

## Intro

CB: Welcome to The Med Thread. We've handed the mic to our pharmacy students once again. They are on this episode to present on topics related to contraception.

MC: A few episodes back, we had Karen, an obstetrics resident, on our podcast, talking about myths related to contraception. This episode will expand on that from a clinical case perspective. Just to recap, our students are answering their questions using evidence-based practice. Evidence-based practice is essentially collecting and evaluating the best available evidence from a variety of sources and putting it together in a meaningful way to make clinical decisions.

CB: Our students have developed short segments based on questions that they've come across in practice. Today, you'll hear from 3 different groups. The first group looks at the impact of body weight and options for contraception in patients who are overweight or obese.

## IUDs and obesity

R: Hello and welcome back! This is Rebecca, Jeremy, Anna, and Seyoung. And we are all students from the MUN pharmacy class of 2020.

Each month The Med Thread, a medication information station from the School of Pharmacy at Memorial University brings you an exciting topic related to medications, disease conditions, pharmacy practice and much more! This episode we as students bring you information on the effectiveness of IUDs versus combined oral contraception in obese women.

J: Alright let's get down to business! With the obesity rate on the rise in this country and in particular in the province of Newfoundland and Labrador, we as healthcare professionals need to start thinking about how this affects medication therapy.

With a large variety of contraceptive methods now available for women, pharmacists may often be faced with the task of recommending an appropriate one. To complicate this matter, the patient may be obese or overweight. Of course, all aspects of a patient need to be taken into consideration when making a recommendation, including the patient's weight.

A: A person who has a 30 or greater body mass index is considered to be obese. In terms of contraception, is one option more effective than another in this specific population? Does body weight have an impact on the efficacy of IUDs or combined oral contraceptives? Well, we will answer this question today!

Before we delve a little deeper, we'd like to speak a little about what the Canadian Contraception Consensus has to say about IUDs and oral contraception effectiveness. It's well known that IUDs are a more effective form of contraception than combined oral contraception. The Canadian Contraception Consensus confirms this in their most recent guidelines. However, does body weight have an impact on their effectiveness?  
(Black, 2016)

S: In terms of our sources and search strategy the following procedure was used to find an answer: Using the ultimate question we searched UpToDate and DynaMed to find relevant information.

Upon feedback we dug deeper into the actual studies that were cited in these summaries to determine their significance. Some of these studies were proven to be less useful than we initially thought. The MESH terms obese, oral contraceptives, IUD and efficacy were searched on PubMed. This allowed us to see if there had been any studies done on our topic as well as review any systematic reviews. Embase proved to be unhelpful even when we used the PICO question search option. Furthermore, we were mindful of the fact that IUDs may sometimes only refer to copper devices, whereas the hormonal ones are often called IUS or intrauterine systems. Thus, we exploded the terms to be inclusive. Overall, relevant evidence was found in UpToDate and DynaMed summaries, as well as PubMed. We found the Canadian Contraception Consensus Guidelines found in PubMed to be particularly useful.

R: In terms of the evidence we found, a systematic review was conducted in 2017 to evaluate the current literature on several forms of contraception and whether they have different effectiveness or failure rates by body weight or body mass index. The study was conducted by searching PubMed and the Cochrane Library databases for all articles, in all languages, published between the start of the study and February 2016. Out of 2874 articles, there were 15 reports included, all of which had fair to poor quality evidence. Out of the 15 reports, 14 of them measured the association of obesity and oral contraceptive failure with 4 (3 fair quality, 1 poor quality) reporting an increase in failure amongst overweight and obese women compared to woman of normal weight. However, 10 (8 fair quality, 2 poor quality) studies did not find an association. Bringing this all together, we can see that the current available evidence addressing the risk of combined hormonal contraception failure in obese compared to normal weight women is limited to fair and poor quality studies. The studies of combined oral contraception available show mixed results.  
*(Dragoman, 2017)*

J: The Canadian Contraception Consensus in 2017 stated that “the majority of qualified studies do not indicate decreased combined oral contraceptive pill efficacy in obese women; however, a small increase in contraceptive failure in women with a body mass index greater than 30 cannot be excluded.” This statement was based on evidence from well-designed cohort (prospective or retrospective) or case-control studies, preferably from more than one centre or research group.  
*(Black, 2017)*

A: We also found, oral contraceptives are generally effective at pregnancy prevention in obese women, but may be less forgiving of imperfect use because the pharmacokinetics of steroid hormones appear to be altered in obese women compared with normal-weight users. Oral contraceptives have been shown to have increased failure rates in obese women compared with normal-weight women. The risk of failure appears to be greatest in those women with the highest BMI (>35 kg/m<sup>2</sup>). Limited data suggests that long-acting reversible contraceptives methods (intrauterine devices) retain excellent contraceptive efficacy in obese women.  
*(Robinson, 2013)*

S: It was interesting that UpToDate stated that there was no evidence of impaired contraceptive efficacy in obese IUD users of copper and hormonal IUDs. However, when we took a closer look at the study the main objective of the study was to look at contraception implants and the IUD results were only a side note. This made us question the reliability of the evidence as no conclusion was made specifically about the IUD results.  
*(Xu, 2012)*

- R: After conducting our research we found that there was a lack of studies done in this specific population. We did not find any specific studies comparing IUD effectiveness versus combined oral contraception effectiveness in obese women or IUD effectiveness in obese vs non-obese women, but we did find a lot of indirect evidence.
- J: Although there is conflicting evidence, the general consensus is that the efficacy of IUD's in obese women is not impacted, while the efficacy of oral contraceptives may or may not be slightly decreased due to the kinetics of the medication. This decrease is reliant on potential adherence issues.
- A: According to our findings, although limited, the use of copper or levonorgestrel releasing IUD would be the best option in the obese population. The hormonal IUD showed greater efficacy compared to copper in the general population, but we did not find specific evidence for users who were overweight or obese. Although we've addressed efficacy, obese patients are quite complex and there are many safety concerns that need to be considered when implementing contraceptives in this population. We did not include safety in our search therefore, further research would need to be done to determine which type of IUD would be the safest option in this specific population.
- S: Overall, there is a general lack of studies done in this demographic and a clear answer is not found in the literature alone. When a topic has not been well studied, we often, as healthcare professionals, make use our own clinical judgement alongside the current evidence to make an informed decision. While the indirect evidence appears to give an appropriate solution, we believe further evidence in this specific population may be warranted.

### Oral contraceptives and migraine

- MC: Next, we have some students discuss a case of oral contraceptives in patients with migraine with aura. What's the risk there?
- Ry: Hello Everyone! We are a group of Pharmacy Students from Memorial Universities Class of 2020. Today we are going to discuss the topic of migraine with aura relating to its risk of stroke with the use of oral contraceptives. My name is Ryan and I will be joined by three of my fellow classmates. To begin today's discussion, I am going to give you guys a brief outline of a scenario we came up with:

A young adult female comes into your pharmacy, and asks to speak to the pharmacist. She asks you "is there any other oral medication I can take for birth control besides this one? My doctor says I can't have any other ones because of my migraines I've been experiencing, but these ones are just not working for me." Upon further investigation, she tells you she has been feeling tired, emotional, and has some breast tenderness. This is from her medication, Movisse, that she's currently prescribed. She also states that her migraines are controlled but she does experience some aura with them.

As we look further into the situation, we noted that the patient was experiencing these migraines with aura, which cause an increased risk of stroke and this is something that we looked further into when trying to come up with a new oral contraceptive that would be acceptable for this patient. The exact mechanism of action of increased stroke risk is unknown,

but it is clear from the information we will explain later, that this risk is independently existing for migraines with aura and also with estrogen contraceptives. If a patient with aura wishes to go on an oral contraceptive, normally the progestin only contraceptive would be recommended to avoid that increase in stroke risk. However, this patient has already tried a progestin only pill and experienced side effects. Therefore, we decided to look into the risk of a combined hormonal contraceptive with different progestin components than previous use. From that scenario and all the information, we gathered, our ultimate question to answer would be, for a young adult female patient who has a history of migraines with aura, and treatment failure due to adverse effects with norethindrone, what would be an appropriate oral contraceptive that does not put the patient at an increased risk for stroke?

Now my classmate Bradley is going to hop in and talk to you about the first part of our search strategy.

B: Hey guys, I'm Bradley. To really wrap our heads around the question, we first took a look at the guidelines to see what prescribers are using to make their decisions. In Canada, the guidelines can be found under the Canadian Contraception Consensus. After looking at the more broad resources, such as Uptodate and Dynamed, we felt that we could not answer our question fully based on the information. In order to really answer the question, we had to read some articles from the primary literature ourselves, so we took a look at some of them in PubMed. Rachel is going to tell you a little bit about this!  
*(Black, 2017)*

Ra: Hey everyone, I'm Rachel. To understand why the guidelines state migraine with aura is a contraindication to combined hormonal contraception, we took a look at the history to really understand where contraception started and why the guidelines say what they do. According to the research, we know that progestin is what actually prevents pregnancy through a couple of mechanisms. So then we wondered, why did the first hormonal contraceptive contain around 75 mcg of ethinyl estradiol, a huge dose compared to today's product? Well, initially in 1957, the first birth control, Enovid-10, contained synthetic estrogen only as a by-product. But it was actually found to improve breakthrough bleeding. Now, current contraceptives contain only a fraction of the original ethinyl estradiol dose, since estrogen does cause adverse effects. Today, 50 mcg is a high dose, and most birth controls don't contain this much. One of our biggest questions after looking into the history, was whether the literature took into account the change in risk with the change in dose of estrogen, since we know this is the link to stroke risk, and whether anyone had assessed this in a primary study. So, Ryan, want to fill us in on what we did next?

Ry: Sure thing. So, we researched the available contraceptives in Canada, from the *Pharmacist's Letter*. We discovered from most of the products on the market, the highest dose of estrogen is actually only 40 mcg. Doses went as low as 10 mcg, which is lower than the first contraceptive at 150 mcg of estrogen, mestranol, which is only about 75 mcg of the active drug, ethinyl estradiol when metabolized in the body as mentioned previously by Rachel. So we began to ask ourselves, is the risk of stroke the same across all of these contraceptives? Or would the results vary? Kristen is going to fill you in on a little bit more about that now.  
*(Pharmacist's Letter Canada: Choosing a Hormonal Contraceptive)*

K: Hi guys, I'm Kristen. So we decided in order to assess the increased risk of ischemic stroke for combined hormonal contraceptives and migraine with aura, we had to look at first, what is the risk in patients without migraines. The Canadian Contraceptive [Consensus] states there is no additional risk of ischemic stroke for patients who do not have additional risk factors which could include smoking or age greater than 35. UpToDate does a really nice job of placing this into context for us, by stating that for every 24,000 people we treat, one person could statistically suffer from a stroke.

Another article we looked at mentioned a study that found a 6-fold increase in ischemic stroke as a combined effect of migraine with aura and use of combined contraceptive, however, the study defined combined oral contraceptive as, a filled prescription for such, patch or ring within 90 days prior to index date. This told us that while they did find an increase risk, they failed to take into account the dose related risk, which we know from prior research actually exists.  
(*Champaloux, 2017*)

There were also some systematic reviews we also looked at in primary literature. Most of the studies we found actually failed to take into account the estrogen component dose and how the different doses could directly affect stroke. Three studies in one systematic review did assess risk of stroke based on dose, but they did so independently of migraine status which meant the data would not help us answer our question. The general trend is that with lowering doses of EE, the odds ratio of stroke risk actually decreases. So, we can conclude, as we previously knew, that independent of migraines, the estrogen dose has a direct effect on risk of stroke, but this does not help our patient's migraine scenario.  
(*Sheikh, 2018*)

Ra: We then looked at a 2016 study: *Hormonal Contraceptives and migraine with aura-is there still as risk*, which is a review of the current literature. For the most part, this review looked at the risks associated with different levels of estrogen, however it's difficult to make a final consensus because each study categorized the various doses of estrogen differently. Essentially, high doses of estrogen will account for the majority of stroke cases, but more research needs to be done with consistent categorizing of current available doses to see if reducing the estrogen component will actually reduce stroke risk.  
(*Calhoun, 2016*)

B: The guidelines outlined in the Pharmacist Letter suggest that patients should avoid the estrogen component all together, and use either a progestin only pill, or a form of protection that is non-hormonal, for example a copper IUD like we mentioned in our introduction. For our specific scenario, they have already tried a progestin only pill, and she would rather an oral tablet. While we cannot recommend to go against guidelines, we may consider an ultra-low dose option for our patient in this case. Some low dose options include Mya, LoLo, and Minestrin. Since she already had adverse effects from a progestin, the studies show that she should switch to a progestin with less activity, such as a drug in the second generation. We would have to outline possible risks to ensure the patient and her physician are informed. We could present varying options and allow them to decide if the benefit is worth the risk.

Ra: While it appears the risk is not increased for ischemic stroke in patients using combined hormonal contraceptives at low estrogen doses, and having migraine with aura, there needs to be further studies done to confirm this evidence.

- K: So to wrap it all up, with more research done in this area, hopefully guidelines will become more flexible, and allow our patient with this condition to have more options. Meanwhile, we can recommend discussing all options, including non-oral formulations, with both patient and physician, and always adhering to guidelines when possible since these do reflect the best evidence.
- Ry: So on behalf of all of us here today, I would like to thank you for listening to our medical scenario and hope you guys enjoy the rest of your day.

### Oral contraceptives and antibiotics

- CB: And the last group will touch on oral contraceptives and antibiotics. Should we be worried about drug interactions or maybe not?
- E: Hi there everyone, welcome back to The Med Thread. Today we are going to talk about a common misconception that many people have regarding antibiotics and oral contraceptives. Do antibiotics really decrease the efficacy of oral contraceptives when the two are taken at the same time? We are going to discuss why many think this, the science behind it, and whether this is something patients, and healthcare professionals, need to worry about. My name is Emily, I'm a third year pharmacy student at Memorial University.
- S: I'm Sarah
- A: I'm Amelia
- H: I'm Hanna
- R: and I'm Rebecca and we are also 3rd year pharmacy students at Memorial University. As Emily mentioned, a common misconception that has been brought up in multiple situations in community pharmacy is if antibiotics affect the efficacy of birth control. This question arises multiple times a day in community practice and it seems that a lot of pharmacists aren't sure how to answer it.
- S: I agree, I think it is safe to say that we have all encountered this question several times in practice so far, especially when individuals are going on vacation. Many physicians will prescribe patients antibiotics before people go down south, such as to the Dominican Republic or Cuba, just in case they pick up something while down there.
- A: As there are so many birth controls out there, we have decided to focus on just one in particular here today—Tri-Cyclen LO or the generic which is Tricira LO, a birth control that we commonly see in practice. Here is some background information on this birth control.
- H: Tri-Cyclen LO is a triphasic birth control, containing norgestimate and ethinyl estradiol which is available in 21 and 28 day packs. The amount of hormone changes each week for 3 weeks, with the fourth week either being no pill or a placebo.
- E: If birth control is taken correctly, it is 99% effective meaning that if 100 women took this birth control for one year, only 1 woman would become pregnant. That being said, there are many

different drugs that can affect the efficacy of Tri-Cyclen Lo, as well as many other oral contraceptives. So the question remains, are antibiotics one of the drugs that affect the efficacy of Tri-Cyclen Lo?

R: Good question! Well, in the past antibiotics have been thought to decrease the efficacy of a variety of birth controls. In addition to antibiotics killing bacteria, it was said to also change the normal gut flora in turn affecting the activation and function of the oral contraceptive medication. As such, it was recommended to use backup contraception, or condoms. Also, if the antibiotics or illness causes vomiting or diarrhea, contraception efficacy could be compromised due to insufficient absorption.

S: However, with further research, evidence shows this is a myth. There is only one antibiotic, rifampin, that interacts with oral contraceptives where secondary contraceptive is recommended. Rifampin is a pretty uncommon antibiotic that is only used for active tuberculosis and meningitis prophylaxis.

E: So, for others working in the pharmacy profession, how can they find this information?

A: Well, it was a little tricky finding primary literature as a randomized control trial would not be ethical in this situation. You are extremely unlikely to find a placebo-controlled randomized control trial that gives some women combined oral contraceptives and antibiotics, and some women combined oral contraceptives and placebo, then see who gets pregnant. We did find a few studies that claimed that Rifampin and Rifamycin antibiotics were the only ones to be concerned with.

H: To begin our search, we looked at RxTx to see what the monograph for Tri-Cyclen Lo stated. It was stated that antibiotics may cause the pills to not work as well and that a back-up method should be used. However, this monograph did not specify whether all antibiotics may cause a decrease in efficacy. As this is where a lot of pharmacists and patients gain information about medications, it is likely the main reason why people are unaware of the effects of antibiotics on birth control use. Therefore, we then went on to explore other sources.

E: Next, we searched UpToDate and DynaMed. Both databases concluded that rifampin is the only antibiotic proven to decrease serum ethinyl estradiol and progestin levels in women taking oral contraceptives. Specifically, DynaMed stated rifampin increases the metabolism of the birth control, affecting its efficacy and therefore non-hormonal contraception is required.

R: To focus on the reliability of these databases, DynaMed and UpToDate are summaries. These databases include the most recent information, where each topic has been searched, evaluated and critically appraised. As the evidence is critically appraised and evaluated, the information has been assessed for bias, confounders, and well researched. It can be concluded that it is a trusted and reliable source.

S: To check for primary research articles on the subject we searched Pubmed. An article titled "Drug interactions between non-rifamycin antibiotics and hormonal contraception: a systematic review" by Simmons, re-enforced that there is no drug interactions between hormonal contraceptives and non-rifamycin antibiotics. There was no difference in ovulation suppression or breakthrough bleeding were observed as well as no significant decrease in any progestin

pharmacokinetic parameters observed during co-administration with any antibiotic.  
(*Simmons, 2018*)

R: Also another article, “Antibiotics and oral contraceptives”, by Scott S DeRossi and Elliot V Hersh stated the concomitant ingestion of ampicillin, tetracycline, doxycycline, metronidazole, erythromycin, fluconazole, and others did not reduce plasma levels of either the estrogen or progestin component of the oral contraceptive. The study looked at retrospective studies and clinical trials. They did note that the sample sizes were relatively small, however the incidence of such a rare interaction would not differ from the accepted normal failure rate of oral contraceptive therapy.  
(*DeRossi, 2002*)

A: Overall our findings concluded that only rifampin and other rifamycin antibiotics decrease the efficacy of birth control as it enhances the liver’s ability to metabolize the birth control resulting in decreased blood levels and therefore decreased efficacy.

H: Other antibiotics don’t interfere with the efficacy of Tri-cyclen Lo unless you experience diarrhea or vomiting. This would be due to the altered GI absorption of the birth control. If your birth control isn’t absorbed properly then it won’t work as effectively. In the situation of having diarrhea or vomiting episodes while taking antibiotics, we recommend using an alternative method of contraception, but once again, this is not directly due to the antibiotic, rather the altered absorption.  
(*Pharmacist’s Letter Canada: Managing Antibiotic and Hormonal Contraceptive Interactions*)

E: Just to conclude and stress the important take home points:

If you have diarrhea or vomiting, which may be a side effect of taking an antibiotic, this may cause interruption in absorption of the Tri-cyclen, therefore decreasing its efficacy. However, this is not due to a drug interaction.

If you are not taking your OC properly, such as missed dose, or taking it at a different time, this may decrease efficacy. However, this is not due to an interaction. In these cases, you should use protection. So if you take your oral contraceptive as directed, don’t experience diarrhea or vomiting, and you aren’t taking rifampin, you do not need to use back up contraception while taking antibiotics. However, if it gives the patient a peace of mind, there is no harm in using it.

MC: We hope you enjoyed the second part of our three-part series where we hear from our students at Memorial School of Pharmacy. Let us know what you think, check us out on Facebook under Memorial School of Pharmacy.

CB: And you can email us at any time. We’d love to hear your feedback and any ideas for future episodes. Our email is [medthread@mun.ca](mailto:medthread@mun.ca).

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