

CB: Welcome to The Med Thread, your monthly dose of all things drugs. I'm Cathy,

MC: and I'm Mike

CB: Today we've got a fascinating and frequently controversial topic to talk about, contraception. The biggest concern I hear is about potential side effects of the hormonal contraceptives or devices that are commonly used for women, so that's what we're getting into today.

MC: Right! And we're going to keep the social, societal, debates aside for now. Instead, we're going to try and find out when these side effects came to the forefront and what we know about them now. Later, we're joined by Dr. Karen Wong, an obstetrics and gynecology resident at Memorial University, who has an interest in contraception and reproductive health, and she'll share some of her insights on these issues with us.

CB: And as always, we'll give a little primer on the history of contraceptives and the pharmacology behind their use. Let's get started.

## History and Pharmacology

*[Mad Men Season 1, Episode 1, Smoke Gets in Your Eyes, 2007]*

MC: That's a few lines strung together from Mad Men, cut from their pilot episode.

CB: The number of contraceptives over human history is extensive but the modern combined oral contraceptive, or 'the Pill' as we know it, was first developed in the late 1950s by a company named GD Searle. In Canada, it came to market in the early 1960s and was eventually allowed to be indicated for contraception in 1969. So for almost a decade, the pill was supposed to be only used for menstrual regulation.

*(Liao, 2012) (<http://www.mum.org/enovid-e.htm>)*

MC: Now, synthetic hormones have been around for much longer and new ones are always being developed and researched. In this first Pill, brand name Enovid, there was a synthetic estrogen called mestranol and a synthetic progestin called norethynodrel. We don't exactly use these two drugs anymore. The most common estrogen in contraceptives now is ethinyl estradiol, which actually was developed in the 1930s.

CB: And interestingly, mestranol, is actually not the active drug. It needs to be converted by the liver into ethinyl estradiol. One of the problems in the past was that this conversion could vary person to person and so there was difficulty in dosing. On the other hand, there are many progestins we use today and as we'll talk about, choosing the most appropriate one can sometimes be difficult.

*(Fotherby, 1996)*

MC: Aside from the actual drug, we have to think about dosages. While we're talking about mestranol, I'll use that as an example. Enovid contained 150 mcg of mestranol, which is approximately 105 mcg of ethinyl estradiol. If you take a look at oral contraceptives today, the highest it goes is 35 mcg, and many are even lower. Over the years, we've realized that we really don't need that high of a dose for them to be effective.

*(Goldzeiher, 1990)*

CB: And that's a good thing, because we know that many side effects are related to the dose.

MC: Right, so how do oral contraceptives work?

CB: Well, there's a few things going on. First off, we can consider that the hormonal contraceptive takes control of the reproductive cycle and if we think back, this is where the menstrual regulation indication comes from. By preventing the production or activity of some of the body's hormones the main effect is that ovulation is suppressed. But there are also effects on thickening cervical mucus which prevents sperm movement and making the uterine lining or endometrium not a good environment for implantation of a fertilized egg.

MC: We also mentioned that there are some devices are also used for contraception and their history is even more interesting. In Ontario, there used to be The History of Contraception Museum, which showcased all the things we used to use before hormones. The collection has moved to Cleveland, Ohio and if you ever make the trip there, you need to visit the Dittrick Medical History Center!

*(<http://artsci.case.edu/dittrick/>)*

CB: Yes, unfortunately, there was a lot of trial and error when they were being developed and there are some rather distressing devices in that collection, but luckily today, the two main types of devices used are much safer. The first one is the copper intrauterine device and the second is the progestin based intrauterine system, both of which really started showing up in the mid to late 1970s. To save on some words, we'll call both of these IUDs.

*(Marguiles, 1975)*

MC: But similar to the oral hormones, there have been many changes to the products since the 70s. For example, one of the first progestin products, Progestasert, required replacement every year, whereas now, there are products effective for up to 5 years. And of all the products available for contraception, intrauterine devices are the most effective.

*(Pharriss, 1974)*

CB: Right, aside from the physical device affecting implantation, the copper also creates a hostile environment for sperm and the progestin ones thicken cervical mucus. And they may also affect ovulation.

MC: And there you have it, a 5 minute history, but we really want to bring in our guest today and get to all these concerns.

## #1 – Blood clots

*[Aside from specific studies cited, information obtained from Williams Gynecology (3rd ed.) and SOGC consensus guidelines (Black, 2017)]*

CB: Time to bring in an expert, Welcome Karen!

KW: Thanks for having me!

CB: Karen, I'm so excited that you are here. I get a lot of questions about birth control from patients, but also from friends. There is a lot of information out there, and some of it is misinformation and I'm glad you're here to help us address some these concerns and look at the evidence.

MC: Starting with our first concern, this one is scary. Contraception causes blood clots. In 1969, an article mentioned that there were some retrospective studies showing a general increased risk and more specifically in women who also smoked. Fast forward almost 50 years and we still here it in the news! What does the evidence say?

*(Ley, 1969) (<https://www.cbc.ca/news/canada/british-columbia/yaz-yasmin-birth-control-pills-suspected-in-23-deaths-1.1302473>)*

KW: That's a great question and that's something that obstetricians and gynecologists are often talking to patients about. Broadly speaking, when we talk about blood clots, we're talking about venous thromboembolism, but we're also talking about arterial clots. So to start off with, in terms of the risk of venous thromboembolism, there are a number of factors that can contribute to this risk for women. Risk factors include, prolonged hospitalization, major surgery, acute illness, obesity, cancer, trauma. Obviously the one we're talking about is the risk associated with hormones.

Specifically, the risk for venous thromboembolism, which includes both deep vein thrombosis and pulmonary embolism is somewhere between 1-5 in 10,000. Studies have shown that the risk of venous thromboembolism in users of combined hormonal contraception, is somewhere in the realm of 7-10 in 10,000, so certainly an increased risk compared to baseline, but overall, the absolute risk remains quite small. The other point to make about this, is that the risk of venous thromboembolism in pregnancy is even greater than that risk associated with combined hormonal contraception, so the risk associated with pregnancy, is somewhere between 10-20 per 10,000 and this risk is actually probably a little bit closer to the higher end, so 20 per 10,000 in the immediate postpartum period. Also associated with pregnancy would be the possibility of Caesarean section and prolonged hospitalization, which would further increase the risk of venous thromboembolism. So overall weighing the risks and the benefits of hormonal contraception and pregnancy, the risk when using combined hormonal contraception, seems to be less than that in pregnancy and overall these risks are quite small. The other point I wanted to make is that there doesn't seem to be an increased risk for venous thromboembolism in the progestin only products such as the intrauterine systems or the intrauterine device.

*(Oedingen, 2018) (Lidegaard, 2009)*

The risk of venous thromboembolism is actually associated with the dose of the estrogen component in CHC. Studies have shown that contraceptives that contain higher doses of ethinyl estradiol, so greater than 50 mcg, are the products that are most associated with an increased risk of venous thromboembolism and this risk is likely dose related. However, the studies that have been done lately, have been looking at the effect of the progestin component as well.

MC: So that's really good to know because, as we said, a lot of the doses for ethinyl estradiol have decreased over the years and we really don't dose up to the 50 mcg anymore.

KW: In terms of arterial embolism, here we're talking about myocardial infarction or heart attacks, as well as cerebrovascular events, meaning stroke. The risk of both of these are increased when ethinyl estradiol is used in doses greater than 50 mcg/day. However, the important thing to

realize about the risk of arterial embolism is that the risk is particularly compounded in those with other risk factors for arterial embolism, so things like, uncontrolled hypertension or smoking.

CB: It's really helpful to hear you talk about the numbers and it really gives me a better sense of what the risk looks like. And there was one study published in 2015 that looked at the use of combined oral contraceptives and the risk of venous thromboembolism and they stated that the risk was higher for newer drugs than for second generation drugs. What is the story here?  
*(Vinogradova, 2015)*

KW: That's a great question as well. There have been a few studies looking at this issue in the past few years as there has been news articles about this as well. Much of the analysis is based on retrospective studies although there have been a few prospective studies as well. And I think a lot of the evidence that there is an increased risk in the later generation pills comes from the retrospective studies. The prospective studies suggest that there may not be this increased risk. So with all of this conflicting evidence, there was a meta-analysis done in 2018 looking at the absolute risks of venous thromboembolism associated with different types of birth control pills. This analysis showed that overall, the risk of venous thromboembolism or VTE was somewhere in the realm of 7-10 in 10,000. The risk associated with levonorgestrel, which is one of the older generation or second generation progestins was on the lower end of the spectrum, 7 in 10,000 whereas the risk associated with the later generation pills such as drospirenone and desogestrel were a little bit higher, closer to 10 in 10,000. So again, the risks are perhaps increased, but overall remain quite small.  
*(Oedingen, 2018)*

## #2 – Cancer

MC: It didn't take long after the Pill was marketed that there started to be articles published about cancer. I'm going to refer back to the 1969 article we mentioned regarding blood clots where it said that studies were underway to compare cancer rates in humans, but we already knew that estrogens were associated cancer in some animal models.  
*(Mills, 1964) (Peckhan, 1969)*

CB: Today, we continue to hear that hormonal therapy in contraception is linked to various types of cancer including endometrial cancer, breast cancer, cervical cancer, ovarian cancer, and more. What do you tell patients about their risk of cancers?

KW: There was a large retrospective cohort study done in 2017 in Denmark, which looked at this issue in quite a lot of detail. This study showed that the risk of breast cancer did seem to be increased in ever-users of hormonal contraception, meaning current users or recent users. However, they also point out that the absolute risk of breast cancer in this study, was 13 per 100,000 so that risk actually remains quite small. In terms of the risk of cervical cancer, again it looks like risk might be increased, however we don't have as many rigorous studies of cervical cancer as we do for breast cancer. What is reassuring about the possible increased risks of breast and cervical cancers is that the risk seems to decrease to baseline after discontinuing hormonal contraception for a number of years. Now to balance these possible increased risks of breast and cervical cancers are the possible decreased risks endometrial and ovarian cancers.  
*(Mørch, 2017)*

MC: And to help us understand where this comes from, can you tell us how the hormones, estrogen and progesterone, could be influencing cancer risk?

KW: Some breast cancers have estrogen and progesterone receptors. These types of breast cancer are susceptible to the effects of both exogenous, meaning coming from the outside and endogenous, meaning coming inside the body, estrogen and progestins. These are the kinds of breast cancer which might be increased with use of exogenous hormones like birth control.

Cervical cancer is different. The main pathological cause of cervical cancer is HPV, or human papillomavirus, which is transmitted through contact. We're not 100% sure why the risk of cervical cancer might be increased with hormonal contraception, but it might be because users of hormonal contraception may not be using barrier contraception such as condoms, which decrease the risk of transmission of human papillomavirus. Another possible reason is that the estrogen or progestin have an effect on the oncogenic potential of cells infected by the HPV virus.

On the other hand, the risk of endometrial and ovarian cancers as we said before, is decreased in users of hormonal contraception. This decreased risk for endometrial cancer is related to regular and controlled growth and shedding of the endometrium. This means that the risk of hyperplasia, which is a disordered growth of the endometrium is decreased. And hyperplasia or disordered growth has a high risk of turning into endometrial cancer. For ovarian cancer, it's believed that ovarian cancer is decreased in users of hormonal contraception because it decreases the number of times a woman ovulates. A lot of ovulation over the lifetime is what is associated with ovarian cancer.

### #3 – Migraines

CB: What about the adage that birth control causes migraines? One of the contraindications to using oral contraceptives is migraine with aura. But does one lead to another? Sometimes we use oral contraceptives to control migraines, but how can it do both?

KW: Certainly as you said, one of the contraindications to using combined hormonal contraception is migraine with aura and the reason this is a contraindication is because there's a thought that this increases the risk for stroke. Now of course, this should be taken into context. The risk for stroke is particularly increased in individuals with migraine with aura but who also are over the age of 35 or who smoke. Importantly, migraine without aura is not a contraindication for combined hormonal contraception and as you said, some people actually use hormonal contraception if they have migraines that are associated with their cycle. In some individuals, their migraines occur with a drop in estrogen so it is cyclical. In these individuals we might treat them with hormonal contraception to maintain levels of estrogen so they don't get that drop in estrogen. In these individuals we might use extended cycle hormonal contraception, so running a few packs back to back or skipping the pill free interval. Or we might switch to options with a different amount of estrogen.

MC: So the idea is that they don't actually cause migraines but they might help to treat the migraines because of those drops in hormone levels.

#### #4 – Weight gain

MC: Before we get to the next question, here's a clip from The Mindy Project.

*[The Mindy Project, Season 2, Episode 20, An Officer and a Gynecologist, 2014]*

CB: Now, this is probably the most common thing I hear about birth control, and that is how it affects a woman's weight. I hear all the time, I gained all this weight on birth control, or, I don't want to use birth control because I don't want to gain weight. Is there any truth to this, and if so, is there any difference between the various methods?

KW: I do spend a lot of time talking to patients about the risk of increased weight or the possible increased weight with various birth control methods. Overall, I would say that there is no increased risk of weight gain. We do have a few placebo controlled trials which show that there's no increased weight gain associated with hormonal contraception. The exception is Depo-Provera, so the injectable progestin only method. With Depo-Provera, there does seem to be a possible increased weight gain, with an average of 11 lbs over 3 years. There's a thought that the weight gain is not due to the contraception itself, but potentially is caused by an increase in appetite and this leads to increased eating, which leads to increased weight gain.

MC: So is there an increased appetite with the combined oral contraceptives?

KW: I would say that some people might think that they have increased weight gain, but our evidence doesn't seem to indicate that there is necessarily a statistically significant or even clinically significant increased risk of more weight gain.

MC: And what would you recommend for your patients that come to you and tell you that they've had weight gain?

KW: I would recommend trying different kinds of birth control. Some people find that they respond differently to different formulations. Some people who don't do well on the combined oral contraception, don't find that they have the same systemic effects with the intrauterine systems, because the dose is lower. I also tell them about the importance of diet and exercise as always. These are mitigating factors if there is any potential increase in appetite.

CB: So I'm glad I can tell my patients that there's really no difference in terms of the various birth control methods other than the Depo-Provera, as you mentioned. And maybe perhaps, the dose of the oral contraceptive pill doesn't matter if it doesn't cause weight gain to begin with.

#### #5 – Infertility

CB: My next questions is about infertility. There have been concerns about infertility and contraception even before hormonal birth control. A paper in 1946 looked at infertility for using things like condoms, diaphragms, and even the withdrawal method. They didn't find much back then.

*(Rubin, 1946)*

MC: I've had patients that were worried about taking contraceptives because they were concerned it would affect their ability to have children in the future. Some are concerned that the longer they are on birth control the harder it will be to have a baby in the future. What do you tell patients?

KW: There doesn't seem to be any evidence for a long-term decrease in fertility with the use of hormonal contraception. There could be a number of reasons for potential associations that people are making between hormonal birth control and difficulty getting pregnant. For example, at baseline, they could have other reasons for having difficulty getting pregnant that haven't been uncovered until they have been actively trying, until they've stopped the birth control that they were on.

Another reason could be that people tend to stop birth control when they are a little bit older and we know that the older a woman is, the more difficulty with fertility she might have, particularly over the age of 35. Finally, there could be a degree of recall bias, in individuals who are struggling with infertility. Individuals who are struggling with infertility for quite a long time often look at all of the things going on in their lives that could contribute to this and lots of people might naturally gravitate to hormones and the birth control pill, but there is no evidence that we can find in the literature for again a long-term decrease in fertility. However, for some methods, it may take a little bit more time to get back to baseline fertility. For example, the Depo-Provera could take up to a year to return to normal ovulation and fertility.

CB: One of the concerns about IUDs is risk of infection and specifically, pelvic inflammatory disease, which we know can affect fertility. What is the story here?

KW: So you're absolutely right that pelvic inflammatory disease can contribute to difficulties with fertility. The risk of infection and pelvic inflammatory disease with modern intrauterine devices is lower now than it was in the past. So the older intrauterine devices, for a number of reasons, were more associated with infection, because of their shape, because of their materials that were used. But again, the current IUDs that we now have on the market don't seem to have such a high risk of pelvic infection. I do tell patients that the risk of infection is highest in the first 3 weeks after insertion but after this there doesn't seem to be too much of an increased risk overall. Another point about IUDs is that the return to fertility is immediate in contrast to say, the Depo-Provera.

CB: So the Depo-Provera seems to be the longest with the return to fertility and all of them seem to be reversible, but varying lengths of reversibility I'll call it.

MC: Right, so if someone is having difficulty conceiving, when should they seek help if they've been on an oral contraceptive?

KW: So for people who haven't been on a contraceptive we define infertility as actively trying to get pregnant and not succeeding in 1 year. For individuals who have been on hormonal contraception, we ask that they seek medical attention after 6 months of trying and not conceiving, not because there's an increased risk with the hormonal contraception, but these individuals tend to be older and we are trying to help them get pregnant sooner.

## 6 – Taking a break

[Semicid advertisement, 1987, [https://www.youtube.com/watch?v=M\\_kqVm518og](https://www.youtube.com/watch?v=M_kqVm518og)]

MC: That's an ad for spermicide in the 80s, as an alternative for birth control and the idea of giving the body a break

CB: I've got another one that I hear a lot, some women say they choose to stop taking birth control, not because they want to get pregnant, but because their body needs a break. There is a thought that the body 'gets used to' the hormones, or that there could be negative consequences if taking the same pill for years. What are your thoughts on this?

KW: I imagine that individuals might be concerned about the efficacy or safety of hormonal contraception with long term use. In terms of the efficacy of hormonal contraception there is no development of tolerance with these medications, so you do not need to stop in order for the body to continue to respond to the medication.

In terms of safety, there might actually be an increased risk to starting and stopping contraception frequently. The risk of venous thromboembolism, which we talked about earlier is highest in the first month after starting a new combined hormonal contraceptive. Therefore, if an individual were to start and then stop and then start a contraceptive repeatedly, she would be exposing herself to that increased risk of VTE multiple times. The risk of VTE decreases and remains constant after that initial month of use. We also spoke about the possible risk of cancer earlier and I had mentioned that any increased risk returns to baseline after discontinuing the medication. Again, this risk applies to breast and cervical cancers, and should be balanced against the decreased risk of ovarian and endometrial cancers with continued use of contraception.

*(Bloemenkamp, 2000) (Poulter, 1995)*

MC: That's really interesting and I know that there are a lot of products, the ones that you mention, about not having a break between packs and to add to that, the Pill was designed to follow a 28-day cycle. But in terms of the science, it really doesn't have to be the case.

*(Marsh, 2008) (St Leger Dowse, 2007)*

KW: To be specific, when we talk about an extended cycle, we mean the use of hormonal contraception for consecutive cycles, skipping any pill free interval. This means that a woman may not have a "period" or withdrawal bleed. Again, we might suggest this for women who have migraines, or severe pain, or bleeding associated with their periods. Women themselves might choose this for convenience.

In terms of safety, we recommend a withdrawal bleed occur after 3 cycles. That is, extended cycles will usually be for 84 days followed by a period of either less hormones or no hormones during which a withdrawal bleed happens. This is a completely safe way to use contraception, since there is controlled growth and shedding of the uterine or endometrial lining.



## 7 – IUD perforations

CB: You've mentioned infections and IUDs, which made me think about the times patients have told me they worry that IUDs will perforate the uterus and cause lots of problems. We've definitely heard that it can happen, but how often and what's the risk?

KW: This is certainly a possible complication that we counsel patients about who are considering IUDs. The risk of perforation is low, about 1 in 1000 insertions and the risk of perforation applies any time instruments are inserted into the uterine cavity. And it relates to individual patient anatomy and other factors such as postpartum or postmenopausal status. So clinically, if we suspect that there was a uterine perforation at the time of insertion, we would have the patient go for a pelvic ultrasound. In the majority of cases, this kind of ultrasound confirms intrauterine placement of the IUD, so no problems. Rarely, the device goes intraabdominal after uterine perforation. In this kind of rare case, we would need to go to the operating room to remove it. Again, this is quite a rare event. In the case that it did happen, it is possible that it would cause damage to neighbouring organs such as bowel or bladder, but again rare event.

CB: And I think people are afraid too, when we actually hand them the box that it comes in. My dispensing job is rearing its head and whenever I hand someone the box, it comes in a much larger box than the IUD, which can be intimidating, but it's certainly not near that size.

KW: Absolutely, the IUD itself is smaller than 2 inches.

## 8 – Pregnancy

MC: We have one last question for you and it's about what happens if someone gets pregnant while on the pill or has an IUD.

KW: In terms of combined oral contraceptives, so the pill, if someone becomes pregnant while using it, there's no increased risk of birth defects, but we would advise that people stop it, not because it's dangerous, but because it has become useless.

The intrauterine devices are a little more difficult. So if someone were to become pregnant while using the intrauterine device, and I will stress that this is a very rare occurrence, the risk of having an ectopic pregnancy, so a pregnancy not located inside the uterus is increased. There's also an increased risk of miscarriage if somebody does become pregnant with an IUD in place and the pregnancy is in the uterus. Depending on when we discover the pregnancy, we may or may not remove the intrauterine device. Early on in the pregnancy, we would try to remove the device, but later on, it becomes much more challenge. So if somebody were to become pregnant while using any kind of contraception, I would advise that they immediately seek medical advice.

## Conclusion

MC: I think we've covered enough concerns for today although there are many, many more. A good website to visit is [sexandu.ca](http://sexandu.ca), that's the letter U, and they have lots of info about contraception and safe sex from the Society of Obstetricians and Gynaecologists of Canada. Thank you, Karen, for coming to our show and having this valuable discussion with us.

KW: Thank you! It was a real pleasure to be there and if you have more questions about contraception, just ask your pharmacist and doctor!

CB: We would love to hear what you think of our podcast, including any topics you'd like us to talk about! So please, send us a message on Facebook via the School of Pharmacy or email us at [medthread@mun.ca](mailto:medthread@mun.ca).

And next month, tune in as we talk about diabetes. Did you know there's more than 10 different types of insulin and more than 20 different medications for diabetes? That is a lot!

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**Contraceptives: The good, the bad and everything in between**

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