e-ISSN 3050-8460
Journal of Dermatology Research

ATHENAEUM SCIENTIFIC PUBLISHERS

Review Article

A Review of Antiherpetic Medications in Pregnancy to Suppress Erythema Multiforme and Risks of Fetal Harm

Joshua J Weyand[1], Maria L Andrzejewski[1], Edward M Klepper[1*], Howard N Robinson[1]

[1]Robinson and Max Dermatology, PA, USA

***Correspondence author:** Edward M Klepper, MS, PA-C, Robinson and Max Dermatology, PA, USA;
Email: edwardklepper@gmail.com

Citation: Weyand JJ, et al. A Review of Antiherpetic Medications in Pregnancy to Suppress Erythema Multiforme and Risks of Fetal Harm. J Dermatol Res. 2026;7(2):1-8.

https://doi.org/10.46889/JDR.2026.7213

Received Date: 30-06-2026

Accepted Date: 27-07-2026

Published Date: 03-08-2026

Abstract

A review of the literature highlights a 2.2% rate of major fetal birth defects in patients exposed to acyclovir, valacyclovir or famciclovir prophylaxis in the first trimester, comparable to a 2.4% rate in those not exposed to the antiviral therapy in a Danish cohort study. In addition, the literature reveals multiple cases of herpes simplex virus associated erythema multiforme occurring during pregnancy, with a wide array of outcomes including significantly decreased oral intake and as severe as fetal demise. The authors are concerned with the morbidity and mortality of unborn fetuses from mothers with recurrent exacerbations of herpes simplex virus induced erythema multiforme that have not been protected with antiviral therapy. Therefore, the following review was conducted to analyze available evidence regarding the impacts of erythema multiforme on pregnancy and the safety of antiviral therapy in expecting mothers.

Keywords: Acyclovir; Erythema Multiforme; Famciclovir; Fetus; Herpes; Valacyclovir

Introduction

Viral induced Erythema Multiforme (EM) is an acute reaction of the skin and mucous membranes that produce characteristic targetoid lesions as a hypersensitivity response to a viral trigger, most commonly herpes simplex virus [1].

Current management of viral-induced erythema multiforme remains largely supportive with an emphasis on ensuring adequate fluid intake [1]. However, in Herpes Simplex Virus (HSV) associated cases of erythema multiforme, viral suppression plays a central role in reducing recurrence and eliminating complications [1]. The three most frequently used antiviral agents include acyclovir, valacyclovir and famciclovir, with acyclovir the most common standard of care [2]. Complications in pregnancy can result from misdiagnosis with Stevens Johnson Syndrome (SJS) or Toxic Epidermal Necrolysis (TEN), viral transmissibility to the neonate or sequelae of malnourishment during gestation.

Previous case reports have shown the outcomes to range from healthy births,vaginal adhesions or fetal demise [2,3]. This research study aims to determine the safety and efficacy of initiating viral suppression with acyclovir or valacyclovir in women at all stages of pregnancy.

Materials and Methods

A literature review was performed April 2, 2026 through July 18, 2026 using the Pubmed database and Cochrane Library. Databases that required a paid membership were not used. Free, full-text and English randomized clinical trials, meta-analysis, case reports and retrospective studies were reviewed by all 4 researchers. An independent review was performed followed by a

consensus meeting. Disagreement was resolved through scholarly discussion. Articles were reviewed Search terms included Erythema multiforme AND pregnancy, valacyclovir AND pregnancy, acyclovir AND pregnancy, famciclovir AND pregnancy, famciclovir AND erythema multiforme, acyclovir AND erythema multiforme, valacyclovir AND erythema multiforme. Studies published between 2006 and 2026 were considered for review. This systematic review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement (Fig. 1).

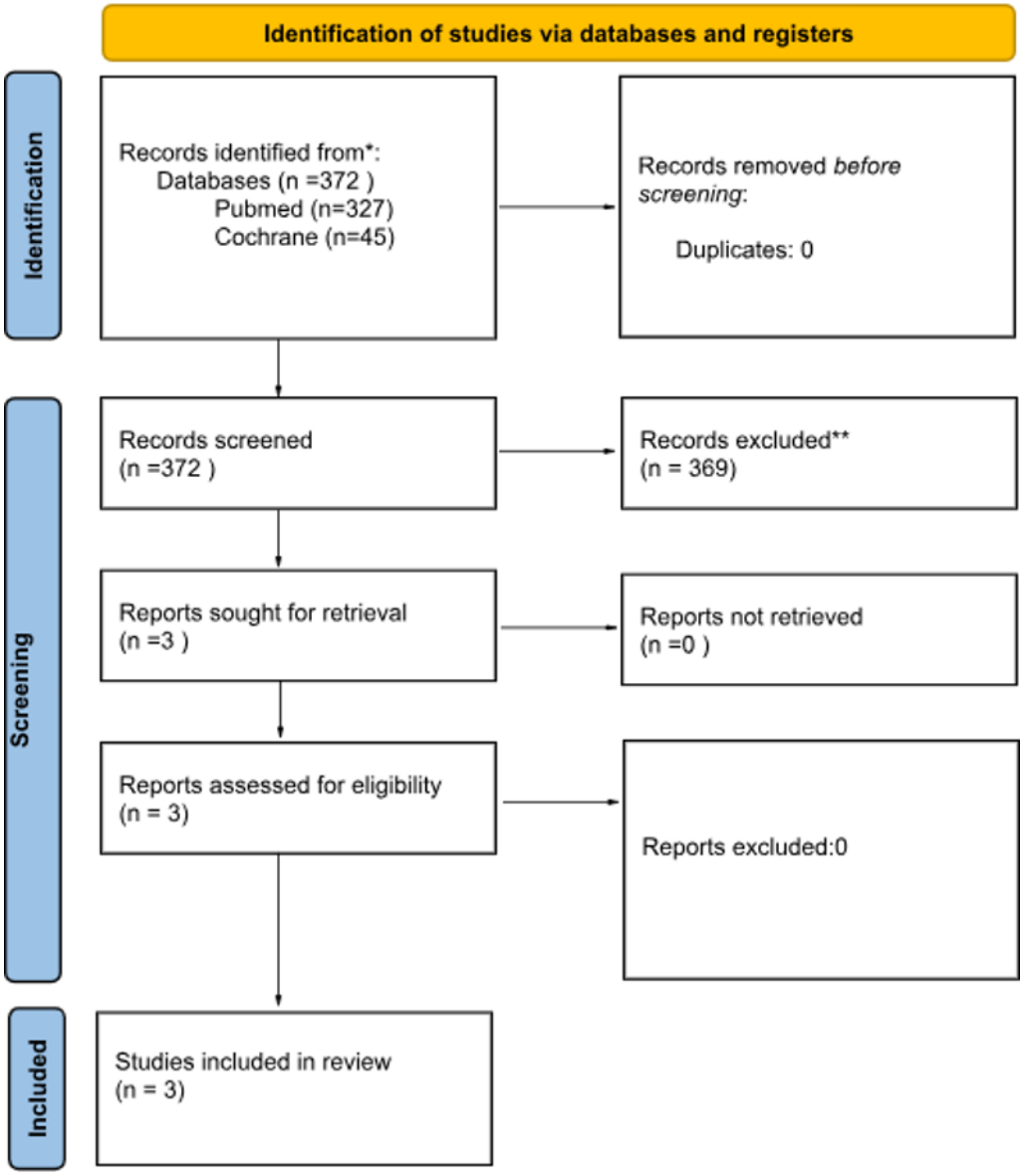

Figure 1: PRISMA 2020 flow diagram.

Results

The incidence of erythema multiforme is detailed in and divided based on subtypes and populations in Table 1. The effects of erythema multiforme on pregnancy are not well defined, with available data largely limited to case reports. However, the safety of antiviral therapy has been well studied throughout pregnancy. Historically, EM had been considered to be on the mild end of a spectrum of cutaneous disorders including SJS and TEN; however, more recently it has been distinguished as its own entity as a dermatologic disorder [4]. Table 2 details the mortality rates associated with erythema multiforme, SJS and TEN. Erythema multiforme is differentiated into two subtypes: Erythema Multiforme Major and Erythema Multiforme Minor. Erythema major describes severe mucosal involvement with lesions greater than 1 cm and potential systemic symptoms such as fevers and joint pains whereas erythema minor is without significant mucosal involvement and absent systemic symptoms [4].

Population	Incidence/Prevalence	Comments/Interpretation
General population (overall EM)	~0.01%–1% annually	Rare condition overall
HSV-associated EM (all patients)	Up to ~90% of EM cases linked to HSV	HSV is most common trigger and dominant cause overall
Males	Slightly lower than females	Mild female predominance
Females (non-pregnant)	Slightly higher incidence	No major sex or racial disparity
Pregnant females	Not quantified	Only case reports, not well studied and likely rare. No studied mortality rate

Table 1: Incidence of Erythema Multiforme [4,5].

Condition	Mortality Rate
Erythema Multiforme	≈0%, Essentially negligible
Stevens Johnson Syndrome	1-5%
Toxic Epidermal Necrolysis	25-30%

Table 2: Mortality rates associated with erythema multiforme, Stevens Johnson syndrome and toxic epidermal necrolysis [6].

The following three cases highlight the range of outcomes of patients with erythema multiforme in pregnancy. The first patient received antiviral treatment strategies while the latter two did not. The recent review literature of erythema multiforme in pregnant patients is limited to single case reports listed below.

The first case described a 28-year-old pregnant patient who presented with herpes-associated erythema multiforme [7]. The patient developed severe, painful oral ulcerations and hemorrhagic crusting of the lips [7]. She reported one month of being unable to consume any food due to painful lesions of her mouth [7]. The patient had a positive history of HSV-associated lesions and upon lab studies was found to have a positive herpes simplex virus IgG [7]. The patient was initially treated with famciclovir and was eventually placed on topical fluocinolone acetonide and benzydamine mouthwash for pain control in order to avoid any potentially negative fetal outcomes [7]. The patient saw complete resolution after one month and in addition, there were no adverse maternal or fetal outcomes, as the patient proceeded with an uncomplicated pregnancy. The patient followed up with the researchers eight months post-partum stating that both herself and her son were in healthy condition with no side effects of treatment to report [7]. This case study highlights the significant potential impacts that are secondary to painful oral involvement of erythema multiforme. This resulted in severely decreased oral intake during the critical period of pregnancy [7]. In addition, this case also emphasizes the importance of adequate management of erythema multiforme in pregnancy and the safety of antiviral and topical corticosteroid therapy in managing severe herpes simplex associated erythema multiforme during pregnancy [7].

The second case analyzed a 33-year-old pregnant patient with a history of recurrent erythema multiforme. The study states that she experienced blisters of oral and cutaneous mucosa and required inpatient hospitalization at 16 and 28 weeks [8]. She was treated with prednisolone, esomeprazole, topical lidocaine and supportive care [8].

Despite recurrent erythema multiforme, the pregnancy progressed to 36 weeks and the patient developed an unassociated hydronephrosis, prompting labor induction [8]. The patient ultimately delivered a healthy infant without complications from erythema multiforme [8]. In this case, the development of recurrent erythema multiforme was associated primarily with transient mucocutaneous discomfort, affecting oral intake [8].

Fortunately, this case ultimately resulted in favorable neonatal outcomes, consistent with the previously discussed case [8,9]. In addition, the case report referenced results from a 1988 study which included four cases of women diagnosed with erythema multiforme during pregnancy. Of those four patients, 100% of them gave birth to live or healthy babies and no incidence of vaginal stenosis was noted [3]. This study noted that only mild consequences of erythema multiforme were described, such as decreased food and fluid intake due to painful eating and drinking from mucosal lesions [8]. From the analyzed studies thus far, decreased oral intake due to irritation and pain from lesions of the oral mucosa is recurrent finding that represents a mild complication of erythema multiforme [8].

The third case report described a 32 year old woman who was diagnosed with erythema multiforme with vulvovaginal involvement in the first trimester of pregnancy. In this case, the patient developed symptoms at roughly 13 weeks gestation with rash and sore throat. She was initially treated with ceftriaxone and amoxicillin/clavulanic acid. Her symptoms progressed and she presented to the emergency department in the United States as she had diffused erosions with yellow crust and purulent drainage of her scalp. In addition, she had numerous targetoid lesions present on her abdomen and trunk. She reported associated eyelid swelling, blurry vision, photophobia and her proximal nail folds of her fingers were swollen and brown and violaceous. The emergency department consulted dermatology and she was diagnosed with erythema multiforme with superimposed bacterial infection, as serology showed elevated IgG titers for mycoplasma pneumoniae and HSV1, with wound cultures growing *Aspergillus flavus, coagulase-negative Staphylococcus, Enterococcus faecalis* and E*scherichia coli.* She was treated with doxycycline, vancomycin and aztreonam, for infection and dexamethasone for inflammation. A multidisciplinary approach was utilized and upon ultrasound, fetal demise at 16 weeks and 6 days was diagnosed. The case was further complicated post fetal demise as tender vulvovaginal erosions and adhesions were appreciated and vaginal triamcinolone suppositories were initiated prior to dilation and evacuation. The patient underwent successful dilation and evacuation in order to avoid further complications such as vaginal stenosis, adhesions and impaired future fertility outcomes. This case highlights the potential severe complications of herpes simplex associated erythema multiforme in pregnancy and emphasizes the importance of initiating reasonable therapy for achieving favorable outcomes [9]. While the literature regarding the outcomes of erythema multiforme in pregnancy are recently limited to numerous case studies, treatment strategies against the most common trigger, herpes simplex virus, have been well studied [4]. The first of which, a large cohort study conducted in Denmark, analyzed the impacts of antivirals throughout the entire duration of pregnancy, including four weeks prior to conception [2]. Out of 837,795 live-born infants, 1,804 were exposed to either acyclovir, valacyclovir or famciclovir [2]. This study found that in the control group, who did not receive antiviral treatment, there was a rate of 2.4% of birth defects [2]. This was compared to a rate of 2.8% in patients exposed to antiviral therapy in the 1 to 4 weeks prior to conception, a rate of 2.2% in patients exposed to antivirals in the first trimester and a rate of 2.1% in patients exposed to antivirals in the second and third trimesters [2]. In addition to the data sets analyzing the timing of exposure to antivirals, the study additionally analyzed adverse effects associated with specific antiherpetic medications [2]. It was found that in utero exposure to acyclovir of 1561 patients was associated with a 2.0% rate of major birth defects, while valacyclovir exposure showed a 3.1% rate of the 226 exposures and famciclovir was associated with 1 birth defect of 26 exposures and a rate of 3.8% [2]. From this data, no significant associations were identified between exposure to acyclovir, valacyclovir or famciclovir and major birth defects. While the rate of defects was slightly elevated in patients exposed to valacyclovir and famciclovir, the sample sizes, 226 and 26 respectively, were not large enough overall to show significant increase in causation [2]. From this study, there was an insufficient sample size of patients treated with valacyclovir or famciclovir to analyze the relationship between the specific antiviral and specific fetal defects [2]. However, the data collected from the sample of patients treated with acyclovir displayed a wide array of birth defects and are analyzed in Table 3 [2]. The results show no specific association between a distinct type of defect and acyclovir use, although it is worth noting that most common types of defects were cardiac, resulting in 0.6% of the patients treated with acyclovir [2]. Overall, exposure to antiviral acyclovir or valacyclovir from four weeks prior to conception until birth was not associated with increased risk of birth defects [2].

Type of Fetal Defect	Number of Cases	Percentage
Cardiac	10	≈ 0.6%
Urinary	8	≈ 0.5%
Nervous System	3	≈ 0.2%
Limb	2	≈ 0.1%
Musculoskeletal	2	≈ 0.1%
Orofacial	2	≈ 0.1%
Genital	2	≈ 0.1%
Eye	2	≈ 0.1%
Digestive System	1	≈ 0.1%
Abdominal Wall	1	≈ 0.1%
Respiratory	0	0.0%
Ear/Face/Neck	0	0.0%

Table 3: Type of birth defects with exposure to acyclovir [2].

The second research study of safety of antiherpetic treatment in pregnancy was a double blinded study that analyzed 200 pregnant women who tested positive for Herpes simplex virus and analyzed outcomes all the way up until birth [10]. Of the sample, 100 women were randomly selected and received acyclovir 400 mg daily and the other 100 women received daily placebo up until 36 weeks [10]. After 36 weeks, both groups were given treatment with acyclovir [10]. While not statistically significant, the study found that of the patients treated with acyclovir in the experimental group 4% developed premature rupture of membranes at 36 weeks gestation, while 10% developed premature rupture of membranes at 36 weeks gestation in the placebo group [10]. The researchers did however find a significant reduction in pre-term delivery in the patients treated with acyclovir compared to placebo, with the rates of preterm delivery being 11.1% in the experimental group versus 23.5% in placebo [10]. The study concluded that in the third trimester treatment of HSV to positive women had no significant impacts on premature preterm rupture of membranes, APGAR scores, admissions to the ICU or fetal demise [10].

In contrast to the previous literature, another case-control study evaluated the association between maternal antiherpetic medication use, genital herpes infection and the risk of gastroschisis in newborns [11]. Among 941 gastroschisis cases and 8,339 controls, maternal use of acyclovir, valacyclovir and famciclovir within three months prior to conception through the first trimester was reported more frequently in cases than controls [11]. The results demonstrated that antiherpetic medication use was associated with a 4.68 increased odds ratio of gastroschisis, compared to a 3.0 increased odds ratio in patients with self-reported genital herpes infection not exposed to antiherpetic medications [11]. These findings suggest a potential association between both antiherpetic therapy and underlying herpes infection with gastroschisis; however, causality cannot be established [11]. It is worth noting that acyclovir is considered to be the antiviral of choice in cases of herpes simplex associated erythema multiforme as seen in Tables 4 and 5. Table 6 highlights the outcomes of reported cases of erythema multiforme in pregnancy. The evidence from the studies above points to the benefits of treating herpes simplex virus associated erythema multiforme in pregnancy to mitigate the potential adverse outcomes on the mother and child.

Type of Antiherpetic	Cases of Fetal Harm
Acyclovir	32 / 1561 (2.0%)
Valacyclovir	7 / 226 (3.1%)
Famciclovir	1 / 26 (3.8%)

Table 4: Incidence of fetal harm after exposure to antiherpetics in the first trimester [2].

Type of Antiherpetic	Cases of Fetal Harm
Acyclovir	47 / 2379 (2.0%)
Valacyclovir	6 / 216 (2.8%)
Famciclovir	0 / 10 (0%)

Table 5: Incidence of fetal harm after exposure to antiherpetics in the second and third trimester [2].

Patient	Patient Age	Treatments Initiated	Adverse Effects and Outcomes
Case 1	28	Famciclovir, fluocinolone acetonide and benzydamine mouthwash	Decreased oral intake, healthy birth
Case 2	33	prednisolone, esomeprazole, topical lidocaine	Decreased oral intake, healthy birth
Case 3	32	ceftriaxone amoxicillin/clavulanic acid	Fetal demise, vaginal adhesions

Table 6: Outcomes of cases of erythema multiforme in pregnancy [7-9].

Discussion

This subject brings up a risk versus benefits discussion to treat versus to not treat the underlying virus. Erythema multiforme can be triggered by a litany of infectious causes, including *Mycoplasma Pneumoniae*, Hepatitis C, SARS-CoV-2 and more [2]. The most common trigger for the rash however is herpes simplex virus, which is the underlying virus in up to 90% of erythema multiforme cases [1,2]. Complications during fetal development in pregnancy have a stronger association with the major subtype,

as the potential misdiagnosis with Stevens johnsons syndrome or toxic epidermal necrolysis is greater and significant involvement of oral or genital mucosa can have outcomes such as decreased oral intake or viral transmissibility to the neonate [8,12]. The cases presented showed outcomes ranging from severe maternal malnutrition to fetal demise [9]. These complications are secondary to changes in mucosal membranes having a direct impact in fetal health. Reviews of literature reveal a balance between the safety of initiating antiviral therapy and the importance of prompt treatment of erythema multiforme in pregnancy.

A common theme surrounding pregnancies is complicated by erythema multiforme surrounds involvement of oral mucosa. Multiple cases reported that their patients were unable to tolerate intake of food and water by mouth due to painful lesions, erosions or crusts within the oral mucosa [7,8]. Decreased intake can complicate pregnancy by leading to decreased absorption of necessary vitamins and minerals in pregnancy. The study which researched cases of gastroschisis and antiherpetic use highlights the risk of gastroschisis with antiherpetic medication use in pregnancy, however, does not illustrate strong enough evidence to endorse whether antiherpetic use or exposure to herpes virus has a stronger cause-effect relationship with the development of gastroschisis [11].

Established risk factors for gastroschisis birth defects include, but are not limited to, low BMI and dietary insufficiency during pregnancy. These risk factors overlap with potential adverse effects of erythema multiforme major with oral mucosa involvement limiting oral intake [7,8]. This raises questions for future studies to analyze the relationship between antiherpetics and gastroschisis and must consider the presence of additional risk factors to provide more significant evidence as to whether antiherpetic medication is causative of or protective for development of gastroschisis potentially associated with herpes simplex infections during pregnancy.

The third case of the patient with fetal demise highlights the importance of prompt identification and adequate management of herpes simplex associated erythema multiforme during pregnancy [9]. The patient started on antibiotic therapy, with IgG titers positive for HSV and the fetus did not survive [9]. This contrasts the 28-year-old patient in the first case who was treated in the first trimester with famciclovir initially, then fluocinolone acetonide and saw complete resolution and delivered a healthy baby [7]. Although these cases demonstrate markedly different pregnancy outcomes, individual case reports cannot establish whether antiviral treatment was directly responsible for favorable outcomes versus fetal demise [7,9]. Nevertheless, they illustrate the need for early diagnosis and careful consideration of antiviral therapy in pregnant patients with suspected HSV-associated erythema multiforme.

The clinical presentation in this third case reveals a multifaceted polymicrobial infection as cultures identified *Aspergillus flavus, coagulase-negative Staphylococcus*, *Enterococcus faecalis* and *Escherichia coli*, while serological testing was reactive for *Mycoplasma pneumoniae* and HSV1. Consequently, this may not represent a classic herpes-associated erythema multiforme and the fetal demise may be attributed to systemic sepsis rather than EM in isolation.

The frequency of these complications can be mitigated safely with initiation of viral suppression using acyclovir, valacyclovir or famciclovir. The results discussed in the above trials detail safety of viral treatment in all three trimesters [2,10]. The research studies analyzed showed no significant increase in birth defects, premature rupture of membranes, low APGAR scores, neonatal sepsis or admissions to the NICU [2,10]. While an association between gastroschisis and antiherpetic use was identified in the third study, at this time the evidence is inconclusive to establish a causation and will require future research to analyze with in depth research parameters [11].

In these circumstances, shared decision making is imperative to allow the patient to weigh risks and benefits to make the safest decision while respecting patient autonomy. The initiation of acyclovir with close monitoring before and during pregnancy appears the most reliable treatment analyzed for decreasing the potential adverse outcomes of erythema multiforme for mother and fetus.

Conclusion

In treating patients with erythema multiforme, shared decision making is a cornerstone of treating the patient. This includes weighing risks and benefits and discussing potentially adverse outcomes of treating versus not treating. Available data is severely limited, as no prospective studies have specifically examined HSV-associated EM during pregnancy. Current

recommendations are predominantly derived from HSV management protocols instead of EM-specific data. Viral suppression therapy should be considered more strongly in pregnant patients with Erythema Multiforme, given the potential consequences and the low risk of antiviral therapy to the pregnancy.

Limitations: Potential weaknesses in this review include the low volume of erythema multiforme cases documented in pregnant populations, a heavy dependence on individual case reports and the possibility of publication bias. Furthermore, the lack of meta-analysis, the presence of diverse study demographics and the reliance on indirect data derived from general herpes simplex virus research may impact the generalizability of these findings.

Conflict of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

Funding Statement

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

Acknowledgement

The authors have no acknowledgments to declare.

Data Availability Statement

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Ethical Statement

The study conducted was a review of existing literature and involved no direct patient interaction or access to medical records. In this case, institutional review board approval and informed consent were not required.

Informed Consent Statement

Informed consent was not applicable.

Authors' Contributions

All authors contributed equally to this paper.

References

1. Wetter DA. Erythema multiforme: Pathogenesis, clinical features and diagnosis. UpToDate. 2025.
2. Pasternak B, Hviid A. Use of acyclovir, valacyclovir and famciclovir in the first trimester of pregnancy and the risk of birth defects. JAMA. 2010;304(8):859-66.
3. Kratzert K, Marks F, Antoine C, Brescia RJ, Parodneck L, Young BK. Pregnancy post-Stevens-Johnson syndrome: Case report and review of the literature. Obstet Gynecol. 1988;72(3 Pt 2):447-50.
4. Trayes KP, Love G, Studdiford JS. Erythema multiforme: recognition and management. Am Fam Physician. 2019;100(2):82-8.
5. Sokumbi O, Wetter DA. Clinical features, diagnosis and treatment of erythema multiforme: A review for the practicing dermatologist. Int J Dermatol. 2012;51(8):889-902.
6. Labib A, Milroy C. Toxic epidermal necrolysis. In: StatPearls. Treasure Island (FL): StatPearls Publishing. 2026.
7. Thongprasom K. Treatment of a pregnant patient with Herpes-Associated Erythema Multiforme (HAEM): A case report. Acta Stomatol Croat. 2016;50(3):265-8.
8. Niemeijer IC, van Praag MC, van Gemund N. Relevance and consequences of erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis in gynecology. Arch Gynecol Obstet. 2009;280(5):851-4.
9. Frisse A, Jobarteh R, Levitt J, Bogaert K, Gerber S. Dilation and evacuation for fetal demise in a patient with presumed erythema multiforme major: A case report. Case Rep Womens Health. 2023;37:e00488.
10. Nakubulwa S, Kaye DK, Bwanga F, Tumwesigye NM, Nakku-Joloba E, Mirembe F. Effect of suppressive acyclovir administered to HSV-2 positive mothers from week 28 to 36 weeks of pregnancy on adverse obstetric outcomes: A double-

blind randomised placebo-controlled trial. Reprod Health. 2017;14(1):31.
11. Ahrens KA, Anderka MT, Feldkamp ML, Canfield MA, Mitchell AA, Werler MM, et al. Antiherpetic medication use and the risk of gastroschisis: findings from the National Birth Defects Prevention Study, 1997-2007. Paediatr Perinat Epidemiol. 2013;27(4):340-5.
12. National Health Service. Neonatal herpes (herpes in a baby). NHS. 2025.