Development of Pharmacokinetic and Pharmacodynamic Models to Assess Efficacy of Contraceptive Pills and Arm Implants in Birth Control

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0 Abstract

In this project, we created a comprehensive pharmacokinetic (PK) model for two distinct methods of birth control: short-term contraceptive pills and long-term arm implants. The primary objective was to explore the dynamics of commonly used birth control forms, enabling a deeper understanding of their effectiveness and risk factors. To achieve this, a 4-compartment and 3-compartment model was developed to simulate the drug transport mechanisms within the body. Additionally, a limited pharmacodynamic (PD) model was constructed to quantitatively assess the contraceptive efficacy of each method. The resulting model exhibited robustness, capturing critical parameters like accumulation ratios without direct input. The study's findings highlighted essential distinctions between the two methods. The model indicated that the pill method demands strict adherence, as missing a single day significantly elevates the risk of unintended pregnancy. According to the model, missing two consecutive days virtually guarantees ovulation. The arm implant proved to be a more consistent birth control option, although the model fails to address concerns about accessibility or equity. The PK model demonstrated resilience, and the PD model proved highly sensitive, potentially susceptible to overfitting. This research contributes valuable insights into the pharmacokinetics of birth control, aiding in better-informed contraceptive choices and safer family planning.

1 Introduction & Background

In the U.S. in 2008, over half of pregnancies were unintended or unwanted, with unintended pregnancy rates being even higher in subset populations such as teens or low-income communities [8]. Such unintended pregnancies can take a major toll on the financial and social statuses of families. As such, access to various forms of contraception, including birth control, has been on the rise. In the U.S. alone, over 88% of women aged 15-44 have or will use some form of birth control[18], such as a daily pill or a long-term implantable drug.

Most modern birth controls suppress pregnancy risk by releasing Estrogen and Progesterone agonists. Naturally produced in a monthly cycle, estrogen and progesterone [16] inhibit the release of Follicle Stimulating Hormone (FSH), among many other hormones, from the hypothalamus. FSH plays a significant role in the development and maturation of follicles, and thus, in suppressing FSH, birth control effectively prevents ovulation. Our mathematical model will utilize different parameters to predict and compare how Yasmin (a pill taken daily), and Nexplanon (a device implanted in the arm for three years) vary in their methodology and effectiveness as birth control options. Yasmin primarily releases ethinyl estradiol (EE) and drospirenone (DRSP) as estrogen and progesterone agonists, whereas Nexplanon utilizes progestin as a progesterone agonist. Our main goal is to determine which method is superior, (a pill or implantable) by analyzing its efficacy and interaction with biological processes within the body.

To accomplish this, we utilize mathematical pharmacokinetic (PK) models to track the concentration of various drugs as they move through organ systems. PK modeling is essential in modeling how different drug dosing patterns and parameters can influence the effectiveness of drugs, and hence can give insight into different strengths and weaknesses of different forms of birth control. The movement of drugs in the body is carefully balanced, and inaccurate estimations in mathematically modeling how birth control interacts with the human body could have impactful consequences, such as unintended pregnancies or infertility.

2 Model Development

2.1 Pill Based Model

2.1.1 Conceptual Model

The compartment model developed for EE and DRSP are identical, since both molecules are absorbed via the same pathway and target similar receptors in the hypothalamus. The difference between the movement of the two molecules lies in the dosing of the drug and various rate constants. To track the movement of EE and DRSP, the following four-compartment model was developed:

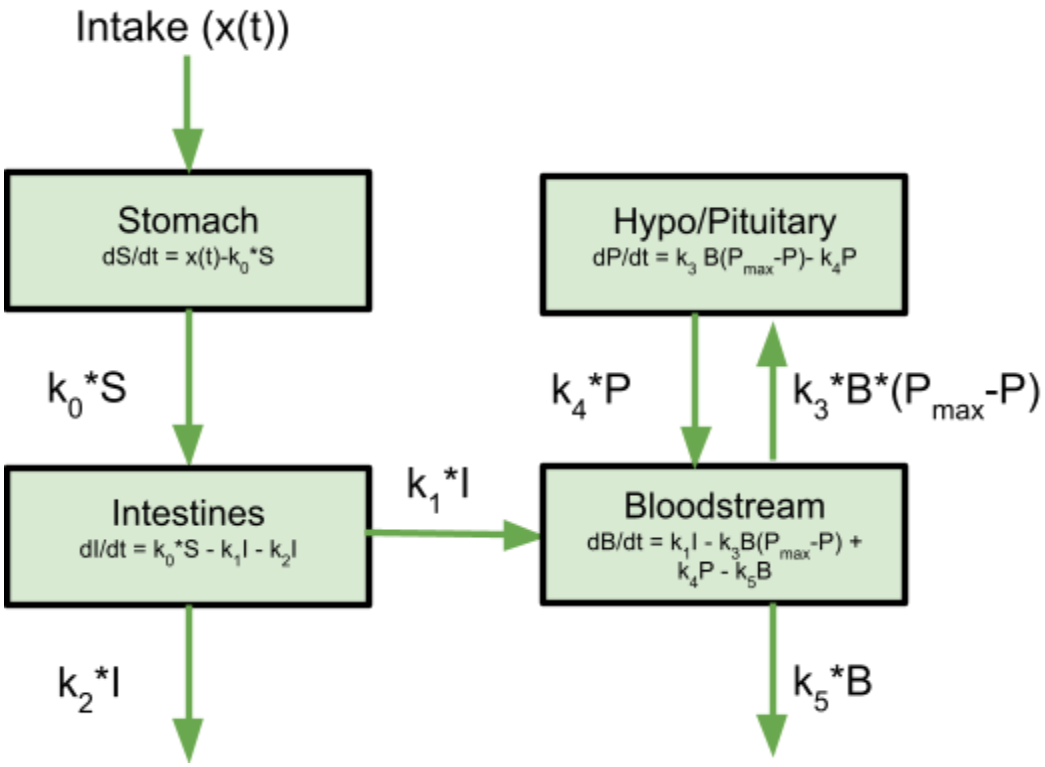


Fig 1: Box and arrow diagram of our four compartment model.

In the model, the synthetic drug of interest is input at a rate of $x[n]$ directly into the stomach. Following entry into the stomach, the drug diffuses by a first order rate into the intestine as per assumption 3. From here, the drug is either directly excreted as waste, equivalent to passing through the GI system, or absorbed into the bloodstream. The ratio of absorption to total drug is equivalent to the bioavailability. Once in the bloodstream, the drug can bind and unbind with target receptors, and any molecules in the bloodstream also decay via metabolism/excretion as per assumptions 2 and 4. Basic enzyme ligand receptor kinetics are utilized here, where the binding rate is proportional to the amount of drug in the bloodstream and the amount of free receptors, while the rate of unbinding is proportional to the amount of bound ligand-receptor complexes. The amount of free receptors will be proportional to the difference between the maximum amount of bound drug with the existing amount of bound drug.

2.1.2 Model Assumptions and Facts

1) All synthetic Estrogen and Progesterone come from an external source. The body does not generate any synthetic drug.

2) Removal of drugs only occurs in the bloodstream. *The majority of drug breakdown occurs in the bloodstream since the bloodstream holds the vast majority of the drug at any given time [Fermi approx. in appendix].*
3) Movement of molecules from one compartment to another is mostly first order with respect to the molecule of interest. *Since movement can be thought of as a reaction where a single molecule moves from one compartment to another, first order with respect to the drug makes the most sense. Even our receptor binding formula, which will be second order overall, is still first order with respect to synthetic drugs.*
4) Removal of drug can be characterized in a single "half-life" term which encompasses both metabolism by the liver and excretion by the kidneys. *Half-life is a commonly measured pharmacokinetic variable in many different models [15].*
5) Receptors for our synthetic drugs of interest are found in the hypothalamus only. *Estrogen and progesterone mainly impact the menstrual cycle by regulating FSH, which is produced and regulated in the hypothalamus [13].*

2.1.3 Model Parameters

Parameter	**Description**
$S_{E/P}$	Amount of synthetic EE/DRSP in the stomach
$I_{E/P}$	Amount of synthetic EE/DRSP in the intestine
$B_{E/P}$	Amount of synthetic EE/DRSP in the bloodstream
$P_{E/P}$	Amount of synthetic EE/DRSP bound to hypothalamus/pituitary receptors
$x_{E/P}(t)$	Input rate of synthetic drug
$k_{0,\,E/P}$	Rate of transfer of synthetic drug from stomach to intestine
$k_{1,\,E/P}$	Rate of absorption of synthetic drug from intestine to bloodstream

$k_{2,\,E/P}$	Rate of excretion of synthetic drug from intestine to body waste
$k_{3,\,E/P}$	Rate of binding of synthetic drug to receptors
$k_{4,\,E/P}$	Rate of disassociation of synthetic drug from receptors
$k_{5,\,E/P}$	Rate of decay of synthetic drug from the bloodstream
P_{max}	Maximum mass of bound synthetic EE/DRSP
$v_{d,\,E/P}$	Volume of distribution for synthetic EE/DRSP

Table 1: Table of parameters used in the conceptual model.

From the parameters above, we derive the following differential equations. Note that subscripts for E/P are removed for clarity, but both E and P will have their own identical set of differential equations with different parameters:

$$\frac{dS}{dt} = x(t) - k_0 S$$

$$\frac{dI}{dt} = k_0 S - k_1 I - k_2 I$$

$$\frac{dB}{dt} = k_1 I - k_3 B \cdot (P_{max} - P) + k_4 P - k_5 B$$

$$\frac{dP}{dt} = k_3 B \cdot (P_{max} - P) - k_4 P$$

As seen above, entry into the stomach is dictated by the input function, x[n], and diffuses at a first order rate into the intestines. Once in the intestines, the drug is either removed at a first order rate into the bloodstream, represented by $k_1 I$, or excreted into waste, represented as $k_2 I$. Bloodstream drug can then bind to the pituitary as described prior at a rate of $k_3 B \cdot (P_{max} - P)$, and unbinds from the pituitary at a rate of $k_4 P$. Lastly, drugs in the blood naturally decay at a rate of $k_5 B$. It is important to note that the rate of binding with the pituitary occurs relatively quickly compared to the timescale we are observing (hours), and the results demonstrate relatively quasi-steady state kinetics.

2.1.4 Parameter Search

For both Estrogen and Progesterone, bloodstream drug concentration peaks at around 1.5 hours [12]. Values for k_0 and k_1 were empirically tuned to match these observations. Bioavailability was used to compute k_2 from k_1, since the ratio, $\frac{k_1}{k_1+k_2}$ gives the ratio of absorption into the bloodstream to total drug consumed. For EE and DRSP, bioavailability was found to be 40% and 76% respectively [4]. k_3 were fit to empirically tested binding rates, while k_4 was calculated using k_d, since $k_d = \frac{k_4}{k_3}$. k_d was found to be around 0.02 nM and 0.19 nM for EE and DRSP respectively [12][25]. k_5 was computed using empirically tested half lives, and is given by $\frac{ln(2)}{t_{1/2}}$, where $t_{1/2}$ is the half life of the synthetic compound. $t_{1/2}$ was found to be 12.2 hours and 30 hours for EE and DRSP respectively [12]. P_{max} was estimated via a fermi approximation shown in the appendix, and v_d was estimated to match our bloodstream concentration with empirically tested values. $x[n]$ was represented as delta functions repeating daily for 21 days on and 7 days off to match the recommended dosing of YASMIN [1]. The exact values computed can be found in the appendix.

2.2 Implant Based Model

2.2.1 Conceptual Model

The following compartments are used to model the movement of progestin released by the arm implantable birth control:

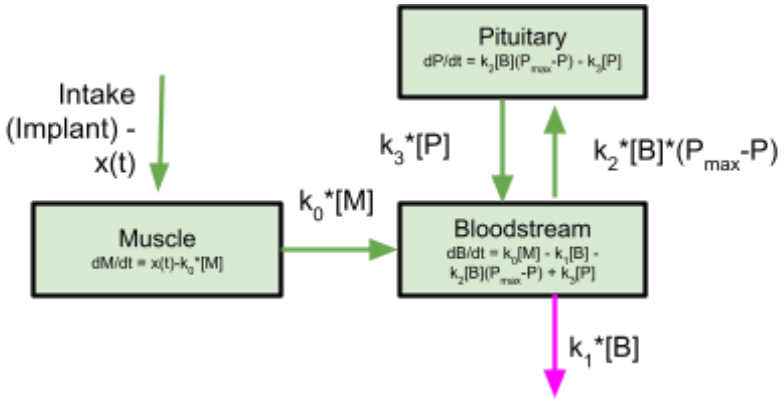


Fig 2: Box and arrow diagram of our three-compartment model.

In the model, progestin is input at a rate of $x(t)$ directly into the muscle, described later in this paper. For the arm implant, the bioavailability of the progestin is ~100% [20]. The hormone is then absorbed into the

bloodstream at a rate of $k_{0,P}$, where it is either broken down into inactive metabolites or travels to the pituitary where it directs FSH. Once absorbed into the bloodstream, the drug can bind and unbind with target receptors in the pituitary gland, and any molecules in the bloodstream also decay via metabolism/excretion. Similar to the pill model, the rate of progestin binding in the pituitary is second order, and first order with respect to both bloodstream drug concentration and free receptors. The amount of free receptors is still proportional to the difference between the maximum amount of bound drug with the existing amount of bound drug.

2.2.2 Model Assumptions and Facts

Along with assumptions 1–5 from 2.1.1 (with a slight modification to assumption 1 being that the arm implant, nexplanon, releases only progestin), we include the following assumptions:

1) The amount of the progestin released by the implant decreases most significantly from 60 ug in the first month of implantation, and decreases at a slower rate as it approaches 30 ug at one year of implantation [20].
2) The entirety of active progestin is released into the muscle/tissue surrounding the implant and completely absorbed into the bloodstream [26].

2.2.3 Model Parameters

Parameter	**Description**
M_P	Amount of synthetic progestin in the muscle
B_P	Amount of synthetic progestin in the bloodstream
P_P	Amount of synthetic progestin bound to hypothalamus/pituitary receptors
$x_P(t)$	Input rate of synthetic drug
$k_{0,P}$	Rate of absorption of progestin from muscle to bloodstream
$k_{1,P}$	Rate of decay of progestin from the bloodstream
$k_{2,P}$	Rate of binding of progestin to receptors

$k_{4,\,P}$	Rate of disassociation of progestin from receptors
P_{max}	Maximum mass of bound progestin
$v_{d,\,P}$	Volume of distribution for synthetic progestin

Table 2: Table of parameters used in the conceptual model.

For our arm implant model, we have derived the following system of ordinary differential equations:

$$\frac{dM}{dt} = x(t) - k_0 M$$

$$\frac{dB}{dt} = k_0 M - k_1 B - k_2 B * (P_{max} - P) + k_3 P$$

$$\frac{dP}{dt} = k_2 B * (P_{max} - P) - k_3 P$$

2.2.4 Parameter Search

The arm implant releases an ovulation-preventing level of progestin within the first day of implantation, and releases 60 ug of progestin each day for the first weeks of implantation, decreasing rapidly until the end of month one, before reaching 30 ug released at month 9 and consistently releasing 30 ug per day for 3-5 years of use. Our input x[n] factors this as a linear relationship in the first 21 days of implantation and another, less steep, decreasing linear relationship from day 21 to the start of month 9. For the value of k_0, we know that the bioavailability of progestin from the arm implant is 100%, so we set a rate value of .5 so as not to overwhelm the model with a delta function-like input. k_1 was computed using empirically tested half lives, and is given by $\frac{ln(2)}{t_{1/2}}$, where $t_{1/2}$ is the half life of the progestin. $t_{1/2}$ was found to be 25 hours for the progestin [20]. The exact values computed can be found in the appendix.

2.3 Ovary Response Model

2.3.1 Model Assumptions and Facts

Along with assumptions 2–4 from 2.1.1, we incorporate the following assumptions:

1) The body only produces FSH as a function of synthetic EE and DRSP, or for the implant model, progestin. *Although FSH is regulated internally, we only focus on the production of FSH that results from exogenous drugs in order to simplify the model.*

2) Steady State FSH levels are around 7 IU/L [14].

3) FSH is produced at the steady state rate when 0% of EE and DRSP or progestin receptors are bound. *In our simplified receptors, none bound should imply no inhibition of FSH.*

4) FSH is linearly inhibited by up to 25% of the base rate when EE and DRSP or progestin receptors are fully bound. *This simplifying assumption encapsulates negative feedback behavior, while also capturing a certain degree of minimum FSH release in the body.*

5) Follicle growth can be modeled as a hill model using FSH. *Hill models are frequently used to model ligand receptor binding, and is particularly useful here since we do not have exact concentrations of FSH. This allows us to create an approximating function where low levels of FSH correspond to little "effect", or growth of follicles, and high levels of FSH correspond to a maximum growth of follicles.*

6) When FSH levels fall below 4.1 IU/L, follicles will fail to grow significantly. *FSH levels govern growth of follicles. The average FSH levels of prepubescent females is around 4 IU/L, and we do not expect follicle growth to occur before puberty completes [21].*

7) Follicle size is reset every month, and cannot exceed or fall below 0 or 100. *After a follicle is fully developed, the released egg will be flushed out, and a new follicle will be chosen to grow.*

2.3.2 Conceptual Model

FSH is modeled in a 2 compartment model, where the hypothalamus generates and distributes FSH to the bloodstream. FSH in the bloodstream naturally decays, and utilizing the Hill model, we convert FSH in the bloodstream to a rate of growth of our follicle.

Although an additional ovary compartment can be used to model FSH binding to receptors, the creation of the Hill model acts as a simplifying model for the percentage of receptor binding. A hill model is used because the amount of "FSH" we model is not truly equivalent to the amount of circulating FSH, but rather a placeholder, as explained in assumption 1, so attempting to use

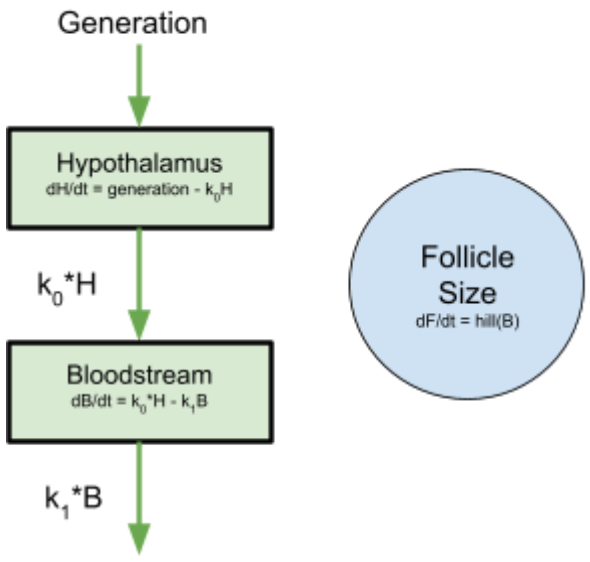


Fig 3: Conceptual model for the ovary and follicle system

enzyme kinetics to model receptor binding would prove to be extremely difficult since there are no empirical trials to base parameters off of.

2.3.3 Model Parameters

Parameter	Description
H	Amount of FSH in the hypothalamus
B	Amount of FSH in the bloodstream
EE_{bound}	Percent of bound EE receptors in hypothalamus/pituitary (from pill model)
$DRSP_{bound}$	Percent of bound DRSP receptors in hypothalamus/pituitary(from pill model)
P_{Bound}	Percent of bound progestin receptors in hypothalamus/pituitary(from implant model)
k_0	Rate of release of FSH from hypothalamus to bloodstream
k_1	Rate of decay of FSH in the bloodstream
c_0	Base/maximum rate of FSH production
EC_{50}	Amount of FSH needed to achieve 50% of the maximum growth of the follicle
E_{max}	Maximum growth rate of follicles
F	Follicle size (as a percentage of being fully developed)

Table 3: Table of parameters used in the conceptual model

From the parameters above, we derive the following differential equations to model the movement of FSH in the body. Note the use of two different generation terms depending on if the PD model is being used for the pill or the arm implant model.

$$gen_{EE/DRSP} = (1 - 0.75 \cdot (\frac{EE_{bound}}{2} + \frac{DRSP_{bound}}{2})) \cdot c_0$$

$$gen_{Progestin} = (1 - P_{bound}) \cdot c_0$$

$$\frac{dH}{dt} = gen - k_0 H$$

$$\frac{dB}{dt} = k_0 H - k_1 B$$

Additionally, the growth of the follicle can be modeled by the following hill equation.

$$\frac{dF}{dt} = \frac{1}{1+(\frac{EC_{50}}{B})^{40}} \cdot E_{max}$$

2.3.4 Parameter Search

E_{bound} and P_{bound} are found via the models developed in 2.1 and 2.2. k_0 was chosen to match the fast acting release rate of FSH from the hypothalamus. Using the half life of FSH, which was found to be ~1.73 hours [15], k_1 was computed to be $\frac{ln(2)}{1.73} = 0.4$. Using assumption 2, we find that $generation - decay = 0$ since the system is at steady state. Therefore, $c_0 = k_1 B = 0.4 * 7 = 2.8 \frac{IU}{L\,hr}$. From assumption 6, we use $EC_{50} = 4.1 \frac{IU}{L}$, since we hope to have $4.1 \frac{IU}{L}$ as our inflection point where we see FSH having an effect on follicle size. E_{max} was found by assuming in uninhibited growth, we expect the follicle to be fully grown in 2 weeks, or 336 hours. Therefore, $\int_0^{336} E_{max} = 100$, so $E_{max} = \frac{100}{336} = 0.3 hr^{-1}$. The exact values computed for each parameter can be found in the appendix.

3.1 Distribution of Ethinyl Estradiol Across Body After Daily Birth Control Pill

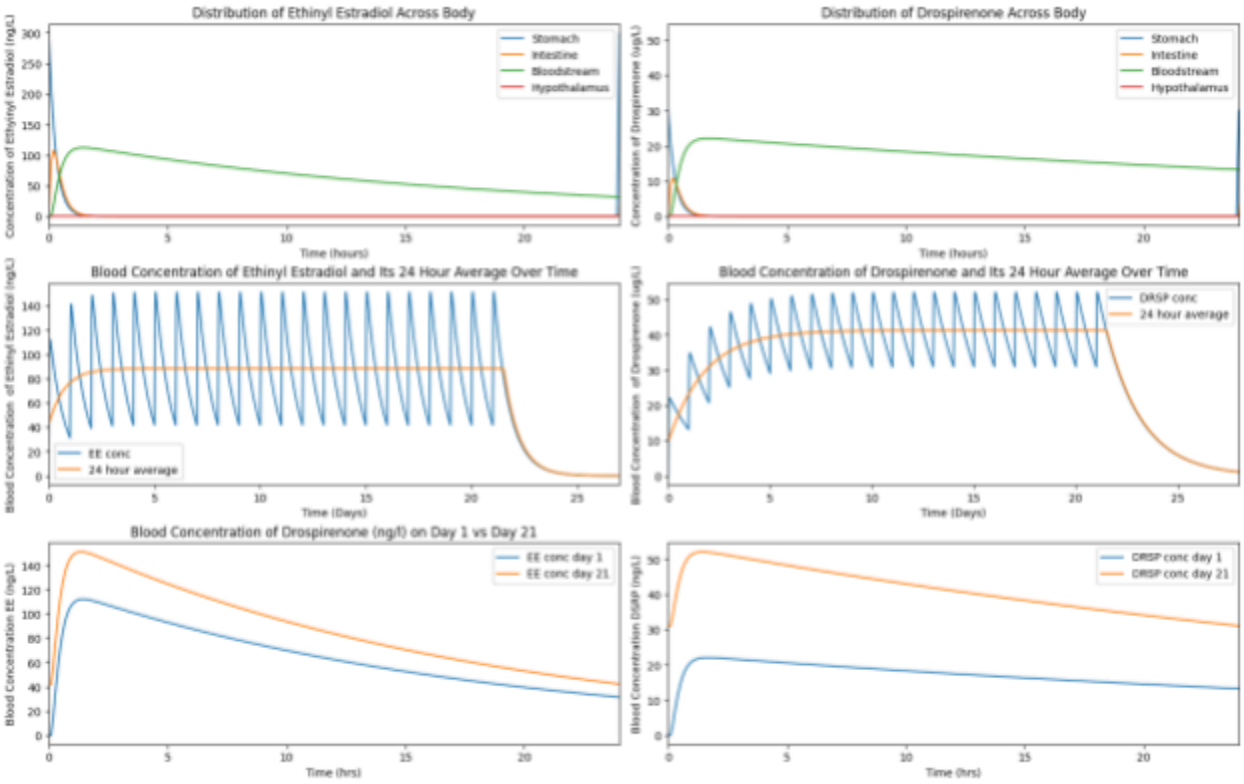


Fig 4: Overview of Pill Model Results

Fig 4.A and 4.B demonstrate the various concentrations of drugs EE and DRSP within each compartment for the first 24 hours of pill administration. The concentration of drugs moves rapidly from the gastrointestinal system to the bloodstream, where we observe a slow decay in concentration over time. The dosage for EE and DRSP are 30 ug and 3mg respectively. The amount of drug bound to the hypothalamus is minuscule relative to the amount of drug in the bloodstream, which is reasonable given our Fermi approximation. The enhanced plot of bound drugs is plotted in the appendix, and follows similar trends to the trends in the bloodstream.

Fig 4.C and 4.D plot the bloodstream concentration over a full month of drug usage. From the plot, we observe that EE reaches steady state bloodstream concentration in around 2 days, while DRSP reaches steady state in around a week. We observe that EE and DRSP doses do not exceed the toxic threshold of 1000 μg/kg body weight and 2000 mg/kg body weight respectively.

Fig 4.E and 4.F compare and contrast the bloodstream concentrations at the beginning of the cycle and at the end of the cycle. Using these results, we determine the accumulation ratio to be ~30% for EE and ~120% for DRSP, which matches closely with existing literature results of 23% and 90% for EE and

DRSP respectively [4][3]. These results help confirm the validity of our model, since the accumulation ratio was not used to fine-tune the model, nor used in any parameter search.

3.2 Distribution of Progestin Across Body Using Nexplanon

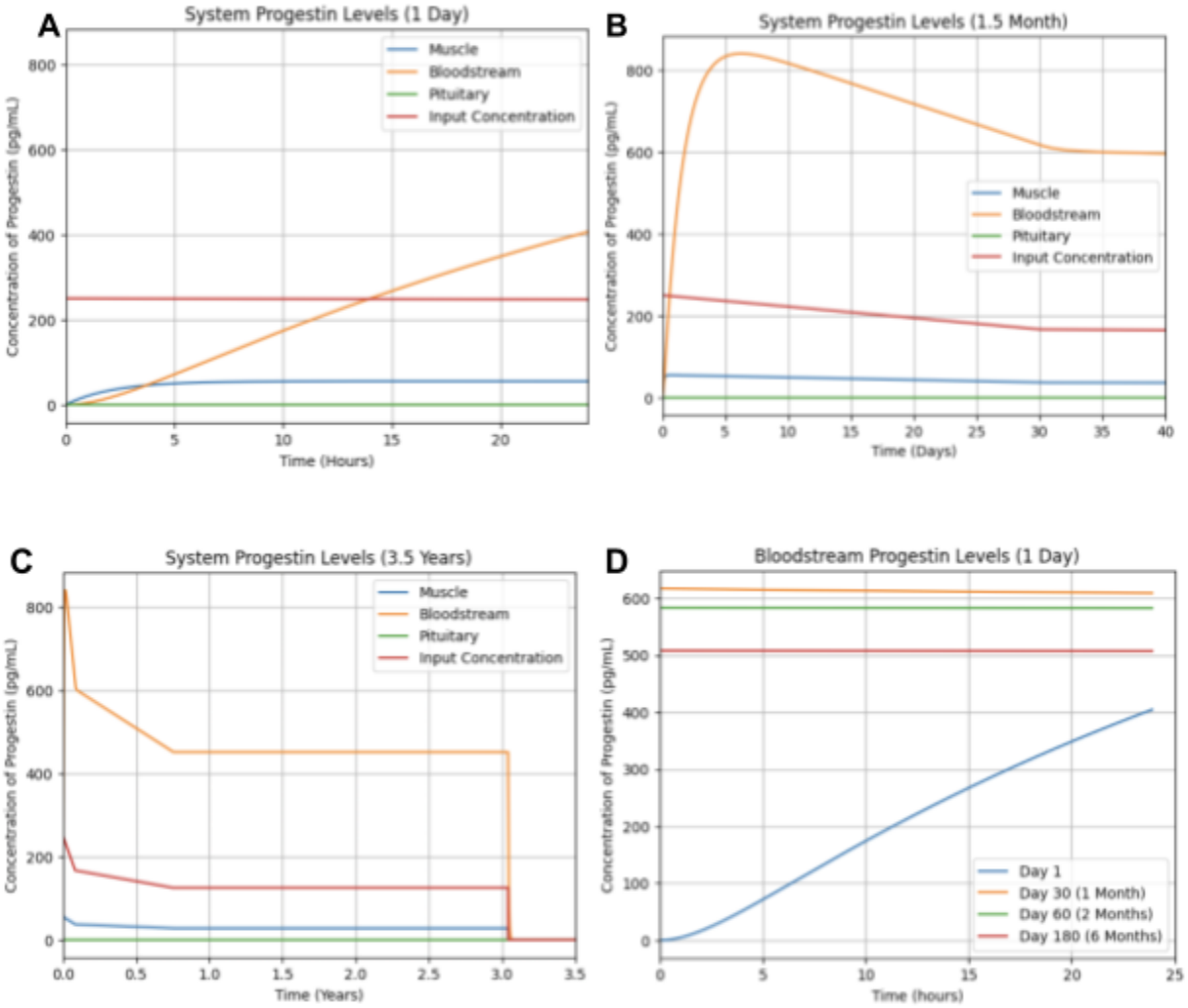


Figure 5: Overview of Implant Model Results

Over the course of a month and a half, the progestin level peaks at three days in the muscle and 7 days in the bloodstream, as seen in fig 5B. Both concentration decreases until reaching steady-state at 31 days and 35 days in the muscle and bloodstream respectively. We observe that these trends for progestin concentrations match closely with experimental data [26], improving the validity of our model.

Over a course of three years, the progestin concentration in the bloodstream in an individual increases for about a month. However, the implant is able to release enough progestin that within the first day of implantation, ovulation-inhibiting levels of progestin are found in the bloodstream. The bloodstream

progestin level rapidly decreases until the second month, and at the ninth month, the concentration reaches steady state. Comparing the bloodstream progestin levels on different days, the first day is the only day that we observe significant changes in bloodstream concentration, which intuitively aligns with our expectations, since by day 30, the arm implant model will have long reached a pseudo steady state. In fact, when in steady state, the bloodstream concentration is in steady state with the input function, and thus the curve of the system progestin levels appears to be a scaled version of the input function, which can be a potential flaw in our model. This also explains the sudden drop in bloodstream concentration at the end of 3 years, which is representative of the removal of the implant. A zoomed in plot of the removal date can be found in section 3.4. We also observe that the concentrations of progestin do not exceed the toxic threshold dosage of between 0.5 and 1.0 g/kg body weight.

3.3 Ovary Model Validity

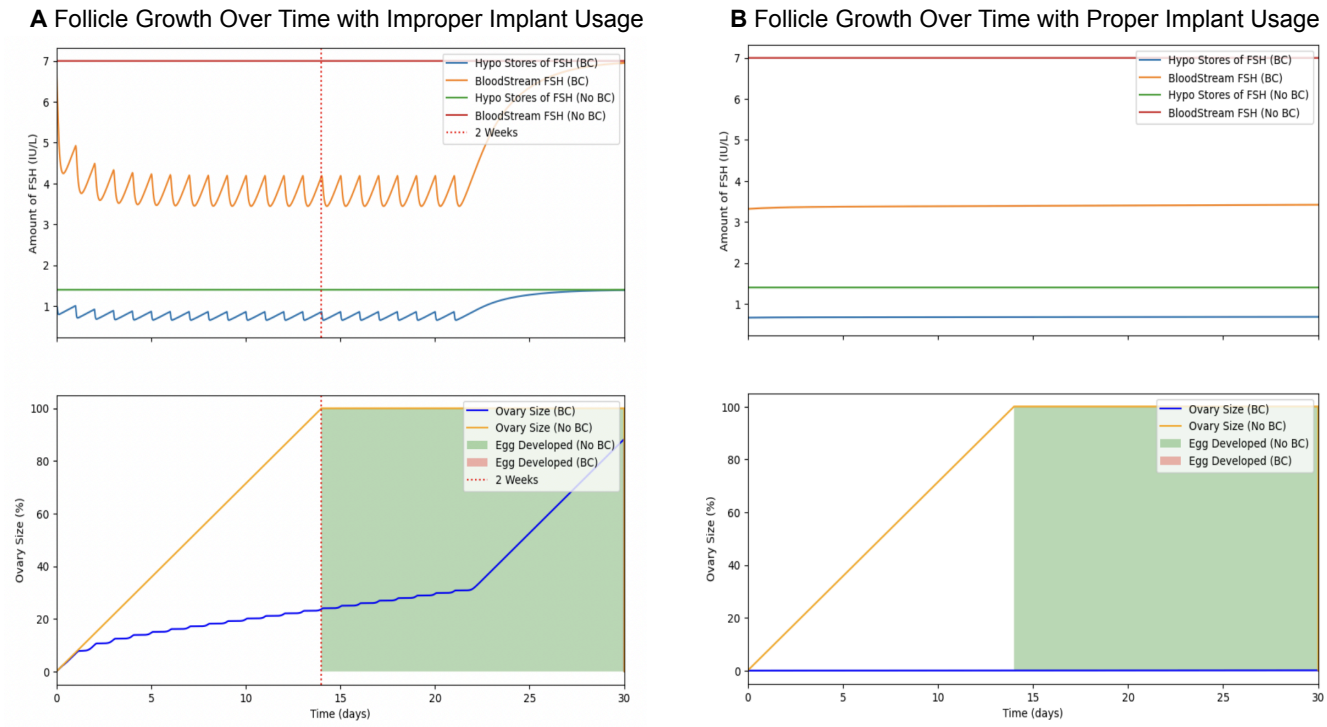


Fig 6: Overview of Ovary Model Results with Proper Birth Control Usage

Applying the results from Fig 4 to the ovarian model yields the graph 6.A. When no birth control is used, a follicle is able to be fully developed at around 2 weeks. Additionally, with how our model is defined, the entire FSH system is in fact at a steady state for the situation where no birth control is taken. With proper birth control usage, we see an oscillatory and suppressed amount of bloodstream FSH, corresponding to the oscillatory amount of EE/DRSP levels in the bloodstream. This ultimately results in decreased follicle

growth such that the model predicts no ovulation to occur in the entire month. The graph showing concentration of FSH vs growth of follicles is in the appendix.

Applying the results from the progestin model from Fig. 5 also demonstrate successful inhibition of ovulation. Due to the long term nature of the progestin release however, we observe no oscillatory FSH release, and overall greater suppression of follicle growth, indicating greater birth control effectiveness.

3.4 Effect of Varying Input Dosages

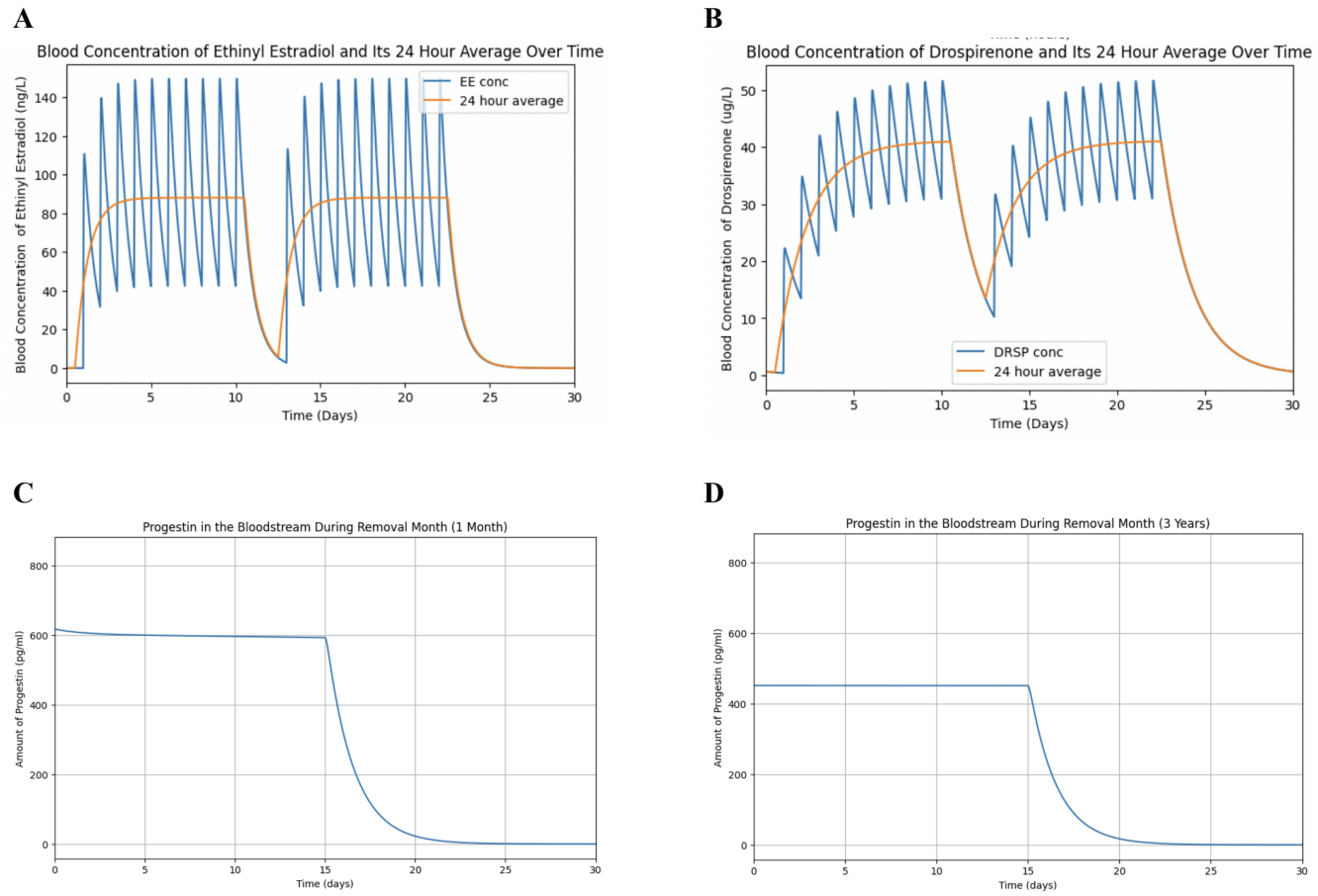


Figure 7: **Model effects of improper pill usage/early removal of implant**

An important factor to analyze is how our model reacts to when individuals fail to adhere to proper dosing. In Fig 7.A and 7.B, the individual forgets to take 2 pills at around the 10 day mark. The resultant change in bloodstream drug concentration is plotted. EE appears to reset almost to 0 concentration levels, whereas DRSP falls by nearly 80%. EE subsequently takes another 3 days to return to steady state levels, while DRSP takes nearly another week to return to steady state levels. Different patterns of dosing schedules are plotted in the appendix as well, such as forgetting for a day, followed by taking twice the recommended dosage, or delaying a dose by half a day.

Figure 7.C and 7.D, reflect the bloodstream progestin levels as a result of removal of the implant. Both implants are removed 15 days into a menstrual cycle. 7.C documents the case of removal after one month of implantation, while 7.D analyzes the effect of removal 3 years after implantation. The major difference between the two cases is that the steady state concentration of drug in the 1 month case is roughly 150 mg higher than the steady state concentration in the 3 year case, highlighting the consistency and reliability of the implant birth control.

3.5 Effect of Varying Drug Dosing Schedules on Ovulation Risk

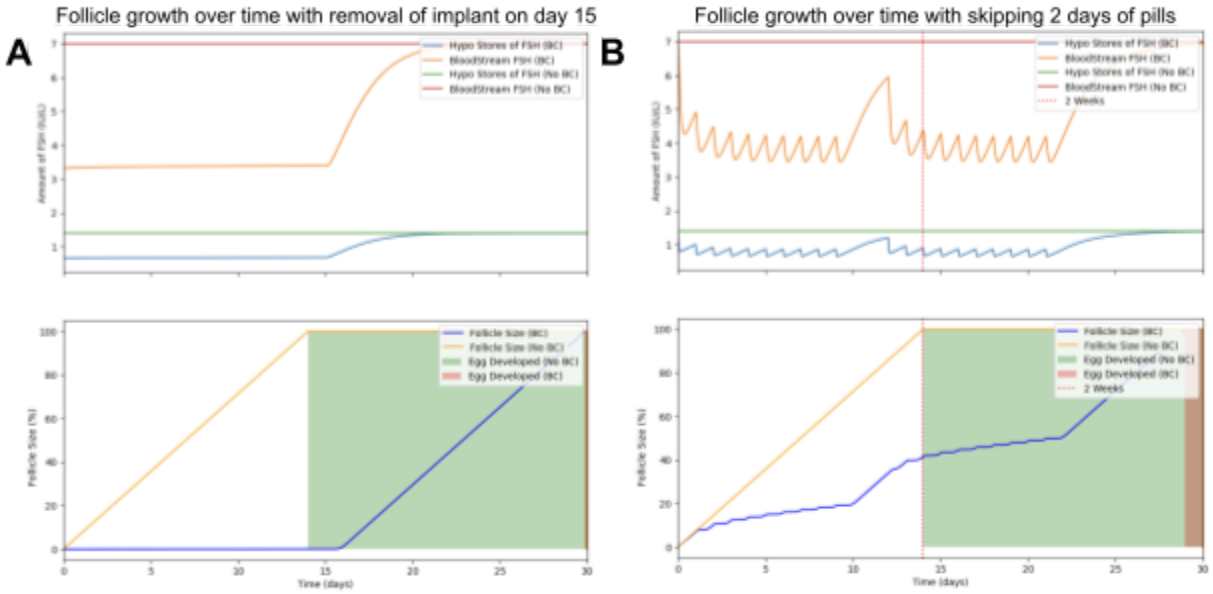


Fig 8: Ovary model predictions with different drug dosings

Figure 8 translates the effects of the improper BC usage from Figure 7 into our ovarian model, to quantify the increased risk in ovulation. As seen, both scenarios result in ovulation occurring at the tail end of the menstrual cycle, indicating failure of complete protection against pregnancy. However, the follicle is still observed to develop at a significantly slower rate than without any birth control at all. Additionally, depending on the day the arm implant is removed in the cycle, there could be entirely no risk of pregnancy involved with the arm implant.

4 Discussion

Both contraceptive pills and hormonal implants are widely used forms of contraception that produce reliable results with the caveat being that they must be utilized properly. The proper use for the implant is trivial as it requires no maintenance, however, the same cannot be said for the pill which requires a careful routine to ensure that it is effective. Details of which are echoed in the results of both of the models. The pill model demonstrates the cyclic nature of dosage, the hormone dependent interactions, and why it is

necessary to remain efficacious. When the pill is taken consistently, FSH is repressed enough to limit the growth of the follicle, i.e. the ovary, and prevent ovulation. However, the model also shows that missing doses widen the window for ovulation, with it only requiring two consecutive missed doses to guarantee ovulation. The implant, in contrast, consistently releases progestin which has the same suppressive effect on FSH and in turn, prevents the ovary from growing and an egg being produced. The only way to produce the conditions for ovulation would be removal of the implant or mechanical (implant) failure.

While birth control has many benefits, there are still risks involved as with any other treatment. For the oral contraceptive, there is a risk of toxicity as well as risk of ovulation. In the long term [16], taking oral hormonal birth control can lead to an increased risk of serious conditions such as cardiovascular diseases as well as cervical and breast cancer. Long-term use of oral contraceptives may also lead to liver damage. There is risk of ovulation as the efficacy of the drug is contingent upon the patient taking it at the correct time everyday. The arm implant also carries separate risks [22]. There may be complications during insertion and removal of the implant as it is able to move through the body. As a result, the implant may end up in the patient's chest which will require surgery to remove and no longer be an effective form of birth control. There may also be complications during recovery such as pain, the implant breaking, and infection. Similar to the pill, the arm implant may increase the risk of blood clots and cancer.

The cost of birth control may also prevent patients from receiving the treatment. A month's worth of birth control pills could cost up to $50 [23] depending on insurance and brand of the medicine. An arm implant could cost up to $1,300 without insurance. However, with insurance, the cost of both treatments could be free or come at a low cost. This does not include the cost of the exam needed in order to receive the pills or arm implant which could be free with insurance or up to $250 without insurance. Additionally, with the arm implant, the patient must pay $300 every three years [23].

In addition to the monetary cost, there is the cost of time. Lower income families/women may not be able to afford to take the time off work to go visit a women's healthcare professional and undergo the procedure for a hormonal arm implant. There may not even be time to schedule and go to an appointment to be examined and be prescribed birth control pills. Thus, birth control is not fully accessible. The cost of scheduling an appointment and paying for the treatment may be a burden to patients without insurance. While there are other options such as using a telehealth provider, the obstacle of time and money still stands.

Each of the treatments has its own disadvantages and advantages. Overall, the arm implant is more effective as the concentrations reach a steady state without the reliance of consistently taking the medication. As long as the implant is inserted during the first five days of the patient's cycle, it is effective immediately. This also applies to oral contraceptives. While the arm implant has a higher cost, it

is a one-time payment for three years. In contrast, the pills incur a monthly cost. Thus, personal preference, economic status, and accessibility must be taken into consideration when deciding the best treatment.

4.1 Sensitivity Analysis

4.1.1 Pill Model

Parameter	% Change in Parameter	% Change in Average Bloodstream Concentration	% Change in t_{max}	% Change in Accumulation Ratio
k_0	+10%/-10%	+0.00%/-0.00%	-4.94%/+6.17%	-0.05%/+0.06%
k_1	+10%/-10%	+5.77%/-6.25%	-0.62%/+1.23%	-0.00%/-0.00%
k_2	+10%/-10%	-5.66%/+6.38%	-1.23%/+1.85%	-0.00%/+0.00%
k_5	+10%/-10%	-9.09%/11.11%	-1.85%/2.47%	-4.05%/+4.99%

Table 4: Sensitivity Analysis of the Pill Model

A sensitivity analysis was conducted on all 3 models to determine the robustness and flexibility of our model. For the pill model, only estrogen was analyzed, as the progesterone model follows an identical set of relationships. Key variables in the model were adjusted by +/-10%, and the changes in various key outputs were measured. For the pill model, we found that no variable played an overwhelmingly significant role in determining the key output values, which indicates flexibility in our model. Additionally, the sensitivity analysis allows us to explore which outcomes certain parameters have the greatest influence over. For example, k_0, the rate of absorption from the stomach into the intestine, has limited effect on the average bloodstream concentration, but does impact t_{max}, or the amount of time needed for the concentration to peak.

4.1.2 Progestin Model

Parameter	% Change in Parameter	% Change in Average Bloodstream Concentration (6 Mo.)

k_0	+10%/-10%	+0.00%/-0.00%
k_1	+10%/-10%	+9.11%/-11.13%

Table 5: Sensitivity Analysis of the Implant Model

The sensitivity analysis of the progestin model reveals k_0 has negligible influence on the average bloodstream concentration 6 months into the implant being inserted. This appears reasonable, since the system would have long reached steady state, so even a slower rate of release from the muscle would likely not impact bloodstream concentration. Rather, the major parameter determining bloodstream concentration is the half life, represented by k_1, which appears to have a large, but reasonable influence on average bloodstream concentration.

4.1.3 Ovary Model

Parameter	% Change in Parameter	% Change in Follicle Size (BC)
k_0	+10%/-10%	+0.09%/-0.12%
k_1	+10%/-10%	-30.6%/+71.85%
c_0	+10%/-10%	+63.77%/-31.85%
EC_{50}	+10%/-10%	-30.79%/+71.26%

Table 6: Sensitivity Analysis of the Ovary Model

The sensitivity analysis of the ovary model reveals high variance when adjusting the input parameters. In fact, in many of the cases, the output becomes nonsensical, as some of these parameter values result in a fully developed follicle even when taking birth control optimally. This indicates a significant weakness in our model, and can be indicative of overfitting of parameters to the data we base our models off of.

4.2 Strengths and Weaknesses

Compared to experimental data, the results, especially pertaining to the modeling of EE/DRSP from the birth control pill and modeling of progestin from the arm implant, are reasonable. A strength of our birth control model is its modular nature. Our model accounts for the typical scenario of the user taking the pill for a thirty day period, with a week in between each thirty day period without birth control. Additionally, we may account for the implications and side-effects when the user skips birth control pills any number of days in a row (we focused on two days, as this was enough to allow ovulation to occur). This includes taking several days for the EE or DRSP to reach steady-state levels or ovulation occurring after skipping. For our hormonal arm implant model, we were able to accurately reflect and model experimental values accepted in literature. The daily, monthly, and yearly amounts of progestin released and subsequently found in the bloodstream was accurate to those found in clinical trials and experiments.

However, a weakness of both the birth control pill model and the arm implant model is the lack of information pertaining to the synthesis of natural estrogen and progesterone. For example, compounds in the birth control pill (such as EE and DRSP) and arm implant (progestin) inhibit production of estrogen and progesterone through a negative feedback loop mechanism. Additionally, another major weakness is the relative sensitive nature of the ovary model. In cases when parameters were altered, the ovary model produced a fully developed follicle, even when the patient had taken birth control regularly. This may have been a result of overfitting the model to existing published literature values, which are based on experimental data. Additionally, our assumption of having a constant value of FSH levels in the individual's bloodstream is not representative of the true system in question. However, a more accurate biological model would display oscillatory behavior of FSH bloodstream levels centered around a constant value (rather than a straight horizontal line as denoted in the FSH model).

In order to make our models more robust and accurate, more experimental data across multiple peer-reviewed studies should be utilized, specifically in representing the body's de novo synthesis of estrogen and progesterone. Additionally, in improving our models, we should consider the different physiologies of individuals using birth control methods (i.e. body composition, age, etc.). Furthermore, additional numerical data pertaining to the relationship of EE and DRSP in birth control pills and FSH levels and follicle size should be incorporated.

5 Conclusion

Our pharmacokinetic model strongly advocates the use of the arm implant for birth control. Due to the relatively constant release profile of the arm implant, the arm implant maintains lower FSH levels and inhibits the development of follicles, minimizing the risk of pregnancy. The arm implant is also able to maintain therapeutic dosages for over three consecutive years after implantation, and poses no risk for failing to follow the dosing pattern, which proves to be a significant risk for pill based birth controls. This

combines to demonstrate that an arm implant not only provides better protection against pregnancy, but also lower overhead maintenance such as the mental toll of taking a pill every day.

However, endorsing this method based solely on mathematical models is risky and shortsighted. Equitable access remains a crucial consideration with any form of drug choice, with challenges like the invasiveness of the implant procedure, associated costs, and time commitments that are challenging to quantify but significant nonetheless.

Moreover, technical risks, although rare, cannot be disregarded. Surgical complications, as mentioned in the discussion section, can occur, and requires the presence of a skilled physician, which is not always accessible to certain populations.

Additionally, our model still has significant flaws. While our PK model has been validated through factors like accumulation ratio and reasonable sensitivity analysis results, the PD model's high sensitivity to input parameters can suggest overfitting. Parameter tuning could potentially introduce unconscious biases into our model as we tune results towards what we expect to occur based on existing data. Future PD models could be significantly improved by analyzing all Estrogen and Progesterone, including Estrogen and Progesterone produced natively in the body. Including this would allow us to validate our PD model with existing data for how we expect FSH to impact the menstrual cycle.

With everything taken into consideration, it is difficult to claim that a certain birth control is "superior" to another. A specific birth control being the better option is likely a nuanced choice that depends on each individual's unique situations. Our model only offers insight into the quantitative comparisons between using a pill based or implant based birth control assuming equitable access to both options.

6 Appendix A

Table A1: Parameter values for pill model.

Parameter	Estrogen	Progesterone
k_0	$3\ hr^{-1}$	$3\ hr^{-1}$
k_1	$2\ hr^{-1}$	$3.8\ hr^{-1}$
k_2	$3\ hr^{-1}$	$3\ hr^{-1}$
k_3	$1\ \mu g^{-1} hr^{-1}$	$0.001\ \mu g^{-1} hr^{-1}$
k_4	$5.93\ hr^{-1}$	$0.696\ hr^{-1}$
k_5	$0.0568\ hr^{-1}$	$0.0231\ hr^{-1}$
P_{max}	$1.47 \cdot 10^{-6}\ \mu g$	$1.81 \cdot 10^{-6}\ \mu g$
v_d	$100\ L$	$100\ L$

Table A2: Parameter values for implant model

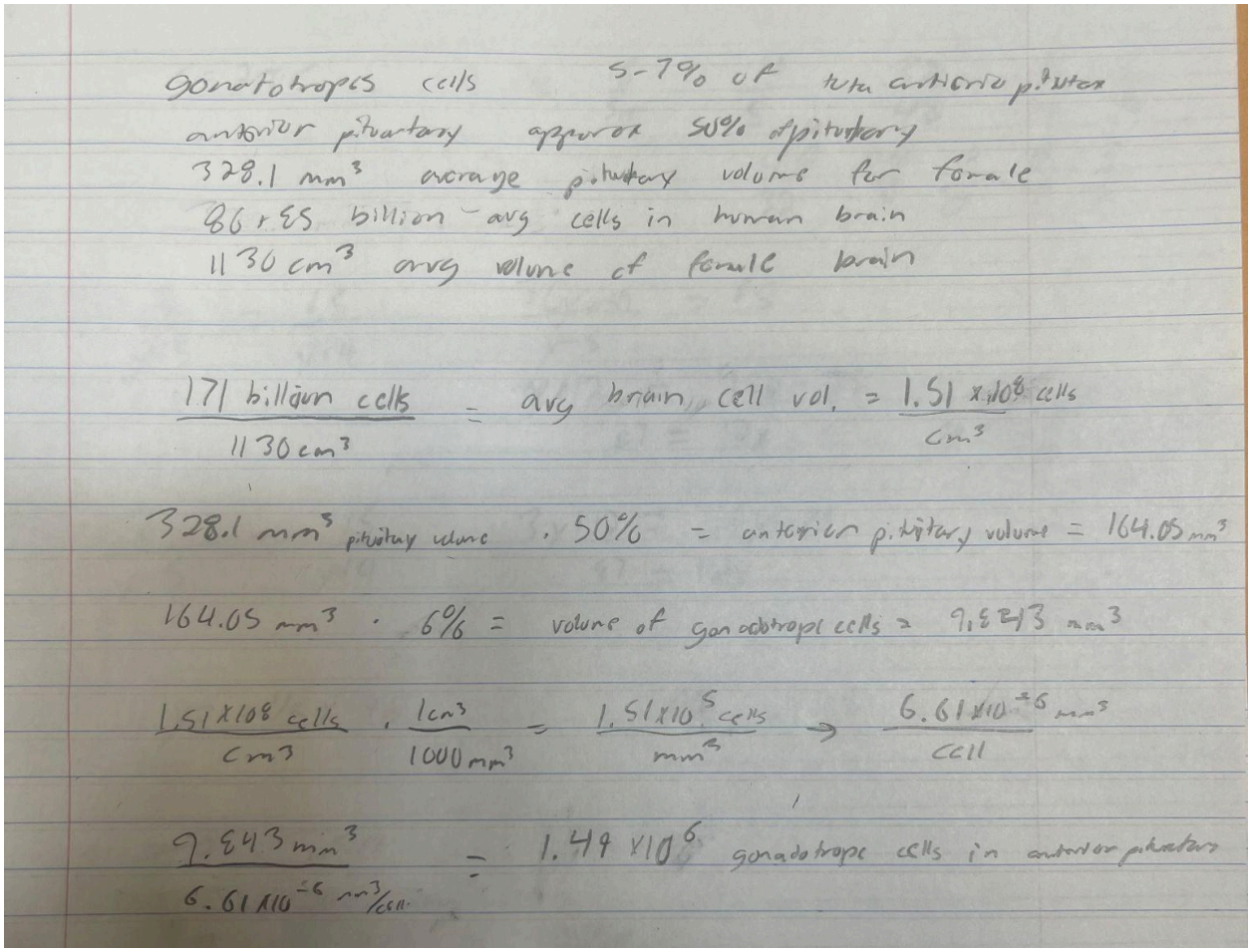
Parameter	Estrogen
k_0	$.5\ hr^{-1}$
k_1	$.0277\ hr^{-1}$

k_2	$.1\ hr^{-1}$
k_3	$10\ hr^{-1}$
v_d	$100\ L$

Table A3: Parameter values for ovary model

Parameter	**Value**
k_0	$2\ hr^{-1}$
k_1	$0.4\ hr^{-1}$
c_0	$2.8\ \frac{IU}{L\ hr}$
EC_{50}	$4.1\ \frac{IU}{L\ hr}$
E_{max}	$0.3\ hr^{-1}$

Fermi A1: Fermi approximation for the number of EE/DRSP/P receptors



$$P_{max} = 1.49 \cdot 10^{6}\ cells \cdot \frac{200\ receptors}{cell} \cdot 6.02 \cdot 10^{23} \frac{mols}{receptor} \cdot MW_{(EE/DRSP/P)} \frac{g}{mol} \cdot 10^{6} \frac{ug}{g}$$

$\frac{2000\ receptors}{cell} = \sqrt{20000\ *\ 200}$ comes from a fermi approximation with a lower bound of 200 and an upper bound of 20,000 [24].

Fig A1: Hill model comparing growth rate of follicle vs. FSH concentration

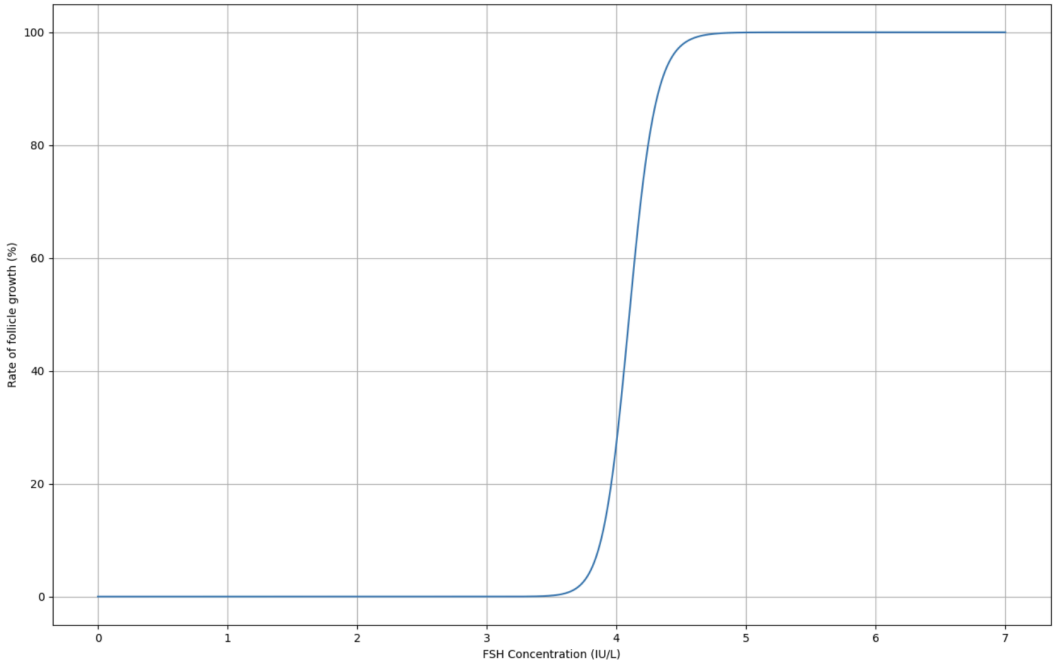


Fig A2: Percent of bound EE receptors over a month of proper pill usage.

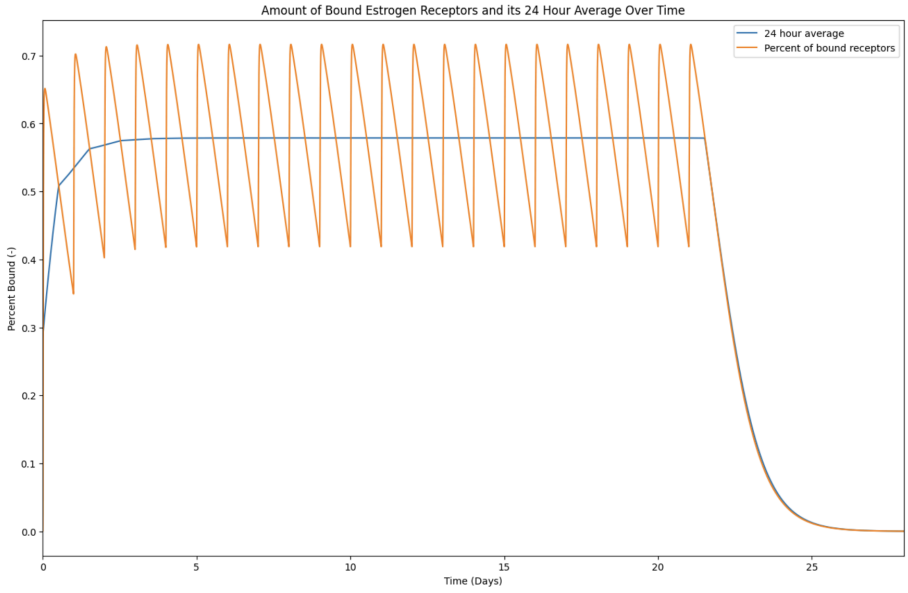


Fig A3: MM kinetics of binding of estrogen Receptors as a function of bloodstream concentration EE

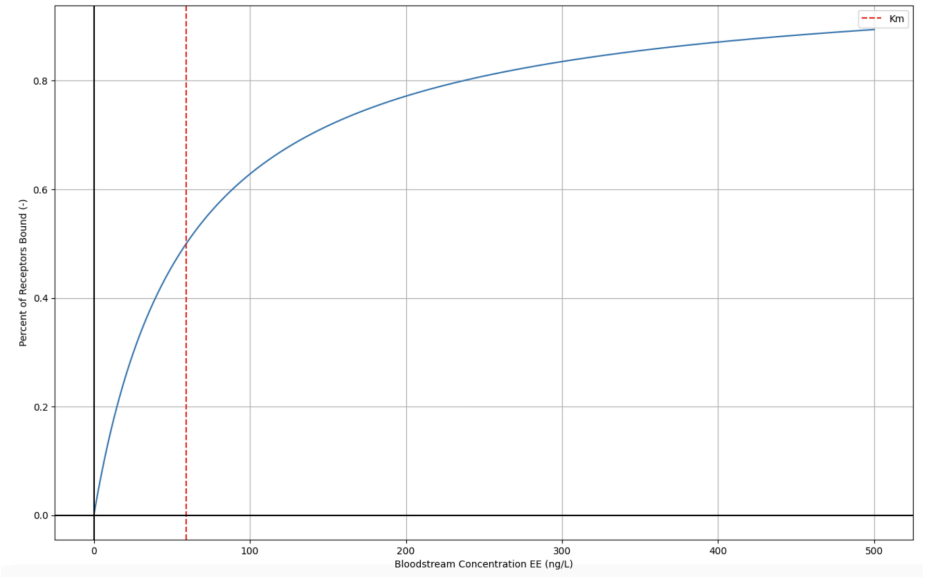


Fig A4: Percent of bound DRSP receptors over a month of proper pill usage.

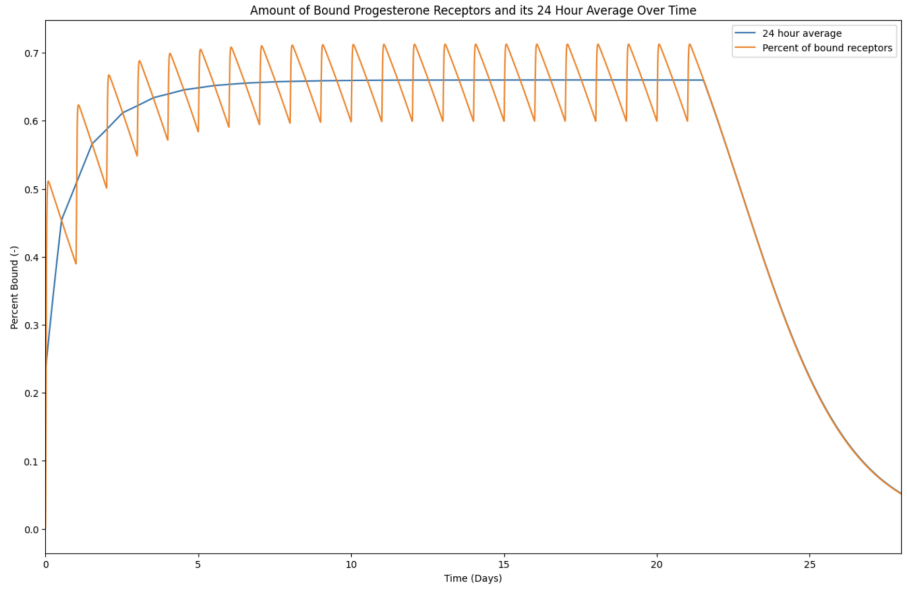
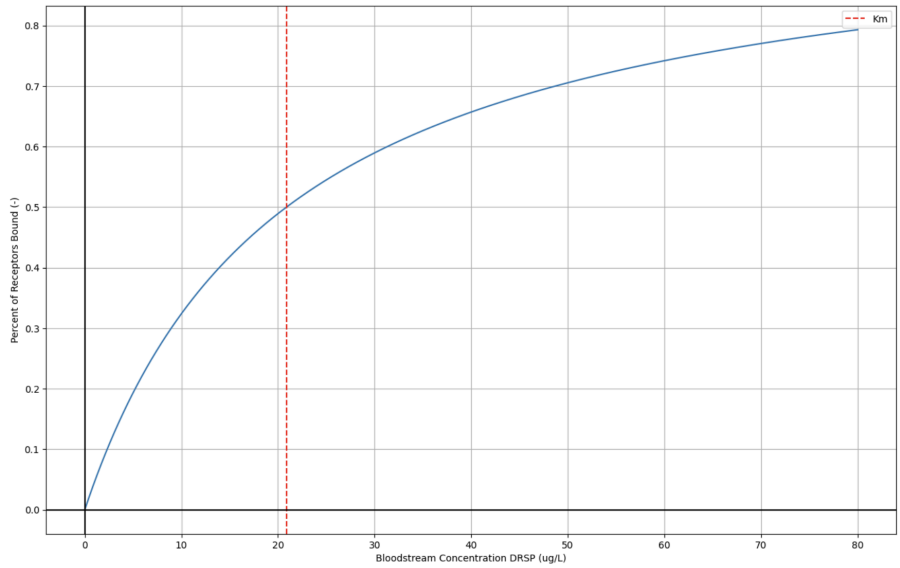


Fig A5: MM kinetics of binding of progesterone receptors as a function of bloodstream concentration DRSP



Code A1: Pill Modeling Code

Final Code Pill

(in case the GUI above doesn't work after being converted to a pdf: https://colab.research.google.com/drive/1joLcEQdzhMOe2XqOYYUBKzWbcT636SGB?usp=sharing)

Code A2: Implant Modeling Code

Arm Implant Final

(in case the GUI above doesn't work after being converted to pdf: https://colab.research.google.com/drive/19SnjJ99QhGMqmQ4lpx0S9rRXsaFsUXGC?usp=sharing)

7 References

[1] S. Reif, N. Snelder, and H. Blode, "Characterisation of the pharmacokinetics of ethinylestradiol and drospirenone in extended-cycle regimens: population pharmacokinetic analysis from a randomised Phase III study," *J Fam Plann Reprod Health Care,* vol. 39, no. 2, pp. e1-13, Apr 2013, doi: 10.1136/jfprhc-2012-100397.

[2] H. Blode, K. Kowal, K. Roth, and S. Reif, "Pharmacokinetics of drospirenone and ethinylestradiol in Caucasian and Japanese women," *Eur J Contracept Reprod Health Care,* vol. 17, no. 4, pp. 284-97, Aug 2012, doi: 10.3109/13625187.2012.677076.

[3] W. H. Richter, R. Koytchev, V. Kirkov, G. Merki, E. Colli, and P. A. Regidor, "Comparative pharmacokinetic estimates of drospirenone alone and in combination with ethinyl estradiol after single and repeated oral administration in healthy females," *Contraception,* vol. 101, no. 2, pp. 137-143, Feb 2020, doi: 10.1016/j.contraception.2019.10.005.

[4] F. Z. Stanczyk, D. F. Archer, and B. R. Bhavnani, "Ethinyl estradiol and 17beta-estradiol in combined oral contraceptives: pharmacokinetics, pharmacodynamics and risk assessment," *Contraception,* vol. 87, no. 6, pp. 706-27, Jun 2013, doi: 10.1016/j.contraception.2012.12.011.

[5] B. Hofmann, I. Reinecke, B. Schuett, M. Merz, and C. Zurth, "Pharmacokinetic overview of ethinyl estradiol dose and bioavailability using two transdermal contraceptive systems and a standard combined oral contraceptive," *Int J Clin Pharmacol Ther,* vol. 52, no. 12, pp. 1059-70, Dec 2014, doi: 10.5414/CP202064.

[6] R. L. Rich *et al.*, "Kinetic analysis of estrogen receptor/ligand interactions," *Proc Natl Acad Sci U S A,* vol. 99, no. 13, pp. 8562-7, Jun 25 2002, doi: 10.1073/pnas.142288199.

[7] J. G. Schenker and V. H. Eisenberg, "Ethical issues relating to reproduction control and women's health," *Int J Gynaecol Obstet,* vol. 58, no. 1, pp. 167-76, Jul 1997, doi: 10.1016/s0020-7292(97)02866-x.

[8] L. B. Finer and M. R. Zolna, "Declines in Unintended Pregnancy in the United States, 2008-2011," *N Engl J Med,* vol. 374, no. 9, pp. 843-52, Mar 3 2016, doi: 10.1056/NEJMsa1506575.

[9] C. S. Borowy and J. V. Ashurst, "Physiology, Zero and First Order Kinetics," in *StatPearls*. Treasure Island (FL), 2023.

[10] C. O. Casteel and G. Singh, "Physiology, Gonadotropin-Releasing Hormone," in *StatPearls*. Treasure Island (FL), 2023.

[11] B. von Schoultz *et al.*, "Estrogen therapy and liver function--metabolic effects of oral and parenteral administration," *Prostate,* vol. 14, no. 4, pp. 389-95, 1989, doi: 10.1002/pros.2990140410.

[12] R. Krattenmacher, "Drospirenone: pharmacology and pharmacokinetics of a unique progestogen," *Contraception,* vol. 62, no. 1, pp. 29-38, Jul 2000, doi: 10.1016/s0010-7824(00)00133-5.

[13] J. W. Goldzieher and S. A. Brody, "Pharmacokinetics of ethinyl estradiol and mestranol," *Am J Obstet Gynecol,* vol. 163, no. 6 Pt 2, pp. 2114-9, Dec 1990, doi: 10.1016/0002-9378(90)90550-q.

[14] A. I. Zablow, P. S. Erba, and L. J. Sanfillippo, "Radiotherapy T1 glottic carcinoma," *N J Med,* vol. 86, no. 11, pp. 879-82, Nov 1989. [Online]. Available: https://www.ncbi.nlm.nih.gov/pubmed/2608210.

[15] D. M. Robertson, L. M. Foulds, R. C. Fry, J. T. Cummins, and I. Clarke, "Circulating half-lives of follicle-stimulating hormone and luteinizing hormone in pituitary extracts and isoform fractions of ovariectomized and intact ewes," *Endocrinology,* vol. 129, no. 4, pp. 1805-13, Oct 1991, doi: 10.1210/endo-129-4-1805.

[16] G. Pandey, S. P. Pandey, and M. Sharma, "Experimental Hepatotoxicity Produced by Ethinyl estradiol," *Toxicol Int,* vol. 18, no. 2, pp. 160-2, Jul 2011, doi: 10.4103/0971-6580.84270.

[17] “Etonogestrel,” National Center for Biotechnology Information. PubChem Compound Database,https://pubchem.ncbi.nlm.nih.gov/compound/Etonogestrel#section=Absorption-Distribution-and-Excretion

[18] L. E. Britton, A. Alspaugh, M. Z. Greene, and M. R. McLemore, "CE: An Evidence-Based Update on Contraception," *Am J Nurs,* vol. 120, no. 2, pp. 22-33, Feb 2020, doi: 10.1097/01.NAJ.0000654304.29632.a7.

[19] S. M. Hawkins and M. M. Matzuk, "The menstrual cycle: basic biology," *Ann N Y Acad Sci,* vol. 1135, pp. 10-8, 2008, doi: 10.1196/annals.1429.018.

[20] "Etonogestrel". Accessed: Oct. 28, 2023. [Online]. Available: https://pubchem.ncbi.nlm.nih.gov/compound/6917715

[21] "FSH levels: Normal ranges, symptoms of high and low, and more". Accessed: Oct. 29, 2023. [Online]. Available: https://www.medicalnewstoday.com/articles/317746

[22] "Risks and Side Effects of NEXPLANON® (etonogestrel implant) 68 mg Radiopaque", Nexplanon. Accessed: Oct. 29, 2023. [Online]. Available: https://www.nexplanon.com/side-effects/

[23]"How Can I Buy the Birth Control Implant & What Does it Cost?". Accessed: Oct. 28, 2023. [Online]. Available: https://www.plannedparenthood.org/learn/birth-control/birth-control-implant-nexplanon/how-can-i-get-the-birth-control-implant

[24]"What are the absolute numbers of signaling proteins?". Accessed: Oct. 28, 2023. [Online]. Available:http://book.bionumbers.org/what-are-the-absolute-numbers-of-signaling-proteins/

[25] "Gynecologic Endocrinology". Accessed: Oct. 28, 2023. [Online]. Available: https://books.google.com/books?id=9vv2BwAAQBAJ&pg=PA25#v=onepage&q&f=false

[26] (2018). *Nexplanon*. [Online] Available: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/021529s018lbl.pdf