Congenital Herpes Simplex Virus: A Histopathological View of the Placenta

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Abstract

Congenital Herpes simplex virus (HSV) infection is considered a common pregnancy pathology that is not always easy to diagnose. This study aimed to present the spectrum of placental histopathological lesions in pregnancies complicated by HSV infection. MEDLINE and Google Scholar databases were searched using the keywords “HSV” and “placental histopathology” up to June 20, 2022. Study inclusion required presenting placental histopathological anomalies in pregnant women diagnosed with HSV infection antenatally, during labor, or postnatally. Herein, we briefly present placental pathogenesis conditions, which have been correlated with congenital HSV infection, providing clinicians with a short review describing herpetic placental pathology.

Introduction And Background

It is widely acknowledged that specific infections during pregnancy may adversely affect both fetus and mother, inducing congenital disorders, intrauterine growth restriction, prematurity, stillbirth, and spontaneous abortions [1]. Vertical transmission is defined as the transmission of a pathogen from mother to fetus in utero through the hematogenous or the ascending route. This may lead to the disruption of organogenesis, which may be related to congenital anomalies in every major organ system [1,2]. Additionally, infection of the fetus through the genital tract during birth may increase the rate of neonatal morbidity and mortality [3].

The acronym “TORCH” which stands for Toxoplasma gondii, other agents, rubella virus, cytomegalovirus (CMV), and herpes simplex virus (HSV) has been proposed to describe the major pathogens, which may be related to the development of congenital disease [1,2]. TORCH pathogens can enter the intra-amniotic space and overcome placental defense mechanisms that protect against vertical microbial transmission [1-3].

HSV is a double-stranded DNA virus and a member of the Herpesviridae family [4], responsible for oral and genital herpes [5]. As a neurotropic virus, it is detected in the dorsal root ganglion, following primary infection [1,6]. The presence of the G1 and G2 glycoproteins in the lipid bilayer envelope can serve as markers that determine the viral serotype, HSV-1 and HSV-2, respectively [7].

It has been estimated that over 15% of the population within the reproductive age has been infected with HSV-2, a phenomenon that establishes HSV-2 as the most common sexually transmitted infection [8,9]. Thus, the risk of fetal or neonatal transmission is increased as numerous women of reproductive age are considered to be infected [7].

HSV could be transmitted to the fetus through the transplacental or the ascending route of acquisition from the vagina or cervix, even when the amniotic membranes remain intact [10,11]. Despite that, the intrapartum transmission of HSV through contact with a virus-shedding lesion in the genital tract tends to be the most commonly detected transmission route [12]. Maternal-fetal transmission may occur in any of the three pregnancy trimesters [13].

The teratogenic effect of HSV on an embryo may provoke a variety of clinical outcomes, namely, ventriculomegaly, microcephaly, intracerebral calcifications, limb dysplasia [1], eye defects [4], and fetal loss [11,14]. As previously reported, primary infection in late pregnancy increases the risk of vertical transmission [13]. The increased rates of fetal loss and the neurodevelopmental disorders regarding fetal neurons and neuronal precursors following HSV infection are associated with poor prognosis [13,15].

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As evidenced by the literature, there are inconclusive results concerning the mechanism responsible for fetus infection by HSV. It has been reported that the expression of HSV entry mediators in syncytiotrophoblast (SYN), namely HveA, HveB, and HveC, provides resistance to viral infection. The inflammation-mediated breakage of the SYN layer allows the virus to reach fetal circulation [1,16]. Furthermore, it has been reported that HSV may be detected in the dorsal root ganglia following the primary infection [17]. Thus, potentially, a transneural migration of HSV to the endometrium may result in uterus transmission during pregnancy [17]. In contrast, the expression of all entry mediators at the extravillous cytotrophoblast (EVT) renders it sensitive to HSV transmission [9,18]. Moreover, the infection of endothelial cells in maternal microvasculature may also induce EVT infection [1,16].

During pregnancy, most of the infected women are asymptomatic or present with nonspecific symptoms. The absence of clinical characteristics could result in a late diagnosis of congenital or neonatal HSV infection, increasing both morbidity and mortality [11,17]. The placenta may be macroscopically normal [19], and its histopathological manifestations may be nonspecific for the HSV infection. Since the placental pathological examination could constitute a strong indication of the viral presence, the current study aims to explore the effects of congenital HSV infection on the placenta’s histopathological profile.

Review

Placenta histopathological findings

Herpetic placentitis constitutes a microscopic feature in the placental pathological examination, indicating hematogenous transplacental HSV transmission. It is characterized by the co-existence of herpetic villitis, chronic intervillitis, and villous necrosis. Particularly, lymphoplasmacytes may penetrate villi [20], while the extensive presence of histiocytes in intervillous space [21] and areas with villous necrosis and granulomatous reaction may be further identified. Moreover, the literature indicates that necrotic Hofbauer cells and syncytiotrophoblast may also be detected [20,22,23]. Additionally, trophoblastic multinucleation may constitute another finding [21], and the characteristic viral inclusion bodies, also known as HSV Cowdry type B, are frequently identified [10]. Due to the degeneration of HSV-infected cells’ nucleus, Cowdry type B may appear in the amniotic epithelium, trophoblast, chorion, and decidual cells like eosinophilic ground-glass areas in the nucleus with margination of nuclear chromatin. All these findings are considered indicative of HSV infection [20,22-25].

Chronic placental inflammation (CPI) constitutes a common histopathologic finding in infections like herpesvirus (HSV-1 and HSV-2) with high maternal-fetal rate transmission. CPI is characterized by the presence of lymphocytic, histiocytic, and plasmacytic infiltration in the villous tree, similar to villitis, as well as in extravascular chorioamniotic membranes, chorionic plate, and basal plate of the placenta [26,27]. It should be noted that the aforementioned placental entities may be regularly observed as separate findings.

Chronic chorioamnionitis constitutes an ascending route of HSV infection, in which amniotic multinucleation, degeneration, and necrosis are described as common histopathological findings. Furthermore, these multinucleated residual cells may be detected in the superficial chorion, while the fetal chorion’s role is considered crucial compared to the amnion. Fetal surface and free membranes may be infiltrated by lymphoplasmacytes and less often by histiocytes, whereas the absence of villitis is not atypical [10]. Plasma cells are sparsely observed in chronic chorioamnionitis, while their presence indicates HSV, CMV, or syphilis infection [20,28-31].

Necrotizing chorioamnionitis, also known as stage 3 of maternal inflammatory response in ascending intrauterine infection, is an acute inflammation of the chorioamnion membranes [28]. Necrotizing chorioamnionitis is accompanied by amnion epithelial necrosis and karyorrhexis of neutrophils. Moreover, thickening and hyperesinophilia may be observed in the amniotic basement membrane [27,32]. Additionally, subamniotic true "blisters" and plasma cells may also be detected [19]. The excessive necrosis of amnion without any evidence of inflammation may be considered as another finding, which has been described as "cloudy membranes" and has been associated with herpetic infection [22,33-36].

Chronic villitis (CV) refers to the detection of maternal lymphocytes, histiocytes, and, in some cases, plasma cells in placental villi and has been associated with congenital viral infection [14,25], as shown in Figure .

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In this case, chorionic villi appear hypovascular, without distinct borders [20]. Diagnosis of CV entails the maternal and fetal investigation for viral infection, including HSV [37–40]. In the case of localization of villitis only on the maternal floor, chorionic villi are defined as basal CV. Identification of severe plasma cell infiltration of chorionic villi may constitute an indication of congenital HSV infection, and further investigation is required [20]. Additionally, CV accompanied by multinucleated giant cells may be linked to HSV, varicella, or toxoplasmosis [41].

Villitis of unknown etiology (VUE) is defined as the lymphohistiocytic infiltration of chorionic villi in the absence of a specific infectious pathogen [28]. It is considered a common lesion, especially in full-term placentas [42]. Grossly, the placenta of VUE may be described as stiff and, if villitis is extensive, the villous tree tends to be molded. Microscopically, the villous tree seems to be intensely infiltrated by neutrophils and granulomas, mainly in the basal villi on the maternal floor. Furthermore, ischemia and infraction may be encountered as secondary findings [19, 42]. This pattern requires a detailed investigation for a possible congenital infection rather than an isolated clinical incident. Since VUE seems to have a high recurrence rate, HSV transmission may be excluded in these cases [43]. The presence of plasma cells and viral inclusions in VUE cases may indicate congenital HSV [20].

Villous necrosis can be presented in a scattered foci pattern and co-exist with decidual necrosis. It has been reported that bland patchy villous necrosis can indicate an ascending herpetic infection, especially if necrotizing deciduitis or funisitis is also detected. An individual finding can be considered nonspecific but can also be the only evidence for a congenital infection [22, 44].

Chronic deciduitis is designated as the focal or diffused detection of lymphocytes and plasma cells in decidua basalis or membranous decidua [20], as presented in Figure 2.
As a chronic inflammatory condition, chronic deciduitis requires maternal and fetal screening for hematogenous infections, including HSV [37,45]. Intervillositis, as a distinct finding in the placental examination, is based on the detection of a characteristic pattern comprising mostly of histiocytic infiltration of intervillous space [46]. Although the underlying etiology remains unclear, the presence of maternal macrophages and the increased incidence of the infection in women with autoimmune disease may provide an insight into the underlying pathophysiological mechanisms, nonetheless. Despite that, chronic intervillositis has been linked to inappropriate activation of the immune response to the semi-allogeneic fetus [46]. Interestingly, intervillositis has also been reported in the placentas of women infected with malaria and/or acute CMV infection [47]. The co-occurrence of chronic intervillositis and malaria has raised questions that an underlying infection could potentially play a role in the onset of chronic intervillositis [47]. As previously documented, infectious intervillositis with a polymorphic infiltrate containing neutrophils and leukocytes indicates acute inflammation [47]. Even not often, among the infectious agents, HSV should be included [32,48]. Considering the high rates of recurrence of intervillositis [28,49], HSV seems to be encompassed in differential diagnosis [19].

Massive perivillous fibrinoid deposition (MPFD) is an extremely rare placenta condition characterized by abnormally extensive fibrinoid deposition in the placental villous parenchyma [50]. Chorionic villi seem to be sclerotic and encased by the extensive deposition of eosinophilic fibrinoid material within the intervillous space. It is characterized by a high rate of recurrence and has also been correlated with autoimmune diseases. Hitherto, the underlying etiology of MPFD remains unclear. Autoimmune disease, infection, toxic reagents, abnormal host-placental interactions, coagulation disorders, and genetic conditions have been proposed as triggering factors for MPFD [50-52]. Regarding infections, coxsackieviruses, syphilis, CMV, syndrome coronavirus 2 (SARS-CoV-2), and congenital HSV infection have been associated with MPFD pathogenesis [53,54]. It has also been reported that this condition represents a final common pathway for a number of miscellaneous disorders culminating in chorionic villus injuries associated with intervillous circulation stasis [50].

Chronic chorionic vasculitis (CCV) is an uncommon placental lesion, rarely affecting multiple vessels. Its diagnosis includes the detection of fetal lymphocytes and eosinophils in the chorionic vessel wall. It constitutes the first stage of fetal inflammatory response and is often associated with CV. In some cases, a thrombus may also be observed as a response to inflammation [45]. It has been reported that transplacental or ascending HSV infection may induce CCV [28,41,55].

Chronic funisitis is also an atypically detected lesion. It is defined primarily as lymphocytic infiltration of...
the umbilical cord due to the establishment of a chronic in-utero viral infection. It has been speculated that HSV may induce chronic funisitis [10,56], while the presence of plasma cells in funisitis requires the exclusion of a herpetic infection [11,20].

Necrotizing funisitis (NF) is characterized by severe umbilical cord inflammation, which could be both grossly and microscopically detected. Under the microscope, NF is depicted as a discontinuous pattern comprising areas with neutrophilic or lymphocytic infiltration and areas enriched with necrotic debris. Additionally, calcium deposits can be frequently detected. Despite that NF is predominantly associated with congenital syphilis, this lesion has been also linked with ascending congenital HSV infection [28,57,58].

Villous agglutination constitutes a nonspecific histopathological finding in the placental examination. It has been described as clusters of adherent distal villi agglutinated by fibrin and/or bridging syncytial knots, which are not separated by maternal blood space [20,59]. It was initially associated with congenital rubella [60] and recently attributed to SARS-CoV-2 [61]. It should be noted that congenital HSV infection cases may also be presented as villi agglutinated without any evidence of villous or membranes’ inflammation [9].

All the findings above should raise suspicions of an HSV infection, which can be confirmed via immunohistochemical staining as presented in Figure 3.

*FIGURE 3: Immunohistochemical staining for HSV-1 in placental tissue complicated with congenital HSV infection (magnification x 200) (Abcam, rabbit polyclonal). Arrows indicate the positively stained cells.*

HSV: Herpes simplex virus.

Source: All placental samples were obtained from the Laboratory of Histology-Embryology Archive, Medical School, Democritus University of Thrace, Greece.

In Table 1, the main histopathological findings associated with congenital HSV infection are briefly presented.
Histopathological findings | L | H | P | E | Necrosis Cowdry type B bodies | Thrombus | Fibrin deposition | Transplacental transmission | Ascending transmission
--- | --- | --- | --- | --- | --- | --- | --- | --- | ---
Chorioamnionitis | + | + | + | + | + | + | + | + | +
Villitis | + | + | + | + | + | + | + | + | +
Intervillositis | + | + | + | + | + | + | + | + | +
Deciduitis | + | + | + | + | + | + | + | + | +
Funisitis | + | + | + | + | + | + | + | + | +
Vasculitis | + | + | + | + | + | + | + | + | +

**TABLE 1: Summary of placental histopathological findings associated with congenital HSV infection and the possible mode of transmission**

L: Lymphocytes; H: Histiocytes; P: Plasma cells; E: Eosinophils; HSV: Herpes simplex virus.

In Table 2, the reported cases concerning the histopathological lesions of the placenta due to HSV infection in pregnancy are summarized.
| Authors, year                  | Gestational age (weeks) | Placenta weight (g)/dimensions | Pathology examination                                                                 |
|-------------------------------|-------------------------|--------------------------------|---------------------------------------------------------------------------------------|
| Edwards et al. [10], 2015     | 29\(^{4/7}\)            | Not presented                  | Chronic chorioamnionitis                                                                |
|                               |                         |                                | Degeneration of amnion epithelium                                                     |
|                               |                         |                                | HSV Cowdry type B intranuclear inclusions                                             |
|                               |                         |                                | Chronic fetal inflammatory reaction on umbilical cord                                   |
| Smith et al. [11], 2020       | 25\(^{1/7}\)            | Not presented                  | Subacute necrotizing inflammation with stromal cell necrosis                          |
|                               |                         |                                | Detection of plasma cells                                                             |
| Pfister et al. [24], 2013     | 27\(^{1/7}\)            | Not presented                  | Viral inclusions in the amniotic epithelium                                          |
|                               |                         |                                | Acute and chronic funisitis                                                          |
|                               |                         |                                | Acute chorioamnionitis                                                               |
|                               |                         |                                | Necrotic abscess in intervillous spaces                                                |
|                               |                         |                                | Intense neutrophilic infiltration                                                    |
| Chatterjee et al. [29], 2001  | 27                      | 229.8 g, 16.3 x 14.7 x 1.2 cm  | Karyorrhexis                                                                          |
|                               |                         |                                | Degeneration                                                                          |
|                               |                         |                                | Chronic inflammation of the membranes (predominantly lymphocytes)                     |
| Kinoshita et al. [31], 2021   | 29                      | Not presented                  | Chronic chorioamnionitis (stage 2): leukocyte infiltration of chorionic membrane      |
| Vasileiadis et al. [33], 2003 | 27\(^{4/7}\)            | Not presented                  | Desquamation of the amnion with areas of necrotizing inflammation                   |
| Barefoot et al. [34], 2002    | 31\(^{2/7}\)            | Not presented                  | Inflammation and necrosis of the fetal membranes                                      |
|                               |                         |                                | Chronic funisitis                                                                     |
| Amidzic et al. [39], 2017     | 31                      | 15 cm in the greatest dimension | Mild chronic villitis                                                                |
|                               |                         |                                | Mononuclear inflammatory infiltration in chorionic villi stroma                      |
| Bedolla and Stanek [44], 2004 | 15                      | 120 g                          | Villous necrosis                                                                     |
|                               |                         |                                | Decidual necrosis                                                                    |
| Bougioukas et al. [55], 2021  | 26\(^{2/7}\)            | Not presented                  | Chorioamnionitis                                                                     |
|                               |                         |                                | Funisitis                                                                            |
|                               |                         |                                | Focal chronic chorionic plate vasculitis                                              |
|                               |                         |                                | Necrotic stromal cells                                                               |
| Demeulemeester et al. [56], 2015 | 28                  | Not presented                  | Acute chorioamnionitis                                                               |
|                               |                         |                                | Acute vasculitis                                                                    |
|                               |                         |                                | Acute and chronic funisitis                                                          |
| Wang et al. [58], 2021        | 31                      | Not presented                  | Acute chorioamnionitis                                                               |
|                               |                         |                                | Necrotizing funisitis                                                               |

**TABLE 2: Summary of the clinical and pathological features of the reported cases diagnosed with congenital HSV infection**

HSV: Herpes simplex virus.
Conclusions

In this narrative review of placental lesions caused by congenital HSV infection, we have summarized the common and rare histopathological findings associated with HSV infection during pregnancy. Reviews relative to HSV congenital infection and case reports were used. The co-existence of villitis, intervillositis, necrosis, and viral inclusion bodies defined as herpetic placentitis is indicative of transplacental transmission but is not often observed. In cases of villitis, VUE, and intervillositis, the detection of plasma cells should guide the differential diagnosis in a viral infection, including HSV. Chorioamnionitis with or without necrotic lesions and funisitis is less often but can also associate with HSV infection. Additionally, findings such as Cowdry type B on fetal tissues, fibrinoid deposition, and villous agglutination should be investigated as they could be part of an atypical manifestation of HSV infection.

The diagnosis of congenital HSV infection is challenging. Data support that clinical findings of HSV infection may not provide an accurate and precise diagnosis. As herpetic transmission rates increase, congenital HSV infection tends to be a more commonly seen phenomenon, attributed to the fact that physicians lack awareness of the true HSV transmission extent. Determining the route of transmission and distinguishing between hematogenous placental or ascending acquisition of HSV may play a key role in the prognosis of the pregnancy outcome. Placental histopathological examination is of utmost importance as it often dictates the subsequent diagnosis and management of HSV. Further investigation into congenital HSV infection may clarify the placental involvement in the pregnancy outcome.

Additional Information

Disclosures

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References

1. Megli CJ, Coyne CB: Infections at the maternal-fetal interface: an overview of pathogenesis and defence. Nat Rev Microbiol. 2022, 20:67-82. 10.1038/s41579-021-00610-y
2. Chan MY, Smith MA: Infections in pregnancy. Comprehensive toxicology. 2017, 856:232-49. 10.1016/B978-0-12-801258-5.64923-9
3. Auriti C, De Rose DU, Santisi A, et al.: Pregnancy and viral infections: mechanisms of fetal damage, diagnosis and prevention of neonatal adverse outcomes from cytomegalovirus to SARS-CoV-2 and Zika virus. Biochim Biophys Acta Mol Basis Dis. 2021, 1867:166198. 10.1007/j.13519-2021-166198
4. Jabłońska A, Studzińska M, Suski P, Kalinka J, Paradowska E: Enhanced expression of IFN16 and RIG-1 in human third-trimester placentas following HSV-1 infection. Clin Exp Immunol. 2018, 195:255-65. 10.1111/cei.13145
5. Finger-Jardim F, Avila EC, da Hora VP, Gonçalves CV, de Martinez AM, Soares MA: Prevalence of herpes simplex virus types 1 and 2 at maternal and fetal sides of the placenta in asymptomatic pregnant women. Am J Reprod Immunol. 2017, 81:e12689. 10.1111/aji.12689
6. Fa F, Laup L, Mandellrot L, Sibiude J, Picone O: Fetal and neonatal abnormalities due to congenital herpes simplex virus infection: a literature review. Prenat Diagn. 2020, 40:408-14. 10.1002/pd.5587
7. Management of genital herpes in pregnancy: ACOG Practice Bulletin, Number 220, Obstet Gynecol. 2020, 135:e192-202. 10.1097/AOG.0000000000005340
8. Felker AM, Nguyen P, Kaushic C: Primary HSV-2 infection in early pregnancy results in transplacental viral transmission and dose-dependent adverse pregnancy outcomes in a novel mouse model. Viruses. 2021, 13:1929. 10.3390/v13101929
9. Heerema-McKenney A: Defense and infection of the human placenta. APMIS. 2018, 126:570-88. 10.1111/apm.12847
10. Edwards MS, Popek EJ, Wise B, Hatzenbuehler L, Arunachalam AR, Hair AR: Ascending in utero herpes simplex virus infection in an initially healthy-appearing premature infant. Pediatr Dev Pathol. 2015, 18:155-8. 10.2350/14-09-1548-CR.1
11. Smith AE, McKenney A, Rabinowitz I, Das A: Diagnosis of neonatal herpes simplex infection from the placenta. Case Rep Pediatr. 2020, 2020:8898612. 10.1155/2020/8898612
12. Magli MC, Jones OM, Lundin K, van den Abbeel E: Atlas of human embryology: from oocytes to preimplantation embryos. Preface. Hum Reprod. 2012, 27:1. 10.1093/humrep/dez219
13. Yockey LZ, Lucas C, Iwasaki A: Contributions of maternal and fetal antiviral immunity in congenital disease . Science. 2020, 568:608-12. 10.1126/science.aaaz960
14. Syridou G, Sapanakis N, Konstantinidou A, et al.: Detection of cytomegalovirus, parvovirus B19 and herpes simplex viruses in cases of intrauterine fetal death: association with pathological findings. J Med Virol. 2008, 80:1776-82. 10.1002/jmv.21297
15. Yamamoto S, Nagamori T, Komatsu S, Shirai M, Suzutani T, Oki J: A case of congenital herpetic infection diagnosed at 8 months of age. Brain Dev. 2020, 42:569-72. 10.1016/j.braindev.2020.01.003
16. Coyne CB, Lazar RM: Zika virus - reigniting the TORCH. Nat Rev Microbiol. 2016, 14:707-15. 10.1038/nrmmicro.2016.125
17. Narang K, Cheek EH, Emminga EA, Theiler RN: Placental immune responses to viruses: molecular and histo-
pathologic perspectives. Int J Mol Sci. 2021, 22:2921. 10.3390/ijms22062921
18. Costa ML, de Moraes Nohrega G, Antolini-Tavares A: Key infections in the placenta. Obstet Gynecol North Am. 2020, 47:153-46. 10.1016/j.ogc.2019.10.005
19. Baergen RN: Manual of Pathology of the Human Placenta. Springer, Berlin, Germany; 2011. 10.1007/978-1-4419-7494-5
20. Heereema-Mckenney A, Popen Ej, De Parpe ME: Diagnostic Pathology: Placenta. Elsevier, Amsterdam, Netherlands; 2018.
21. Faye-Petersen OM, Reilly SD: Demystifying the pathologic diagnoses of villitis and fetal thrombotic vasculopathy. Neo Reviews. 2008, 9:399-410. 10.1542/neo.9-9-e399
22. Baergen RN, Burton CJ, Kaplan GG: Benirschke’s Pathology of the Human Placenta. Springer, Berlin, Germany; 2012.
23. Bittencourt AL, Garcia AG: The placenta in hematogenous infections. Pediatr Pathol Mol Med. 2002, 21:401-52. 10.1080/1202795026157768
24. Pfister KM, Schleiss MR, Reed RG, George TN: Non-immune hydrops fetalis caused by herpes simplex virus type 2 in the setting of recurrent maternal infection. J Perinatol. 2015, 35:817-20. 10.1038/jp.2015.68
25. Turovskii G, Rollag H, Roald B: Viral infection in placenta relevant cells—a morphological and immunohistochemica study. APMS. 2015, 125:60-4. 10.1111/apm.12307
26. Goldstein JA, Gallagher K, Beck C, Kumar R, Germand AD: Maternal-fetal inflammation in the placenta and the developmental origins of health and disease. Front Immunol. 2020, 11:551543. 10.3389/fimmu.2020.531543
27. Kim CJ, Romero R, Chaemsaithong P, Chaiyasit N, Yoon BH, Kim YM: Acute chorioamnionitis and funisitis: definition, pathologic features, and clinical significance. Am J Obstet Gynecol. 2015, 213:529-52. 10.1016/j.ajog.2015.06.040
28. Khong TV, Mooney EE, Ariet J, et al.: Sampling and definitions of placental lesions: amsterdam placental workshop group consensus statement. Arch Pathol Lab Med. 2016, 140:698-715. 10.5858/arpa.2015-0225-CC
29. Chatterjee A, Charttrand SA, Harrison CJ, Feltly-Duckworth A, Bevrta C: Severe intrauterine herpes simplex disease with placititis in a newborn of a mother with recurrent genital infection at delivery. J Perinatol. 2001, 21:559-64. 10.1038/sj.jp.7210573
30. Jacques SM, Qureshi F: Chronic chorioamnionitis: a clinicopathologic and immunohistochemical study. J Hum Reprod Sci. 1998, 29:1457-61. 10.1096/jrsm.1998.1457-61
31. Kinoshita T, Hatanaka A, Mori J, Akaiwa K, Imazumi H: Multimodal imaging of a severe case of neonatal acute retinal necrosis and lens vacuoles associated with herpes simplex virus infection. Ocul Immunol Inflamm. 2022, 30:1009-15. 10.1080/09273948.2020.1841803
32. Oliveira GM, Pascoal-Xavier MA, Moreira DR, Guimarães VS, Aguiar RA, Miranda DM, Romanelli RM: Detection of cytomegalovirus, herpes virus simplex, and parvovirus b19 in spontaneous abortion placentas. J Matern Fetal Neonatal Med. 2019, 52:768-75. 10.1080/14767058.2017.1597778
33. Vasileiadis GT, Rokkema HW, Romano W, Walton JC, Gagnon R: Intrauterine herpes simplex infection. Am J Perinatol. 2005, 22:55-8. 10.1055/s-2005-38319
34. Barefoot KH, Little GA, Omvold KT: Fetal demise due to herpes simplex virus: an illustrated case report. J Perinatol. 2002, 22:86-8. 10.1055/s-2002-38388
35. Hain J, Doshi N, Harper JB: Ascending transcytactic herpes simplex infection with intact fetal membranes. Obstet Gynecol. 1980, 56:106-9.
36. Ozer E: Placenta in Preterm Birth. IntechOpen, London; 2013. 10.5772/54887
37. Matsika A: Clinical correlates of histopathologial entities of the placenta. Aust J Gen Pract. 2021, 50:62-9. 10.31128/AJGP-11-19-5154
38. Redline RW: Placental inflammation. Semin Neonatol. 2004, 9:265-74. 10.1016/s880-2003-02.005
39. Amidic J, Vukovic N, Capo I, Levakov AF: Congenital cytomegaly inclusion disease with disseminated herpes simplex infection. Malays J Pathol. 2019, 41:75-8.
40. Cinillo A, Lacobone AD, Calvino IG, Alberi I, Gardella B: The role of the placenta in feto-neonatal infections. Early Hum Dev. 2014, 90 Suppl 1:57-9. 10.5151/ehd/120157
41. Crum CP, Lee KR, Nucci MR, et al.: Diagnostic Gynecologic and Obstetric Pathology. Elsevier, Amsterdam, Netherlands; 2019.
42. Chan JS: Villitis of unknown etiology and massive chronic villitis. Surg Pathol Clin. 2015, 6:115-26. 10.1016/pat.2012.11.004
43. Chen A, Roberts DJ: Placental pathologic lesions with a significant recurrence risk - what not to miss! . APMS. 2018, 126:589-601. 10.1111/apm.12796
44. Bedolla G, Stanek J: Intrauterine hematogenous herpetic infection. Arch Pathol Lab Med. 2004, 128:1189-90. 10.5858/2004-128-1189-IIHI
45. Avgil M, Ornoy A: Herpes simplex virus and Epstein-Barr virus infections in pregnancy: consequences of neonatal or intrauterine infection. Reprod Toxicol. 2006, 21:436-45. 10.1016/j.reprotox.2004.11.014
46. Brady CA, Williams C, Sharps MC, Shieh J, HeuZell AE, Crocker IP: Chronic histiocytic villitis: a breakdown in immune tolerance comparable to allograft rejection? Am J Reprod Immunol. 2021, 85.e13373. 10.1111/ajri.13373
47. Bos M, Nijkels PG, Cohen D, et al.: Towards standardized criteria for diagnosing chronic villitis of unknown etiology: a systematic review. Placenta. 2018, 61:60-8. 10.1016/j.placenta.2017.11.012
48. Doss BJ, Greene MF, Hill J, Hefferen LJ, Bibeer FR, Genest DR: Massive chronic villitis associated with recurrent abortions. Hum Pathol. 1995, 26:1245-51. 10.1016/S0046-8177(95)90201-5
49. Freitag L, von Kaisenberg C, Koepe H, Hussein K: Expression and function of leukocytes attracting cytokines in chronic histiocytic villitis of the placenta. Int J Clin Exp Pathol. 2013, 6:1105-11
50. Qi M, En Chang K, Lian DQ, Kho C, Tan K: Placental massive perivillous fibrinoid deposition is associated with adverse pregnancy outcomes: a clinicopathological study of 12 cases. Case Reports in Perinatal Medicine. 2016, 12:55-59. 10.1515/crpm-2015-0087
51. Raspolini MR, Oliva E, Roberts DJ: Placental histopathologic features in patients with thrombophilic mutations. J Matern Fetal Neonatal Med. 2007, 20:113-23. 10.1080/1476705060118345
52. Romero R, Whitten A, Korzeniewski SJ, et al.: Maternal floor infarction/massive perivillous fibrin deposition: a manifestation of maternal antifetal rejection?. Am J Reprod Immunol. 2013, 70:285-98. 10.1111/aji.12143
53. Feist H, Turowski G, Hussein K, Blöcker T, Heim A: Massive perivillous fibrin deposition of an enterovirus A-infected placenta associated with stillbirth: a case report. Pediatr Dev Pathol. 2019, 22:142-5. 10.1177/1093526618798772
54. Robb JA, Berirschke K, Mannino F, Voland J: Intrauterine latent herpes simplex virus infection: II. Latent neonatal infection. Hum Pathol. 1986, 17:1210-7. 10.1016/s0046-8117(86)80562-7
55. Bougioukas L, Psoinos RB, Jones DC, Morris EA, Hale AJ: Disseminated herpes simplex virus 2 as a complication of pregnancy. JCases. 2021, 24:e01107. 10.1016/j.jcder.2021.e01107
56. Demeuemeester V, Voeten M, Jacqunenyn Y, Mahieu L: A rare infectious cause of severe neonatal skin lesions. BMJ Case Rep. 2015, 2015:bcr2015209460. 10.1136/bcr-2015-209460
57. Heifetz SA, Bauman M: Necrotizing funisitis and herpes simplex infection of placental and decidual tissues: study of four cases. Hum Pathol. 1994, 25:715-22. 10.1016/0046-8177(94)90506-9
58. Wang W, Zhang M, Gong L, Wu Q: Necrotizing funisitis and calcification of umbilical vein: case report and review. BMC Pregnancy Childbirth. 2021, 21:296. 10.1186/s12884-021-03743-3
59. Jaiman S, Romero R, Pacora P, et al.: Disorders of placental villous maturation in fetal death [IN PRESS]. J Perinat Med. 2020, 10.1515/jpm-2020-0050
60. Garcia AG, Marques RL, Lobato YY, Fonseca ME, Wigg MD: Placental pathology in congenital rubella. Placenta. 1985, 6:281-95. 10.1016/s0143-4004(85)80038-2
61. Zaga-Clavellina V, Diaz L, Olimo-Ortiz A, Godínez-Rubi M, Rojas-Mayorquín AE, Ortuño-Sahagún D: Central role of the placenta during viral infection: immuno-competences and miRNA defensive responses. Biochim Biophys Acta Mol Basis Dis. 2021, 1867:166182. 10.1016/j.bbadis.2021.166182