**Episode 7: Contraception – Part 2**

By Dr. Joe Chappelle

Hello everyone, and welcome back to the OB/GYN Podcast. Today, we are soldiering on with our contraception topic. In our last episode, we spent some time discussion the role of contraception in history and throughout society. I hope that I was able to illustrate how important access to contraception is, and how important it is to society and the future of our civilization. In today’s episode, I want to give an overview of the amazing biology behind ovulation and menstruation, and how some very smart people figured out how to highjack it to provide contraception. There is some great history here, so I hope you’ll indulge me if I spend a little extra time on it today. We will then move on to the different types of hormonal contraception that utilize these findings. So, let’s get started with Episode 7: Contraception – Part 2.

The menstrual cycle is an amazing series of interconnected feedback loops that reminds me of an intricate clock or watch. There are so many moving pieces and they interlock in these complex intricate ways to produce the pathways for human reproduction. The menstrual cycle really starts in utero, with the formation of eggs in the ovary. By 20 weeks of gestation, each female fetus has its entire lifetime supply of eggs, about 4 to 5 million. But the number decreases substantially, and by the time she reaches puberty, most women will only have about 180,000 eggs. These eggs are recruited in batches during each cycle, with only the fittest being utilized for ovulation. This means that of those millions of eggs that she started with each woman will use only about 400 of them during her reproductive years.

So, how does this process work? Well, I actually tried recording this next part a few different ways, and it was confusing no matter how I tried to organize it. It is just difficult to describe such a complex system without visual aids. With that in mind, I have linked to a couple of nice graphics that do a good job of visually explaining what I’m going to try to do verbally. So, if you can, you might want to look at those images while I go over it.

There are a few important players in this process that I want to introduce. The first is gonadotropin-releasing hormone, which is produced by the hypothalamus. GNRH, as it’s abbreviated, acts on the anterior pituitary to stimulate the release of follicle-stimulating hormone and luteinizing hormone. One of the interesting things about GNRH is that it is not just the presence or absence of it that matters, but rather how it is secreted. If it is released in pulses, then it stimulates production of FSH and LH. And if it released continuously, it inhibits the production of them. We also have estrogen, progesterone and inhibin acting at different times of the ovulation cycle to stimulate or suppress the production of FSH and LH.

So, those are the players. Now, how do they all come together? Well, at the beginning of each cycle, GNRH is released in a pulsatile manner, which stimulates the production of FSH and LH. The rising levels of FSH recruit a cohort of eggs to begin maturing. Each of these maturing follicles is surrounded by two types of cells: granulosa cells and theca cells. The theca cells are controlled by LH, and as the levels of LH rise throughout the early phase of the cycle, they stimulate the theca cells to make androgens, which are then converted to estrogen by the neighboring granulosa cells.

Okay, so, so far, we have rising FSH, LH and estrogen levels, which was all kickstarted by GNRH. Now, here is where things get interesting. The rising estrogen levels exert a positive feedback on the production of FSH and LH, causing their levels to rise further, which causes estrogen levels to rise further, and so on, and so on. The FSH levels, however, do not rise as high or as fast as LH because the estrogen effect on FSH is being counterbalanced by the release of inhibin, which is also made from granulosa cells. Inhibin actually has a stronger effect on the pituitary than estrogen, and so the net result is a slow drop in FSH levels. This is key to the egg maturation process, because it is controlled by FSH. As the FSH levels drop, all but the fittest egg in the recruited cohort atrophies, and we are left with one dominant follicle for ovulation.

So, here we are now, about mid-cycle. The FSH levels have slightly dropped, the dominant follicle is ready for ovulation and all we need is the trigger. The trigger is LH. Because LH has no negative feedbacks at this point, its levels rise quickly and culminate in a huge spike around day 10 of the cycle. This is known as the LH surge and causes release of the egg into the oviduct. The huge levels of estrogen now cross a threshold where they flip from being a positive feedback to a negative feedback, and the levels of FSH and LH both plummet. Exploiting this threshold is one of the keys to suppressing ovulation, and therefore, to hormonal contraception.

The remnants of the dominant follicle switch production from estrogen to progesterone, and this new hormone has two important effects. The first is to inhibit the pulsatile release of GNRH, which, thereby, suppresses FSH and LH even further. The second, is to prepare the endometrium for implantation if fertilization occurs. Progesterone does this by increasing blood flow to the newly formed endometrium, which was stimulated by estrogen in the beginning of the cycle. It also reduces the contractility of the smooth muscle of the uterus, which inhibits contractions, which could lead to expulsion of a newly fertilized egg.

Okay, so where are we now? We are slightly after ovulation. The FSH and LH levels are plummeting, GNRH is being suppressed, progesterone levels are on the rise and we are awaiting fertilization. Here, we encounter another piece of the clockwork. The progesterone-secreting corpus luteum is supported by LH, whose levels, you’ll remember, are now dropping quickly due to the actions of that very same progesterone. This death spiral for the corpus luteum continues unless the egg is fertilized and implants. This is because a newly implanted egg immediately starts to produce human chorionic gonadotropin, or HCG, which is structurally similar to LH and allows it to keep producing progesterone until the newly formed placenta can take over that roll at around 10 to 11 weeks. If no fertilization occurs, then the corpus luteum degrades and the progesterone levels drop. This causes the endometrium, along with the unfertilized egg to be shed and menstruation occurs. Once the progesterone levels fall far enough for GNRH to resume its pulsatile release, FSH starts to rise again, and the whole process starts over.

Now, wow. Like I said, it is an amazing process, but it is certainly not easy to explain succinctly. Each part of the process interconnects with the others in the most intricate ways. The more I learn about the human body, the more I am humbled. It seems that the further down we go, the more we learn how complex things actually are. Even the things that seem simple on the surface are controlled at the protein, gene and molecular levels in these amazingly complex ways. In any case, understanding the basis of the menstrual cycle is the key to understanding how hormonal contraception works, and what I find amazing is that the people who created the first hormonal contraceptives didn’t understand what I just laid out for you. In fact, it wasn’t even until 1975 that we knew for sure that estrogen and progesterone were synergistic in preventing pregnancy.

Now that we’ve laid the groundwork for the mechanisms responsible for hormonal contraception, let’s go back and talk about how we ended up with the pill at all. Well, the story starts with the corpus luteum, which was first described in the 1600s during autopsies of pregnant women. By the late 1800s, it was known to be important for pregnancy, and that it was histologically similar to other endocrine organs, suggesting that it secreted something. By the early 1900s, when a young physiologist from Austria, Ludwig Haberlandt began experimenting on rabbits, it was well known that whatever the corpus luteum secreted, it had some effect on menstruation.

Haberlandt spent years studying the corpus luteum, but his story really begins in 1919, when he began experimenting with transplanting this corpus luteum from pregnant rabbits into non-pregnant rabbits. He found that after transplantation, these rabbit recipients could not get pregnant for two to two and a half months despite regular intercourse. He then followed up these studies by feeding mice pieces of corpus luteum and placenta and found that they also could not get pregnant. Now he knew he was on to something. He still didn’t know what the corpus luteum produced, but he now knew that he could prevent pregnancy with it.

Haberlandt’s goal was really to provide contraception in the belief that it would create potentially beneficial societal effects. He wrote about his passion in his 1931 book on the subject, in which he wrote, “unquestionably, practical application of the temporary hormonal sterilization in women, would markedly contribute to the ideal in human society. Theoretically, one of the greatest triumphs of mankind would be the elevation of procreation into a voluntary and deliberate act.”

After his discoveries in mice and rabbits, he spent the remainder of his short life trying to recruit doctors to do human trial of purified hormones from corpus lutea. He was mercilessly hounded for his beliefs and was ultimately unsuccessful in his attempts to test his ideas in humans. His untimely death at the age of 47 from either a heart attack or suicide, would leave it to others to pick up where he left off, but his dedication to the idea of temporary sterilization would make him the father of modern contraception. His work would be continued by many others over the next 20 years. In fact, two separate groups would ultimately isolate what we now call progesterone from corpus lutea.

The first group consisted of George Corner and Willard Aller, who worked at the University or Rochester. As an interesting historical aside, in order to isolate it, they turned for help from the Eastman Kodak Company for some of the equipment. It’s interesting to think that the photography company also played an important role in our understanding of human fertility and contraception. Anyway, they called their newly isolated substance progestin and would end up butting heads with another group working in Europe, where two men, Butenandt and Westphal called their newly isolated substance luteosterone.

This naming controversy would be resolved in 1935 at a dinner party in London hosted by Sir Henry Dale, who was a renowned physiologist from England, who would himself go on to win the Nobel Prize for his work on acetylcholine. He was able to convince the two groups to combine their names and share samples. They would end up taking the beginning of progestin and the end of luteosterone and mashing them together to form progesterone, the hormone we have all come to know and love.

These early years of progesterone production were rough though. The yields were extremely low, and consequently the cost was high. They would start with one ton of cholesterol, in these days, that was only obtainable in large quantities from cattle brains and spinal cords, and after the initial processing, would only end up with about 20 pounds of the starting material for their reaction. The small quantities of progesterone obtained cost about $1,000 per gram in 1930s money, which would be about $14,000 per gram today. This obviously limited the amount of research that could be done, and we would need to wait for a cheaper process before Haberlandt’s dream could become reality.

This major turning point occurred in 1945 thanks to a chemist at Penn State University. His life story is worthy of an entire episode by itself, and I might to a bonus one to cover it in detail because it is that fascinating. In shorth, though, he found a way to convert a compound from the sarsaparilla root into progesterone. But the yield was low, so he then spent the next four years searching through the U.S. southwest and Mexico for a better starting material. He finally found it in Mexico, and in 1945 he started a company to make progesterone with his new process. He started selling it for $50 a gram, which substantially undercut the competition, which you’ll remember, was selling theirs for $1,000 a gram. His price would fall to $5 per gram within a few years, and this reduction in price finally removed the last barrier to research into progesterone, and from here on out, the progress moves fast.

With this newly found supply of relatively cheap progesterone, several people were able to prove that progesterone could suppress menstruation and ovulation. The one hang-up for human trials was that, at the time, progesterone could only be injected, and not taken orally. An orally available progesterone was first created by Carl Djerassi in 1949. He had developed a technique to make estrogen by aromatizing testosterone. When he applied this method to progesterone, he got a progesterone-estrogen hybrid that unfortunately had no biological activity. He then applied a brand-new chemical technique from an Austrian chemist to dearomatize his new compound and ended up with a modified version of natural progesterone that was eight times more potent than that progesterone, and more importantly, it was orally available. This was the first of the synthetic progesterones, and though it has gone through a few names over the years, today we call it norethindrone.

Before I continue with the story of progesterone, whose story is really the story of the first oral contraceptive, let me take a moment to talk about estrogen, Research on estrogen and its contraceptive abilities was being conducted at the same time but little attention was being paid to it. So little in fact, that people who did the first trials of OCPs had no knowledge of this work. Estrogen had in fact been isolated, and an orally available compound, estradiol, had been synthesized prior to progesterone by the same teams that worked on progesterone. Estradiol itself was used clinically throughout the ‘30s and ‘40s to treat menorrhagia and dysmenorrhea due to its ability to stop menstruation. Though they didn’t know it, these women were also getting contraception, but the idea of using estrogen as a contraceptive would not find a firm foothold until 1960 and its place in our story of oral contraception is quite by accident, which we’ll get to in a minute.

Now, back to progesterone. By the early 1950s, all the pieces for a hormonal contraceptive were in place, and all we needed were the players. This started with a physiologist, Gregory Pincus, who in 1937, had performed the first in vitro fertilization working with rabbits. Now, another dinner party comes into our story. This time it’s in Manhattan. Dr. Pincus would meet Margaret Sanger, the founder of Planned Parenthood. After discussing his work with her, he would receive a small grant from Planned Parenthood to start research into creating an oral contraceptive pill. His meager funding was amplified 50-fold by a one Katharine McCormick, a well-known women’s rights advocate and philanthropist, who at the time, like Sanger, felt that contraception was one of the keys to achieving their goals of gender equality.

After obtaining and testing progesterone samples, Pincus and his team recruited Dr. John Rock from the Women’s Free Hospital in Boston to begin clinical trials in women. At this time, there were three oral progesterones available: norethisterone, made by Djerassi, and noretynodrel and norethandrolone, both made by Frank Colton at a company called Searle in Illinois. They found that doses above 5 milligrams for the first two and any dose for the last suppressed ovulation, but at doses lower, there was considerable breakthrough bleeding. The group ended up choosing noretynodrel for their first largescale study because it had no androgenic activity compared the small amounts in the other two compounds.

As one of the quirks of fate, they found that their chosen progesterone was actually contaminated with about 7% mestranol, and estrogen, which was an intermediate in the synthesis. This team asked Colton at Searle to purify his hormone, and when they tested a sample that had less than 1% contamination, they found that it worked as well as the original sample for contraception but led to increased breakthrough bleeding. So, when they started their trial in Porto Rico in 1955, they purposely added 2.2% mestranol to their pills to prevent breakthrough bleeding and increase acceptance of the pill. Up until 1975, when the synergistic effects of estrogen and progesterone were solidified, all OCPs had estrogen in them, not for contraception, but to prevent breakthrough bleeding.

The successful trial in Porto Rico led to the first FDA approved pill in 1960, called Enovid 10. The doses of hormones in Enovid and those that followed were in order of magnitude higher than today, because they did not know at the time that they could use much lower doses when using estrogen and progesterone together. These high doses were responsible for severe side effects and at least three deaths due to blood clots in the trial. There has been considerable controversy about the Porto Rican trial, because the women were not educated or informed about the potential risk, or even that they were participating in a trial of a new drug.

Before I move into the different types of pills and their efficacy, let me take a minute to talk about estrogen only OCPs. These actually existed for a short time, but as any gynecologist today can tell you, unopposed estrogen is generally a bad idea. These pills had a host of side effects, including nausea and headaches amongst others. And also carried an increased risk of breast cancer and uterine cancer. These pills were quickly killed by the FDA and never appeared on the scene again.

So, how exactly do combined hormonal contraceptives work? Well, there are actually several actions going on at once. The first is progesterone which, as we described before, suppresses the pulsatile secretion of GNRH, which severely reduces the amount of FSH and LH produced by the anterior pituitary. This inhibits both the recruitment of eggs during the follicular phase and stops ovulation from occurring as well. The lack of follicular development also means that there is less estrogen to positively feedback on LH, which gives us two mechanisms for stopping ovulation, even if follicular recruitment occurs.

The progesterone also alters the mucus secreted by the cervix, making the mucus more viscous, which inhibits the penetration of sperm through the cervix and into the uterus and fallopian tubes. The estrogen in most pills is high enough to negatively feedback on FSH and adds another suppressive mechanism. Estrogen also has one other effect that was noted by Pincus and his team. Estrogen stabilizes the endometrium and reduces the amount of breakthrough bleeding that is associated with progesterone-only contraception.

Each OCP has the same estrogen, ethinylestradiol, which was first made in 1938 and started to replace mestranol in OCPs in 1964. Different OCPs do have different progesterones, which can have different side-effect profiles, but which mainly differ by their androgenic activity. There is even one progestin with antiandrogenic activity, drospirenone, which also, unfortunately, conveys an increased risk of blood clots as compared to the other synthetic progesterones.

I should also mention that there are two non-oral forms of combined contraception in the forms of the patch and the ring. For all intents and purposes, they work the same. I will only mention the patch to say that it’s been associated with higher risks of blood clots and should be used cautiously in women with a baseline increased risk.

The low and low-low pills are named in reference to the amount estrogen. As I mentioned, there are many different ways that pills prevent pregnancy, and we have learned that given the synergistic effects of estrogen and progesterone, that we can use much smaller doses of estrogen without a significant decrease in efficacy. These lower-dose pills do come with a downside. As you’ll remember, estrogen was initially put into the pills to decrease the amount of breakthrough bleeding, so you can probably guess what the consequence of lower estrogen dosage is: increased breakthrough bleeding.

What is the upside to lowering the estrogen dose? Well, many of the side effects we’ll talk about in a second are due to estrogen, and estrogen is also the major cause of blood clots. So, it makes sense that decreasing the amount of estrogen may be beneficial. This is also the rationale behind the multiphasic pills, where the amount of estrogen is varied by week in order to decrease the overall monthly dose. As a note, there is no evidence that low or low-low pills are any safer than the normal strength pills. But if you do have a patient that is very sensitive to estrogen, low and low-low pills may be appropriate.

Alright, so I mentioned side effects. What are they? You probably won’t be surprised to know that the most common side effect is breakthrough bleeding, with women taking the pill having about 32% more spotting compared to those using other methods. Other common side effects include nausea, vomiting, headache, bloating, breast tenderness and swelling. More serious side effects include blood clots and worsening of hypertension. This is why combined oral contraceptive pills should be avoided with women with an increased risk of blood clots, such as those who smoke and those with hypertension. Women who have classic migraines with aura also are encouraged not to use estrogen-containing pills due to an increased risk of stroke.

Lastly, I want to touch on OCPs and cancer. Birth control pills, at least modern ones with their lower doses, have not been found to increase the risk of breast cancer. They have, however, been found to decrease the risk of endometrial and ovarian cancer if taken for at least five years.

Now that we have spent a considerable amount of time talking about how we got here and how the pill works, we should talk about how effective they are at preventing pregnancy. As it turns out, that is a slightly difficult question to answer, because it comes down to how well a woman uses it. If the pill is taken every day without missing any, only 0.3% of women will get pregnant within one year, compared with 85% of women using no method. As a callback to the last episode, remember that only 4% of women will get pregnant when using the withdrawal method perfectly. Some methods are easier to use perfectly than others, and what researchers talk about is typical use. For typical use with the pill, the pregnancy rate is about 9%, while typical use with the withdrawal method is 22%. Big difference. Now, they’re both still much better than no method, which is 85%, but I don’t think anyone will argue that the pill is far superior.

So far, we’ve been talking about combined estrogen and progesterone pills because that is how they were first marketed. There are however progesterone-only forms of contraception as well. These take several forms, from pills to shots to implants. The pills work by inhibiting ovulation, but only about 50% of the time. So, they also rely on the cervical mucus action we talked about before. The progesterone-only pill is about as effective as the combined pill when taken perfectly, which for these pills means taking the pill at the exact same time every day. This is in contrast to the combined pill, which has much more leeway in doe timing.

The other forms of progesterone-only contraception have much higher doses and therefore suppress ovulation more reliably. The Nexplanon subdermal implant suppresses about 97% of ovulatory cycles and the Depo-Provera shot eliminates about 100%. They also both have the same effects on the cervical mucus, which make them very effective forms of contraception. These high doses of progesterone do come with drawbacks though. For the Nexplanon, it is breakthrough bleeding, with approximately 80% of women having irregular bleeding for the entire 3-year life of the implant, and 7% reporting frequent bleeding. Bleeding is not a common problem with Depo-Povera shot, however. Well, at least not after the first few months. But rather, weight gain and loss of bone mass are associated with prolonged use.

I should also mention that progesterone-only treatment has been associated with worsening of underlying depression and should be used with caution in women with major depressive episodes. The allure of these two methods is that perfect use is easier to come by because they either live inside the person or are given by a healthcare professional every 12 to 14 weeks. For Nexplanon, the pregnancy rate is 0.05% and for Depo 0.2%. There is one other caveat for these two methods that is worth mentioning. For both, body mass is a huge influence on pregnancy rates. The higher the BMI, the lower the effectiveness, and all these progesterone-only methods should be used carefully in obese women.

The last hormonal contraceptive I want to talk about today is breastfeeding. As I mentioned in the last episode, this is the most ancient form of birth control. Breastfeeding works via a similar mechanism as progesterone. When the infant suckles the nipple during breastfeeding, the stimulation causes the posterior pituitary to produce prolactin. Prolactin, as the name implies, is essential in stimulating the breast to make milk. It also has the added effect of suppressing the pulsatile release of GNRH and decreases estrogen levels. Breastfeeding can be highly effective in the first six months of life if it is done exclusively. In fact, only about 1% of women will get pregnant using this method. If not breastfeeding exclusively, or when food starts to be introduced at around six months, the effectiveness drops quickly, and a backup method should be used.

In what will become a theme for today’s episode, each of the birth control mentioned today come to its own set of pros and cons. And the interesting part for providers is getting to know the women we care for and to recommend what we think best fits their needs and lifestyles. As you can see, there is a lot of information for women to soak in when thinking about contraception.

To get on my soapbox for a minute, I want to address the idea of nondirective counseling. This is the concept that you give people all the information they want and then let them decide what to do without steering them towards any one particular method. Frankly, I think that nondirective counseling is wrongheaded in most situations. In fact, I think the opposite is true. We practitioners spend so much time learning about not only the underlying physiology, but also the particular benefits and side effects of procedures and medications. Our patients come to us for exactly that knowledge and experience.

I often take the analogy to an accountant. If I go to an accountant to get my taxes done, I expect them to know all the ins and outs of the tax code and come up with the best solution for my taxes. Now, of course I want them to explain all the consequences of the choices, and of course the ultimate choice is mine. But at the end of the day, I want them to say, “I recommend you do this.” I think that our patients except the same of us. I do, however, also believe that we need to be very careful and always make sure that we are recommending what is best for them and not what is best for us.

To sum up today’s episode, I just want to say again how fascinating and amazing the complex interplay between hormones is in the human body. Only slightly less impressive are the people who figured out how to hack that system to provide contraception. My hat goes off to Ludwig Haberlandt and Margaret Sanger for believing in the transformative effects of contraception on women’s lives and for their role in bringing us the future that we live in today. I firmly believe that they and my mentor, Dr. Gentile, would’ve been fast friends, for they shared the same passion.

What is a little disheartening, however, is that almost a hundred years after Haberlandt started his crusade, that people like Dr. Gentile are still needed to carry that banner forward. I imagine that he hoped that by the early 21st century, that access to affordable and effective contraception for all women in the world would no longer be something that people even talked about. It would be taken for granted. So, I am sure that he would also tip his hat to Dr. Gentile and to all the people like her all over the world who dedicate their lives to making that dream a reality.

And on that note, I think I’ll stop here for today. I hope you enjoyed our trip through history with the little pill that could. And I hope that you will join me again on the next episode, where we’re going to talk about barrier contraception and IUDs.

On a technical point, I want to let everyone know that I have added this podcast to both the Google Play library as well as Stitcher. So, if you know anyone who uses those, please consider recommending the show. Also, and I hate to do this because it feels weird to ask people to promote your show for you, but if you do like this show, please consider leaving a review on iTunes or wherever you listen, because it does help new people find the show. And with all that done, I say happy New Year, and thanks for listening.