

## Placental Morphology of Pregnant Iraqi Women with Rheumatic Heart Disease

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### Abstract

**Background:** Placental morphology and cellular arrangement can be altered in maternal diseases. Rheumatic heart disease (RHD) is a chronic heart condition that can lead to death in pregnant women. The aim of this study is to determine the histological changes of the placenta in pregnant women suffering from RHD. **Methods:** Placentae were collected from 10 healthy pregnant women, and 31 pregnant women with heart conditions (26 with RHD and 5 with NRHD) who had been admitted to the Baghdad Teaching Hospital. Placental tissues were fixed in 10% formal-saline and were processed for light microscopy. Measurements including the placental weight and diameter of the chorionic villi capillaries were recorded. **Results:** The results indicate that there are many histological changes in pregnant women with RHD such as hyalinisation, fibrosis of the chorionic villi, proliferation of trophoblastic cells, and thickening of its membrane. Additionally, expectant mothers with RHD experience a reduction in capillary diameter and thickening of the capillary walls, and decreased size and weight of their placenta when compared with the control. **Conclusions:** Heart diseases, especially RHD, are associated with developmental damage of the placenta in pregnant women by injuring the endothelial cells of the placentas capillaries.

*Keywords: chorionic villi, placenta, pregnancy, rheumatic heart diseases*

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### Introduction

The placenta is a short-lived organ interposed between the mother and foetus, and it is essential for the growth and survival of the foetus in the uterus.<sup>1</sup> The placenta develops in the uterus during pregnancy and is composed of two different surfaces; the maternal surface and the fetal surface. The placentas anatomical and functional features come from both the mother and foetus and it functions as an endocrine organ, a barrier, and a transporter of substances between the maternal and fetal circulation.<sup>2,3</sup> There is increasing evidence that pathophysiological changes in maternal homeostasis may modify placental structure and function, thus influencing the fetal growth rate and causing potential complications.<sup>4,5</sup> The architecture of the placenta can be altered in many maternal diseases such as diabetes mellitus, hypertension, pre-eclampsia, eclampsia, etc.<sup>6</sup>

Maternal cardiac disease complicates 1% to 3% of all pregnancies and is responsible for 10% to 15% of maternal

mortality.<sup>7</sup> Rheumatic heart disease (RHD) describes a group of heart disorders that occur as a result of rheumatic fever.<sup>8</sup> Epidemiologic studies show that RHD is the most common cause of valvular disease in industrialised countries such as the USA, Germany, and the UK.<sup>9-11</sup> It is a current public health concern around the world, with 90% of all heart disorders found in women of childbearing age being rheumatic in origin, in developing countries. However, an accurate estimation of trends of rheumatic fever in these countries is not possible due to an absence of reliable health statistics.<sup>9</sup> RHD is a major cardiac concern in pregnant woman and affected individuals are susceptible to higher maternal and neonatal mortality rates, as found in studies in Eritrea, India, and Iran.<sup>12-15</sup> Mitral stenosis (MS) is the most common manifestation of RHD. Damaged valves may result in heart failure and abnormal valves can increase the risk a trial fibrillation and valvularinfections.<sup>8</sup> MS remains the most common acquired valvular lesion in pregnant women and the most common cause of maternal death due to cardiac complications.<sup>16</sup>

Examination of the placenta is important to understand the pathophysiology of maternal and fetal diseases. Many disorders found in pregnant woman are accompanied by pathological changes in the placenta and are associated with high perinatal morbidity and mortality.<sup>6,17</sup> The purpose of this study is to investigate the histopathological changes that occur in the placenta of pregnant women with RHD.

## Methods

41 placentas were collected at the Department of Obstetrics and Gynaecology, Baghdad Teaching Hospital in Baghdad City. 10 placentas were collected as a control group, from healthy pregnant woman with no associated diseases, who were aged between 19 and 35. 31 placentas were collected from pregnant women, aged between 20 and 39 years, with a provisional diagnosis of heart disease. Of these 31 patients, 26 had a diagnosis of RHD and 5 were patients with non-rheumatic heart disease (NRHD). This research project was conducted in compliance with the humane care standards outlined in the National Institute of Health Guide for Care, with the ethic approval from the Al-Mustansiriah University.

Placentae were collected immediately after delivery, and were washed to remove any clotted blood. The placental weights were recorded and tissue samples from the maternal portion were fixed in a 10% formal-saline solution for 8 hours. They were then dehydrated using a series of ethanol products, cleared using two changes of xylene, impregnated, and embedded in paraffin wax. Paraffin sections of 5  $\mu\text{m}$  thick were stained with Haematoxylin and Eosin and periodic acid-Schiff. The diameters of the chorionic villi capillaries were measured using ocular micrometre.

Results were analysed using standard methods to determine the mean and standard error of the mean. In addition, one-way analysis of variance was used to test the significant differences between the study sample and the control group. *p* values less than 0.05 were considered to be significant.

## Results

**Placental weight.** Results showed no significant difference ( $p \geq 0.05$ ) in the mean values of placental weight of patients with RHD ( $516.23 \pm 24.94$ ) and NRHD ( $522.86 \pm 23.35$ ) when compared with the subjects in the control group ( $624.00 \pm 73.12$ ) (Table 1).

**Capillary diameter.** There were no significant reductions in the capillary diameter of the placentae of patients with RHD ( $0.973 \pm 0.015$ ) and NRHD ( $0.944 \pm 0.023$ ) when compared with the control group ( $1.008 \pm 0.027$ ) (Table 2).

**Histological observation.** Light microscopy examination of the placenta of the control group showed normal structural features. The bulk of the chorionic villi consisted of connective tissue containing fetal capillaries, bundles of collagen fibres, and a variety of connective tissue cells mostly fibroblasts and macrophages. The villi are surrounded by syncytiotrophoblasts which stain dark blue, and are separated by inter-villous spaces that contain maternal blood cells and clumps of fibrinoid (Figure 1A).

Histological investigation of the placentae collected from the patients with heart disease showed multiple degenerative changes. There was an increased incidence of hyalinisation and fibroid necrosis of the villi, and crowded and degenerating villi with decreased inter-villous spaces and fibrin deposition. Additionally, there were numerous arteriosclerotic and congested blood vessels with endothelial degeneration of the endothelial cells, thickened walls of fetal blood capillaries with associated progressive fibrosis, degeneration of trophoblastic cells, and haemorrhage in the inter-villous spaces (Figure 1 B, C, D and Figure 2).

**Table 1. The Mean Values of Placental Weight (gm), of Control, RHD and NRHD Pregnant Women**

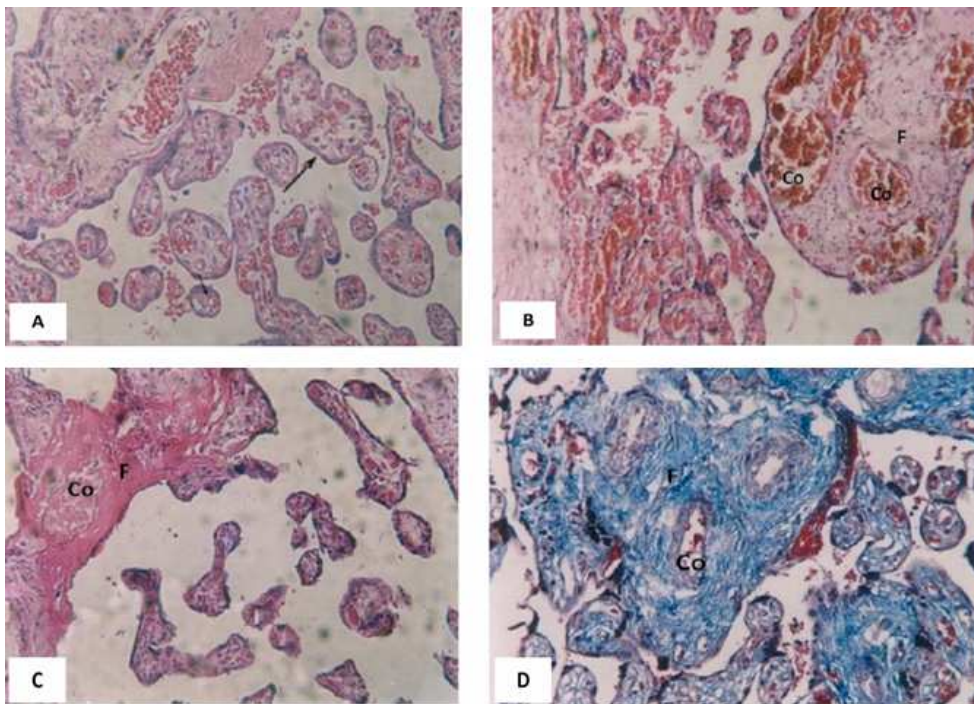
Group	No.	Mean(gm) $\pm$ S.E.M.
RHD	26	516.23 $\pm$ 24.94*
NRHD	5	522.86 $\pm$ 23.35*
Control	10	624.00 $\pm$ 73.12

Data are presented as mean  $\pm$  SEM. \*: None significantly ( $p \geq 0.05$ ) different from their control

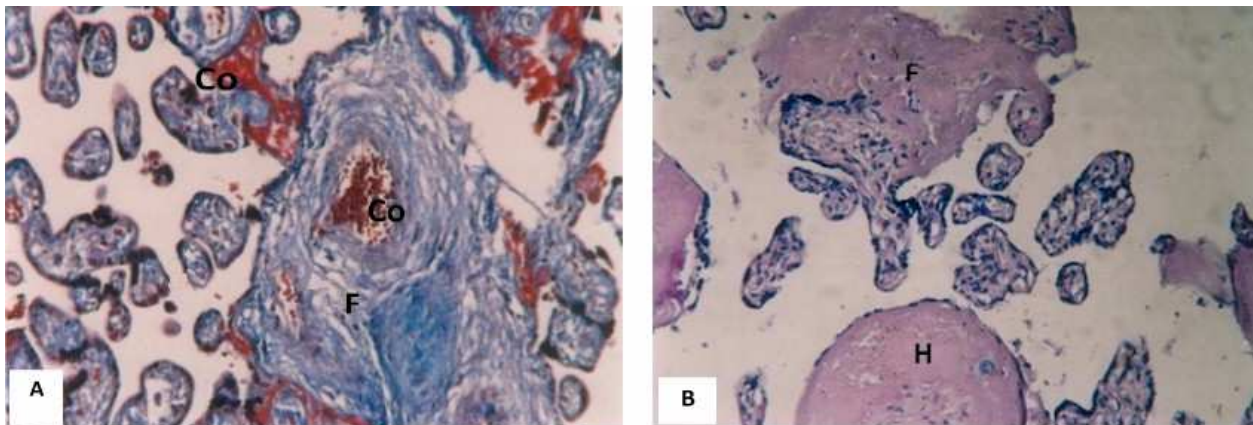
**Table 2. Capillaries Diameter ( $\mu\text{m}$ ) in RHD, NRHD and Control Pregnant Women**

Group	No.	Mean( $\mu\text{m}$ ) $\pm$ S.E.M.
RHD	26	0.973 $\pm$ 0.015*
NRHD	5	0.944 $\pm$ 0.023*
Control	10	1.008 $\pm$ 0.027

Data are presented as mean  $\pm$  SEM. \*: None significantly ( $p \geq 0.05$ ) different from their control



**Figure 1.** Photomicrograph of sections from human placentae of: (A) A control group showing normal architecture structure with normal trophoblast “arrow”; (B, C, D) Patients with RHD (mitral stenosis) showing degenerating villi with thickened fetal congested blood capillaries (Co), marked fibrosis (F), and exfoliated trophoblast cells (dark spots). A, B and C, “H&E”; D “trichrome”, x 200



**Figure 2.** Photomicrograph of sections from human placentae of: (A) Patient suffering from Patent Ductus Arteriosus (PDA); (B) A case of mitral regurgitation showing degenerating villi with thickened fetal congested blood capillaries (Co), marked fibrosis (F), hyalinization (H) and exfoliated trophoblast cells (dark spots). A, “trichrome”; B, “PAS” x 200

## Discussion

The placenta is a vital organ that connects the developing foetus to the maternal uterine wall. It plays a critical role during pregnancy including permitting nutrient entry, waste removal, and respiratory gas exchange via the mother's blood supply. The placenta also fights against internal infection, synthesises and releases

various hormones, and facilitates maternal metabolic adaptation to the different stages of pregnancy.<sup>18</sup> The quality and quantity of maternal blood transported to the intervillous spaces of the placenta controls the development of foetus.<sup>19</sup> The human placenta is a highly vascular organ that acts as the fetal lung, and the amount of blood flow through the placenta is moderated by its vascular arrangement.<sup>20</sup>

Previous studies have demonstrated the morphological and histological changes of the placenta in mothers with cardiac disease. These changes include a decrease in the absolute volume of the placental parenchyma, placental weight, thickness, diameter, and surface area. Additionally, thickened walls of fetal blood capillaries, crowded degenerating villi with decreased intervillous spaces, and intravillous and perivillous fibrinoid deposition has also been reported.<sup>4</sup> Numerous syncytial knots and exfoliated trophoblast cells were also observed and a thickened layer of subchorionic fibrinoid in the placenta of pre-eclamptic mothers.<sup>6,21</sup> The presence of infarction, retroplacental haematomas, calcification, and a significant decrease in the diameter of blood vessels and placental diameter has been noted in the placenta of hypertensive mothers.<sup>17,22</sup>

In this study a placental morphometrical analysis was completed and the placentas in the RHD and NRHD group had lower mean placental weights than those in the control group. A previous study found that placental weight in pre-eclamptic mothers in India is directly proportional to neonatal birth weight.<sup>6</sup> Furthermore, another study of Indian women with pre-eclampsia found that decreased placental weight, thickness, and diameter of villi and vessels are related to the pathogenesis of maternal and fetal morbidity and mortality.<sup>22</sup> A similar study of pre-eclamptic Bangladeshi mothers found that a decrease in the weight and volume of the placenta was related to a substantial decrement of parenchymal tissue due to a significant reduction in peripheral villous tissue mass, fetal capillary, and intervillous space volume by approximately 50% in the placenta.<sup>4</sup> Conversely, the placenta of diabetic pregnant women in India weighed more, and experienced associated syncytial knots, fibrinoid necrosis, villous oedema, villous fibrosis, and capillary proliferation when compared with normal pregnancies.<sup>23</sup> Diabetes mellitus also induces oedematous stroma, an apparent increase in the number of syncytial knots, and perivillous fibrin deposition in the villous tissues was found in gestational diabetes mellitus placentas.<sup>18</sup>

Results from this study found a reduction in capillary diameter and increased wall thickness of fetal blood capillaries in the placentae of RHD and NRHD patients. This finding is consistent with the thickened walls of fetal blood capillaries, increased density of collagen fibres around fetal blood capillaries, and the decrement of their lumen associated with decreased fetal blood capillaries found in the placentae of pre-eclamptic mothers.<sup>21</sup> A significant decrease in the diameter of blood vessels was observed in the placentae of hypertensive mothers, leading to a complete lack of capillaries in the terminal villi in most areas of the placenta, with subsequent formation of a vascular villitis.<sup>22</sup> The structural and functional changes in the villous capillaries of the placenta, such as hypoxia and epigenetic influences, can interrupt embryo development.<sup>24</sup> Additionally, increasing

numbers of villous capillaries and thickening of their walls has been observed in the placentae of diabetic mothers and is considered to be a sign of chronic hypoxic changes.<sup>25</sup>

Results from this histological study have demonstrated clear placental changes in pregnant women who suffer from heart diseases. Examination of RHD and NRHD placentae revealed ruptured villi with congested and thickened walls of fetal blood capillaries, degeneration of the chorionic villi with diminished intervillous spaces, and associated extravasation of fetal RBCs into the maternal space. The degeneration of the villi and subsequent haemorrhage into the intervillous spaces with intravillous fibrinoid deposition correlate with previous findings in pregnant women with pre-eclampsia, toxemia and eclampsia.<sup>3</sup> These changes are thought to impair blood flow in the intervillous spaces and lead to placental hypoxia, infarction, and retarded fetal growth.<sup>21,26</sup> The increased vasculosyncytial membrane thickness and decreased area of exchange, as a result of fetal hypoxia, can subject the foetus to extensive risks.<sup>27</sup> It was found that extensive infarction, in cases of toxemia, were associated with low birth weight, placental weight, and increased fetal death.<sup>27</sup>

Previous electron microscopic studies have related the pathological changes of placental tissue in pre-eclampsia to the changes in endothelial cells, reduced perfusion by maternal blood, or to the mitochondrial damage that leads to trophoblast apoptosis in pre-eclampsia.<sup>28-30</sup> Further electron microscopic studies are needed to elucidate ultrastructural changes in the placenta of pregnant mothers with RHD.

## Conclusions

Heart diseases, especially RHD, are associated with developmental damage of the placentae in pregnant women by injuring the endothelial cells in the placentas capillaries.

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## Conflicts of Interest Statement

The authors have no conflicts of interest to declare.

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