The uteroplacental circulation in hypertensive disorders of pregnancy; Doppler ultrasound and histopathological studies
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1 HYPERTENSIVE DISORDERS OF PREGNANCY

1.1 DEFINITIONS

Perhaps the only thing scientists in the field of hypertensive disorders of pregnancy agree on, is that they disagree on virtually everything else. The very name of the disease complex (toxaemia, pre-eclampsia, hypertensive disease of pregnancy, pregnancy-induced hypertension, EPH-gestosis), the difficulty to define the symptoms, the various clinical forms, and the pathophysiology that becomes more complex every time new evidence is found, are all subject to the controversy. The difficulty arises from the great variation in clinical expression of the syndrome, and the inability to distinguish symptoms induced by pregnancy from underlying (but often latent) maternal disorders. Still, a consensus is badly needed if only to enable comparison of research work\(^1\). But also in clinical practice, a comprehensive and easily obtainable classification will improve prognostics and decision making.

Most classifications focus on diastolic blood pressure, or changes in diastolic blood pressure. Proteinuria is not always included in the diagnosis, and levels for significant proteinuria tend to vary between classifications. Oedema has become markedly unpopular as a clinical sign of pre-eclampsia as it is hard to measure quantitatively and is commonly associated with normal pregnancy.

The gold standard for decades has been the classification proposed by Nelson in 1955\(^2\). A diastolic blood pressure of 90 mmHg after the 20th week was used as a cut-off point, regardless of earlier blood pressure values. Proteinuria was used to
divide between mild and severe pre-eclampsia. Although it is an accurate and simple classification, the main flaw is that it tends to include women with pre-existing hypertension. In more recent years, a number of organisations and individual research workers have proposed improved classifications, resulting in the various systems now currently used in different parts of the world. Table 1.1 gives an overview of the classification systems currently in use.

The World Health Organisation (WHO)\(^3\), like Nelson’s classification, uses the limit of 90 mmHg diastolic blood pressure, but specifies that the woman should be normotensive before the 20th week; in a previously hypertensive woman, pre-eclampsia is diagnosed if there is an increment of 15 mmHg in diastolic pressure and/or the development of proteinuria. The International Society for the Study of Hypertension in Pregnancy (ISSHP)\(^4\) also recommends a diastolic pressure of 90 mmHg, but measured twice at least 4 hours apart, diminishing the influence of “white-coat hypertension”. A diastolic pressure of 110 mmHg is sufficient for the diagnosis if measured only once. A different approach is used by the American College of Obstetricians and Gynecologists (ACOG)\(^5\); their definition is based on increment of blood pressure (more than 30 mmHg increase in systolic pressure or more than 15 mmHg increase in diastolic pressure) rather than a set value. The same approach is also used by Redman and Jefferies in their proposed revised definition\(^6,7\). Their criteria, however, are much more stringent, requiring an increment of 25 mmHg of diastolic pressure. The definition of the ACOG has been evaluated by North et al\(^8\), for association with fetal and maternal complications. They report good risk stratification based on the ACOG classification system but found that women who have a rise in blood pressure ≥30/15 mmHg but remain normotensive had uncomplicated pregnancies. They propose a modification which includes a cut-off value of ≥140/90 mmHg in addition to an increment of ≥30/15 mmHg for the diagnosis of gestational hypertension.

In 1976, Page and Christianson introduced the mean arterial pressure (MAP) as a prognostic sign\(^9\); their definition of pre-eclampsia is based on a MAP of 105 mmHg or more in the third trimester, in a previously normotensive woman.
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(defined as a mean arterial pressure of less than 90 mmHg). Interestingly, they also evaluated the value of MAP changes instead of cut-off values and found that poor pregnancy outcome was predicted better by the cut-off values they used. Proteinuria is usually defined as 0.3 grams/litre or 0.3 grams/24 hours (WHO, ISSHP, ACOG) but in Redman and Jefferies’ classification, 0.5 grams/litre is considered significant. The use of dipsticks is also included in most classifications. One ‘+’ is generally accepted as the equivalent of 0.3 grams/litre, but the ISSHP and Page/Christianson’s definition require ‘++’ as significant proteinuria. In their evaluation of the ACOG's definition, North et al⁸. found that ‘+’ proteinuria was associated with a 3.8 fold increase in "severe maternal disease” compared to gestational hypertension with no proteinuria, supporting the use of ‘+’ as a prognostic sign.

Pre-eclampsia, in most classifications, consists of proteinuria and hypertension, although the in the ACOG classification system an increment of blood pressure and proteinuria or oedema are required; Redman and Jefferies’ classification consider pre-eclampsia as an increment of diastolic pressure even without proteinuria. Most classification systems, however, also include hypertension without proteinuria as “gestational” or “pregnancy-induced” hypertension.

This view is supported by the finding of Saudan et al⁴. that only 15-25% of women with gestational hypertension will eventually develop pre-eclampsia (as defined by gestational hypertension and proteinuria ≥ 0.3 grams/24 hrs or ≥ ‘++’).

Attempts have been made to differentiate between mild and severe pre-eclampsia; the WHO and ACOG agree in this, diagnosing “severe” pre-eclampsia if one or more of the following signs occur: systolic blood pressure over 160 mmHg, diastolic blood pressure over 110 mmHg, thrombocytopenia, renal failure, icterus, epigastrial pain, severe headache and/or visual disturbances, retinal haemorrhage, or pulmonary oedema. The ISSHP uses only blood pressure criteria, defining severe pre-eclampsia as a diastolic pressure of 110 mmHg or more measured twice, or 120 mmHg or more measured once. Interestingly, gestational age at presentation

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is not included in any definition of "severe" pre-eclampsia although it is strongly correlated to adverse maternal and fetal outcome\textsuperscript{10}.

Eclampsia is defined as the occurrence of convulsions during pregnancy for which no other cause can be found; eclamptic insults can occur without significant hypertension or proteinuria. The HELLP-syndrome\textsuperscript{11-13} traditionally consists of hemolysis, elevated liver enzymes and thrombocytopenia, but in practice the hemolysis component is often less prominent. A number of definitions for the HELLP-syndrome is currently in use\textsuperscript{14-16}. They all include thrombocytopenia (a platelet count < 100 x 10\textsuperscript{9}/l), elevated transaminase levels, and elevated lactic dehydrogenase (LDH).
<table>
<thead>
<tr>
<th>Hypertension criteria</th>
<th>Nelson(^2)</th>
<th>WHO(^3)</th>
<th>ISSHP(^4)</th>
<th>ACOG(^5)</th>
<th>Redman/Jefferies(^6)</th>
<th>Page/Christianson(^7)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≥ 90 mmHg diastolic</td>
<td>≥ 90 mmHg diastolic*</td>
<td>≥ 90 mmHg diastolic* or ≥ 110 mmHg diastolic</td>
<td>Increase of ≥ 30 mmHg systolic or ≥ 15 mmHg diastolic</td>
<td>Increase of ≥ 25 mmHg diastolic</td>
<td>Mean Arterial Pressure ≥ 105 mmHg</td>
</tr>
<tr>
<td>Proteinuria Criteria</td>
<td>-</td>
<td>0.3 g/l or +</td>
<td>0.3 g/24h or ++</td>
<td>0.3 g/24h or +</td>
<td>0.5 g/l</td>
<td>++</td>
</tr>
<tr>
<td>Pre-eclampsia criteria**</td>
<td>Hypertension</td>
<td>Hypertension/proteinuria</td>
<td>Hypertension/proteinuria</td>
<td>Hypertension/ proteinuria or oedema</td>
<td>Hypertension</td>
<td>Hypertension/proteinuria (in third trimester)</td>
</tr>
<tr>
<td>“Super-imposed” pre-eclampsia criteria</td>
<td>-</td>
<td>Increase ≥ 15 mmHg diastolic or development of proteinuria</td>
<td>Proteinuria in pre-existent hypertension</td>
<td>Increase of ≥ 30 mmHg systolic or ≥ 15 mmHg diastolic and proteinuria</td>
<td>-</td>
<td>MAP ≥ 90 mmHg in 2nd trimester and MAP ≥ 105 mmHg in 3rd trimester and proteinuria</td>
</tr>
<tr>
<td>“Severe” pre-eclampsia criteria</td>
<td>Hypertension and proteinuria</td>
<td>≥ 160 mmHg systolic or ≥ 110 mmHg diastolic icterus thrombocytes &lt; 100 oliguria proteinuria ≥ 3 g/l epigastrial pain scotoma/frontal headache retinal haemorrhage pulmonary oedema coma</td>
<td>≥ 110 mmHg diastolic</td>
<td>≥ 160 mmHg systolic or ≥ 110 mmHg diastolic icterus thrombocytes &lt; 100 elevated creatinine proteinuria ≥ 2 g/24h epigastrial pain headache retinal haemorrhage pulmonary oedema coma</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 1.1. Classification systems for hypertensive disorders in pregnancy.

* Measured at least twice 4 hours apart
** Occurring after the 20th week of pregnancy unless otherwise specified.

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1.2 EPIDEMIOLOGY

Prevalence

For the greater part of the world, we have no accurate figures about the prevalence of hypertensive disorders of pregnancy. Even if reliable information is available, it is usually based on hospital populations and therefore biased, especially in countries where access to health care is low. Another problem is caused by differences in classification and definitions. Thus, it is not surprising that figures concerning the prevalence of hypertensive disorders of pregnancy show great variation, sometimes even between reports from the same region. Figures from larger, population-based studies show an incidence of hypertensive disorders of pregnancy between 2 and 26 per 100 births (table 1.2)\(^{3,17-19}\). Geographic variations in incidence have been reported to be significant even after correction for population bias and with standardised classification\(^{20,21}\).

<table>
<thead>
<tr>
<th>Country or area</th>
<th>Period</th>
<th>Hypertensive disorders of pregnancy per 100 births</th>
<th>Eclampsia per 1000 births</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cuba</td>
<td>1973</td>
<td>18.4</td>
<td>2.0</td>
</tr>
<tr>
<td>Great Britain</td>
<td>1958</td>
<td>25.8</td>
<td>0.9</td>
</tr>
<tr>
<td>Great Britain</td>
<td>1970</td>
<td>26.0</td>
<td>1.3</td>
</tr>
<tr>
<td>Jerusalem</td>
<td>1964-66</td>
<td>2.0</td>
<td>0.6</td>
</tr>
<tr>
<td>USA</td>
<td>1959-68</td>
<td>22.3</td>
<td>0.55</td>
</tr>
<tr>
<td>USA</td>
<td>1979-86</td>
<td>26.1</td>
<td>0.56</td>
</tr>
<tr>
<td>USA</td>
<td>1988-92</td>
<td>3.8</td>
<td>0.1</td>
</tr>
<tr>
<td>Sweden</td>
<td>1987-93</td>
<td>9.6</td>
<td>NA</td>
</tr>
</tbody>
</table>

Table 1.2. Reported incidences of eclampsia and hypertensive disorders of pregnancy and eclampsia from population-based surveys, 1958-1993\(^{3,17-19}\). NA = not available.
In developed countries, hypertensive disorders of pregnancy are responsible for a third to a tenth of all maternal deaths, mostly the result of eclampsia. Other possibly fatal complications are disseminated intravascular coagulopathy, abruptio placentae, pulmonary oedema, acute renal failure, and intracerebral haemorrhage. In underdeveloped countries, maternal mortality due to hypertensive disorders of pregnancy is even higher (150 or more per 100,000 births), even though complications of illegal abortion and peripartum haemorrhage are the major causes of maternal death. Maternal death rate is inversely related to access to health care.

In a study conducted in the USA between 1974 and 1978, eclampsia ranked as the second cause of maternal mortality (after venous thrombo-embolism), causing 2.6 deaths per 100,000 births in the entire population, and 5.7 deaths per 100,000 births in the black population. In a recent enquiry, hypertensive disorders of pregnancy constituted the largest single cause of maternal mortality in the Netherlands. One particularly threatening complication is the HELLP-syndrome which consists of hemolysis, elevated liver enzymes, and a low platelet count. In a study from 1986 describing 112 patients with this syndrome, 38% had disseminated intravascular coagulopathy, 8% had acute renal failure and 2 patients (2%) died.

In addition to its impact on maternal mortality, hypertensive disorders of pregnancy account for a perinatal death rate of 1.2 per 1000 total births. The risk of perinatal death depends mainly on the severity of the disease, and gestational age at the onset of symptoms. In a group of 303 severely pre-eclamptic patients, a perinatal death rate of 14.5% and a prematurity rate of 92% was found. If the gestational age at onset of symptoms is before 37 weeks, 18.2% of fetuses are small for gestational age, and perinatal death occurs in 10.4%. A particularly high rate of perinatal mortality (37%) is associated with the HELLP-syndrome. Little is known about the development of children who survive the perinatal period; Ounsted found only a slight developmental delay in children from pre-eclamptic
mothers at the age of four, and no delay at all in growth and development at age 7½\textsuperscript{28}.

The remote prognosis women with a history of hypertensive disorders of pregnancy has been extensively studied by Chesley\textsuperscript{29-31}. He describes an increased risk of cardiovascular mortality, chronic hypertension and diabetes mellitus in women who suffered from eclampsia as multiparas. In contrast, women who suffered from eclampsia in their first pregnancy did not have an increased risk of cardiovascular disease later in life. Sibai followed 406 women who had severe pre-eclampsia/eclampsia in their first pregnancies. He found a higher incidence of pre-eclampsia in subsequent pregnancies. In addition, he found a significantly higher risk of subsequent chronic hypertension in patients who developed pre-eclampsia/eclampsia before 30 weeks of gestation, and in patients who suffered from pre-eclampsia in more than one pregnancy\textsuperscript{32,33}. Based on these results, Chesley proposes the theory that many patients diagnosed as having (mild) pre-eclampsia actually have latent chronic hypertension or renal disease which becomes manifest during pregnancy. This group of women naturally has an increased risk of hypertension and cardiovascular mortality later in life. In contrast, severe pre-eclampsia or eclampsia in nulliparas -Chesley uses the term "true (pre-)eclampsia"- does not appear to be related to latent or subsequent hypertension. The HELLP-syndrome also appears to belong in this second category, as it is not associated with subsequent hypertension\textsuperscript{34}.

North\textsuperscript{35} compared the remote prognosis of 50 women with pre-eclampsia to 50 normotensive pregnant women; all of these women were from the Samoan population, which has a strong ethnic predisposition for hypertension and diabetes mellitus. He found a high incidence of hypertension (40%) and proteinuria (40%) in the group of women with a history of pre-eclampsia, which was significantly different from the control group. In light of the theory presented by Chesley and described above, these women probably have latent hypertension or renal disease and are thus "misdiagnosed" as having pre-eclampsia.

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Risk factors

Women in their first pregnancy are at increased risk of hypertensive disorders of pregnancy. Previous pregnancies appear to have a protective effect, even if they ended early in abortion. In contrast, women with a history of hypertensive disorders in previous pregnancies are at increased risk. Extremely young (teenage) or relatively old (over 35) women, and those with a positive family history, also have a higher risk. African-American women in the US have a higher incidence of hypertensive disorders of pregnancy compared to white women. This difference is at least partially explained by the increased incidence of underlying chronic hypertension among African-American women. Maternal disorders predisposing for hypertensive disorders of pregnancy are those disorders generally associated with increased cardiovascular risk. Women suffering from essential hypertension, renal disease, systemic lupus erythematosus, and type I diabetes mellitus have an increased risk, as well as obese women and those with hypercholesterolemia. In addition, an unusually high proportion of coagulation abnormalities and autoantibody syndromes has been reported in association with hypertensive disorders of pregnancy.

Lately, the association between hypertensive disorders of pregnancy and the Insulin-Resistance Syndrome has been investigated. The Insulin-Resistance Syndrome (or " Syndrome X", "the metabolic syndrome") consists of decreased insulin sensitivity, hypertriglyceridemia, and obesity and is associated with an increased risk of essential hypertension, diabetes mellitus and coronary artery disease. Several authors have reported a significant association between hypertensive disorders of pregnancy and this syndrome, but this association has been disputed by others. Other significant associations have been reported with a history of infertility and headaches, particularly migraine. Interestingly, smoking appears to have a protective effect; the lowest incidences have been reported in women who had a
smoking history but quit smoking in early pregnancy\textsuperscript{19,36}. Factors associated with the pregnant state itself that increase the risk of hypertensive disease are twin pregnancy, polyhydramnion, mola pregnancy\textsuperscript{37}, and a high serum alpha-foeto-protein\textsuperscript{49}.

1.3 PATHOLOGIC FINDINGS

Pre-eclampsia is a systemic disorder, involving organs like the kidney, liver and brain. The systemic manifestations are generally attributed to widespread endothelial damage or activation. Subsequent events include activated coagulation, increased vascular permeability and vasoconstriction, compromising the microcirculation of the organs involved. The pathologic findings are consistent with this theory and indicate that abnormalities are often present even before organ dysfunction becomes clinically apparent. However, most observations obtained by invasive techniques are based on studies in patients with severe disease or even on post-mortem findings; there is no conclusive evidence that all these organs are involved in mild pre-eclampsia or pregnancy-induced hypertension. The most extensive and characteristic abnormalities associated with hypertensive disorders of pregnancy are found in the placenta and uteroplacental vasculature; these abnormalities will be described in detail in Chapter 2.

\textit{Blood}

In normal pregnancy, a great number of changes take place in the bloodstream. Red cell mass increases, but plasma volume increases even more, a phenomenon known as “physiological hemodilution”. This results in a decreased hematocrit and decreased blood viscosity, facilitating uteroplacental blood flow\textsuperscript{50}. In pre-eclampsia, the hematocrit is increased compared to normal pregnancy, due to failure of the adaptive mechanism of volume expansion. The increase in hematocrit
is of prognostic value in severe disease. Blood viscosity is increased in pre-eclampsia, associated with an increase in all major determinants of blood viscosity; hematocrit, plasma fibrinogen, and plasma viscosity. Not all pre-eclamptic patients, however, have significantly raised viscosity. The increase in viscosity alone is not sufficient to explain the increase in placental vascular resistance. The findings on erythrocyte deformability are conflicting due to differences in methodology. The pro-thrombotic state of normal pregnancy is even more aggravated in pre-eclampsia, as indicated by an increase in plasma levels of thrombin-antithrombin III complexes and lower levels of antithrombin III. In severe disease, disseminated intravascular coagulation is present, characterised by thrombocytopenia and accumulation of fibrin degradation products. Thrombocytes in pre-eclamptic patients undergo increased consumption. Thrombocyte production is also accelerated as indicated by an increase in platelet size and distribution of platelet sizes as well as an elevated thromboglobulin level. There is evidence that this increased platelet turnover is caused by oxidative damage to the platelet membrane. Interestingly, the presence of reticulated thrombocytes (a marker of increased thrombopoiesis) has been reported in the sera of pre-eclamptic women several weeks before the onset of clinical symptoms.

**Hemodynamics**

In normal pregnancy, plasma volume increases and arterial vasodilatation occurs, as indicated by decreased diastolic blood pressure and increased cardiac output due to afterload reduction. Pre-eclampsia, compared to normal pregnancy, is associated with a decreased cardiac output and increased systemic peripheral resistance, indicating systemic vasoconstriction. However, recent research work indicates that this low-output state is preceded in the pre-clinical phase by a hyperdynamic state with a high cardiac output. Thus, around the time when clinical symptoms develop, there is a "hemodynamic cross-over" from a high-output to a
low-output state\textsuperscript{71}. Interestingly, this “cross-over” does not occur in women who develop non-proteinuric gestational hypertension\textsuperscript{70,71}. The same pattern is also found in the pulmonary circulation of pre-eclamptic patients: pulmonary artery pressure is increased, right ventricle output is decreased and pulmonary vascular resistance is increased. Filling pressures in pre-eclampsia are unchanged compared to normal pregnancy, supporting the hypothesis that pre-eclampsia is primarily characterised by systemic vasoconstriction and contradicting earlier descriptions of pre-eclampsia as an “overfilled” or “underfilled” state.

\textit{Kidney}

The renal lesions in pre-eclampsia are characteristic and have been extensively studied\textsuperscript{72}. The severity of the abnormalities correlates with the duration of proteinuria. The most characteristic findings are endothelial cell swelling (“glomerular endotheliosis”) and the presence of deposits of fine collagen fibres and fat in the endothelium. “Foam cells”, either endothelial cells or macrophages filled with fatty vacuoles, are also a predominant feature. The basement membrane appears thickened. Subendothelial fibrin deposits and mensangial proliferation have been described by some authors\textsuperscript{73}. These changes lead to swelling of the glomerular tufts and expansion of the capillary wall resulting in complete or partial obliteration of the capillary lumen (figure 1.1). The role of the immune system is not yet clear, but there is evidence that complement and IgM\textsuperscript{74} are present in the capillary loops in pre-eclampsia. Recent Doppler ultrasound findings in the interlobar arteries suggest that vasospasm or arterial stenosis may play a role\textsuperscript{75}. The result in terms of renal function impairment is in the first place proteinuria, with albumin as the main protein excreted. In severe cases, angiospasm leads to acute tubular necrosis and acute renal failure\textsuperscript{76}, sometimes requiring hemodialysis even after delivery.
Figure 1.1 Renal pathology in pre-eclampsia: increase of endothelial and mesangial cell size with compression of the capillaries; the wall of capillary loops appear thickened (Haematoxylin and Eosin x 845). *J Clin Pathol* 1979; 32: 681-692, with permission from the BMJ Publishing group.

*Liver*

Hepatic involvement of the liver in pre-eclampsia is clinically evident in the HELLP-syndrome, which was first described by Weinstein in 1982 and consists of hemolysis, elevated liver enzymes and a low platelet count\(^{13}\). Paradoxically, the HELLP-syndrome does not always co-exist with hypertension and proteinuria\(^{14,77}\). Histopathologically, the HELLP-syndrome is characterised by periportal granulocytic infiltration, focal haemorrhagic necrosis, and deposition of fibrin-like hyalin material. (figure 1.2). Using immunofluorescence techniques, fibrin depositions can be made visible in the sinusoids of almost all patients\(^{14,78}\).
Figure 1.2. Hepatic pathology in the HELLP-syndrome. Periportal haemorrhage and necrosis in addition to fibrin deposition and granulocytic infiltration (Haematoxylin and eosin x 100). *Am J Obstet Gynecol* 1992; 167: 1538-1543, with permission from Mosby, Inc.

The histopathological condition does not significantly correlate to the biochemical severity.78 Liver biopsies from a significant proportion of pre-eclamptic patients who do not have symptoms of the HELLP-syndrome show the same abnormalities on light microscopic examination.14 In addition, immunofluorescence studies show that fibrin deposition is present in the majority of patients with pre-eclampsia, although it is less extensive than in cases with the HELLP-syndrome.14,79 These findings indicate that there is hepatic involvement in most cases of pre-eclampsia even though it is not clinically apparent. The nature of the histopathological abnormalities suggest that ischemia of hepatic tissue plays a major role, perhaps due to microthrombi or vasospasm. Doppler ultrasound analysis of the hepatic
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artery supports this view. Increased resistance to blood flow was found in pre-eclamptic patients with and without the HELLP-syndrome\textsuperscript{80}.

Interestingly, some authors report that the histopathological abnormalities in both pre-eclampsia and the HELLP-syndrome show similarities with another threatening complication of pregnancy, acute fatty liver of pregnancy. Periportal fatty infiltration was observed in four out of eleven cases of the HELLP-syndrome studied by Barton\textsuperscript{78} and in ten out of ten cases of pre-eclampsia studied by Dani\textsuperscript{81}. This view is however not generally accepted.

Potentially fatal complications are subcapsular haemorrhage and acute rupture of the hepatic capsule\textsuperscript{82}. In 34 cases of the HELLP-syndrome, hepatic imaging by CT-scanning and ultrasound was used to detect 13 cases of subcapsular haematoma and six cases of intraparenchymal haemorrhage\textsuperscript{83}. The presence of these complications was significantly related to the severity of thrombocytopenia.

\textbf{Brain}

Central nervous system involvement in pre-eclampsia often presents as visual disturbances, which may arise from retinal artery vasculopathy, abnormalities in the visual pathway, or the occipital lobe. Seizures in pre-eclamptic patients without concomitant neurological disease warrant the diagnosis of eclampsia; these seizures may be focal motor or generalised tonic-clonic\textsuperscript{84}.

The cerebral changes as diagnosed by computer tomography in eclampsia but also severe pre-eclampsia consist mostly of cerebral oedema, especially in the posterior parietal and occipital areas\textsuperscript{85}. This characteristic image has been described as the posterior leukoencephalopathy syndrome\textsuperscript{86}. Subarachnoidal, subcortical and petechial haemorrhages, as well as small infarctions of the cortex, corona radiata, basal ganglia and brain stem are less frequent. Hypoxic ischemic brain damage is also found. In some instances, cerebral oedema and raised intracranial pressure can lead to transtentorial herniation of the occipital lobe, or even brain stem herniation. On post-mortem examination\textsuperscript{85}, vasculopathy with perivascular fibrinoid necrosis
is a predominant feature, accompanied by perivascular micro-haemorrhages and micro-infarcts.

**Myocardium**

Cardiac abnormalities found in pre-eclampsia are mostly secondary to concomitant chronic hypertension or longstanding renal disease. Heart failure, conduction disturbances and cardiac arrest are rarely seen in the absence of pre-existent cardiovascular disease. On post-mortem examination, findings consist of left ventricular hypertrophy, and subendocardial haemorrhages.

**Lungs**

Pulmonary oedema in pre-eclampsia is a serious complication, but in many patients it may well be the result of vigorous intravenous fluid treatment rather than a complication of the disease itself. Interestingly, pulmonary oedema tends to develop post-partum in most patients, probably caused by the volume shift after delivery. As with cardiac abnormalities, pulmonary complications in the absence of pre-existent pulmonary abnormalities are rare. In very severe cases, the Adult Respiratory Distress Syndrome may follow pulmonary oedema or periods of hypoxia.
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