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Etiology of cholelithiasis

Donald Martin Petersen
University of Nebraska Medical Center

The Role of Estrogen and Progesterone in the Edema of Pregnancy

By
Donald M. Petersen

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Introduction

From the time of conception to the time of delivery, the maternal organism undergoes many fundamental modifications during pregnancy. These changes take place not only in the reproductive organs but also in the organism generally. These changes are influenced by the hormones elaborated during this period. Recent advances in the field of Endocrinology have suggested that a knowledge of abnormalities in the endocrine balance during pregnancy might throw light on the pathalogical states affecting reproduction, and might suggest appropriate therapeutic procedures.

One of these changes which takes place in the organism is the tendency to retain water in the tissues. In the toxemias this tendency is further exaggerated and results as a rule in greater degrees of edema. The causes for the maternal organism to retain water in the tissues have guided research in two fields. One field of research has been in the endocrines, for it seems hardly possible that a substance which is responsible for the physical changes of pregnancy should not in some sense be responsible for the disease which occurs only in pregnancy. The other field of research has been in the physical and chemical phenomena of water and electrolytic changes as a cause of edema in the normal and toxemic pregnant woman.

Recent experiments have been undertaken showing that the estrogens and progesterone may cause the retention of sodium and water in the tissues during pregnancy. Thus the hormonal and physicochemical conception of the retention of water in the edema of a normal or toxemic pregnancy may be reconciled. Taylor (53)

Water and Sodium Metabolism in Pregnancy

The retention of water in a normal pregnancy is manifested by an increased gain in weight and by the frequent pitting edema of the lower extremities. Another indication of water retention is an increase in the volume of blood plasma. Dieckman (18) in a series of cases found that the blood and plasma volumes began to increase in the first tri-mester, and by the thirteenth week the gain amounts to 16% and 18% respectively. The increase continues throughout the pregnancy until the ninth lunar month there is some dimunition. During the ninth lunar month, there is some decrease in volume. Thompson (57)

Feldman (20) in attempting to find a reason for the anemias of pregnancy made studies on a rat and found that in part it was due to the blood dilution. That water content was markedly increased but not in proportion to the decrease in hemaglobin, red cell count, and hematacrit which he also found. These findings were corrobarated in studies made by Oberst (36) and Dieckman (16) on the human female and can be explained by physiologic dilution of the blood associated with an increased blood volume. Rise in plasma volumes is further manifested by a reduction in the plasma proteins. During normal pregnancy the plasma proteins begin a gradual drop at the third month and the minimum is reached at the ninth month. There is a subsequent rise in the tenth month and again during labor. Plass(39,40)

This increase in plasma volume is said to reach its maximum value at the ninth month. This amounts to an increase of 65% above the average normal non-pregnant value. During the tenth month there is a definite decrease to 50% above the normal non-pregnant level. Thompson(57)

The increase of extra cellular water is also an indication that there is a retention of water in a normal pregnancy. Chesley (8), as cited by Taylor (54) The usual proportion of available extra cellular water in pregnant women weighing less than 120 pounds has been found to range from 33-37 per cent of the total body weight, as compared to an average of 20-26 per cent in non pregnant women.

Denis (14) made numerous studies on the concentration of sodium and chlorides in normal and toxemic patients, and found them to be unchanged as to concentration. This work was doneiin the early twenties when methods of chemical analysis were not as exact as they are today. We now know that sodium and chlorides are increaseddduring pregnancy, and that sodium retention is also an important factor in the edema of pregnancy. Large fluctuations in body weight result from significant changes in body water, which accompany parallel shifts in sodium balance. Thompson (56) Freyberg (22) found that when a pregnant wowan would ingest 5 gms. of sodium chloride daily for 6 days, there

was a marked retention of water during the first three days. This response is identical with that in normal non-pregnant women but with this it would seem to indicate that the same factors that govern water balance in normal non-pregnant individuals would be of similar importance during pregnancy. It is a known fact that the sodium ion is increased above normal in the latter months of pregnancy. Thompson (56) and Taylor (61) No doubt a part of this positive balance can be attributed to the needs of the developing tissues of mother and fetus, but the capacity to eliminate sodium is still diminished in the pregnant woman. Janney (30) presented results to show the great capacity of the kidney to eliminate water. They also showed that this capacity declines progressively in normal pregnant women from the twelfth week of pregnancy. These observations show further evidence that the pregnant woman has an altered capacity to eliminate sodium.

During the tenth lunar month, labor, and parturition certain changes in the relationship of plasma volume and sodium concentration takes place. There is a definite increase in blood concentration during the first few days ante partum and during labor, as is shown by hematacrit values in normal patients. Crawford (13) Part of this concentration of the blood may be due to blood loss,

muscular activity, or dehydration. This period of blood concentration continues until after labor and then following delivery there is a rapid blood dilution during the first three days. After this period of blood dilution the blood gradually returns to normal Thompsen (57). When the blood volume again rises following the blood concentration the first few days post-partum, diuresis commences.

During this period of diuresis following delivery there is an increased amount of sodium in the urine. Taylor (53) Thus indicating that the sodium retained in the tissues above the normal level is being eliminated to the normal level. The water held in the tissues with the sodium is also being eliminated because there is a considerable loss of extracellular water. Chesly (8) as cited by Taylor(54) The extracellular water probably contributes to the increase in plasma following delivery. This fluid is moving from the tissues to the vascular spaces. This in turn leads to diuresis. Within a week or two after delivery, the blood volumes return to normal and blood volume studies at this time will show a loss of a liter or more while according to obstetrical reports the loss was only 300 cc. Keith (31) This decrease in the blood volume following delivery can be explained on the basis of hydremia. The water which was increased

during the antepartume period has been eliminated through the urinary tract with a resulting concentration of the blood to its normal level.

In the specific toxemias of pregnancy, eclampsia and pre-eclampsia, the degree of weight gain, edema, and water retention is exaggerated more than in a normal pregnancy. In a normal pregnant woman, when a large amount of salt is taken, there is at once a large positive water and salt balance. Freyberg (22) It is the failure of this adjusting mechanism which makes off the toxemias from the normal. If sodium salts are retained so is water, even to the point of edema. Harding (27) Harding (27,28) in a series of toxemic patients used 10% saline intravenously and found that the albuminuria was increased and systolic and diastolic blood pressure increased. Giving 10% saline intravenously can even precipitate convulsions. The observations were the same with sodium bicarbonate, thus proving it is the sodium ion which causes the retention of water. Diet high in sodium will affect these toxemic patients in a like manner. It is the retention of water along with this electrolyte sodium that causes edema and an exacerbation of the symptoms. These observations of Harding's were substantiated by Strauss (49,50,51,).

It is a known fact that in eclampsia or pre-eclampsia, there is a reduction in urine volume and that complete suppression is one of the sequelae to be feared. As I have mentioned previously, Janney (30), there is a diminishing urinary capacity for the normal pregnant woman from the 12th ante-partum week. In the toxemias of pregnancy the ability to eliminate water was markedly diminished. McManus (35) in a series of cases ran kidney functions on normal and toxemic pregnant women and also found that there was a more marked reduction in the urinary output of a toxemic patient.

The blood in pre-eclampsia does not go through the same changes as in normal pregnancy. There is a definite increase in the blood concentration as is shown by the increase in the cell volume, hemaglobin, and proteins. In a normal pregnancy there is an increased blood concentration but this occurs in the last week before delivery. In patients suffering from pre-eclampsia toxemia, they have a definite increased blood concentration for a week or more before delivery. Crawford (13) Clinical improvement occurs with dilution of the blood during the course of the toxemia in pregnancy. Schwarz (42) Pre-eclampsia or eclampsia patients who show edema, albuminuria, and high blood pressure will show definite

signs of clinicla improvement within twenty four hours postpartum or after death of the fetus. Schwarz (42) This is because blood dilution occurs within twenty four hours postpartum or after death of the fetus. Clinical improvement is also manifold during the course of the toxemia whenever blood dilution occurs. Blood dilution occurs when therapy is carried out using Ammonium chloride or dehydration therapy. In either procedure acidosis results and water bound in tissues is released. There is an increase in urinary output, decrease in edema, and albuminuria. Blood dilution occurs when water moves from tissues to the vascular system. It is during this period of blood dilution following death of fetus or delivery with its accompanying physico-chemical changes that the greatest clinical improvement, greater diuresis, and greatest weight loss takes place. Schwarz (42) The cell volume drops 15-25%, while the protein decreases 25-35%. The serum proteins return to normal within a week or two but the cell volume percentage and haemaglobin return to normal more slowly. There is no good explanation for this increased concentration of water in the tissues or for the decreased concentration of the blood in a toxemic patient, but there is the suggestion of a barrier of some kind between blood stream and kidney. If a barrier of some kind is not present

between blood stream and tissues, edema would not result and all excess water would be eliminated through the kidney. Taylor (53)

Effect of Estrogen and Progesterone on Sodium and Water Metabolism in Pregnancy

Numerous observations have been made on the water and sodium retaining effects of estrogens and, to a lesser extent, progesterone. Krohn (32) investigated the water metabolism in a fully mature female pig-tailed monkey which has a menstrual cycle of approximately thirty days. The sexual skin of the animal regularly swelled during menstruation, resorption of the swelling beginning shortly before the middle of the cycle. The animals body weight also fluctuates in accordance with the state of the sexual skin, increasing throughout the first half, and decreasing in the second half of the cycle. The increase in weight amounted in one cycle to as much as 18% of the animals body weight when her sexual skin was quiescent. The intake of water was lower during the phase of sexual skin swelling than during the phase of sexual skin subsidence. There was an increase in urinary output during the phase of sexual skin subsidence. The conclusions drawn from such observations are that the sodium and water retention is the greatest when the concentration of estrogen is the highest. The estrogenic concentration is the highest during the middle of the menstrual cycle. The swelling of this skin is also due partly to an increased imbibition of water by the tissues. Fisher (21) In a group of fifty normal subjects 48%

were observed to have a marked fluctuation in body weight during the premenstrual period in the menstrual cycle. Twenty-six per cent were observed to have a marked fluctuation at or about the time of ovulation. Renal excretion of sodium and water was decreased preceding menstruation but increased after menstruation. Thorn(59)

Injections of the sex hormones, notably estrogen and progesterone, causes the renal excretion of sodium and chloride in dogs to be markedly diminished. Thorn (58) The potency of these two compounds differs. Estrogenic injections causes more markedly diminished renal excretion of sodium and chloride than progesterone. Thorn (58) also found that renal excretion of potassium was increased following administration of progesterone and estrone. Guthketch(26) using monkey's, also found that water and sodium was retained when estrogen was injected. He used ovariectomized animals. After nine courses of estrin injections into these animals, the sexual skin swelled during the course of injections and subsided gradually when the injections were stopped. The red cell count also increased during the course of injections, thus indicating some hemoconcentration of the sexual skin. The count thus rises and falls after periods in which estrin is injected into these spayed females. The hemo-

concentration can be explained on the basis of water loss into the tissues. The fluids for this edema in the sexual skin comes from the vascular system and passes into the tissues causing hemoconcentration in the vascular system and edema of the sexual skin.

Numerous investigators found the reproductive organs to contain a portion of this unexcreted water. Astwood (1) and Aykroy (2) injected estrogen into an immature female rate and found the uterus to have an increase in weight. This increase was due to the accumulation of water in this organ. Water is found in excess in the stroma of the uterus and to a lesser extent in between the muscle layers. The concentration of the sodium had risen quite high. Talbot (52) The potassium concentration decreased. Thirty-six hours after the administration of estrogen, the uterus was much larger than the control but was no longer edematous. The electrolyte pattern was essentially the same as in the control. There is also a large amount of water that is retained in the sexual skin of the pig-tailed monkey as I have previously stated. Fisher and Zuckerman (21) Clark (10,11) stated that the sexual skin of the baboon achieves its state of edema with little if any change in its cellular volume. The greater part of the increase in weight of this organ is due to the increase in interstitial

fluid. The increase in weight of the sexual organ is in part contributed from its own body but the greatest is from the outside. The animals exhibit thirst and relative oliguria when the swelling occurs and the reverse while the resorption is going on. Clark (10,11) also noticed a slight hemoconcentration during the period of sexual skin swelling.

The observations made by Clark (10,11) in regard to blood volume changes are in contrast to those made by Friedlander (23,24,25). Friedlander (23) working on cats found a marked reduction in blood volume following the removal of both ovaries and made the conclusions that the ovary exerts a controlling influence on the blood volume. Changes are also produced in women by bilateral oophorectomy. When this operation is performed blood volumes are reduced about twenty-five per cent. A control group, consisting of women with normal and natural menopauses, show no changes in blood volume or chemistry. Friedlander (24) Friedlander (25) administered estrogenic hormones into castrated women and raised the blood volumes to normal. This is another observation that the estrogens influence the retention of sodium and water. Friedlander (25) also came to the conclusion that these elevations of blood volume are not due to changes in the capillary permeability.

The diuretic effect of progesterone is also difficult to understand along with the other observations. Using rats as experimental animals Selye and Basset (44) found that injections of progesterone increased the urinary output in both normal and hypophysectomized animals. The water elimination is slower in hypophysectomized animals than in the normal, but nevertheless progesterone stimulates water excretion much more markedly in the absence than in the presence of a hypophysis. Cantarow (6) in a recent article found that desoxycorticosterone and progesterone administered to dogs resulted in an increase in concentration of sodium and chloride ions in the peritoneal fluid. The cause for this could be the result of passage into the fluid of large amounts of these elements or a decrease in the volume of intraperitoneal fluid. These observations support the hypothesis that the effect of these agents is exerted upon the membranes in general, and their action in producing a decreased renal elimination of sodium and chloride ions may constitute a part of their generalized action.

Taylor (53) made observations on six pregnant women for at least ten days before labor, during labor, and ten days after delivery in regard to their sodium balances. In three cases these observations were made on normal pregnant women. Certain factors were common to the three

normal cases. Estrogens before labor gave values in the urine varying from 200 to 3000 rat units per liter. These values dropped very abruptly after labor and by the third day the amounts obtained were reduced practically to those of non-pregnant women. The sodium balance was slightly, but almost consistently positive in all three cases up until the time of labor. There was a negative sodium balance in each on the fifth and sixth postpartum days, but this can be ascribed to the increase putput in the urine. This diuresis along with the increased sodium putput, occurred shortly after the estrogen and progesterone level had fallen to non-pregnant levels. In the case of the pre-eclamptic patients, the hormone concentrations of estrogen and progesterone were similar to those for the normal cases. Taylor (53) There was a retention of sodium before delivery as in the normal cases. There was a greater loss of sodium in the postpartum period. This greater loss of sodium is no doubt due to the elimination of extra-cellular fluid. The period of greatest sodium loss closely followed the disappearance of the hormones from the circulation.

The injection of large doses of estrogens in a normal pregnancy increased the antepartum sodium retention, and this suggests that the administration of estrogens has a physiological effect on sodium retention. Taylor (53)

This patient was given 180,000 rat units of estradiol benzoate in six injections on two successive days ante-partum and on each of the first five post-partum days she received two injections of 30,000 rat units of estradiol benzoate. In the case of the normal pregnancy, after the ante-partum injection of estradiol benzoate, sodium retention was quite marked. During the post-partum period the loss of sodium was similar to that of a normal person. In the postpartum period there is evidence of a slight net gain in sodium. The substance used in this experiment was estradiol benzoate whose effect is slower to develop than that of the simple hormone.

From the observations that Taylor has made, it seems probable that the estrogens are one of the causes of sodium retention. Progesterone is also reported as being able to cause salt retention although evidence shown far is not conclusive. The manner in which these hormones act is debatable. It might be through the kidney, which in some manner inhibits its excretion, or it might be through some other gland as the adrenals or pituitary gland.

In attempting to find an explanation for the increased excretion of sodium and watef during the puerperium one must think of the physiologice change which

occurs when the baby is born and the placenta is detached from the uterus. The sodium and water loss is no doubt connected with this change. The sodium retaining properties of the estrogens and progesterone seems a satisfactory explanation but others must be considered. One possible explanation is the disappearance of the placental circulation. Burwell (3,4) has shown that there is some similarity between an arterio-venous fistula and the circulation of the placenta. In the placenta arteries connect with the veins by way of relatively large vascular spaces and without the interposition of either arteries or capillaries, so there is some similarity between the two. Burwell has also shown that in an arterio-venous fistula, symptoms of increased blood pressure in veins adjacent to fistula, increase in cardiac output, increase in total blood volume have also been shown to be present in pregnant women. This could be a satisfactory explanation for the increased blood volume and increased venous pressure in the lower extremities, and hence a factor in the retention of water. It was hoped that by administering large amount of estrogens in the puerperium, concentrations of these substances could be elevated to those of pregnancy. If the sodium loss and water diuresis could be prevented the association of water and sodium retention with the estrogens in the ante-partum period

would be more or less established. Taylor (54)

Smith (46) advocates the use of estrogen and progestin in the treatment of pre-eclampsia. He based his conclusions on observations made in a series of cases treated this way. His studies indicate that there is an increased destruction of these hormones which characterizes the stages of toxemia at which the first clinical signs appear and is more pronounced when toxic signs progress. There was no beneficial effect derived from replacement therapy upon the clinical picture unless large injections of estrogen and progesterone were given, and continued for six or more days. He believes that this steroid deficiency is due to changes in kidney physiology which causes excessive destruction of these placental hormones.

The excretion of the estrogens for example is dependent upon a great variety of conditions. The first is the rate of production which occurs during the placenta. The second is the degree of destruction or conversion into an inactive form which may occur in the liver and kidneys. There is finally the factor of kidney excretion, although there is less belief than formerly in a renal threshold. With the amount of estrogen in the urine dependent on placental renal and hepatic function it is not surprising that the values in blood and urine

may be altered in such a disease as toxemia of pregnancy. Taylor (55) Smith (46) gave a total of nine women, including one diabetic, showing the clinical signs and symptoms of pre-eclampsia, and urinary findings indicative of rapid steroid destruction intramuscular injections of 10 milligrams of estradiol benzoate and 30 to 50 milligrams of progesterone together with sodium pregnandiol gluoronidate by mouth (100-200 milligrams a day). Pregnandiol by mouth enhances the beneficial effect of estrogen and progesterone metabolism. In only two of the patients was clinical improvement and a normal steroid metabolism maintained for the duration of the injections. The other seven patients with severe eclampsia to whom progesterone, estradiol benzoate, and pregnandiol were given have been less encouraging. There was some clinical improvement immediately but before the seventh day there was a return of the clinical and hormonal abnormality. Smith believes that these patients would have been helped if they had been seen earlier in the course of the disease.

Smith (48) also reported in another paper that uterine contractions and the resultant embarrassment of placental circulation was a possible cause for immediate reduction in the supply of progesterone and estrogen, and the accompanying shift in the urinay distribution of estrogens

was indicative of deficient progesterone metabolism.

Smith (45) makes the statement that a certain toxin is produced during menstruation, the formation of which appears to be closely allied to rapid destruction of the estrogens, and that the same shift of steroid metabolism in pregnancy results in the formation, on a larger scale, of a similar toxin. The albuminuria of pre-eclampsia might be ascribed to the effect of such a toxin acting on the kidney glomeruli. The hypertension maybe an actual Goldblatt phenomena from renal arteriolar constriction due to this same toxin. Even though the pathalogical changes may be ascribed to the action of some specific toxin, an important aspect of these changes is the circulatory deficiency which must, in itself, interfere with the vascular supply of the placenta. Thus a vicious circle is set up in which circulatory and hormonal changes are amplifying one another. In breaking up this vicious circle two methods may be approached. The first is to neutralize the hypothetical toxin and the second to prevent it further formation by restoring adequate blood supply to the placenta and replacing the progesterone and estrogen deficiency. The more advanced the case, the more difficult it is to replace estrogen and progesterone deficiency.

Smith (47) has recently made urinary studies in a

patient with severe eclampsia during a four day period when veratrum viride a temporary vaso dilator, was given. These studies indicate that there is an increased metabolic conversion of the estrogens. These hormonal affects are of short duration as are the chemical. There is reason to believe that the relationship between the sex hormones and their production, metabolism, and general vascular supply is reciprocal.

Marsden(34) used large doses of progestrin alone in toxemic patients and discovered that none of the patients developed convulsions but in only one of the patients was there a drop in blood pressure. All of the patients had toxic symptoms.

White(63) advocates the use of progesterone and estrogen in the therapy of certain cases of pregnancy. He uses estrogen and progesterone in the treatment of diabetic pregnant women when there are indications that they will have premature births, still births, or neonatal deaths. He believes that after the twentieth week a diabetic will have an accident such as I have just mentioned if the chorionicgonadatropin level rises to more that 200 rat units per 100 cc. of blood. These accidents can be prevented by continuous substitutional estrogen and progesterone therapy in replacement doses. The estrogens probably fail to be produced in sufficient

quantities or there might be a failure in the metabolism of estrogen and progesterone. These accidents are not due to an improperly controlled diabetic but to an abnormal hormonal balance.

Watts and Adair (64) found the twenty-four hour excretion of estrogen and gonadatropin shows significant difference between a group of normal patients and the groups with either pre-eclampsia and eclampsia in whom the disease is considered peculiar to pregnancy. There was an extreme individual variation of the excretion of both estrogen and gonadatropin. The values for each group of patients show a lowered excretion of estrogen in the pre-eclamptic and eclamptic group, and an increased excretion of gonadatropin in the pre-eclamptic and eclamptics. The values obtained by different investigators differ because of the variation in technique of extraction and assay of the estrogen and gonadatropin. In general there seemed to be a relationship between the amount of estrogen and gonadatropin excreted. When the estrogen was high, gonadatropin was high. This relationship has been expressed as the estrogen to gonadatropin ratio. The mean ration was the lowest in the pre-eclamptic and eclamptic group. There was a significant difference between the normal and pre-eclamptic group. These results thus indicate that these hormones are in some way associated with the toxemias of pregnancy. There is an

increased excretion of gonadatropin and a lowered excretion of estrogens in pre-eclampsia and eclampsia. The question for the future seems to be to determine the cause of these hormonal changes whether or not they are attributed to change in the production of these hormones, to disturbance of their ratios or to altered excretory, metabolic, and storage functions of the kidney, liver, or placenta.

Although there is a slight dimunition in the estrogens in a pre-eclamptic patient, Taylor (53) still does not believe in this replacement therapy as Smith (46) advocates. He believes that the individual is already suffering from an abnormal retention of sodium and water, and if estrogen and progesterone were given in large doses as Smith gives, further damage might result..

Taylor (54) attempted to alter the postpartum decline of urinary estrogens by daily injections of 30,000 units of estradiol benzoate or 5 milligrams of estradiol benzoate but failed to alter this decline. No change in the ratio of decline of urinary pregnandiol was brought about by the use of 50 milligrams of progesterone daily. Under normal conditions the concentration of estrogens in the urine falls rapidly and immediately after delivery a level characteristic of the non-pregnant woman is reached in three to five days. Nevertheless, it appears that the doses were physiological for there was a com-

plete suppression of lactation in those women treated with hormones through the early puerperium. The dosages of both estradiol and progesterone were also comparable to those used by Thorn and Engel (58) in their experiments on the effect of sex hormones on the renal excretion of electrolytes. Due consideration was taken in regard to body weight relationship of dog and human in considering adequate dosages of hormones.

Hormone administration after the termination of labor caused a retention of sodium. Using as control a group of normal pregnant women who had not had any hormones administered, a comparison was made with cases treated with estradiol benzoate, or progesterone and in each, sodium loss was less than in the controls. The average loss of sodium for the first ten post-partum days in the three patients serving as controls was 4.89 grams, the individual loss in each case being 4.00, 6.59, and 4.08 grams. In one case a total of 300,00 rat units of estradiol benzoate was administered during the first five post-partum days. The sodium retention in this patient was 2.78 grams before the tenth post-partum day. Estrdiol 45 milligrams was given to another patient for a week, beginning two days before delivery. Only 1.87 grams of sodium was lost in the first ten days, indicating that the preparation is more effective in retaining sodium

than estradiol benzoate. Progesterone was effectual if doses as high as 1.25 milligrams were given. When this dose was given the loss of sodium before the tenth day was only 2.34 grams. Taylor (54)

In a patient suffering from toxemia there is an excessive loss of sodium and water during the first few days of the puerperium. Taylor (53) There is also a marked variation in the readings obtained from these patients. Of course much of this excessive loss of sodium and water depends on the amount of the previous edema. Taylor (54) experienced great difficulty in setting up controls for his experiements on hormones administered before the termination of toxemic pregnancies because of this great variation in edema. The sodium loss in one patient before and after delivery amounted to 17.34 grmas of sodium. The loss in another patient amounted to only 2.56 grams in ten days, but this patient had begun to lose sodium nearly three weeks before delivery. The loss of sodium nearly three weeks before could be explained on the probability of an impending intra-uterine death. If the sodium loss in this particular patient were taken from the very first day of negative sodium loss, then the total sodium loss including the first ten post-partum days would be a loss of 19.44 grams. Two other patients received hormones on the day of labor. One received 300,000 units of estradiol benzoate and the

other 200 milligrams of progesterone. In both instances the sodium loss was lower than in the other two untreated cases of toxemia. The patient receiving estradiol benzoate lost 7.34 grams while the patient receiving 200 milligrams of progesterone lost 3.77 grams of sodium. In each of the untreated patients there was a negative sodium loss on the tenth post-partum day, while in those patients receiving hormones there was still a positive balance on the tenth post-partum day. There is thus some proof that estrogen and progesterone have some sodium and water retaining properties.

Taylor (54) in a series of three patients administered hormones before the termination of pregnancy to determine whether sodium excretion could be influenced under there administration. The results were not to conclusive for in none of the three cases treated was there any change in the sodium excretion under these conditions. The reason these hormones had no influence on the course of sodium excretion following delivery is probably to be found in the fact that the hormones administered was only a small fraction of the amount being constantly manufactured by the patient. The large doses of estrogen and progesterone that were administered in the latter stages of pregnancy may also have represented an insignificant increase over their normal supply.

One patient with toxemia received doses of 50-200 milligrams of progesterone over a period of two days. the doses were given over a period of two days.before delivery. The doses were given on three separate occasions. Another patient who had a normal pregnancy received a total of 180,000 rat units of estradiol benzoate distributed over a three day period beginning sixteen days before the onset of her labor. Another toxemic patient received the same amount of estradiol over a periol of three days, beginning fourteen days before labor. In none of these patients was there any marked change in urinary excretion of sodium or changes in urine volume. In each of the three patients treated there was a slight decrease in the sodium retention during the first three days. This was followed by a slightly increased positive balance. The results of using estrogen and progesterone in preventing diuresis and sodium loss in the puerperium of patients who had toxemia are not too convincing but only suggestive. Taylor (54)

Other Factors to be Considered as a Cause of Edema in Pregnancy

Many factors have been offerred as a basis for explaining the edema of pregnancy. As a result of the work done in the past few years on the effects of estrogen and progesterone on sodium and water retention, and their ability to cause edema, these factors must be re-evaluated. Either of the factors offerred could still be a cause of edema in combination with the effects of the estrogens and progesterone.

A. Excessive retention of sodium: Straus (49) and Harding (28) have pointed out that ingestion of large amounts of sodium in the form of sodium chloride may cause an exacerbation of the symptoms of toxemia such as edema, nausea, and vomiting and increase in blood pressure. This retention of sodium and increase of extra-cellular fluid when it is administered in large amounts is not a peculiarity of pregnancy byt will occur to some degree in normal persons. Harding (29) That which is characteristic of both normal and toxemic patients is the delayed elimination of the sodium. Thus a given quantity of sodium will cause a greater degree of edema in the toxemic or normal pregnant woman than in a healthy non-pregnant woman. Strauss (49) administered large amounts of sodium to patients in the last tri-mester of pregnancy who also had an associated hypoproteinemia,

and found that visible edema appeared. When this sodium administration was stopped, the visible edema disappeared. These conclusions were verified by Harding (27,28). Harding put a pre-eclamptic patient on a high salt diet and this resulted in an increase in edema. Edema diminished when the patient was put on a low salt diet. Taylor (54) believes that this immediate cause of edema is due to the increased tendency to sodium retention. Therefore the problem is to transfer this cause of edema to the cause for the increased sodium retention. The cause for this physiologic change can be explained by the concentration of estrogens and progesterone.

B. Reduction of plasma proteins: For many years it was thought that a decrease in colloid osmotice pressure, due to a reduction in plasma proteins, was a factor in causing edema in the latter months of a normal pregnancy. In certain cases of edema there maybe a very pronounced nutritional deficiency which causes a very low concentration of plasma proteins but this is very rare. These cases are neither examples of normal pregnancy nor of pre-eclampsia. Dieckman (17) determined the serum proteins and albumin concentrations and colloid osmotic pressure in a number of normal pregnant and toxemic pregnant patients before and after delivery. He found that the colloid osmotic pressure in a normal pregnant patient is 28.7 centimeters, 26.5 centimeters in toxemic patients without edema, and 24.9 centimeters in those

toxemic patients with edema. There are many factors to be considered in the formation and disappearance of edema, but the concensus of opinion is that edema is likely to occur if the oncotic pressure is less than 20 centimeters and likely to disappear if the pressure exceeds this. There are thus no changes in the serum proteins which might account for the edema. Low plasma proteins are not even a primary or important contributory factor in the ordinary case of toxemia of pregnancy.

C. Altered kidney function as a cause of edema:

Numerous observations have been made on the renal functions in normal and toxemic pregnancy in an attempt to correlate the edema with altered kidney function. Dieckman (17) suggested that the renal function was altered in normal pregnancy. The evidence for such observations is not quite clear. Studies made by Chesley (7), and Welsh (62) indicate no disturbance in kidney function in a normal pregnancy. Chesley (9) showed the effective renal blood flow in toxemia of pregnancy as determined by the diodrast clearance to be the same as that of normal pregnant and non-pregnant women. Welsh (62) found the filtration rate (inulin clearance), effective renal blood flow (diodrast clearance), tubular excretory mass and phenol red clearance are not altered in pregnancy or in the puerperium of normal women. Renal func-

tion as revealed by these tests is unaltered by normal pregnancy and undergoes no change in the days immediately following delivery. Water and salt retention of normal pregnancy therefore can not be explained on the basis of a decreased filtration rate. There is no evidence of any hormonal effect on kidney function which might accompany the morphological change known to follow the injection of similar substances into small laboratory animals. Some patients with toxemia of pregnancy have a decrease in glomerular filtration rate. Corcoron (12), Dill (18), and Wellen (61) found this to be true in some of their patients with toxemia. Wellen (61) compared the renal function in fourtenn pregnancies complicated by specific toxemia to that of a control group and found the clearance below the normal range in two, while the filtration fraction increases, in part because of an increase in inulin clearance. The group with clinical cure have figures within the normal range. Cases of late toxemia of pregnancy in which filtration fraction is increased or clinical and functional grounds may be classified as essential hypertension, pre-existing or formerly latent. Corcoran (12) These changes found in toxemic patients may contribute to the tendency to retain water. This would not hold true for the non-pregnant patient, because this observed degree

of reduction in kidney function would be inadequate to produce any edema. Further notice is to be taken of that fact that some of the patients in whom edema was present had normal filtration rates. Such observations made on kidney funtion strongly suggests that extra renal factors cause edema in both normal and toxemic pregnant patients.

D. The factor of capillary permeability: The question of capillary permeability must be considered on this question of factors in causing edema of pregnancy. Numerous indirect tests have been made on question of capillary permeability. Such tests are said to have shown an increase in permeability in the subcutaneous tissues. Lash (33) found that intradermally injected salt solution in normal pregnant women disappeared faster than in patients with toxemia of pregnancy. The disappearance time was more marked in those patients having convulsions. The degree of decrease in the time varies with the degree in severity of the toxemia, increasing with the general clinical improvement. The factors that produce edema, hypertension, and albuminuria in the late toxemias of pregnancy apparently produces the condition in the tissues which give a decreased disappearance time. The rapid disappearance is due to an increase affinity of the tissues for water. This change in the tissue

affinity might be assumed to be due to a general intoxication involving the tissues in these areas. Petersen and Lash (38), and Oberst and Plass (37) found the capillaries of the skin to be less permeable and that relatively more of the antepartum cases are in the group of lowered permeability. The pathalogic cases predominate in the groups of greatest permeability. If there were an increased capillary permeability in pregnancy, proteinuria would be present in such patients. Such is not the case. If there was a general tendency to capillary injury, the effect should show in the glomerular capillaries and protein should appear in the urine. In the toxemic patient, however, there must be an increased capillary permeability to plasma proteins because of the appearance of proteins in the urine. Such a change in the capillaries of the glomerulus may affect all of the capillaries more or less universally and be an explanation for the great increase in fluid retention which takes place when the normally pregnant women becomes toxemic.

E. Edema in the legs as a result of increased venous pressure: Edema in the legs may be due to an increase in venous pressure in the veins of the legs during pregnancy. This pressure may be due to the structure of the placental circulation in which a capillary bed is largely absent. Burwell(4) has likened this con-

dition to approximate those found in an arterio-venous fistula. There is a close similarity of changes observed in pregnant women to those known to occur in patients with a large arterio-venous connection. Such patients show tachycardia, increase in cardiac output, increase in blood pressure in veins adjacent to fistula, increase in total blood volume, continuous bruit with systolic accentuation in region of fistula. These phenomena have been shown to be present in pregnant women, although not always in as striking a degree as they may show in arterio-venous fistula. Burwell (4) The increased pressure in the lower limbs may also be ascribed to the pressure of the enlarging gravid uterus on the veins of the pelvis. The increased pressure on the veins offers obstruction to the return of venous blood and undoubtedly favors the appearance of edema in the feet and ankles. Burwell (4) also made the suggestion that the high femoral venous pressure in the femoral vein may be due to inflow of blood via the placenta. The water that is retained in the edema of the lower extremities, and that accounted for by the increased blood volue, may represent a significant part of the total retained in normal pregnancy.

F. Tendency of normal pregnant women to retain sodium and water: The general tendency of normal preg-

nant women to retain sodium and water appears to be best explained by the experiments of Taylor (53,54). His explanation and experiments appear to be conclusive that sodium and water are constantly under the influence of enormous quantities of estrogens and progesterone. The effect is so predictable from the known physiologic properties of these substances that were the tendency to sodium and water retention not present, one would have to find an explanation for its absence. The increase in the tendency to sodium and water retention, which takes place with the onset of toxemia, does not, however, find a complete explanation on the basis of a further rise in hormone effectiveness. Taylor (54) The sudden appearance of proteinuria and of hypertension, and the change from hydremia toward hemoconcentration indicates that a new mechanism is at work. In most cases of pre-eclampsia, the rate of formation and excretion of the sex hormones are not actually increased but decreased. Rakoff (4) Although the estrogens and progesterone constitute a contributory factor in the retention of sodium and water in pre-eclampsia, the greater edema seen in this type of a patient cannot be considered simply an exaggeration of that found in normal pregnancy.

G. Briggs(5) believes that most types of edema can be explained on a basis of a disturbance between

capillary blood pressure and the osmotic pressure of the plasma proteins. In eclampsia there is usually an increased venous pressure as well as reduction of serum albumin each of these factors tend to prŏduce edema.

Conclusions

1. A review of the literature has been made on the sodium and water retention capacity of the estrogens and progesterone.

2. From the evidence given, the retention of sodium and water which causes edema in normal pregnant women is dependent upon the physiologic influence of the estrogens and progesterone. Estrogen has more sodium and water retaining properties than progesterone.

3. The concentration of the estrogens and progesterone determines the rate of excretion of sodium and water in the normal pregnant women. The manner in which the estrogens and progesterone may act to prevent sodium excretion can only be guessed at. They may displace sodium into the tissues, prevent its excretion by the kidney, or act through some other gland, as for example the posterior pituitary.

4. The reason for edema of toxemia of pregnancy is not to conclusive. There are additional factors at work but if the pregnant woman is under the influence of estrogen and progesterone, as in a normal pregnancy, she is already conditioned to retain water, readily. Estrogen and progesterone thus may contribute greatly to the clinical manifestations of the disease.

5. Numerous hormonal changes have been found to be present in the toxemic patients which are different than in the normal patients. The ration of estrogen

and gonadatropin was determined in some patients and found to be lower in the pre-eclamptic and eclamptic group, than in normal pregnancy. This indicates that these hormones are in some way associated with the toxemias of pregnancy.

6. The rapid destruction of estrogen and progesterone is probably a significant factor as a cause of edema and other clinical manifestations in toxemia of pregnancy

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