Water Metabolism in Pregnancy

Current Research in Obstetrics and Gynaecology

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<**Opening titles**>

<**Mr Geoffrey Chamberlain to camera**>

Good day and welcome to another edition of our series on current research in obstetrics and gynaecology. This series, you'll remember, is being run jointly by the Audio-Visual Centre of the University of London and the Blair Bell Research Society. Today we're going to talk about water metabolism and we are fortunate enough to have with us not just a prominent member of the university, but an ex-chairman of the Blair Bell Society himself. Professor Frank Hytten is from the Division of Perinatal Medicine at the Clinical Research Centre in Northwick Park, and he's going to discuss with us water metabolism. Professor Hytten.

<**Professor Frank Hytten to camera**>

There are just two aspects of water metabolism I think it's worth talking about. One of these is the way the body handles water in pregnancy, and it centres around a really quite extraordinary phenomenon […]

<**Hytten, seated, shows a series of graphs and diagrams on a flip chart beside him, camera moves between long shots including Hytten and close shots of the graphs and diagrams**>

[…] namely a very abrupt fall in plasma osmolality which takes place quite early in pregnancy, probably within the first six weeks, and it's a fall of about 10 milliosmoles. Now there really isn't time to talk about why this should happen but it all centres, in fact, on the change in respiratory control which takes place in pregnancy.

The baby, <*next diagram*> using progesterone, resets the respiratory centres, and the mother over-breathes, simply to reduce the pCO_2 – I don't want to go into this in any detail, it makes it easier obviously for the baby to offload carbon dioxide across the placenta. But the pCO_2 comes down dramatically in early pregnancy by a considerable amount, and because the mother is allowed to maintain her pH, then she has to discard bicarbonate and with it goes sodium and that is, to a large extent, what cools down the plasma osmolality. It's not the only reason but it is one of the major reasons, I think, why plasma osmolality falls.

Now, a fall of the dimensions we're talking about 10 milliosmoles, is the kind of fall you get when you drink a litre of water, it's a very big fall in osmolality. And it's worth considering just what happens when a fall of osmolality of that degree takes place. This <*next graph*> is all physiological work and it simply shows that we tend to maintain osmolality within very narrow limits indeed, around about + or – 1 or 2 milliosmoles. If it drops by as much as even 5, which is less than we're talking about, then the release of anti-diuretic hormone ceases and there is a maximum diuresis. If, on the other hand, there is an increase in osmolality, there's an increasing release in

anti-diuretic hormone, and thirst, and both of these things tend to correct the osmolality.

Well, what happens, the point is really that in pregnancy we have this really low osmolality all the time and the question arises as to why the woman isn't permanently in a state of having no anti-diuretic hormone, in fact in having diabetes insipidus. In fact, why does she not have this throughout the pregnancy? Well, let me just show you the kind of thing that happens. If you or I drink a litre of water quickly, then we get this sudden fall in <*draws with marker pen on blank graph*> plasma osmolality, say from 290-280. And then what happens is that the kidney excretes water at a maximum rate of perhaps 15ml a minute and back comes the osmolality to where it should be. Now what happens if you are living permanently at this low level. It can be done – people in the old days did experiments to bring their osmolality permanently down by going onto a salt-free diet, for example, for many weeks. And if you were permanently down here then if you drink a litre of water, again it goes down by 10 milliosmoles, but the characteristic of this circumstance is that it takes a tremendously long time to come up, with a maximum ability to excrete water of no more than about 5ml a minute.

But pregnancy is quite different. The pregnant woman, too, you see is living down here permanently at about 280 and she goes down to 270 too, if you give her a litre of water to drink, but she comes back with the most astonishing speed. The pregnant woman has a quite exceptional ability to excrete free water.

This is just to show you an example of one such woman who we studied. And this is a quarter-hourly <*next graph*> urine output in response to a water lowered of a litre, and you can see that in early pregnancy this girl was able to excrete 30ml a minute at the height of her diuresis; now this far and away exceeds anything that a normal person can do. So the pregnant woman is entirely different, something has happened here which is unusual.

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And, if I can just put this caption back again. I think what she has done, among other things, <*next diagram*> is to reset osmoreceptors, to put it in a rather over-simplified way, so that she is now coming to accept and preserve this new low level of osmolality in the same way that she's had to learn to accept and preserve a new low level of pCO_2 . But the interesting thing is, I think, that there is a lag in the resetting of these osmoreceptors so that for a little while she does behave like a diabetic insipidus and the pregnant woman characteristically has a polyuria in early pregnancy and in some woman it's really a great polyuria, they don't complain about it very much, but it's very common. And, the interesting thing again is that after the placenta has been discarded, the progesterone level drops extremely quickly, all of this resetting goes into reverse: the woman stops over-breathing, CO_2 comes up, bicarbonate comes up, the osmolality rises and it rises very quickly after the pregnancy. You find then that there is a rising osmolality with reset osmoreceptors for a lower osmolality. And the consequence of that is water retention. And this is what happens in the first few days of the puerperium; the pregnant woman tends to retain water and the diuresis which is said to happen after delivery does not in practice happen until 5 or 6 days after delivery. So that really is the story of what happens, I think, in the handling of water in just this one respect.

<**Camera moves onto Chamberlain, seated nearby, who begins a discussion with Hytten. Camera moves between them**>

There's one aspect I don't quite follow. With the low osmolality, and the haemodilution that occurs during pregnancy, why is it they are thirsty? Shouldn't their thirst desire be suppressed?

<**Hytten**>

Well, you're quite right, I think it's one of the interesting paradoxes of pregnancy that the pregnant woman has this low osmolality and, as far as the brain's concerned, a dilute plasma, and yet she's also thirsty because thirst is a very characteristic phenomenon for pregnant women. I think we don't know the answer but it could be that the very high angiotensin levels in pregnancy are controlling her feelings for

thirst, and that of course is concerned with a whole other part of pregnancy metabolism concerning sodium.

<**Chamberlain**>

It's also concerned with another programme we're having later in the series with Fiona Broughton-Pipkin, coming down from Nottingham, but we won't talk about that now. But there's one point, can you help us … how does one reset an osmoreceptor? Is it a biochemical change in the cells? Can you measure how it's reset?

<**Hytten**>

No, you can't, I presume it is biochemical resetting, I presume, nothing at the moment is known about this, a little bit of work is going on, but it's a very difficult thing to investigate, and it's a difficult concept in a way and I don't think we really understand it. What I've said is really a pretty gross over-simplification of what happens, I'm sure.

<**Chamberlain**>

Like physiology always is as it moves on, it cuts things down a bit. Well, let's go on to the second part now, the water storage.

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<**Hytten, seated, shows a series of graphs and diagrams on a flip chart beside him, camera moves between long shots including Hytten and close shots of the graphs and diagrams**>

Well, the next thing I want to talk about is the question of the storage of water by pregnant women which is a well-known phenomenon, of course, and all tissue contains water and therefore as the pregnant woman grows a baby with its placenta

and amniotic fluid and extrauterine muscle and so on and so forth, of course she is storing water in all those components, and we can see the extent of that in this graph <*next graph*> that the pregnant woman is storing something of the order of 6 litres in total in the product of conception – the baby and the amniotic fluid and so forth, and in added maternal tissue and the increased plasma volume and one thing and another. So that is the amount of water that you would expect the woman to store. But, of course, when clinicians talk about accumulations of body water, what they really are talking about is excess accumulation, oedema if you will.

Now, in pregnancy, the normal woman does store excess water outside those defined sites and the amount depends on the amount of clinical oedema. The information I'm showing you here is the result of a big study of body water which was done <*next graph*> in Aberdeen just a few years ago, and if you look at the amount of water that has been stored by the 3 oedema groups, and perhaps I'd better just digress for a moment and tell you what these are. When it says 'none' that means that there was no clinical oedema apparent; 'leg oedema' simply means what you all understand it to mean, namely swelling of the legs and so forth, nothing above the knee; 'generalised oedema' means what obstetricians mean by generalised oedema, it doesn't mean anasarca, it just means a tight wedding ring, a puffy eyelid, it's a very trivial thing in general terms; gross generalised oedema is most uncommon in pregnancy and there's no gross generalised oedema here. So that by 30 weeks of pregnancy you can see that, unless the woman has gross generalised oedema, there's no excess water stored at all. All of the water that was found to be stored by this body water study could be accounted for in those zones. It's only at term that there's an excess and that is something like 2 / 2 ½ litres. But you see that women with generalised oedema have very much water storage. It's apparent at 30 weeks and by term it's really grossly excessive and averages something of the order of 5 litres, but can be as much, in individual women, as 8 litres, in excess of what we would expect. So it's very big.

Now, there are several questions that are raised by this but the first and most important question that occurred to us was: why did so many women in this study which was of absolutely normal, healthy primigravid girls, why did something like

50% of them have oedema at all because in the days when we did this, oedema was still considered to be a sinister sign of something going wrong? And I defended this study which I had done because those girls with oedema were perfectly normal, they'd been perfectly healthy in every respect throughout the pregnancy and when I did a quick calculation I even found that the babies were, if anything, a little bigger than the women who didn't have oedema, so it seemed to me that there was every reason to believe that this was normality. But the only way to find out whether it was as common as this and whether it was normal was to look at it in epidemiological terms.

Now, in Aberdeen we were lucky because Aberdeen is an exceptional place, as you will know, and where there is an extremely homogeneous and stable population which all delivers in one hospital. And there's been a tradition of research there for many years and the notes are kept, the clinical records, are extremely good, so we were able to look at all deliveries in the whole of a defined population for 10 years to see what the incidence of oedema was. I may say that oedema had never been looked at as something we did research on, so the notes weren't kept for research purposes, they were just good ordinary notes where oedema was noted in the usual places. And in those cases <*next graph*> we found that something like 40%, not quite as much as in that study I just referred to, but about 40% of pregnant women were recorded as having oedema, and in about 15% of them it was generalised. It is, of course, much commoner if there are hypertensive complications; if there is just hypertension it's something about 70%; if there's hypertension with proteinuria, it's something of the order of 90%.There's still 10% of women, even in this group, who do not have oedema. But the numbers, as you can see, are quite different, and while 70% of women with hypertensive complications will have oedema, 70% of women with oedema will not have hypertension.

Well, that was to some extent a relief to me, it did show that oedema was commonplace. The question still arose to whether it was normal. Let me just say in passing, quickly, <*next graph*> that the fatter a woman is, the more oedema she has and the more of that oedema is generalised. Well, the only way we could look at normality in any sensible fashion was to see whether foetal growth was affected and

the babies all weighed more when the woman was oedematous and that didn't matter whether there was or there wasn't hypertensive complication, I won't go into details about that. But you may well say, ah of course, fat women have more oedema, fat women have big babies and that's the connection. It isn't as simple as that because at any weight for height, <*next graph*> women with oedema have bigger babies than women without oedema. These babies are not oedematous themselves, they don't lose weight after delivery more than any other baby, we believe this is simply enhanced foetal growth in women with oedema. So, if it's common and if, as we now believe, it's normal, what is this water doing and where is it – this is the problem.

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Well, you might expect there to be an excess of fluid stored as a result of simply starling phenomenon: high venous pressure in the lower limbs and water being squeezed out, because not just that increase in pressure but also because there's a fall in colloid osmotic pressure, a very substantial fall, due to the fall in serum albumin. You can see albumin falls, colloid osmotic falls absolutely in parallel with it, and femoral venous pressure rises so that one would expect water to accumulate as a result of this in the lower limbs where venous pressure is high.

And it does, but <*next graph*> only, you see, to the extent of about half a litre, that is the increase in leg volume which occurs during pregnancies. So, the 2 ½ litres we are looking for are not in the lower limbs, this is not as simple as that. The fact is that this water is distributed much more generally. This is a study which took place in Newcastle a few years ago. Four groups of women: <*next graph*> group one having no oedema at all clinically and two having very slight oedema, these having rather more oedema, but you can see in all of these groups that the increase in finger circumference, which was simply judged by using jewellers' ring sizes, increased steadily.

So, we believe that there is a general distribution of body water, of increased body water, in pregnancy. And the feeling now is that this is in the connective tissue

ground substance. There isn't really time to talk about this in any detail, <*next illustration*> but here we have an extremely important and valuable organ of the body, very much concerned with homeostasis. In this diagrammatic representation of it, I'll show you three cells stuck together with connective tissue ground substance, or they could be collagen fibres, or one could be a capillary wall. This is standing between the blood and the tissues, it's an extremely important organ which can take up water and let it go, it can take up electrolytes and let it go – it is the organ of homeostasis. And it exists in two phases: a jelly-like matrix and little globules of low colloid, high water content, which are visible by electron microscopy. And when the ground substance takes up a lot of water, it does so not by diluting the jelly which then becomes sloppy but by increasing the number of droplets, and you can push it in this direction by a number of ways; it's hormone dependent, it will move in this direction in the sex skin of the monkey with oestrogen, in the cock's comb with testosterone, it can be pushed backwards with corticosteroids and we believe that this effect is happening in women, that connective tissue ground substance all over the body is being caused to become wetter and swell in this fashion by oestrogen. It's a very important thing to happen in pregnancy because is the ligaments of the pelvis, in the cervix, the vagina, all these things have to become extremely stretchable compared to the non-pregnant state; nipple anchorages, that kind of thing, so that it's an important change to take place but it shows up in the skin where a lot of the ground substance as oedema.

So, here is something which is a normal phenomenon, probably very normal in pregnancy, but which has, as an external manifestation, swelling, which we've all regarded as an abnormality. So, I think I'll stop there and there's a lot more one could say about this, there's a lot of interesting side effects like flat feet and spongy gums – the increase in periodontal disease has undoubtedly been added to by this, the fact that women have difficulty getting contact lenses to fit because of corneal changes, it's all part of the same pattern.

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<**Camera moves onto Chamberlain, seated nearby, who begins a discussion with Hytten. Camera moves between them**>

<**Chamberlain**>

Yes, and these of course occur with the taking of the pill when you get the other oestrogen increase don't you?

<**Hytten**>

Indeed, indeed.

<**Chamberlain**>

I wonder, in this, you've used incidence of oedema several times in your studies, I'm sure you agree that the actual incidence of oedema varies very much. For instance if it's a warm day clinic or a cold day clinic, with an afternoon clinic or a morning clinic. Do you notice these very great swings?

<**Hytten**>

I think you do, I just think we haven't been paying a lot of attention to it in the past. If you ask women about swelling I think you get a more accurate view because they're integrating whatever they've noticed over the week since you've last seen them and I think that's probably a better measure than looking for it yourself.

<**Chamberlain**>

Yes, I've always thought that leg oedema, is, as you rightly said, almost a normal finding when there's a swelling in the abdomen and a girl is a vertical creature, and probably more accurate is hand oedema of the ring, or, as you rightly say, of the face when the girl notices it herself. I'm interested in what you were saying about pre-eclampsia and oedema: do you have any comments to make on that 10%, I didn't

realise it was as high as 10%, of pre-eclamptics who don't get oedema. You may remember Fred Gibberd used to always say "Beware the dry eclamptic", it was one of his favourite sayings, it is undoubtedly, they are very sick people aren't they?

<**Hytten**>

They are indeed, yes.

<**Chamberlain**>

What happens to their water mechanisms do you suppose?

<**Hytten**>

Well I don't know. I think women who don't get oedema are presumably lacking, at its simplest, oestrogen and I think you see pre-eclamptics occasionally, or pregnant women in general, who aren't pre-eclamptic who just don't appear to be pregnant, they've not made any of the changes. Their hands aren't warm, they don't have an increased plasma volume, they've just got a baby growing there and they've made no arrangements for it. They do badly, these babies, and the women, if they have a hypertensive complication on top of it, do extremely badly, there's no doubt about that.

<**Chamberlain**>

Are the babies smaller after gestation? These dry pre-eclamptics?

<**Hytten**>

Yes, that's right. Yes, they are, yes.

<**Chamberlain**>

I see. How do you think this fits into the story, the treatment of oedema in pregnancy, our American colleagues give quite a lot of diuretics, something we don't do very often in this country; do you think this affects things?

<**Hytten**>

Well, I think the treatment of oedema is pointless and I think to treat this kind of oedema in the ground substance with diuretics is equally pointless because this is not accessible to the kidney. You will have a diuresis from the use of diuretics and it won't be from here and this is why there have been some extremely serious consequences from its use, and reported, particularly in the American literature, women have died as a result of the use of diuretics in pregnancy. The question of whether oedema should be regarded as a bad sign in the context of pre-eclampsia is, I think, a very difficult one. I have one more picture which points this out. This <*shows diagram on previous flip chart*> caption shows you that in that study that we did of a hundred women where we measured body water, the grey zone here shows the extent of water storage in women who had generalised oedema and there were quite a lot of them, and the individual lines are six women who, in that group, became pre-eclamptic with proteinuria. And you can see that they all had generalised oedema but their water storage was no greater than it was in normal women with generalised oedema. What I can't say, and what nobody can say, is whether the oedema or the water is stored in a different place in pre-eclampsia, it may be, I can't say that – there may be cerebral oedema, there may be all kinds of things, there is absolutely no way in which this can be discovered at the moment, we have no techniques.

<**Chamberlain**>

There is no physiological way of measuring cerebral oedema is there?

<**Hytten**>

Not that I know of, no.

<**Chamberlain**>

Nor I, that's why I'm asking. This again is the Aberdeen study. We're all very jealous of Aberdeen studies in the south here because our follow-ups are so poor compared with what you get in Aberdeen. And the story, of course, goes round in this part of the world that there's the community medicine police patrol the outskirts of Aberdeen and send back an essay: <*Chamberlain adopts a Scottish accent*> "Go back and get a part of someone's follow-up, you've got to go back!" And also there's an official protection vessel going three miles off-shore sending back anyone that wants to leave Aberdeen so they have to join in the studies. I'm sure it isn't true, but …

<**Hytten**>

<*laughs*> That's not entirely true …

<**Chamberlain**>

… We are jealous of those … And, do you remember Philip Rhodes did a study in St Thomas' Hospital and he related using weight increase as a measure of water retention. And he showed, very nicely, that the people who had very small weight increase were very often associated with those with no pre-eclampsia; as pre-eclampsia got worse, measured by blood pressure, so the weight of people got worse until the very severe group – and the severe group had a very sharp down go in weight increase. Do you remember that piece of work?

<**Hytten**>

I don't remember that, no, that's very interesting, that would fit in …

<**Chamberlain**>

Yes, that fits exactly with what you were saying, I thought, as a clinical estimate.

<**Hytten**>

Yes.

<**Chamberlain**>

Well, thank you very much Professor Hytten for coming with us today You've explained a study, you've explained work to us which sometimes we have difficulty with getting over and we have difficulty in getting someone to talk about it clearly. It isn't well laid out in the textbooks and so we're grateful to you today to talk to us about water metabolism. Thank you very much.

<**End credits**