Review Paper

# Prevalence of Cardiac Anomalies in Fetuses Diagnosed With Intracardiac Echogenic Foci: A Systematic Review and Meta-analysis

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**Citation** Taksande A, Jameel PA, Rao R, Taksande B, Damke S. Prevalence of Cardiac Anomalies in Fetuses Diagnosed With Intracardiac Echogenic Foci: A Systematic Review and Meta-analysis. Journal of Pediatrics Review. 2023; 11(3):193-208. http://dx.doi.org/10.32598/jpr.11.3.1110.1

http://dx.doi.org/10.32598/jpr.11.3.1110.1

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**Article info:**
Received: 02 May 2023
First Revision: 03 Jun 2023
Accepted: 10 Jun 2023
Published: 01 Jul 2023

**Key Words:**
Intracardiac echogenic foci, Cardiac anomalies, Prevalence, Calcification

## ABSTRACT

**Objectives:** The exact prevalence of cardiac anomalies in diagnosed cases of echogenic foci is still unknown, as various studies have been carried out across multiple populations with different methodologies.

**Objectives:** The primary objective of this study was to determine the precise prevalence of cardiac anomalies found in cases with intracardiac echogenic foci.

**Methods:** The authors manually searched the electronic databases (Cochrane Library, PubMed, EMBASE, Scopus, Web of Science). Two reviewers independently did data extraction and quality control; a third reviewer resolved any raised conflicts. The data were analyzed by comprehensive meta-analysis software version 2. Risk of bias assessment and strobe checklist were used for quality assessment.

**Results:** Out of 531 articles identified, 32 studies met the inclusion criteria and were included in the meta-analysis with a total sample size of 7568. The pooled prevalence of cardiac anomalies in the fetuses with intracardiac echogenic foci was 4.8% (95% CI, 3.6%-6.4%). Subgroup analysis was done according to the geographical distribution of cases, maternal age, gestational age, year of publication, risk of bias, and ultrasonography operator.

**Conclusions:** The current study represents the first and only meta-analysis concerning the prevalence of cardiac anomaly in fetuses diagnosed with intracardiac echogenic focus (ICEF). This study supports a definitive relationship between ICEF and underlying congenital heart disease. We recommend increased training of individuals performing this ultrasonography to improve early detection, ultimately enhancing the care given to infants immediately post-birth.

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## Introduction

Intracardiac echogenic focus (ICEF) is demonstrated by ultrasound inside the fetal heart with a brightness comparable to that of the bone. It was first described by Schechter et al. [1] in 1987 in the left ventricle of a fetal heart, which they attributed to a thickening of the chordae. Usually, the focus has no acoustic shadow and is located near or within the papillary muscles. It moves in synchronization with the atrioventricular valves. It can be visualized in a 4 chambers view when performing a basic echocardiogram [2]. ICEF is most frequently visualized in the left ventricle and less commonly on the right side or both ventricles. While a single ICEF in the left ventricle is the most frequent finding, multiple foci may be seen often. These foci vary in size but are usually less than 6 mm [1, 2]. Echogenic foci suggest micro-calcification of the chordae and papillary muscles. Echogenic foci are increasingly associated with cardiac structural anomalies and chromosomal abnormalities.

When diagnosed, echogenic foci bring a clinical conundrum as their origin, and definitive significance are not yet completely understood. However, echogenic foci are increasingly considered markers for chromosomal abnormality and underlying structural cardiac defect in the fetus, especially in high-risk women [3, 4]. Therefore, the detection of ICEF warrants further investigations, such as fetal echocardiography. Fetal echocardiography has proven to be an invaluable tool for the early and accurate detection of fetal structural heart defects. Despite its challenges, fetal echocardiography helps in the early detection of ICEF. The importance of detecting ICEF can be highlighted by the fact that some clinicians recommend performing fetal echocardiography in all cases of ICEF [3-5].

The exact prevalence of ICEF is difficult to ascertain because of the different populations and methodologies used across various studies. In addition, several studies have included both high- and low-risk populations, while others have reported retrospective and prospective studies including a wide range of gestational ages [6]. The prevalence of ICEF varies between 0.17% and 20% according to the populations studied, gestational age, fetal position, and equipment quality. The highest prevalence is among Asian, Middle-Eastern, and African-American populations [5, 7]. There are few systematic reviews and meta-analyses on the diagnostic performance of the presence of echogenic cardiac foci for detecting chromosomal anomalies. Still, there is a lack of strong evidence about the prevalence of cardiac anomalies in ICEF. This study aims to conduct a systematic review and meta-analysis of published studies on detecting cardiac anomalies in fetuses with ICEF in clinical practice.

## Methods

This systematic review followed the recommendations of the meta-analyses in observational studies (MOOSE) guidance statement [8].

### Search strategy for identifying relevant studies

The search strategy was implemented in two stages.

### Bibliographic database search

Electronic databases (Cochrane Library, PubMed, EMBASE, Scopus, and Web of Science) were used as data sources. The search was restricted to English language publications involving human subjects but not limited by date or publication type. Studies with insufficient data, only abstracts, and duplicate publications were excluded. Two reviewers (PZJ and RR) independently performed data extraction and quality control. A third reviewer (AT) was involved in any conflict that occurred. The following search keywords were used: “Intracardiac”[All Fields] AND (“echogeneity”[All Fields] OR “echogenic”[All Fields] OR “echogenicities” [All Fields] OR “echogenicity”[All Fields] OR “echogenity”[All Fields]) AND “foci” [All Fields] AND (“fetus”[MeSH Terms] OR “fetus” [All Fields] OR “fetuses” [All Fields] OR “fetus s” [All Fields] OR “foetu”[All Fields] OR “fetus” [All Fields]) AND ((“cardiacs” [All Fields] OR “heart”[MeSH Terms] OR “heart” [All Fields] OR “cardiac” [All Fields]) AND (“abnormalities” [MeSH Subheading] OR “abnormalities”[All Fields] OR “malformations”[All Fields] OR “congenital abnormalities” [MeSH Terms] OR (“congenital”[All Fields] AND “abnormalities” [All Fields]) OR “congenital abnormalities” [All Fields] OR “malformation” [All Fields] OR “malformational” [All Fields] OR “malformative” [All Fields] OR “malformed” [All Fields])). The last electronic search was carried out on May 30, 2021.

### Searching other sources

We conducted a manual search, scanning the reference lists of eligible papers, other relevant review articles, and specialist journals. Reference lists of included articles and relevant reviews were searched for additional articles. All studies were imported to the literature management software Endnote X7 to eliminate duplicate records. Two authors (AT and PZJ) independently conducted a preliminary screening of studies by reading titles and abstracts. After screening titles and abstracts, the full texts of potentially relevant articles were downloaded. Additionally,

we conducted a second round of screening by reading full texts. Studies were selected if they met the inclusion criteria. Methods were adapted as per PRISMA (preferred reporting items for systematic reviews and meta-analyses) guideline for meta-analysis [9].

### Eligibility criteria for studies

Studies considered in this meta-analysis were observational studies reporting the prevalence of cardiac anomalies associated with ICEF seen in fetuses. These studies had to provide the total number of patients with ICEF and the number of children with cardiac anomalies occurring in the cohort of ICEF in the fetuses.

The inclusion criteria were all cross-sectional, case-control, or cohort studies reporting the prevalence of ICEF and detecting structural cardiac defects later on in the fetuses and published from January 1, 1980, to June 30, 2020. The exclusion criteria were studies not performed on human participants, case reports, reviews, letters, commentaries, and editorials, studies with insufficient data, abstracts, and duplicate publications, and studies whose key data were not accessible even after a request from authors.

### Selection of studies for inclusion in the review

Two investigators (PZJ and RR) independently identified articles and sequentially screened their titles and abstracts for eligibility. Full texts of articles deemed potentially eligible were acquired. These investigators further independently assessed the full text of each study for eligibility and consensually retained studies to be included. Disagreements were resolved by a third author (AT). We used a screening guide to ensure all review authors reliably applied the selection criteria. The agreement was measured using the kappa (κ) statistic [10].

### Data extraction and management

A standard data extraction form was used to extract relevant information and data from each study included in the analysis. Two review authors (PZJ and RR) participated in data extraction independently. PZJ and RR extracted data with general information (authors, year, and country), study design, ultrasonography operator, number of ICEF in the fetus, and cardiac anomalies. Studies with only primary data (sample size and number of outcomes) were used to calculate the prevalence estimates. Data were extracted using a preconceived and standardized data abstraction form. Studies with un-interpretable data were excluded from the analysis. The agreement was measured using the κ statistic [10].

### Appraisal of the quality of included studies

Two investigators (PZJ and RR) evaluated all the included studies for methodological quality and risk of bias using an adapted version of the Risk of Bias Tool for Prevalence Studies developed by Hoy and associates [11]. Furthermore, the reporting quality of each study was assessed using the STROBE checklist [12]. Two authors performed the reporting of observational studies in epidemiology (STROBE), scoring from 0 to 22, with 22 reflecting the highest quality. The STROBE statement is a checklist of 22 items. These items refer to the article's title and abstract (item 1), the introduction (items 2 and 3), methods (items 4–12), results (items 13–17), discussion sections (items 18–21), and other information (item 22 on funding). The agreement was measured using the κ statistic [10].

### Statistical analysis

In each study, the prevalence of cardiac anomalies associated with ICEF in fetuses was considered the probability of binomial distribution. Forest plots were drawn to visualize the combined prevalence and extent of heterogeneity between studies. Owing to the differences across patients in the studies, a random-effects meta-analysis was used to pool prevalence data [13, 14]. To evaluate the heterogeneity of the studies, Cochran's Q test and $I^2$ index were used [15]. There are three categories for the $I^2$ index: Heterogeneity lower than 25%, heterogeneity between 25% and 75%, and heterogeneity more than 75%. Considering the heterogeneity of the studies, a random effects model was used to combine cardiac anomaly prevalence. Sensitivity analysis was performed to identify the influence of a single study on the combined result prevalence. To determine the cause of heterogeneity of cardiac anomaly prevalence, sub-group analysis of cardiac anomaly in the fetuses with ICEF was carried out based on geographical region, etiology, and quality of studies. The meta-regression model (method of moments) was carried out based on the year of studies [16]. Subgroup analysis was conducted by geographical distribution, maternal age, gestational age, year of publication, and ultrasonography operator. Egger and Begg's tests were used to identify publication bias. Data analysis was performed using comprehensive meta-analysis software version 2, and the significance level in the test was considered lower than 0.05 [17].

**Table 1.** Characteristics of studies included in the meta-analysis

| S. No. | First Author | Year | Country | Study Design | Total Study Population | Intracardiac Echogenic Focus Studied | Cardiac Anomaly | Prevalence of Cardiac Anomaly (%) |
|---|---|---|---|---|---|---|---|---|
| 1 | Schechter et al. [1] | 1987 | USA | Observational | 738 | 26 | 0 | 0 |
| 2 | How et al. [18] | 1994 | USA | Observational | 5395 | 25 | 1 | 4 |
| 3 | Petrikovsky et al. [19] | 1995 | USA | Observational | 1139 | 41 | 0 | 0 |
| 4 | Sepulved et al. [20] | 1995 | UK | Observational | 36 | 7 | 4 | 57.14 |
| 5 | Bronshtein et al. [7] | 1996 | Israel | Retrospective | 25725 | 44 | 3 | 6.81 |
| 6 | Bronshtein et al. [7] | 1996 | UK | Prospective | 3290 | 228 | 1 | 0.43 |
| 7 | Dildy et al. [22] | 1996 | USA | Prospective | 506 | 25 | 1 | 4 |
| 8 | Achiron et al. [23] | 1997 | Israel | Observative | 2214 | 163 | 0 | 0 |
| 9 | Bromley et al. [24] | 1998 | USA | Cohort | 290 | 290 | 6 | 2.06 |
| 10 | Wolman et al. [25] | 2000 | Israel | Case-control | 3744 | 138 | 1 | 0.72 |
| 11 | Tennstedt et al. [26] | 2000 | Germany | Prospective | 6 | 6 | 3 | 50 |
| 12 | Barsoom et al. [27] | 2001 | USA | Retrospective | 10406 | 230 | 1 | 0.43 |
| 13 | Liu et al. [28] | 2002 | Taiwan | Prospective | 547 | 43 | 1 | 2.32 |
| 14 | Carrico et al. [29] | 2004 | Portugal | Retrospective | 753 | 61 | 5 | 8.1 |
| 15 | Rebarber et al. [30] | 2004 | USA | Cohort | 149 | 22 | 1 | 4.54 |
| 16 | Wax et al. [31] | 2004 | USA | Retrospective | 139 | 25 | 2 | 8.00 |
| 17 | Bradley et al. [32] | 2005 | USA | Prospective | 10875 | 176 | 19 | 10.79 |
| 18 | Petrikovsky et al. [33] | 2005 | USA | Observative | 9 | 9 | 1 | 11.11 |
| 19 | Lim et al. [34] | 2006 | USA | Prospective | 1543 | 76 | 3 | 4 |
| 20 | Gonclaves et al. [35] | 2006 | Brazil | Cross-sectional | 23756 | 373 | 10 | 2.68 |
| 21 | Shanks et al. [36] | 2009 | USA | Retrospective cohort | 62111 | 218 | 16 | 7.33 |
| 22 | Hilal et al. [37] | 2012 | Pakistan | Descriptive | 8000 | 138 | 9 | 6.5 |
| 23 | Shakoor et al. [4] | 2013 | Pakistan | Retrospective | 8226 | 24 | 2 | 8.33 |
| 24 | Chitra et al. [38] | 2016 | India | NM | 478 | 103 | 0 | 0.00 |
| 25 | Tian et al. [39] | 2016 | China | Retrospective | 1690 | 696 | 37 | 5.31 |
| 26 | Guo et al. [40] | 2017 | China | Retrospective | 14846 | 2647 | 101 | 3.8 |
| 27 | Chiu et al. [41] | 2018 | China | Retrospective cohort | 9782 | 758 | 24 | 3.2 |
| 28 | Chiu et al. [42] | 2019 | China | Retrospective | 8120 | 531 | 12 | 2.25 |
| 29 | Akinmoladun et al. [43] | 2020 | Africa | Cross-sectional | 1986 | 20 | 5 | 25 |
| 30 | Ozsurmeli et al. [44] | 2020 | Turkey | Retrospective | 8300 | 233 | 8 | 3.43 |
| 31 | Usta et al. [45] | 2020 | Turkey | Retrospective cohort | 2590 | 66 | 2 | 3.03 |
| 32 | Song et al. [46] | 2021 | China | Retrospective | 571 | 144 | 9 | 6.25 |

**Table 2.** Characteristics of the ICEF in the foetus of the included studies

| S. No. | 1st Author | Year | Mean±SD | | Location of ICEF | | | ICEF Diagnosed by | Number of Abnormal Karyotype |
|---|---|---|---|---|---|---|---|---|---|
| | | | Maternal Age (y) | Gestation (wk) | Left Ventricle | Right Ventricle | Both Ventricles | | |
| 1 | Schechter et al. [1] | 1987 | 34.24 | 18.12 | 26 | 0 | 0 | Fetal sonographer | 1 (Trisomy 21) |
| 2 | How et al. [18] | 1994 | 25.5±5.3 | 19.4±3.7 | 24 | | 1 | NM | 0 |
| 3 | Petrikovsky et al. [19] | 1995 | NM | NM | 38 | 2 | 1 | NM | 0 |
| 4 | Sepulved et al. [20] | 1995 | NM | NM | 5 | 1 | 1 | NM | T21-3<br>T18-1<br>T13-3 |
| 5 | Bronshtein et al. [7] | 1996 | NM | NM | 35 | 5 | 4 | NM | NM |
| 6 | Simpson et al. [21] | 1996 | NM | 19 (14.32) | 173 | 16 | 39 | Fetal cardiologist | 2 (Trisomy 21, unbalanced translocation between chromosomes 4 and 6) |
| 7 | Dildy et al. [22] | 1996 | NM | 20.6±1.6 | 19 | 6 | 0 | Fetal medicine specialist | 0 |
| 8 | Achiron et al. [23] | 1997 | 24.6 | 14 | 75 | 25 | 0 | NM | 0 |
| 9 | Bromley et al. [24] | 1998 | Anneuploidy-33.4<br>Euploidy-33 | A-18.6<br>E-18.2 | 254 | 14 | 22 | NM | 14 |
| 10 | Wolman et al. [25] | 2000 | 27.4 | NM | 109 | 25 | 5 | NM | 0 |
| 11 | Tennstedt et al. [26] | 2000 | NM | 20-24 | 5 | 0 | 1 | NM | T21-2,<br>T13-1,<br>Triploidy-1 |
| 12 | Barsoom et al. [27] | 2001 | NM | 23.1±4.5 | NM | NM | NM | Pediatric cardiologist | NM |
| 13 | Liu et al. [28] | 2002 | NM | NM | 17 | NM | 3 | Pediatric cardiologist | NM |
| 14 | Carrico et al. [29] | 2004 | 29.0 | 23.4 | 44 | 9 | 8 | Fetal cardiologist | Excluded |
| 15 | Rebarber et al. [30] | 2004 | 30.7±3.9 | 19.8±1.6 | 19/3 | 0 | 0 | Ultrasonographer followed by fetal medicine specialist | 0 |
| 16 | Wax et al. [31] | 2004 | 32±7 | 18.9±1.2 | NM | NM | NM | NM | T21=61; T18=14; T13=13; Triploidy=10; Numerical sex chromosome=13; Others= 28 |
| 17 | Bradley et al. [32] | 2005 | 31.8 | 19.1 | NM | NM | NM | Maternal fetal medicine specialist | Abnormal karyotype-3 |
| 18 | Petrikovsky et al. [33] | 2005 | NM | 16-18 | 1 | 0 | 8 | NM | 0 |
| 19 | Lim et al. [34] | 2006 | 27.8±6.6 | 20.6±1.8 | 71 | 2 | 1 | Foetal medicine specialist | T21-1 |

| S. No. | 1st Author | Year | Mean±SD | | Location of ICEF | | | ICEF Diagnosed by | Number of Abnormal Karyotype |
|---|---|---|---|---|---|---|---|---|---|
| | | | Maternal Age (y) | Gestation (wk) | Left Ventricle | Right Ventricle | Both Ventricles | | |
| 20 | Gonclaves et al. [35] | 2006 | 29.7±5.4 | 22±3.4 | NM | NM | NM | Foetal medicine specialist | T21-9<br>T13-2<br>T18-2<br>Triploidy-1 |
| 21 | Shanks et al. [36] | 2009 | 30.65 | 19.4±1.9 | NM | NM | NM | Fetal sonographer | T21-218 (34) |
| 22 | Hilal et al. [37] | 2012 | NM | NM | 111 | 21 | 6 | NM | NM |
| 23 | Shakoor et al. [4] | 2013 | 26.9±3.9 | 20.3±2.2 | 46 | 3 | 9 | Radiologists | 0 |
| 24 | Chitra et al. [38] | 2016 | 24.7±4.3 | 24.8±4.6 | NM | NM | NM | NM | NM |
| 25 | Tian et al. [39] | 2016 | 26.9 | 24.5 | 41 | 19 | 142 | NM | 7 |
| 26 | Guo et al. [40] | 2017 | 28.9 | 24.5 | 2498 | 45 | 104 | Foetal cardiologist | T21-2,<br>47+XXY-1 |
| 27 | Chiu et al. [41] | 2018 | 27.2±5.4 | 23±3.1 | 643 | 27 | 88 | NM | NM |
| 28 | Chiu et al. [42] | 2019 | 25.7±3.6 | 22.8±3.2 | 455/9 | 29/1 | 47/2 | Pediatric cardiologist | Excluded |
| 29 | Akinmoladun et al. [43] | 2020 | 18-51 | 18-22 | 41 | 2 | 1 | Pediatric cardiologist | T18-1 |
| 30 | Ozsurmeli et al. [44] | 2020 | 29.7 | 22 | 210 | 11 | 12 | Ultrasonographer | Chromosome anomalies=7 |
| 31 | Usta et al. [45] | 2020 | Isolated-27.8±5.8<br>Non iso-28.6±6.3 | I-38.5±1.2<br>NI-38±2.9 | NM | NM | NM | Trained obstetrician | 2 |
| 32 | Song et al. [46] | 2021 | 29.72 | NM | 113 | 31 | 6 | NM | 44 |

NM: Not mentioned.

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## Results

### Characteristics of included studies

Initially, 531 articles were identified (Figure 1). After eliminating duplicates, screening titles, and abstracts, 385 papers were found completely irrelevant and excluded. Agreement between investigators on abstract selection was high (κ=0.90, P<0.001). Full texts of the remaining 43 studies were scrutinized for eligibility, among which 11 studies were excluded. There was no disagreement between investigators for full-text selection. Overall, 32 studies were found eligible and included in the meta-analysis (Figure 1).

All 32 studies reported the number of cardiac anomalies in fetuses with ICEF without any detailed analysis. The included studies were published from 1987 to 2021. While 13 studies retrospectively collected data, the remaining 19 studies collected the data prospectively. Characteristics of these studies are summarized in Table 1 and Table 2. The studies varied in sample size between 6 to 2647 subjects, with a total sample size of 7568 inclusive of all the studies.

### Quality of studies

The quality assessment results are presented in Table 3. None of the studies met all the criteria of the quality assessment score. Based on the criteria enlisted in the STROBE checklist, studies varied in their quality score from 10 to 16. A score of <14 was considered low quality, and >14 was considered good/fair quality. The reporting quality was low for 13 studies while good/fair for the remaining 19 studies. Of the 22 items from the STROBE assessment, the most common problems were a failure to estimate the required sample size and the poor generalizability of the results.

**Table 3.** Quality assessment of the included studies STROBE quality of reporting

| S. No. | 1st Author | Title and Abstract (Item 1) | Introduction (Items 2 & 3) | Methods (Item 4-12) | Results (Item 13-17) | Discussion and Other Information (Items 18-22) | Quality Score (0-22) |
|---|---|---|---|---|---|---|---|
| 1 | Schechter et al. [1] | 0 | 2 | 3 | 3 | 2 | 10 |
| 2 | How et al. [18] | 1 | 1 | 5 | 3 | 2 | 12 |
| 3 | Petrikovsky [19] | 0 | 2 | 4 | 4 | 0 | 10 |
| 4 | Sepulved et al. [20] | 1 | 2 | 4 | 3 | 1 | 11 |
| 5 | Bronshtein et al. [7] | 1 | 2 | 4 | 4 | 2 | 14 |
| 6 | Simpson et al. [21] | 1 | 2 | 5 | 4 | 2 | 14 |
| 7 | Dildy et al. [22] | 1 | 2 | 5 | 4 | 2 | 14 |
| 8 | Achiron et al. [23] | 1 | 2 | 5 | 3 | 1 | 12 |
| 9 | Bromley et al. [24] | 1 | 1 | 4 | 3 | 1 | 10 |
| 10 | Wolman et al. [25] | 1 | 2 | 5 | 4 | 2 | 14 |
| 11 | Tennstedt et al. [26] | 1 | 2 | 5 | 6 | 2 | 16 |
| 12 | Barsoom et al. [27] | 0 | 2 | 5 | 5 | 2 | 14 |
| 13 | Liu et al. [28] | 1 | 2 | 3 | 2 | 2 | 10 |
| 14 | Carrico et al. [29] | 0 | 2 | 5 | 4 | 1 | 12 |
| 15 | Rebarber et al. [30] | 1 | 2 | 4 | 3 | 1 | 11 |
| 16 | Wax et al. [31] | 1 | 2 | 5 | 4 | 2 | 14 |
| 17 | Bradley et al. [32] | 1 | 2 | 6 | 5 | 2 | 16 |
| 18 | Petrikovsky et al. [33] | 1 | 2 | 3 | 3 | 2 | 11 |
| 19 | Lim et al. [34] | 1 | 1 | 4 | 4 | 1 | 11 |
| 20 | Gonclaves et al. [35] | 1 | 2 | 6 | 4 | 1 | 14 |
| 21 | Shanks et al. [36] | 1 | 3 | 5 | 4 | 1 | 14 |
| 22 | Hilal et al. [37] | 0 | 2 | 4 | 2 | 2 | 10 |
| 23 | Shakoor et al. [4] | 1 | 2 | 6 | 4 | 2 | 15 |
| 24 | Chitra et al. [38] | 1 | 2 | 5 | 4 | 2 | 14 |
| 25 | Tian et al. [39] | 1 | 2 | 5 | 3 | 1 | 12 |
| 26 | Guo et al. [40] | 1 | 2 | 5 | 5 | 2 | 15 |
| 27 | Chiu et al. [41] | 1 | 2 | 5 | 4 | 2 | 14 |
| 28 | Chiu et al. [42] | 1 | 2 | 5 | 5 | 1 | 14 |
| 29 | Akinmoladun et al. [43] | 1 | 2 | 6 | 4 | 1 | 14 |
| 30 | Ozsurmeli et al. [44] | 1 | 2 | 5 | 4 | 2 | 14 |
| 31 | Usta et al. [45] | 1 | 2 | 5 | 4 | 2 | 14 |
| 32 | Song et al. [46] | 1 | 2 | 5 | 4 | 3 | 15 |

**Table 4.** Risk of bias assessment of included studies using the Hoy et al. [11] 2012 tool

| S. No. | 1st Author | Representation | Sampling | Random Selection | Non Response Bias | Data Collection | Case Definition | Reliability and Validity of Study Tool | Method of Data Collection | Prevalence Period | Numerator and Denominator | Summary Assessment |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Schechter et al. [1] | LR | LR | LR | HR | LR | LR | HR | HR | HR | HR | MR |
| 2 | How et al. [18] | LR | LR | LR | LR | LR | LR | HR | LR | LR | LR | LR |
| 3 | Petrikovsky [19] | LR | LR | HR | HR | LR | LR | HR | LR | LR | HR | MR |
| 4 | Sepulved et al. [20] | LR | LR | HR | HR | LR | LR | HR | LR | HR | HR | MR |
| 5 | Bronshtein et al. [7] | LR | LR | HR | HR | HR | LR | HR | LR | LR | HR | MR |
| 6 | Simpson et al. [21] | LR | LR | HR | HR | LR | LR | HR | LR | LR | LR | LR |
| 7 | Dildy et al. [22] | LR | LR | HR | HR | LR | LR | HR | LR | LR | LR | LR |
| 8 | Achiron et al. [23] | LR | LR | HR | HR | LR | LR | HR | HR | LR | HR | MR |
| 9 | Bromley et al. [24] | LR | LR | HR | HR | LR | LR | HR | LR | LR | HR | MR |
| 10 | Wolman et al. [25] | LR | LR | HR | HR | LR | LR | HR | HR | LR | LR | MR |
| 11 | Tennstedt et al. [26] | LR | LR | HR | HR | LR | LR | HR | LR | HR | HR | MR |
| 12 | Barsoom et al. [27] | LR | LR | HR | HR | HR | LR | LR | LR | LR | LR | LR |
| 13 | Liu et al. [28] | LR | LR | HR | HR | LR | LR | HR | HR | LR | HR | MR |
| 14 | Carrico et al. [29] | LR | LR | HR | HR | LR | LR | HR | HR | LR | HR | MR |
| 15 | Rebarber et al. [30] | LR | LR | HR | HR | HR | LR | HR | LR | LR | HR | MR |
| 16 | Wax et al. [31] | LR | LR | HR | HR | HR | LR | HR | LR | LR | HR | MR |
| 17 | Bradley et al. [32] | LR | LR | LR | HR | LR | LR | HR | LR | LR | HR | LR |
| 18 | Petrikovsky et al. [33] | LR | LR | HR | HR | LR | LR | LR | HR | LR | HR | MR |
| 19 | Lim et al. [34] | LR | LR | HR | HR | LR | LR | HR | LR | HR | HR | MR |
| 20 | Gonclaves et al. [35] | LR | LR | HR | HR | LR | LR | LR | LR | LR | LR | LR |
| 21 | Shanks et al. [36] | LR | LR | HR | HR | LR | LR | LR | LR | LR | HR | LR |
| 22 | Hilal et al. [37] | LR | LR | HR | HR | HR | LR | HR | LR | LR | HR | MR |
| 23 | Shakoor et al. [4] | LR | LR | HR | HR | LR | LR | LR | LR | HR | LR | LR |
| 24 | Chitra et al. [38] | LR | LR | HR | HR | LR | LR | HR | HR | LR | HR | MR |
| 25 | Tian et al. [39] | LR | LR | HR | HR | HR | LR | HR | LR | LR | HR | MR |
| 26 | Guo et al. [40] | LR | LR | HR | HR | LR | LR | HR | LR | LR | LR | LR |
| 27 | Chiu et al. [41] | LR | LR | HR | HR | LR | LR | LR | LR | LR | LR | LR |
| 28 | Chiu et al. [42] | LR | LR | HR | HR | LR | LR | LR | LR | LR | HR | LR |

| S. No. | 1st Author | Representation | Sampling | Random Selection | Non Response Bias | Data Collection | Case Definition | Reliability and Validity of Study Tool | Method of Data Collection | Prevalence Period | Numerator and Denominator | Summary Assessment |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 29 | Akinmoladun et al. [43] | LR | LR | HR | HR | LR | LR | LR | LR | LR | LR | LR |
| 30 | Ozsurmeli et al. [44] | LR | LR | HR | HR | LR | LR | LR | LR | LR | HR | LR |
| 31 | Usta et al. [45] | LR | LR | HR | HR | HR | LR | LR | LR | LR | LR | LR |
| 32 | Song et al. [46] | LR | LR | HR | HR | HR | LR | HR | LR | LR | HR | MR |

Abbreviations: HR: High risk; MR: Medium risk; LR: Low risk LR.

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## Risk of bias and heterogeneity

Quality assessment was also conducted for each study in 10 items using the risk of bias assessment tool11we required a tool to assess the risk of study bias. Our objectives were to (1. Of the 32 included studies, our summary assessment (Table 4) showed a low risk of bias for 14 studies (43.75%), a moderate risk of bias for 18 studies (56.25%), and no studies with a high risk of bias. Agreement between investigators on the quality assessment of studies was high (κ=0.90, P<0.001). The included studies exhibited high heterogeneity according to the Cochrane Q test (Q test P=0.00001) and $I^2$ test (73.50%), which indicates using the random-effects model.

## Prevalence of cardiac anomalies associated with ICEF in fetuses

Prior studies have estimated a large variation, ranging from 0% to 57%, in reporting the prevalence of cardiac anomalies in fetuses diagnosed with ICEF. However, definitive data from large population sizes are lacking. According to the Der Simonian-Laird random-effects model, the overall prevalence of the meta-analysis of 32 studies revealed that the pooled prevalence of cardiac anomalies in the fetuses with ICEF was 4.8% (95% CI, 3.6%-6.4%). The forest plot is shown in Figure 2. There was a wide variation in cardiac anomalies prevalence in the fetus with ICEF. The heterogeneity was high ($I^2$=73.50%, P<0.000).

## Sensitivity analysis

A sensitivity analysis (Figure 3) was performed to assess the stability of the meta-analysis. The results remained largely unchanged. The statistically similar results indicated the stability of this meta-analysis. However, sensitivity analysis did not identify any factors that substantially influenced the heterogeneity of the results.

## Subgroup analysis

To reduce the heterogeneity, subgroup analysis was performed. The pooled estimates of the prevalence in different subgroups are shown in Table 5. There were significant differences for subgroups of geographical regions, maternal age, gestational age, study publication year, risk of bias, and ultrasonography operator (P<0.05 for all).

## Region

The prevalence of cardiac anomalies among fetuses with ICEF from the Africa continent (25%; 95% CI, 0.108%-0.478%) was higher than in other continents. The European continent's prevalence of cardiac anomalies among fetuses with ICEF was 4.3% (95% CI, 0.018%-0.579%), followed by the American continent and then Asia.

## Maternal age

According to the maternal age group, 21 studies were divided into two categories: Studies conducted in maternal age less than 30 years (15 studies) and those conducted in maternal age more than 30 years (6 studies). The prevalence of cardiac anomalies among fetuses with ICEF in maternal age of >30 years groups (5.81%; 95% CI, 0.03%-0.10%) was higher than studies conducted in maternal age <30 year groups (3.57%; 95% CI, 0.03%-0.04%).

## Gestational age

According to the gestational age group, 24 included studies were divided into two categories: Studies conducted in the gestational age group <20 weeks (10 studies) and studies conducted gestational age group >20 weeks (14 studies). The prevalence of cardiac anomalies among fetuses with ICEF in gestational age group <20 weeks groups (3.97%; 95% CI, 0.02%-0.07%) was higher

**Table 5.** Prevalence in different subgroups

| Variables | Stratification Group | Number of Studies | Total Number of Subjects | Total Number of Events | $I^2$ | P | Prevalence (%) | 95% CI |
|---|---|---|---|---|---|---|---|---|
| Region | Asian | 14 | 5728 | 209 | 49.902 | 0.000 | 3.93.6 | 0.030-0.050 |
| | America | 13 | 1568 | 61 | 62.391 | 0.000 | 4.23.8 | 0.025-0.069 |
| | Europe | 4 | 302 | 13 | 88.951 | 0.095 | 13.84.3 | 0.018-0.579 |
| | Africa | 1 | 20 | 5 | 0 | 0.033 | 2525 | 0.108-0.478 |
| Maternal age | <30 year | 15 | 6829 | 244 | 43.715 | 0.000 | 3.53.5 | 0.030-0.047 |
| | >30 year | 6 | 757 | 44 | 65.560 | 0.000 | 5.85.8 | 0.031-0.105 |
| Gestational age | <20 weeks | 10 | 1182 | 47 | 67.687 | 0.000 | 4.23.9 | 0.022-0.079 |
| | >20 weeks | 14 | 6404 | 241 | 64.782 | 0.000 | 3.93.7 | 0.029-0.053 |
| Study published | Before 2000 | 9 | 849 | 16 | 76.200 | 0.000 | 1.881.8 | 0.010-0.097 |
| | 2001 - 2021 | 23 | 6737 | 272 | 73.408 | 0.000 | 4.034.03 | 0.038-0.068 |
| Risk of bias | Low risk | 14 | 5474 | 196 | 77.801 | 0.000 | 4.23.5 | 0.028-0.061 |
| | Moderate risk | 18 | 2112 | 92 | 67.861 | 0.000 | 5.64.3 | 0.036-0.068 |
| Operator | Pediatric cardiologist | 8 | 2097 | 77 | 78.046 | 0.000 | 4.13.67 | 0.023-0.072 |
| | Fetal cardiography | 1 | 61 | 5 | 0 | 0.000 | 8.18.1 | 0.035-0.182 |
| | Fetal medicine specialist | 2 | 252 | 22 | 65.192 | 0.000 | 7.58.7 | 0.028-0.183 |
| | Sonographer | 2 | 255 | 9 | 0 | 0.000 | 3.53.5 | 0.019-0.067 |

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than studies conducted in gestational age group >20 weeks group (3.76%; 95% CI, 0.02%-0.05%).

### Published studies

The prevalence of cardiac anomalies among fetuses with ICEF was lower among the published studies before 2000 (1.88%; 95% CI, 0.01%-0.09%) than those published after 2000 (4.03%; 95% CI, 0.03%-0.06%).

### Risk of bias

Subgroup analyses showed the prevalence of cardiac anomalies among fetuses with ICEF in moderate risk studies (3.91%; 95% CI, 0.03%-0.06%) was higher than in studies with low risk of bias (3.11%; 95% CI, 0.028%-0.061%).

### Operator

According to the operator performing fetal echocardiography or sonography to detect cardiac anomalies, 13 studies were divided into 4 categories: pediatric cardiologist, fetal cardiography, fetal medicine specialist, and ultrasonographer. The higher prevalence of cardiac anomalies among fetuses with ICEF was detected by a fetal medicine specialist (8.73%; 95% CI, 0.02%-0.18%) and fetal cardiography (8.19%; 95% CI, 0.03%-0.18%) versus the pediatric cardiologist and ultrasonographer.

### Publication bias

The Egger weighted regression statistics (P=0.873) and Begg rank correlation statistics (P=0.57) indicated no evidence of publication bias. There was no publication bias or asymmetry in the funnel plot (Figure 4).

Meta-regression model in Figure 5 shows that the prevalence of cardiac anomalies among fetuses with ICEF is increasing according to the year of study. However, this relationship is not statistically significant (meta-regression coefficient: 0.0022, 95% CI, -0.0319% to 0.0362%, P=0.900).

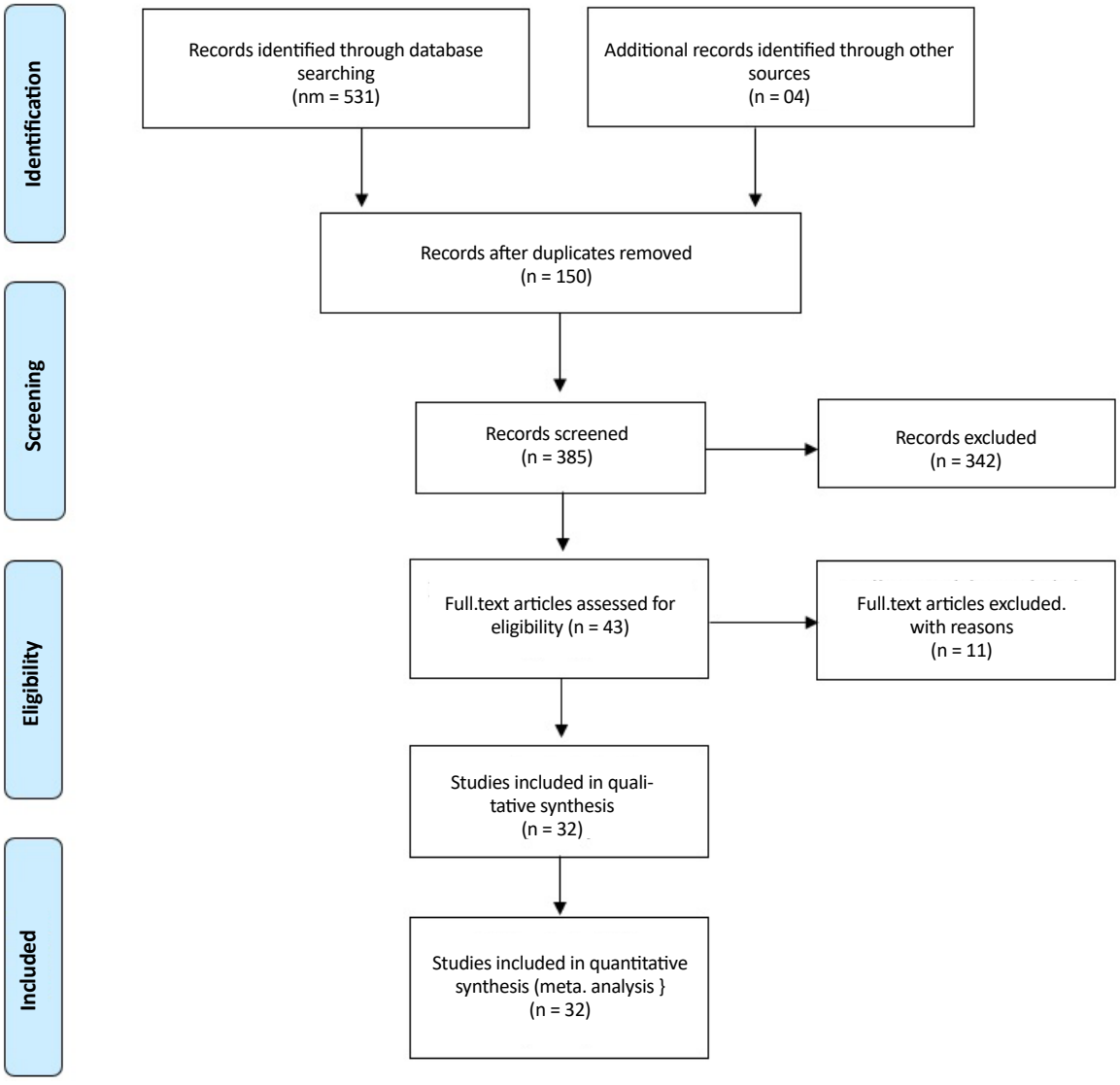


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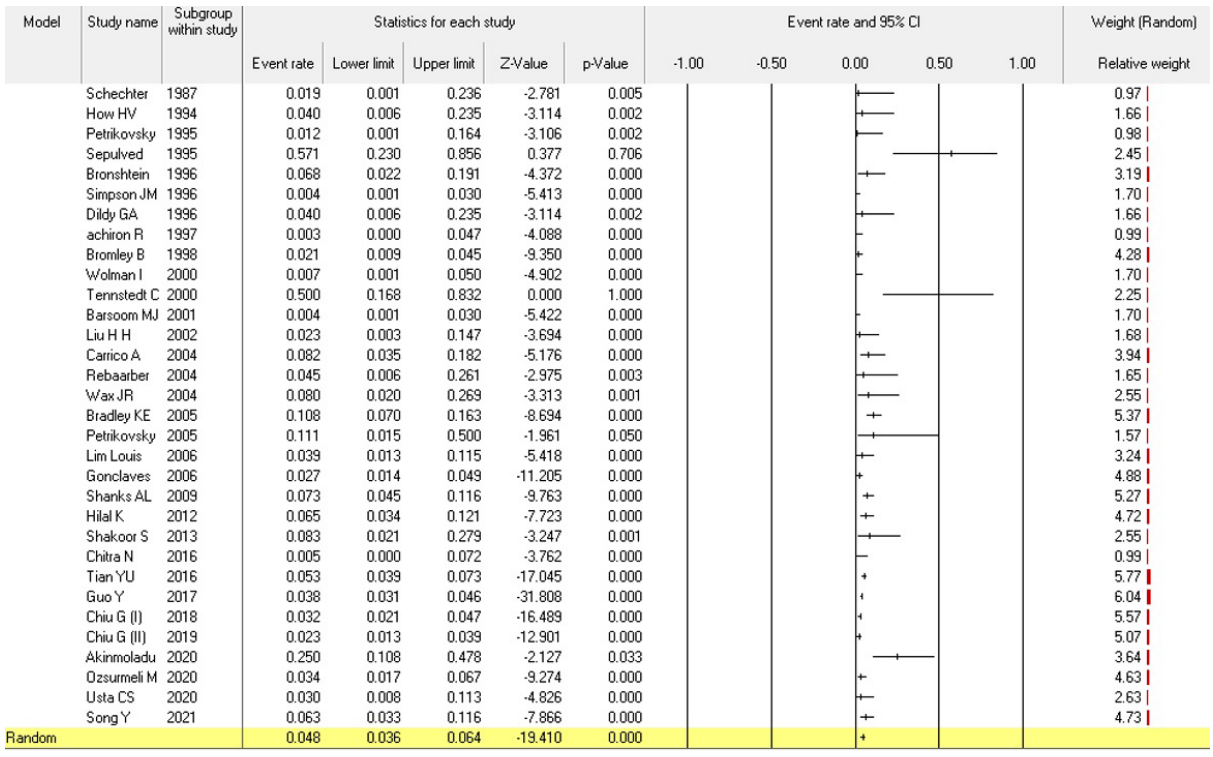
**Figure 1.** PRISMA flow chart diagram describing process of identification and selection of studies for inclusion in the review

## Discussion

Diagnosis of echogenic foci is increasingly associated with an underlying structural cardiac defect and chromosomal abnormalities. Despite various previous studies, the relationship of ICEF with the cardiac anomaly is unclear [29, 47, 48]. Most studies show that the presence of ICEF should be interpreted as a possible risk factor for congenital heart defects. While some studies have found that fetal echogenic foci were not associated with underlying congenital heart disease, structural heart defects, or extra-cardiac anomalies [1, 23, 33, 38]. Sotiriadis et al. [49] conducted the first meta-analysis associating intracardiac echogenic foci to trisomy 21 and observed a 5-7 times higher risk in patients diagnosed with echogenic foci. Another meta-analysis by Lorente et al. [50] confirmed the association of echogenic foci with chromosomal anomalies. The identification rate of trisomy 21 in children diagnosed with echogenic foci was low (21.8%), with a low false positive rate (4.1%). In addition, the determined likelihood ratios in their study showed that echogenic foci have an important role in confirmation rather than ruling out trisomy 21 [50]. This meta-analysis assessed the prevalence of cardiac defects in fetuses diagnosed with echogenic foci. The present study found the overall prevalence to be 4.8% (95% CI, 3.6%-6.4%) from a pool of 32 studies that met the inclusion criteria. In addition to this analysis, sensitivity analysis was performed to assess the stability of our meta-analysis showed largely unchanged results suggestive of stable and widely applicable results.



| Model | Study name | Subgroup within study | Statistics for each study: Event rate | Lower limit | Upper limit | Z-Value | p-Value | Event rate and 95% CI: -1.00 -0.50 0.00 0.50 1.00 | Weight (Random): Relative weight |
|---|---|---|---|---|---|---|---|---|---|
| | Schechter | 1987 | 0.019 | 0.001 | 0.236 | -2.781 | 0.005 | | 0.97 |
| | How HV | 1994 | 0.040 | 0.006 | 0.235 | -3.114 | 0.002 | | 1.66 |
| | Petrikovsky | 1995 | 0.012 | 0.001 | 0.164 | -3.106 | 0.002 | | 0.98 |
| | Sepulved | 1995 | 0.571 | 0.230 | 0.856 | 0.377 | 0.706 | | 2.45 |
| | Bronshtein | 1996 | 0.068 | 0.022 | 0.191 | -4.372 | 0.000 | | 3.19 |
| | Simpson JM | 1996 | 0.004 | 0.001 | 0.030 | -5.413 | 0.000 | | 1.70 |
| | Dildy GA | 1996 | 0.040 | 0.006 | 0.235 | -3.114 | 0.002 | | 1.66 |
| | achiron R | 1997 | 0.003 | 0.000 | 0.047 | -4.088 | 0.000 | | 0.99 |
| | Bromley B | 1998 | 0.021 | 0.009 | 0.045 | -9.350 | 0.000 | | 4.28 |
| | Wolman I | 2000 | 0.007 | 0.001 | 0.050 | -4.902 | 0.000 | | 1.70 |
| | Tennstedt C | 2000 | 0.500 | 0.168 | 0.832 | 0.000 | 1.000 | | 2.25 |
| | Barsoom MJ | 2001 | 0.004 | 0.001 | 0.030 | -5.422 | 0.000 | | 1.70 |
| | Liu H H | 2002 | 0.023 | 0.003 | 0.147 | -3.694 | 0.000 | | 1.68 |
| | Carrico A | 2004 | 0.082 | 0.035 | 0.182 | -5.176 | 0.000 | | 3.94 |
| | Rebaarber | 2004 | 0.045 | 0.006 | 0.261 | -2.975 | 0.003 | | 1.65 |
| | Wax JR | 2004 | 0.080 | 0.020 | 0.269 | -3.313 | 0.001 | | 2.55 |
| | Bradley KE | 2005 | 0.108 | 0.070 | 0.163 | -8.694 | 0.000 | | 5.37 |
| | Petrikovsky | 2005 | 0.111 | 0.015 | 0.500 | -1.961 | 0.050 | | 1.57 |
| | Lim Louis | 2006 | 0.039 | 0.013 | 0.115 | -5.418 | 0.000 | | 3.24 |
| | Gonclaves | 2006 | 0.027 | 0.014 | 0.049 | -11.205 | 0.000 | | 4.88 |
| | Shanks AL | 2009 | 0.073 | 0.045 | 0.116 | -9.763 | 0.000 | | 5.27 |
| | Hilal K | 2012 | 0.065 | 0.034 | 0.121 | -7.723 | 0.000 | | 4.72 |
| | Shakoor S | 2013 | 0.083 | 0.021 | 0.279 | -3.247 | 0.001 | | 2.55 |
| | Chitra N | 2016 | 0.005 | 0.000 | 0.072 | -3.762 | 0.000 | | 0.99 |
| | Tian YU | 2016 | 0.053 | 0.039 | 0.073 | -17.045 | 0.000 | | 5.77 |
| | Guo Y | 2017 | 0.038 | 0.031 | 0.046 | -31.808 | 0.000 | | 6.04 |
| | Chiu G (I) | 2018 | 0.032 | 0.021 | 0.047 | -16.489 | 0.000 | | 5.57 |
| | Chiu G (II) | 2019 | 0.023 | 0.013 | 0.039 | -12.901 | 0.000 | | 5.07 |
| | Akinmoladu | 2020 | 0.250 | 0.108 | 0.478 | -2.127 | 0.033 | | 3.64 |
| | Ozsurmeli M | 2020 | 0.034 | 0.017 | 0.067 | -9.274 | 0.000 | | 4.63 |
| | Usta CS | 2020 | 0.030 | 0.008 | 0.113 | -4.826 | 0.000 | | 2.63 |
| | Song Y | 2021 | 0.063 | 0.033 | 0.116 | -7.866 | 0.000 | | 4.73 |
| Random | | | 0.048 | 0.036 | 0.064 | -19.410 | 0.000 | | |

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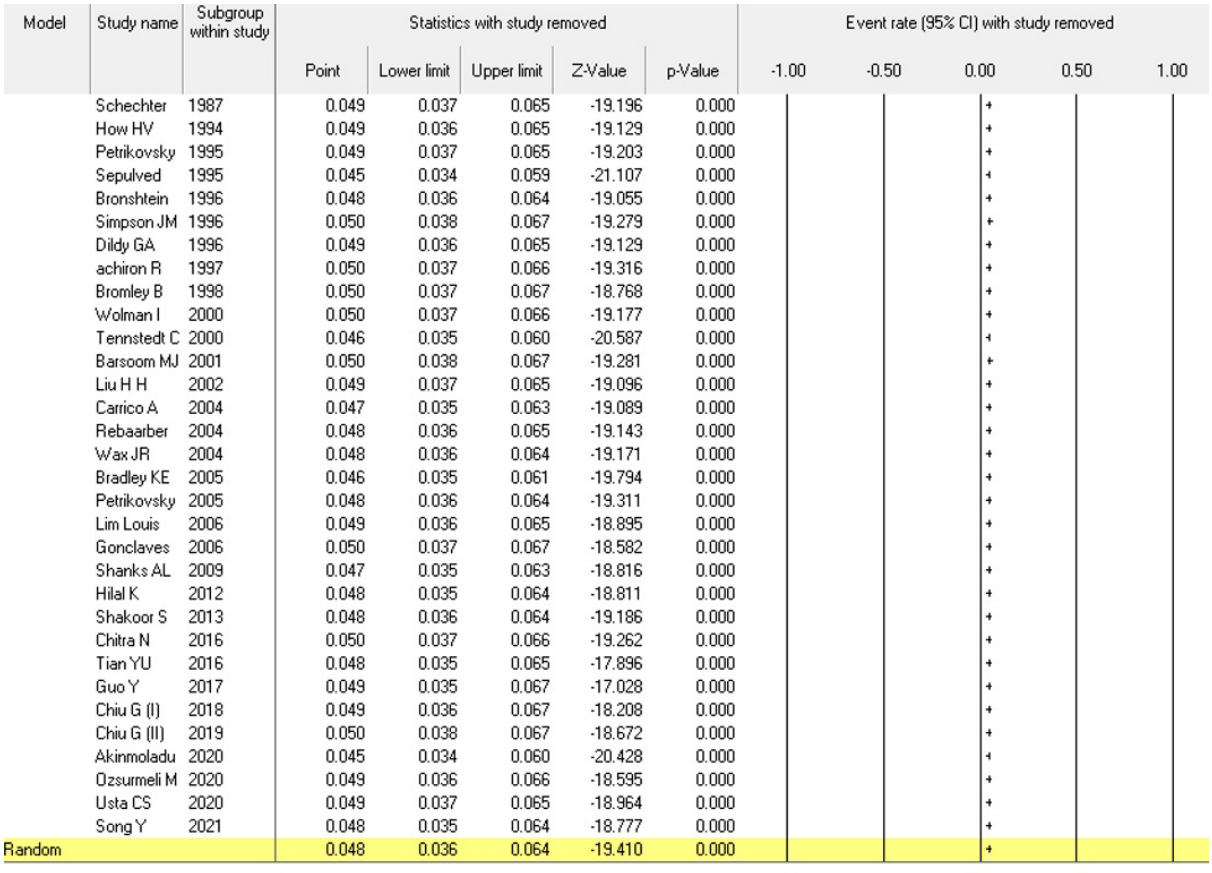
**Figure 2.** Forest plots of cardiac anomalies prevalence among foetus with ICEF



| Model | Study name | Subgroup within study | Statistics with study removed: Point | Lower limit | Upper limit | Z-Value | p-Value | Event rate (95% CI) with study removed: -1.00 -0.50 0.00 0.50 1.00 |
|---|---|---|---|---|---|---|---|---|
| | Schechter | 1987 | 0.049 | 0.037 | 0.065 | -19.196 | 0.000 | |
| | How HV | 1994 | 0.049 | 0.036 | 0.065 | -19.129 | 0.000 | |
| | Petrikovsky | 1995 | 0.049 | 0.037 | 0.065 | -19.203 | 0.000 | |
| | Sepulved | 1995 | 0.045 | 0.034 | 0.059 | -21.107 | 0.000 | |
| | Bronshtein | 1996 | 0.048 | 0.036 | 0.064 | -19.055 | 0.000 | |
| | Simpson JM | 1996 | 0.050 | 0.038 | 0.067 | -19.279 | 0.000 | |
| | Dildy GA | 1996 | 0.049 | 0.036 | 0.065 | -19.129 | 0.000 | |
| | achiron R | 1997 | 0.050 | 0.037 | 0.066 | -19.316 | 0.000 | |
| | Bromley B | 1998 | 0.050 | 0.037 | 0.067 | -18.768 | 0.000 | |
| | Wolman I | 2000 | 0.050 | 0.037 | 0.066 | -19.177 | 0.000 | |
| | Tennstedt C | 2000 | 0.046 | 0.035 | 0.060 | -20.587 | 0.000 | |
| | Barsoom MJ | 2001 | 0.050 | 0.038 | 0.067 | -19.281 | 0.000 | |
| | Liu H H | 2002 | 0.049 | 0.037 | 0.065 | -19.096 | 0.000 | |
| | Carrico A | 2004 | 0.047 | 0.035 | 0.063 | -19.089 | 0.000 | |
| | Rebaarber | 2004 | 0.048 | 0.036 | 0.065 | -19.143 | 0.000 | |
| | Wax JR | 2004 | 0.048 | 0.036 | 0.064 | -19.171 | 0.000 | |
| | Bradley KE | 2005 | 0.046 | 0.035 | 0.061 | -19.794 | 0.000 | |
| | Petrikovsky | 2005 | 0.048 | 0.036 | 0.064 | -19.311 | 0.000 | |
| | Lim Louis | 2006 | 0.049 | 0.036 | 0.065 | -18.895 | 0.000 | |
| | Gonclaves | 2006 | 0.050 | 0.037 | 0.067 | -18.582 | 0.000 | |
| | Shanks AL | 2009 | 0.047 | 0.035 | 0.063 | -18.816 | 0.000 | |
| | Hilal K | 2012 | 0.048 | 0.035 | 0.064 | -18.811 | 0.000 | |
| | Shakoor S | 2013 | 0.048 | 0.036 | 0.064 | -19.186 | 0.000 | |
| | Chitra N | 2016 | 0.050 | 0.037 | 0.066 | -19.262 | 0.000 | |
| | Tian YU | 2016 | 0.048 | 0.035 | 0.065 | -17.896 | 0.000 | |
| | Guo Y | 2017 | 0.049 | 0.035 | 0.067 | -17.028 | 0.000 | |
| | Chiu G (I) | 2018 | 0.049 | 0.036 | 0.067 | -18.208 | 0.000 | |
| | Chiu G (II) | 2019 | 0.050 | 0.038 | 0.067 | -18.672 | 0.000 | |
| | Akinmoladu | 2020 | 0.045 | 0.034 | 0.060 | -20.428 | 0.000 | |
| | Ozsurmeli M | 2020 | 0.049 | 0.036 | 0.066 | -18.595 | 0.000 | |
| | Usta CS | 2020 | 0.049 | 0.037 | 0.065 | -18.964 | 0.000 | |
| | Song Y | 2021 | 0.048 | 0.035 | 0.064 | -18.777 | 0.000 | |
| Random | | | 0.048 | 0.036 | 0.064 | -19.410 | 0.000 | |

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**Figure 3.** Sensitivity analysis of cardiac anomalies prevalence among foetus with ICEF

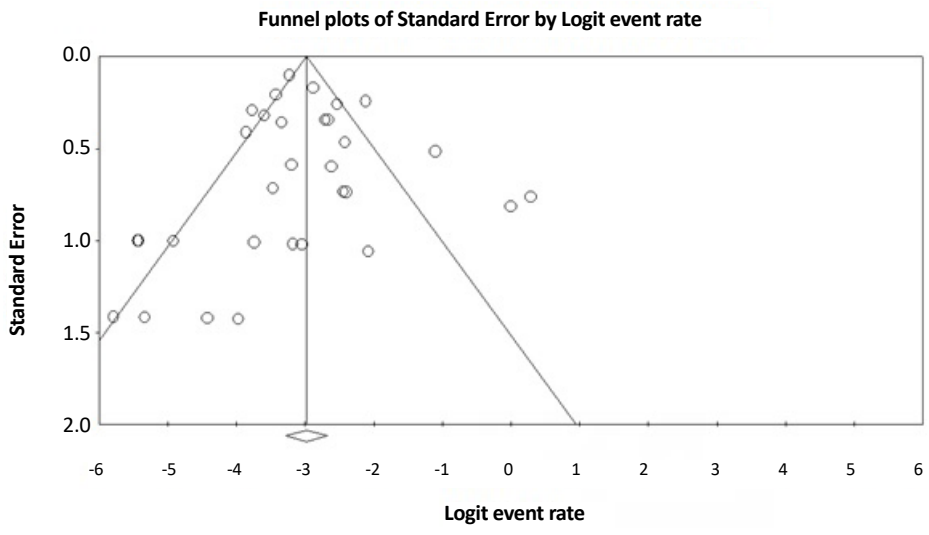


**Figure 4.** Funnel plots of cardiac anomalies prevalence among foetus with ICEF

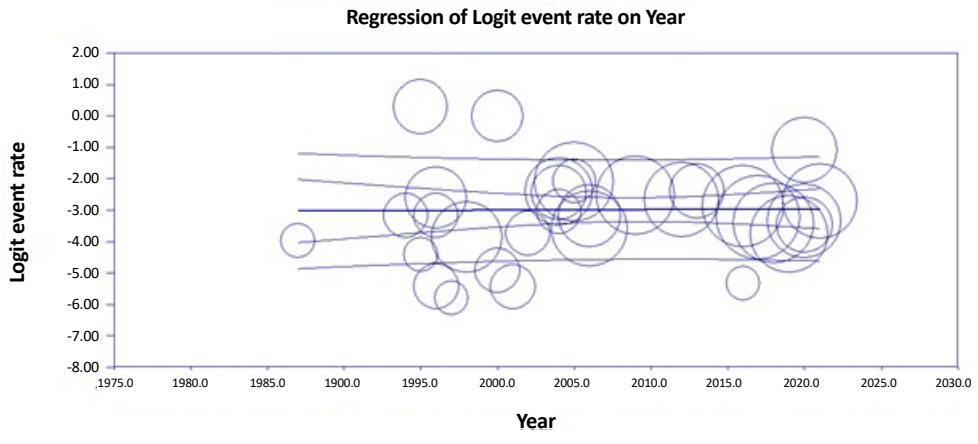


**Figure 5.** Meta-regression of cardiac anomalies prevalence based on years of studies

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In the meta-analysis, significant heterogeneity among studies was reported, and we tried to address heterogeneity with a sensitivity and sub-group analysis that needs to be considered when interpreting the results of this review. The large heterogeneity found in all types of prevalence indicates the existence of characteristics of the studies causing this variability. Furthermore, subgroup analysis was done according to regions, age of the mothers, year in which the study was published, risk of bias, and individual performing ultrasonography to reduce heterogeneity. As per the geographic distribution, the European population (4.3%) was found to have the highest prevalence, followed by the Asian (3.8%) and American people (3.6%). In the included studies in our meta-analysis, no analysis by ethnicity was possible because these articles did not assess this population's characteristics concerning cardiac anomaly and echogenic foci. Therefore, further studies on this aspect would be advisable. In addition, subgroup analysis also showed a higher prevalence of cardiac anomalies associated with ICEF when diagnosed in mothers over the age of 30 years (5.8% vs 3.5%) and at less than 20 weeks of gestational age (3.9% vs 3.7%). In evaluating the studies on gestational age, those studying fetuses during later gestational ages are more sensitive and specific. This outcome could be attributed to increased heart sizes, possible enlargement of the focus with gestational age, and the persistence of EIF display during pregnancy. In the literature, the persistence of EIF in ultrasound scans ranges from 25% to 92.3% [48, 51]. The publication year influenced the lifetime prevalence rates, with the higher prevalence rates reported in the most recent studies. This result seems to be very solid, as in the multiple meta-regression models, publication year was one of the two predictors that achieved a statistically significant relationship with the lifetime prevalence once controlled

by the methodological quality of the studies. A higher prevalence was also observed in studies published after 2000, probably due to improved imaging modalities and increased personnel experience. The same subgroup analysis also shows that prevalence is highest when a fetal medicine specialist performs ultrasonography; thus, showing operator experience is vital in identifying ICEF. The echogenic foci detection sensitivity is higher in medium-/high-quality studies, although not statistically significant; the false positive ratio is also higher. This outcome may be attributable to a greater population selection and ultrasound studies being performed by more trained professionals.

### Strengths and weaknesses of the study

This study's strength is its use of multiple databases to avoid missing any eligible research. Data extraction was also done reproducibly using a pre-set and pre-tested checklist to minimize errors that could affect the estimate. This systematic review and meta-analysis also included studies from different geographical regions worldwide. However, the study is not free from potential limitations, as it is restricted to articles published in English. Also, the articles included in this review are weak to establish a causal relationship between the associated factors and the outcome because they are cross-sectional. As a result, this meta-analysis is helpful if interpreted considering both the inherent limitations of the original studies and the current meta-analysis. There was significant clinical and statistical heterogeneity. The heterogeneity was mainly related to the gestational age at assessment, maternal age, different operators, and the sample size (which ranged from 6 to 2647). Because heterogeneity was anticipated, we used a random-effects model for the meta-analysis. The high statistical heterogeneity was due to the varied prevalence of cardiac anomalies in the fetuses with ICEF in the included studies. Our results enable us to make recommendations for future research in this field.

## Conclusion

The current study represents the first and only meta-analysis concerning the prevalence of cardiac anomaly in the fetus diagnosed with ICEF. Most recent studies seem to show higher prevalence rates than the older ones, and studies with a better methodology tend to show higher lifetime prevalence rates than methodologically poor ones. This study supports a definitive relationship between ICEF and underlying congenital heart disease and chromosomal anomalies such as trisomy 21. We recommend increased training of individuals performing this ultrasonography to improve early detection, ultimately enhancing the care given to infants immediately after delivery. In addition, further longitudinal studies with long follow-ups are necessary to better explore the determinants of cardiac anomaly in the study subjects in resource-limited settings for successful interventions.

## Ethical Considerations

### Compliance with ethical guidelines

The protocol for this systematic review and meta-analysis was registered at the International Prospective Register of Systematic Reviews PROSPERO (Code: #CRD42021253664).

### Funding

This research did not receive any grant from funding agencies in the public, commercial, or non-profit sectors.

### Authors contributions

All authors equally contributed to preparing this article.

### Conflicts of interest

The author declared no conflict of interest.

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