Water and Electrolyte Balance During Pregnancy

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ONE of the most profound changes that takes place in a pregnant woman is the retention of salt and water. The retention of fluid and electrolytes starts almost immediately when a woman becomes pregnant. This inevitably influences the management of pregnancy and those diseases which complicate pregnancy. Prenatal care is based partly on the control of weight gain and the restriction of salt. Toxemia, that peculiar disease of pregnancy, is associated with edema and hypertension and its control is associated with an understanding of the pathophysiology of pregnancy and salt and water metabolism. There is controversy as to whether salt is good or bad for the pregnant woman. Lately the association of prematurity with small maternal heart volume [1] and the failure of plasma volume to expand in pregnancy [2] has made the whole matter of water and electrolyte control an important consideration.

Weight Gain

As a gross indication of the retention of fluid and progress in gestation, weights are regularly recorded during prenatal visits. Weight gain at term will consist of the total weight of the reproductive organs and contained fetus, plus retained fluid. In a large series, Chesley found that the mean weight gain of pregnant women at term was 24 pounds (11 kg.).[3] Assuming that the fetus, placenta, amniotic fluid and uterus and breast are the major sites of weight gain, Rhodes has summarized the relative data as follows [4]:

	Pounds	Kg.	
Fetus	7½	3.5	(2.5–4.5 kg.)
Placenta	1	0.5	(Fetus: Placenta 6.35–7.9:1)
Amniotic fluid	2	1.0	(500–2,000 ml)
Uterus	2	1.0	Estimates
Breasts	2	1.0	

This leaves 4 kg. (9 pounds) unaccounted for. This accumulation of weight which is lost postpartum cannot be accounted for by the fetus and products of conception, or by alterations in the reproductive tissues alone. This increase in weight takes place as a result of retained fluid with accompanying electrolyte. There is an increase in blood volume, intracellular and extracellular fluid, which result from altered renal function apparently initiated by humoral factors.

Blood Volume

Blood volume expands during pregnancy; both plasma volume and red cell mass show significant increases. Classical studies have demonstrated that mean blood volume increases to levels of 30 to 50 per cent above nonpregnant values between 28 and 34 to 36 weeks, then diminishes gradually to term.[5] Red cell mass increases about 40 per cent and plasma volume undergoes a similar increase although to a more variable degree. Where the body hematocrit is determined by dividing the red cell mass by the plasma volume (the former using ^{32}P, the latter by Evans-Blue dye T-1824), the ratio between venous hematocrit and body hematocrit has been shown to vary between 0.87 and 1.08.[6] This is confirmed by the extreme variation (25 to 80 per cent) in increase of plasma volume, when the increment is related to the size of the fetus and placenta. Also women with smaller plasma volumes when not pregnant (measured postpartum, as their own controls) have a greater increment in pregnancy [7] than women with larger plasma volumes in the nonpregnant state.

Immediately postpartum, about one-half of patients increase their plasma volume by greater than 15 per cent. All patients with toxemia of pregnancy increase their plasma volumes postpartum by more than 15 per cent and patients with severe anemia have similar increases. The hematocrit is therefore of little clinical value postpartum (*e.g.*, to determine

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blood loss) for at least 48 to 96 hours after delivery.[8]

In the management of pregnant patients with cardiac disease or severe anemia, the gradual increase of plasma volume to a maximum at 28 to 34 weeks gestation may lead to more severe manifestations such as heart failure, tachycardia or degrees of anemia which make the administration of anesthesia and delivery extremely hazardous. Immediately postpartum, there is a danger of congestive heart failure and the risk of excessive transfusion. It is of interest that, in spite of removal of the placenta and the involution of the uterine circulation, plasma volume remains elevated disproportionately to red cell mass for at least 96 hours, and in toxemic pregnancies for as long as one or two weeks. This emphasizes the profound influence that pregnancy and diseases of pregnancy exert on the normal control systems of the body.

Water Retention

Of the total weight gain in pregnancy, a considerable portion is retained water. This can be measured by estimating the extracellular fluid space. Chesley estimated fluid loss at delivery to be 6.1 liters and thiocyanate space as 6.3 liters. The water loss at delivery is calculated to represent 30 per cent of a 3.2 kg. fetus (available water 30 per cent), 82 per cent of placental weight, 83 per cent of 0.75 kg. blood loss plus 1 kg. of amniotic fluid which equals 3 liters. The additional 3 kg. loss postpartum, is largely water comprising a total of approximately 6 liters.

In summary Rhodes has shown the water retained in a pregnant woman at term to be distributed as follows.[4]

	Liters of Water
Fetus	0.96
Placenta	0.41
Amniotic fluid	1.00
Blood	1.00
Uterus	0.60
Breasts	0.50
Maternal tissues	1.40

Water is retained in the presence of sodium and the ratio of the mean sodium (^{22}Na) space to the mean water (D_2O) space corresponds closely to the nonpregnant value. Thus pregnant women have a mean sodium and water space of 26.4 per cent and 53.3 per cent of body weight, respectively, which are equivalent to those of the nonpregnant woman. The mean total body water for non gravid women has been shown to be 52.8 ± 6.9 per cent of body weight; for obese women, 38.2 ± 3.7 per cent and for underweight women, 70.1 ± 2.3 per cent.[9] The same variation, with less extreme values has been shown for pregnant women (mean 53.3 per cent; women over 80 kg., 45.4 per cent and women less than 60 kg., 58.7 per cent). Although there is a reduction in the mean sodium space in the overweight woman and an increase in underweight women, both maintain a normal sodium : water distribution.[10]

Immediately postpartum, the fluid volumes determined by T-1824, ^{24}Na and sucrose remained elevated (at 4 hours), but only the ^{24}Na space is significantly higher. The 24 hour exchangeable sodium value was found to be the same in postpartum and in normal pregnant patients. Seven days later, the sucrose and the 4 hour sodium spaces diminished by approximately 2 liters in the postpartum women. In normal pregnancy, it is concluded therefore that there is no significant hydration of maternal tissues or storage of osmotically active sodium.[11]

In preeclamptic patients, although the water space remains normal, the sodium space increases to give a disproportionate balance between sodium and water; whereas in normal pregnant women the sodium space is 50 per cent of the D_2O space, in preeclamptic women this ratio rises to 56 per cent. This could be either a result of the storage of osmotically active sodium, which seems unlikely,[11] or an expansion of extracellular fluid with a reduction of the intracellular space.

Of considerable importance is the recent observation that salt administration cannot influence the amount of sodium retained by a normal pregnant woman.[12] It has been known for a long time that preeclamptics are unable to excrete a salt load; indeed, this has been used as a test for preeclampsia.[13, 14, 15] However, Robinson's work,[16] repeatedly quoted, in which a large group of patients was treated with salt without alteration of incidence of toxemia, can now be reasonably explained. It would take a very large group to show a significant difference, because the incidence of

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toxemia is very low. Mengert's study [17] using large doses of salt in preeclamptic patients is a little more difficult to explain. He found no difference between preeclamptics treated with 10 g. of salt and another group receiving 1.0 g. of salt intake per day. Variation in absorption and the short length of the study might have influenced these results.

There is still controvery about whether the disparate concentrations of salt and water in toxemia is primarily a defect in salt or water metabolism. This will be considered below.

Sodium and Potassium

In pregnancy there is a shift of the *p*H of blood from 7.39 to 7.42. Total cation is reduced from 155 to 145 mEq. per liter.[18] Primarily this represents a reduction in serum sodium concentration (142 to 135 mEq. per liter). Both P_{CO_2} and the CO_2 content of venous blood are reduced in pregnancy. (P_{CO_2} drops about 5 mm. to 40 mm. of mercury and CO_2 content decreases from 27 to 23 mEq. per liter). There results a compensated metabolic acidosis. All these changes are apparently initiated by hormone-stimulated pulmonary hyperventilation.

This slightly altered balance takes place in the presence of a total increase of retained sodium of about 756 mEq. (17.5 g. Na). This can be accounted for as follows: [19]

	Na^+ mEq.
Mother	
Intravascular compartment	160
Extravascular compartment	308
Infant 7 pounds 43% Na	168
Placenta	12
Amniotic Fluid (788 ml.)	99

This agrees with 20.5 g. of retained sodium, calculated by Rhodes from nonradioactive sodium data.[4]

In pregnancy there is also a total retention of potassium of somewhat less than 10 g. Theoretically this may be shown to be distributed among fetus, placenta, uterus, breasts and extracellular fluid.[4] This corresponds well with the value 6.7 g. (171 mEq.) of increased total exchangeable potassium measured by means of isotope dilution techniques.[19]

Total exchangeable sodium expressed in kilograms of body weight is generally considered to be increased during pregnancy from a value of 40.1 mEq./kg. to 41 or 42 mEq./kg. (mean of studies quoted by McGillivray).[19] There is no significant difference in these figures, but McGillivray has indicated higher values for pregnancy as term approaches (46.2 to 48.3 mEq./kg.) and Gray *et al.* have demonstrated a trend toward increase in exchangeable sodium. Both McGillivray and Gray *et al.* agree that there is a slight increase in both sodium space and total body water but the relative increase in body water exceeds that of sodium space.

With the slight increase in exchangeable sodium and drop in serum sodium, it appears that, in spite of the increased sodium space,[10] there is greater fluid than salt retention in the latter portion of pregnancy and in preeclampsia. This is important in considering preeclampsia where total exchangeable sodium/kg. drops but edema develops with water retention. The fine adjustments and minimal alterations with increasing gestation or disease may be sufficient to affect the clinical picture, with the rapid rate of turnover of Na^+ and K^+. This very important observation must be considered in the management of toxemic patients with edema. The usual procedures for salt and water diuresis in patients with cardiac disease and cirrhosis cannot be expected to result in the same improvement in pregnant toxemic women and may even lead to deterioration.

Total exchangeable sodium has been measured throughout pregnancy (16 to 36 weeks) with a demonstrable mean rate of increase of 23 mEq. per week. Patients with essential hypertension showed values of total exchangeable sodium equivalent to those of normal pregnant women; however, because of excess weight (presumably fat) they had a smaller exchangeable sodium per kg. of body weight. Preeclamptics demonstrated a significantly greater total body sodium at 16 weeks gestation and an excessive increase, from 16 to 26 weeks. Total body sodium fell when symptoms and signs of preeclampsia appeared.[20] This alteration in sodium metabolism in the presence of preeclampsia creates hazards in inducing sodium diuresis. Although as much as 300 mEq. sodium and 3.6 liters of water may be lost after diuretic therapy, there may be no improvement in hypertension or proteinuria.[21] Sodium binding resins have been used with

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some improvement. After resin therapy there occurs a 40 per cent reduction of total body sodium at the expense of a compensated metabolic acidosis with depression in carbon dioxide combining power.[22] Hutchinson and Plentl point out the danger of confusing sodium deficiency with severe preeclampsia.[23] Apparently chlorthiazide, although its continuous administration will not prevent toxemia, has no serious adverse effects.[24]

The alteration in sodium and water metabolism in preeclampsia has been investigated, measuring inulin, antipyrine and ^{24}Na spaces. The results suggest that in this and other abnormal pregnancies there is an increased intracellular penetration of sodium.[25] The complexities of sodium metabolism in preeclampsia make it unwise to rely only on values which measure the static state of sodium balance. As emphasized by Kellar and reiterated by Mahran, there is need for measurement of the dynamic aspects of the changes in sodium balance in the development and progress of preeclampsia.[26]

The importance of sodium and potassium in uterine muscular physiology has been known for some time. Calcium modulates the excitatory process at the level of the cell membrane, affecting cellular permeability to sodium which leads to muscle contraction. Estrogen and progesterone affect the permeability and transport of sodium in the myometrium. Oxytocin exerts its effect on calcium, facilitating sodium transport across the cell membrane, thereby increasing myometrial contraction.[27] These effects have been investigated in relation to uterine inertia. After 24 hours of prolonged labor, plasma water decreases; after 48 hours, serum sodium rises, potassium and chloride fall. It is believed that the fall in serum K^+ might contribute to inertia.[28] In a subsequent study of biopsies of the nonpregnant uterus and at term, Hawkins and Nixon demonstrated a progressive hydration of myometrial cells, with increase in intracellular Na^+ and no change in K^+. No differences in water or electrolyte composition were detected up to 23 hours of labor; but between 40 to 90 hours of labor, reduced total intracellular calcium could be demonstrated.[29] It is unlikely that administration of intravenous K^+ or Ca^+ solutions would alter the myometrial cellular *milieu*, but rest and rehydration of patients during prolonged labor is a good conservative alternative.

Renal Function

Chesley has recently reviewed the changes in renal function during pregnancy.[30] It is well known that there are elevated and maintained increases in inulin and para-aminohippurate (PAH) clearance.[30, 31] The glomerular filtration rates (inulin clearance) during pregnancy were shown by Sims and Krantz [32] and Sohar *et al.*[33] to increase about 50 per cent, falling in the last week toward normal. They also showed that renal plasma flow (PAH clearance) increased by one third in early and mid pregnancy, and fell to normal values at term and subnormal values postpartum.

Tubular reabsorption must adjust itself to the increased glomerular filtration rate in order to maintain sodium balance. The 50 per cent increase in GFR represents a fivefold increment in the normal exchangeable sodium presented to the tubules for reabsorption. Although during pregnancy about 23 mEq. of Na^+ are retained per week, this is considerably less than the increased amount undergoing glomerular filtration.

The increase in glomerular filtration reduces the blood concentration of those substances primarily cleared by glomerular filtration (*e.g.*, creatinine concentration 0.46 mg. per 100 ml. and urea 8.7 mg. per 100 ml. in pregnancy [32, 34]). Likewise tubular reabsorption may not rise in parallel with increased glomerular filtration (*e.g.*, glucose leading to glycosuria [35]). The balance between the increased glomerular filtration and tubular reabsorption of sodium and water is however maintained, except in diseases of pregnancy.

In preeclamptic and pregnant hypertensive patients sodium clearance is independent of absolute filtered load or the increment after salt loading which results in sodium retention [36]; in comparison, normal pregnant women respond by an increase in sodium clearance. Thus renal tubular absorption is altered in preeclampsia and to a lesser degree in hypertensive patients. Salt retention in preeclamptics, therefore, is not the result of reduced glomerular filtration alone but of changes in tubular reabsorption as well.[36] This observa-

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tion is slightly different from the conclusions of De Alvarez *et al.*[37] who compared renal sodium absorption in normal pregnant women and preeclampsia, using each patient as her own control, postpartum. They found that there was no difference in renal sodium resorption, but a significant decrease in renal water absorption. The alteration in tubular function in preeclampsia, therefore, appears to affect water metabolism *per se*, and sodium metabolism under conditions of salt loading.

In spite of increased GFR, tubular reabsorption of salt and water increases to provide for the needs of the fetus and the retained fluid of pregnancy, including increased blood volume. This increase is effected by humoral substances which are secreted by the placenta, or results from the placental stimulus to maternal hormone production. Preeclampsia, probably beginning as a placental disease, leads to alterations in the fine control of renal sodium and water balance, resulting in altered sodium and water retention, particularly in patients whose renal and vascular systems are already compromised. Beginning in a simple manner this becomes extremely complex by the time symptoms and signs of preeclampsia develop.

Hormonal Control

There has been considerable interest in antidiuretic hormone (ADH) as being responsible for the retention of water in pregnancy. ADH has not been found in the blood of normal pregnant women, but it is known that a strong stimulus is required to produce detectable levels in peripheral blood.[38] Some studies have demonstrated that extracts of plasma or placenta from normal pregnant women inactivate ADH *in vitro*.[39, 40, 41] This would indicate that women are less responsive to ADH during pregnancy, an observation borne out by the management of pregnant patients after hypophysectomy or with diabetes insipidus[42-45] who require larger doses of vasopressin than when not pregnant. The intravenous administration of vasopressin in pregnant women produces a marked fall in urine output, with a fall in GFR, renal plasma flow, and a reduction in the output of sodium chloride and solute.[46] This is quite different from the response in nonpregnant patients in whom vasopressin administration leads to salt excretion with only slight increase in GFR.[47] The dynamic balance between ADH and anti-ADH substances seems to be altered in pregnancy. The fine adjustments of the ADH control systems appear to be set slightly differently in pregnancy and interrelate with the other humoral mechanisms of salt and water control to affect renal function directly and to maintain a positive water balance relative to Na^+.

Estrogen, which is secreted in such increased amounts during pregnancy, is known to alter sodium and water ouptut. Estradiol administration has been shown to decrease urinary sodium and water, but only in a transient manner. Plasma sodium concentration is unaltered after estrogen injection although the hematocrit falls and the plasma volume increases (8 to 10 per cent). The effects of estrogen administration are more marked in the presence of cirrhosis with ascites and cardiac failure.[48] Although intravenous estradiol has no effect (presumably because of its rapid inactivation), intramuscular estradiol does produce a fall in renal plasma flow (RPF) and GFR with lowered sodium and chloride output (potassium is variably affected).[49] In pregnancy, liver blood flow is equivalent to that in the non-pregnant woman but a diminished rate of inactivation, possibly in the presence of a greater concentration of secreted circulating steroids, may lead to an equally prolonged influence of estrogens similar to the effects of cirrhosis or cardiac failure. Although it is known that the hepatic extraction of aldosterone is reduced in patients with cardiac disease,[50] the comparable effect of pregnancy has not been studied.

Growth hormone (HGH) may play a part in the retention of sodium and potassium in pregnancy. Increases in GFR and RPF[51] with a retention of sodium and potassium[52] are known to occur after its administration. Although HGH has not been shown to be elevated in maternal blood, there is an increase in placental "lactogen"[53] with growth hormone-like prolactin-like properties.[54]

Aldosterone which is the major adrenocortical hormone controlling electrolyte balance is excreted in increasing concentration in the urine throughout pregnancy, to elevated values at term (15 to 125 μg./24 hours).[55-60] This

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concentration has been shown to vary considerably with the amount of sodium intake.[59] The secretion rate of aldosterone has been shown to increase during pregnancy to a mean value of 1100 μg. per day on an intake of 80 to 190 mEq. per day.[61] The secretion rate varies inversely with salt intake. The pattern of urinary metabolites has been shown to be changed in pregnant subjects,[62] although this observation has been contested.[61] However, the ratio of the secretion rate to the urinary free aldosterone indicates that the metabolic rate was not altered.[62] This is confirmed by the metabolic clearance rate (MCR) of aldosterone which in pregnancy is equal to that in the nonpregnant woman.[63] If the secretion rate (or production rate as it is more properly defined [64]) is increased and the MCR remains the same, this implies an increased circulating concentration of free hormone. [MCR = Production Rate/Blood Concentration.[64]] Since there is no significant increase in binding of aldosterone to plasma proteins in pregnancy,[65, 66] this would suggest a slight hyperaldosterone influence in pregnancy. The increased secretion of aldosterone is greater than that required for the normal maintenance of sodium balance, on a diet of 80 to 190 mEq. sodium per day. Prolonged administration of large doses of salt retaining hormones (desoxycorticosterone,[67] *d,l*-aldosterone [68] and 9α-flurohydrocortisone [69]) lead to salt and water retention for only a limited period of time. These pharmacologic doses, greater than the increased secretion rate of aldosterone, do not lead to sufficient sodium retention comparable to a normal pregnancy; humoral factors other than aldosterone therefore must play a part.

Among the factors which could inhibit aldosterone effect and lead to increased secretion is the increased progesterone secretion in pregnancy; progesterone is natriuretic in nonpregnant subjects.[70] Also the 50 per cent increase in GFR and the consequent increase in sodium presented to the tubules, could require an increased secretion of aldosterone to maintain the balance of sodium; but the aldosterone secretion rate does not vary directly with GFR,[61] and this postulate therefore is not likely.

A competitive interaction of aldosterone and progesterone has been suggested to explain the elevated aldosterone levels of pregnancy [56] and a direct correlation between pregnanediol excretion and aldosterone secretion seems to bear this out.[62] In nonpregnant subjects progesterone will stimulate aldosterone secretion,[71] but natriuresis did not follow the administration of 50 to 100 mg. progesterone in pregnancy,[72] suggesting that progesterone was exerting a maximum effect. There is a ten-fold increase in the progesterone production rate in pregnancy [73] with an even greater elevated plasma concentration [74]; and, though plasma binding of progesterone in pregnancy and its metabolic effect is not yet clear,[75] these all suggest a maximal stimulus to aldosterone metabolism in pregnancy.

Angiotension II exerts a considerable effect on aldosterone metabolism.[76] Likewise in nonpregnant subjects it causes a considerable reduction in sodium and chloride excretion with lowered GFR and RPF.[77] In pregnancy this effect is much less marked,[78] but angiotension may play a greater role in renal control of sodium and water balance in abnormal pregnancies, but not necessarily in sodium retention. The paradox of sodium and chloride diuresis after angiotension administration in cirrhotics, compared to normal subjects who retain sodium, is not understood.[79] The known reduced hepatic extraction of steroids in patients with elevated retention of bromsulfthalein [50] and the possible changes in the control of the liver's hormonal metabolism in pregnancy may be the reason for the diminished angiotension effect in pregnancy. In complications of pregnancy, this saluretic effect of angiotensin may be even greater.

Summary and Conclusions

The retention of electrolyte and water is the result of complex dynamic alterations in hormonal metabolism, exerting their effects on the kidney. In pregnancy GFR is markedly increased. Sodium reabsorption is similarly increased but humoral controls result in an increased retention of salt and water over and above the increase in GFR (50 per cent) to provide for the needs of the fetus and altered reproductive tract (a total of 763 mEq. of sodium and 6 liters of water during pregnancy). An increase in the secretion rate of any single hormone is not responsible; but the

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development of many subtle humoral changes affecting the endocrine glands and the organs which control hormonal metabolism (*e.g.*, the liver) and their resulting effect on kidney function, combine to retain salt and water in pregnancy. In complications of pregnancy, particularly preeclampsia, altered water and electrolyte balance take place long before the appearance of clinical signs and symptoms. The control of salt intake apparently does not affect sodium and water balance measureably until preeclampsia has appeared clinically: even then there is doubt that salt administration will adversely affect the outcome. However, the fine adjustments of all hormonal and electrolytic controls are closely interrelated and the early benefits of sodium restriction apparent clinically, may not be measureable with present methodology.

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H-ION Cardiac output, carotid, coronary, and renal flows have been measured in the following acid-base variations: respiratory acidosis and alkalosis, compensated respiratory acidosis, and metabolic acidosis and alkalosis to delineate the effect of P_{CO_2} and hydrogen ion concentration on distribution of blood flow. Cardiac output, carotid flow, and coronary flow correlate directly with the carbon dioxide tension in the blood, irrespective of the hydrogen ion concentration. Renal blood flow varies inversely as the carbon dioxide tension, irrespective of the hydrogen ion concentration. (*Kittle, C. F., and others: The Role of pH and CO_2 in the Distribution of Blood Flow, Surgery 57: 139 (Jan.) 1965.*)

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