**Episode 22: PCOS – Part 1**

By Dr. Joe Chappelle

Hello everyone, and welcome back. I’m Joe Chappelle and you’re listening to Episode 22 of the OB/GYN Podcast. Before we get started with today’s topic, I want to thank all of you who sent in an email about post-caesarean pain management. And if you haven’t had a chance to send something in, please take just a minute and write in to feedback@obgyn.fm with how your practice or hospital manages pain after a caesarean delivery in both the immediate setting and once the woman goes home. Once I get enough responses, I’ll put them together into a little show and I’ll share all that knowledge back with you. But today, we’re going to start a new topic. That is, polycystic ovarian syndrome. I think it’s fascinating. It’s also, however, extremely complex. So, bear with me, and I hope I can do a good job with it. So, let’s get started with Episode 21: Polycystic Ovarian Syndrome – Part 1.

As I said, this is a complex topic, and we could choose one of any multiple entries into this story. But by the 1920s, it was well established that women with oligomenorrhea were sub- or infertile. There was, however, a subset of this women with no menses or amenorrhea that had gone relatively unnoticed and unstudied, and that is where I’m going to start my story today.

In 1935, Drs. Stein and Leventhal published a case series in the American Journal of Obstetrics and Gynecology, in which they reported on seven women with amenorrhea and infertility, and I want to dive right into one of those cases. They wrote, “Case 1. M. G., aged twenty-two, married one and a half years, gravida 0, was first seen Oct. 3rd, 1928. Her chief complaints were sterility and amenorrhea. Menses began at age thirteen, irregular, two to seven months, five-day duration, moderate, no pain.” She was treated with IM estrogen to regulate her menses for several years. And then, the story picks up in November of 1929. “Menstruated about every seven weeks. Examination reveals minor obesity and slight struma.” An examination revealed a normal sized retroverted uterus and a palpably cystic right ovary. The authors then performed a transabdominal pneumoperitoneum x-ray, which showed very cystic and enlarged ovaries. The authors then went on to perform a laparotomy and wedge resection of both ovaries. As a historical note, that woman remained in the hospital for twelve days after her surgery. That’s a long time by today’s standards. In any case, the woman began having monthly menses one month after the surgery and went on to have two children. And four years later, was still having normal menstruation.

I think that most of us would immediately recognize this presentation as being polycystic ovarian syndrome, and the other six women presented are similar. Now, before I really start breaking this down, I want to spend a moment talking about that transabdominal pneumoperitoneum x-ray, because it’s something I’d never heard of before. In fact, the author of the paper I was just quoting was one of the firs people to describe its use in gynecology. His description of the technique is as follows. First, a woman is given a high enema to remove fecal matter from the colon. Then, she is given Demerol for pain and a urinary catheter to drain the bladder. A small incision is made to the left of the umbilicus and a 20-gauge spinal needle is inserted into the peritoneal cavity. 500 ccs of carbon dioxide is used to insufflate the abdomen to a pressure of 10 to 20 millimeters, Now, as a side note, all of this should sound familiar to laparoscopists. And then, the woman is placed into a modified knee-chest position and x-rays are taken of the pelvis. The CO2 allows the outlines of the pelvic organs to be visualized, and therefore, can give an idea of the relative size and shape of the uterus and ovaries.

In a time with limited imaging modalities, this technique was very useful for deciding who would benefit from laparotomy. This technique was eventually eclipsed by the use of the pneumoperitoneum to directly visualize the structures, and as I mentioned, you can see the genealogy of laparoscopy in the methodology they used here. This is not very important to today’s discussion, but I just couldn’t pass up the opportunity to share that little historical nugget. Anyway, let’s go back to PCOS.

Here we are in the late ‘20s, early ‘30s, and people were starting to realize that women with irregular menses and infertility had similar ovarian findings and could be potentially helped by a wedge resection of the ovary. Stein and Leventhal were unsure why this helped. They wrote, “The ovarian change in bilateral cystic ovaries is most probably a result of some hormonal stimulation and very likely related to the anterior lobe of the pituitary gland.” They continue, “Oddly enough, the surgical treatment directed to the ovary in our series adjusted the endocrine balance to the extent of restoring normal menstruation and reproductive function. Theoretically, one would expect that if the cystic portion of the ovary were removed without also removing the abnormal stimulus which produced the ovarian change, the same factors would still be operative, resulting in reformation of the polycystic change. Thus far, this has not been our experience.”

I’m going to keep quoting from them because there is no way I could sum up the mystery of PCOS better. They continued, “Whenever one attempts to correlate the function or dysfunction with the structure of any of the endocrine glands, one is apt to encounter grave difficulties. The association of amenorrhea with polycystic ovaries in our series is no exception to this statement. The pathologist is unable to conclude from a study of the sections taken from the ovaries in our patients that amenorrhea was a symptom. He can demonstrate no anatomic structure or characteristic change in the ovary which enables him to describe the clinical picture. The only consistent pathologic finding is the presence of follicle cysts lined by theca cells. The fact remains, however, that when we remove the cystic portions of the ovary, normal function is restored to the sex apparatus.”

What they are describing is the very definition of a syndrome. A constellation of signs and symptoms that are associated with a phenotype. This means that we do not know the underlying cause, and in fact, there might be several different causes, all converging on a similar phenotype. For another example of this, you can think of the short cervix in pregnancy. In practical terms, this means that it makes it difficult to even ascertain what the underlying mechanisms are, because first we need to be able to split them into neat boxes for research purposes. Over the years, we’ve actually managed to do this a little bit, and I’ll get there. But it’s important to understand what a barrier this is in both research and clinical terms.

Stein and Leventhal’s work resulted in a syndrome of amenorrhea and cystic ovaries being named after them, and their approach of laparotomy and wedge resection being one of the primary treatments for the next two decades. In their 1935 paper, they mostly focused on amenorrhea, but didn’t mention that some of these women displayed signs of masculinization. Stein kept working on PCOS, and by 1945 had expanded his work and his description of the signs and symptoms starts to include items we still use today. In his 1945 paper in AJOG, he defines the syndrome as follows. “The characteristics of this syndrome are menstrual irregularity, featuring amenorrhea, a history of sterility, masculine type of hirsutism, and less consistently, retarded breast development and obesity.” This was the first time that we really had hirsutism being named as a main component, and he states that about 50% of the women that he cared for presented with some form of it.

As far as diagnosis at this time, Stein recommended history and physical exam as the main elements, focusing on menstrual pattern, infertility, hirsutism and abnormal development of the breasts. If some or all of these findings were present, he recommended the pneumoperitoneum x-ray, which he now call gynecography, to confirm the presence of cystic ovaries before proceeding to laparotomy for treatment. To give you an idea of how varied the presentations were, he studied 53 women, 43 had amenorrhea, 5, irregular bleeding, 25 were hirsute, and 6 were obese. And after treatment with wedge resection, none of the women had a recurrence of cystic ovaries.

For me at least, it is hard to make a whole lot of sense from this. The only thing that seems to tie all these women together are cystic ovaries. But how did they get that way? Why are there different symptoms? And why does removing part of the ovary fix the symptoms, never to return again? Dr. Stein thought it had to do with recruitment of follicles. We already discussed how this process works in the contraception episodes, and so I won’t go through it again. But he thought that somehow, many follicles were being activated at once and then getting stuck in a half-matured state. He hypothesized that this layer of half-mature, non-functional follicles created a physical barrier to the normal maturation of follicles. To him, this made sense, because when this layer of abnormal follicles was removed, normal function was restored. Alternatively, perhaps, these multitude of cysts, produce some substance or hormone that affects the menstrual cycle. Unfortunately for both Dr. Stein and us, the answer is not that easy, as we’ll see.

By 1958, when the other half of their duo, Dr. Leventhal, wrote a review for AJOG, they had already started to tease apart some of the cases by attributing them to other causes. By then, it was known that women with severe virilization most often had congenital adrenal hyperplasia, as diagnosed by urinary 17 alpha-hydroxyprogesterone. In the same paper, he also summarized the advances in the hormonal studies in the previous ten years. He presented data from a group at Iowa University. They found that women with PCOS had low or normal FSH but elevated LH. Interestingly, at the time there was no way to directly measure these compounds, and so they devised an ingenious experiment.

They took urinary samples from each women and extracted the gonadotropins. These extracts were then injected into immature female mice. The mice were then sacrificed, and the ovaries examined histologically. If the theca cells were stimulated to hypertrophy, with little stimulation of the granulosa, this was considered a primarily LH in character. If the reverse were true, with the formation of many cystic follicles, the extract was considered to be primarily FSH. Now, hardly ironclad evidence, but a brilliant hack to get at the underlying cause.

Next, he got the reader up to speed regarding the androgenic effects. Given that about half the women with PCOS had hirsutism, many thought that part of the problem might arise from the adrenals. The discovery of congenital adrenal hyperplasia served to squash this theory, because the levels of 17 alpha-hydroxyprogesterone were normal in these PCOS women, which means that Leventhal and his contemporaries were stuck with the LH theory, which even they found inadequate.

Now, I want to take a break here for a second and talk about the treatment during these early times. Leventhal and Stein, as we already discussed, advocated for surgical treatment given the strong results they observed in terms of fertility. Leventhal in particular cautioned that all other potential causes should be ruled out before laparotomy was performed, given the risks associated with the procedure, and it was because of these risks that other treatment modalities were explored. The most notable of which was irradiation of the ovaries.

The primary proponent of this modality was Dr. Ira Kaplan from New York. Starting in the mid-1920s, he started treating women with the same complaints as seen by Stein and Leventhal. Whereas they chose laparotomy and wedge resection, he chose to use x-rays. 75 to 150 rads were applied to 4 areas in the pelvis once per week for 3 weeks. In his 1937 paper, he describes the outcome in 128 women. 76 of the women started menstruating normally again, and 44 became pregnant, with 17 doing it more than once. These pregnancies resulted in 47 living children, 9 miscarriages and 1 stillbirth of an abnormal fetus. The children were followed for up to 10 years and were all normal. They also reported no adverse effects to the mothers due to the radiation. Like the wedge resection championed by Stein and Leventhal, the mechanism of action was unknown, but it appeared to work.

Although radiation didn’t work as well as wedge resection, it also didn’t require surgery, and both were in use through the ‘30s and ’40s. Kaplan acknowledged that radiation therapy had a bad reputation, and this was even before Hiroshima, after which radiation became to be very feared. After World War II, the use of radiation for the treatment of PCOS fell out of favor and completely disappeared from the medical literature, most likely due to the two nuclear bombs dropped by the U.S. in Japan and the horrific aftereffects from radiation poisoning that were documented. This meant that until we knew more about the etiology of the syndrome, that we were stuck with brute force methods of management, such as the wedge resection.

Speaking of etiologies, the early ‘60s brought with it new studies and new theories. Dr. Short in London from England, published a small trial where they obtained ovarian cyst fluid from both PCOS and non-PCOS women and determined the relative amounts of progesterone, 17 alpha-hydroxyprogesterone, androstenedione, estrone and estradiol. They found that women who fit the clinical definition of PCOS, or Stein-Leventhal syndrome as it was still called, had much lower concentrations of estrone and estradiol and much higher concentrations of the androgens. This lead them to believe that a defect in the conversion of androstenedione to estrogen was the primary cause of PCOS, and they were further encouraged because androstenedione can cause hirsutism.

Further studies during that decade found that the LH levels in these women had a much higher baseline than the unaffected women and much smaller spikes. But other studies in the early ‘70s found that some women with all the hallmark symptoms had completely normal LH, and so the mystery, confusion and arguments continued. In the mid ‘70s there came a breakthrough that would not only change the way we think about PCOS, but also would fundamentally change medicine to its roots. Things we do every day are the result of it, but yet we hardly think about, and most don’t know anything about it. What I’m talking about is radio amino acids. Not what you were guessing, was it?

Well, it is just important, as I stated, and the pioneering work was done by Rosalyn Yalow and Solomon Berson in the 1950s. They were actually studying insulin when they came across their breakthrough. At first, they just wanted to know what happens to insulin when diabetics inject it. So, they added iodine-125 to bovine insulin and found that the longer the patient had been using the insulin, the longer it stayed in the body. They hypothesized – correctly, I might add – that the cattle insulin was causing an immune reaction in these patients and slowing down the metabolism of the insulin. This led them to an aha! moment. So, they created an assay where known amount of radio labelled hormone or other substance of interest was bound to antibodies. This mixture was then added to the patient substance. The key here is that these antibodies would much rather bind to the non-labelled substance, and so the antibodies will dissociate from the radio-labelled versions and bind the naturally occurring variant. The antibody pairs are then isolated, and the radioactivity is measured, and the difference between before and after can be used to calculate the amount of the studied substance.

This was huge. For the first time we had the means to directly determine the amount of hormone in a given sample. Prior to this, all our methods had been roundabout ways and required large investments in time. Now, in a matter of hours you could get an answer. This work would get Yalow the Nobel Prize in 1977. Berson, unfortunately, died in 1972, and therefore Yalow went to Stockholm by herself, but did name her lab after him, so that his name would continue to be on all of her work for the rest of her career. I know this was a tangent, but this is the kind of medical history I love, and I wanted to share it with you.

In any case, let’s get back to PCOS and let’s see what her work accomplished. One of the more interesting papers is from Howard Judd et al. in 1976. Using these new tools, they measured estrogen, androgen and LH/FSH levels in women with PCOS before and after wedge resection. What they found was that wedge resection caused an immediate reduction in androstenedione and testosterone, with no difference in LH and FSH. In the women afterwards who ovulated, there was a spike in LH midcycle, as one would predict, along with a preovulatory rise in estrogen. This team suggested that due to the lack of change in gonadotropins, that their assumption of ovulation due to wedge resection must be due to changes in the ovaries themselves, and that the abnormalities seen in the hypothalamic hormones is due to the miscommunication between them and the ovaries. So, now we’re starting to see that it was the ovaries most likely causing the issue and not the hypothalamus.

The second paper that starts to illuminate this complex process is one by Gregory Erickso et al. from 1979. They looked at the ability of granulosa cells to aromatize androgens into estrogen. As you’ll remember, there are two main types of cells in the ovarian follicles. The theca cells produce androstenedione and then the granulosa cells aromatize it into estradiol. They found that when FSH is added to granulosa cells cultured after wedge resection, they responded appropriately and concluded that in women with PCOS, that they many small follicles are stuck at a stage before they normally start to produce significant amounts of aromatase. This results in a large amount of excess androstenedione and low levels of estrogen. What they could not figure out is why the cells were not responding appropriately to the otherwise normal levels of FSH. And the breakthroughs into this question wouldn’t happen for two more decades.

A series of papers from 1996 to 2007 found that androgens that had been reduced by 5-alpha reductase can cause follicular arrest and leads to increased ovarian androgen production in the theca cells. Hyperinsulinemia also was found to contribute to hirsutism by decreasing hepatic sex hormone production, which thereby increases free testosterone, which as you can guess, leads to worsened hirsutism. Insulin also turns out to be a major contributor to the follicular arrest, which leads to polycystic ovaries. Several papers from the early 2000s found that excess insulin causes follicles to luteinize prematurely by causing the granulosa cells to differentiate and respond to FSH too early. This arrests cell proliferation and growth and leaves them stuck in the small state we often see in these women. Additionally, as we discussed a moment ago, these small time-frozen follicles don’t produce estrogen in meaningful amounts. But as these researches discovered, they do continue to produce anti-mullerian hormone, which also has an additional antagonistic effect on FSH action on those very same follicles. What we see here is a negative feedback cycle, which results in persistent anovulation and hyperandrogenism.

So, now that we know what the underlying mechanisms are in the ovaries and the other systemic effects, we still don’t understand what the inciting agent is. We know there must be at least some genetic component, because if a woman is diagnosed with PCOS, then about a third of her first-degree female relatives will also have it. What that gene or genes are, we don’t know. And to make it even more confusing, there is likely a component of incomplete gene penetration at work as well. And lastly, in women with low penetration, it is possible that environmental factors may push that woman over the edge into PCOS.

This variability in presentation makes it difficult to pinpoint a concrete set of diagnostic criteria. But of course, that doesn’t stop people, and the first consensus attempt was in 1990 by the NIH and NICHD. The focus at this time, especially in the U.S., was on the biochemical aspect of the syndrome, and so they leaned heavily on that. The agreed upon criteria ended up being oligoovulation, signs of androgen excess and the exclusion of other disorders that can result in menstrual irregularity and hyperandrogenism. Well, if you are paying attention, you might see that something is missing from this diagnosis, namely, the presence of polycystic ovaries. The other thing that wasn’t included in the NIH conference were their European colleagues.

So, in 2003, the European Society of Human Reproduction and Embryology, and the American Society of Reproductive Medicine held a meeting in Rotterdam to come up with their own criteria. They recognized the overall lack of knowledge and decided to be much more inclusive. They therefore chose oligo- or anovulation, excess androgen activity, polycystic ovaries by ultrasound, and with only two out of the three needed to make the diagnosis. These two definitions emphasized different aspects of the syndrome.

To quote from a Nature Review article in 2011, Goodarzi et al. wrote about the NIH criteria the following. “It makes PCOS a hyperandrogenic disorder of exclusion, with an ovarian etiology and/or consequences.” It continues, “The 1990 NIH and Androgen Excess-PCOS Society criteria emphasize hyperandrogenism, which is closely interrelated with hyperinsulinism, which makes these definitions valuable in understanding metabolic dysfunction in PCOS. The Rotterdam criteria are useful for the diagnosis of PCOS in ethnic groups who do not exhibit clinical hyperandrogenism.”

This push and pull between narrow and broad definitions, is a familiar issue in medicine, especially when dealing with syndromes. In the early days, as I mentioned, congenital adrenal hyperplasia was included under this umbrella, but as we learned more about the underlying molecular pathways, we moved things out from underneath that umbrella. That being said, the Rotterdam criteria are probably the most widely used, so let’s dive into them a little bit more.

Let’s start with androgen excess. First off, if the woman has obvious signs of hirsutism, then it is not necessary to do any biochemical tests, but if absent, then total and free testosterone, as well as DHEAS levels can be evaluated. It’s important to note that these tests are very variable and a 2006 survey of 25 different labs found 12 different methodologies and reference ranges that differed by up to 350%. Therefore, it is important to use a lab with good quality data or, if available, a reference lab. Second, is oligo- or anovulation. Again, if the woman has irregular menses or amenorrhea, then no further testing is needed to verify an abnormality in ovulation. If, however, the woman reports regular menstruation but still has signs of androgen excess, then a luteal phase progesterone can be performed to verify ovulation, as approximately 40% of these women will not ovulate despite regular menses. Next is a sonogram to evaluate for the presence of polycystic ovaries, and that’s pretty straightforward. Last is an evaluation for other causes, such as hypothyroid, hyperprolactinemia and non-classic adrenal hyperplasia, which can best be evaluated by obtaining a morning 17 hydroxyprogesterone level during the follicular phase of the cycle. If elevated, then an acute adrenal stimulation test can be performed to rule it out.

Using the Rotterdam criteria, if two out of the three are present, then a diagnosis can be made, and we can start working on the management, which I’m going to hold off for the next episode. In many ways, PCOS reminds me of the onset of labor. We have learned so much about the underlying mechanisms but still don’t know what the inciting agent is. And then even when it starts, it takes on all shapes and sizes. I’m confident that we will someday get there, but until then, I agree with the Rotterdam approach, and let’s keep the diagnosis broad. In reality, it’s not much of a diagnosis anyway, because what we end up treating are the symptoms. In the next episode, we will get into the long- and short-term consequences of PCOS and how we can go about managing them. Like so many things in medicine, a good and thorough medical history can get you most of the way towards a diagnosis, with labs and imaging confirming the initial impression.

I hope you all enjoyed this journey down the history and diagnosis of PCOS, and I hope you’ll join me next time for the management. So, until then, thanks for listening.