

# Number of Hofbauer Cells in Placentae from Normal and Pre Eclamptic Gestation

Ifra Saeed<sup>1</sup>, Ayesha Yousaf<sup>1</sup>, Shaista Ali<sup>2</sup>

1. Department of Anatomy Rawalpindi Medical University; 2 Department of Anatomy, HBS Medical and Dental College

## Abstract

**Background:** To compare the number of Hofbauer cell in placenta from normal pregnancy with placenta complicated by pre eclampsia

**Methods:** For this comparative study, fifty placentae were taken from normotensive mothers (Normotensive group) and fifty placentae were taken from mothers with hypertension (Hypertensive group). Placentae were fixed in formalin for 48 hours. Placentae were divided into four parts, after fixation and 5mm tissue was taken from the center of randomly selected two parts. After tissue processing and staining, number of Hofbauer cells was counted in both groups.

**Results:** The number of Hofbauer cells was increased in hypertensive group. The quantitative difference between number of Hofbauer cells in normotensive and hypertensive groups were statistically significant.

**Conclusion:** Number of Hofbauer cells was increased in hypertensive group and it may be the result of placental hypoxia which is a common finding in pre eclampsia

**Key Words:** Placenta; Pre-eclampsia; Hofbauer cells

## Introduction

Preeclampsia is a spectrum of pregnancy related illness which includes eclampsia and HELLP syndrome. Without intervention, it can lead to seizures (eclampsia) and carries a high mortality for mother and baby.<sup>1</sup> Preeclampsia is defined as the presence of systolic blood pressure (SBP) greater than or equal to 140 mm Hg or a diastolic blood pressure (DBP) greater than or equal to 90 mm Hg or higher, on two occasions at least 4 hours apart in a previously normotensive patient.<sup>2</sup> In addition to the blood pressure, diagnostic criteria for pre eclampsia is proteinuria greater than 0.3 grams in a 24-hour urine specimen

In patients who develop hypertension during pregnancy without proteinuria, the new onset of any of the signs and symptoms like platelet count less

than 100,000/ $\mu$ L, serum creatinine level greater than 1.1 mg/dL, liver transaminase levels at least twice the normal concentrations. Pulmonary edema and cerebral or visual symptoms have significant diagnostic value in preeclampsia.<sup>3</sup>

Exact cause and pathogenesis of pre eclampsia remains unclear, although much research has taken place. There is a strong evidence that abnormally implanted placenta predisposes susceptible women to pre eclampsia, removal of which ends the disease in most cases.<sup>4</sup>

During normal pregnancy, the placenta becomes highly vascular to allow exchange of gases, water, nutrients and wastes, between maternal and fetal blood. Abnormally developed placenta has poor placental perfusion. The placenta of women with pre-eclampsia is characterized by abnormal and poor trophoblastic invasion, that leads to oxidative stress, hypoxia, and the release of factors that cause endothelial dysfunction and inflammation.<sup>5</sup>

Important and major cells in the human placenta include the syncytiotrophoblast, the cells that are in direct contact with maternal blood and line the intervillous space. Other important cells are fibroblasts (FIBs), and Hofbauer cells (HBCs), also known as fetal macrophages

The number of Hofbauer cells in placenta of normal pregnancy becomes less after fourth week of gestation. Hofbauer cells were first described in the placental villi 150 years back but in the early 1900s, extensive studies by Hofbauer and other investigators revealed that these large (10–30  $\mu$ m), pleiomorphic cells have granular cytoplasm and are highly vacuolated. Hofbauer cells (HBCs), are present in the core of the placental villi from the early stage of pregnancy until term. These cells express high levels of CD163 (a member of the scavenger-receptor cysteine-rich family of proteins)<sup>(6)</sup>. By the fourth or fifth month of pregnancy, their identification becomes difficult, as villous stroma become compressed.<sup>6</sup>

The origin of Hofbauer cells in the placental villi has been proposed to change during gestation. HBCs appear in the placental villi before the development of

fetal circulation, so it is thought that HBCs originates from villous mesenchymal stem cells in early pregnancy, whereas in late pregnancy they are supposed to differentiate from fetal monocytes. Functions of tissue macrophages are phagocytosis of cellular debris and antigen presentation in response to infectious agents and inflammation. However, the regulation of these functions in HBCs during normal pregnancy, as well as their dysfunction in pre eclamptic pregnancy, has not been explored yet.<sup>7</sup>

Direct role of Hofbauer cells in early placental development is established. Immunohistochemical analysis, of first trimester placentas, showed that endothelial progenitor cells were in close contact with HBCs indicating their role in vasculogenesis in placenta. HBCs also express vascular endothelial growth factor at higher levels than other macrophages and this finding supports its angiogenic role in placenta.<sup>7</sup> Time-lapse photography of placental stromal cell cultures showed significant Hofbauer cells morphology plasticity and FIBs paracrine support, suggesting that HBCs also promote development and maturation of the mesenchyme in placenta.<sup>8</sup>

### Patients and Methods

Fifty normotensive mothers (Normotensive group) were selected from Gynaecology/Obstetrics Department of Holy Family Hospital, and Combined Military Hospital Rawalpindi with blood pressure 120/80 throughout pregnancy while Hypertensive group included fifty mother having preeclampsia with blood pressure 140/90 mm of Hg to 160/100 of Hg at two different occasions six hours apart. Gestational age was between 34-38 weeks in both groups. Mothers who had history of pre-gestational hypertension were excluded. After delivery placentae were carefully collected and fixed in formalin. After fixation the placentae were divided into four parts and 5mm tissue was taken from the center of two randomly selected parts. After tissue processing and staining the number of Hofbauer cells were counted in both groups Hofbauer cells were identified as round to ovoid cells with eccentric nuclei and granular cytoplasm. Number of Hofbauer cells was counted in three high power fields per slide at 40X magnification from regions A and B. Mean was calculated. Histology of placental tissue was similar in both normotensive and hypertensive groups. Complete circular cross-sections of the terminal villi were considered and number of Hofbauer cells were counted in three different fields in each section.

### Results

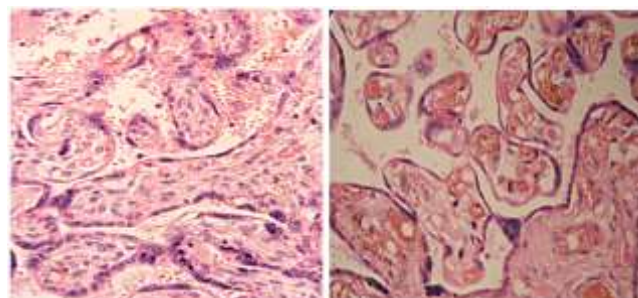
Mean number of Hofbauer cells in A and B regions in hypertensive group was  $17 + 0.802$  and  $18 + 0.090$  respectively (Table-1, Fig-1). The quantitative difference between the mean number of Hofbauer cells in A and B region was statistically insignificant ( $P > 0.05$ ). In normotensive group mean number of Hofbauer cells in A and B regions was  $11 + 0.973$  and  $9 + 0.755$  respectively (Table-1, Fig-2). Mean number of Hofbauer cells in normotensive and hypertensive group was  $69.96 + 1.395$  and  $126 + 1.378$  respectively (Table-2). The quantitative difference between mean number of Hofbauer cells in normotensive and hypertensive groups was statistically significant ( $P$  value  $< 0.05$ ).

**Table 1: Number of Hofbauer Cells**

Parameters	Placental Regions	Normotensive group Mean+SE n=50	Hypertensive group Mean+SE n=50
Number of Hofbauer cells	Region A	11+0.973	17+0.802
	Region B	9+0.755	18+0.90

**Table 2: Quantitative difference between number of Hofbauer cells in normotensive and hypertensive group**

Parameter	Normotensive Group (NG) n = 50 Mean + SE	Hypertensive group (HG) n = 50 Mean + SE	Statistical significance
Hofbauer Cells	69.96 + 1.395	126 + 1.378	$P < .001$



**Fig1: Hypertensive group, Placental tissue showing villi with Hofbauer cells**

**Fig2: Normotensive group. Placental tissue showing villi with Hofbauer cells**

Colour

## Discussion

Feto-maternal interface immune tolerance is a complicated phenomenon. Although macrophages in maternal decidua are competent and well-known immune cells, little is known about Hofbauer cells (fetal-derived macrophages) present within chorionic villi. The immunological role of maternal decidual macrophages is well known in preeclampsia (PE), leading cause of maternal mortality.<sup>9</sup>

In this study the number of the Hofbauer cells in hypertensive group were increased as compared to normotensive group and difference is statistically significant. Results of present study are in accordance with study performed by Evsen MS. They found that number of Hofbauer cells in the placental villi of patients with HELLP syndrome were significantly increased in comparison to normotensive group.<sup>10</sup>

Sizes of the Hofbauer cells were almost similar and not statistically different between groups. Another study performed by Yang SW compared properties of Hofbauer cell between normal and Preeclamptic placental chorionic villi and to evaluate the existence of Hofbauer cells. did sequential staining of CD14, DC-SIGN and CD68 Furthermore, they evaluate the immunological function by staining the cells for CD163. <sup>9</sup> They also explored the expression of cytokine interleukin (IL)-10, which is produced by M2 macrophages. The results showed that levels of CD14, DC-SIGN, CD163, and IL-10 were significantly low in pre eclampsia compared with normal pregnancy. Additionally, Hofbauer cells were significantly less frequent in placenta complicated by pre eclampsia than in normal placenta. Thus, they suggested that Hofbauer cells play an important role in maintaining immune tolerance during pregnancy. This important function of macrophages become defective in pre eclampsia indicating their role in development of this lethal condition.

Another study performed by, Zhonghua Tang et al supported that alterations in appearance and number of Hofbauer cells are associated with different complications of pregnancy. <sup>11</sup>

The Results of our study are also supported by Demir et.al, and Kondi-Pafiti et. al that in pathological placentas due to gestational diabetes mellitus or intrauterine growth restriction, the number of Hofbauer cells seems to be increased while in placentas from uncomplicated pregnancies, Hofbauer

cells either disappear or become less in number after the fourth month of gestation. <sup>12,13</sup>

## Conclusion

Alterations in appearance and number of HBCs is associated with different complications of pregnancy. The increased number of Hofbauer cells in villi of placenta of pre eclamptic mothers can be due to adaptive mechanism at fetal side or due to increased inflammation.

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