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HIV infection and adverse perinatal outcomes – a meta-analysis of premature births, low birth weights, and small for gestational age newborns

HIV infekce a nepříznivé perinatální výsledky – metaanalýza předčasného porodu, nízké porodní hmotnosti a novorozenců malých na gestační věk

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Summary: HIV remains a significant global public health challenge, affecting millions of individuals with a disproportionate burden in sub-Saharan Africa. Despite advancements in antiretroviral therapy (ART) and global efforts to control transmission, the impact of HIV on pregnancy outcomes remains a topic of concern. **Aim:** This study aims to evaluate the association between maternal HIV infection and adverse pregnancy outcomes, specifically preterm birth (PTB), low birth weight (LBW), and small for gestational age (SGA) infants through a comprehensive meta-analysis. **Materials and methods:** A systematic search of English-language databases, including Medline, Web of Science, Ovid, Scopus, and Google Scholar, was conducted to identify relevant studies published between 2014 and 2024. Eligible studies included retrospective and prospective cohort studies with well-defined control groups of HIV-negative mothers. Studies that lacked appropriate control groups, included multiple pregnancies, or did not report adjusted statistical outcomes were excluded. A total of eight studies met the inclusion criteria for PTB analysis, five studies for LBW analysis, and five studies were selected for SGA analysis. **Results:** Meta-analysis using a random-effects model demonstrated a statistically significant association between maternal HIV infection and PTB (OR = 1.55; 95% CI 1.38–1.74; $p < 0.001$), LBW (OR = 1.57; 95% CI 1.24–1.98; $p < 0.001$), and an increased risk of SGA (OR = 1.24; 95% CI 1.10–1.40; $p < 0.001$). Heterogeneity was moderate for PTB ($I^2 = 38.2\%$) and LBW ($I^2 = 55.9\%$) while it was low for SGA ($I^2 = 7.6\%$), indicating consistency across studies. Egger's test showed minimal publication bias. **Discussion:** These findings highlight the adverse effects of HIV on pregnancy outcomes, emphasizing the need for continued monitoring and optimization of ART regimens to mitigate risks. Further research is warranted to explore the influence of different ART combinations and immune system dynamics on fetal development.

Key words: HIV – preterm birth – antiretroviral therapy – low birth weight – small for gestational age – SGA meta-analysis

Introduction

HIV remains a public health problem all over the world. It is estimated that 42.3 million HIV-positive individuals were alive by mid-2024. The spread of HIV involves all countries globally, and 65% of those affected live in sub-Saharan Africa. In 2023, 630,000 people died from HIV-related causes, and around 1.3 million people were infected. Even though there is no definite treatment, the trend of stopping HIV multiplication in the body and infecting other people could, according to World Health Organization (WHO) plans, help end the HIV epidemic by 2030 [1]. According to the WHO strategy, by 2030, 95% of people living with HIV should receive a diagnosis, 95% of those diagnosed should be taking life-saving antiretroviral treatment, and 95% of those treated should have therapy that suppresses their viral load to reduce further virus transmission and benefit their health status. In 2023, these percentages were 86%, 89%, and 93%, resp. WHO presently defines advanced HIV disease as a CD4 cell count lower than 200 cells per mm^3. It also includes WHO stage 3 or 4 HIV in adolescents and adults

Souhrn: HIV zůstává významnou globální výzvou v oblasti veřejného zdraví, která postihuje miliony lidí, přičemž největší zátěž připadá na subsaharskou Afriku. Navzdory pokroku v antiretrovirové terapii (ART) a globálním snahám o kontrolu přenosu zůstává vliv HIV na těhotenské výsledky důvodem k obavám. **Cíl:** Tato studie hodnotí souvislost mezi mateřskou infekcí HIV a nepříznivými těhotenskými výstupy, zejména předčasným porodem (PTB – preterm birth), nízkou porodní hmotností (LBW – low birth weight) a novorozenci malými vzhledem k danému gestačnímu věku (SGA – small for gestational age), prostřednictvím komplexní metaanalýzy. **Materiál a metody:** Systematické vyhledávání v anglicky psaných databázích (Medline, Web of Science, Ovid, Scopus a Google Scholar) identifikovalo relevantní studie publikované v letech 2014–2024. Zahrnuty byly retrospektivní a prospektivní kohortové studie s dobře definovanými kontrolními skupinami HIV-negativních matek. Vyloučeny byly studie bez odpovídajících kontrol, s vícečetnými těhotenstvími nebo bez adjustovaných statistických výsledků. Celkem bylo zahrnuto osm studií zaměřených na PTB, pět na LBW a pět na SGA. **Výsledky:** Metaanalýza prokázala významnou souvislost mezi mateřskou infekcí HIV a PTB (OR = 1,55; 95% CI 1,38–1,74; p < 0,001), LBW (OR = 1,57; 95% CI 1,24–1,98; p < 0,001) i SGA (OR = 1,24; 95% CI 1,10–1,40; p < 0,001). Heterogenita byla mírná u PTB (I^2 = 38,2 %), LBW (I^2 = 55,9 %) a nízká u SGA (I^2 = 7,6 %), s minimálním publikačním zkreslením dle Eggerova testu. **Diskuze:** Výsledky zdůrazňují negativní dopad HIV na těhotenství a potřebu optimalizace ART ke snížení rizik. Další výzkum by měl sledovat vliv různých režimů ART a dynamiku imunitního systému na vývoj plodu.

Klíčová slova: HIV – předčasný porod – antiretrovirová terapie – nízká porodní hmotnost – malý vzhledem ke gestačnímu věku – SGA metaanalýza

and all HIV-positive children under the age of 5. Maternal HIV viral load is categorized as undetectable (HIV viral load ≤ 20 copies/mL), low-level viremia (21–999 copies/mL), or high-level viremia (viral load ≥ 1,000 copies/mL). A substantial problem is mother-to-child transmission (MTCT), also referred to as vertical HIV transmission during pregnancy and birth [2]. Many maternity hospitals previously tried to solve this problem by performing a primary cesarean section [3,4]. At present, as mentioned above, the vast majority of pregnant women worldwide receive suitable antiretroviral therapy (ART), which significantly lowers the possibility of vertical transmission to the child during pregnancy and delivery. Moreover, ART improves the mothers quality of life and decreases the probability of transmitting the infection to her sexual partner [1]. Other notable obstetrical problems are frequently discussed [5]. One such concern is adverse pregnancy outcomes, including preterm birth (PTB) or preterm delivery (PTD), low birth weight (LBW) and small for gestational age (SGA) newborn babies in HIV-positive women. Several studies have been conducted on these topics, often with contradictory results. According to WHO, PTB is defined as the delivery of a live-born baby before completed 37 weeks of gestation. It is often associated with poorer neonatal adaptation and many other important complications. According to WHO, LBW is defined as the delivery of a live-born baby with a weight of < 2,500 g. In conformity with WHO, SGA newborns are smaller than expected for a particular gestational age, mostly defined as having a weight below the 10th percentile for gestational age, adjusted for gender and geographical factors. Due to these adjustments, SGA is often considered a very accurate method of evaluation. Babies born preterm or classified as LBW or SGA are at an increased risk of perinatal mortality, lung disease, hypotension, necrotizing enterocolitis, poor thermoregulation, hypoglycemia, and polycythemia. Long-term risks of LBW and SGA include insulin resistance, type II diabetes mellitus, cardiovascular disease, chronic kidney disease, neurodevelopmental delays, cognitive impairment, and short adult stature [1,6–9].

Aim

The aim of our research was to gather plausible studies that include birth data on PTB, LBW and SGA in HIV-positive mothers, comparing them with control groups of HIV-negative mothers who gave birth to their babies. We evaluated these data using a meta-analysis technique in order to elucidate the debated adverse effect of HIV on delivery outcomes.

Materials and methods

Study selection

English-language databases were searched via Medline, Web of Science, Ovid, Scopus, and Google Scholar. The relevant articles were gathered from 2014 to 2024 (inclusive). Earlier trends were often influenced by a large percentage of planned primary C-sections, sometimes performed before completing 37 weeks of pregnancy [3]. Even now, the probability of a caesarean section is two times higher in HIV-positive patients compared to HIV-negative patients [4]. We selected retrospective and prospective cohort studies that included comparable control groups of HIV-negative patients. Unsystematic studies, case-control studies, or case series were excluded from our analysis. Similarly, studies without an appropriate control group were also excluded. Only studies published in peer-reviewed journals were considered. Additionally, studies involving multiple pregnancies were excluded due to potential bias.

We searched for PTB, LBW and SGA studies [9]. All included studies reported statistical outcomes using adjusted odds

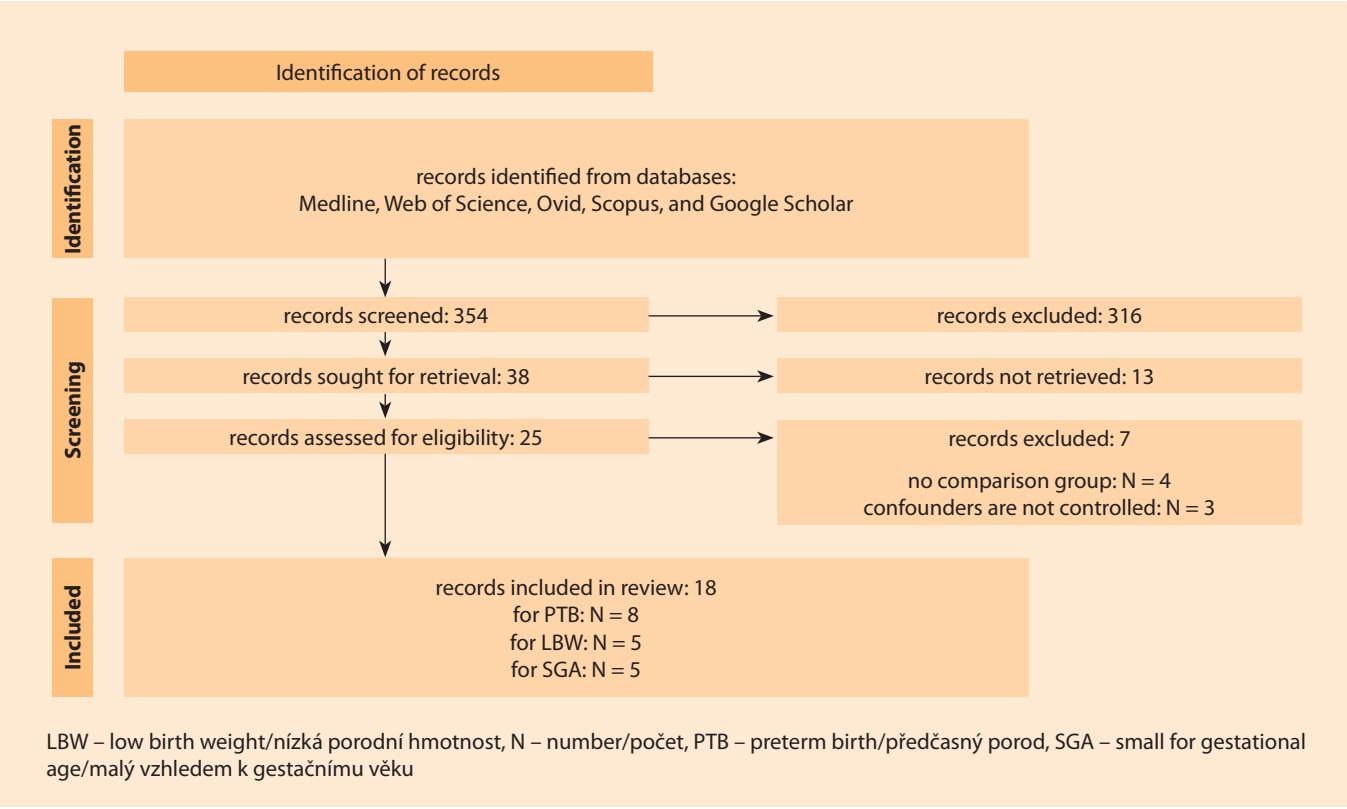

Fig. 1. Flow chart diagram.
Obr. 1. Plovoucí diagram.

ratios (OR) and 95% confidence intervals (CI) and p-value. Studies that did not adjust for covariates were also excluded.

The selected search techniques and results are presented in the Flow Diagram for meta-analyses.

Statistical analysis

Comprehensive Meta-Analysis (CMA) software and SPSS were used for calculations. A random-effects model for binomial meta-analysis was chosen. The OR and CI from individual studies were transformed into their natural logarithm form for more precise meta-analysis calculations. The pooled overall results are presented in exponential form, including OR and 95% CI. P values are presented.

Heterogeneity was evaluated using the I^2 statistic, which measures the percentage of variability between studies not due to chance. It describes how cohesive the particular components of the study are. The interpretation is as follows:

- 0–30% = not important;
- > 30–60% = moderate heterogeneity;
- > 60–80% = substantial heterogeneity;
- > 80–100% = considerable heterogeneity.

Egger's test was used to perform weighted regression analysis. A significant intercept with $p < 0.05$ (considered statistically significant) suggests the presence of publication bias.

The forest plot provides a graphical representation of the included studies. The boxes represent study sample sizes, while the CI whiskers indicate the range of dispersion within each study. The red diamond-shaped structure in the lower section of the plot represents the overall study impact, as indicated by its OR and CI.

Heterogeneity and bias were also assessed using a funnel plot. Sensitivity analysis was conducted on all datasets. After sequentially removing individual studies, no significant change in results was observed.

Results

Recognized studies

A total of 18 records were identified during the database search. Eight studies focused on PTB, while five addressed LBW and five examined SGA [10–17]. The Flow Chart Diagram describes the technique used for specifying the selected studies (Fig. 1).

PTB meta-analysis

For the PTB meta-analysis, eight studies were selected. They are listed in (Tab. 1), ranked according to the year of publication. Their adjusted OR and CI are specified in the table, resp., along with their percentage influence on the overall analysis (totaling 100%), which is presented in the last column.

The overall pooled effect size for PTB is OR = 1.55; 95% CI 1.38–1.74; and

Tab. 1. PTB study-results and overall-result.
Tab. 1. PTB výsledky studie a celkové výsledky.

ID	Year	OR	95% CI		Weight (%)
			Lower	Upper	
Macdonald et al. (1)	2015	1.76	1.381	2.242	14.9
Gagnon et al. (2)	2016	1.4	0.5	3.6	1.4
Moodley et al. (3)	2016	1.33	1.193	1.483	30.1
Malaba et al. (4)	2017	2.03	1.33	3.099	6.4
Arab et al. (5)	2017	1.57	1.387	1.777	28
Sebitloane et al. (6)	2017	1.65	1.169	2.328	9
Tukei et al. (7)	2021	1.41	0.642	3.09	2.1
Duffy et al. (8)	2024	1.6	1.107	2.32	8.1
Overall	**p < 0.001**	**1.55**	**1.377**	**1.74**	**100**

PTB – preterm birth/předčasný porod

$p < 0.001$; indicating the statistical significance of the PTB meta-analysis. The study's homogeneity remains intact ($p = 0.24$). This p-value indicates a lack of statistical significance, suggesting that there is no homogeneity distortion. The measure of heterogeneity is $I^2 = 38.2\%$, which indicates moderate heterogeneity in the overall analysis. Egger's test, with a significant intercept of $p = 0.007$, reveals mild publication bias.

The forest plot provides a graphical interpretation of the PTB analysis, with the diamond-shaped marker in the lower section representing the overall effect size and 95% CI (Fig. 2).

The funnel plot illustrates the cohesiveness of the studies and minimal bias, as it appears nearly complete without significant distortion (Fig. 3).

The PTB meta-analysis confirms a significant influence of HIV positivity on preterm births.

LBW meta-analysis

For the LBW meta-analysis, five studies were selected. They are listed in (Tab. 2), ranked according to the year of publication. Adjusted OR and CI are specified in the table, along with their percentage influence on the overall study.

The overall pooled effect size for LBW is OR = 1.57; 95% CI 1.24–1.98; and $p < 0.001$; confirming its statistical significance. The study's homogeneity is slightly affected ($p = 0.04$). The measure of heterogeneity is $I^2 = 55.9\%$, indicating moderate heterogeneity in the analysis. Egger's test, with $p = 0.22$, suggests no publication bias.

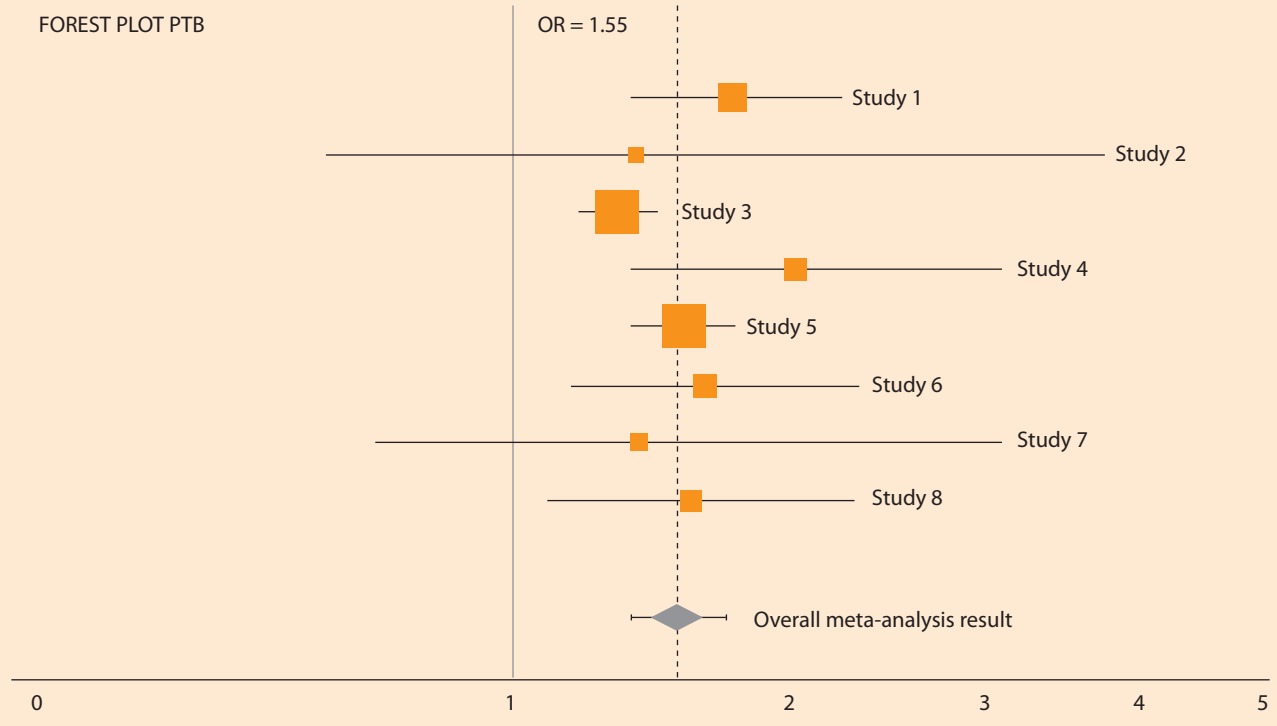

Fig. 2. PTB forest plot.
Obr. 2. PTB forest graf.

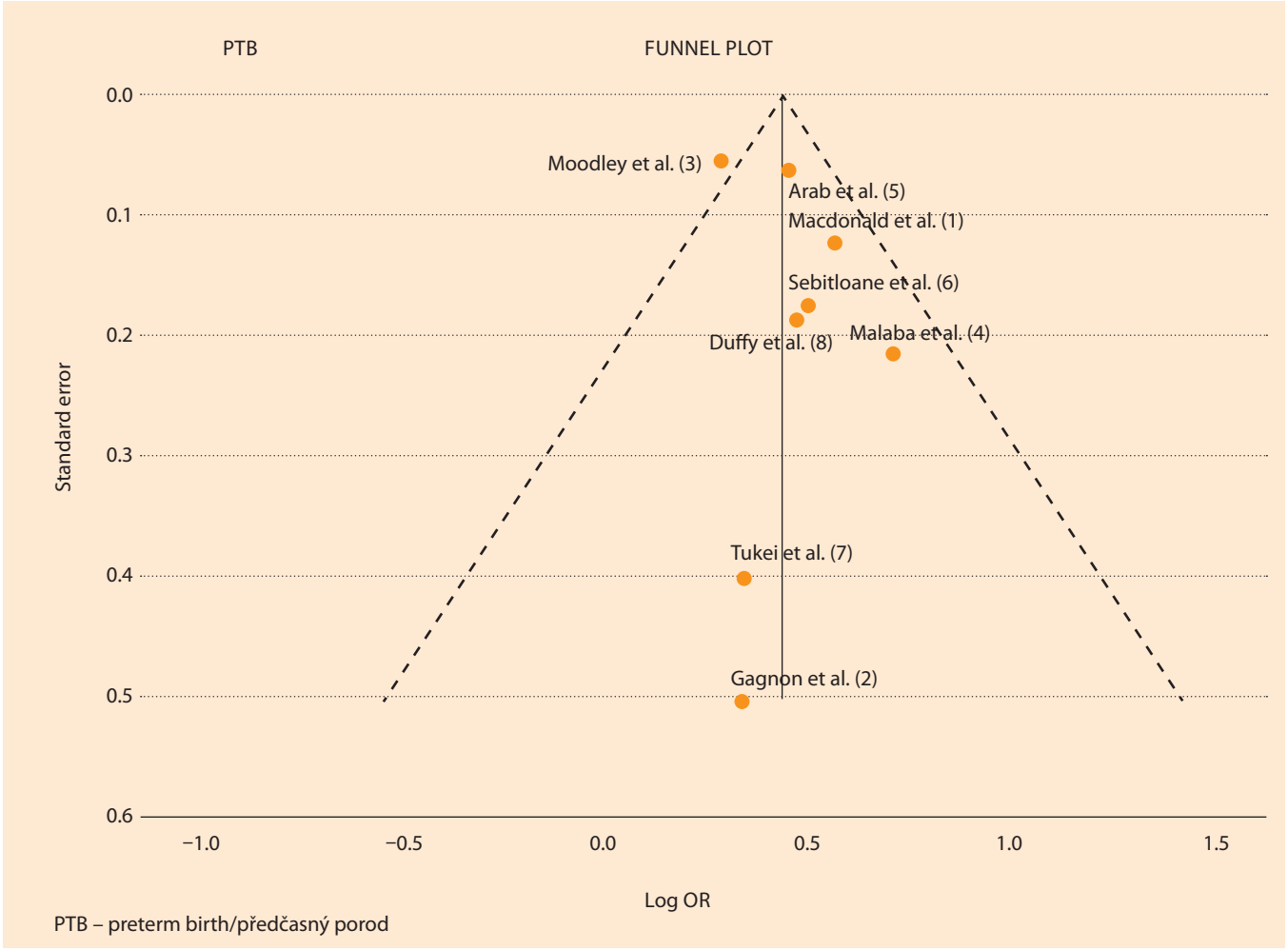

Fig. 3. PTB funnel plot.
Obr. 3. PTB trychtýřový graf.

The Forest plot provides a graphic interpretation of the LBW analysis, with the diamond-shaped marker representing the overall OR and CI (Fig. 4).

The funnel plot demonstrates high cohesiveness and minimal bias. Nearly all studies fall within the funnel, with no evidence of distortion (Fig. 5).

The LBW meta-analysis confirms a significant influence of HIV positivity on the presence of LBW at the time of delivery.

SGA meta-analysis

For the SGA meta-analysis, five studies were selected. They are listed in (Tab. 3), ranked according to the year of publication. Adjusted OR and CI are specified in the table, along with their percentage influence on the overall study.

The overall pooled effect size for SGA is OR = 1.24; 95% CI 1.10–1.40; and $p < 0.001$; confirming its statistical significance. The study's homogeneity remained intact ($p = 0.47$). The measure of heterogeneity is $I^2 = 7.6\%$, indicating very low heterogeneity in the analysis. Egger's test, with $p = 0.46$, suggests no publication bias.

The forest plot provides a graphical interpretation of the SGA analysis, with the diamond-shaped marker representing the overall OR and CI (Fig. 6).

Tab. 2. LBW study-results and overall-result.
Tab. 2. LBW výsledky studií a celkové výsledky.

ID	Year	OR	95% CI		Weight (%)
			Lower	Upper	
Macdonald et al. (1)	2015	1.90	1.47	2.45	28.30
Gagnon et al. (2)	2016	1.90	0.60	5.50	4.10
Moodley et al. (3)	2016	1.26	1.11	1.44	37.60
Malaba et al. (4)	2017	1.47	0.90	2.40	15.00
Tukei et al. (5)	2021	1.89	1.16	3.09	15.00
Overall	**p < 0.001**	**1.57**	**1.24**	**1.98**	**100**

LBW – low birth weight/nízká porodní hmotnost

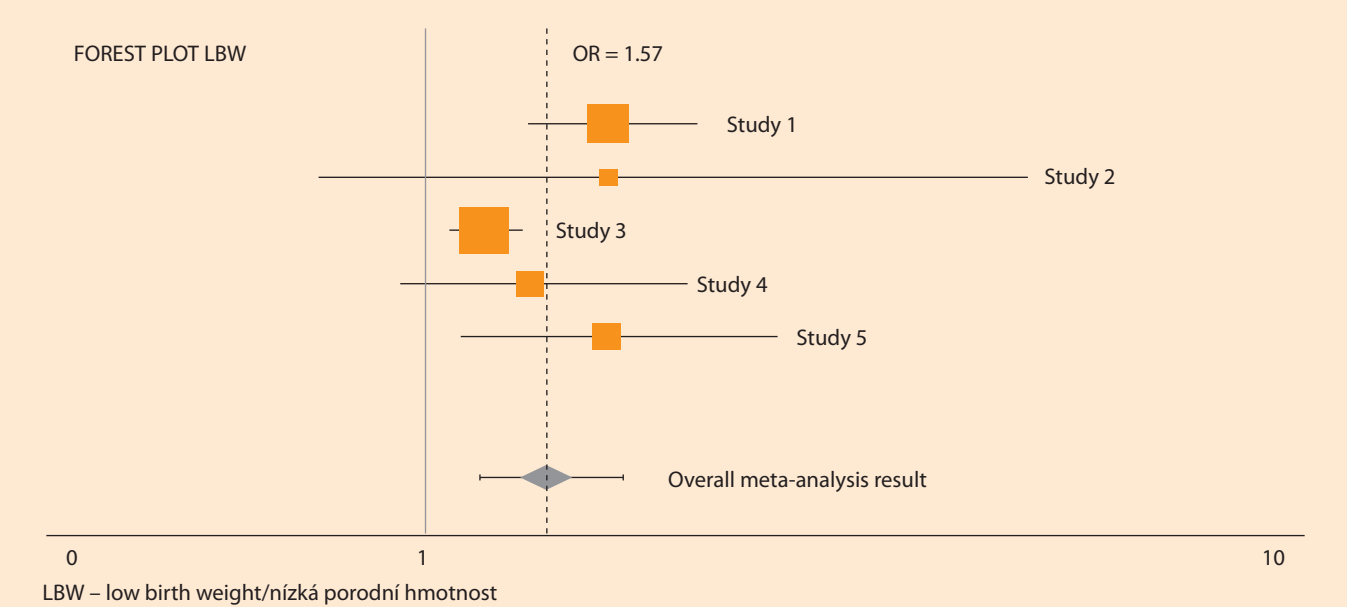

Fig. 4. LBW forest plot.
Obr. 4. LBW forest graf.

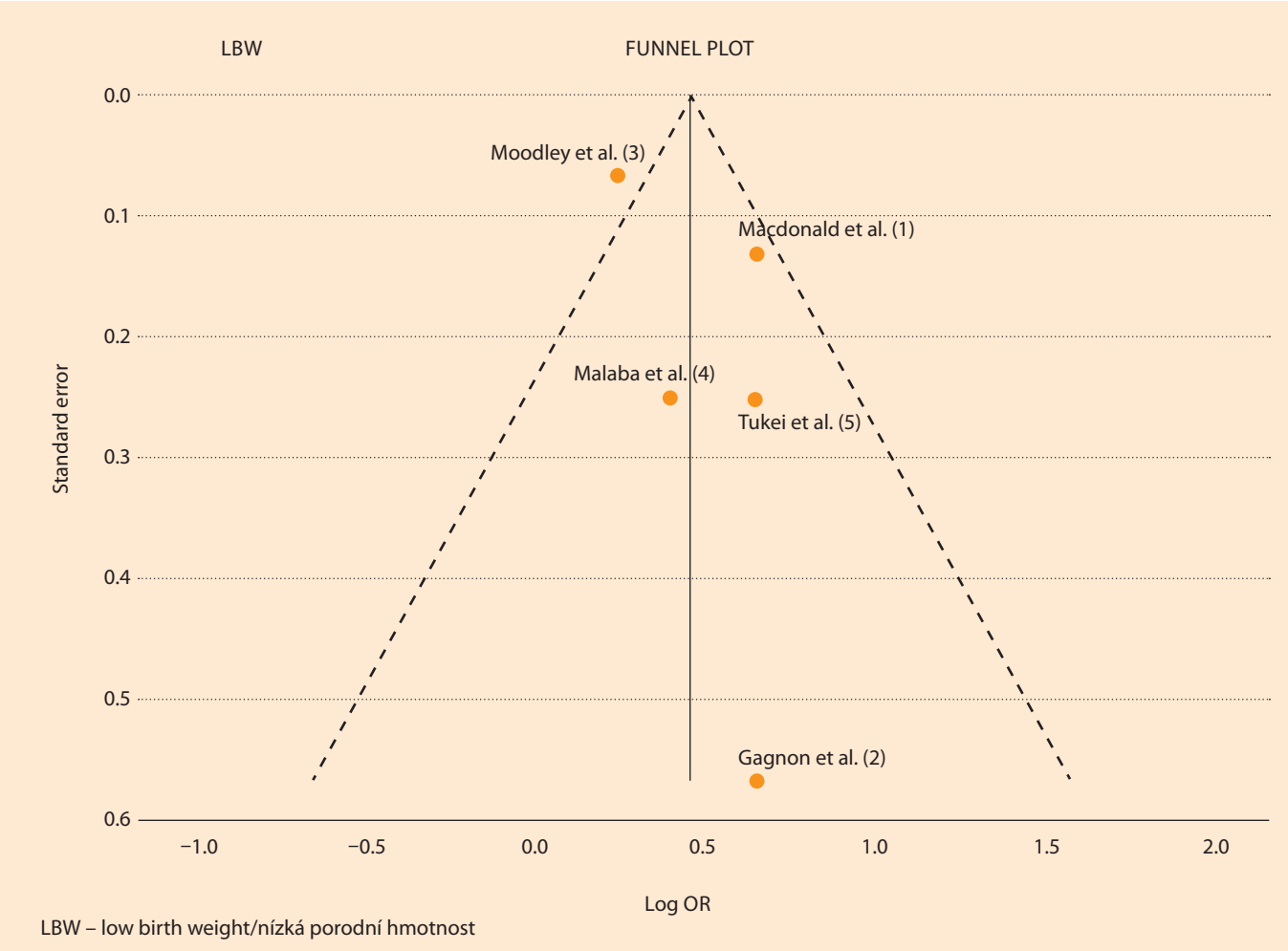

Fig. 5. LBW funnel plot.
Obr. 5. LBW trychtýřový graf.

The funnel plot demonstrates high cohesiveness and minimal bias. All studies fall within the funnel, with no evidence of distortion (Fig. 7).

The SGA meta-analysis confirms a significant influence of HIV positivity on the presence of SGA at the time of delivery.

Discussion

We conducted meta-analyses to compare the adverse events of PTB, LBW and SGA between HIV-positive pregnant women and HIV-negative controls. In both cases, a statistically significant influence of HIV positivity on PTB, LBW and SGA at birth was proven. For our meta-analysis, adjusted data were used to ensure accurate results.

The global ART intervention has been highly successful in saving many lives, reducing HIV transmission within the population, improving quality of life (QoL), and having a significant positive effect on vertical HIV transmission [18–20].

The influence of different ART combinations on adverse delivery outcomes is not yet fully understood. Some studies report conflicting results [21–24].

Tab. 3. SGA study-results and overall-result.
Tab. 3. SGA výsledky studie a celkové výsledky.

ID	Year	OR	95% CI		Weight (%)
			Lower	Upper	
Macdonald et al. (1)	2015	1.43	1.12	1.81	23.70
Gagnon et al. (2)	2016	1.80	0.80	4.60	2.00
Moodley et al. (3)	2016	1.15	0.98	1.35	47.20
Malaba et al. (4)	2017	1.06	0.71	1.61	8.70
Duffy et al. (5)	2024	1.29	0.98	1.70	18.40
Overall	**p < 0.001**	**1.24**	**1.10**	**1.401**	**100**

SGA – small for gestational age/malý vzhledem k gestačnímu věku

There are several explanations for the occurrence of PTB, LBW and SGA in newborns [25–27]. One widely accepted theory suggests that HIV-related damage to the human immune system, particularly a reduced CD4 T-cell count and immunosuppression, plays a role. It has been shown that women with CD4 cell counts below 350 cells/mm^3 have an increased risk of giving birth to LBW infants [27–30]. One explanation is that pregnant women are naturally immunocompromised, and when combined with HIV infection, this condition could negatively affect the placenta and impair fetal development [31–33]. Additionally, lower levels of progesterone may influence fetal development, potentially leading to an earlier onset of labor. This hypothesis is supported by some studies [25].

Limitations

Naturally, not all studies are fully comparable. Studies conducted in developing countries carry certain risks, particularly when evaluating newborn weight. Therefore, we believe that adjusted SGA measurements provide the most reliable criterion for assessing newborn size. We aimed to select studies with well-presented and adjusted results to minimize bias.

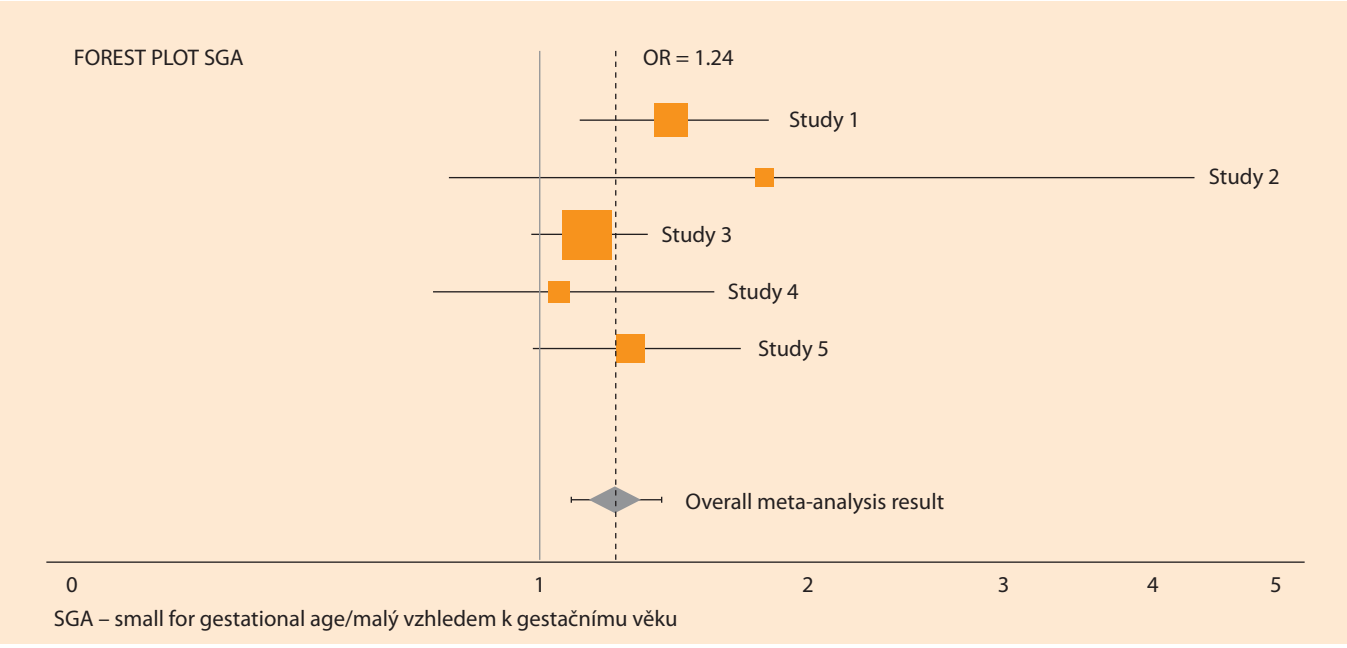

Fig. 6. SGA Forest Plot.
Obr. 6. SGA Forest Graf.

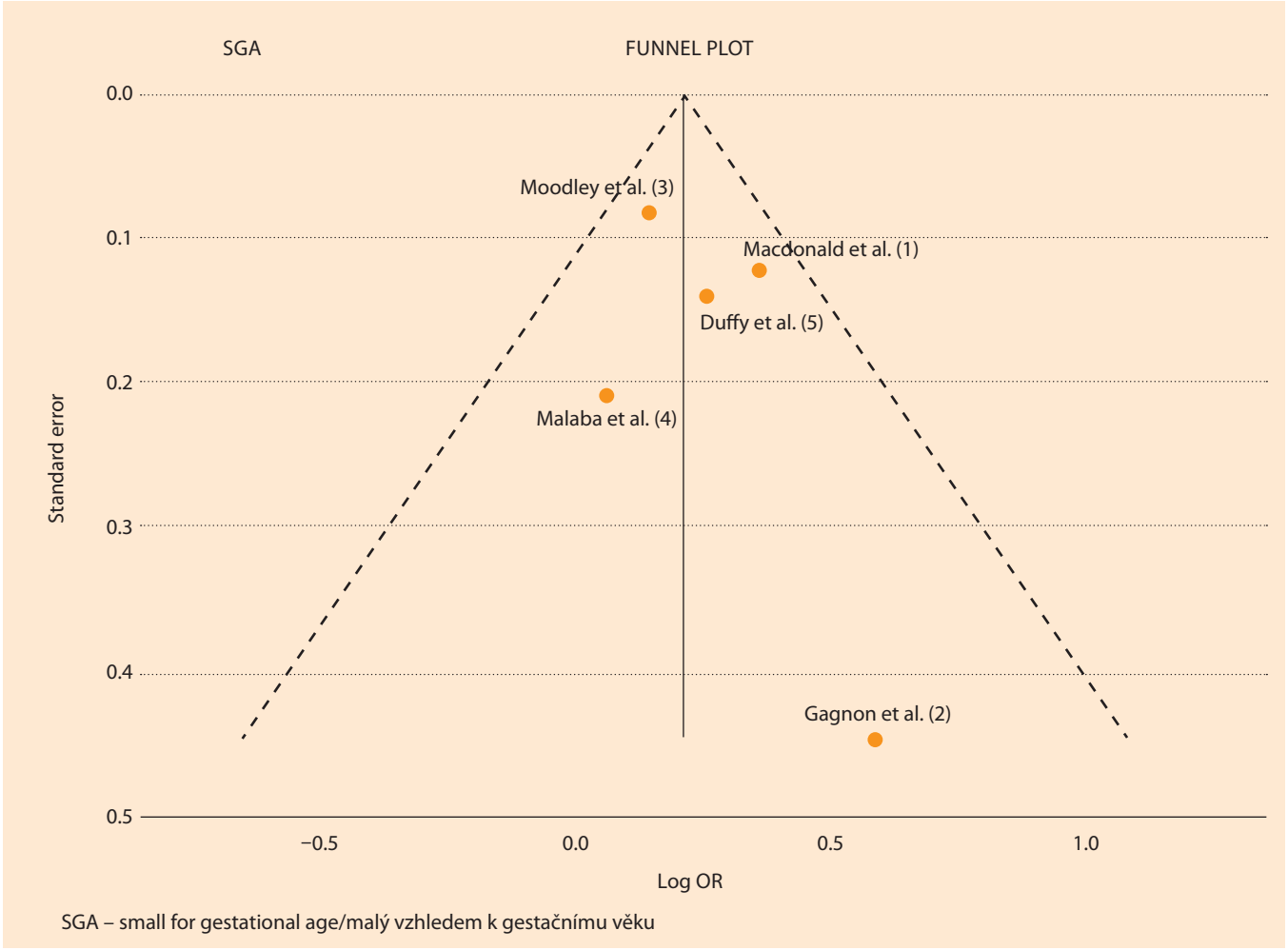

Fig. 7. SGA funnel plot.
Obr. 7. SGA trychtýřový graf.

Another limitation is the potential bias introduced by authors and publishers. It is well known that studies with groundbreaking results are more likely to be published than those that yield inconclusive findings.

Conclusion

The findings of our meta-analysis indicate that maternal HIV infection is statistically associated with an increased probability of preterm birth, low birth weight, and having a small for gestational age newborn.

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