Adnexal Mass Risk Assessments: Do Algorithms Improve Care?

OnMedicalGrounds

PODCAST 8

Dr. Jill Sellers:
Welcome to the *On Medical Grounds* podcast. I'm Jill Sellers, your host. *On Medical Grounds* is a casual, friendly place where you can find an authentic, audible blend of timely scientific and medical knowledge. We talk with experts about their experiences and knowledge, the utilization of new therapies and challenges within the world of healthcare. Select podcasts offer continuing medical education credits for those of you needing an additional why you should listen. We provide perks to all posted podcasts by linking content so you can drink in more if you so choose.

Assessing, diagnosing, treating and monitoring adnexal masses can be complicated, yet our guest today will simplify it for us. Dr. Laura Hanks is a board eligible OB/GYN, currently serving as an attending physician for Olympia Obstetrics and Gynecology in Olympia, Washington. She received her Doctor of Medicine degree from the University of Wisconsin School of Medicine and Public Health and completed her OB/GYN residency training at the University of Rochester in New York. I will link to a more complete bio in the show notes. We are very pleased to have her with us. Welcome to the *On Medical Grounds* podcast, Dr. Hanks.

Dr. Laura Hanks:
Thanks so much for having me, so happy to be here.

Dr. Jill Sellers:
I always like to start at the beginning, so let's start by defining an adnexal mass.

Dr. Laura Hanks:
Sure. That's actually a more complicated question than you might realize. The adnexa actually refers to the area just adjacent or adjoining to the uterus. This can include ovaries, fallopian tubes, uterine serosa or surrounding tissue, which means that these type of masses can be gynecologic, gastrointestinal or urologic in origin. They can also be benign or malignant. We generally divide these kind of masses into four different categories. The first would be a gynecologic benign adnexal mass, which could include functional ovarian cysts, endometriomas, tubo-ovarian cysts, mature teratomas or dermoids, serous cystadenomas, mucinous cystadenomas, hydrosalphinx, paratubal cyst, leiomyomas, also known as fibroids or mullerian anomalies. And then another kind of adnexal mass is the gynecologic malignant, which is obviously the more concerning and these are usually ovarian cancers and can include epithelial carcinomas, germ cell tumors, metastatic cancers, sex cord and stromal tumors. And then examples of non-gynecologic benign adnexal masses can be diverticular abscesses, appendicular abscesses or mucocele, nerve sheath tumors, ureteral diverticulum, a pelvic kidney or bladder diverticulum. Lastly, you have your malignant non-gynecologic adnexal masses, which can include GI cancers, retroperitoneal sarcomas and metastatic cancer.

Dr. Jill Sellers:
How do patients with an adnexal mass present clinically?

Dr. Laura Hanks:
Most adnexal masses are found incidentally on physical exam, which is why patients going for their yearly exams are so important. They can also be found at the time of pelvic imaging, usually by a transvaginal ultrasound and they can also present as acute or intermittent pain.

Dr. Jill Sellers:
Is a transvaginal ultrasound common practice? Or does that happen when there's a problem or maybe someone they think is at high risk?

Dr. Laura Hanks:
That's a great question. Transvaginal ultrasound is really the best imaging modality for organs of the pelvis but not everyone's aware of that. Sometimes we have patients that come from the ER that have had the CT scan and then we'll do the transvaginal ultrasound. But really, I try to stress to my ER colleagues that if they have a woman with pelvic pain, that it's really is best to start with a transvaginal ultrasound.

Dr. Jill Sellers:
Oh, excellent. Are you as an OB/GYN typically the one who finds the mass? Or are you evaluating patients referred to you for an adnexal mass?

Dr. Laura Hanks:
Usually, it's the latter. The majority of the patients that I see with adnexal masses have been referred either by the PCP or one of the midwives in our clinic or as I mentioned, the ER consult. That being said, I do identify some adnexal masses on exams, either incidentally or after referral. And sometimes they will present with abnormal bleeding or pelvic pain, which is why when I see those patients, an exam is so important. And a lot of times patients are surprised that I'm going to do a pelvic exam when they're having pelvic pain or bleeding, but it really is important to be able to assess if there's the reason for that.

Dr. Jill Sellers:
Right. I think that would be the first thing you'd do with that but that's just me. What is your initial clinical workup for an adnexal mass?

Dr. Laura Hanks:
The main goal of working up an adnexal mass is to figure out if it's benign or malignant. Unfortunately, there's no screening method for ovarian cancer, such as for cervical cancer we have our pap smears, but there really isn't any kind of screening like that for ovarian cancer, which means that epithelial ovarian cancer is most commonly first detected when it's already an advanced stage. That's 65% of cases will initially be found when they're already stage three and stage four, which is pretty horrible. And at that point, the cure rate is only 18%. Having said that, it is important to remember that the age is the most important independent risk factor for ovarian cancer in the general population. Whereas the most important personal risk factor for ovarian cancer is a strong family history of breast or ovarian cancer. And I only stress that for the OB/GYNs that are listening because that will be on your boards.

Dr. Jill Sellers:
Good.

Dr. Laura Hanks:
And then as far as working up an adnexal mass, you should consider individual patient characteristics such as medical and family history as I mentioned and women with the strong family history of ovarian, breast or colon cancer may have hereditary breast and ovarian cancer syndrome, which is the BRCA mutation or hereditary nonpolyposis colorectal cancer, Lynch syndrome. A physical exam, as we mentioned, is also very important and this should include palpation of the cervical and supraclavicular, axillary and groin lymph nodes, as well as abdominal palpation auscultation and pelvic exam, which includes visual inspection of the perineum, cervix and vagina, as well as the bimanual exam. And exam findings that are concerning for malignancy on your bimanual exam would include an adnexal mass that's irregular, firm, fixed, nodular, bilateral or any associated ascites.

And we kind of talked about before, the transvaginal ultrasound is really the best imaging modality and not to jump straight to the CT or MRI, but the ultrasound should document size and composition of the mass, such as if it's cystic, solid or mixed, which side or laterality the mass is on, presence or absence of septations, mural nodules, papillary excrescences or free fluid in the pelvis. And then lastly, serum markers can be ordered to help distinguish benign from malignant masses. I also want to stress, please don't forget to order the beta-hCG or the pregnancy test in reproductive-age women.

Dr. Jill Sellers:
Good reminder.

Dr. Laura Hanks:
Everyone has their story about missing that adnexal mass. That is a very important part of the workup. And then if there's an infectious etiology that is suspected, we should also do CBC or complete blood count and swabs for gonorrhea and chlamydia.

Dr. Jill Sellers:
I can imagine it would be a little bit embarrassing for, I don't know, you and the patient if a fetus was mistaken for an adnexal mass.

Dr. Laura Hanks:
Yeah, don't be that guy.

Dr. Jill Sellers:
Yeah, don't be that person. What percent of adnexal masses require surgery?

Dr. Laura Hanks:
Well, 20% of women are going to be diagnosed with an adnexal mass at some point in their lifetime and of those women, only five to 10% will end up needing surgery. And of those women, 13 to 21% of the masses will be found to be malignant.

Dr. Jill Sellers:
Why is preoperative malignancy assessment of an adnexal mass important?

Dr. Laura Hanks:
Ovarian cancer is the second most common type of female reproductive cancer and more women die from ovarian cancer than from cervical and uterine cancer combined and survival is related to the adequacy of surgery, which means that women that have an adnexal mass that is concerning for a malignancy really do need to be referred to a GYN oncologist in a timely fashion. For me as a generalist, I'm trained to remove ovarian cysts and perform oophorectomies, salpingectomies and hysterectomies. However, in cases of ovarian malignancy, women will need further surgery such as lymph node sampling, omentectomy, debulking and so on. Basically, a more complicated surgery than I received training for. Later stages of ovarian surgeries can also be complicated by metastatic adhesions, and these complex cases are really best managed by the GYN oncologist as they have that specialized training or fellowship training to handle those kind of situations. If a patient that I'm concerned for an ovarian malignancy, I find it most appropriate to refer them to the gynecologic oncologist to ensure they have that appropriate surgery and then to avoid additional surgeries as well as early detection and improval of survival rate.

Dr. Jill Sellers:
And that's really the point. We don't want to put people through unnecessary surgeries.

Dr. Laura Hanks:
Exactly.

Dr. Jill Sellers:
What do the American College of Obstetricians and Gynecologists, commonly known as ACOG, guidelines say about the use of the biomarkers and malignancy assessment algorithms?

Dr. Laura Hanks:
First kind of taking a step back, I do want to mention that I sometimes see providers, and this is not only in my area but all over the country, that will use a transvaginal ultrasound and a serum tumor marker CA-125, either together or alone for early detection of ovarian cancer in women without adnexal masses, and I really want to stress that ACOG and USPSF do not recommend this or any screening for ovarian cancer in asymptomatic women with average risk because neither of these have been proven to reduce mortality and harms do exist from invasive testing, such as surgery when you get a false positive from one of these.

That being said, CA-125 is found to be elevated in 80% of women with epithelial ovarian cancer. Specificity and positive predictive value of CA-125 are consistently higher in postmenopausal women compared to premenopausal women. Currently, ACOG recognizes that CA-125 is most useful in evaluating postmenopausal women with an adnexal mass and suggests that you use an abnormal cutoff level of 35 units per milliliter. When using CA-125 to evaluate premenopausal women with an adnexal mass, ACOG previously set a threshold of over 200 units per milliliter but this threshold was based on expert opinion and no current evidence-based thresholds have actually been identified for these women. And part of that is I mentioned the false positives before. Women that have endometriomas or endometriosis can actually have a super elevated CA-125 up to the thousands. That's why that cutoff level is there's a little more gray area for our premenopausal women.
ACOG suggests that providers integrate CA-125 level in our premenopausal population with other clinical factors to determine if there's a need for referral to GYN oncology. And additionally, CA-125 has a low sensitivity for detection of ovarian cancer because it is elevated in only half cases of early-stage epithelial

ovarian cancer. As we talked about, that we often detect epithelial ovarian cancer at stage three and stage four and it's rarely elevated in cases of germ cell, stromal or mucinous ovarian cancers. Regarding assessment algorithms, the US Food and Drug Administration has approved two different serum tumor marker panel tests to further assess the likelihood of ovarian cancer in adult women with a pelvic mass. The first one is a multi-variant index assay, which is a qualitative serum tumor marker panel, and the second is the risk of ovarian malignancy algorithm or ROMA for short.

Dr. Jill Sellers:
I'm going to talk about ROMA. How does ROMA fit into your clinical workup?

Dr. Laura Hanks:
Sure. As I just mentioned, ROMA stands for risk of ovarian malignancy and it includes three data points, the patient's pre or postmenopausal status. The second is the cancer antigen 125 or CA-125 that we just mentioned as well. And then the third is human epididymis protein or HE4. We've talked about CA-125 before, but just to review, CA-125 is the most extensively studied serum marker regarding ovarian cancer. It's a protein associated with epithelial ovarian malignancies, yet it can also be elevated in nonmalignant conditions such as I mentioned, endometriosis, pregnancy or pelvic inflammatory disease. CA-125 is most useful when evaluating postmenopausal women and identifying non-mucinous epithelial ovarian cancers. HE4 is actually a novel serum marker that is now being used for ovarian cancer monitoring. It's a member of a family of protease inhibitors that function in protective immunity. The HE4 protein is expressed by epithelial ovarian malignancies and can be detected in the serum of ovarian cancer patients and has been shown to be a sensitive marker for the differentiation of benign ovarian tumors from those that are malignant and as well as a marker for adenocarcinomas of the endometrium. Recent studies have found that the combination of the HE4 and the CA-125 is more sensitive than either of the marker used alone.

Dr. Jill Sellers:
It's amazing that these biomarkers are so sensitive, and I love it that they are now even more specific when you're using them together. And in this ROMA, this algorithm, has it changed the way that you assess the likelihood of malignancy?

Dr. Laura Hanks:
Yeah. For me personally, not really because I used ROMA in my residency training and it's kind of what I grew up with. But when I first started practicing in Olympia, I was ordering it just right away because it was what I was used to and many of the physicians and midwives of my practice were kind of like, "What is this? What are you doing?" It was really great to kind of have that conversation and introduce and spread the word about ROMA, just kind of in this area.

Dr. Jill Sellers:
Yeah. It's nice that you had that experience and exposure to it in your residency training.

Dr. Laura Hanks:
Yeah, absolutely.

Dr. Jill Sellers:
How has the use of ROMA impacted your practice regarding patient care?

Dr. Laura Hanks:
I've often had patients with a pelvic mass and an elevated CA-125 but then when I calculate their ROMA score, it comes out as a low likelihood of cancer. I'll still review that case with our GYN oncologist, but, usually, we're able to avoid those major surgeries we talked about, not to mention the anxiety and stress that comes along with giving a patient a possible cancer diagnosis.

Dr. Jill Sellers:
Right. Yeah. While we're talking about the science, we really have to keep the patient in mind too while we're talking about this so that is what this ROMA app, it kind of embodies. How do you order the ROMA test? And what is the turnaround time to get your results?

Dr. Laura Hanks:
Every lab is going to be different. It's really important to communicate with your lab and to find out what they have available. Turnaround time is also going to depend on the lab and if you're in the middle of a pandemic or not. Currently our lab takes about two to three days to receive our results. But again, just kind of keeping in touch with them about what their availability is.

Dr. Jill Sellers:
Do you order the CA-125 and the HE4 and calculate the score yourself? Or do you order the ROMA test?

Dr. Laura Hanks:
Again, some labs are calculating the ROMA test for you, ours isn't but remember that if you do have a lab that calculates the ROMA test, then you obviously need to let them know what the patient's menopausal status is. That needs to be on the form when you send in the order. Currently, in our lab, I order just the CA-125 and HE4 and then I calculate the ROMA score on a super simple app on my phone, and it'll give you a low or high risk for ovarian malignancy score. And the ROMA app can be downloaded free on the Apple Store just by searching ROMA calculator.

Dr. Jill Sellers:
I actually saw that.

Dr. Laura Hanks:
Yeah, it's super great. Super easy.

Dr. Jill Sellers:
Yeah. Do you refer all adnexal mass patients to GYN/OC for evaluation? I know this is a loaded question so go ahead.

Dr. Laura Hanks:
Definitely not. Definitely not every single, as I listed off kind of that extensive list in the beginning, if I sent them every single one of those, I'd be out of a job. ACOG recommends that women with an adnexal mass only be referred to a GYN oncologist if they are A, postmenopausal with an elevated CA-125, an ultrasound finding suggestive of malignancy, such as the ascites, nodular, fixed pelvic mass or evidence of distant metastases. B would be a premenopausal woman with a very elevated CA-125 and one of the before-mentioned findings. Lastly, would be a pre or postmenopausal woman with an elevated ROMA score.

It is so important, I can't stress this enough for generalists to have a good working relationship with your GYN oncologist. I was super fortunate to have trained with amazing GYN oncologists at the University of Rochester and at the University of Wisconsin when I was there for medical school. And now I work with a super fantastic GYN oncologist in Olympia and we communicate regularly about patients. It's rarely just a straightforward send the facts over referral. It's usually a conversation and it's great continued learning for me. In my practice, I feel comfortable managing endometriomas, TOAs, dermoids, hydrosalpinx, ectopic pregnancy and fibroids. But if an imaging workup at all points towards a malignancy, I'm going to refer or at least have a conversation with my GYN oncologist. Even in cases that it appears to be more complicated, like extensive endometriosis or a large rapidly growing fibroid uterus, I'll often discuss that with my GYN oncologist and we may just go to the OR together. So, I'm really fortunate to have that kind of situation where I am.

Dr. Jill Sellers:
Yeah. I think networking and building those relationships within your profession, having that discussion is only going to benefit, well, the two of you for one, but the patient most of all. That's encouraging.

Dr. Laura Hanks:
And patients really do appreciate that when we can meet both of us and know that we're both there and helping each other out in the OR and it's just a really great situation all around.

Dr. Jill Sellers:
Right. Well, in a survey of OB/GYNs, 83% did not know that malignancy assessment algorithms are included in the ACOG guidelines for the evaluation of adnexal masses. That was surprising to me, 83%. How do we educate clinicians that evaluate women with these masses about implementing this important assessment tool into their practice?

Dr. Laura Hanks:
Well, I think what we're doing here on this podcast is a great start.

Dr. Jill Sellers:
Good, good, good. That's what we want.

Dr. Laura Hanks:
Yeah, absolutely. And then, just as I mentioned, getting the word out, starting to order it and have the conversation with your local providers. Dr. Richard Moore is also a great resource. I trained with Dr. Moore at the University of Rochester where he's chief of GYN oncology, and he studied the HE4 protein extensively as a biomarker for pelvic cancers, and he helped create the app actually for the ROMA score today. He has this excellent PowerPoint presentation regarding this very subject, and he can do it virtually at any clinic or practice. And he's actually given the presentation via Zoom to our clinic and local area providers, and it was a huge success. I'm happy to help people set up one of these presentations if they're interested.

Dr. Jill Sellers:
Well, I'm going to post the contact information in the show notes for the person who can assist in setting up a virtual presentation by Dr. Moore.

Dr. Laura Hanks:
Great.

Dr. Jill Sellers:
In addition, I'll list a few sources that you, Dr. Hanks, have provided as reference material for this podcast.

Dr. Laura Hanks:
Perfect.

Dr. Jill Sellers:
In closing, is there anything else that you want our audience to know about assessing, monitoring, treatment? Well actually, I guess, assessing, diagnosing, monitoring, treating these adnexal masses.

Dr. Laura Hanks:
Remember that women do ovulate every month, generally, and that they can have cysts on their ovaries and that can be very normal. Before referring to a GYN or even a GYN oncologist, it is reasonable to repeat that ultrasound at a different time in their cycle, at least a month away, and to see if the cyst has resolved because that is something that we see quite often and can avoid a referral or again, unnecessary anxiety. That's one thing as far as just kind of the benign side of it falls.

Dr. Jill Sellers:
That's good.

Dr. Laura Hanks:
But really as far as ROMA goes, I think that just remembering that there is a more sensitive testing out there and that your CA-125 often be elevated in benign conditions and that this could help avoid unnecessary anxiety and surgeries and so on. And it really is a great advance that we have.

Dr. Jill Sellers:
Anytime a patient can avoid going under the knife or having unnecessary testing done because even unnecessary CTs or MRIs, those can be full of anxiety for the patient too, especially when they think they're facing a cancer diagnosis. This has been great. Dr. Hanks, thank you for being our guest and educating us on adnexal masses and the importance of accurate assessment from malignancy via the ROMA app, and it is my hope that other primary care physicians and OB/GYNs will utilize this valuable tool in their practice.

Dr. Laura Hanks:
Yeah. Thank you so much for taking the time and glad to get the word out.

Dr. Jill Sellers:
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