

PHYSIOPATHOLOGY OF TOXEMIAS OF PREGNANCY *

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The present discussion will be limited to acute toxemia of pregnancy in its stages known as preeclampsia and eclampsia. This limitation excludes conditions which might coincide with pregnancy such as chronic hypertensive, cardiovascular or renal diseases. It should be realized, however, that acute toxemia might become superimposed on anyone of these conditions and its recognition as such might present certain difficulties.

For the purpose of this discussion, we shall define acute toxemia as a disease characterized by hypertension, edema and/or proteinuria which usually appears in the latter part of gestation. In addition to the above triad, convulsions and coma are present in the eclamptic stage of the disease. In the past, it was the general belief that toxemia was peculiar to the pregnant woman. In recent years, evidence has been accumulating to indicate that certain animal species such as the sheep and primates may have a form of toxemia closely similar to that of human subjects.

The classification of preeclampsia as mild and severe should be avoided as much as possible because of the false sense of security that might be implanted in the mind of the practicing physician. It is not infrequent to see a case labeled as mild preeclampsia rapidly progress into eclampsia with convulsions and coma. This eventuality can be prevented to a great degree by considering all cases of preeclampsia as potentially dangerous requiring utmost attention and care.

From the diagnostic point of view, the presence of hypertension is essential for classifying a case as acute toxemia; for a certain degree of proteinuria and edema may be found in an otherwise normally pregnant woman. It has been recently shown that the edema of normal pregnancy may be related to hemodynamic and renal factors brought into play by the tendency to venous pooling when a pregnant woman assumes the standing position.

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This type of edema subsides rapidly with bed rest in contrast to that of toxemia which requires a more vigorous treatment. The importance of blood pressure elevation in the diagnosis of toxemia has, unfortunately, been misunderstood and neglected by many physicians and investigators. One of the main reasons for the confusion has been the rigid ceiling of 140/90 mmHg which was established many years ago by the American Committee on Maternal welfare as a borderline between normal and abnormal blood pressure. While this level might be of some help in following the pressure of a nonpregnant individual, in pregnancy it has done more harm than good. For, it is well known that many pregnant women exhibit a diastolic blood pressure of 60 mmHg or less throughout most of their pregnancy. A sudden rise to 80 or 90 mmHg may represent a substantial increment of 45 to 50% and in certain instances may be present with a galloping convulsive eclampsia. Yet this pressure may still fall somewhat short of the established ceiling and may lead to a certain hesitation on the part of the physician to make a diagnosis and treat a case as toxemia. For this and other reasons, we have repeatedly advised physicians to disregard the ceiling of 140/90 mmHg and to accept as indicative of hypertension any sustained diastolic rise of 25 to 30% over the patient's own baseline blood pressure during her present pregnancy.

It is not the object of this report to discuss the many hypotheses which have been advanced to explain the etiology of toxemia. A brief mention, however, will be given to the theory of uterine ischemia since this has been for many years and is still in vogue. This theory states that mechanical or pathological vascular factors produce ischemia of the uterus and placenta. This leads to the elaboration of pressor or "toxic" substances by the ischemic chorionic villi which in turn evoke a generalized vasoconstriction and toxemia. In favor of this hypothesis are the facts that toxemia is more frequent in primiparas with a tight abdomen and uterus, in multiple pregnancy and hydramnios, in the presence of hydatiform mole and in the presence of cardiovascular or degenerative diseases such as diabetes, essential hypertension etc. Experimentally, this hypothesis received some support from two series of studies in which the total blood flow to the pregnant uterus in toxemic patients was measured and found to be less than that of normal pregnant women of the same period of gestation. Despite the clinical and experimental evidence in its favor, the hypothesis of uterine ischemia still remains unproven. First, it has not been conclusively demonstrated that the mechanical or pathological conditions listed above produce any uterine ischemia. Second, no pressor or any other abnormal substances have as yet been identified in the blood of toxemic patients. Third, the measurements of uterine blood flow, upon which much hope has been placed, were performed on patients with frank toxemia and it is impossible at this time to state whether the diminished flow which

was found was related to the cause of the disease or was merely a part of the generalized vasoconstriction which undoubtedly exists in toxemia

Despite the lack of knowledge regarding the etiology of toxemia great progress has been made during recent years toward understanding its pathophysiology. It is generally agreed now that the basic underlying abnormality in preeclampsia and eclampsia is a generalized arteriolar vasoconstriction which affects such major organs as the kidney, the brain and the pregnant uterus. The systemic as well as the regional vascular resistances are elevated. In the kidney, the increase in vascular resistance is more marked in the afferent segment. Renal blood flow and glomerular filtration rate in toxemia are diminished when compared to those of normal pregnancy of the same period of gestation. It is possible that the decreased filtration rate in toxemia may be related to the mechanism of edema formations in toxemia. For, a fall in filtration rate would lead to a fall in the filtered load of sodium. This latter factor is thought to stimulate increased reabsorption of this ion by the renal tubules. This together with the action of the mineralocorticoids which have been found to be elevated in toxemia favor accumulation of edema. The proteinuria of toxemia has also been attributed to excessive leakage of protein by the ischemic glomerular membranes. In the brain, increased vascular resistance has been shown to exist in preeclampsia as well as in eclampsia. However, whereas in the absence of convulsions, cerebral blood flow and oxygen consumption may not be affected, in eclampsia these are significantly reduced. Thus, a certain relationship between cerebral ischemia and convulsions seems to exist. In fact, such a relationship has been established in the experimental animal by Byron and his group in England. These investigators followed the changes in the caliber of the cerebral vessels in rats with renal hypertension and observed reduction in their caliber when the animal convulsed. This reduction was to a large degree independent of the blood pressure level. In the pregnant uterus, the marked increase in uterine vascular resistance results in a diminished blood flow and oxygen consumption of the uterus and its content. This may account for the high incidence of placental infarcts of prematurity and of stillbirth in toxemia. The evidence gathered during the last 10 years seems to indicate that the vasoconstriction of acute toxemia of pregnancy is maintained by humoral factors rather than by activity of the sympathetic vasoconstrictor impulses. Inhibition of these latter by autonomic blocking agents or by spinal anesthesia has failed to affect materially the hypertension of toxemic patients. Furthermore, toxemia of pregnancy has been observed to occur in patients who had been subjected to extensive sympathectomy for essential hypertension.

The concept of generalized vasoconstriction and of its humoral support as being an important pathogenetic factor in toxemia has had a great impact

on the management of this disease. Ideally, the treatment of any illness would be that which is directed to its etiology. But since the etiology of toxemia is not known, we should be satisfied to direct our treatment to its underlying abnormality which is vasoconstriction. In the past, the emphasis was placed on heavy sedation with one form of drug or other. Heavy sedation, however, does not relieve the vasospasm and clouds the issue more than it helps it. For, besides the respiratory depression that sedation produces, it deepens the comatous condition in such a way that it becomes difficult to determine how much of the unconsciousness is due to the sedation and how much is caused by the disease itself. For these and other reasons, the use of heavy sedation as the main form of treatment of toxemia of pregnancy has been de-emphasized. More reliance has been placed on the use for vasodepressor drugs in conjunction with triazide diuretics and mild sedation. This approach has simplified considerably the management of toxemia and has contributed significantly to the reduction of maternal death caused by this disease.