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Original Article

Monkeypox infection in pregnancy, maternal and fetal outcomes: a systematic review

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Abstract

Introduction: Monkeypox (mpox) is an emerging infectious disease with increasing global incidence. Limited evidence exists regarding its impact on pregnancy and perinatal outcomes, especially in low-resource settings. The objective was to systematically synthesize current evidence on maternal and fetal outcomes associated with mpox infection during pregnancy.

Methodology: A systematic review was conducted following the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines. PubMed, Scopus, Web of Science, and Embase (as of 4 September 2024) databases were searched. Case reports, case series, cohorts, and observational designs were included. Duplicates were removed using Rayyan. Only 6 studies (out of 471) met the eligibility criteria. A descriptive analysis was conducted due to heterogeneity and small sample sizes.

Results: A total of 6 studies were included (4 from US, 1 from Spain, 1 from Democratic Republic of Congo), comprising 33 pregnant women aged 18–29 years. Mpox was confirmed by polymerase chain reaction (PCR) in 32 cases. The clinical symptoms included vesicular rash, genital lesions, and systemic manifestations. No maternal deaths were reported. Adverse fetal outcomes included miscarriage (9.1%), stillbirth (6.1%), and 4 intrauterine deaths. Most pregnancies (84.8%) resulted in live births. The reported complications included oligohydramnios, cholestasis, chorioamnionitis, and fetal tachycardia. One study confirmed vertical transmission via placental and fetal tissue analysis.

Conclusions: Mpox infection during pregnancy is associated with significant risk of adverse perinatal outcomes. Although current evidence is limited, these findings highlight the urgent need for more robust data to inform clinical and public health guidance.

Key words: monkeypox; MPOX; pregnancy; perinatal; fetal outcomes, maternal health.

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Introduction

Monkeypox virus (MPXV) is a linear double-stranded DNA virus that belongs to the Poxviridae family, subfamily Chordopoxvirinae, and genus Orthopoxvirus [1–3]. It is responsible for causing monkeypox (mpox) in humans. The first case of mpox was described in 1970 in the Democratic Republic of Congo (DRC) in a 9-month-old boy who developed fever, a centrifugal rash, cervical lymphadenopathy, and mastoiditis [1,4,5].

Since then, sporadic outbreaks and isolated reports of mpox in humans have primarily occurred in Central and West Africa, overlapping with the waning of herd immunity due to smallpox vaccination cessation in 1980 [4,5], since both viruses share antigen and genetic similarities because they belong to the same genus [1]. The mpox outbreak in 2022 began on May 6 in the United Kingdom and prompted the World Health Organization (WHO) to declare mpox a global health emergency on July 23. This outbreak resulted in 3000 reported infections in 50 countries across 5 regions [2,4,5].

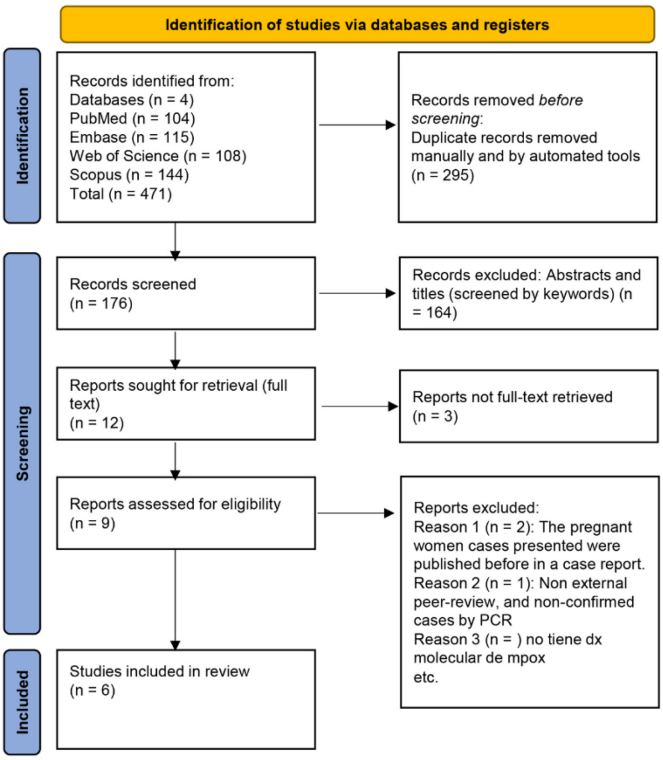
It was hypothesized that transmission was largely associated with sexual networks because a disproportionately high proportion of men who have sex with men (MSM) were affected during the outbreak [1,3]. However, it was soon recognized that mpox transmission primarily occurred through close physical contact with skin, mucosal, and anogenital lesions; and not necessarily by contact with sexual fluids, as positive polymerase chain reactions (PCR) may result from non-competent replication specimens [4,5].

Vertical transmission has been proposed for MPXV. In 2008, positive PCR results were noted from the umbilical vein blood of a 21-week gestation stillborn female fetus in DRC [6]. Further reports

described cases ranging from chorioamnionitis without additional complications to fetal demise, presenting with skin rashes similar to mpox and hydrops fetalis [7–9]. However, further characterization of the mother-fetus binomial is deemed necessary to include the morbidity caused by the more transmissible clade Ib, which has caused a sharp increase in incidence in DRC since 2023, and prompted WHO to declare a public health emergency of international concern on 14 August 2024 [10]. Therefore, this study aimed to conduct a systematic review of the literature to characterize the clinical outcomes of mpox infection during both pregnancy and perinatal periods.

Fetal outcomes in pregnant women with MPXV infection include stillbirth, miscarriage, and preterm birth [8,11,12]. The fetal mortality rate of MPXV clade I infection in the DRC ranged from 50–75%, based on studies conducted in Sankuru from 2007 to 2011, and South Kivu from 2023 to 2024 [8,11]. Both studies reported that fetal losses occurred during the first or second quarter of pregnancy [8,11]. The incidence of infection among pregnant women was relatively low during the multinational MPXV clade IIb infection outbreak from 2022 to 2024. Studies conducted in the United States reported that in 2022 only 3% of 769 women infected with MPXV were pregnant; 3 full-term deliveries and 1 spontaneous abortion were also documented [12]. The Pan American Health Organization (PAHO) reported that as of 24 February 2023, there were1.6% pregnant women among 2,278 confirmed cases in the Region of the Americas, with 35.1% of them required hospitalization [13].

Figure 1. PRISMA flow diagram for mpox in pregnancy systematic review.



There has been a significant increase in cases of MPXV infection as a result of a new, more transmissible, and genetically distinct clade Ib of the virus reported in the DRC. The current outbreak (since 14 August 2024) has been considered a Public Health Emergency of International Concern (PHEIC) in the DRC and neighboring countries [14].

Therefore, the aim of this study was to review the existing literature about the impact of MPXV on fetal outcomes; maternal complications during pregnancy; childbirth; and the postpartum period and placental outcomes.

Methodology

Protocol, information sources, and literature search

A systematic review was conducted in line with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines. The population, intervention, comparison, outcome, and study design (PICOS) framework (Supplementary Table 1A) was employed to structure the research strategy (Supplementary Table 1B).

The PubMed, Scopus, Web of Science, and Embase databases were searched electronically on 4 September 2024, utilizing combinations of entry terms and selected keywords (Figure 1).

Eligibility criteria

Original studies that reported individual clinical cases of MPXV infection during pregnancy, regardless of outcome, were included. Eligible study designs were case reports, case series, cross-sectional studies, cohort studies, and case-control studies; provided they included extractable maternal, fetal, or neonatal data. No restrictions were applied on the language or country of publication. Articles that did not present primary clinical data, such as narrative reviews, systematic reviews, commentaries, opinion pieces, and letters to the editor without original case descriptions, were excluded.

Outcome measure, study selection, and data collection

The search results were exported to Rayyan (Cambridge, Massachusetts, USA) [15] after eliminating duplicates. The automated search yielded 471 records from the 4 electronic databases. Of these, 295 records that were duplicates were removed, and

176 records were screened. Of these, 164 were excluded because they lacked keywords in their titles and abstracts. The remaining 12 reports were selected for retrieval (full-text); however, 3 could not be retrieved. Nine full texts were assessed for final eligibility, and 3 were excluded (these cases were part of previously included studies). Finally, 6 studies were included in this review (Figure 1).

Quality assessment and risk of bias

The quality of included studies was assessed considering their full-text versions. In order to minimize selection bias, 3 investigators independently screened each record for eligibility. They adopted the following process to resolve any conflicts. One investigator conducted a full review of potentially eligible full texts. When the first investigator deemed a record ineligible, a second investigator screened it. The three investigators discussed any discrepancies and reached a consensus.

A meta-analysis was not feasible due to the limited number of cases, and the heterogeneity in diagnostic methods and reported outcomes. Instead, a descriptive analysis was conducted to provide a comprehensive overview of the pregnancy outcomes associated with mpox infection.

Results

Study selection and characteristics

A total of 471 articles were identified from the initial search. The articles were screened after removing duplicates and abstracts, and only 6 articles were included in the systematic review. The studies included were reported from the United States (n = 4), Spain (n = 1), and the DRC (n = 1). Most of the studies were case reports (n = 4), and there was 1 retrospective observational and 1 cross-sectional observational study. A total of 33 pregnant women were reported with ages between 18 and 29 years. The coinfections reported included malaria, herpes, and human immunodeficiency virus (HIV). Mpox was confirmed by PCR in most of the studies. However, two studies reported using PCR for Orthovirus as a diagnostic confirmation. One study failed to mention the diagnostic method used to identify mpox infection.

Synthesis of the results

All the cases (n = 33) included in the present systematic review were reported as mpox infection. Thirty-two mpox patients were diagnosed by PCR, while the confirmation method for 1 case was not specified. The most common sample used for PCR was a vaginal swab (n = 5), followed by blood or other body fluids (n = 4), and an unknown sample (n = 1) (Table 1).

At the time of sampling, the symptoms were described as vesicular rash, enanthem, papule with central umbilication and rash (n = 28); genital lesions (n = 6); vaginitis (n = 2); asymptomatic (n = 2); and others (fever, myalgia, lymphadenopathy, etc.). Pregnant women (n = 3) reported severe pruritus following sample collection (Table 1).

No maternal death was reported. Miscarriage occurred in 9.09% (n = 3), stillborn (defined as intrauterine fetal death after the 20th week) occurred in 6.06% (n = 2), and live births occurred in 84.85% (n =

Table 1. General characteristics of pregnant women infected with monkeypox (mpox).

Publication year	Country	Study type	No. of patients	Age (years)	Gestational age	US	No of pregnancies	Gyn-obstetric history	Comorbidities	Coinfections	Symptoms at diagnosis	Symptoms weeks After	Prepartum complications
2023	USA	Observational retrospective	1	19	24 weeks	Not indicated	Not indicated	No	No	HIV -	Vaginitis	Pruritus, cholestasis, fever	No
			2	23	36 weeks	Not indicated	Not indicated	No	No	HIV -	Asymptomatic	Fever	No
2023	USA	Case report	1	19	24 weeks	Not indicated	1	No	No	HIV-, NG-, CT-, STI-	Vaginal itching	Severe diffuse pruritus	Intrahepatic cholestasis
			2	22	36 weeks	Not indicated	1	No	No	HIV-, NG-, CT-, STI-	Asymptomatic	Asymptomatic	Oligohydramnios
2017	Democratic Republic of Congo	Case report	1	20	6 weeks	Not indicated	Not indicated	No	Not indicated	Not indicated	Vesicular rash and/or enanthems in the oral cavity and fever history	Not indicated	Not indicated
			2	25	6–7 weeks	Not indicated	Not indicated	No	Not indicated	Not indicated		Not indicated	Not indicated
			3	29	14 weeks	Not indicated	Not indicated	No	Not indicated	Not indicated		Not indicated	Not indicated
			4	22	18 weeks	Not indicated	Not indicated	No	Not indicated	Malaria		Not indicated	Not indicated
2023	USA	Case report	1	20	31 weeks	Not indicated	Not indicated	Gonorrhea, Chlamydia, pyelonephritis	Not indicated	Herpes	Dysuria, vaginal bleeding, 1 vaginal lesion, 3 lesions in the abdomen, 1 lesion in the right leg	No	No
2024	Spain	Case report	1	24	Since conception	Ultrasound 4 days after conception	Not specified. nulliparous	No	Not indicated	*Chlamydia trachomatis* (PCR) was found 27 days after mpox confirmation	Asthenia, localized lymphadenopathy, burning rash in the genital region	Genital lesion persisted, and a burning sensation. nausea and vomiting	Not indicated

HIV: human immunodeficiency virus; NG: Neisseria gonorrhea; CT: *Chlamydia trachomatis;* STI: sexually transmitted infections.

28) of the cases. A total of 4 fetal deaths were reported, and there was no case of neonatal death within 30 days of birth (Table 2).

Among all the medical complications reported during pregnancy (n = 33), 6.06% (n = 2) presented oligohydramnios, and 6.06% (n = 2) presented cholestasis. Chorioamnionitis (n = 4), fetal tachycardia (n = 3), fever (n = 3), and late decelerations (n = 1) were reported during labor. Mpox symptoms appeared within 3 days after delivery (n = 2) (Table 2).

One of the studies reported a case of intrauterine fetal death [11]. The researchers extended their diagnostic analysis to the dead fetus and the placenta. Diffuse cutaneous maculopapular lesions involving the skin of the head, trunk, abdomen, back, chest, and extremities, including the palms and soles; hydrops fetalis; and hepatomegaly with peritoneal effusion were reported in the fetus. Hemorrhages on the maternal cotyledon surfaces and numerous punctate and diffuse abnormalities were reported on the placenta. Both the samples were positive for MPXV PCR.

Discussion

Molecular diagnosis of MPXV: specificity and limitations

MPXV is a DNA virus belonging to the genus *Orthopoxvirus*. It is primarily diagnosed through real-time polymerase chain reaction (RT-PCR) targeting MPXV-specific genes such as *J2R*. These assays offer high specificity by avoiding cross-reactivity with other orthopoxviruses. RT-PCR can detect 4 copies of MPXV DNA per microliter, thus making it highly sensitive for biological samples. However, some studies have utilized a *Orthomyxovirus* PCR that does not distinguish MPXV from other orthopoxviruses. The most reliable diagnosis is achieved through MPXV-specific PCRs or by confirming through next-generation sequencing (NGS), particularly in epidemiological surveillance or atypical presentations [16].

Confirmed, suspected, and probable cases according to the Centers for Disease Control and Prevention (CDC) guidelines or case definitions

The CDC classifies mpox infection as suspected, probable, or confirmed; based on clinical, epidemiological, and laboratory criteria. Confirmed cases require MPXV DNA detection by PCR or virus isolation. Nearly all the studies in this review followed these criteria, with the exception of one [9] that lacked clear diagnostic methods despite being labeled as "confirmed." Another study relied only on *Orthopoxvirus* PCR without MPXV-specific testing [17], underscoring the need for greater standardization in diagnostic protocols to improve reliability in clinical and epidemiological reporting.

Limitations in current evidence regarding vertical transmission

Although there are reports of vertical transmission of mpox and its different outcomes, the exact mechanism of this transmission is unknown [18]. Proposed mechanisms include hematogenous spread, ascending infection from genital lesions, and placental invasion through infected trophoblasts [18,19]. However, these are hypotheses based on limited case reports and extrapolated data, and should be interpreted cautiously.

In contrast to the results of this study, another systematic review reported that fetal loss occurred in up to 39% of pregnancies with complications of mpox infection. The study reported that intrauterine fetal death had an incidence of 23%, and total fetal loss could reach 77%. Vertical transmission, due to the immunological weakness in pregnant women, allows the virus to enter through the maternal uterine spiral

Table 2. Fetal outcomes in pregnant women infected with monkeypox (mpox).

Year of publication, country	No. of patients	Gestational age at birth	Complications during labor	Fetal complications	Placental outcome
2023, USA	1	37 3/7 weeks	Chorioamnionitis, fetal tachycardia	No	Not indicated
	2	39 4/7 weeks	Loss of amniotic fluid, chorioamnionitis, oligohydramnios, fetal tachycardia	No	Not indicated
2023, USA	1	37 3/7 weeks	Fever, chorioamnionitis	No	Corioamnionitis stage 1
	2	38 4/7 weeks	Chorioamnionitis, Fever, Fetal tachycardia, late decelerations	No	Not indicated
2017, Democratic Republic of Congo	1	Not indicated	Not indicated	Miscarriage	Not indicated
	2	Not indicated	Not indicated	Miscarriage	Not indicated
	3	a term	Not indicated	Live birth	Not indicated
	4	Not indicated	Not indicated	Fetal death	Placental hemorrhages on the maternal cotyledon surfaces, which were numerous, punctate, and diffuse
2023, USA	1	39 2/7 weeks	No	No	Histopathologically normal
2024, Spain	1	38 5/7 weeks	2 peaks of fever, Chorioamnionitis	No	Not indicated

arteries, infecting trophoblast cells and eventually reaching fetal blood cells. This has proven to be a significant risk in 62% of the cases. The incidence of premature birth is low at around 8% [20].

Comparison with other congenital viral infections

Other congenital viral infection such as cytomegalovirus (CMV), rubella, and Zika virus carry varying risks depending on the timing of maternal infection. Specifically, the spontaneous abortion rate for CMV is estimated at 10–20% [21], while intrauterine fetal death occurs in approximately 13% of cases [22]. Fetal death has been reported in up to 90% of rubella infections occurring 11 weeks prior to gestation [23]. In support of this, a study in Brazil analyzing 25 rubella cases in pregnancy reported fetal death or spontaneous abortion in 40% of cases [24]. Moreover, vertical transmission of CMV occurs in about 30–40% of primary maternal infections [25–26]. Finally, rubella infection during early pregnancy, particularly in the first trimester, poses significantly higher risks, with vertical transmission rates reaching up to 90% [27].

Based on available reports, mpox in pregnancy appears to be associated with high rates of fetal loss; therefore, caution must be exercised when comparing it to better-characterized infections. However, since this review included a limited number of cases, inconsistent gestational timing, and lack of neonatal follow-up data significantly limited the strength of such comparisons. More systematic data are urgently needed to confirm the true burden and risks associated with MPXV in pregnancy

Epidemiological and clinical evolution of mpox before and during the 2022 outbreak

Mpox has caused outbreaks, mainly in Central and West Africa, since 1970. The largest recorded outbreak prior to 2022 occurred in the DRC (1996–1997) with over 500 cases [28], and 19,273 suspected cases were reported between 2000–2015 [29]. During that period, clinical presentation was characterized by a 5–34-day incubation, followed by fever, chills, headache, and myalgia for 2–13 days. Subsequently, a centrifugal rash progressed to ulcers or necrotic lesions over 7–24 days [30]. Outside Africa, mpox was uncommon, typically linked to travel or animal importation. Notably, the first mpox case reported outside Africa occurred in Wisconsin, USA in 2003, linked to prairie dogs exposed to African rodents. By July, 72 cases were identified in three states [31].

The 2022 mpox outbreak (clade IIb) was characterized by predominantly sexual transmission, with lesions on genital, perianal, oral, and perioral regions. The incubation period averaged 7–10 days, shorter than that reported in earlier outbreaks. Additionally, patients often presented with proctitis, pharyngitis, urethritis, or ocular involvement [32]. In this review, pregnant women presented with vaginitis, genital rash, vaginal bleeding, dysuria, and lymphadenopathy—symptoms distinct from classical forms, but without maternal deaths.

Comparison with other Orthopoxvirus infections in pregnancy

Smallpox, another *Orthopoxvirus*, carries high maternal risk. One study reported a 34.3% mortality rate, often resulting in fetal death, preterm birth or neonatal mortality [33]. Moreover, hemorrhagic forms of smallpox produced severe complications resembling disseminated intravascular coagulation. In one series, unvaccinated pregnant women with smallpox had a case fatality rate of 61.1%, higher than in nonpregnant women (34.7%) and men (30.2%) [34].

Although mpox lesions mimic smallpox (maculopapules, vesicles, pustules, proctitis) [35], this review identified additional features—severe pruritus, cholestasis, and chorioamnionitis. Furthermore, while congenital smallpox caused near-total mortality [36], two neonatal mpox cases and one stillbirth with lesions were observed. Similarly, a 2021 cowpox case led to fetal demise with localized hand and facial lesions [37], whereas mpox lesions in this review appeared more widespread.

Limitations

Several limitations should be considered when interpreting this review. First, publication bias is inherent to systematic reviews, particularly in the context of emerging diseases, where severe or atypical cases are more likely to be reported. Second, study heterogeneity in diagnostic methods and outcome reporting also affects comparability. Third, journal selection bias and unmeasured confounding factors, including potential selection bias, cannot be completely excluded. One of the included sources in this review was a report from the CDC's Morbidity and Mortality Weekly Report (MMWR). Although MMWR is not a traditional academic journal, it is a trusted public health bulletin that provides timely and authoritative epidemiological data. Its inclusion reflects the limited availability of detailed reports on mpox in pregnancy and contributes valuable early insights.

Conclusions

Mpox during pregnancy is a public health concern that must be addressed due to its potential to cause severe maternal and fetal complications. Diagnostic tools such as PCR using *J2R* gene-specific primers provide accurate detection and differentiation from other orthopoxviruses. Infected pregnant women may present with gynecological symptoms such as vaginitis, vaginal bleeding, and dysuria; as well as systemic signs like lymphadenopathy and genital rash. Intrapartum complications, particularly chorioamnionitis, fetal tachycardia, and maternal fever, suggest maternal-fetal stress. Alarmingly, high rates of miscarriage and stillbirth were observed; and while vertical transmission remains uncertain, some neonates showed mpox-like lesions and one case of fetal malformation was documented.

Recommendations

Clinicians should conduct thorough evaluations of pregnant patients presenting with skin rashes, especially in early pregnancy; and consider the possibility of mpox infection during labor, particularly in areas with known epidemiological risk. Prospective studies are urgently needed to elucidate the mechanisms of vertical transmission and fetal complications associated with mpox.

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Conflict of interests

No conflict of interests is declared.

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Annex – Supplementary items

Supplementary Table 1. PICOS criteria and search strategy.
A. PICOS criteria

Population of interest	Pregnant women
Intervention	Monkeypox (mpox) confirmed by polymerase chain reaction (PCR)
Comparator	Not measured
Outcomes of interest	Miscarriage, stillbirth, fetal anomalies detected at ultrasound or birth, preterm birth (before 37 weeks of gestation), complications during the pregnancy, complications during the childbirth or postpartum period, anomalies in the placenta detected during ultrasound or histopathology, or maternal death.
Study designs	All study designs reporting primary data on maternal mpox in humans in any setting and any country in any period.

B. Search strategy
English language searches: 471; Database: Pubmed (MEDLINE)

(n = 104)	**("monkeypox"[TIAB] OR "monkey pox"[TIAB] OR "mpox"[TIAB]) AND ("pregnant women"[TIAB] OR "pregnancy"[TIAB] OR "pregnant"[TIAB])**

Database: EMBASE

(n = 115)	('monkeypox':ti,ab,kw OR 'monkey pox':ti,ab,kw OR 'mpox':ti,ab,kw) AND ('pregnant woman':ti,ab,kw OR 'pregnancy':ti,ab,kw OR 'pregnant':ti,ab,kw)

Database: Scopus

n = 144	(TITLE-ABS-KEY ("monkeypox") OR TITLE-ABS-KEY ("monkey pox") OR TITLE-ABS-KEY ("mpox")) AND (TITLE-ABS-KEY ("pregnant women") OR TITLE-ABS-KEY ("pregnancy") OR TITLE-ABS-KEY ("pregnant"))

Database: Web of Science

(n = 108)	TS=("monkeypox" OR "monkey pox" OR "mpox") AND TS=("pregnant women" OR "pregnancy" OR "pregnant")

PICOS: population: intervention: comparison: outcomes and study design.