

Stillbirth and its Association with Early Rupture of Membranes in Sub-Saharan Africa: Systematic Review and Meta-Analysis

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Abstract

Background: Stillbirth rate is an important indicator of access to quality antenatal and delivery care services. Many previous pocket studies were conducted to assess the magnitude of stillbirth and its association with premature rupture of membrane. However, the level of stillbirth, as well as its relationship with Premature Rupture of Membrane (PROM) varies from study to study.

Objectives: This systematic review and meta-analysis was conducted to estimate the pooled prevalence of stillbirth and its association with the early rupture of membranes in sub-Saharan Africa. Search strategy: Electronic databases such as PubMed Central PMC, Cochrane library, Medline via Virtual Health Library (VHL), HINARI (Health Inter Network Access to Research Initiative) portal, and Google scholar were used for searching for original articles.

Selection criteria: All Published and unpublished observational studies (prospective and retrospective cohort studies, case-control studies, and cross-sectional studies) that deal with stillbirth and their association with early rupture of membranes in sub-Saharan African women were included.

Data collection and analysis: The extracted data analyses were done using STATA (version.16.0) software. Texts, figures, and tables were used to describe the included original articles. The heterogeneity of the studies was checked by I-squared statistics. A Random-effects method was applied to estimate the pooled prevalence of stillbirth and the effect size of the early rupture of membranes in sub-Saharan Africa. Subgroup analysis was performed based on region (East, West, Central, and Southern Africa) and year of study (before 2015 and after 2015). A funnel plot and Egger's regression test was used to see publication bias.

Main result: Pooled prevalence of stillbirth in sub-Saharan Africa was 6.4% (95% CI: 5.5-7.3). In sub-group analysis, Southern African regions had a higher stillbirth prevalence and the western African regions had a lower than East and Southern Africa. The prevalence of stillbirth in the region is increased from 4.1% (95% CI: 2.2-6.0) before 2015 to 7.1%(95% CI: 5.8-8.3) after 2015. The pooled odds ratio results from seven studies showed the non-significant effect of early rupture of membrane on stillbirth (pooled OR=1.54, 95% CI: 0.26-2.82). According to the regression test (Egger test), there was no small study effects or publication bias (P=0.108).

Conclusions: The pooled prevalence of stillbirth in sub-Saharan Africa was relatively high. The analysis establishes the minimal effects of early rupture of membrane on stillbirth. Therefore, we recommend that strengthening the testing intervention is crucial to reduce the still relatively high stillbirths.

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Keywords: Stillbirth • Early Rupture of Membranes • Sub-Saharan Africa

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Introduction

Stillbirth is defined as a baby born dead (without spontaneous respiration or heartbeat) with >1000 grams' birth weight or after 28 weeks' gestation [1]. The stillbirth rate is an important indicator of access to quality antenatal and delivery care services [2]. Over 2.6 million stillbirths occur each year worldwide and 98% were in low-income and middle-income countries [3]. Among these over two-thirds were in sub-Saharan Africa and southern Asia [4]. Different studies showed that shorter inter-pregnancy intervals are one of the determinant factors for stillbirth [5].

Preterm Premature Rupture of Membranes (PPROM) is defined as rupture of the amnion and chorion before the gestational age of 37 weeks [6]. Premature Rupture of Membranes (PROM) also represents the same problem that occurs, but after the gestational age of 37 weeks [7]. The etiologies of PPRM or PROM are multifactorial, and the prognosis depends on the gestational age [8]. Any kind of infection seems to play a major role, being either a cause or a result of PPRM/PROM [9].

In sub-Saharan Africa Estimate that babies die before the onset of labor or antepartum stillbirths, account for two-thirds of all stillbirths in countries where the mortality rate is greater than 22 per 1,000 births [10].

Stillbirths occur every year at least 2.6 million worldwide [11]. The majority (98%) of stillbirths occurs in low and middle-income countries and more than half (55%) of these happen in rural sub-Saharan Africa [12].

Numerous factors have been associated with an increased risk of stillbirth [13]. Most risk factors of stillbirth that occur during the antepartum and intrapartum period are preventable [14]. From previous studies, preterm birth, increasing maternal age, history of stillbirth, reported preterm and term PROM, hypertension, extremes of neonatal birth weight, cesarean delivery, operative vaginal delivery, and assisted breech delivery were all significantly associated with stillbirth [15].

The fetal outcome varies with the gestational age [16]. The stillbirth rates are 15-43% in PPRM in the 2nd trimester, whereas the stillbirth rate is reduced to 4.5% in PPRM managed expectantly at the gestational age between 24 weeks and 28 weeks [17].

Even though stillbirth represents a large proportion of perinatal death, risk factors and prevalence of stillbirth are lack of pooled data [18]. Therefore, this study thus aimed to evaluate the pooled prevalence of stillbirth and the effect of early rupture of membranes

on stillbirth in sub-Saharan Africa using a more comprehensive database [19]. The findings of this study will be useful in enhancing the capacity of planning and decision making to look for possible solutions to solve the problem in collaboration with concerned stakeholders so as to provide future high-quality antenatal and intrapartum care within the continuum of care for women and children [20]. In addition, the paper may be useful to other researchers as reference while conducting further studies [21].

In this review, Premature Rupture Of Membranes (PROM) risk factors for stillbirth will be discussed [22]. Early identification of PROM risk for stillbirth and appropriate antenatal management may reduce preventable stillbirths and improve general outcomes of pregnancy [23].

Materials and Methods

The protocol and registration

The results of this systematic review and meta-analysis were reported based on the Preferred Reporting Items for Systematic Review and Meta-Analysis statement (PRISMA) guideline [24]. The researchers tracked the flowchart from the PRISMA guideline recommendation to show the selection process from initially identified records to finally included studies [25]. The protocol for this review was registered on the International Prospective Register of Systematic Reviews (PROSPERO) with registration number CRD42020171329 [26].

Data sources and searching strategy

Comprehensive searching for articles began on August 15-30, 2020 [27]. Articles from Electronic databases such as PubMed Central® (PMC), Cochrane library, Medline via Virtual Health Library (VHL), HINARI (Health Inter Network Access to Research Initiative) portal, and Google scholar search were searched without time restriction of the publication date [28].

In addition to this, the references list of relevant studies and manual searching of the relevant publication are retrieved [29]. The search was based on the combination of the following special index search terms using Medical Subject Headings (MeSH) and Boolean operations was applied [30].

The Mesh term was stillbirth or perinatal death or perinatal mortality and sub-Sahara countries (Figure 1)[31,32].

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PMC (((stillbirth[MeSH Terms] OR perinatal death) OR perinatal mortality) AND
PROM) AND Africa south of the Sahara

(((stillbirth[MeSH Terms] OR ("perinatal death"[MeSH Terms] OR ("perinatal"[All
Fields] AND "death"[All Fields]) OR "perinatal death"[All Fields]) OR ("perinatal
mortality"[MeSH Terms] OR ("perinatal"[All Fields] AND "mortality"[All Fields]) OR
"perinatal mortality"[All Fields] OR "perinatal death"[MeSH Terms] OR ("perinatal"[All
Fields] AND "death"[All Fields]) OR "perinatal death"[All Fields] OR ("perinatal"[All
Fields] AND "mortality"[All Fields]))) AND ("fetal membranes, premature
rupture"[MeSH Terms] OR ("fetal"[All Fields] AND "membranes"[All Fields] AND
"premature"[All Fields] AND "rupture"[All Fields]) OR "premature rupture fetal
membranes"[All Fields] OR "prom"[All Fields])) AND ("africa south of the
sahara"[MeSH Terms] OR ("africa"[All Fields] AND "south"[All Fields] AND
"sahara"[All Fields]) OR "africa south of the sahara"[All Fields])

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Figure 1. Terms used in PubMed search.

Inclusion and exclusion criteria

All Published and unpublished observational studies (prospective and retrospective cohort studies, case-control studies, and cross-sectional studies) that deal with stillbirth and their association with early rupture of membranes in sub-Saharan African women were included [33]. Articles, case series/reports, patient stories, expert opinions, discussion papers (guidelines), letters, and Citations without abstract and/or full-text, anonymous reports, editorials, systematic re-views, and meta-analyses and qualitative studies which published other than the English language were excluded from the analysis [34].

Study selection

In the selection of this study, the following procedures were followed [35]. At first, retrieved studies were exported into Endnote Citation Management Software (Endnote x8) [36]. Then, they were imported to covalence Software for screening the title and abstract, full-text as per inclusion and exclusion criteria, and to assess the quality of the studies, then remove duplicate studies [37]. After that, the two independent reviewers screened the title and abstract, then full-text as per inclusion and exclusion criteria [38]. Two independent authors conducted the abstract and full-text review [39]. The disagreement between the two reviews was handled through a discussion [40]. Finally, in the case of further disagreement, other authors (BS) made the final decisions [41].

Quality assessment

Two independent authors (BS and TY) appraised the quality of studies to assess the extent of quality and eligibility of the study and to determine the extent to which a study has minimized the possibility of bias at the designing, conducting, and analyzing stage [42]. The Joanna Briggs Institute (JBI) quality appraisal checklist was used. Studies were considered low risk when it scored more than half of the quality assessment indicators [43]. Thus, the inter observer agreement for data abstraction was measured using weighted kappa statistics [44].

Data extraction

Two independent reviewers extracted data using a structured data extraction form of Microsoft Excel spreadsheet include the author's name, year of publication, the country; where the study was undertaken, the study design, the sample size, the objective of the study, statistical model, and measure of association of odd ratio with its confidence interval are also extracted using the above form, and whenever variations of extracting data were observed, the phrase was repeated [45]. If discrepancies between data extractors continued, the third reviewer would involve [46]. The name of the first author and year of publication, study design, sample size, the objective of the study, quality, statistical model, and effect size were collected [47].

Statistical analysis

The extracted data analyses were done using STATA (version. 16.0) software [48]. Texts, figures, and tables were used to describe the included original articles [49]. Random-effects methods were applied to estimate the pooled prevalence of stillbirth and the effect size of early rupture of membranes in sub-Saharan Africa was presented with a 95% Confidence Interval (CI) [50]. Considering the relatively high variance between studies, the random effect model was used to report the effect size [51]. Additionally, subgroup analysis was performed based on region (East, West, Central, and Southern Africa) and year of study (before 2015 and after 2015) [52]. Heterogeneity and Publication bias were observed using I-squared statistic and funnel plot respectively, I^2 values 25%, 50%, and 75% are classified as low, medium, and high heterogeneity, respectively [53]. Publication bias was checked by the funnel plot and more objectively through Egger's regression test (Figure 2) [54].

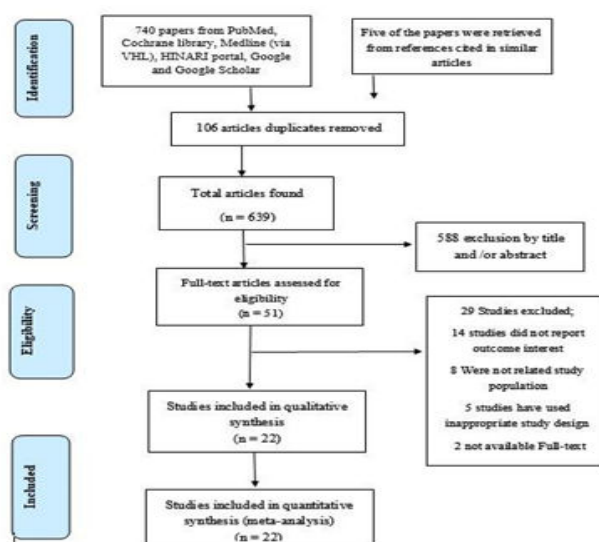


Figure 2. Funnel plot of the pooled effect of early rupture of membrane on stillbirth.

Results

Study characteristics

About 745 studies were retrieved through the electronic database search [55]. Among these, 106 duplicated were removed, and 588 were excluded based on the screening of titles and abstracts [56]. Still the remaining 51 full-text articles and 29 articles were excluded based on various criteria [57]. Many studies have been excluded due to different reasons: Fourteen studies did not report the outcome of interest; 8 were not related to study population; five studies have used inappropriate study design (case series/reports, systematic reviews, and meta-analyses and qualitative studies) [58]. Still, the

other five studies have used inappropriate study design and two have not available in full-text (Figure 1) [59].

On the other hand, of the 22 studies included in this review, 10 of them were found in Ethiopia, the others two in Zambia, Nigeria, and Cameroon, one in South Africa, Tanzania, Guinea-Bissau, Ghana, Kenya, and Zimbabwe [60]. Regarding the quality of studies assessed by JBI quality appraisal criteria established for cross-sectional, case-control, and cohort studies were used [61]. The quality of the studies included in this systematic review and meta-analysis had no considerable risk (Table 1) [62].

First publication year	author,	Country	Study design	Sample size	Statistical model	Effect size Measure	Quality
Tilahun D and Assefa T		Ethiopia	Cross-sectional	422	Logistic regression	OR	Low risk
Anu N.B et al.		Cameroon	Retrospective cross-sectional	3563	Not use statistics		Low risk
Dassah E.T et al.		Ghana	Retrospective cross-sectional	12190	Logistic regression	OR	Low risk
Suleiman B.M et al.		Nigeria	Case-control	176	Logistic regression	OR	Low risk
Gwako G.N et al.		Kenya	unpaired case-control	642	Logistic regression	OR	Low risk
Adane A.A et al.		Ethiopia	Cross-sectional	481	Logistic regression	OR	Low risk
Kassahun E.A et al.		Ethiopia	Cross-sectional	462	Logistic regression	OR	Low risk
Mengesha S and Dangisso M.H (2020)		Ethiopia	Cross-sectional	374	Logistic regression	OR	Low risk
Stringer E.M, et al.		Zambia	Retrospective cohort	100,454	Logistic regression	OR	Low risk
Chuwa F.S, et al.		Tanzania	Retrospective cohort	38,568	Logistic regression	OR	Low risk
Bjerregaard-Andersen M. et al.		Guinea-Bissau	Retrospective cohort	7731	Logistic regression	Prevalence Ratio	Low risk
Mengistie A and Andualem M		Ethiopia	Cross-sectional	310	Logistic regression	OR	Low risk
Madhi SA, et al.		South Africa	Prospective cross-sectional	354	Not use statistics		Low risk
Berhe T, et al.		Ethiopia	Cross-sectional	573	Logistic regression	OR	Low risk
Lakew D, et al.		Ethiopia	Cross-sectional	2555	Logistic regression	OR	Low risk
Yadeta T.A, et al.		Ethiopia	Cross-sectional	1688	Logistic regression	OR	Low risk
Chaibva B.V, et al.		Zimbabwe	Retrospective Cross-sectional	346	Logistic regression	OR	Low risk
Miyoshi Y, et al.		Zambia	Retrospective Cross-sectional	1704	Not use statistics		Low risk
Okonofua F.E, et al.		Nigeria	Cross-sectional	4416	Logistic regression	OR	Low risk
Mesfin F, et al.		Ethiopia	Cross-sectional	574	Logistic regression	OR	Low risk
Worede D.T and Dagnew G.W		Ethiopia	unmatched case-control	420	Logistic regression	OR	Low risk
Egbe T.O, et al.		Cameroon	unmatched case-control	576	Logistic regression	OR	Low risk

Table 1. Summary characteristics of the included studies in systematic review and meta-analysis.

In general, 22 studies were included in the systematic review out of which 18 are used for the meta-analysis. Eighteen studies were used for prevalence and 7 studies for the effect of PROM. All the included studies utilized data were collected from health facilities.

Because of the high heterogeneity observed across studies ($Q=1011.806$, $p<0.0000$; $I^2=98.320\%$ and Tau-squared, $p=0.000$), both inverse-variance fixed-effect and a random-effects model was

used for the meta-analysis to estimate the pooled prevalence of stillbirth and the effect of early membranes rupture on stillbirth (Figure 3).

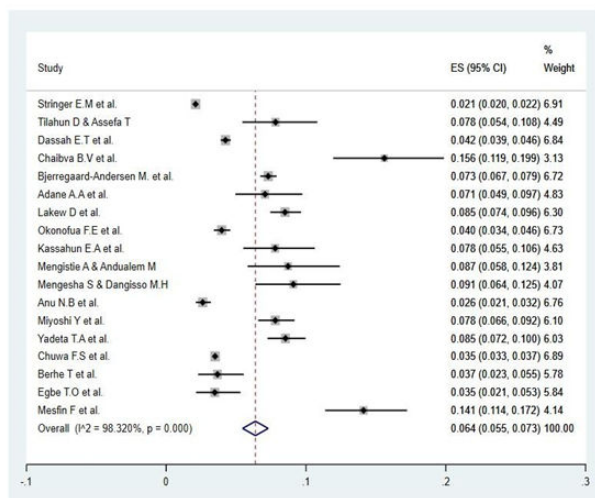


Figure 3. The meta-analysis and forest plot of pooled prevalence of stillbirth in sub-Saharan Africa.

After detail review was done, 22 studies (15 cross-sectional, 3 retrospective cohort studies, and 4 case-control studies) met the inclusion criteria. Of the included studies, the maximum sample size was 100,454 and 176 minimum sample size. Overall, the studies included in our review were of high quality.

Meta-analysis of stillbirth

The meta-analysis of 18 studies, according to the random-effects model, revealed that the pooled prevalence of Stillbirth in sub-Saharan Africa was 6.4% (95% CI: 5.5-7.3) (Figure 1).

The subgroup analysis by geographical region indicated 7.8% (95% CI: 5.6-10) pooled prevalence of Stillbirth in Eastern Africa (Ethiopia and Tanzania), 8.2% (95% CI: 2.5-13.8) in Southern Africa (Zambia and Zimbabwe), and 4.3% (95% CI: 2.8-5.9) in Western Africa (Nigeria, Guinea-Bissau, Ghana, and Cameroon) (Figure 4).

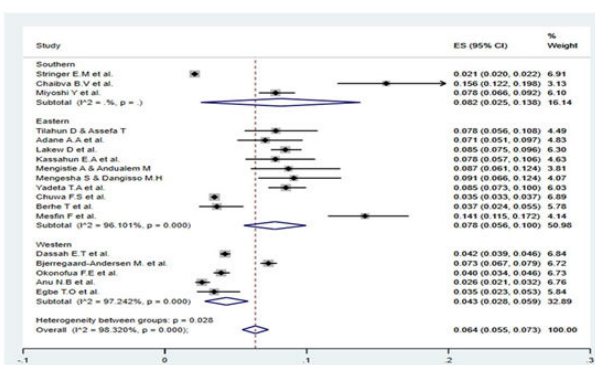


Figure 4. PRISMA flow diagram for article selection and screening.

The pooled prevalence before and after Sustainable Developmental Goals (SDGs) or before 2015 was 4.1% (95% CI: 2.2-6.0) and found 7.1% (95% CI: 5.8-8.3) after (SDGs). The

heterogeneity observed across group ($p=0.028$; $I^2=98.320\%$ and Tau-squared, $p=0.000$). (Figure 3) In before, (SDGs) 3 studies and 15 studies include after (SDGs) or 2015. The heterogeneity observed across group ($p=0.012$; $I^2=98.320\%$ and Tau-squared, $p=0.000$) (Figure 5).

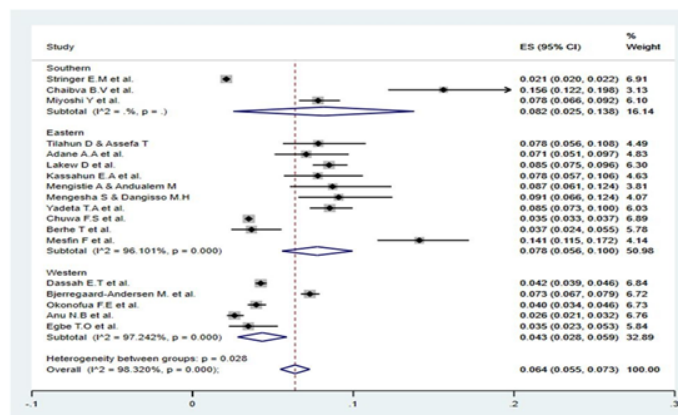


Figure 5. A subgroup meta-analysis of Stillbirth prevalence by geographical region.

The Cumulative random-effects meta-analysis of 18 studies showed the pattern of prevalence on stillbirth and its significance over time of publications.

The Cumulative meta-analysis showed a decreasing trend of the effect of early rupture of membrane on stillbirth (Figures 6 and 7).

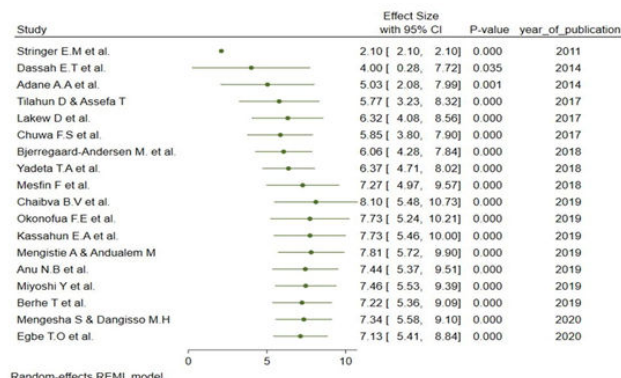


Figure 6. Cumulative meta-analysis of prevalence on stillbirth based on years of publication.

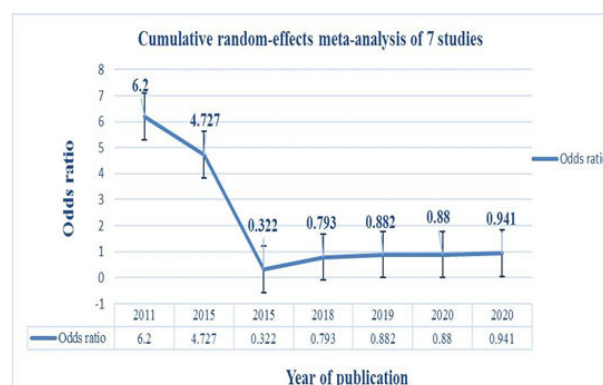


Figure 7. Cumulative meta-analysis of stillbirth based on years of publication.

An effect of early rupture of membrane on stillbirth

The pooled effects of seven studies that were analyzed according to the random-effects model in sub-Saharan Africa revealed that the pooled odds ratio results showed the non-significant effect of early rupture of membrane on stillbirth (pooled OR=1.54, 95% CI: 0.26-2.82). Therefore, the analysis establishes the minimal effects of early rupture of membrane on stillbirth. Low heterogeneity observed across studies ($Q=13.14$, $p=0.041$; $I^2=54.3\%$ and Tau-squared, $p=0.018$) and a random-effects model was used to report the pooled effect (Figure 8).

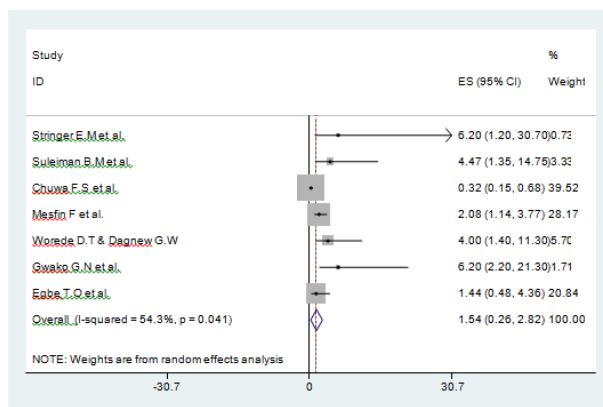


Figure 8. A subgroup meta-analysis of stillbirth prevalence by the year of study.

Publication bias

The presence of small-study effects/publication bias was examined using a regression test (Egger test). The test result indicated that the minimal small study effects or publication bias ($P=0.108$)

Discussion

The current meta-analysis estimated the pooled prevalence of Stillbirth, 6.4% (95% CI: 5.5-7.3) in sub-Saharan Africa using 18 studies (Figure 9).

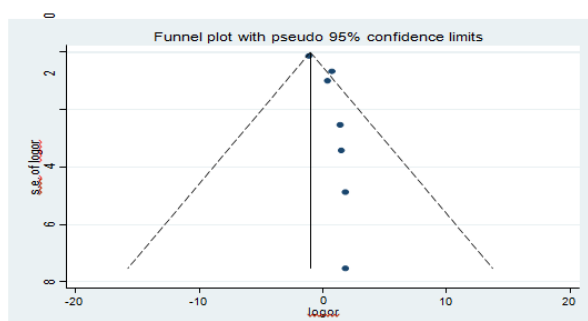


Figure 9. The meta-analysis of the pooled effect of early rupture of membrane on stillbirth in sub-Saharan Africa.

The current finding is higher than a systemic review from sub-Saharan African countries where the prevalence of stillbirth ranged

from 2.1 to 3.3% (53). However, studies reported in East and Southern African regions had a higher stillbirth prevalence among pregnant women 7.8% (95% CI: 5.6-10), 8.2% (95% CI: 2.5-13.8) respectively. The differences in the prevalence of stillbirth mainly reflect the risk profiles of the populations included in the studies.

Moreover, the findings indicate that certain regions in sub-Saharan Africa exhibit a particularly higher prevalence of stillbirth. The current review also showed that the prevalence of stillbirth has remained to be high in the South African region. Even though a decreasing trend was observed, the prevalence of stillbirth was the highest in East Africa followed by the Southern part of Africa. The regional differences in the prevalence of stillbirth could be because of differences in the strength of programs for primary prevention, quality of ANC follow-up, and delivery service programs.

Furthermore, most of the studies that were included in the analysis were facility-based studies. The included studies heterogeneity of the results might have biased the true estimate of stillbirth in the region; the review protocol for the current review has been registered. Any disagreements between the reviewers were resolved through discussion, and inter-observer agreement between the reviewers was assessed using the Cohens Kappa coefficient the kappa statistics 77% (0.77) which showed substantial agreement between the reviewers with regard to study quality score.

Conclusion

Generally, the analysis showed a high prevalence of stillbirth in Sub-Saharan Africa, and it revealed that the pooled odds ratio results showed the non-significant effect of early rupture of membrane on stillbirth. Therefore, the analysis establishes the minimal effects of early rupture of membrane on stillbirth. Therefore, we recommend Implications for policy and practice while these findings showed, the pooled odds ratio results showed the non-significant effect of early rupture of membrane on stillbirth. Therefore, the analysis establishes the minimal effects of early rupture of membrane on stillbirth. Many stillbirths could be prevented if pregnant women had access to quality peri-conceptional care and ANC during pregnancy, skilled attendance at birth, and emergency obstetric care for complications. Proper antepartum care, manage medical and obstetric conditions Interventions with a proven and potential effect on stillbirth prevention care, and strengthening the testing are recommended. In strategically advocating for stillbirth prevention, existing maternal and newborn health initiatives can and must be galvanized to include stillbirth prevention as part of their advocacy for resources. Many of the interventions that can impact stillbirths are also of benefit to mothers and newborns. Even in developed countries, the fact that stillbirths constitute close to 1% of all births should alert policy-makers to initiate audit procedures to identify avoidable cases and take action.

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