed an overall good score regarding the selection and comparability of the study groups, and for ascertainment of the outcome of interest. The main weaknesses of these studies were their retrospective design, small sample size, different

Table 1. General characteristics of the included studies.

Author	Year	Country	Study design	Period analyzed	Inclusion criteria	Fetal anomalies	GA at US	Definition of small thymus	Pregnancies (*n*)	Outcomes observed
Brandt (20)	2016	USA	Prospective	2013	All women undergoing routine second-trimester scan	Excluded	$18–23^{+6}$	A-P and transverse diameters <25th centile; thymic–thoracic ratio	520	Preterm birth, pregnancy-related hypertension, SGA
Ekin (21)	2015	Turkey	Prospective	2012–2015	Singleton pregnancies with intact membranes between 24 and 40 weeks	Excluded	24–40	Transverse thymus diameter <5th centile	293	IUGR
Aksakal (22)	2014	Turkey	Retrospective	2010–2011	Singleton pregnancies with PPROM at 24–37 weeks	Excluded		Transverse thymus diameter <5th centile; thymus area <331 mm^2	100	Chorioamnionitis
Cetin (23)	2014	Turkey	Prospective	2009–2011	Singleton pregnancies with PPROM	Excluded	$26^{+1}–36^{+6}$	Transverse thymus diameter <5th centile	40	Neonatal sepsis
Musilova (24)	2013	Czech Republic/ Norway	Prospective	2008–2011	Singleton pregnancies with PPROM at 24–37 weeks	Excluded		Transverse thymus diameter <5th centile	216	Chorioamnionitis
Olearo (25)	2012	Italy	Prospective	2010–2011	Singleton pregnancies at 20–37^{+6} weeks of gestation	Excluded	28.3 (20–37)	Not provided (thymus volume/AC ratio)	63	IUGR
Eviston (26)	2012	Australia	Prospective	2006–2011	Singleton pregnancies at 24–40 weeks of gestation	NS		Not provided (thymus diameter)	173	Preeclampsia
Mohamed (10)	2011	Australia	Prospective	2008–2009	Singleton pregnancies at 24–40 weeks of gestation	NS	NS	Not provided (thymus diameter and perimeter)	109	Preeclampsia
Cromi (9)	2009	Italy	Prospective	2006–2007	Singleton pregnancies >20 weeks of gestation	Excluded	$22^{+5}–39$	Thymus perimeter ≤5th centile	120	IUGR
El-Haieg (27)	2008	Egypt	Prospective	2006	Singleton pregnancies with PPROM, 28–34 weeks of gestation	Excluded	Weekly till delivery	Thymus perimeter ≤5th centile, according to fetal thymus normogram	56	FIRS, PTB
Yinon (28)	2007	Israel	Prospective	2003–2004	PPROM at 24–35 weeks	NS	24–35 weekly	Thymus perimeter ≤5th centile	21	Chorioamnionitis
Di Naro (29)	2005	Italy	Prospective	2003–2004	Women with preterm labor and intact membranes at 24–32 weeks	Excluded	At admission	Thymus perimeter ≤5th centile	33	Intra-uterine infection

AC, abdominal circumference; A-P, antero-posterior; FIRS, fetal inflammatory response syndrome; GA, gestational age; NS, not stated; US, ultrasound; SGA, small-for-gestational age; IUGR, intrauterine growth restriction; PPROM, preterm premature rupture of the membranes; PTB, preterm birth.

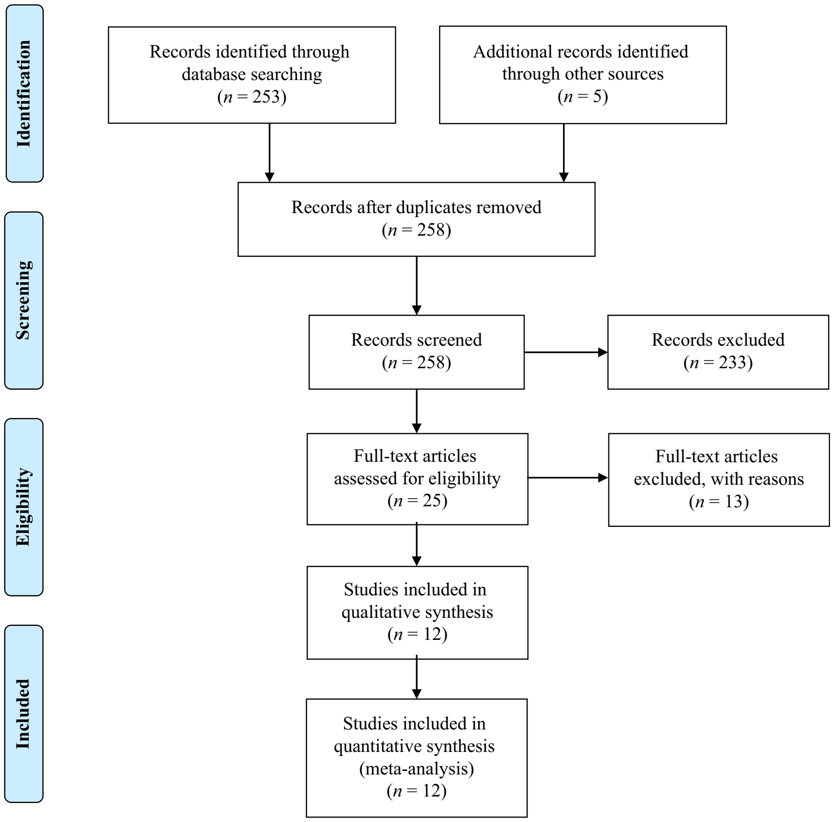


Figure 1. Systematic review flowchart. [Color figure can be viewed at wileyonlinelibrary.com].

gestational ages at scan, large heterogeneity in the definition of abnormal cut-offs for small thymus and lack of information on maternal and biochemical characteristics of the included cases (15).

Synthesis of the results

Preterm birth and gestational age at delivery. Two studies including 551 fetuses explored the strength of association between small thymus and the occurrence of spontaneous PTB <37 weeks of gestation, reporting no difference between the two groups (OR 2.2, 95% CI 0.2–23.6) (20,29). However, these two studies differed as regards their inclusion criteria. The study by Brandt et al. (20), included women undergoing second-trimester scans and did not report any difference in the occurrence of PTB between fetuses with a small and a normal thymus (OR 0.7, 95% CI 0.3–1.7), whereas the study by Di Naro et al. (29) included women with symptoms and signs of PTB and reported an increased risk for PTB in those with a small fetal thymus (OR 8.3, 95% CI 1.7–41.2), with a sensitivity of 75.0% (95% CI 47.6–92.7), a specificity of 73.3% (95% CI 44.9–92.2), an LR+ of 2.8 (95% CI 1.29–7.11), an LR− of 0.34 (95% CI 0.13–0.76) and a DOR of 73.3% (95% CI 44.9–92.2) (Figure 2, Table 3).

Three studies explored the strength of association between a small fetal thymus and the occurrence of PTB before 34 weeks of gestation (20,27,29). The study by Brandt et al. (20) included all women undergoing routine second-trimester scans and a cut-off of <25% to define the thymus as small, whereas the studies by El Haieg et al. (27) and Di Naro et al. (29) included pregnancies affected by PPROM or presenting with symptoms of preterm labor and adopted a perimeter < 5th centile as a cut-off for a small thymus. When pooled together, there was no difference in the risk of PTB before 34 weeks of gestation in fetuses with compared to those without small thymus (OR 5.2, 95% CI 0.9–31.2) (Table 3). However, when considering only those studies including women at risk (27,29) there was a higher risk of PTB <34 weeks of gestation in pregnancies with a small fetal thymus compared with control, with an OR of 12.5 (95% CI 4.3–36.8; I^2 0%). When translating these figures into predictive accuracy a small fetal thymus had a sensitivity of 81.3% (95% CI 63.6–92.8), a specificity of 72.5% (95% CI 58.3–84.1), an LR+ of 2.86 (95% CI 1.78–4.58), an LR− of 0.27 (95% CI 0.13–

Table 2. Quality assessment of the included studies according to the Newcastle–Ottawa Scale. A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability.

Author	Year	Selection	Comparability	Outcome
Brandt (20)	2016	★★	★	★★
Ekin (21)	2015	★★	★	★★
Aksakal (22)	2014	★★	★	★★
Cetin (23)	2014	★★	★	★★
Musilova (24)	2013	★★	★	★★
Olearo (25)	2012	★★	★	★
Eviston (26)	2012	★★	★★	★★
Mohamed (10)	2011	★★	★	★★
Cromi (9)	2009	★★	★	★
El-Haieg (27)	2008	★★	★	★
Yinon (28)	2007	★★★	★★	★★
Di Naro (29)	2005	★★	★	★★

0.56) and a DOR of 11.03 (95% CI 3.7–32.6) in detecting PTB before 34 weeks of gestation in women at risk for these conditions such as those affected by PPROM or presenting with symptoms of PTB (Figure 2, Table 3).

When assessed as a continuous variable, there was no difference in the mean gestational age at birth between fetuses with and those without a small thymus (mean differences 1.48, 95% CI −0.93 to 3.90; p = 0.2), although the three included studies differed as regards their inclusion criteria (20,21,28). The study by Brandt et al. (20) includes all fetuses routinely screened during the second trimester of pregnancy and did not report any difference in gestational age at birth between pregnancies with small fetal thymus compared with controls, whereas those by Ekin et al. (21) and by Yinon et al. (28) include cases affected by IUGR and pregnancies with PPROM respectively and reported lower gestational age at birth in pregnancies with small fetal thymus (Table 4, and see Supplementary material, Figure S1) (20,21,28).

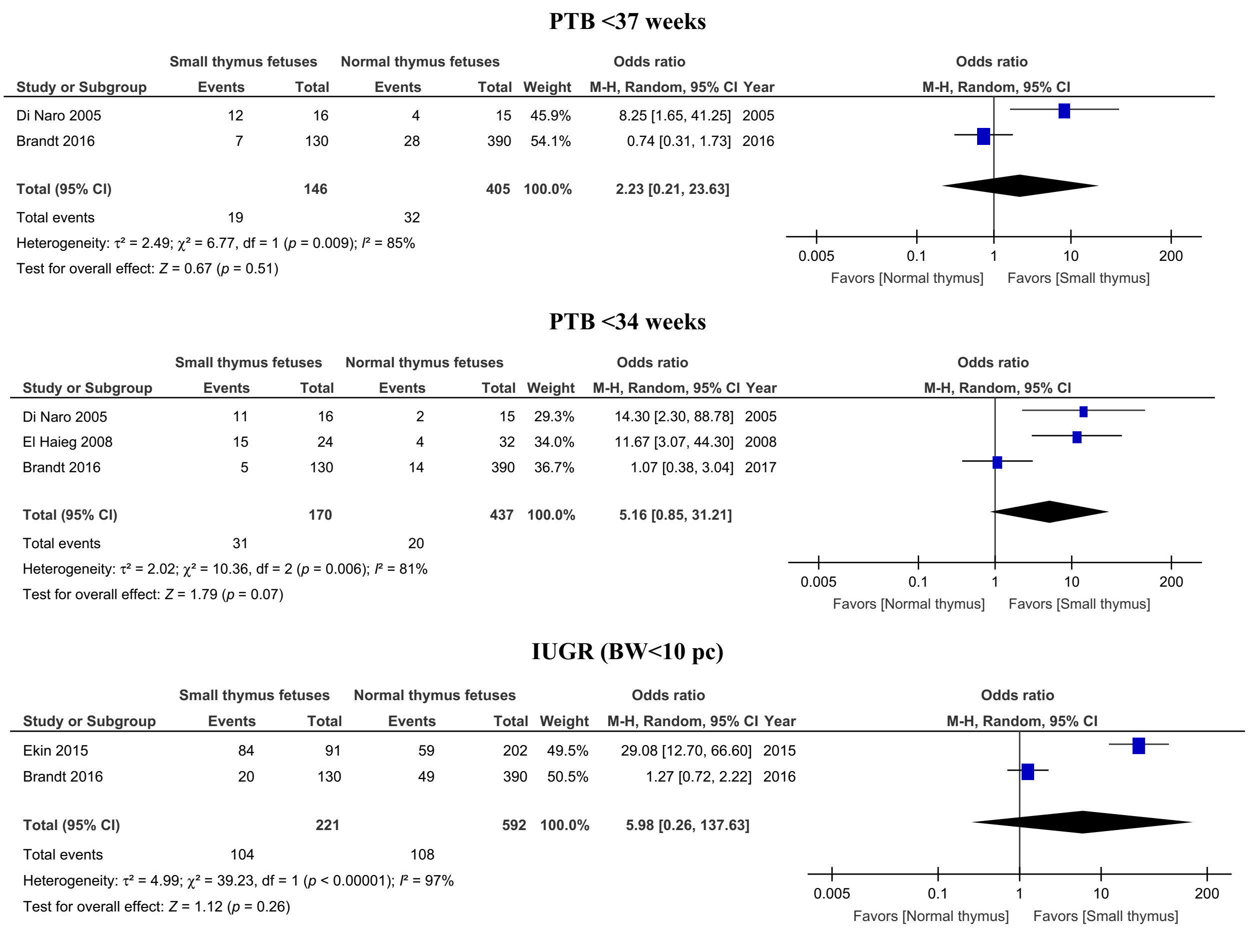
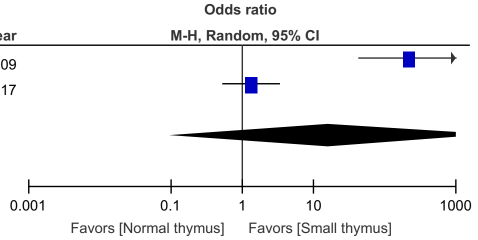


Figure 2. Results of the meta-analysis comparing the likelihood of preterm birth (PTB), intrauterine growth restriction (IUGR), chorioamnionitis, neonatal sepsis, neonatal morbidity and preeclampsia before 37 weeks in fetuses with small thymus vs. fetuses with normal thymus. BW, birthweight. [Color figure can be viewed at wileyonlinelibrary.com].

IUGR (BW<5 pc)

Study or Subgroup	Small thymus fetuses Events	Small thymus fetuses Total	Normal thymus fetuses Events	Normal thymus fetuses Total	Weight	Odds ratio M-H, Random, 95% CI	Year
Cromi 2009	58	65	2	55	49.2%	219.57 [43.67, 1103.98]	2009
Brandt 2017	7	130	16	390	50.8%	1.33 [0.53, 3.31]	2017
Total (95% CI)		**195**		**445**	**100.0%**	**16.38 [0.09, 2839.21]**	
Total events	65		18				

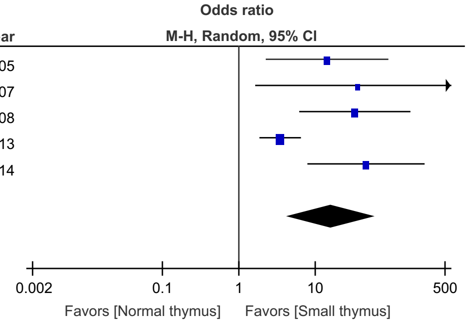
Heterogeneity: $\tau^2 = 13.39$; $\chi^2 = 30.93$, df = 1 ($p < 0.00001$); $I^2 = 97\%$
Test for overall effect: $Z = 1.06$ ($p = 0.29$)



Chorioamnionitis

Study or Subgroup	Small thymus fetuses Events	Small thymus fetuses Total	Normal thymus fetuses Events	Normal thymus fetuses Total	Weight	Odds ratio M-H, Random, 95% CI	Year
Di Naro 2005	11	16	2	15	19.3%	14.30 [2.30, 88.78]	2005
Yinon 2007	9	13	0	8	11.7%	35.89 [1.67, 769.09]	2007
El Haieg 2008	22	24	8	32	20.7%	33.00 [6.31, 172.51]	2008
Musilova 2013	106	150	27	66	28.4%	3.48 [1.90, 6.36]	2013
Aksakal 2014	22	27	2	23	19.9%	46.20 [8.07, 264.65]	2014
Total (95% CI)		**230**		**144**	**100.0%**	**16.02 [4.18, 61.36]**	
Total events	170		39				

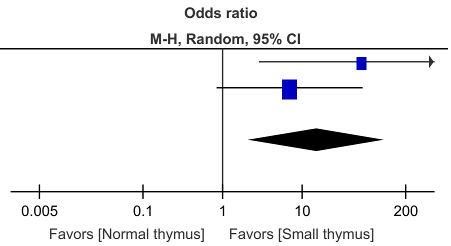
Heterogeneity: $\tau^2 = 1.56$; $\chi^2 = 14.77$, df = 4 ($p = 0.005$); $I^2 = 73\%$
Test for overall effect: $Z = 4.05$ ($p < 0.0001$)



Neonatal sepsis

Study or Subgroup	Small thymus fetuses Events	Small thymus fetuses Total	Normal thymus fetuses Events	Normal thymus fetuses Total	Weight	Odds ratio M-H, Random, 95% CI	Year
Cetin 2014	10	18	0	22	37.1%	55.59 [2.92, 1056.48]	2014
Ekin 2015	9	84	1	59	62.9%	6.96 [0.86, 56.51]	2015
Total (95% CI)		**102**		**81**	**100.0%**	**15.05 [2.10, 108.04]**	
Total events	19		1				

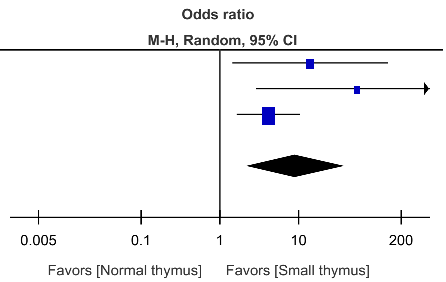
Heterogeneity: $\tau^2 = 0.47$; $\chi^2 = 1.27$, df = 1 ($p = 0.26$); $I^2 = 22\%$
Test for overall effect: $Z = 2.70$ ($p = 0.007$)



Neonatal morbidity

Study or Subgroup	Small thymus fetuses Events	Small thymus fetuses Total	Normal thymus fetuses Events	Normal thymus fetuses Total	Weight	Odds ratio M-H, Random, 95% CI	Year
Di Naro 2005	8	16	1	15	26.0%	14.00 [1.47, 133.23]	2005
Cetin 2014	10	18	0	22	17.9%	55.59 [2.92, 1056.48]	2014
Ekin 2015	30	84	7	59	56.2%	4.13 [1.67, 10.22]	2015
Total (95% CI)		**118**		**96**	**100.0%**	**9.02 [2.15, 37.81]**	
Total events	48		8				

Heterogeneity: $\tau^2 = 0.74$; $\chi^2 = 3.49$, df = 2 ($p = 0.17$); $I^2 = 43\%$
Test for overall effect: $Z = 3.01$ ($p = 0.003$)



Pre-eclampsia

Study or Subgroup	Small thymus fetuses Events	Small thymus fetuses Total	Normal thymus fetuses Events	Normal thymus fetuses Total	Weight	Odds ratio M-H, Random, 95% CI	Year
Brandt 2016	8	130	25	390	100.0%	0.96 [0.42, 2.18]	2016
Total (95% CI)		**130**		**390**	**100.0%**	**0.96 [0.42, 2.18]**	
Total events	8		25				

Heterogeneity: Not applicable
Test for overall effect: $Z = 0.10$ ($p = 0.92$)

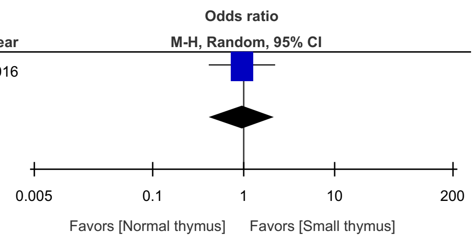


Figure 2. Continued.

Table 3. Head-to-head meta-analyses comparing the risk of selected gestational outcomes in fetuses with small thymus vs. fetuses with normal thymus (see also Figure 2).

Outcomes	No. of studies (total sample) (ref.)	OR (95% CI)	p	I^2, %	Sensitivity % (95% CI)	Specificity % (95% CI)	DOR (95% CI)	LR+ (95% CI)	LR− (95% CI)
1. Preterm birth									
<37 weeks (overall)	2* (551) (20,29)	2.23 (0.21–23.6)	0.5	85	37.3 (24.1–51.9)	74.6 (70.5–78.4)	2.23 (0.21–23.6)	1.44 (0.41–5.03)	0.65 (0.19–2.21)
<37 weeks (women at risk)	1 (47) (29)	8.3 (1.7–41.2)	0.01	–	75.0 (47.6–92.7)	73.33 (44.9–92.2)	8.25 (1.3–56.2)	2.81 (1.29–7.11)	0.34 (0.13–0.76)
<34 weeks (overall)	3* (607) (20,27,29)	5.16 (0.85–31.2)	0.07	81	60.8 (46.1–74.2)	75.0 (71.2–78.5)	5.16 (0.85–31.2)	2.23 (1.10–4.50)	0.42 (0.11–1.61)
<34 weeks (women at risk)	2 (87) (27,29)	12.52 (4.3–36.8)	<0.001	0	81.3 (63.6–92.8)	72.5 (58.3–84.1)	11.03 (3.7–32.6)	2.86 (1.78–4.58)	0.27 (0.13–0.56)
2. IUGR									
a. <10th centile	2* (813) (20,21)	5.98 (0.26–138)	0.3	97	52.0 (45.3–58.7)	82.3 (79.0–85.3)	2.81 (0.01–557)	1.91 (0.04–82.6)	0.68 (0.10–4.60)
b. <5th centile	2* (640) (9,20)	16.4 (0.09–2839)	0.3	97	78.3 (67.9–86.6)	76.7 (72.9–80.1)	16.4 (0.09–2839)	3.18 (0.44–22.7)	0.19 (0.00–28.4)
3. Chorioamnionitis	5† (374) (22,24,27–29)	16.0 (4.18–61.4)	<0.001	73	81.6 (74.3–87.2)	73.5 (55.2–86.2)	12.3 (4.81–31.5)	3.08 (1.68–5.64)	0.25 (0.16–0.38)
4. Neonatal sepsis	2* (183) (21,23)	15.1 (2.10–108)	0.007	22	95.0 (75.1–100)	49.1 (41.2–57.0)	15.1 (2.10–108)	2.28 (0.93–5.59)	0.15 (0.03–0.71)
5. Neonatal morbidity[a]	3* (214) (21,23,29)	9.02 (2.15–37.8)	0.003	43	85.7 (73.8–93.6)	55.7 (47.6–63.6)	9.02 (2.15–37.8)	2.25 (1.36–3.72)	0.28 (0.12–0.66)
6. Preeclampsia	1 (520) (20)	0.96 (0.42–2.18)	0.9	–	–	–	–	–	–

DOR, diagnostic odds ratio; IUGR, intrauterine growth restriction; LR+ and LR−, positive and negative likelihood ratios; OR, odds ratio.
For each outcome, summary estimates of sensitivity, specificity, LR+ and LR− and DOR to predict the presence of a small thymus were also computed. Depending on the number of studies, computations were based upon DerSimonian–Laird random-effect (*) or hierarchical summary receiver operating characteristic model (†).
[a]Composite outcome of: sepsis, respiratory distress, abnormal brain imaging.

Intrauterine growth restriction and birthweight

Three studies explored the association between a small fetal thymus and the risk of IUGR. All these studies included apparently uncomplicated pregnancies and reported no increased risk of IUGR (OR 6.0, 95% CI 0.3–138 and 16.4, 95% CI 0.1–2839 for IUGR <10th and <5th centiles, respectively) in fetuses with compared to those without a small thymus on ultrasound (9,21,25).

Three studies explored the mean difference in birthweight between fetuses with small thymus compared with controls (20,21,28); these three studies differed in the inclusion criteria with that of Brandt et al. considering all pregnancies screened during the second trimester whereas those by Ekin et al. and Yinon et al. included pregnancies affected by IUGR and PPROM, respectively. Overall, there was no difference in the mean birthweight between fetuses with and those without a small thymus at the scan (mean difference 322, 95% CI −241 to 886; $p = 0.3$). However, when analyzed separately, the study by Brandt et al. reported no difference in mean birthweight between fetuses with small compared to those with normal thymus, whereas those by Ekin et al. and Yinon et al. reported a smaller birthweight in fetuses with small thymus compared with controls (Figure 2, Table 4, and see Supplementary material, Figure S1).

Chorioamnionitis

Five studies explored the risk of chorioamnionitis in fetuses with small thymus compared with controls (22,24,27–29). All these studies included pregnancies at high risk for chorioamnionitis; four studies included women with PPROM (22,24,27,28), whereas that by Di Naro et al. included women presenting with symptoms of PTB (29). The studies by Aksakal, Musilvoa and El Haieg and their colleagues (22,24,27) used a transverse diameter <5th centile whereas those by Yinon et al. (28) and Di Naro et al. (29) used a perimeter <5th centile to define a thymus as small. Overall, the risk of chorioamnionitis was significantly higher in pregnancies affected by PPROM, showing small thymus at the scan (OR 16.0, 95% CI 4.18–61.4). Furthermore, when translated into a predictive model, the presence of a small fetal thymus at the scan had a moderate diagnostic accuracy in identifying pregnancies affected by chorioamnionitis in women at risk, with a sensitivity of 81.6% (95% CI 74.3–87.2), a specificity of 73.5% (95% CI 55.2–86.2), an LR+ of 3.1 (95% CI 1.7–5.6), an LR− of 0.25 (95% CI 0.16–0.38) and a DOR of 12.3 (95% CI 4.81–31.5) (Figure 2, Table 3).

Table 4. Results of the head-to-head meta-analyses comparing selected gestational outcomes in fetuses with small thymus vs. fetuses with normal thymus (see also Supplementary material, Figure S1).

Outcomes	No. of studies (total sample) (refs)	*n*/*n*	Mean difference (95% CI)	*p*	I^2, %
1. Birthweight (g)	3 (684) (20,21,28)	227/457	322 (−241 to 886)	0.3	95
2. Gestational age at birth (weeks)	3 (684) (20,21,28)	227/457	1.48 (−0.93 to 3.90)	0.2	93
3. Length of hospital stay (days)	2 (77) (28,29)	37/40	4.76 (1.10–8.42)	0.01	0

Length of stay, neonatal outcome and preeclampsia

Two studies explored the difference in length of in-hospital stay between pregnancies with compared to those without a small thymus on ultrasound (28,29); both studies included pregnancies affected by PPROM and reported an overall longer stay in the hospital in women with small fetal thymus compared with controls, mainly as the consequence of the higher occurrence of chorioamnionitis (mean difference 4.76, 95% CI 1.10–8.42; $p = 0.01$) (see Supplementary material, Figure S1).

The presence of a small fetal thymus increased the risk of neonatal sepsis (OR 15.1, 95% 2.10–108), with a sensitivity and specificity of 95.0% (95% CI 75.1–100) and 49.1% (95% CI 41.2–57.0), respectively (Table 3). The two included studies (21,23) had different populations, with that of Cetin et al. (23) including women with PPROM, whereas that by Ekin et al. (21) included fetuses affected by IUGR. Despite this, the risk of neonatal sepsis was higher in fetuses with small compared to those with normal thymus diameter in both studies. However, a small fetal thymus had overall poor diagnostic accuracy in detecting neonatal sepsis, with a specificity of 49.1% (95% CI 41.2–57.0), despite a sensitivity of 95.0% (95% CI 75.1–100) (Figure 2).

Three studies explored the risk of neonatal morbidity in fetuses with small thymus (21,23,29). The study by Ekin et al. (21) included IUGR fetuses, whereas those by Cetin et al. (23) and Di Naro et al. (29) included pregnancies affected by PPROM and threatened preterm labor, respectively. When pooled together, a small fetal thymus was also associated with a higher risk of neonatal morbidity, with an OR of 9.0 (95% CI 2.15–37.8), a sensitivity of 85.7% (95% CI 73.8–93.6), a specificity of 55.7% (95% CI 47.6–63.6), an LR+ of 2.3 (95% CI 1.36–3.72), an LR− of 0.28 (95% CI 0.12–0.66) and a DOR of 9.0 (95% CI 2.15–37.8) (Figure 2).

Finally, two studies explored the association between fetal thymus and preeclampsia (20,26). The study by Eviston et al. reported that thymus diameters were significantly smaller in preeclamptic pregnancies vs. healthy control pregnancies (26). Furthermore, the authors reported a significant association between the mean fetal thymus diameter and the risk of preeclampsia (OR 0.73, 95% CI 0.63–0.84, $p < 0.001$) and that this association remained statistically significant after adjustment for maternal body mass index, gestational age at ultrasound, and fetal anthropometry at ultrasound. The study by Brandt et al. assessed the risk of preeclampsia in fetuses compared with those without a small thymus at ultrasound defined as a categorical variable (anteroposterior and transverse diameters <25th centile) reporting no difference between the study groups (Figure 2, Table 3) (20).

Discussion

The findings from this systematic review show that a small fetal thymus increased the risk of PTB, chorioamnionitis, neonatal sepsis and neonatal morbidity in women at risk, such as those affected by PPROM or presenting with symptoms and signs of preterm labor. The diagnostic accuracy of small fetal thymus in detecting PTB or chorioamnionitis was moderately good. Conversely, a small fetal thymus in uncomplicated pregnancies either during the second or third trimester was not associated with any of the adverse outcomes explored in this systematic review and should not be used in clinical practice to stratify the obstetric and perinatal risk.

The strengths of this study are its robust methodology for identifying all possible studies for inclusion, assessing data quality and synthesizing all suitable data. The small number of cases in some of the included studies, their retrospective nonrandomized design, different periods of follow up, dissimilarity of the populations (due to various inclusion criteria) and lack of standardized criteria for the antenatal management represent the major limitations of this systematic review. Assessment of the potential publication bias was also problematic because of the nature of the outcome evaluated (outcome rates, with the left-side limited to a value of zero), which limits the reliability of funnel plots, and because of the scarce number of individual studies, which strongly limits the reliability of formal tests.

The very small number of included cases did not allow a precise estimation of the strength of association between small thymus and the observed outcomes and it may be entirely possible that the lack of association between small fetal thymus in uncomplicated pregnancies and some of the outcomes explored was due to the low power of the analysis. Several cut-offs to define a thymus as small during pregnancy have been reported in the recently published literature; although we aimed to explore the strength of association between each cut-off and the outcomes observed, the very small number of included cases precluded such assessment. Gestational age at assessment was another peculiar issue; the majority of the included studies did not stratify the analysis according to the gestational age at ultrasound and it was not possible to elucidate whether the strength of association between small fetal thymus and perinatal outcome was higher in a specific gestational age window. Finally, inclusion criteria differed among the studies, with some including uncomplicated pregnancies, whereas others only included women at risk such as those with threatened preterm labor or cases affected by PPROM; in this scenario, meta-analysis of the data would not give a precise estimate of the strength of association between small fetal thymus and adverse perinatal outcome. Therefore, although we stratified the analysis according to the type of population analyzed, the small number of cases included in each sub-analysis may have biased the results.

Ultrasound assessment of fetal thymus has been reported to be feasible from the first trimester of pregnancy. Despite this, identification of fetal thymus may be challenging. Paladini et al. described a simple and reproducible way to identify fetal thymus through the visualization of internal mammary arteries in the three-vessel and trachea view of the fetal heart: the “Thy box”. Using color Doppler in a three-vessel and trachea view of the fetal heart allows visualization of the internal mammary arteries, a branch of the subclavian artery, which run lateral to the sides of the sternum; in this way, the Thy-box can be depicted, with the thymus highlighted on both sides by the two internal mammary arteries, on the front by the sternal plate, and on the back by the three vessels and the trachea (7).

The thymus plays a major role in the fetal inflammatory response syndrome, a condition characterized by an elevation of pro-inflammatory cytokines in the fetal circulation, which can occur in a subset of patients with preterm labor or PPROM and it is associated with an in utero multiorgan involvement eventually leading to septic shock and fetal demise (8). Postnatal studies have shown that children affected by fetal inflammatory response syndrome showed decreased thymus size at X-ray. Although the pathophysiological explanation of small thymus size in fetuses affected by infectious-related morbidities has not been fully elucidated, it is thought to be the result of a nonspecific steroid-mediated response to infection (8).

The findings from this systematic review confirmed those from postnatal studies and showed that fetuses with a small thymus had a higher risk of developing complications related to chorioamnionitis. Furthermore, a small thymus increased the risk of PTB, neonatal sepsis and neonatal morbidity in women with PPROM or presenting with symptoms of preterm labor.

However, despite this association, we still do not support the practice of ultrasound assessment of thymus to predict perinatal outcome in pregnancies at risk, such as those affected by PPROM. The multitude of reported cut-offs and thymus measurements, differences in gestational age at scan and lack of correlation with maternal clinical symptoms and biochemical markers do not allow us to extrapolate an objective predictive model to adopt in clinical practice. Therefore, active management in women affected by PPROM, such as iatrogenic delivery, should not be based upon the thymus size but should be tailored according to maternal, fetal and biochemical status.

Conversely, assessment of fetal thymus at the time of the routine second- and/or third-trimester scan should not be undertaken to predict the outcome of the pregnancy, in view of the lack of the association between small fetal thymus and adverse perinatal outcome in uncomplicated pregnancies.

Further large studies combining maternal characteristics, clinical status at presentation and prenatal imaging are needed to ascertain whether fetal thymus can be integrated into clinical practice to ascertain the short-term risk of women at risk of infection-related morbidities.

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Supporting information

Additional Supporting Information may be found in the online version of this article:

Table S1. Search strategy.

Table S2. Excluded studies and reason for the exclusion.

Figure S1. Results of the meta-analysis comparing the mean weight and gestational age at birth of fetuses with small thymus vs. fetuses with normal thymus, and length of in-hospital stay of women with fetuses with small thymus vs. fetuses with normal thymus.