Renal Excretion Of Nutrients In Pregnancy

The Scientific Basis of Medicine

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Introduced by Ian Gilliland.

University of London Audio-Visual Centre, 1972.

Made for British Postgraduate Medical Federation.

Produced by Peter Bowen.

Black-and-white
Duration: 00:16:08:12

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<Gilliland to camera>

Professor Frank Hytten is Professor of Human Reproductive Physiology in the University of Newcastle upon Tyne, where he is also Deputy Director of Medical Research Council's Unit on Reproduction and Growth. Prior to this, he worked in the University of Aberdeen with the Medical Research Council's Unit in the Department of Midwifery. He has made many important contributions to the physiology of pregnancy, particularly to the renal excretion during pregnancy of nutrients. Professor Hytten.

<Hytten to camera, seated. During lecture, Hytten frequently refers, with indicator stick, to diagrams and charts on display stand>

Let's begin by looking at the scene of the action. <*Hytten stands up and indicates diagram*> Here's a diagram of a nephron of which each kidney has about a million, and arterial blood, skimmed very largely of its red cells and therefore predominantly arterial plasma, comes into this capillary tuft which is the glomerulus at a rate in the non-pregnant woman of something approaching half a litre a minute. For the whole of pregnancy that arterial plasma flow is raised by something like a half to 750 to 800 ml a minute, and about a fifth of it, 20%, is filtered from that tuft out into the capsule and down into the tubular system. In other words, in pregnancy the glomerular filtration rate is about 150 ml a minute.

Now that's an easy figure to say and a lot of people know it <*Hytten sits back down at table*> and I think that unless you visualise this, it's not very easy to know just what it involves. I'm going to empty a 20 ml syringe, which will take 8 seconds, into here and that, as you can see and perhaps hear, is the glomerular filtration rate. And that is going on day and night, day after day, week after week. <*Refers to diagram*> It's a great deal of fluid and quite clearly the body cannot afford to throw away all that filtered plasma, so what happens is that the arterial plasma, having dropped a fifth of itself through the capsule here, rushes around and comes down past the tubules here to recover from the tubules what perhaps it should never have thrown away in the first place.

So this is where the scene is set: the first half of the proximal tubule, and that is where most of the nutrients are recovered and the recovery is remarkably efficient. <*To camera*, *Hytten seated at table with measure of glucose*> For example, in that gushing glomerular filtrate there is every day about that much, about 150 grams, of glucose and all that appears in the urine is about this much, about 100 milligrams, so that the efficiency is better than 99.9%. But, in pregnancy the whole picture changes, and it's one of the more bizarre and unexpected features of normal pregnancy that nutrients are excreted in much bigger amounts than that.

Well now, let's begin with glycosuria because that's a well-known one; it's been known for more than a hundred years that pregnant women excrete glucose in their urine and, indeed, at the beginning of this century it enjoyed a certain vogue as a pregnancy test. An efficiency of something like 95% was claimed for the diagnosis of pregnancy if the woman had glycosuria after eating 100 grams of glucose. Now the data I'm going to show you comes from a serial study of 30 perfectly healthy, normal women in Newcastle. They all had normal glucose tolerance and what they did was this: for one week every month, they tested every sample of urine they passed with the paper strip reagent, Clinistix, and at the end of that week they collected the whole of the urine they'd passed as a 24 hour sample and we estimated the glucose in that.

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Now I'm going to begin by looking at just at the 24 hour excretions – the total glucose excreted in 24 hours in these women. And we'll look at it first not serially but cross-sectionally and you can see here <*narrates over chart using indication stick*> that in the non-pregnant state, that's the same women postpartum, none of them excreted more than 100 milligrams during 24 hours. But during pregnancy, there is a huge range of much higher excretions, many women stretching up towards a gram a day and some going as high as 10 grams a day.

Now if you look at them individually, <*to camera*> the interesting thing is that some women don't make this adjustment at all; some women don't excrete any more glucose than normal. <*Refers to charts*> Here, for example, is a group of 4 women – there were more than this – who really don't show any increase in glucose excretion during the course of their pregnancies. On the other hand, here's another group where there was a considerable increase: up between half a gram and a gram at the peak. Note the tremendous irregularity always which is associated with this. Here's another group yet, who are – note this is a logarithmic scale – these women are now up about between 1 and 10 grams: 5 grams, 6 grams, 7 grams commonly.

Now you may get the impression from these that there is a steady increase in the amount of glycosuria as pregnancy progresses; that is by and large the case, although it's very irregular, but there are at the same time a number of women who have their maximum excretion in the first half of pregnancy. Here are 4 of those and you can see that the maximum excretion took place quite early in pregnancy after which they went up and down a little bit, but never reached that peak again.

<*To camera*> So, the most obvious thing about this is that women vary tremendously among themselves, and individual women vary tremendously from time to time during their pregnancies. Now when you come to look at the variation within the week that they did this, this is even more remarkable. And we'll now have a look at some of the results which we got with the testing by Clinistix. <*Refers to charts*> These diagrams look terribly complicated and I don't want you to be bamboozled by them, but broadly speaking what has happened is this: these are 6 weeks – the week is numbered 26, 30, 33, 35, 38 and 39 – of a single patient, and that block represents her week of urine testing. Each line is one day in that week, it goes from midnight to midnight, and every time she passed urine she tested it. If it was negative, you get a white blob; if it's positive, you get a black blob. There's nothing much in the first half of the block because she's asleep by and large during that time. And then on the seventh day, she not only tested every sample, she also collected it as a 24 hour sample and that is the total as measured in that 24 hour sample.

So, here's the first one, for example, and you can see a great scattering of positive results here. A gram and a quarter in that day. In week 30, almost all positive, and 3½ grams on the seventh day. <*Indicates week 33*> Again, largely positive. And then you see it all disappears and there's only the occasional positive one.

<*Next chart*> And here's yet another patient with the same sort of pattern you see. And the thing which stands out is that you get days or groups of days, parts of days, where glycosuria is the rule and then days and parts of days where there is no glycosuria. <*Seated, to camera*> The picture that really stands out here is of tremendous intermittency of tubular function. Now, we haven't any idea why this occurs; this is just a failure of tubular reabsorption for which the cause is totally unknown.

It's worth making the point, I think, from the clinical point of view, that all these women were absolutely normal and had normal glucose tolerance. Conversely, we have had women who have unequivocally abnormal glucose tolerance, who have shown very little or no glycosuria and this raises the whole question, I think, of the value of urine testing for sugar in antenatal clinics as a screening procedure.

Well now, another very well-recognised example of nutrient excretion in pregnancy is the excretion of amino acids. And in distinction to glycosuria, as far as we know, all women, not just a few but all women, excrete much more amino acids in their urine. The total excretion is up by about 4 times but all the amino acids don't behave in the same way.

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<*Refers to charts*> Here is an example of a serial study which we did of 10 subjects and you can see that these are the 5 amino acids which are excreted in greatest amount: glycine, histidine, threonine, serine and alanine. And there were frequent samples taken and you can see it's pretty irregular. Now for the rest of the diagram, I've smoothed this out simply by averaging all the points in each 10 week period of pregnancy, but remember when you see them in their smooth state that, in fact, there is a tremendous variation from time to time in the same subject.

If we look at the amino acids, they divide into 3 groups, roughly speaking. There are the 5 I've just talked about: glycine, histidine, threonine, serine and alanine, which are in any event excreted in the greatest amount in the non-pregnant person, up to 1000 micromoles in 24 hours for glycine. And there is an immediate rise in quite early pregnancy, this happens before 10 weeks as a matter of fact, and then it rises and goes on rising until at the end of pregnancy the excretion is anything from 4 to 6 times what it was in the non-pregnant state.

Then there's a second group: lysine, tyrosine, cystine, leucine, valine, phenylalanine and taurine, which also rise at about the same rate in early pregnancy but then they tend to fall off and their excretion at the end of pregnancy tends to be less than it is at the beginning of pregnancy. And the remainder of the amino acids really don't show any notable change at all.

Now in terms of renal clearance which we can calculate because we know the blood levels of amino acids in this series, you can see that of the five big spenders which we'll concentrate on now, renal clearance goes up to 20 or 30 ml per minute for glycine and histidine at the end of pregnancy. And for people who aren't used to thinking in terms of renal clearance, we can also calculate the amount, the proportion of the filtered amino acids which are lost in the urine. And I've done that over here and you can see that for histidine and glycine again, something like 20% of filtered amino acid is lost in the urine. And it goes up to about 7% for serine and so on, much less obviously for the other ones. But for some individual women, odd examples have shown that they can lose 50% of filtered glycine from time to time.

<*To camera, seated*> Now we have absolutely no idea why this happens. It doesn't bear any relation, as far as we can see, to the biochemical configuration of the amino acid or to its biological function, nor does it seem to be related to specific transport mechanisms; for example, we know that cystine, <*refers to diagram*> ornithine, lysine and arginine are all carried by a single transport mechanism. But, you can see here that in terms of renal clearance, these four behave quite differently so that particular transport system isn't being specifically interfered with by itself. <*To camera*> The mechanism is not at all clear although you can duplicate this phenomenon in men by giving cortisol and the high levels of free cortisol in pregnant women may have something to do with this.

Now the next group which is very well known too, of the nutrients to be excreted in the urine are the water soluble vitamins. Vitamin C is excreted in large amounts and so are all the B vitamins. We've looked at folic acid and you can see here that the normal non-pregnant person secretes about 5 micrograms in 24 hours <*refers to chart*>. In pregnancy again, rather like the glycosuria, the values stream away and you get great irregularity from time to time in the same person, and from person to person, but individual women, not being supplemented I may say with folic acid, can excrete up to 50 micrograms of folic acid in 24 hours.

<*To camera, seated*> Well, what are the implications of this clinically? It's difficult to know. One thing which does stand out, of course, is that the urine is a tremendously nutritious fluid with all these nutrients in it and that may in part explain why urinary tract infection is much more common in pregnancy. But to throw away 2 grams of amino acids and 50 micrograms of folic acid may be all right in Western society, where women are living on good diets, but there are many parts of the world where that kind of extravagance could be very serious. And it would be of great interest to know whether the kidney is capable of curbing its spendthrift tendencies in areas of the world where nutrients are scarce.

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