Published in final edited form as:

Ann N Y Acad Sci. 2011 March ; 1221: 103–108. doi:10.1111/j.1749-6632.2010.05932.x.

Placental Hofbauer cells and complications of pregnancy

Zhonghua Tang, Vikki M. Abrahams, Gil Mor, and Seth Guller

Department of Obstetrics/Gynecology and Reproductive Sciences, School of Medicine, Yale University, New Haven, Connecticut

Abstract

Hofbauer cells (HBCs) are placental macrophages that are present in the villus across gestation. Despite their identification more than 100 years ago, their specific role in placental function remains largely unelucidated. We initially review aspects of their history and biology as well as evidence for putative sites of origin. To gain insight into their potential function, we then describe complications of pregnancy including villitis of unknown etiology (VUE) and histological chorioamnionitis (HCA), in which alterations in numbers, gene expression, or other characteristics of HBCs have been documented to occur. We further review methods for isolation of HBCs and *in vitro* studies that explore their role in relation to other major cell types in the placenta and examine their actions in cytokine-mediated inflammation. We conclude that HBCs play a key role in placental pathophysiology, and future advances in their isolation and culture would enable mechanistic insight into their villus function.

Keywords

placenta; Hofbauer cells; fetal macrophages; preterm delivery; villitis of unknown etiology; chorioamnionitis

Introduction

Major cell types in the human placenta include the syncytiotrophoblast (SCT)—the cell layer that lines the intervillous space and is in direct contact with maternal blood—underlying stromal cells adjacent to fetal capillaries largely consisting of fibroblasts (FIBs), and Hofbauer cells (HBCs) or fetal tissue macrophages.^{1,2} More than 150 years ago, cells later known as HBCs, were first described in the placental villus by several investigators; in the early 1900s, morphological studies by Hofbauer and others revealed these large (10–30 μ m), pleiomorphic cells to be highly vacuolated with a granular cytoplasm.^{1,2} HBCs normally appear on the 18th day of gestation and can be found until term.³ However, due to the compression of the villous stroma, by the fourth or fifth month of gestation, their identification becomes more difficult and requires the use of immunohistochemistry with antibodies that recognize macrophage proteins (e.g., CD68).^{4,5} HBCs were shown to be of fetal origin using Y chromosome-specific probes in pregnancies with male fetus.^{5,6} The cellular source of HBCs in the placental villus has been proposed to change across gestation.¹ Since HBCs appear in the placental villus prior to the appearance of a fetal circulation, it is suggested that HBCs are derived from villous mesenchymal stem cells early

© 2011 New York Academy of Sciences.

Address for correspondence: Seth Guller, Dept. OB/GYN, School of Medicine, Yale University, 333 Cedar Street-339 FMB, P.O. Box 208063, New Haven, CT 06520-8063. seth.guller@yale.edu.

Conflicts of interest

The authors declare no conflicts of interest.

in pregnancy, whereas later in pregnancy they are suggested to largely arise following differentiation of recruited fetal monocytes.^{1,5,6} The function that specific placental cell types play in the generation and/or recruitment of HBCs remains unknown. General functions of tissue macrophages include phagocytosis of apoptotic bodies and cellular debris as well antigen presentation in response to inflammation and infectious agents.⁷ However, the specific regulation of these processes in HBCs during normal pregnancy, as well as their potential dysfunction in complications of pregnancy, remains unexplored.

Several studies suggest that HBCs may play a direct role in early placental development. Immunohistochemical analysis, using double staining of first trimester placentas, indicated that HBCs were in close contact with endothelial progenitor cells and primitive vessels, suggesting that they play a role in early placental vasculogenesis.⁸ Support for an angiogenic role of HBCs is the finding that they express vascular endothelial growth factor at higher levels than peritoneal macrophages.⁹ Sprouty proteins, regulators of branching morphogenesis, were localized to HBCs in placental tissue by double-immunofluorescence microscopy,¹⁰ suggesting that this cell type plays a critical role in the development of the placental villous tree. A recent study using time-lapse photography of mixed placental stromal cell cultures showed significant plasticity of HBC morphology and paracrine support of FIBs, suggesting that HBCs may promote the maturation and development of the placental mesenchyme.¹¹

HBCs and complications of pregnancy

Villitis of unknown etiology (VUE) is a destructive inflammatory lesion of the chorionic villi occurring in approximately 10% of pregnancies, and is associated with intrauterine fetal growth restriction, significant perinatal morbidity, and mortality.^{12,13} From an immunological standpoint, it is characterized principally by villus infiltration of CD8⁺ maternal T lymphocytes and CD68⁺ fetal macrophages, i.e., HBCs^{5,6,14,15} (see Table 1 for representative examples of changes in HBC expression related to pregnancy complications). In contrast to histological chorioamnionitis (HCA, see below), no clear infectious agent has been implicated in VUE, and investigators have attributed villus damage in these pregnancies to a maternal immunological response against the fetus akin to graft rejection.^{5,6,14,16} A recent study compared levels of placental messenger RNA expression of chemokines and cytokines as well as their corresponding protein levels in maternal and cord bloods in VUE and HCA.⁶ Their conclusion was that VUE, and not HCA, was a distinct immunological condition resulting from both maternal allograft rejection, and fetal graft-versus-host disease.

In contrast to VUE, HCA is most often caused by ascending genital tract microorganisms that promote infiltration of neutrophils in maternal decidua and fetal membranes, with or without a neutrophil response in the placenta and fetus.¹⁷ Of note is the connection between HCA, cerebral palsy, and related neurological disorders, which occur in approximately 3/1,000 live births and results in significant neonatal mortality, morbidity, and long-term disability.^{18,19} In some individuals, cerebral palsy is associated with preterm delivery, low birth weight, and HCA when accompanied by fetal inflammatory response syndrome, a multisystemic fetal response manifested by septic chemokine expression as well as funisitis, or umbilical cord inflammation.^{17,20,21} To date, the appearance or role of HBCs in HCA and neurodevelopmental delay in children remains largely unexplored.

In a recent study by our group using immunohistochemistry, we surprisingly noted that term placentas with HCA (the presence of polymorphonuclear leukocytes in the Wharton jelly [funisitis], in the walls of umbilical cord vessels, in the chorionic plate stroma and/or vessels [chorionitis and/or vasculitis], or in the amniotic membranes [amniosis]²²) manifested a

two- to threefold increase in CD68⁺ HBCs in the placental villus stroma compared to gestational age-matched controls.²³ This is consistent with the results of other investigators demonstrating increased levels of CD68⁺ cells in the placental villous stroma and fetal membrane choriodecidua in pregnancies with HCA that were delivered at term.²⁴ They documented that HCA was also accompanied by increased levels of TNF- α converting enzyme (TACE) in placenta and fetal membranes, suggesting that TNF- α released by TACE is an integral part of an inflammatory pathway in HCA. Conversely, a second group documented decreased levels of CD68⁺ cells in the placental villus in association with both advancing gestational age as well as HCA.²⁵ In this report, CD68⁺ cells were systematically quantitated by computerized imaging. In the recent study from our laboratory,²³ we noted that CD68⁺ cells were not homogeneously distributed among different villi in placentas from pregnancies with HCA as well as in controls. Therefore, we only quantitated HBCs in those areas in which more than one HBC was noted in terminal villi and five or more were observed in intermediate villi. When considering all three studies, we suggested that HCA was associated with focal increases in numbers of CD68⁺ cells in the placental villus even though total numbers of HBCs may not change or decrease.²³ Further experiments by our group used primary cultures of SCTs and FIBs to gain insight into which placental cell types may recruit HBCs to placenta.²³ Regulation of monocyte chemotactic protein-1 (MCP-1) by bacterial products and inflammatory cytokines was studied since this chemokine is a major monocyte chemoattractant that is expressed in placenta and other gestational tissues.^{26–28} Immunoassays and quantitative PCR revealed that bacterial products and inflammatory cytokines promoted the synthesis and release of MCP-1 by FIBs, but not SCTs, suggesting that fibroblast-derived MCP-1 promotes the migration of fetal monocytes to the placentas in pregnancies with HCA.²³ In addition, since FIBs and HBCs are both localized to the fetal stroma, which is adjacent to fetal capillaries, it is more likely that factors released by FIBs will more profoundly alter fetal monocyte recruitment compared to the SCT, which is separated from fetal capillaries by a basement membrane and the villus stroma.¹ Increased HBC expression of Toll-like receptor-4, the receptor for the Gram-negative bacterial constituent lipopolysaccharide, was noted in HCA.²⁹ Similarly, *in situ* PCR and immunohistochemistry localized bacterial and viral DNA and protein to HBCs in pregnancies associated with newborn mortality and morbidity.³⁰ In addition, HBCs from infection-associated second trimester spontaneous abortions possessed large phagosomes with increased acid phosphatase, a marker of activated macrophages.³¹ These studies support a direct role of HBCs in infection-related inflammatory processes during pregnancy and the neonatal period.

In addition to VUE and HCA, there are several other less common complications of pregnancy that are associated with alterations in the characteristics of HBCs (Table 1). They include hydrops fetalis, a dangerous accumulation of fluid in the fetus, that may be due Rh incompatibility in mother and fetus as well as nonimmune causes.³² In these pregnancies, either an excessive number of HBCs or HBCs with a foamy appearance or numerous vacuoles (indicative of inflammatory processes) have been reported.^{33–35} It is of note that fetal metabolic storage diseases including GM1 gangliosidosis, β -gluronidase deficiency, and type VII mucopolysaccharidosis with and without hydrops fetalis are also associated with increased HBCs or foamy appearance of HBCs.^{33,34,36} These results demonstrate that several complications of pregnancy are characterized by alterations in the appearance and/or number of HBCs in placenta.

Use of *in vitro* culture systems would facilitate mechanistic investigations of HBC cell function leading to a better understanding of their role in the pathophysiology accompanying complications of pregnancy. Indeed, several studies have focused on the biological responses of HBCs using *in vitro* systems.

Isolation and culture of HBCs

Early methods for the isolation of HBCs from term placentas were described almost 30 years ago^{37–39} (Table 2 describes the findings from representative reports using several different culture techniques). These initial protocols used digestion and homogenization to disrupt placental tissue, and then Percoll and Ficoll gradients. The observation of relatively strong adherence of HBCs to tissue culture plastic compared to other leukocytes was used in purification strategies as well.^{9,38,40} Rosetting, a technique used for embedding antibodies in the membranes of erythrocytes, that were raised against proteins found on the surface of HBCs, was also used to facilitate purification of HBCs.^{41,42} A disadvantage of this technique, as well as positive immunoselection in general, is that they may activate HBCs. As such, later developments include the use of negative immunoselection techniques employing antiepidermal growth factor receptor antibodies and magnetic beads to remove contaminating cytotrophoblasts.^{43,44} There are several conclusions that can be drawn regarding the techniques used to isolate HBCs over the years. First, unlike protocols to isolate cytotrophoblasts, which have remained largely unchanged for 20 years,^{45–49} there appears to be no consensus regarding a specific methodology that can be consistently used to isolate these cells in high yield and purity (Table 2). Thus, we conclude that no standard technique is currently available. Some contributing factors precluding its development may include the loss of macrophage-specific markers during the digestion process that may complicate verification of purity, activation of macrophages during isolation that may alter their function during subsequent culture, and long-term culture may be compromised by outgrowth of FIBs. Thus, it is clear that the field would benefit from the development of a more universally adopted protocol for the isolation of HBCs in high yield and excellent purity from human placenta.

Despite the absence of uniform protocols for isolation and culture of HBCs, there have been several *in vitro* studies that have provided insight into potential HBC function. Early studies demonstrated their phagocytotic properties,^{38,39} as well as the expression of the receptor for IgG-Fc and class I and class II MHC antigens.^{37,38,41} It was noted that HBCs stimulated the proliferation of maternal and paternal lymphocytes, but there was no evidence of lymphocyte priming by HBCs, suggesting they perform a stabilizing function in the villus.⁴¹ Cultures of HBCs possessed higher levels of triglyceride-hydrolyzing and lipoprotein lipase activity compared to trophoblasts, suggesting that these cells play an important role in uptake of triglycerides and transfer of fatty acids to the fetus.⁵⁰ A later study demonstrated that the addition of HBCs to cultures of cytotrophoblasts increased the expression of hCG- β , a marker of trophoblast differentiation, and promoted the proliferation of trophoblasts.⁵¹ A second study demonstrated that conditioned culture media from HBCs promoted the proliferation and fusion of cytotrophoblasts into syncytia as well as a concomitant increase in expression of hCG and placental lactogen.⁹ These studies suggest that HBCs play an important role in the development of the placental syncytium. Other studies indicated that culture of HBCs under hypoxic conditions promoted decreased levels of prostaglandin E_2 ,⁴⁴ an important mediator of inflammatory responses in macrophages.⁵² This finding is of specific significance in preeclampsia, a condition associated with placental hypoxia.^{53,54} Taken together these results suggest that factors released by HBCs play an important role in the proliferation and differentiation of trophoblasts and HBC function may be altered under conditions in which the placenta is exposed to a suboptimal intrauterine environment.

Conclusions

Based on several reports, it is clear that alterations in levels and appearance of HBCs are associated with several complications of pregnancy. While it is evident that VUE is associated with increased levels of HBCs in the placental villus, it is suggested that HCA is

associated with focal increases in the numbers of these cells in the placental stroma. In VUE, it is proposed that a graft-versus-host response is critical for recruiting fetal monocytes to the placental villus and their subsequent differentiation to HBCs. In HCA, microbial infection is stated to promote focal increases in the release of MCP-1 by placental FIBs that lead to increased recruitment of fetal monocytes. Several methodologies have been employed over the last 25 years to isolate and culture HBCs from human placenta, yet no consensus has been reached on one that will yield cultures with high yield and purity. In spite of this limitation, *in vitro* studies have demonstrated an important role for HBCs in trophoblast differentiation, development of the placental mesenchyme, and in the regulation of inflammatory responses across gestation. Optimization of culture techniques to isolate HBCs is a priority for future studies designed to mechanistically dissect their potential role in complications of pregnancy.

Acknowledgments

This work was supported in part through NIH ARRA funding grant HD33909-13(S.G.) and program grant P01 HD054713-01 (G.M.)

References

1. Castellucci, M.; Kaufmann, P. Pathology of the Human Placenta. Springer-Verlag; New York: 2000. Basic Structure of Villous Trees.
2. Georgiades P, Ferguson-Smith AC, Burton GJ. Comparative developmental anatomy of the murine and human definitive placentae. *Placenta*. 2002; 23:3–19. [PubMed: 11869088]
3. Castellucci M, Zaccheo D, Pescetto G. A three-dimensional study of the normal human placental villous core: I. The Hofbauer cells. *Cell Tissue Res*. 1980; 210:235–247. [PubMed: 7407868]
4. Fox H. The incidence and significance of Hofbauer cells in the mature human placenta. *J Pathol Bacteriol*. 1967; 93:710–717. [PubMed: 6054069]
5. Kim JS, et al. Involvement of Hofbauer cells and maternal T cells in villitis of unknown aetiology. *Histopathology*. 2008; 52:457–464. [PubMed: 18315598]
6. Kim MJ, et al. Villitis of unknown etiology is associated with a distinct pattern of chemokine up-regulation in the feto-maternal and placental compartments: implications for conjoint maternal allograft rejection and maternal anti-fetal graft-versus-host disease. *J Immunol*. 2009; 182:3919–3927. [PubMed: 19265171]
7. Wynn TA, Barron L. Macrophages: master regulators of inflammation and fibrosis. *Semin Liver Dis*. 2010; 30:245–257. [PubMed: 20665377]
8. Seval Y, Korgun ET, Demir R. Hofbauer cells in early human placenta: possible implications in vasculogenesis and angiogenesis. *Placenta*. 2007; 28:841–845. [PubMed: 17350092]
9. Khan S, et al. Human villous macrophage-conditioned media enhance human trophoblast growth and differentiation in vitro. *Biol Reprod*. 2000; 62:1075–1083. [PubMed: 10727280]
10. Anteby EY, et al. Human placental Hofbauer cells express sprouty proteins: a possible modulating mechanism of villous branching. *Placenta*. 2005; 26:476–483. [PubMed: 15950061]
11. Ingman K, et al. Characterisation of Hofbauer cells in first and second trimester placenta: incidence, phenotype, survival in vitro and motility. *Placenta*. 2010; 31:535–544. [PubMed: 20347485]
12. Becroft DM, Thompson JM, Mitchell EA. Placental villitis of unknown origin: epidemiologic associations. *Am J Obstet Gynecol*. 2005; 192:264–271. [PubMed: 15672035]
13. Robillard PY, et al. Etiology of preeclampsia: maternal vascular predisposition and couple disease-mutual exclusion or complementarity? *J Reprod Immunol*. 2007; 76:1–7. [PubMed: 17997164]
14. Myerson D, et al. The pathogenesis of villitis of unknown etiology: analysis with a new conjoint immunohistochemistry-in situ hybridization procedure to identify specific maternal and fetal cells. *Pediatr Dev Pathol*. 2006; 9:257–265. [PubMed: 16944988]
15. Redline RW, Patterson P. Villitis of unknown etiology is associated with major infiltration of fetal tissue by maternal inflammatory cells. *Am J Pathol*. 1993; 143:473–479. [PubMed: 8342596]

16. Labarrere CA, McIntyre JA, Faulk WP. Immunohistologic evidence that villitis in human normal term placentas is an immunologic lesion. *Am J Obstet Gynecol.* 1990; 162:515–522. [PubMed: 2137969]
17. Redline RW. Placental inflammation. *Semin Neonatol.* 2004; 9:265–274. [PubMed: 15251143]
18. Hagberg B, et al. Changing panorama of cerebral palsy in Sweden. VIII. Prevalence and origin in the birth year period 1991–94. *Acta Paediatr.* 2001; 90:271–277. [PubMed: 11332166]
19. Greenwood C, et al. Cerebral palsy and clinical negligence litigation: a cohort study. *Br J Gynaecol.* 2003; 110:6–11.
20. Redline RW, et al. Placental diagnostic criteria and clinical correlation—a workshop report. *Placenta.* 2005; 26(Suppl A):S114–S117. [PubMed: 15837060]
21. Romero R, Chaiworapongsa T, Espinoza J. Micronutrients and intrauterine infection, preterm birth and the fetal inflammatory response syndrome. *J Nutr.* 2003; 133:1668S–1673S. [PubMed: 12730483]
22. Shatrov JG, et al. Chorioamnionitis and cerebral palsy: a meta-analysis. *Obstet Gynecol.* 2010; 116:387–392. [PubMed: 20664400]
23. Toti P, et al. Focal increase of fetal macrophages in placentas from pregnancies with histological chorioamnionitis (HCA): potential role of fibroblast monocyte chemotactic protein-1 (MCP-1). *Am J Reprod Immunology.* 2010 Advance online publication. 10.1111/j.1600-0897.2010.00927.x
24. Hung TH, et al. Tumour necrosis factor-alpha converting enzyme in human gestational tissues from pregnancies complicated by chorioamnionitis. *Placenta.* 2006; 27:996–1006. [PubMed: 16376986]
25. Vinnars MT, et al. The number of CD68+ (Hofbauer) cells is decreased in placentas with chorioamnionitis and with advancing gestational age. *Pediatr Dev Pathol.* 2009; 13:300–304. [PubMed: 19642814]
26. Abrahams VM, et al. Divergent trophoblast responses to bacterial products mediated by TLRs. *J Immunol.* 2004; 173:4286–4296. [PubMed: 15383557]
27. Abrahams VM, Mor G. Toll-like receptors and their role in the trophoblast. *Placenta.* 2005; 26:540–547. [PubMed: 15993703]
28. Esplin MS, et al. Monocyte chemotactic protein-1 expression is increased in human gestational tissues during term and preterm labor. *Placenta.* 2005; 26:661–671. [PubMed: 16085045]
29. Kumazaki K, et al. Immunohistochemical distribution of Toll-like receptor 4 in term and preterm human placentas from normal and complicated pregnancy including chorioamnionitis. *Hum Pathol.* 2004; 35:47–54. [PubMed: 14745724]
30. Satosar A, et al. Histologic correlates of viral and bacterial infection of the placenta associated with severe morbidity and mortality in the newborn. *Hum Pathol.* 2004; 35:536–545. [PubMed: 15138926]
31. Matsubara S, et al. Hofbauer cell activation and its increased glucose-6-phosphate dehydrogenase activity in second trimester-spontaneous abortion: an ultrastructural dual staining enzyme-cytochemical study. *Am J Reprod Immunol.* 2003; 49:202–209. [PubMed: 12852494]
32. Ojala TH, Hornberger LK. Fetal heart failure. *Front Biosci (Schol Ed).* 2010; 2:891–906. [PubMed: 20515832]
33. Delbecque K, Gaillez S, Schaaps JP. Histopathological diagnosis of a type vii mucopolysaccharidosis after pregnancy termination. *Fetal Pediatr Pathol.* 2009; 28:1–8. [PubMed: 19116811]
34. Nelson J, et al. Foamy changes of placental cells in probable beta glucuronidase deficiency associated with hydrops fetalis. *J Clin Pathol.* 1993; 46:370–371. [PubMed: 8496396]
35. Pilz I, Schweikhart G, Kaufmann P. Problems of distinction of normal, arteficial and pathological structures in mature human placental villi: III. Morphometric studies in rhesus incompatibility (author's transl.). *Arch Gynecol.* 1980; 229:137–154. [PubMed: 7369801]
36. Roberts DJ, Ampola MG, Lage JM. Diagnosis of unsuspected fetal metabolic storage disease by routine placental examination. *Pediatr Pathol.* 1991; 11:647–656. [PubMed: 1946081]
37. Hunt JS, King CR Jr, Wood GW. Evaluation of human chorionic trophoblast cells and placental macrophages as stimulators of maternal lymphocyte proliferation in vitro. *J Reprod Immunol.* 1984; 6:377–391. [PubMed: 6097681]

38. Uren S, Boyle W. Isolation of macrophages from human placenta. *J Immunol Methods*. 1985; 78:25–34. [PubMed: 3981018]
39. Wilson CB, Haas JE, Weaver WM. Isolation, purification and characteristics of mononuclear phagocytes from human placentas. *J Immunol Methods*. 1983; 56:305–317. [PubMed: 6300249]
40. Pavlov OV, et al. Production of cultured human placental macrophages. *Biull Eksp Biol Med*. 1998; 125:579–582. [PubMed: 9644565]
41. Sutton LN, Mason DY, Redman CW. Isolation and characterization of human fetal macrophages from placenta. *Clin Exp Immunol*. 1989; 78:437–443. [PubMed: 2532993]
42. Zaccheo D, et al. Isolation and characterization of Hofbauer cells from human placental villi. *Arch Gynecol Obstet*. 1989; 246:189–200. [PubMed: 2482706]
43. McIntire RH, et al. In vitro models for studying human uterine and placental macrophages. *Methods Mol Med*. 2006; 122:123–148. [PubMed: 16511979]
44. Wetzka B, et al. Isolation of macrophages (Hofbauer cells) from human term placenta and their prostaglandin E2 and thromboxane production. *Hum Reprod*. 1997; 12:847–852. [PubMed: 9159455]
45. Douglas GC, King BF. Isolation of pure villous cytotrophoblast from term human placenta using immunomagnetic microspheres. *J Immunol Methods*. 1989; 119:259–268. [PubMed: 2470826]
46. Guller S, et al. Placental expression of ceruloplasmin in pregnancies complicated by severe preeclampsia. *Lab Invest*. 2008; 88:1057–1067. [PubMed: 18679377]
47. Guller S, et al. Glucocorticoid suppression of human placental fibronectin expression: implications in uterine-placental adherence. *Endocrinology*. 1993; 133:1139–1146. [PubMed: 8365358]
48. Kliman HJ, et al. Purification, characterization, and *in vitro* differentiation of cytotrophoblasts from human term placentae. *Endocrinology*. 1986; 118:1567–1582. [PubMed: 3512258]
49. Petroff MG, et al. Isolation and culture of term human trophoblast cells. *Methods Mol Med*. 2006; 121:203–217. [PubMed: 16251745]
50. Bonet B, et al. Metabolism of very-low-density lipoprotein triglyceride by human placental cells: the role of lipoprotein lipase. *Metabolism*. 1992; 41:596–603. [PubMed: 1640846]
51. Cervar M, et al. Paracrine regulation of distinct trophoblast functions in vitro by placental macrophages. *Cell Tissue Res*. 1999; 295:297–305. [PubMed: 9931376]
52. Nagamatsu T, Schust DJ. The immunomodulatory roles of macrophages at the maternal-fetal interface. *Reprod Sci*. 2010; 17:209–218. [PubMed: 20065301]
53. Redman CW, Sargent IL. Latest advances in understanding preeclampsia. *Science*. 2005; 308:1592–1594. [PubMed: 15947178]
54. Sharma S, Norris WE, Kalkunte S. Beyond the threshold: an etiological bridge between hypoxia and immunity in preeclampsia. *J Reprod Immunol*. 2010; 85:112–116. [PubMed: 20236707]

Table 1

Hofbauer cells and complications of pregnancy

Complication	Observation	Reference
VUE	Increased HBCs	15
VUE	Increased HBCs	5
VUE	Increased HBCs	6
HCA	Focally increased HBCs	23
HCA	Increased HBCs	24
HCA	Decreased HBCs	25
HCA	Increased TLR4 in HBCs	29
HCA	Increased microbial DNA in HBCs	30
SA	Activation of HBCs	31
EF	Increased HBCs	35
FMSD	Excessive HBC vacuolization	36
FMSD	Excessive HBC vacuolization	33

VUE = villitis of unknown etiology; HCA = histological chorioamnionitis; SA = spontaneous abortion; EF = erythroblastosis fetalis; FMSD = fetal metabolic storage disease.

Table 2

Protocols for isolation of Hofbauer cells

Purity	Yield (per gram)	Methodology	Reference
95%	1×10^5	Digestion/Ficoll/Percoll/adherence	39
75%	UKN	Digestion/Ficoll	37
65–100%	2×10^7	Digestion/Ficoll/adherence	38
90%	UKN	Homogenization/Ficoll/Percoll	42
77–95%	$0.77\text{--}5.5 \times 10^6$	Digestion/Percoll/Rosetting	41
95%	UKN	Digestion/Percoll	50
91%	5×10^4	Digestion/Ficoll/Percoll/IP	44
66–90%	2×10^6	Digestion/Ficoll/adherence	40
UKN	UKN	Digestion/Percoll/IP	51
UKN	UKN	Digestion/adherence	9
UKN	3×10^4	Digestion/Ficoll/IP	49

UKN = unknown; IP = immunopurification.