AMNIOTIC FLUID CREATININE

by

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The presence of creatinine in amniotic fluid is known for a long time (Amberg and Rowntree, 1905; Tankard, 1934). Recent analysis of liquor creatinine have depicted rising values with advancing gestation (Pitkin and Zwirek, 1967; Droegenmuller *et al*, 1969; Doren *et al*, 1970; Roopnarainsingh and Morris, 1971). Coupled with the observations of higher concentrations of creatinine in liquor amnii than in maternal serum these findings lend support to the fetal origin of amniotic fluid creatinine. Thus, during the last decade estimation of liquor creatinine values have been made use of in assessing fetal maturity (Begneaud *et al*, 1969; Roopnarainsingh, 1973). However, in complicated pregnancies associated with pre-eclamptic toxaemia, eclampsia, diabetes mellitus, etc. there have been varying observations on the liquor creatinine values. While PitKin and Zwirek (1967) and Begneaud *et al* (1969) did not observe any significant difference between uncomplicated and complicated pregnancies, Roopnarainsingh and Morris (1971) and Roopnarainsingh (1973) found higher mean values in diabetes and pre-eclamptic toxaemia than in normal pregnancies at corresponding periods of gestation. In view of these reports it was decided to investigate the levels of amniotic fluid creatinine at various stages of gestation and to find out the relationship between maternal serum creatinine and amniotic fluid creatinine in normal pregnancies and those complicated by pre-eclamptic toxaemia or eclampsia and finally to find out the possible application of such determinations in assessing fetal maturity.

Material and Methods

Eighty women in their second half of pregnancy were included in this study. The cases were randomly selected from outpatients department, antenatal clinics, or while in labour. From each patient liquor amnii was collected either from the hind waters using a Drew-Smythe catheter or by aspiration of forewaters under direct vision using a dry syringe with a thick bore needle or during hysterotomy or caesarean section or by transabdominal amniocentesis. At the same time 3 ml. of blood was collected from the antecubital vein from each patient. All specimens of amniotic fluid were centrifuged and stored at —20°c till creatinine estimation was carried out by the Folin-Wu (1965) adaptation of the Jaffe reaction. Blood and meconium stained samples were discarded.

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The stage of pregnancy in each patient was estimated by menstrual history and fundal height. Where accurate menstrual history was not available patients were left out of the study.

Serial estimations of amniotic fluid creatinine and maternal serum creatinine were conducted in 8 of these patients at different stages of their gestation making a total of 92 determinations.

Results

There were 62 patients with normal pregnancy and 18 complicated by toxaemia (pre-eclamptic toxaemia P.E.T. or eclampsia).

(a) Relationship between the Amniotic fluid creatinine and maternal serum. Creatinine:

Creatinine

Figure 1 shows the results of 92 determinations of the creatinine concentration in amniotic fluid as well as maternal serum carried out simultaneously in the 80 patients studied.

FIGURE 1

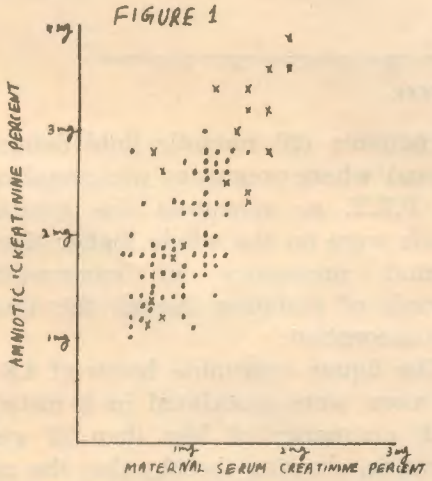


FIGURE 1 Showing simultaneous Maternal and Amniotic fluid creatinine Concentration (92 Samples)
• → Normal Pregnancy
X → Pre-eclampsia and Eclampsia

The serum creatinine levels were within the range of 0.5 to 1.4 mg% in normal pregnancies with the amniotic fluid creatinine in the range of 1.0 to 3.2 mg per cent.

In pregnancies associated with toxaemia (P.E.T. or eclampsia) the serum creatinine as well as the liquor creatinine levels were generally higher, the range being 0.5 to 2.0 mg per cent for the former and 1.2 to 3.9 mg per cent for the latter. However, these higher values were not present in all cases of toxaemia.

In all the determinations the concentration of creatinine in amniotic fluid was higher than the concentration in maternal serum. And as pregnancy advanced this ratio also increased. Between 37-40 weeks of gestation the amniotic fluid creatinine concentration was more than twice the value of maternal serum creatinine concentration in 84 per cent determinations.

(b) Serial Amniotic fluid creatinine levels at different stages of gestation:

This is depicted in figure 2 representing

FIGURE 2

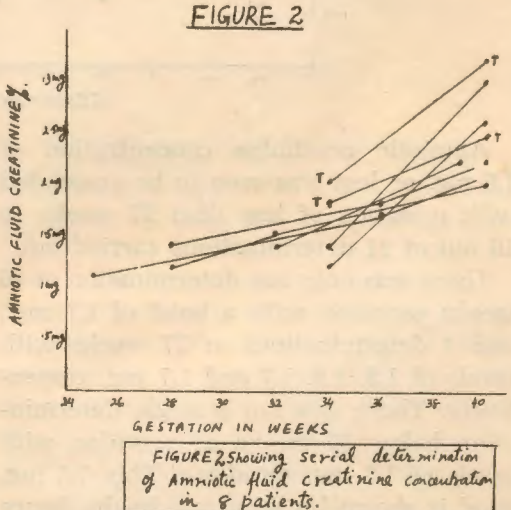


FIGURE 2 Showing serial determination of Amniotic fluid creatinine concentration in 8 patients.
T → Patients with PET or Eclampsia.

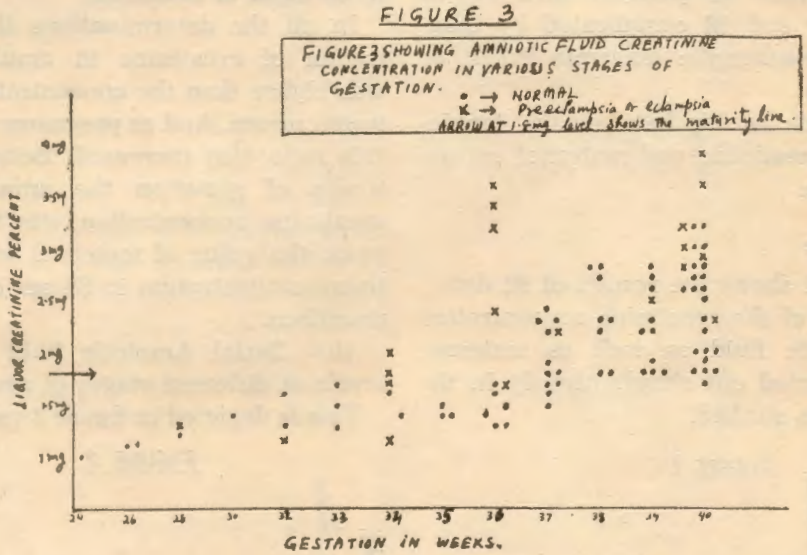
19 serial determinations in 8 patients. The creatinine concentration was seen to rise

with advancing gestation. The rise became most pronounced in the last four weeks of pregnancy, especially at and after the 37th week. Two patients marked T represent cases of toxaemia.

(c) Amniotic fluid at various stages of gestation in normal pregnancy:

Figure 3 (dots) shows that of the 51 amniotic fluid creatinine determinations in patients with gestation of 37 weeks and above, 46 (90%) had creatinine concentration of 1.8 mg. per cent or more.

FIGURE 3



Amniotic creatinine concentration of 1.5 mg. or less was seen to be associated with gestation of less than 37 weeks in 16 out of 21 determinations carried out.

There was only one determination at 40 weeks gestation with a level of 1.7 mg., and 4 determinations at 37 weeks with levels of 1.5, 1.6, 1.7 and 1.7 mg. respectively. There was not a single determination below 37 weeks of gestation with levels of 1.8 mg. or above. This 1.8 mg. level is shown by an arrow in the figure and with amniotic fluid concentration of creatinine at or above this level one can safely say that gestation has proceeded to the 37th week or more. Levels of 1.6 mg or 1.7 mg are associated with either side of this gestational period and can be said to be indefinite or borderline so far as the decision about maturity of the fetus is concerned.

(d) Amniotic fluid creatinine at various stages of gestation in pregnancy associated with pre-eclamptic toxaemia (PET) or eclampsia:

Again figure 3 (crosses) depicts that in 18 patients (20 amniotic fluid determinations) where pregnancy was complicated by P.E.T. or eclampsia the creatinine levels were on the whole higher than in normal pregnancy at corresponding periods of gestation though this finding was inconstant:

The liquor creatinine levels of 1.8 mg or more were associated in 6 instances with pregnancy of less than 37 weeks duration, showing thereby that the criteria of fixing a liquor creatinine level of 1.8 mg or more as an index of fetal maturity cannot be relied upon in P.E.T. or eclampsia as in normal pregnancy.

Discussion

Our data on the relationship between liquor creatinine and maternal serum levels confirm earlier reports (Makepeace *et al,* 1931; Begneaud *et al,* 1969; Roopnarainsingh, 1970, 1973) that amniotic fluid creatinine levels are always higher than maternal serum creatinine levels.

Our observations further confirm the findings of these investigators that creatinine concentration in the amniotic fluid rises gradually with advancing gestation till at about the 37th week of pregnancy when the rise becomes pronounced and is maintained upto term. This makes the difference in the amniotic fluid and maternal serum creatinine level more marked in the last 3 weeks of gestation where in creatinine concentration becomes twice or more than the maternal serum creatinine concentration.

This observation brings in the question of the origin of liquor creatinine. There is ample evidence to suggest that fetal micturation occurs especially in the later weeks of gestation and that fetal kidneys excrete the waste products of the fetus at this stage (Serr *et al,* 1963; Thomas *et al,* 1963; Chez *et al,* 1964). It appears that the increase in amniotic fluid creatinine concentration that occurs around the 37th week of gestation is the result of increasing maturation of fetal kidneys at this stage. It also appears that during this late gestational period the fetal kidneys have to excrete the metabolic waste of a larger muscle mass of the fetus resulting in higher concentration of creatinine in the amniotic fluid.

Our data further shows that in normal pregnancy amniotic fluid creatinine concentration of 1.8 mg per cent or more is associated with gestation that has advanced to the 37th week and suggests an advanced degree of fetal maturity. Conversely liquor creatinine values of 1.5 mg per cent or less indicate that the fetus has not reached an advanced stage of maturity compatible with viability. Viability is at 28 weeks values less than 1.5 mg are seen many weeks after that (Fig. 3). Liquor creatinine values in the 1.6 mg and 1.7 mg per cent range have a limited clinical usefulness as a definite estimate of fetal maturity cannot be made. This value of amniotic fluid creatinine of 1.8 mg per cent which we suggest as a safe index of fetal maturity is slightly less than the value of 2 mg per cent established in reports from Western studies (Begneaud *et al,* 1969; White *et al,* 1969; Roopnarainsingh, 1970, 1973). This may be explained by the fact that on the whole Indian neonats have a lower birth weight than their Western counterparts and the fetal kidneys have to excrete the metabolic load of a lesser muscle mass of the smaller infant. Unfortunately, we did not make the birth weight recordings though there are studies to bear out this relationship between birth weight and amniotic fluid creatinine levels (Begneaud *et al,* 1969; Roopnarainsingh, 1970).

So far as the study on pregnancies complicated by toxaemia goes we observed that the maternal serum as well as liquor creatinine concentration showed wider fluctuations than in normal pregnancy. On the whole the values are higher than at corresponding periods of normal gestation. It is obvious that the maternal serum levels in toxaemia may rise as a result of reduced glomerular filtration by the mother (Pollak and Netdes, 1960). What causes a higher level in the liquor in many cases of toxaemia inspite of fetal immaturity is only a conjecture. Whether diminition in the rate of creatinine transfer from the fetal compartment (Roopnarainsingh, 1973) is responsible or the

evlevation of maternal serum creatinine leading to an osmotic gradient across the placental barrier (McGaughey *et al*, 1960) or some other factor is at work can possibly be shown only by amniotic fluid turnover studies in future. At the moment it appears that in pregnancies complicated by pre-eclampsia or eclampsia it may be hazardous to depend on the determination of amniotic fluid creatinine values for assessing fetal maturity.

Conclusions

1. Creatinine concentration in amniotic fluid is almost always higher than in the maternal serum in the second half of pregnancy.

2. The creatinine concentration in amniotic fluid increases with advancing pregnancy and the increase becomes pronounced when the fetus attains maturity at about the 37th week of gestation.

3. From 37th week of gestation the ratio of liquor creatinine to maternal serum creatinine is 2:1 or more in about 84 per cent cases.

4. Liquor creatinine concentration of 1.8 mg per cent is a fairly reliable guide to fetal maturity in Indian patients.

5. In pregnancy complicated by toxaemia the liquor creatinine values show wider fluctuations and are higher on the whole.

As such, levels of 1.8 mg per cent may be attained earlier than 37 weeks of pregnancy and are unreliable for assessing fetal maturity.

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