>> Steve Langjahr: May 23rd, 2012. Tonight, a lot of ground to cover. We finished with the male reproductive system. So, it's only right that we launch into the feminine side of things. What are the gonads in women? Of course, they are the ovaries. And at least from puberty throughout adulthood, ova are produced and released on a monthly basis, until menopause. Ova or eggs are the female gametes. And certainly, their production is dependent on reproductive hormones. Namely, estrogens and progesterone. Both of which are, chemically speaking, steroids. So, what is the way in which ova are produced? Actually, it turns out to be not so much production of ova, but maturation of ova. Which are already in place. And then the very carefully orchestrated release of ova, once a month. So, it's a very different system than in men. In men, we're making sperm constantly. And releasing them often, shall we say. But in women, we are not so much making, but maturing. Maturing gametes that are already in place. And then releasing them in a very precise timed sequence in the middle of the menstrual cycle, as we'll see. So, looking at this process, which is called oogenesis. It begins with some nondescript stem cells called oogonia. Which actually divide and populate the ovary, during fetal life. In other words, the oogonia are dividing and filling up the ovary, even before the girl child is born. And by the time she is born, she has already in place, about 400,000, what are called, primary oocytes. So, during her fetal existence, her ovaries essentially produced 400,000 primary oocytes. And nothing happens to them for at least the first ten years of this child's life. That is, they're dormant. In fact, if anything happens to them, many of them die or disappear. So, even though a woman is born with 400,000 primary oocytes, nothing much happens to them, until the onset of puberty. And so, when does that happen? Why does that happen? What are the causes of puberty? Well, of course, it's that acronym, FSH. What's FSH?

>> Follicle Stimulating Hormone.

>> Steve Langjahr: Follicle Stimulating Hormone. Which arrives on the scene, shall we say, at age ten. And begins to promote, not the mitosis, but the miosis of these primary oocytes. And you know that miosis doesn't just produce more cells. But actually, reduces the chromosomal number of these potential gametes. So, miosis ultimately produces four cells from a single cell. And the chromosomal count is reduced from the diploid state. Which is what? Forty-six. To the haploid number. Which is? Twenty-three. The interesting and very different thing about this kind of miosis in women, is even though it produces four cells, only one of them is viable. And that's a curious and somewhat mysterious thing. Notice that we get four cells. One, two, three, four. One of them is huge. The others are pathetic. And essentially, incapable of being fertilized. So, this process of miosis, even though it generates four cells, each with 23 chromosomes. Only one of them is suitable as a gamete. Why would the ovary do it this way? Well, it's really not hard to understand. Because unlike sperm, is there any nutritive source for an ova, when it's released into the oviduct? Is there anything like semen in the female reproductive tract that can support the cell respiration of this gamete? No. And so, the strategy here

seems to be this. Let's put all the cytoplasm into one. So, that its survival, so that its viability is increased. And therefore, improving the chances of it being fertilized. And so, that for better or worse, is the way it works. Finally, we should also point out that all of these cells, even the so called polar bodies, all have the X chromosome. After all, a woman, a woman's genotype, when it comes to the sex chromosomes, is two X's, right? So, just to remind you, who determines the sex of a child at conception?

>> The male.

>> Steve Langjahr: It's the father. And the sperm which have that capacity to decide whether the conceived embryo is male or female. Now, the process of generating and releasing an egg on a monthly basis is complicated and tightly orchestrated. But this synopsis, which can be viewed in a counterclockwise fashion. Shows, the existence of a collection of what are called primary follicles. Which contain these so called primary oocytes. And under the stimulation of FSH, some of them grow and undergo miosis. And typically, in any given month, one of them will reach this status, which is designated the mature follicle. Also known as the Graafian follicle. Many of them may be simulated, but only one will reach this status. And notice that this unit, which is a cluster of cells surrounding a single gamete, is pushing its way to the surface of the ovary. And eventually, for reasons that we'll mention tonight, it is forced to explode at the surface. Releasing, at that point, what is a secondary oocyte. Along with many other cells to be captured and catapulted into the oviducts. And then this remnant of the Graafian follicle, essentially assumes another role for the rest of the menstrual cycle. As it becomes known as the corpus luteum. Eventually to fade away. And so, the cycle repeats. So, we're going to focus on these events. Which are shown nicely in this illustration. So, to review again, what are the ovarian structures and changes and stages that take place, as we move through the female cycle? Primary follicles, by definition, are clusters of cells that contain a primary oocyte. And they are promoted. That is to say, they grow in response to what hormone?

>> FSH.

>> Steve Langjahr: FSH. And usually quite a number of these, quite a number of these primary follicles will respond to FSH. But only one receives this distinction or reaches this stage called the Graafian follicle stage. And then, as we've already said, it will rupture, literally exploding through the surface of the ovary. And it will cast out into the oviduct, something called the secondary oocyte. Which will, at some point, be available for fertilization. What remains behind in the ovary is a remnant of the Graafian follicle. And it assumes the name and the function of something called the corpus luteum, which we'll get into. But to repeat then, these are the primary events, the names. The stages that take place in the liberation, the ovulation of an ovum. That said, what's the hormonal backdrop? What are the hormones, aside from FSH, that instigate, orchestrate, make this all possible? What's the role of the anterior pituitary? It's really no different from the role of the anterior pituitary in men. Because

remember, the hormones are the same, regardless of gender. It turns out, as we've already said, that when a female child is born, she already has in place, how many primary follicles?

>> Four hundred thousand.

>> Steve Langjahr: Four hundred thousand. And we mentioned that there is no FSH in those childhood years. So, you would assume that those 400,000 would be there later, as she enters puberty. But it actually is not the case. There's a huge attrition. When a woman has her first period, whenever that is, it's call menarche. Menarche is the girls first menstrual period. For discussion, let's say it's at age ten. And believe it or not, she's lost a considerable number of these primary follicles. Down from 400,000 to what? Ten thousand. Strictly as a result of attrition. In other words, death of these otherwise healthy cells. And what is the hormone that's released at this time that's going to have an effect on these remaining follicles? Well, it's FSH. And in any given month, a number of these primary follicles then, will respond to rising levels of FSH. One of them will achieve a distinction known as the Graafian follicle. And one of them then, will provide an egg for ovulation. The other hormone that occurs and that's important in the menstrual cycle, just as it is in men, is LH. But LH stimulates the follicle cells. Those that are not contributing to the egg itself. And those cells produce estrogens. The primary feminine steroid, which supports the female reproductive tract. And indeed, the growth and maturation of follicles, per say. LH is also important in maintaining the corpus luteum. Indeed, what the initials LH stand for? [inaudible answer]. Luteinizing hormone. So, it's main effect is to sustain and maintain the corpus luteum. Which produces progesterone and estrogen, especially during the last two weeks of the menstrual cycle, as we'll see. Now, with that said, let's take a step backwards. It's one thing to outline what the anterior pituitary does. But why and when does the anterior pituitary release these hormones? Well, clearly, it's under the thumb of the hypothalamus. So, just as with men, the hypothalamus releases GNRH. Which stimulates the cells of the anterior pituitary that make and release FSH and LH. Those hormones arrive and have an effect on the ovary. FSH stimulating ovum development. LH stimulating, at first, the follicle cells. And later, the corpus luteum. All of which promote and make possible oogenesis and eventual ovulation. And from this, especially from the corpus luteum, progesterone will be produced later as well. Do these ovarian hormones circulate throughout the body? Do estrogens and progesterone, produced here in the ovary, circulate throughout the body? Yes. And do they have effects on these hypothalamic and pituitary cells? Yes. And what do you call it when hormones, produced here, having an effect there, exerts that sort of control. It's the F word? Feedback. Now, this feedback, in this loop, is quite a bit more complex, than in men. So, we need to take it slow and in steps. It turns out that whenever there's high levels of estrogen and or high levels of progesterone, they have a negative effect on the hypothalamus. And what do you call that negative effect?

>> Negative feedback.

>> Steve Langjahr: Negative feedback. And what would that lead to? Well, if we inhibit the hypothalamus, then it wouldn't release GNRH. Therefore, the pituitary would not release FSH or LH. And therefore, these hormones that produced or that are produced by the ovary would be diminished and brought back into, shall we say, a lower level. So, this is classic negative feedback. The second possibility, which is quite different, is when there's low levels of estrogen and progesterone, tend to exert a positive influence. That sounds like positive feedback, but it's just the removal of negative feedback. In other words, when these levels are low, we're taking away negative feedback. And therefore, allowing the hypothalamus to release GNRH. And so, the pituitary will produce and release FSH and LH. So far, this is sort of standard. But here's the twist. When there's high estrogens alone, that produces a positive stimulus to the hypothalamus. And what do you call it when high levels of any hormone promote even more production of that same hormone? That's positive feedback. So, in summary, from top to bottom, we have classic negative feedback. The removal of negative feedback. And a pure case of positive feedback. The importance of which we'll see in a minute. So, this system is well, needless to say, complex. When this was fully understood, in the mid twentieth century, it became almost immediately obvious to some clever scientists that this knowledge could be used in a practical way. Because wouldn't it be possible to provide estrogens and or progesterone to women in an oral form. And if they took a pill that contained estrogens and progesterone, what would that daily consumption do to their hypothalamus? And the inhibition of the hypothalamus would in turn decrease the release of? FSH and LH. Therefore, prevent and stop ovum development. And what is the name for that strategy? Contraception, oral contraception. Introduced in the 1960s and widely popular around the world. It is effective. It's safe. And you could argue it's natural. Why is it natural? Because the hypothalamus normally responds in a negative way to any increase of these two hormones. But let's go on. Let's actually talk about the menstrual cycle. Because we have to understand this to integrate how things are coordinated, when it comes to reproductive issues in normal individuals. What is the menstrual cycle? Well, first, we have to look at it from the ovary standpoint. What is the menstrual cycle, as far as the ovary is concerned? We know the menstrual cycle is a 28-day repetitive cycle. So, with those 28 days in mind, the first two weeks, as far as the ovary is concerned, is designated the follicular phase. The follicular phase is when follicles are developing. Under the influence of what hormone, you think? FSH. And even though FSH has no way to single out any one follicle. After all, it's just a hormone arriving in the ovary from the blood. It turns out that maybe two dozen, at most, ten to 15 primary follicles are provoked every month from FSH. But do all ten or 15 of those reach the Graafian follicle state?

>> No.

>> Steve Langjahr: No. Not usually. How many of these 10 to 15 are actually developed to that mature state and are ready and able to be ovulated in any

given month? Well, usually one, maybe two. In the case of octomom, well, that's another story. But normally one, maybe two. So, ovulation, as far as we know, is usually a singular event. And I say, as far as we know, because we really don't know. What do we base that knowledge on? We say it's a singular event. But we're saying it's a singular event because most births are what?

>> Singular.

>> Steve Langjahr: But does that make it impossible that there might have been two or even three ovulatory events? The other two might not have been fertilized. Might have died on the way to the uterus. So, this statement is a bit speculation. But let's go with it. Ovulation, the rupture of one Graafian follicle. Which releases a secondary oocyte into the oviduct about midcycle. Now, what happens to the cells that provided that secondary oocyte? What happens to those cells that remain behind in the ovary? Well, they reform into something new, something important. Something that exists for the next two weeks. Something called the corpus luteum. And that's why this final two weeks is known as the what? Luteal phase. This is the hay day of the corpus luteum. Which is not unimportant. Because what does the corpus luteum provide during these two weeks? Progesterone and estrogens. Which, as we'll see, support the endometrium, maintaining then the condition of the uterus, ready for a conceivable implantation. Now, with that as a backdrop, let's look at this somewhat quantitatively. And somewhat chronologically, spreading out these days from zero to 28. And pacing down here below, the ovarian changes that we've implied. And now we're going to plot the hormonal changes that occur during the first week, second week, third week and fourth week. Down here, we'll plot the ovarian hormones. Up here, we'll plot the pituitary hormones. So, hope you have some pencils handy. First, let's just consider progesterone. Where did we even mention progesterone? Where is progesterone even shown here, during these 28 days that revolve around the ovary? [inaudible answers]. Only in the luteal phase. And the luteal phase, by definition, is day 15 through 28. So, would there be any progesterone during the first two weeks of the menstrual cycle? No. So, progesterone, here in green, is pretty flat, pretty nonexistent, for the first two weeks. But what develops after ovulation, is of course, the corpus luteum. And with it, progesterone and estrogen. But notice this, what happens to the corpus luteum, which is at first very robust? What do these illustrations suggest about the viability or the longevity of the corpus luteum? How long does the corpus luteum last? [inaudible answer]. Two weeks. And eventually, very soon really, it degenerates. And with it, what happens to the progesterone and estrogen, which it produced at first, so well? So, what's going to be the progesterone story for these final two weeks? Will progesterone go up? Yes, it will. Will it come back down?

>> Yes.

>> Steve Langjahr: Yes, it will. So, there you are, progesterone. Why does it go up? Because of the corpus luteum. Why does is go down? Because of the death of the corpus luteum. So, that's the rise and fall of the progesterone, associated

with the corpus luteum. The next one I want to plot here and need to plot is estrogen. Estrogens come from the corpus luteum. But notice they're also produced or at least in part produced, by the cells of the developing follicles. So, as we look through the first two weeks, these follicles are growing. And therefore, estrogen supply is increasing accordingly. So, estrogens will escalate, as you can see, in response to the growing size and number of follicle cells. What happens at day 15? Day 15, day 14? An event called what? Ovulation. And ovulation is the physical act of releasing an egg. And does the follicle, which provides this egg, suffer some injury, as a result of that explosion? Do some cells die in the course of ovulation? Yes. So, what's going to happen to estrogen, which was being produced by these cells up to then? Well, it's going to come down. But never fear because what is going to be resurrected from these remanences left behind after ovulation? And what does the corpus luteum produce, aside from progesterone? Estrogens. So, you can pretty much anticipate what's going to happen. Progesterone, I should say, estrogen, will decline at first. But then it will rebound when the corpus luteum is active. But it will follow progesterone in this downward path. Why does estrogen dip, along with progesterone, to almost nothing at the end of the menstrual cycle? Why are these coming down? [inaudible answers]. The corpus luteum is dying off. And thus, we return to day zero and repeat the cycle. All right, now, with these, with these data, what's going to happen? That is, what will these hormones do to the release of the pituitary hormones? Which are directly influenced by the feedback mechanisms we've already mentioned? So, what's happening to estrogen or let's put it this way. What's happening to both estrogens and progesterone during the first two weeks? Progesterone's are almost nothing, right? But estrogens are going up, up, up, up. So, look back a page and tell me, how does the pituitary or hypothalamus respond to rising levels of estrogen alone? Rising levels of estrogen alone, is positive feedback. So, if we were to plot FSH, what would FSH be doing, in response to rising levels of estrogen alone? FSH is going to really get going here. Especially as estrogens peak at or around the day of ovulation. And the same is true for LH. Both of these, after all, are controlled by GNRH of the hypothalamus. So, this is not just interesting, it's fundamentally important. Because it's one thing to say all of this happens. It's another thing to explain why ovulation itself actually happens so reliably on or around day 14 or 15. And it's no longer a mystery. It hasn't been a mystery for some time. Because what pituitary hormones are spiking at or around day 14 and 15? LH and FSH. And it turns out that that's exactly what causes ovulation. It's known as the LH surge, LH surge. Which represents a spike of LH, as a result of positive feedback, due to the increasing levels of estrogen. In fact, this knowledge can be exploited. There are products on the market that you can test your urine for the presence of LH. And why would a woman want to know whether she's got a sudden surge of LH in her urine? [inaudible answers]. She'd say, well, sudden surge here. That means I'm about to what?

>> Ovulate.

>> Steve Langjahr: So, she can avoid or sex or get into sex, whatever she's

interested in, in order to be pregnant, get pregnant or not get pregnant. So, it's a way of obviously being aware of what's going on and timing things accordingly, the LH surge. Without that, ovulation won't happen. Now, what's happening in the last two weeks? Notice that this estrogen dips, in response to some destruction of follicle cells. But then it rebounds. But it rebounds, not by itself, it comes up with progesterone. Once again, look back a page. And how does the hypothalamus respond to rising levels of estrogen and progesterone together?

>> Negative.

>> Steve Langjahr: Negative. So, these spikes, which went up, are going to come right back down, in response to that negative feedback. And notice that their decline will eventually end up at the same level that they began on day one. Thus, the cycle repeats itself. So, at first, I'm sure these changes seem weird or not necessarily significant. But they're all finely tuned to bring about ovulation. And then the development of the corpus luteum. Especially for the secretion of progesterone and estrogen, for the maintenance of the endometrium. Before we go on to the next part of the story, let's pause and at least reflect on estrogen. Just as we did testosterone. Isn't estrogen the male or I should say the female counterpart to testosterone in men? So, what are the overall actions of estrogens? First, as you know, they're produced by and simulate development of follicles. Second, they are important for the support and maintenance of the genitalia. Which means the female reproductive tract, as well as the breasts. After all, what's the condition of the genitalia and the breasts in a prepubescent female? And what's the condition of the genitalia and the breasts in a postmenopausal woman? So, the condition of the genitalia and the breasts, definitely estrogen dependent. Promotes growth. By that I mean skeletal growth. And the maintenance of secondary sexual characteristics. So, do girls of age five, have feminine sexual characteristics? They don't. What are female secondary sexual characteristics?

>> Breasts.

>> Steve Langjahr: Breasts. A certain distribution of adipose. A certain distribution of body hair and so forth. All of these are estrogen dependent. Item D, interestingly and you could argue without any apparent purpose or function, but a footnote of sorts. Estrogens increase the level of renin and angiotensin two. Now, you might say, what good is that? Well, the short answer is nothing. But why worth the mention? When are estrogens especially high, based upon the data you just plotted? They are high from ovulation through the rest of the menstrual cycle, aren't they? And if they have this affect on renin and angiotensin two, what comes from that? What does angiotensin two do, but stimulate the? [inaudible answer]. Adrenal cortex, to release aldosterone. And what effect does that have? Well, that increases sodium reabsorption. What effect does that have? [inaudible answers]. Water reabsorption. Where are we going with this?

>> Bloating.

>> Steve Langjahr: Bloating. You know, I'm glad you provided the word. Because it's so indelicate. But you've seen enough commercials to know that yes, there's this issue of what? Water retention. And when does water retention happen? And why does it happen? Because of high estrogens. Again, there's no known advantage of that. It's just a pharmacological effect of estrogen. Another interesting side note, is that probably estrogens protect against atherosclerosis, to a degree. Question mark, we're not sure. But certainly, if you look at heart attacks across gender lines, which gender tends to develop heart attacks sooner in their lifespan?

>> Men.

>> Steve Langjahr: Men. And why are women late comers, when it comes to atherosclerosis? Well, some people think it's because of the estrogen. Do women eventually succumb from heart attacks, in some cases? Yes. And that's usually post menopause. And what happens at menopause is a decline of?

>> Estrogen.

>> Steve Langjahr: Estrogen. So, this might sound all sort of circumstantial. But it is, never the less, statistically supported. And there's also even some evidence that estrogens delay the onset of Alzheimer's. So, if all of this is only slightly true, it might argue for what, in women entering menopause? Women entering menopause have a decision to make. And what is that decision?

>> Hormones.

>> Steve Langjahr: Go natural or replace these hormones. HRT, Hormone Replacement Therapy. And in this context, we're talking about replacing or not estrogen. And there's compelling reasons to at least consider that. Even though there's some suspicion that estrogens may support or promote breast cancer. So, it's not an easy decision to make. Estrogens may also be responsible for PMS. Which is an acronym for what? Punish my spouse? [brief laughter]. I didn't make that up. But I like it. No, I tell you what I really like, is Webster's definition of PMS, which I happen to have. Webster's dictionary, you know, always sort of cut and dry. But here's their definition of premenstrual syndrome. "Physical, psychologic or behavioral changes, distressing enough to impair interpersonal relationships or interfere with usual activities." [brief laughter]. All right. All right, moving on. Estrogens may also be anti – well, not maybe. Estrogens are, very definitely, anti-acne. Because it makes sebum, the cause of acne, watery. And why is that worth mentioning? Well, sometimes mothers bring their adolescent girls in for acne concerns. And what might be prescribed, much to the chagrin of the mother?

>> Oral contraceptives.

>> Steve Langjahr: Oral contraceptives. Well, how dare you. Well, would this be in fact a therapy for acne? Of course. And whether it provides an additional

benefit it is, well, maybe secondary. But indeed, even adult women sometimes have acne, right? Yes, they do. And would they benefit from estrogens, in the form of oral contraceptives? Well, yes. It depends on, you know, how distressed you are about this. But it's just a fact. And let's go on. In the time we have left and it looks like we have plenty of it. We can finally get down to the interplay. That is, the processes which lead to successful reproduction. But before we talk male and female, we need to expand our knowledge of the menstrual cycle, to look beyond the ovary. The uterus has a point of view. That is, it has a concern in this game. And before we get to details, should the uterus be informed or at least be aware of what's going on in the ovary, shall we say? Of course. If the uterus is doing its own thing and the ovary is doing its thing, they wouldn't be synchronized or timed or otherwise able to pull this all off. So, what are the changes, during the 28 days of the menstrual cycle, that are different here in the uterus? Before we go, before we go there, what is the uterus actually made of? We know it's smooth muscle. But the lining of the uterus is the endometrium. Which is glandular epithelium. Which undergoes quite substantial change, day to day throughout the menstrual cycle. The myometrium, not so much. They myometrium is the contractile component of the uterus. And it's made of what? Smooth muscle. So, these are ideas you know from anatomy. But we had to review those quickly. So, from the uterine standpoint, the menstrual cycle looks totally different. Day one through five, menstruation. What is menstruation? And why is it happening now? Well, as you look back to the graph that we prepared, what are the ovarian hormones present in the early days of the menstrual cycle? Is there any estrogen? No. Is there any progesterone? No. And without estrogen and progesterone, the endometrium simply shrivels and sluffs. That means, comes loose and leaves the uterus through the cervix. What do we call this discharge of endometrial cells and blood that occurs during this time? We call it menstruating or having one's period. And it's all the fault of what hormones?

>> Estrogen and progesterone.

>> Steve Langjahr: The decline in estrogen and progesterone. But never mind because the next ten days, are going to be the rebuilding phase of this lost endometrium. And for that reason, it's called the proliferation phase. To proliferate means to make more. And what hormone, what hormone is responsible for this phase? Estrogen. Why not progesterone? [inaudible answer]. Progesterone doesn't come on the scene until after ovulation. And only then, as a result of the corpus luteum. So, the rebuilding, the repair of the endometrium is entirely the result of what? Estrogen. Which is increasing in response to the growing follicles in the ovary. In response to FSH from the pituitary. And this is logical? I mean, think about it. Do we want the endometrium to be developing as the follicles are doing the same? Of course. In case it's not clear, what is the function of the endometrium? The function of the endometrium is to provide a nesting ground, if you will. A site for the I word? Implantation. So, the endometrium has got to be ready, ready to take on this responsibility. And it's the proliferation phase, which guarantees that readiness. Now, let's

say that ovulation comes and goes. And let's say, sadly, that the egg is not fertilized. Well, what then happens to the corpus luteum, you think, if the egg that was ovulated is not fertilized? The corpus luteum will what? [inaudible answer]. And what hormones will decline as a result?

>> Estrogen and progesterone.

>> Steve Langjahr: And so, what happens to the endometrium, despite its earlier proliferation? Well, it's going to end up being sluffed. But at least, in the final two weeks, while there still is progesterone and estrogen, it's going to be enjoying an even higher level of production. It's called the secretory phase. And here is where it's not only lush and ready, so to speak. But it's also putting away a lot of carbohydrate. That is the cells are storing and producing glycogen. Now, just think, why would it be a good idea for these endometrial cells to synthesize and store glycogen? Glycogen, isn't that a complex carbohydrate that could be useful for what? Energy source for an implanted embryo. So, it's exactly the goal of the secretory phase. Not only is it storing glycogen, it is increasing in its vascularity. So, it's doing everything it can to get ready for what? To get ready for possible arrival of a zygote or a blastocyst in the uterus. But if that doesn't happen, as we've already said, if that doesn't happen, what happens to the corpus luteum? Dies. What happens to the estrogen and progesterone? What happens to the endometrium? And so, we repeat the cycle again and again. So, these are the phases of the menstrual cycle, from the uterine standpoint. So, finally, we can talk about how we successfully create new life. Of course, involving both male and female participation. We know about spermatogenesis. We know about erection. We know about ejaculation. So, with that information, we know that sexual activity occurs. Let's say, with some degree of timing or synchronization. And the ejaculate, which is deposited in the vagina, is deposited rather high up in the vagina, as we mentioned. Semen will coagulate. Remember that? Which helps prevent it from leaking out. And sperm then, will have access now to the uterus. If this is going to be successful, we know that this act or this effort has to occur midcycle. And so, let's assume that that's the case. And by no coincidence, at midcycle, the cervix, which is normally tightly plugged with mucus. Develops a different kind of mucus at this point, which is more liquid. Why is that conversion of a solid plug to a liquid plug appropriate, indeed necessary at this time? Well, sperm aren't going to get through, unless there's an open door. And so, the status of the cervix can be inviting or not inviting. And therefore, deny or permit access to the uterus. We also know that semen has prostaglandins. And we mentioned their function. Prostaglandins cause smooth muscle to contract. And so, this may assist in the uptake of sperm into the uterus. Those are points of speculation. But one thing for sure, the semen, the bulk of the semen, is left behind in the vagina. And the only thing that gains access into the uterus are sperm cells by the millions. And they do what sperm cells are famous for. They swim against the tide, so to speak. And it turns out that this swimming, this flagella action is important. Because actually, the head of the sperm is covered with a glycoprotein coat. Which really prevents sperm from penetrating an ova. So,

this might seem primitive and even unexpected. But it turns out that sperm have to actually rub up against the uterine lining, in order to scrape off this glycoprotein coat. That process is called sperm capacitation. And until the advent of invitro fertilization, nobody had a clue that this was necessary or that it even occurred. And how did invitro fertilization lead to this discovery? Well, in the early days of invitro fertilization, they would just take an ova. And then they'd dump in some sperm and hope for the best. But it rarely worked. And it turns out that the sperm weren't, what's the C word? They weren't capacitated. So, now we know that you just can't dump in sperm and hope for the best. You've got to scrape off this glycoprotein coat, in order that they can successfully penetrate the ovum. Anyway, sperm are pretty good swimmers. And they have been detected in oviducts within a half an hour after sex. So, they arrive in the oviducts within 30 minutes. And what might be there or could be there waiting for their arrival? An egg. I don't know that they're waiting. But they're at least there. And as far as we know, once sperm are in the female reproductive tract, beyond the vagina, their time is running out. How long can they survive? Nobody really knows, but here's a number. I won't hold you to it, but less than what? Seventy-two hours. What is that? That's three days, isn't it? Pretty impressive. Which means that maybe they live as long as three days in the female reproductive tract. Again, nobody knows. And certainly, some last less than that, for sure. Meanwhile, what's going on and what are the issues surrounding ovum transport? We know that ovulation occurs when in the menstrual cycle? Day 14, day 15, all right. And ovulation indecently, is not a singular event. What I mean is, a single cell doesn't get ovulated. Ovulation is like a volcano, in that it blows out many cells. One of which is a potential ovum. And all of these cells are captured and manipulated by those tentacle like projections at the end of oviducts. You might recall from anatomy, those fimbriae. And so, literally, the fimbria capture, manipulate and guide the cells into the oviduct. How does the oviduct itself, contribute to the movement of these cells? Remember, these cells don't have any flagella or a means of propulsion. And they're not just going to roll down the oviduct. Because there is no down an oviduct. So, how then do these cells move through the fallopian tube? Well, they move because the oviduct has what? Cilia. And also, what?

>> Peristalsis.

>> Steve Langjahr: Peristalsis. And this process is slow and steady. But it is pretty reliable. Meaning, faithfully moving the cells toward the uterus. But it is very slow. How slow? How long does it take these cells to go from the beginning of the oviduct to an entry point in the uterus? Four days. So, that's about an inch per day. That's pretty slow. And why is that even worth commenting on? Well, the interesting fact is, that the ovum, despite its bonus supply of cytoplasm – remember how the ovum's got a line share of cytoplasm. Even despite that, it's viability, as far as we know, is less than a day. So, what does that mean? If an egg hasn't been fertilized within this window, then it's dead. Even though it continues to roll on toward the what? Even though it continues to roll on toward the uterus. So, with these two factoids, what about fertilization can we

really say? Well, first of all, it has to happen in the oviduct. It can't happen in the uterus. At least not on paper. Why can't it happen in the uterus? By the time the cells that have been ovulated are in the uterus, they've been dead for three days. So, fertilization almost always occurs in the oviduct. And usually that means then that the sex act or insemination, must occur no more than three to four days before ovulation. And certainly, no more than one day after ovulation. Which really means the opportunity for fertilization is actually kind of brief. But looking at world population, I don't think this has been any kind of impediment. In fact, we're lucky that it's that brief. Incidentally, I don't know I'm flashing on this, but what animal species is famous for lots of offspring?

>> Rabbits.

>> Steve Langjahr: Rabbits. And it's not coincidence because remember that LH surge we talked about? In rabbits, that LH surge is caused by copulation. So, what does that mean? Every time you copulate, LH surge. Bingo. So, luckily that's not the way it happens in humans. But you know, anyway, back to our story. Remember, we said that ovulation is not a singular event, but many cells have been blown out of the ovary. And so, literally, the ovum is surrounded by an entourage. Kind of like Madonna with a bunch of body guards. So, what has to happen, if all these sperm, which you consider sort of like paparazzi or autograph seekers. If they're going to get to the egg, they first have to get past what? All of these F words here. All of these follicle cells. It might seem counterproductive, literally. But there's no way around it. And again, we emphasize a single egg doesn't by itself just sort of dance down the oviduct. It's surrounded by this cluster of cells that got blown out at the same time. And so, these follicle cells have to be, what's the D word? They have to be dispersed, in order to gain access. In order to get close to the egg itself. Luckily, the sperm are equipped with a mechanism to do that. The sperm release a proteolytic enzyme, which dissolves some of the glue, which is holding and keeping these cells in contact with the ovum. And this is more than just interesting. Because isn't it technically true that it only takes one sperm to fertilize an egg? That's technically true. But yet, it takes millions to get the job done. Why does it take millions? Even though only one will get the privilege of actually fertilizing that egg? Well, it takes millions to do this, to disperse the follicle cells. So, men who have low sperm numbers, may in fact be infertile. Not because they don't have a single sperm. But because they don't have enough sperm to accomplish this step here, follicle cell dispersal. Once those cells have been dispersed, then the coast is clear, so to speak. And one sperm, who knows which one, certainly by chance, will actually have the opportunity to make contact with the cell membrane of this ovum. And it may not be widely known. And maybe it doesn't seem important to you. But the sperm itself does not go inside the ovum. After all, what's the goal here? We don't need to put a sperm inside an ovum. All we really need to do is inject what? What is the sperm carrying that needs to go in?

>> Chromosomes.

>> Steve Langjahr: The chromosomes. And so, that's called the male pronucleus. So, if you want to create a vision of what's happening here, all of the apparatus of the sperm is left at the doorstep. And the only thing that gets inside are the chromosomes. That's all we need. How many chromosomes are the sperm carrying?

>> Twenty-three.

>> Steve Langjahr: How many chromosomes is the egg carrying?

>> Twenty-three.

>> Steve Langjahr: Twenty-three. So, there you have it. In fact, anything but that, would be lethal. What do I mean? What if two sperm were to hit the cell membrane at the same time? And what if we shoot in 23 and 23? Then we'd end up with way too many chromosomes, right? And that would be catastrophic. Indeed, it simply wouldn't work. So, the interesting and amazing thing is, that when a single sperm docks and penetrates, something happens immediately to the area around the ovum, called the zona pellucida. It becomes hardened. And therefore, prevents access to and penetration by anymore sperm. Therefore, it prevents this word, polyspermia. What would that mean polyspermia?

>> Many sperm.

>> Steve Langjahr: Many sperm. polyspermia would be deadly and incompatible. So, in fact, only one sperm is allowed entry. Now, this might be confusing to some because they might say well, wait a minute. What about twins? Well, what about twins? What are the two kinds of twins that you know? What are the two designations for human twins? There's fraternal twins, which is certainly not polyspermia. What's the deal with fraternal twins? [inaudible answers]. Two eggs. Two sperms. Two different fallopian tubes, we don't know. Two different days. Two different fathers. All these things are possible. Am I making this up? No. Two different sexes, right? So, all you have there ultimately, are just well, I can't resist, womb mates. That is [brief laughter] two different events, sharing the same uterus. What is that called again? Fraternal twins. What's the other kind?

>> Identical.

>> Steve Langjahr: Now, identical twin is one egg. One sperm. One zygote. But then, very early, instead of doing its normal mitotic deal, it splits into two. And they develop separately. Thus, they have the same genes. Thus, they are what?

>> Identical.

>> Steve Langjahr: Identical. Identical in every way. So, anyway, polyspermia is uniformly bad and prevented by the hardening of the zona pellucida. So, remember what we've just described is the injection of the male pronucleus, which will make contact with the female pronucleus. And 23 plus 23 is what?

>> Forty-six.

>> Steve Langjahr: And so, we have restored the diploid number. The name of this entity, at this time, is called a zygote. A zygote. How many cells is a zygote?

>> One.

>> Steve Langjahr: One. One cell. But how's it different from the ova that was there a minute ago? [inaudible answers]. Instead of being haploid, it's suddenly diploid. And it's a new potential human being. And where physically has this happened? Where in the female's reproductive tract has this event occurred? Oviducts. And at what point in the menstrual cycle.

>> Midcycle.

>> Steve Langjahr: Midcycle. Is the woman aware of this occurrence? Does she have any clue that this has happened?

>> No.

>> Steve Langjahr: No. What's her earliest clue or at least at hint that something might be different?

>> Missed menstruation.

>> Steve Langjahr: Her first clue is still two weeks away. And what is that clue? Oh, I missed my period. All right. But by then, that's zygote has had how much time? Two weeks. And considerable things have happened in two weeks. So, let's carry on. This has happened at midcycle. And the cell we have here is a zygote. And it wastes no time. One cell becomes what? Two. And two become four. And four become sixteen. And 16 become 32. This is ordinary, rapid, amazing mitosis. Multiple mitotic divisions of the zygote, almost from the get go. And in the early stages, really nothing remarkable. In fact, these are mitotic divisions, which produce nothing bigger than what was the original zygote. It's just more cells. And so, the first recognizable or otherwise important stage, which occurs even before this unit reaches the uterus, is called a blastocyst. And what makes it different or remarkable or worthy of a name, is that it's not a solid ball of cells, but what? [inaudible answers]. A hallow ball of maybe 100 cells. And these 100 cells are no bigger than the original zygote, there's just more of them. The key word there is hollow. Hence the name blastocyst. A blastocyst is unremarkable. Except that it has the first clear-cut physiological distinction in these cells. And as you can see, here's a magnified view of a blastocyst. Which consists of two basic cell types. Those around the perimeter, which are called trophoblasts. And those that occupy the center, which are called what? Inner cell mass. Without getting into complex embryology, the trophoblasts will become the membranes. And structures which contribute to the development of the placenta. The inner cell mass, will become the embryo itself. Eventually, the fetus. Now, blastocysts are valuable, in a sense. In fact, blastocysts can be harvested, even frozen. Why would a woman produce a bunch of blastocysts, only to have them frozen in liquid nitrogen? Why would a woman want to put away a bunch of blastocysts?

[inaudible answer]. Okay, she wants to have another child by the same father, down the road. And are there blastocysts sitting in liquid nitrogen around the world waiting for that possibility? Sure. Can you take these blastocysts out, thaw them and stick them in an endometrium and hope for the best? Yeah, okay. So, this is the basis for essentially banking blastocysts. It's also a source of controversy. Because I know you've heard the term stem cells, as it applies to embryonic stem cells. And embryonic stem cells are these inner cell masses, currently residing in blastocysts. And during the Bush administration, you remember, Bush. He forbade – is that a word? I think it is. The government use of blastocysts for stem cell research. And I know I'm getting into political science here or certainly shaky ground. But his notion was that these were somehow sacred. And this would be killing life. And therefore, shouldn't be sanctioned by the U.S. Government. So, you may have your own opinion on that. But as soon as Barack Obama was elected, that went away. So, we are now allowing government funding for stem cell research. Using what source? Using these. And you might say well, that's terrible. You might say that's good. I don't know. But what's going to happen to these blastocysts if you don't do anything with them? [inaudible answer]. They're going to be thrown out. So, I guess it's just a matter of point of view. But I thought you'd want to know a background story about blastocysts. Never the less, let's resume to blastocyst. It's going to roll into the uterus, literally, at about day five. Does the woman know she's pregnant?

>> No.

>> Steve Langjahr: No. Now, the blastocyst is how many cells? One hundred. And does mitosis take up a lot of energy? And so, you could say this blastocyst is on it's last leg. Which you really can't because it doesn't have legs. But is it about ready to parish? Yeah. So, what's waiting and hopefully ready in the uterus, which will rescue. Which will really save this blastocyst from certain death is the status of that lining. What is that lining?

>> Endometrium.

>> Steve Langjahr: Endometrium. And is it ready? And if so, what is it ready with?

>> Glycogen.

>> Steve Langjahr: Glycogen, all right. So, the blastocyst rolls into the uterus at day five. Is the woman aware she's pregnant or any of this is going to happen? Again, five days, she's still got what? I don't know, 11 days left before she misses her period. So, anyway, what happens at this point, is that the trophoblasts secrete enzymes, which literally dissolve some of the surface cells of the endometrium. Trophoblasts secreting enzymes, digest or breakdown endometrial cells. And essentially create a pocket. Which is very much like planting a seed. How do you plant a seed in the garden? You dig a hole, throw the seed in and what? Cover it up. So, it's kind of like that. What digs the hole are the enzymes from the trophoblasts. Then the trophoblast falls into the

hole. And then it's covered up with cells. So, this process, what do you call it, the whole thing? I word.

>> Implantation.

>> Steve Langjahr: Implantation. And this is happening about six days after ovulation. Still at least a week before the first missed period. And what is the first order of business, after implantation? I mean, what is the desperate status of this blastocyst, as it's running out of energy. So, what's awaiting there is the glycogen. And so, that will rescue and provide nutrition for the early further mitosis of this blastocyst. Which never really stopped. But now is escalating with the supply of glucose. Now, the stages that happen in these early days are complex, mysterious. And we could devote a whole semester of study to. It's called embryology. And we'll skip that. So, let's fast forward to a developmental stage of some significance. Which is earlier than you think. But never the less, the creation of something very important called the placenta. Now, you think of a placenta as something commonly called the afterbirth. And you imagine this object being delivered after the baby. And indeed, it is a massive structure at that point. But early on, the placenta is very fragile, very feeble, very small. Its origin is from these cells called trophoblasts. Which at first, as we've said, release proteolytic enzymes. Which dissolve and breakdown endometrial tissue. And not only endometrial cells, but endometrial capillaries. Remember, the endometrium has a blood supply. And what happens to capillaries if you open them up? Bloods going to come pouring out. And so, what happens, as a result of this statement, is that the area around the blastocyst becomes flooded with maternal blood, maternal blood. So, now the blastocyst is literally surrounded by, not its own blood, but what? Maternal blood. What normally happens to blood when it's outside a blood vessel?

>> It coagulates.

>> Steve Langjahr: It coagulates. With that appropriate or good here? No. So, there are anticoagulants that prevent that. But never the less, the blastocyst is surrounded by blood. Now, notice these earlier outcroppings of the blastocysts, develop like roots, developing from an early plant in soil. And these projections are called chorionic villi. To me, as an analogy, it looks like a chia pet. I don't know if you've seen the commercials. But you know, those things you can buy and you water and grass comes out. So, anyway, a bunch of these projections, projecting into maternal blood pools. And this happening within the first month. Certainly, by this time, the woman's aware of what? She's pregnant. Why? Because her periods have been interrupted and rightly so. But never the less, at this point, the embryo is sending out blood vessels into these chorionic villi. Its own blood vessels. But this is important. The maternal blood pool, never really leaks in or makes contact with the embryonic blood. There's an interface there, but blood never what? Never mixes. Fetal blood and maternal blood never make physical contact, except and finally only when?

>> Delivery.

>> Steve Langjahr: At delivery. But all through nine months, these bloods are kept separate. That doesn't mean there isn't exchange. There is exchange. But blood cells never really move across this barrier. With that said, what are the functions of the placenta that persist and must be maintained for at leas nine months? First, the placenta provides an exchange site for gases. What gases does the embryo have to acquire? What gases does the embryo have to get rid of? Obviously, CO2 and oxygen. And an interesting question would be, why would the fetal blood have any greater claim or affinity to oxygen than maternal blood? What I'm saying is, why would oxygen from the mother's blood cells, decide to leave that and go into the baby's circulation? Well, it wouldn't. But the amazing thing about fetal hemoglobin, is that it has fetal hemoglobin has what? [inaudible answers]. A grater affinity. So, literally, it steals what? Steals oxygen from the mother's hemoglobin. And that's the only way that it's able to get enough oxygen. Because after all, a fetus doesn't have any working lungs. And even if it did, there's no air down there to breathe. So, fetal hemoglobin is the only way in which the developing embryo, later a fetus, can ever acquire enough oxygen. The rest of the story is pretty simple. Are there other commodities in the maternal blood that the fetus would benefit from? And are there commodities in the fetal blood that need to be disposed of or introduced into the mother's blood? Is it a two-way street? Yes. So, nutrient and waste exchange occurs across the placental interface here. So, in short, what's in it for the fetus? What's in it for the fetus? Maternal glucose. Maternal amino acids. Maternal FFA. What's that?

>> Free fatty acids.

>> Steve Langjahr: Free fatty acids. Does the maternal blood have antibodies? Would those be useful for the fetus? Well, yes and no. What does that mean? Does the fetus have any need for maternal antibodies, during its stay in the uterus?

>> No.

>> Steve Langjahr: No. Why not? [inaudible answers]. That's a sterile environment, right? So, what would be the benefit of antibodies that the mother made, reaching the fetus, as they do? [inaudible answer]. Yeah, important on the day of birth, right? So, it provides a head start. And then of course, the name of that is passive immunity, isn't it? Does the mothers blood have iron? Does the mothers blood have calcium? Does the mothers blood have various vitamins? All of which the fetus craves or otherwise needs for survival? Yes. Does the mothers blood have drugs that she may have consumed? Therapeutically or otherwise? Yes. So, any drug that might be in the mother's blood stream will end up in the baby's blood. Will nicotine get through and provide some sort of high or satisfaction for the fetus? Well, the answer is yes. What about cocaine? Yeah. What about heroine? All goes straight in. And how does it go in? What's the process by which these things enter or I should say fetal circulation? It's passive diffusion, from what? High concentration to a low concentration. Why does glucose move from mother's blood into fetal blood? High to low.

Why is it low in the fetal blood? Baby's using it. So, it's pretty natural, pretty ordinary, passive diffusion. What's in it for the mom? What does the mom get out of this? Well, nothing terribly useful to her. That is, the mothers blood picks up all the nitrogenous waste products. Creatinine, uric acid. But that's not really a burden. That is, what will the mother do with these, regardless of their source? Doesn't the mother herself make creatinine? Doesn't the mother herself make uric acid? And how are those dealt with, but certainly by the kidneys. So, in short, it's a good deal for the fetus. And essential, of course, for the growth of the fetus. But there's some good news. There are certain things that don't get through the placenta. And that's basically large proteins, such as albumins and so forth. Blood cells, certainly not. And most bacteria are too big. Now, let's be clear, there's not normally bacteria in mother's blood. But if there were bacteria in mother's blood, would they get into fetal circulation? No. And is that good? Yes. But viruses, as you know from microbiology, are way smaller than bacteria. So, can viruses because of their smaller size, get into fetal circulation? Yes. And what's a notorious and unfortunate virus that has this capacity and therefore leads to tragic consequences, is HIV. So, are babies born already infected, as a result of their mother's infectious state? Yes. The good news is, is that it's not obligatory. And statistically, the last time I looked this up, only about 25% of babies born to HIV positive mothers are actually themselves actually HIV positive. So, that means that this barrier is even pretty good at resisting what? Even pretty good at resisting viruses. So, that's good. The other thing to say about the placenta is that it's an endocrine gland. It's an endocrine gland. We've got to go at least five more minutes. It produces estrogen and progesterone. And what's the importance of estrogen and progesterone? Remember, what's keeping this fetus where it's at? What is it embedded in? What is it buried in? What is it dependent on, is the endometrium. And if anything causes estrogens and progesterone to decline, what's going to happen? [inaudible answers]. And that's called menstruation. And by any other name, that's called an abortion, right? That's called a miscarriage. So, is it important to maintain these estrogens and progesterone for nine full months? Yeah. So, let's skip ahead. What keeps this level of estrogen and progesterone so strong? Well, the early placenta, which at that point is called the chorionic villi, produces a hormone. Which you've heard of or should have heard of, called hCG. Chorionic gonadotropin. Chorionic gonadotropin comes from the early placenta. And its target is the ovaries. Specifically, the corpus luteum. It basically keeps the corpus luteum going for up to how long? And without that, how long would the corpus luteum normally last? How long would the corpus luteum normally go for?

>> Two weeks.

>> Steve Langjahr: Two weeks. But now it's going to go for up to what? [inaudible answers]. And is this important? Yes. So, hCG is the signal from the placenta, which tells the ovary, hey, we're pregnant here. So, let's keep that corpus luteum going. And this same hormone, naturally, like any hormone, will circulate around the female's body. And eventually be filtered by the kidneys.

So, will that hormone, at some point, show up in the urine of this woman? And would the presence of that hormone, in any urine, have some significance? It would tell you what?

>> You're pregnant.

>> Steve Langjahr: You're pregnant. And are there ways to detect this hormone that are cheap and easy? Yeah. Every time I go to the 99 cents store, I go on through the checkout stand, right there, pregnancy test, 99 cents. Yeah. I feel like I should just get some just to pee on them for fun [brief laughter]. I mean, 99 cents, I mean. I'm just sort of a product tester. But I mean, yeah, when these first came out, they were horribly expensive. Now, they're what, 99 cents. They're practically giving them away at theatres and stuff, I don't know. But anyway, if you have hCG, what does that mean?

>> You're pregnant.

>> Steve Langjahr: You're pregnant. If you don't, what does that mean? [inaudible answers]. You still might be pregnant. How can you still be pregnant and not have hCG? Well, you just haven't detected it yet, right? So, anyway, I'm sorry to bog down on that. Interestingly, hCG also suppresses maternal lymphocytes. Why is that important? Remember, this blastocyst is a foreign cell. Why is it a foreign cell? It's not mom. It's a brand-new set of androgens, right? And what is the lymphatic system trained to do or at least focused on doing is eliminating this. So, suppressing lymphocytes, pretty important to maintain the early survival of this early embryo. Now, the corpus luteum, as we said, will go up to three months. And it produces not only progesterone and estrogens, but also some androgens. But eventually it burns out. And if it burns out, what goes with it are estrogens and progesterone. So, the good news is, the placenta keeps up the faith there. And why do we need to keep up estrogens and progesterone? [inaudible answers]. Maintain the endometrium. And therefore, maintain the pregnancy. I don't know, I'm going to press this, but let's just go through it quick. Sooner or later we have something called, there's the word, parturition, labor and delivery, nine months. Amazingly well timed. Predictable, almost down to the day. Here's the story of hCG. It rises and gets really heavy. But then it almost disappears. Why is its level, after three months, almost unnecessary? It disappears to almost nothing. But why is that okay? what was the purpose of hCG? And why is its disappearance at three months okay? The purpose of hCG was to stimulate the corpus luteum and keep it going for three months. And what took over the responsibility of making estrogens and progesterone, after three months?

>> The placenta.

>> Steve Langjahr: The placenta. So, the function of hCG is limited to the first trimester. Estrogens go up in this fashion. Progesterone's go up in this fashion. Both of these effects smooth muscle, among other things. Estrogens tend to depolarize smooth muscle. Therefore, causing what? Estrogens depolarize

smooth muscle, therefore cause contraction. Progesterone tends to hyperpolarize smooth muscle. Therefore, what?

>> Relaxing.

>> Steve Langjahr: Relaxing it. What's the ratio of these two, according to these lines? Which one dominates throughout? Progesterone. Why are we happy about that? Why are we happy that progesterone is dominant over estrogen? Because that prevents the uterus from contracting too soon or too early. What then does happen at delivery? Well, there is at the end of gestation, a reduced sensitivity to progesterone. That means, the myometrium becomes less sensitive to progesterone. And therefore, more sensitive to what?

>> Estrogen.

>> Steve Langjahr: And what does estrogen do to smooth muscle? And so, what does the babies head do, in response to uterine contraction? [inaudible answer]. It shoves its face into the cervix, right? What does that do? The cervix has stretch receptors, which respond to guess what? Stretch. And those stretch receptors feedback impulses, action potentials, to the hypothalamus. Now, what does the hypothalamus have to do with this story? What hormone does the hypothalamus have that's going to be important here?

>> OT.

>> Steve Langjahr: OT, oxytocin. And that's going to reach the uterus. And what's the uterus going to do? Contract. What's the babies head going to do? [inaudible answers]. And what's that going to do to the stretch receptors? What's that going to do to the action potential back to the hypothalamus? What's that going to do to the oxytocin? What do we call this?

>> Positive feedback.

>> Steve Langjahr: Positive feedback. More, getting more, getting more. And what stops this cycle? What prevents this from going on endlessly, heaven forbid? [inaudible answers]. The baby is delivered, end of story. So, that's natural. Increased sensitivity, increased release of oxytocin, as a result of positive feedback. At the same time, we're getting prostaglandins from the placenta. Which further assists in this contraction. And also, perhaps of less importance, relaxin from the ovary. Relaxin softens the cartilage between the pubic bones. Why is that good? [inaudible answers]. Pubic bones fall away a bit. Therefore, bigger space for the baby to come out. Oxytocin is sometimes given in hospital settings. Why would oxytocin be given now, even though oxytocin is already there? [inaudible answers]. To stimulate. To make it more forceful. To expedite this whole thing. So, that everybody can get on with their day. And also, to deliver, not just the baby, but deliver what?

>> The placenta.

>> Steve Langjahr: The placenta. And prevent uterine bleeding. The end.