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The Impacts of Fluconazole on Invasive Fungal Infection, Colonization, and Overall Mortality in Preterm Infants: An Updated Systematic Review and Meta-Analysis

Tiehui Huang[1*], Xue Zhang[1], Xueqiao Lei[1]

[1] Department of Pediatrics, Zhongshan Hospital of Traditional Chinese Medicine, Zhongshan City, China

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ABSTRACT

Objective: Invasive fungal infection is not uncommon in preterm infants, and fluconazole has been reported to prevent fungal infection. The impacts of fluconazole on invasive fungal infection in preterm infants can be evaluated using an updated systemic review and meta-analysis of randomized clinical trials.

Methods: The log risk ratio was transformed using the risk ratio and 95% confidence interval to assess the impacts of fluconazole on fungal infection in preterm infants. After selection, eleven randomized clinical trials of 1097 preterm infants with fluconazole prophylaxis and 953 preterm infants in the control group were enrolled. The focused outcome was the risk ratio and 95% confidence interval of fungal infection in each included study.

Results: In the fluconazole prophylaxis group, the significantly lower risk of invasive fungal infection was found in preterm infants. In addition, a similar significantly lower risk of colonization or mortality was found in preterm infants with fluconazole prophylaxis. However, the significantly high heterogeneity was observed in the pooled synthesis of invasive fungal infection.

Conclusion: In the updated systematic review and meta-analysis, the preterm infants with fluconazole prophylaxis had a lower risk of invasive fungal infection, colonization, and mortality when compared to the control group. However, the substantial heterogeneity of invasive fungal infection should be considered during the interpretation of our meta-analysis results.

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*** Corresponding Author:** Tiehui Huang, *Hth18933389288@outlook.com*

Introduction

Preterm infants are vulnerable to multiple kinds of complications, especially those with very low birth weight or extremely low birth weight. Among the complications, invasive fungal infection, invasion to the human body by fungi, leads to inflammatory reactions, intraventricular hemorrhage, neurological sequelae (around 60%), tissue damage, injury of myocardium, injury of kidney and liver, retinopathy, and chronic pulmonary disease, and even death in preterm infants with very low birth weight or extremely low birth weight.[1,3] Invasive fungal infection occurred in 2-8% of preterm infants with very low birth weight, which might lead to the mortality rate of 19.3%.[4] It also occurred in 10-16% of preterm infants with extremely low birth weight. The most popular pathogen of invasive fungal infection is Candida.[5] According to the latest report of Engbers et al., the increase of invasive fungal infection in neonatal intensive care units might be related to the following phenomenon in the modern style of pediatric treatment: the increased use of antibiotics, more preterm infants in neonatal intensive care units, increased use of invasive procedures, and advanced life support systems.[6] Therefore, it is very important for the clinicians to focus on this issue and develop the prophylaxis to prevent the invasive fungal infection in preterm infants.

Fluconazole is an option for the prophylaxis of invasive fungal infection. It has been proven to be effective to reduce the fungal colonization in the gastrointestinal system, respiratory system, and skin.[7,8] It might be related to the antifungal activity of fluconazole via the interaction with lanosterol-14-alpha-demethylase, a kind of cytochrome P450 enzyme that is responsible for ergosterol formation.[9] In addition, the previous randomized clinical trial (RCT) also revealed that fluconazole prophylaxis might provide the advantage of decreasing the risk of invasive fungal infection and consequent mortality due to invasive fungal infection.[10] However, the fluconazole prophylaxis was still not routinely given in preterm infants with low birth weight, which might be due to the concerns of an increased risk of conjugated hyperbilirubinemia or impaired liver function.[11] To investigate the effectiveness of fluconazole prophylaxis, the authors designed an updated systematic review and meta-analysis for the prophylactic use of fluconazole in the risk of invasive fungal infection, fungal colonization, and overall mortality in the preterm infants with very low birth weight and extremely low birth weight. According to the above literature, the authors hypothesized that fluconazole prophylaxis might reduce the risk of invasive fungal infection, fungal colonization, and overall mortality in the preterm infants.

Methods

Inclusion criteria

The following keywords: “preterm”, “premature”, “infant”, “very low birth weight”, “extremely low birth weight”, “fluconazole”, “antifungal”, “invasive”, “fungal”, “fungus”, “infection”, “prevention”, “treatment”, “prophylaxis”, “prophylactic”, or “randomized”, “clinical”, “trial”, “study”, “control”, “comparison” were used to search and collect the related prospective RCT articles in Web of Science, PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), ScienceDirect, and EmBase. The published deadline of included articles was before July 2024.

The eligible criteria in the included studies were as follows:[1] The comparison between fluconazole prophylaxis and control in preterm infants with very low birth weight or extremely low birth weight.[2] The studies focused on the outcome profile for the invasive fungal infection risk, fungal colonization risk, or overall mortality risk in adjusted risk ratio (RR) due to multiple confounding factors.[3] The studies focused on the outcome of the invasive fungal infection risk in the adjusted RR-associated 95% confidence interval (95% CI).[4] Published in the English language style in the journals of science citation index database.[5] Diagnostic criteria for invasive fungal infection and preterm infant were based on hospital records or a national database.[6] Very low birth weight criteria were set below 1500 g, and extremely low birth weight criteria were set below 1000 g.

Risk of bias assessment and data collection

The meta-analysis study was conducted based on the Cochrane Handbook for Systematic Reviews and Interventions. The results were reported according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines.[12] The risk of bias for each included study was assessed by using the Cochrane Collaboration Revised Risk of Bias tool for randomized clinical trials (RoB 2.0, version 22 August 2019, facilitated by Cochrane RoB 2:

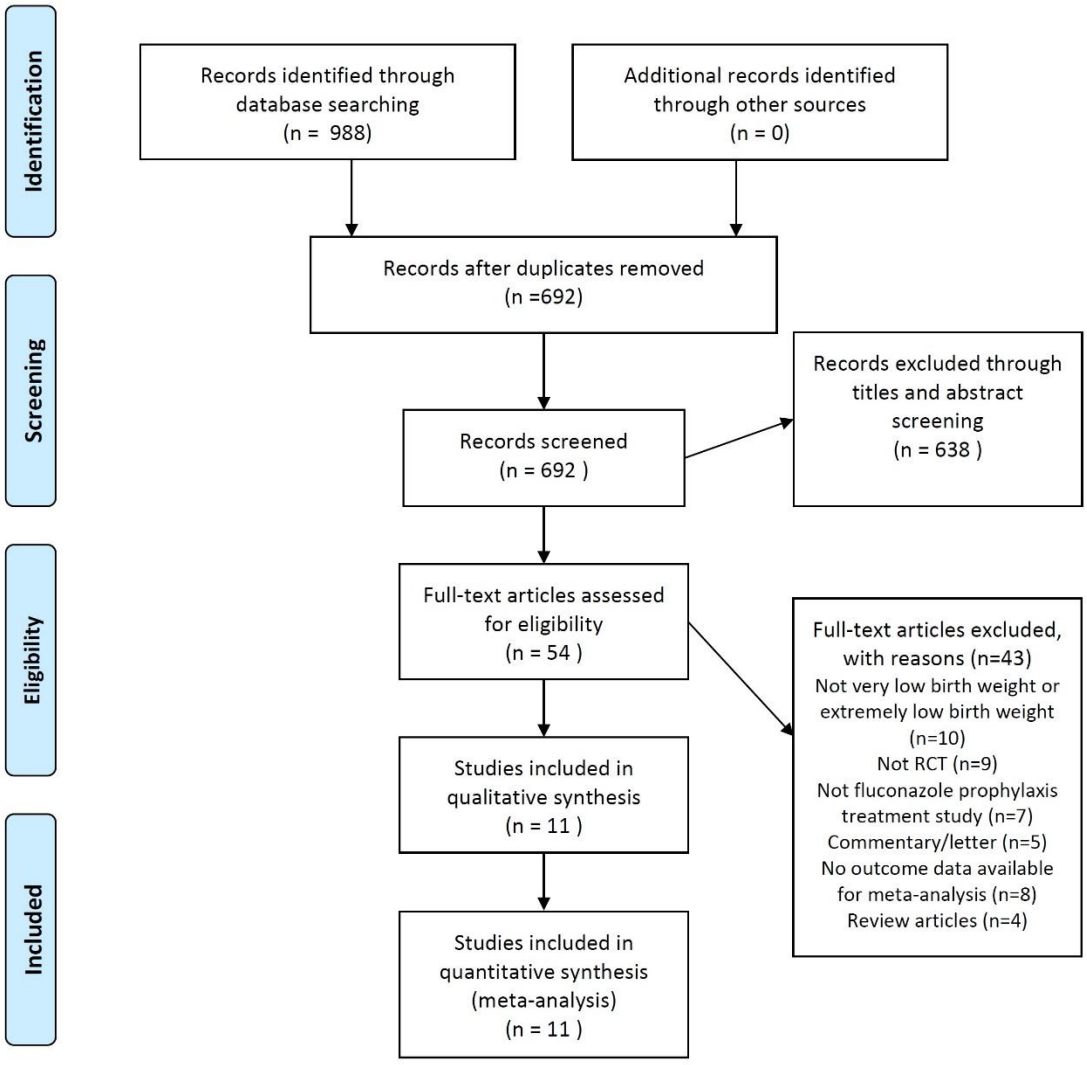

Figure 1. The PRISMA flow diagram of current meta-analysis

Learning Live series). (https://www.riskofbias.info/).

The following data were collected: First, the RR and 95% CI of invasive fungal infection risk for preterm infants with fluconazole prophylaxis when compared to preterm infants with control treatment. Second, the RR and 95% CI of fungal colonization risk for preterm infants with fluconazole prophylaxis when compared to preterm infants with control treatment. Third, the RR and 95% CI of overall mortality risk for preterm infants with fluconazole prophylaxis when compared to preterm infants with control treatment.

Data extraction and critical appraisal

HT and ZX independently screened the abstracts and collected the full text version of the selected citations. Then the extraction of clinical outcome data from the text, tables, and figures of the included articles was performed independently by each reviewer for the data of the adjusted RR and 95% CI of depression for the invasive fungal infection risk, fungal colonization risk, or overall mortality risk of preterm infants with fluconazole prophylaxis and with control treatment. Then a collaborative review was performed by the authors, and the agreement reached kappa=0.9. All authors also reviewed the final results.

Meta-analysis and statistical analysis

For the invasive fungal infection risk, fungal colonization risk, and overall mortality risk, we generated pooled estimates of RR along with the associated 95% CI. Due to the lack of patient-level data, we used summary statistics for each trial by extracting the reported RRs. The Cochrane Collaboration Review Manager Software Package (Rev Man Version 5.4, The Cochrane Collaboration, London, United Kingdom) was applied in the current meta-analysis, and the Mantel-Haenszel OR using

DerSimonian and Laird's random-effect models was calculated. The Mantel-Haenszel method was used to calculate and estimate the adjusted RR of the overall and adjusted effect for prophylactic fluconazole treatment by pooling specific adjusted RR. DerSimonian and Laird's random-effect models were applied under the assumption that different studies were investigating different but related intervention effects and were used to incorporate the heterogeneity among the between-study intervention effects. The log-RRs were obtained from the adjusted RR and the start of the 95% CI using the Rev Man calculation function. The risk estimates of individual studies were combined via an inverse variance weighed average of log RRs in the random-effects model. In addition, the random and fixed effects models were used with an inverse variance function weighted log RR. The Chi-square tests and derived I^2 statistics were used to estimate the statistical heterogeneity of the included studies in the current meta-analysis.

Results

The included studies

The selection process for the included articles is presented in **Figure 1.** The qualitative analysis of the included eleven articles,[10,32,22] was performed, and the eleven studies were included in the current meta-analysis **(Table 1).**

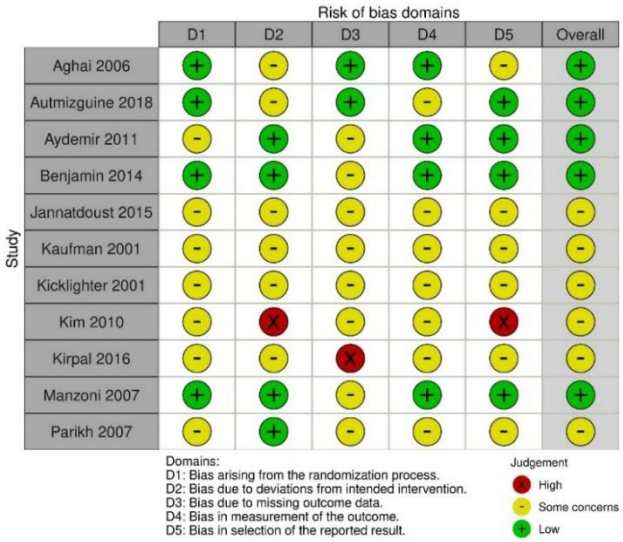

Figure 2. The risk of bias assessment

The risk of bias assessment

The risk of bias assessment was presented in **Figure 2.** The funnel plot was presented in **Figure 3** to evaluate the publication bias.

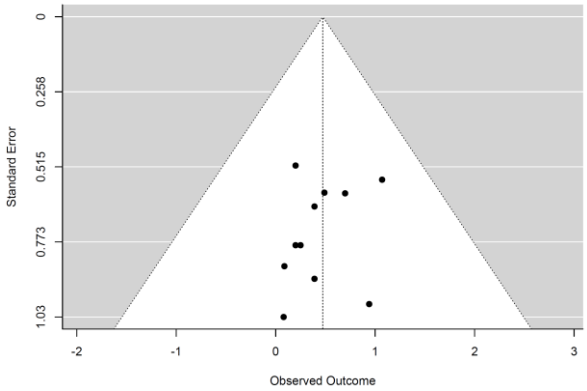

Figure 3. The funnel plot

Meta-analysis results

The risk of invasive fungal infection in preterm infants with fluconazole prophylaxis

The I^2 was 63 %, which demonstrated substantial heterogeneity. The test for overall effect was Z=3.67 (p=0.002) and the meta-analysis results showed that preterm infants with fluconazole prophylaxis had the significantly lower log RR of invasive fungal infection (RR: 0.40, 95% CI: 0.25~0.65) when compared to the control group under the random effects model **(Figure 4).**

The risk of fungal colonization in preterm infants with fluconazole prophylaxis

The I^2 was 0 %, which indicated the low heterogeneity. The test for overall effect was Z=9.15 (p<0.00001) and the meta-analysis results showed that preterm infants with fluconazole prophylaxis had the significantly lower log RR of colonization risk (RR: 0.31, 95% CI: 0.24~0.40) when compared to the control group under the random effects model **(Figure 5).**

The risk of overall mortality in preterm infants with fluconazole prophylaxis

The I^2 was 0 %, which indicated the low heterogeneity. The test for overall effect was Z=2.55 (p=0.01) and the meta-analysis results showed that preterm infants with fluconazole prophylaxis had the significantly lower log RR of overall mortality risk (RR: 0.76, 95% CI: 0.62~0.94) when compared to the control group under the random effects model **(Figure 6).**

Subgroup analysis of extremely low birth

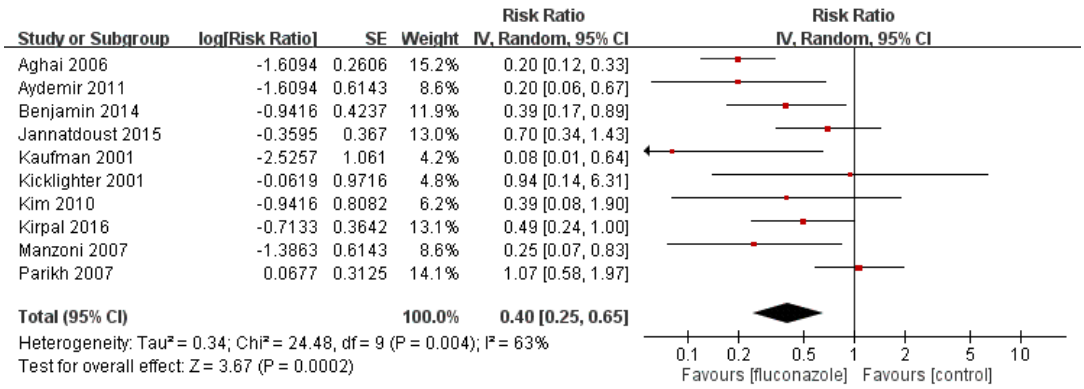

Figure 4. A lower risk of invasive fungal infection in preterm infants with fluconazole prophylaxis

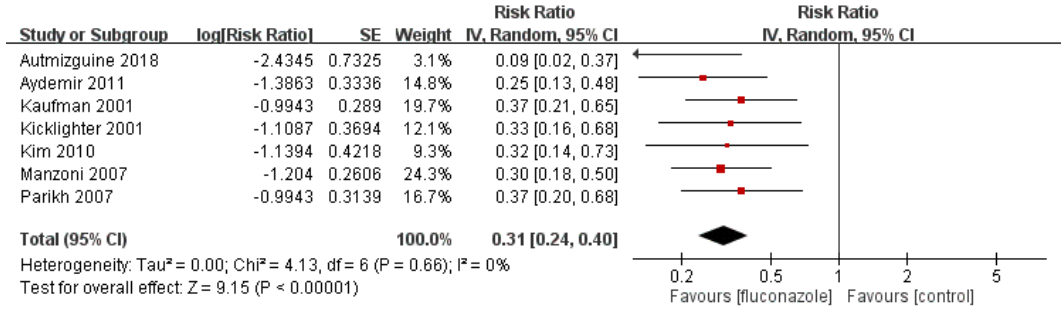

Figure 5. A lower risk of fungal colonization in preterm infants with fluconazole prophylaxis

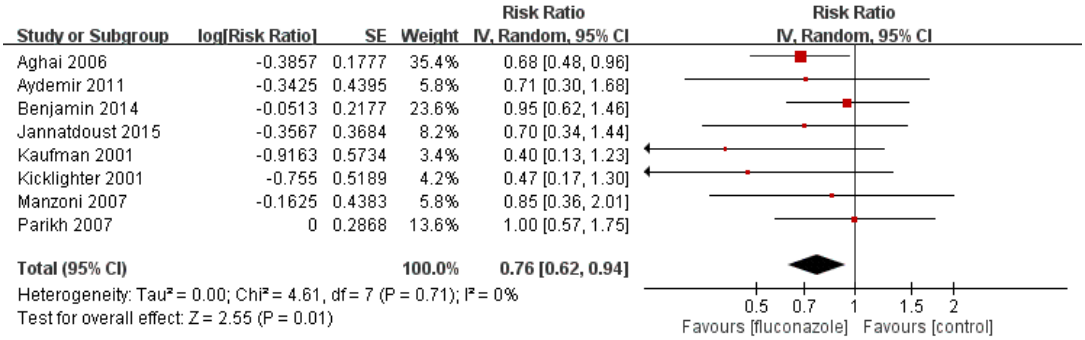

Figure 6. A lower risk of overall mortality in preterm infants with fluconazole prophylaxis

Weight subgroup and very low birth weight subgroup

The subgroup analysis findings of the extremely low birth weight subgroup remained significant in the reduction of the risk of invasive fungal infection, fungal colonization, and overall mortality. However, the subgroup analysis findings of the very low birth weight subgroup only remained significant in the reduction of the risk of invasive fungal infection and fungal colonization. The subgroup analysis findings of the very low birth weight subgroup were not significant in the reduction of the risk of overall mortality (p=0.29).

Sensitivity analysis results

The sensitivity analysis showed the robustness of the meta-analysis results, which were not skewed by a single study.

Certainty of evidence

Our research staff judged that the risk of bias in individual studies was not significant enough to influence the risk of bias in the body of evidence. Low imprecision and indirectness were found in the body of evidence. However, a high level of inconsistency was observed. The publication bias was moderate based on the impression of the funnel plot. The quality of evidence assessed by GRADE for the body of evidence was moderate.

Discussion

The current results suggested that prophylactic fluconazole treatment might be beneficial for decreasing the risk of invasive fungal infection, fungal colonization, or overall mortality in preterm

Table 1. Summary of included studies

	Subjects (fluconazole prophylaxis vs control)	Fluconazole prophylaxis dose and administration	Study design	Outcome
Aghai 2006	140 vs 136 Extremely low birth w eight	3 mg/kg, Intravenous or through a gastric tube, once every three days for 6 weeks	Fluconazole vs. placebo	Invasive fungal infection, overall mortality
Autmizguine 20 18	188 vs 173 Preterm infants with birth weight < 750 g	6 mg/kg Intravenous or through a gastric tube for 6 weeks	Fluconazole vs. placebo	Fungal colonization
Aydemir 2011	93 vs 91 Very low birth weight	3 mg/kg, Intravenous or through a gastric tube, once every three days for 6 weeks	Fluconazole vs. placebo	Invasive fungal infection, overall mortalit-y, fungal colonizat-ion
Benjamin 2014	188 vs 173 Preterm infants with birth weight < 750 g	6 mg/kg Twice weekly, Intravenous or through a gastric tube for 6 weeks	Fluconazole vs. placebo	Invasive fungal infection, overall mortality
Jannatdoust 201 5	43 vs 50 Birth weight < 1250 g and gestational age < 32 weeks	3 mg/kg, Intravenous; Once every 3 days for the first 2 weeks, once every 2 days for the second 2 weeks and once daily for the thir d 2 weeks for 6 weeks	Fluconazole vs. placebo	Overall mortality
Kaufman 2 001	41 vs 40 Extremely low birth w eight	3 mg/kg Mode A: Every 3 days * 2 weeks, then every 2 days * 2 weeks; e very day * 2 weeks; Mode B: twice weekly, Int ravenous For 6 weeks	Fluconazole vs. placebo	Invasive fungal infection, overall mortality, fungal colonization
Kicklighter 200 1	53 vs 50 Very low birth weight	6 mg/kg Every 72 h for the first we ek and every 24 h for weeks 2-4; intraveno us or oral for 4 weeks	Fluconazole vs. placebo	Invasive fungal infection, overall mortality, fungal colonization

Kim 2010	28 vs 27 Very low birth weight	3 mg/kg Intravenous For 4-6 weeks	Fluconazole vs. placebo	Invasive fungal infection, overall mortality, fungal colonization
Kirpal 2016	38 vs 37 Very low birth weight	6 mg/kg Intravenous, every other day for week 1 and daily for weeks 2-4 or until discharge for 4 weeks	Fluconazole vs. placebo	Invasive fungal infection, overall mortality
Manzoni 2007	216 vs 106 Very low birth Weight Extremely low birth w eight	112 (6 mg/kg) 104 (3 mg/kg) Every 3 days for the first 2 weeks, then daily for a total of 6 weeks for extremely low birth weigh t and 4 weeks for very low birth weight, Intravenous or through a gastric tube for 6 weeks	Fluconazole vs. placebo	Invasive fungal infection, overall mortality, fungal colonization
Parikh 2007	60 vs 60 Very low birth weight	6 mg/kg Once every 3 days for wee k 1 and once a day for weeks 2-4. Intravenous first, then oral with total enteral nutrition for 4 weeks	Fluconazole vs. placebo	Invasive fungal infection, overall mortality, fungal colonization

infants with very low birth weight or extremely low birth weight. The RR was below 1 and the 95% CI was also below 1 in the preterm infants with prophylactic fluconazole treatment compared to the control group. It indicated that the lower RR and 95% CI supported the advantages of prophylactic fluconazole treatment to reduce the risk of invasive fungal infection, fungal colonization, or overall mortality in preterm infants. The strength of the meta-analysis is that the included studies were RCTs with prophylactic fluconazole treatment vs. control treatment in preterm infants. The results provide the evidence for the clinical staff to conduct the prophylactic fluconazole treatment in preterm infants to avoid the risk of invasive fungal infection, fungal colonization, and overall mortality in preterm infants. However, the substantial heterogeneity, which might include clinical heterogeneity, methodological heterogeneity, and statistical heterogeneity, in the invasive fungal infection should be considered when interpreting the meta-analysis results. The clinical heterogeneity might include the extremely low birth weight subgroup, the very low birth weight subgroup, variations in the characteristics of invasive fungal infection, preterm infant populations, and outcome measurements for invasive fungal infection, such as the different severity and duration. In addition, the different prophylaxis regimens between the studies might contribute to the clinical heterogeneity. For example, the different kinds of fluconazole prophylaxis dose and interval in the included studies might influence the results of individual included studies, which might contribute to the clinical heterogeneity in the current meta-analysis. The methodological heterogeneity might be related to the variations in RCT design and the risk of bias. The statistical heterogeneity might be associated with the variability in the risk effects being evaluated in the different studies. For the meta-analysis of fungal colonization and overall mortality, the lack of heterogeneity might be another strength in the current study. It suggested that the homogeneity of included RCTs, clinical population, and statistical risk effects in the meta-analysis of fungal colonization and overall mortality. It might be more persuasive for the prophylactic fluconazole treatment to reduce the risk of fungal colonization and overall mortality in preterm infants, which should be considered in clinical practice. The current meta-analysis included the update study, such as Autmizguine et al.'s study in 2018,[14] which has not been included in the past meta-analysis studies.[4,23] In addition, the previous meta-analysis study of Ericson et al.[4] just included 4 trials, which were lower than the number of included studies in the current meta-analysis. Therefore, the current meta-analysis can provide more updated information and evidence for the fluconazole prophylaxis in the invasive fungal infection in preterm infants. The current meta-analysis results endorse the significant role of fluconazole prophylaxis to prevent the invasive fungal infection in preterm infants, which might be related to the reduction of fungal colonization. The reduction of invasive fungal infection might be linked with the lower risk of overall mortality in preterm infants. However, the causal relationship between invasive fungal infection, fungal colonization, and overall mortality still needs more studies to confirm. Invasive fungal infection usually leads to overall mortality and morbidity in preterm infants with very low birth weight.[24] From this point, the current meta-analysis indicated the reduction of the risk of invasive fungal infection, which might contribute to the decrease in the risk of overall mortality. In the results of the current meta-analysis, fluconazole prophylaxis reduces the risk of fungal colonization. The mechanism of anti-fungal activity of fluconazole might be the following:[1] The reduction of cell numbers and aggregated phenotype of fungus.[2] Inhibit the fungal colonization, invasion, and host immune evasion effects.[3] Inhibit the biofilm formation from the fungus-host cell interaction via the production of behenyl alcohol and decanoic acid.[4] Inhibit fungus growth activity via the activation of 2-palmitoyl glycerol, 1-tetradecanol, and 1-nonadecene.[5] Interaction with 14-demethylase to influence the conversion of lanosterol to ergosterol.[9,25] In addition, fluconazole prophylaxis has been reported to decrease the fungal colonization index, which might predict less invasive fungal infection.[26] The bacterial decontamination activity of fluconazole treatment might inhibit the anaerobic intestinal bacteria, which might be associated with the decrease in the fungal colonization[27] In the neonatal intensive care unit, the rate of fungal colonization in the preterm infants with extremely low birth weight is more than 10 % with fluconazole colonization,[24] which might be due to that the fluconazole-releasing surface coatings inhibit the formation of fungus biofilm.[28] Therefore, the fluconazole prophylaxis will be recommended to reduce the risk of fungal colonization, which is proven in the current meta-analysis. In addition, The reduction of overall mortality will not be surprising due to the findings of reductions in the invasive

fungal infection and fungal colonization. Therefore, more RCTs will be needed in the future to confirm the benefits for reducing the invasive fungal infection, fungal colonization, and overall mortality in preterm infants.

This study has several limitations. First, the imbalance of sample size in the included studies might be a concern. Some of the included RCTs had small sample sizes, and others had large sample sizes. The heterogeneity of the sample size might also lead to clinical heterogeneity. The substantial heterogeneity in the current meta-analysis results might be related to this issue. The authors applied a weighting method to decrease the bias. However, the impact of an imbalanced sample size should not be ignored. Second, there were variations in age, prophylactic fluconazole treatment doses, control treatment content, and treatment duration, which are also potential sources of bias. Third, the lack of patient-level data may be another concern and prevented us from performing a full evaluation of patient-level covariates. Fourth, the definition and severity of invasive fungal infection in the included RCTs also differed. Some included RCTs were also double blinded, while some were single blinded, and the timing of invasive fungal infection was also variable between studies, which could also affect the results. This issue was also needed to be considered when we reported such a significant result of lower RR in preterm infants with very low birth weight or extremely low birth weight. Sixth, after 2018, there was no RCT of this topic to be reported or published in scientific journals. The limitation of publication date and no latest RCTs should not be ignored in the current meta-analysis.

Conclusion

The systematic review and meta-analysis results showed that fluconazole prophylaxis might provide benefits to the preterm infants with very low birth weight or extremely low birth weight, such as a lower risk of invasive fungal infection, fungal colonization, and overall mortality. Future studies with a less inhomogeneous design and content of rehabilitation should be warranted to clarify and confirm the benefits of fluconazole prophylaxis in preterm infants.

Declarations

Consent for publication

Not Applicable.

Availability of data and materials statement:

Data available on request from the authors.

Competing interests

None

Funding

None

Author Contributions

Research ideas and study design: HT and ZX; data acquisition: HT and ZX; data analysis/interpretation: HT and ZX; statistical analysis: HT, ZX, LX; supervision or mentorship: LX. All authors take responsibility that this study has been reported honestly, accurately and transparently, and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

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