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Navigating the Myths and Truths Behind Pharmacological Drug and Herbal Supplement Use: A Guide for Pregnant Women

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Navigating the Myths and Truths Behind Pharmacological Drug and Herbal Supplement Use: A Guide for Pregnant Women

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Chapter 1: Herbal Supplements – A Personal Tradition

Growing up as a Vietnamese-American, I am well versed in the idea of cultural differences. Early on, I realized that culture permeates everything – including the way we approach our health. In many ways, the dichotomy between Western and Eastern medicine mimics the contrast between the different cultures. I experienced this first hand with my grandma. To this day, her medicine cabinet remains stock full. Granted, about half of this cabinet is filled with prescription medications, over the counter drugs, and multi-vitamins. However, the other half is filled with herbal supplements. Many of these herbal supplement bottles are brightly decorated with CGI images of human anatomy or with a photo of an unspecified plant and most, if not all, contain non-descriptive names such as "Kidney" or "Livertox." The vague descriptions and the limited ingredients list raised a lot of questions about the safety and efficacy of these supplements. While I remained wary and skeptical about these herbal remedies, I became aware of the wide range of possible physiological effects of these supplements. My grandma introduced me to a different side of medicine, one often ignored by researchers and providers.

While traditional western medicine often excludes alternative or Eastern medicine, many people worldwide rely on complementary alternative medicine (CAM) which can include herbal supplements, dietary supplements, acupuncture, among other therapies. A significant number of women worldwide use these natural therapies at least once during their reproductive age. Interestingly, women who use CAM and herbal

remedies tend to be 31-40 years old with higher education levels and higher income levels, (Kennedy, Lupattelli, Koren, & Nordeng, 2013). The uptick in alternative medicine can be attributed to a multitude of different factors. Women often cite that alternative medicine techniques such as herbal medication promotes holistic health care by introducing the use of natural products, a method they prefer to the clinical side of Western medicine. Herbal therapy proponents hold that these natural therapies exist in a separate category compared to pharmaceutical or OTC drugs and appear to be synonymous to safe (Warriner et al., 2014). Using the power of the internet and personal testimonies, the surge in CAM and herbal supplement use continues into the current day.

Currently, there are thousands of herbal supplements readily available to the general public and due to a little niche in FDA regulation, these supplements remain largely unregulated and unstandardized. In comparison, thousands of over the counter medications and pharmacological drugs exist, but many of these substances may be limited via prescriptions. Given their accessibility and increasing popularity, many women take a combination of pharmacological drugs and herbal supplement. The use of one or both methods are evident during pregnancy because women experience a whole slew of different symptoms. However, unregulated combinations result in potential herbal and pharmacological interactions, leading to a host of unintended physiological and biochemical effects on the maternal and fetal system. I believe that pregnant women need a comprehensive guide on how to navigate this complicated system. Women should be aware of the benefits, adverse side effects, and the possible interactions of both

pharmacological methods and herbal remedies, which allows them to make an informed decision on the course of their healthcare.

Throughout the course of this thesis, I will comment on current Federal Food and Drug Administration (FDA) guidelines on the regulation of herbal supplements and compare them to international guidelines. I will elucidate on how gaps in these regulations can be detrimental to the health of patients and use this as a platform to introduce an extensive guide denoting the major biochemical changes occurring antepartum and postpartum as an explanation for symptoms often experienced during pregnancy. I will then use this as a background to detail the mechanism of the active ingredients in these supplements and comment on the effectiveness of the relating FDA regulations. I hope that this thesis will help raise awareness about common herbal supplements and serve as a resource grounded in scientific facts for women looking into alternative medicine during pregnancy.

Chapter 2: Differential Regulation of Pharmaceutical Drugs and Herbal Supplements Creates a Public Health Hazard

International Laws and Regulation

The use of herbal supplements originated in the East, and currently, countries all over the world employ alternative medicine, especially the use of herbal supplements to treat certain ailments. In such a global society, the exchange of data information and regulatory remains a major part of international communication. While the World Health Organization (WHO) isn't an official regulator of herbal medication and supplements, this association serves as a hub for information exchange regarding different national regulations. The WHO also supports the International Regulatory Cooperation for Herbal Medication (IRCH), an organization developed in 2006 by several countries who expressed interest in sharing research and regulatory issues. The IRCH, whose main purpose includes providing a global network of regulatory authorities responsible for regulating and promoting herbal supplements, includes 33 national and regional members who conduct annual meetings to discuss issues revolving around herbal medication and complementary medicine (Alostad, Steinke, & Schafheutle, 2018).

From the importation of herbal plants and supplements to their distribution, the regulation of these substances takes on different faces across the globe. For example, Germany has a well-established regulatory and registration system that even predates the policy enforced by the European Union. As a result, some reports suggest that

approximately 70% of German physicians claim to feel confident in prescribing herbal medications to their patients. In contrast, India lacks a reliable regulation system. The mainframe of their system relies on poorly enforced policies and manufacturers can take advantage of many loopholes (Alostad et al., 2018). In comparison to many other countries, the United States employs a rather simplistic and broad approach towards regulation of these substances. Countries such as Germany and the UK have employed a more structured and reasoned system for registering herbal supplements and medication as seen in Figure 1. The United States differs from the structure and order of these different regulation systems in three main categories: evidence for safety and efficacy as well as registration requirements.

Main registration requirements	Regulatory authority				
	UK	Germany	USA	UAE	Kingdom of Bahrain
Evidence of quality	GMP standards and QC tests for THR and MA	GMP standards and QC tests for THR and MA	Not required for dietary supplements GMP standards and QC tests for botanical drugs	GMP standards and QC tests for traditional HMs and HMs Declaration of pork-free contents Declaration of alcohol content	GMP standards and QC tests for health products and medicines with a vegetable substance Declaration of pork-free contents Declaration of alcohol content
Evidence of safety	Bibliographic data for THR Toxicological tests for MA	Bibliographic data for THR Toxicological tests for MA	Not required for dietary supplements unless it is a NDI Toxicological tests for botanical drugs	Bibliographic data for traditional HMs Toxicological studies for HMs	Bibliographic data for health products Toxicological studies for medicines with a vegetable substance
Evidence of efficacy	Long tradition of use for at least 30 years (including 15 years in the EU) for THR Clinical studies for MA	Long tradition of use for at least 30 years (including 15 years in the EU) for THR Clinical studies for MA	Not required for dietary supplements Clinical studies for botanical drugs	Copies of at least two traditional HMs for each herbal ingredient for traditional HMs Clinical studies for HMs	Copies of published scientific literature or international monographs for health products Clinical studies for medicines with a vegetable substance
Label requirement	For THR: must include a statement that the product is exclusively based on long-standing use Must include a certification mark (THR)	For THR: must include the words "traditional medicines" and "traditionally used"	For dietary supplements: must include a disclaimer: "This statement has not been evaluated by the FDA. This product is not intended to diagnose, treat, cure, or prevent any disease" Must state on the label that it is a dietary supplement	No requirements	No requirements

EU European Union, *FDA* US Food and Drug Administration, *GMP* Good Manufacturing Practice, *MA* marketing authorisation, *NDI* new dietary ingredients, *QC* quality control, *THR* traditional herbal registration

Figure 1. *Summary comparison of herbal medication registration and regulation requirements set by the different regulatory agencies of the UK, USA, United Arab Emirates, Germany, and the Kingdom of Bahrain. This table looked at the differences between evidence requirements and labeling requirements between these countries. Figure adapted from Alostad, A. H., Steinke, D. T., & Schafheutle, E.I. (2018). International Comparison of Five Herbal Medicine Registration Systems to Inform Regulation Development: the United Kingdom, United States of America, United Arab Emirates and the Kingdom of Bahrain. Pharmaceutical Medicine, 32 (1), 39-49. Doi:10.1007/s40290-018-0223-0.*

Perhaps most notably, as Figure 1 denotes, the regulatory authority in the U.S. or the FDA requires no evidence for safety, efficacy, or efficiency for dietary and herbal supplements. Conversely, many other countries require herbal medication to adhere to pre-marketing registration laws including laboratory standards, manufacturing standards, and storage requirements. Without the requirement for pre-marketing evaluation, the United States sets up a system where FDA intervention doesn't begin until the herbal supplement enters the market and proves to be detrimental to patient health. This almost backward approach disavows any change for preventative regulation of herbal medications and leaves the door open for loopholes that manufacturers can take advantage of. The US notably requires no evidence from herbal manufactures or sellers other than a disclaimer on the box or bottle. In contrast, all of the other 4 countries used in this study require at least some form of validation for each of the main registration components.

Secondly, the United States employs different registration requirements compared to its international counterparts. In countries apart of the European Union, herbal supplements and medication registered by the one-member state will be accepted by all other states in the union. However, under this directive, each member's regulatory agency will employ pre-marketing checks and quality assessment. This system tried to ensure that each country can benefit from these herbal medications while also maintaining the proper quality assessments. Countries such as Germany also consider traditional usage as

evidence of efficacy, thus reducing the need for extensive clinical trials to validate their efficacy (Alostad et al., 2018). In the U.S., herbal supplements can make certain nutritional support claims, however, should a supplement claim to treat or cure a disease, it will be regarded as a botanical drug and undergo the same rigid requirements and standards imposed on conventional drugs. Because of this, between 2004 and 2013, only two botanical drugs have received FDA approval out of over 400 applicants (Avigan, Mozersky, & Seeff, 2016). Given the drastic differences between FDA policies and foreign policies, we will take a closer look into the specific policies that regulate dietary and herbal supplements.

History of FDA Regulation

The FDA is a regulatory agency for food and drugs in the U.S. Established by Harvey Washington Wiley, the head of the Bureau of Chemistry in the Department of Agriculture, this agency enforced regulations regarding the safety and quality of food products and pharmaceutical drugs. Prior to its establishment, the 1800s gave rise to a corrupt food and drug market. Many products sold during this era boasted claims with no backing and most commodities failed to disclose all of the ingredients in the product (Seamon & Clauson, 2005). The height of the crisis came in the form of the 1906 novel *The Jungle*, where Upton Sinclair elucidated the adulteration issues in the food industry, particularly the meat industry. With the public's attention focused on the unsanitary conditions of food preparation and the danger of mislabeling, Congress passed the Pure

Food and Drug Act, which prohibited the misbranding and adulteration of food and drug products. In 1938, the government passed the FDCA (Food, Drug, and Cosmetic Act) to further elucidate the regulations placed on manufacturers and distributors. Under this act, no new drug can be marketed until it passes safety benchmarks set by the FDA and labels are required to contain adequate instructions and warnings. The 1938 bill also broadened the scope of the FDA to encompass cosmetics and therapeutic devices and therapies. Just two years after the enactment of this policy, the FDA issued dozens of safety warnings against various drug products and even deemed some products unsafe for distribution (Chhabra, Kremzner, & Kiliany, 2005). This bill creates the foundation for current food and drug regulation, and the FDA continues to modify and adjust its regulatory principles and systems today (Spies, 2006).

DSHEA: Distinguishing Herbal Supplements from Pharmacological Drugs

On October 25, 1994, President Bill Clinton passed the Dietary Supplement Health Education Act of 1994 (DSHEA) to establish standards for dietary and herbal supplements. The act starts in Section 3 by defining dietary and herbal supplements by law through a very rigid and specific definition:

> "(1) means a product (other than tobacco) intended to supplement the diet that bears or contains one or more of the following dietary ingredients:
>
> - "(A) a vitamin;
> - "(B) a mineral;
> - "(C) an herb or other botanical;
> - "(D) an amino acid;

- "(E) a dietary substance for use by man to supplement the diet by increasing the total dietary intake; or
- "(F) a concentrate, metabolite, constituent, extract, or combination of any ingredient described in clause (A), (B), (C), (D), or (E)" (FDA, 1994)

This act requires that all substances adhering to the definition of the dietary or herbal supplement must comply with some regulations. For example, the FDA prohibits distribution of adulterated or misbranded products and manufacturers must comply with the Current Good Manufacturing Practices as defined by the FDA (Curry, Schaffer, & Yoon, 2016).

However, under these conditions, these substances are automatically placed in their own category, removing them from the regulations imposed on pharmaceutical drugs. In fact, this act mandates that dietary supplement regulation mirrors that of a specialized food group rather than a drug. By placing dietary and herbal supplements under the broad umbrella of food regulation, these substances are excluded from the stringent requirements that govern pharmaceutical drugs. The most prominent exclusion revolves around the notion of premarket approval and pre-clinical data and trials. Pharmaceutical drugs, before even approaching distribution in the market, are required to provide sufficient data on the effectiveness and the potential side effects of the product to gain premarket approval by the FDA. A significant amount of research and thorough clinical trials predate the release of any modern drug. In contrast, the DSHEA dictates that manufacturers are responsible for determining the safety of the product and its claims (Spies, 2006). Thus, the burden lies with the FDA to provide proof that a dietary or

herbal supplement poses significant harm before the substance can be removed from the market.

The DSHEA also allows dietary supplements to make certain nutritional support claims. Taken from the FDA:

> "(A) the statement claims a benefit related to a classical nutrient deficiency disease and discloses the prevalence of such disease in the United States, describes the role of a nutrient or dietary ingredient intended to affect the structure or function in humans, characterizes the documented mechanism by which a nutrient or dietary ingredient acts to maintain such structure or function, or describes general well-being from consumption of a nutrient or dietary ingredient (FDA, 1994).

In other words, under this section of the DSHEA, there are four main claims that dietary supplements can make without causing the FDA to consider the product as a drug. To make these claims, the seller must provide data supporting the claims and to ensure that these claims contain no false or misleading information. The FDA also requires all dietary and herbal supplement labels to bear the disclaimer, "This statement has not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease" (FDA, 1994; Spies, 2006). Despite the disclaimer, this section gives dietary supplements a looser leash, allowing them to publish certain types of claims that regimented drugs are prohibited from making. For example, a seller can claim that cranberry supplements can increase the acidity of urine to improve urinary tract function, but they cannot claim that these supplements decrease the likelihood of urinary tract infections, nor can they claim that these supplements prevent an individual

from contracting a UTI. By changing the wording of the claim, herbal and dietary supplements can publish and market certain nutritional support claims without adhering to the governing factors of traditional drugs (Spies, 2006).

Criticisms of DSHEA: Biochemical Impact of Active Ingredients and Potential Side Effects

Despite their seemingly benign reputation, herbal supplements rely on active chemical compounds extracted from plants to induce physiological changes in the body, which mimics the mechanism that drugs employ. Especially in the presence of certain active compounds in pharmaceutical drugs, herbal products can have pharmacodynamic interactions that result in adverse side effects. Thus, herbal medications can also pose a significant health risk, in the right conditions and should be regulated as such. While the current policies in place keep the price of herbal medications significantly lower compared to conventional drugs, the almost hands-off approach significantly increases risk towards the consumers due to poorly defined and manufacturing processes. Many herbal compounds have been proven to have pharmacodynamic interactions with the active components in commonly used conventional drugs. For example, St. John's Wort, an herbaceous perennial plant commonly used for the treatment of depression, has been proven to interact with a number of drugs, including immunosuppressants, contraceptives, anticoagulants and more. St. John's Wort has been found to significantly reduce the pharmacological effect of warfarin when taken in combination. While many of these herb-drug interactions exist, poor regulation and research behind these adverse side

effects hinder the scientific process in gathering accurate data and implementing the appropriate response to minimize consumer risk.

While the FDA seems to be the hallmark for conventional drug regulation, its approach to herbal medication leaves the door open to many different loopholes that might increase the health risk for many consumers. Based on the analysis of the DSHEA, the main regulatory policy enforced by the US, herbal supplements receive more lax regulations compared to their drug counterparts. Without rigorous screening and strict manufacturing restrictions, herbal medication manufacturers require less testing and the overall process from development to distribution remains less regulated. As a result, many of the herbal supplements and medications on the market may pose a significant health risk towards consumers as the quality of the ingredients that many sellers claim to be present are not properly accessed. In fact, a study conducted by researchers in Toronto analyzing the ingredients contained in 44 different herbal supplements sold in the United States and Canada revealed that less than half of these supplements contained any herbal substances disclosed on the label and more than half of these substances contained ingredients not disclosed on the label (Alostad et al., 2018). The fact that many herbal medications currently on the market contain undocumented materials poses a significant risk for consumers, especially if that ingredient can cause an allergic reaction or other adverse side effects or if that material is of poor quality.

The DSHEA along with all other FDA regulation policies allows manufacturers and sellers to use fillers or substitutions in their products, which once again, constitutes not only as food fraud but also poses health issues for consumers. Current analytical and quantification techniques fail to identify all the active ingredients in most herbal supplements, partly due to the combination of organic chemicals that many of these products contain. Even with standard chemical practices used by all manufacturers for analyzing the number of active ingredients in the supplement, there is still not enough information to discern whether these active components exhibit an adverse side effect (Newmaster, Grguric, Shanmughanandhan, Ramalingam, & Ragupathy, 2013). In comparison to many other countries, who require herbal supplements to pass pre-market approval, the current U.S. regulatory system, when it comes to herbal medicine, is severely lacking. Rather than a preventative approach, the FDA allows unproven supplements to enter the market and directly reach consumers.

The current regulation system puts consumers at risk because these policies seemingly downplay the potential effects of herbal medications; rather, the regulation should reflect the potential risk posed by consumption of these products. Currently, the FDA encourages voluntary recall of the supplements they find adulterated or contaminated. In 2018, the FDA issued its first mandatory recall for herbal products containing kratom, an herb that has psychotropic effects, produced by the manufacturer Triangle Pharmanaturals LLC (FDA, 2018). However, this only affects a small number of

supplements on the market. Taking a preventative approach, these products should have to undergo pre-market approval and at the very least, provide data that demonstrates its safety in consumption. The burden of proof, therefore, shouldn't lie with the FDA, but manufacturers and sellers alike should play an active role in elucidating the efficacy, safety, and quality of their products.

Chapter 3.1: The complexity of Pharmaceutical Drugs and Herbal Supplement Use During Pregnancy

Pregnancy is marked by large changes to both the maternal physiology and environmental changes. On top of navigating numerous prenatal visits, scans, and tests, women must also rethink their medication regiment. The FDA has established a categorical system to delineate the safety of different medications during pregnancy, which can be summarized in

Table 1. This system allows healthcare providers to identify which medications to recommend or prescribe, considering the associated side effects. Only a small number of herbal supplements have been categorized using this system. The development of the fetus and hormonal changes during all three trimesters of pregnancy alters the effect of many different drugs. This complicates the trajectory of care. To better understand the hazards of medications on both the development of the fetus and the maternal system, we will first look at the multitude of hormonal changes that occurs during each trimester of pregnancy. These fluctuations cause many of the symptoms experienced, and hence, opens the door to treatment by pharmacological and/or herbal therapies. We will then

compare the pharmacological therapies with the herbal remedies, looking specifically at the mechanism of action, the side effects, and the potential interactions with other substances.

Table 1: *FDA pregnancy risk categories for different medications with examples of drugs that fall into each category. Information obtained from Survey, J. & Chang, J. (2014). Over-the-counter medications in pregnancy. American Family Physician, 90(8), 548-555. https://doi.org/10.1016/j.acthis.2015.01.004*

Category	Description	Examples
Category A	Adequate and well-controlled studies have failed to demonstrate a risk to the fetus in all trimesters	
Category B	Animal reproduction studies have failed to demonstrate a risk to the fetus There are no well-controlled studies in pregnant women	Acetaminophen Benadryl
Category C	Animal reproduction studies have shown adverse effects on the fetus There are no well-controlled studies in humans Potential benefits may warrant the use of the drug during pregnancy	Guaifenesin (Humibid L.A.) Miconazole (Monistat) Calcium Carbonate (Tums)
Category D	There is evidence of human fetal risk based on adverse reaction data from studies in humans	Aspirin (in the third trimester) Ibuprofen (in the third trimester)
Category X	Studies in animals or humans have demonstrated fetal abnormalities The risks involved clearly outweigh the potential benefits	Castor oil

Changes in Maternal Hormones and Metabolism

To successfully develop a zygote, a fertilized egg, into an infant requires complete rewiring of maternal metabolism. Throughout the approximately 280 days of a normal human pregnancy, changing biochemical parameters dictate a whole orchestra of physiological changes to support a pregnancy. Steroid hormones, peptide hormones, and prostaglandins help to establish a protective environment for fetal growth and develop a system for the transportation of nutrients between maternal and fetal systems (Lockitch, 1997). Disruptions to the normal function of these interactions may cause serious side effects in both the fetus and the mother. Thus, pregnancy presents an interesting dilemma in terms of the use of medicines and alternative medicines. Side effects and the molecular influence of both pharmaceutical drugs and herbal medications should be stringently documented and researched to prevent adverse interactions and side effects.

The four main hormones that govern pregnancy are estrogen, progesterone, human placental lactogen (hPL), and human chorionic gonadotropin hormone (hCG). These hormones are synthesized by the placenta throughout most of the pregnancy and

rely on the metabolic relationship between the maternal and fetal systems. The patterns of estrogen, progesterone, and hCG can be summarized in Figure 2. It should be noted that estrogens, progesterone, and hLP follow a similar pattern with lower levels during the beginning of the pregnancy before gradually increasing and peaking near term (Blackburn, 2007).

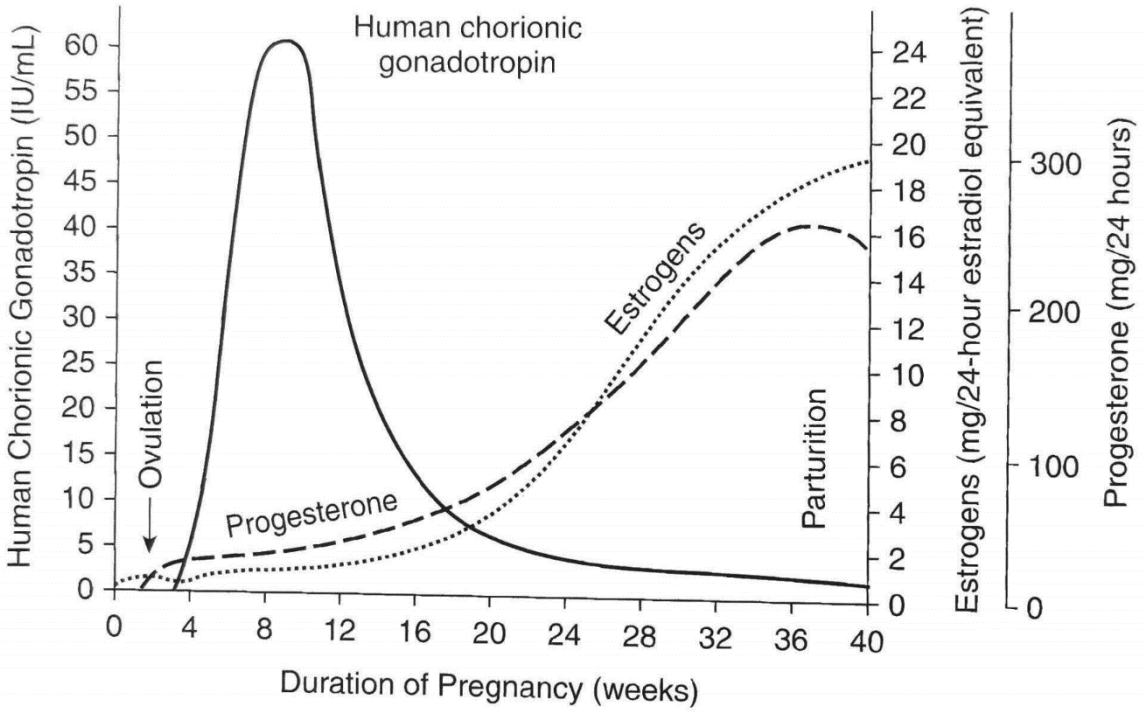

Figure 2: *Graph depicting patterns of estrogen, hCG, and progesterone levels during pregnancy from fertilization to labor. Figure adapted from Guyton, A.C (1987). Human Physiology and mechanisms of disease (4th ed.). Philadelphia: Saunders.*

In the weeks following conception, hCG levels can be detected in the blood in 7 days after ovulation, and substantially increases until concentrations in the maternal serum peaks at around 8 and 12 weeks before slowly declining. The sudden rise in hCG extends the functionality of the corpus luteum (CL), a structure that allows for the production of progesterone, into a couple of weeks allowing the body to sustain the pregnancy until the placenta takes over. Moreover, studies indicate that hCG may play a role in the implantation of the embryo to the uterine wall. Receptors on the endometrium (the uterine lining) promote the secretion of relaxin and progesterone by the CL, which stimulates the physiological changes required in early pregnancy. Abnormalities in the expression of hCG receptors and abnormal levels of the hormones itself can be associated with issues in female reproduction and pregnancy (Keay et.al., 2004; Lockitch, 1997).

With hCG maintaining the functionality of the corpus luteum, levels of progesterone, a steroid hormone in the maternal serum remains elevated. Under the influence of hCG, progesterone is produced by the CL until its production is sustained by the placenta 6-8 weeks after fertilization. Progesterone combats the labor-inducing effects of other hormones such as estrogen, prostaglandins, and oxytocin, allowing for the pregnancy to sustain. In addition to preventing menstruation, which would shed the

uterine lining needed for implantation of the ovum, progesterone, a pro-gestational hormone, maintains pregnancy by promoting uterine quiescence. The myometrium, the smooth muscle of the uterus, plays a large role in the duration of pregnancies and in the birthing process. Through most of the pregnancy, the myometrium remains in a relaxed state, stretching to accommodate the growing fetus mainly sustained by the presence of progesterone. At the time of birth, rhythmic contractions of the myometrium allow for the expulsion of the fetus and placenta. After 8 weeks of pregnancy, the main production of progesterone shifts from the CL to the placenta and placental trophoblasts, where the levels of progesterone remain elevated until the placenta is lost following parturition. Interestingly, disruption in the production of progesterone initiates labor by stimulating uterine contractions. Clinical studies indicate that progesterone supplement may decrease preterm labor in women with high risk for preterm labor, however, more research is needed before this treatment can be applied clinically (Mesiano et.al., 2011; Tuckey, 2005). Progesterone also serves as a substrate for the production of corticosteroids by the fetal adrenal gland. Due to insufficient levels of enzymes required to form several different corticosteroids, the fetus is unable to use the main metabolic pathway to form these components. Thus, they rely on progesterone produced by the placenta using precursors from the maternal system to form mineralocorticoids and corticosteroids, which are hormones that hold physiological importance (Blackburn, 2007).

Estrogen exists within the body in three major forms: estrone, estradiol, and estriol. During pregnancy, levels of all three major estrogens substantially increase.

Notably, levels of estradiol production increase almost 1000 times baseline levels by the third trimester of the pregnancy. Estrogen, like hCG and progesterone, is mainly produced by the placenta, however, unlike progesterone, 90% of the precursors are derived from the fetus instead of the maternal system. Furthermore, while progesterone decreases myometrial activity and promotes myometrial constriction, estrogen provides the opposite effect – enhancing myometrial activity and promoting myometrial vasodilation. In addition to effects on the uterine wall, estrogen derivatives also increase maternal sensitivity to carbon dioxide and secretion of other hormones such as prolactin and serum binding proteins (Blackburn, 2007).

Another key component in developing the environment to sustain a pregnancy revolves around changing maternal metabolism to support the development of fetal metabolism, as task mediated by the hormone hPL. Almost exclusively secreted by the placenta into the maternal circulation, hPL is hypothesized to be responsible for the rise in maternal plasma insulin-like growth factor (IGF-1). During early pregnancy, hPL and other placental hormones drive an increased appetite and food intake as well as energy storage leading to an increase in the deposition of fat reserves. As the pregnancy progresses towards term, hPL mobilizes these reserves to support fetal growth (Magon & Kumar, 2012).

Use of Medicine During Pregnancy: An Upward Trend

With a whole slew of changes occurring, pregnant women often experience a whole array of different symptoms, ranging from emesis to constipation to fatigue. Because of the complex physiological changes coupled with dynamic shifts in hormones and metabolic homeostasis, the use of medication to address symptoms in pregnancy proves to be difficult for providers to navigate. Providers must balance not only the effects of these medications on the mother but also an unintended subject, the fetus. Perhaps one of the biggest medical disasters revolves around the severe birth defects affecting over 10,000 children globally from 1957 to 1962. At the center of this tragedy lies Thalidomide, a drug prescribed to women to treat morning sickness. Administration of this drug caused severe birth defects including limb development and significant organ tissue damage in infants worldwide (Ghoreishi, 2014). The thalidomide crisis greatly impacted the dynamic of medication use during pregnancy.

For the past several decades, the use of both over the counter medications as well as prescription medicine during pregnancy shows a substantial increase. As depicted by the figure below, in 2008, 93.9% of women reported taking at least one medication anytime during the pregnancy, a substantial increase from around 50% in 1967-1981. Moreover, this figure also supports the notion that the average number of medications taken follows a similar upward trend, from an average of 2.5 drugs in 1976 to over 4 in 2008. The number of women taking four or more medications also increased, from 23.3% in the late 1970s to 50.1% in 2008. Interestingly, this trend continues into the current day (Mitchell et al., 2011). In a 2018 study, out of 9,546 women surveyed, 95.7% took

medication during the first trimester with 30.5% meet the requirements for polypharmacy, defined as taking five or more medications. Excluding vitamins and herbal supplements, 74.4% of women took at least one medication during pregnancy (Haas et al., 2018; Lee et al., 2006). \

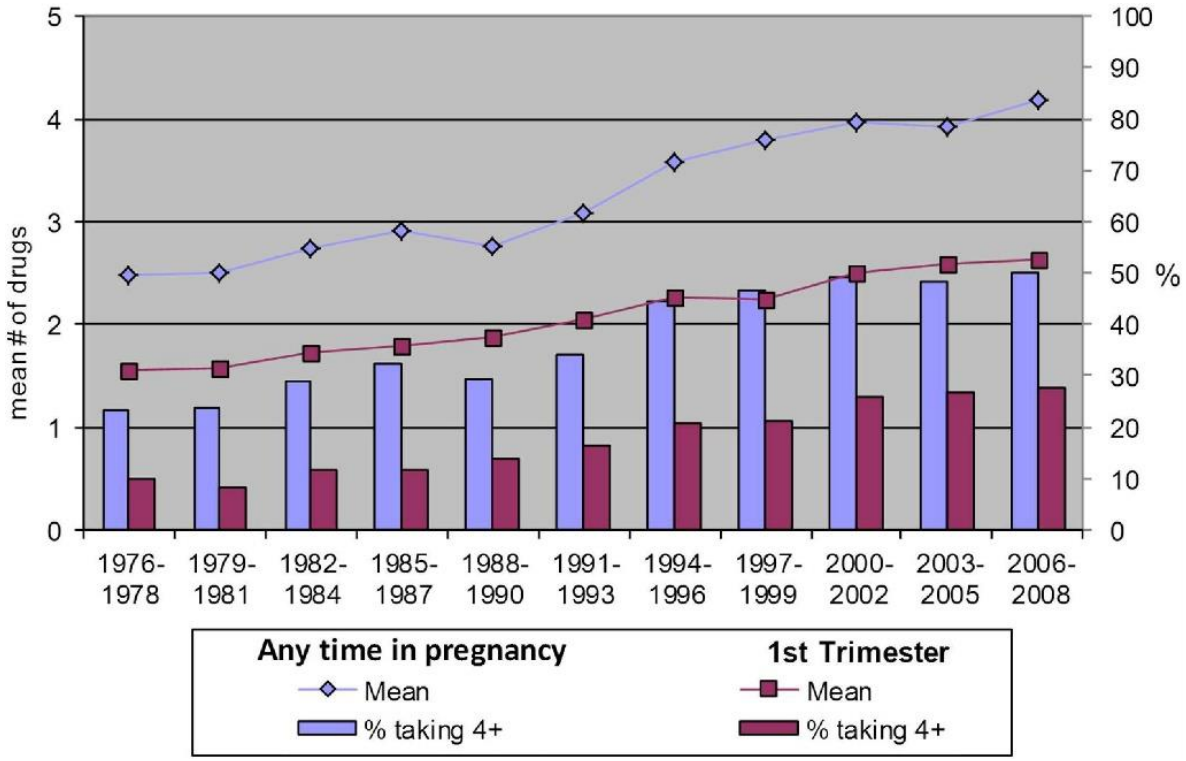

Figure 3*. Average medication uses during pregnancy and the first trimester. The chart shows an upward trend in medication usage throughout the duration of pregnancy. Figure adapted from Mitchell, A. A., Gilboa, S. M., Werler, M. M., Kelley, K. E., Louik, C., & Hernandez-Diaz, S.. (2011). Medication use during pregnancy, with particular focus on prescription drugs: 1976-2008. American journal of Obstetrics and Gynecology, 205(1), 51.e1-51.e8. http://doi.org/10.1016/j.ajog.2011.02.029.*

Drug safety thus remains a major priority for both researchers and providers. Since the thalidomide crisis, many pharmaceutical drugs have been classified as teratogens, a substance that can cause malformations in a developing embryo. Warfarin, an anticoagulant medication, valproic acid, an anticonvulsant, and isotretinoin, an acne medication serves as examples of teratogens. As a result, many of these pharmaceutical drugs are strictly modulated and monitored by pharmacists and healthcare workers. However, the regulation of over the counter medications (OTC) use poses a difficult task, relying mostly on patient disclosure. While the prevalence of OTC and their easy accessibility suggests usage safety by nonpregnancy populations, this doesn't extend to safety during pregnancy (Servey & Chang, 2014). Little to no data exists detailing the long-term effects of most OTC medications. Thus, given their prevalence in routine obstetric care, stringent research on the potential side effects and interactions should be conducted to ensure the safety of both the mother and the fetus.

The upward trend in medication use during pregnancy also extends to herbal supplement use during pregnancy. In fact, a vast range between 7% to 55% of expectant mothers globally reported using herbal remedies or other types of natural health products during pregnancy and lactation (Facchinetti et.al., 2015; Yusof et.al., 2016). Prevalence

of usage is dependent on geography as well as demographics. According to various studies, the top four herbal medicines used by pregnant women globally are ginger to treat nausea, valerian to aid with insomnia, and raspberry to induce labor (Abebe, 2002; Holst et.al., 2011; Kennedy et.al., 2013).

Table 2 provides a summary of several herbal supplements commonly used during the first three trimesters of pregnancy with their intended benefits, the risks associated with usage, and documented interactions with other medications. Like OTC medications, the regulation of complementary and alternative medicine proves a difficult task. Without a prescription requirement, these substances can be readily purchased at different stores and sources without stringent quality control by the FDA. Moreover, often, women

neglect to inform their midwife or physician about herbal medicine use, increasing the chances of herb-drug interactions during pregnancy (Hall et.al., 2011; Kennedy et al., 2013).

***Table 2**: Common herbal supplements used by women during pregnancy.[1] (Abebe, 2002), (Tiran, 2012); [2]* (Holst et al., 2011)*; [3] (Abebe, 2002) [4] (Holst, Haavik, & Nordeng, 2009); [5]* (Dugoua, 2010), (Dugoua, Seely, Perri, Mills, & Koren, 2008)*; [6] (Dugoua, Jean-Jacques; Mills, Edward; Perri, Daniel; Koren, 2006); [7]* (Newmaster et al., 2013)

Herbal Supplement	Reason for use	Benefits	Associated risks	Interactions
Ginger [1]	To treat morning sickness, cold and flu-like symptoms,	Diaphoretic properties	Stomach irritant, Heartburn	Anticoagulant effects that might interfere with

	gastrointestinal diseases		No reported increase in birth malformities	anticoagulant drugs
Cranberry [2] 	To treat UTIs, colds, water retention	Research shows questionable efficacy in preventing recurrent UTI in pregnancy	No significant side-effects reported	
Valerian [3] 	To treat insomnia and restlessness	Induce mild sedation and hypnosis	No reported risk to the fetus Valerian withdrawal mimics withdrawal of ben Benzodiazepines	Can potentiate the sedative effects of other central nervous system drugs
Raspberry Leaf [4] 	Flu and cold symptoms, to prime the uterus for labor, stimulate labor	Research shows contradictory results for the efficacy; the active component remains unidentified	None documented No evidence of fetal malformities	
Blue Cohosh [5]	To prepare for labor	Evidence of initiating	Several cases of in vivo evidence	

		uterine contractions	of teratogenic, embryotoxic, and oxytocic effects	
Ginkgo [6] 	To use for premenstrual syndrome (PMS)	Strong evidence for therapeutic use for intermittent claudication, dementia, altitude sickness, and vertigo	The antiplatelet activity could prolong bleeding during delivery No risk associated with consumption during lactation	May potentiate anti-clotting effects of anticoagulant medications
Senna[7] 	To treat constipation	Evidence of laxative effects	Prolonged use can cause chronic diarrhea, liver damage, abdominal pain	(Sennosides) Interact with immune cells in the colon

Dangers of Medication Use During Pregnancy

As mentioned, drug use during pregnancy poses an imminent challenge to the current healthcare system. A portion of this issue is attributed to holes in clinical practice and FDA regulation, but another compounding factor comes from the changes in maternal drug metabolism. Expanding on the hormonal changes, pregnancy is also hallmarked by distinct physiological changes including a significant increase in a plasma

volume expansion of erythrocyte mass, altered distribution of cardiac output, and an increase in plasma protein synthesis (Lockitch, 1997).

Table 3 shows changes in absorption, distribution, metabolism, and excretion that occurs during pregnancy. Alterations in the maternal system change the way drugs and supplements are metabolized, thus changing the effect and potency of many drugs. For example, an increase in renal blood flow and pulmonary function during pregnancy may decrease the effectiveness of medications, due to the increase in excretion efficiency. Due to large metabolic changes and hormonal changes, prescribing drugs during pregnancy remains a difficult task for healthcare providers. They must consider a multitude of changes and factors to ensure the safety for the mother as well as the fetus while also treating various symptoms that arise during pregnancy.

Table 3: *Changes to factors that influence metabolism of drugs during pregnancy. Adapted from Reed, MD * Blumer, J.L. (2006). Pharmacologic treatment of the fetus. In R.J. Martin, A.A. Fanaroff & M.C. Walsh (Eds.). Fanaroff and Martin'sneonatal-perinatal medicine: Diseases of the fetus and infant (8th ed.), Philadelphia: Saunders*

Influence of Pregnancy on Physiological Aspects of Drug Disposition	
Pharmacokinetic Parameter	**Change in Pregnancy**
Absorption	
Gastric emptying	Increased
Intestinal Motility	Decreased

Cardiac Output	Increased
Distribution	
Plasma Volume	Increased
Total body water	Increased
Plasma proteins	Decreased
Body fat	Increased
Metabolism	
Hepatic	Increased or Decreased
Extrahepatic	Increased or Decreased
Plasma proteins	Decreased
Excretion	
Renal blood flow	Increased
Pulmonary function	Increased

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Chapter 3.2: Treating Symptoms During Pregnancy: A Look at Common Pharmacological and Herbal Options

Morning Sickness: An Imbalance of hCG

Nausea and vomiting or emesis are some of the most common symptoms experienced by expectant mothers with nausea affecting 75% of pregnant women and emesis occurring in 50% of pregnant women. In a small number of patients, hyperemesis gravidarum, a condition characterized by persistent vomiting leading to dehydration and

weight loss, may develop. Typically manifesting in the early weeks of the first trimester and peaking at around 9 weeks of gestation, most instances resolve by the end of the first trimester. The severity of nausea and vomiting of pregnancy (NVP) can range from mild to unbearable instances, lasting throughout the day, contrary to the public term of morning sickness (M.L., S.M., & J.A., 2006; Niebyl, 2010). Interestingly, the clinical course for NVP correlates with the levels of hCG. In theory, an increase in hCG, especially during pregnancy, may stimulate the production of estrogen, a hormone known to increase instances of nausea and emesis (Niebyl, 2010). The vomiting center, when activated, mobilizes motor neurons that descend down the cranial nerves to the upper gastrointestinal tract before reaching the vagal nerve, a cranial nerve controlling the digestive tract. The activation of this center causes the contraction of the abdominal muscles and the diagram, initiating the action of vomiting. Irritants are known to activate this center. In addition, the presence of certain hormones and neurotransmitters might trigger this center (Becker, D.E., 2010).

An Overview of Treatments for NVP

Clinically, multiple methods can be used to alleviate NVP and improve the quality of life for expectant mothers. Broken into two general groups, providers may employ a pharmacological approach or a nonpharmacological approach, each treatment containing a different set of benefits and disadvantages. The first approach to NVP treatment generally involves behavioral and environmental changes. While the efficacy

of this approach remains unproven, women are often encouraged to shift their diet – consuming smaller meals and avoid spicy foods. In addition, providers might encourage women to take their prenatal vitamins at night and suspend iron therapy (M.L. et al., 2006).

The use of herbal medicine also falls within the category of nonpharmacological approaches. The most common herbal supplement used to treat nausea is ginger (*Zingiber officinale*). Widely used as a spice to enhance the flavor of food, ginger is among the top 20 selling herbal supplement in the United States. Various preparations of ginger exist, including extract in teas, capsules, or root powder. Due to a lack in federal oversight, the dosages present in these different preparations and brands may vary greatly – from 250 mg to 1000 mg (Borrelli et.al., 2005; Ebrahimi et.al., 2010). While the mechanism employed by ginger has not been fully elucidated, the antiemetic effects are attributed to gingerol. Other components such as galanolactone are thought to act as serotonin and vasopressin antagonists to decrease tachygastric activity especially in the ileum, a portion of the small intestine. Interestingly, some prescription anti-emetics employ the same mechanism (Tiran, 2012). Multiple studies indicate that ginger is effective in reducing the severity of NVP (Borrelli et al., 2005; M.L. et al., 2006; Ozgoli et.al., 2009; Westfall, 2004).

If symptoms persist or worsen, providers turn towards pharmacological therapies. A number of different drug categories can be considered to manage nausea and vomiting

during pregnancy. Antihistamines, such as meclizine and diphenhydramine (Benadryl ®), directly inhibit the action of a histamine receptor, thus indirectly decreasing the stimulation of the vomiting region. The effectiveness of antihistamines has been proven over a series of tests conducted in the 1960s. Another class of drugs typically used to treat NVP is dopamine antagonists (Metoclopramide), serotonin antagonists (Ondansetron), and cholinergic antagonists (dicyclomine and scopolamine). These antagonists block certain receptors in the vomiting center or certain digestive sites to decrease stimulation or triggers that might activate these areas (Becker, D.E., 2010).

Risks/Interactions Associated with Nonpharmacological Methods

Despite limited research, many clinical studies indicate that ginger proves to be an effective and safe method to manage NVP. However, limited data exists on the appropriate dosage of ginger to achieve optimal results. One study indicates that a daily dose of 1000 mg, in the form of a capsule achieves a reduction in the intensity of nausea and vomiting in women (Ozgoli et al., 2009). Generally, a dosage of 1000 mg or less per day is deemed safe. Multiple randomized controlled trial studies show a reduction in symptoms with infrequent side effects overall (Ebrahimi et al., 2010). There is still a lack of studies detailing the effects of extended use of these supplements on the mother and the fetus. Moreover, as mentioned before, due to a lack of FDA regulation, each preparation of ginger may contain different amounts of active ingredients, thereby altering the effectiveness of the treatment. Additionally, minimal federal oversight into

the quality and manufacturing of herbal medicines, including ginger, leaves the door open of adulterations.

The use of ginger may result in a multitude of symptoms, many due to interactions with other medications. Recently, several studies indicate that ginger contains anticoagulant effects. When taken in tandem with other anticoagulant therapies such as Warfarin or aspirin, the effects of these drugs can substantially increase. Thus, women with a past medical history of vaginal bleeding or clotting disorders are encouraged to avoid taking ginger during their pregnancy. In addition to interactions with anticoagulants, ginger also shows potential to interact with other classes of drugs such as benzodiazepines, beta blockers, barbiturates, and other herbal medications (Tiran, 2003).

As one of the most popular and studied herbal supplement, the use of ginger in primary care and in pregnancy seems to be a safe and inexpensive option. However, despite promising research, the lack of regulation in purity coupled with lenient dosage management by the FDA should raise concerns. Ginger can exacerbate the effects of anticoagulants and interact with other drugs. Due to the tendency of patients to exclude the use of herbal supplements from healthcare providers, the risk of herb-drug interactions substantially increases. While generally safe to use during pregnancy, caretakers should monitor ginger and other herbal supplements similar to the way to manage pharmaceutical drugs.

Risks/Interactions Associated with Pharmacological Methods

Compared to their herbal medicine counterparts, the pharmacological methods are better researched in terms of their exact mechanism, teratogenic effects, and safety. Multiple studies on the safety and effectiveness of dopamine, serotonin, and cholinergic antagonists indicate almost no teratogenic effects or adverse side effects for the mothers (Ebrahimi et al., 2010; M.L. et al., 2006; Niebyl, 2010).

Biochemical Changes Associated with Sleep Disturbances in Pregnancy

Another common symptom reported by 66% to 94% of pregnant women reports sleep disturbances, including insomnia. Due to marked mechanical changes coupled with hormonal fluctuations, the quality and length of sleep change profoundly. Ailments such as lower back pain, leg pain, and abdominal discomfort affect the architecture of sleep. Pregnant women tend to have increased light sleep (stage 1 sleep) and suppression of REM or deep sleep. Importantly, as seen in

Figure 4, the marked elevation of progesterone and estrogen due to pregnancy plays a large role in changing the quality of sleep. Estrogen decreases REM sleep as well as increase upper airway resistance by causing swelling. The increased difficulty breathing might play a role in sleep disruption. Progesterone, on the other hand, increases non-REM sleep. Similar to the effect of estrogen on the airway, progesterone increases ventilation and respiratory alkalosis, leading to instability in the airways and disruption in sleep. Furthermore, because progesterone shares binding sites on corticosteroid binding globulin, an increase in progesterone level directly correlates to an increase in free cortisol. This disturbance in the cortisol-melatonin ratio is hypothesized as a cause of

sleep disturbances and insomnia (Kizilirmak et. al., 2012; Reichner, 2015; Sharma et. al., 2004).

Interestingly, the typical sleeping pattern of expectant mothers' changes and shifts throughout the trimesters. During the first trimester, the rise in progesterone may cause daytime sleepiness. However, even though there is a meaningful increase in sleep duration, the efficiency and quality of sleep remain depressed, thus, common complaints during this period may also include fatigue. In the second and third trimesters, the total night-time sleep duration falls, resulting in an increase in non-REM sleep and a reduction of REM sleep. Nocturnal disturbances become increasingly common. Some women can develop insomnia or difficulty falling asleep (AM, SK, SK, & IS, 2016; Pien & Schwab, 2004; Sharma et al., 2004).

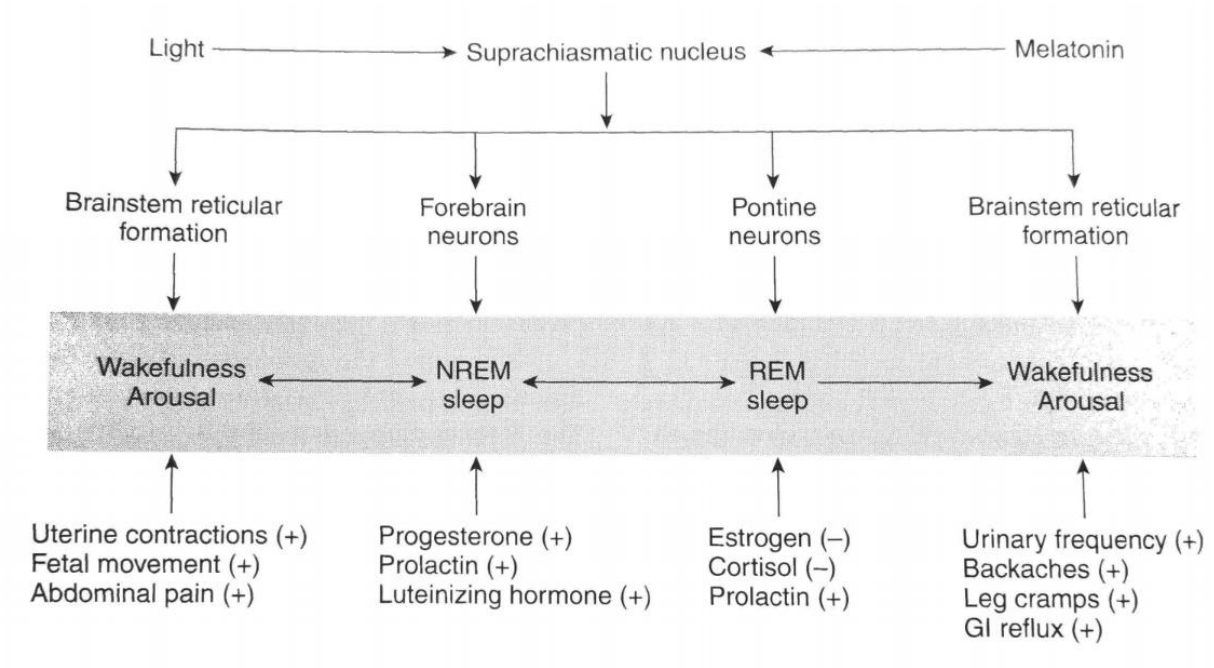

Figure 4: *Impact of different hormones on the quality of sleep in pregnancy. Figure adapted from Guyton, A.C (1987). Human Physiology and mechanisms of disease (4th ed.). Philadelphia: Saunders.*

Overview of Treatments for Insomnia During Pregnancy

Similar to the treatment for NVP, sleep disruptions can be mediated by nonpharmacological methods and pharmacological therapies. Nonpharmacologic interventions include sleep hygiene and sleep education as well as behavioral therapy. Changing the surrounding environmental factors by avoiding certain foods, dimming the lights, and changing sleeping position may help promote a restful night of sleep. A step above sleep hygiene and education involves behavioral therapies that promote relaxation, employ sleep restriction, and decrease anxiety and stimulus through cognitive therapy (AM et al., 2016). Another major alternative or nonpharmacological therapy utilizes herbal supplements to promote sleep. Valerian (*Valeriana officinalis*) is an herb commonly recognized for its sedative effect often available in many different preparations including extracts, infusions, and tinctures. With a mixture of active ingredients, the main mechanism of valerian is attributed to valerenic acid and sesquiterpenes. By inhibiting the breakdown of the enzyme charged with the degradation of GABA, valerian causes a decrease in activity in the central nervous system resulting in a sedative effect (Abebe, 2002; Houghton, 1998).

If insomnia persists, a limited number of pharmacological therapies may be considered for short-term use. Most sedative-hypnotics remains unsafe for use during pregnancy, however, diphenhydramine (Benadryl) or zolpidem (Ambien) when used infrequently are currently considered safe for the mother and the fetus. Similar to the

proposed mechanism for valerian, zolpidem acts on GABA receptors to induce sedation (Doble, 1996). The medical community still remains divided on the use of Zolpidem during pregnancy due to uncertainty about dosage and potential side effects. Diphenhydramine, a known histamine receptor antagonist, induces sedation by altering the regulation of the sleep-wakefulness continuum (Turner, Handford, & Nicholson, 2006). Insomnia remains a difficult disorder to treat, and stringent drug management is imperative in preventing adverse side effects.

Risks/interactions Associated with Nonpharmacological Therapies

Only a handful of clinical trials and experiments have been conducted on the effectiveness and safety of valerian. Both clinical and animal studies can have sleep-inducing and tranquilizing effects in-vivo. With a mixture of different constituents, valerian utilizes several different mechanisms to cause a tranquilizing or sedative effect. However, the activity of valerian is dependent on the concentration of its constituents. Due to a variety of different preparations, the effectiveness of this herbal supplement greatly varies from company to company. With current FDA regulations, no formal standardization for the preparation of valerian currently exists, which raises concerns about safety.

Limited research exists studying the pharmacokinetic and pharmacodynamic interactions between valerian and other herbal medications or pharmaceutical drugs. Due to its effect on GABA, interactions with barbiturates and opioids are plausible. Valerian

may exert an additive or antagonistic effect in response to tranquilizers, other sedative medications, and opioids. In addition, some studies indicate that valerian potentially reduces the effect of antidepressants when taken in tandem. In vitro evidence also suggests that valerian might inhibit CYP, opening the door for potential interactions with CYP substrates such as warfarin and atorvastatin. (Abebe, 2002; Cramer et.al., 2006; Houghton, 1998).

Risks/Interactions Associated with Pharmacological Therapies

In general, pharmacological treatments for insomnia and sleep difficulty during pregnancy should be short-term. Most sedatives may be teratogenic, posing a significant risk towards the fetus. Currently, no official pharmacological therapy for insomnia is classified as safe during pregnancy. Zolpidem has been shown to increase symptoms of depression when combined with central nervous system acting drugs such as Tramadol and Alprazolam. This indicates that Zolpidem might influence the metabolism and hence the function of other medications. Due to its interactions with GABA receptors in the brain, potent interactions between Zolpidem and illicit drugs that interact with the central nervous system may cause catastrophic side effects. Other categories of sedative pharmaceutical therapies also pose a major risk to the fetus, such as drug withdrawal symptoms following birth (Jazbar et. al., 2018).

Chapter 3.3: Induction of Labor: A Review of Pharmacological and Herbal Methods

Induction of Labor: Biochemical changes

The initiation and development of a pregnancy, as discussed earlier, relies on a whole orchestra of hormones and molecules. Similarly, the initiation and stimulation of labor are greatly dependent on several major proteins: progesterone, prostaglandins, interleukin-8, and oxytocin receptors. As mentioned above, progesterone levels remain high during pregnancy to combat labor-inducing effects. This steroid hormone inhibits the ripening of the cervix, governed by another hormone, as well as combat the effects of labor promoting hormones. While there is no noticeable progesterone withdrawal during human pregnancy, some studies indicate that progesterone might undergo a "functional" withdrawal. Speculation into the role of progesterone during labor remains debated and postulated. Another important hormone in inducing labor is prostaglandins, which stimulate myometrial contractility and cervix ripening. Changes in the synthesis and the metabolism of prostaglandins fluxes over the duration of the pregnancy and plays a role in governing the labor process. Up-regulation of prostaglandins near the end of pregnancy stimulates contractions during labor. The hormone interleukin-8 is produced by the endometrium, myometrium, decidual cells, and the placenta. The expression of this hormone correlates with increasing gestational age, suggesting that interleukin-8 might play a role in ripening the cervix prior to cervical dilation. The final key player in the induction of labor in humans is the oxytocin receptors. Increased sensitivity to

oxytocin in the myometrium plays a large role in promoting uterine contractions, thus, biochemical changes both the levels of oxytocin and the affinity of oxytocin receptors to their substrate largely contributes to the induction of labor (Mohan et. al., 2004). Figure 4 shows a summary of the regulators involved in labor induction. This figure also shows that other secondary factors such as nitric oxide and ion channels, while not discussed thoroughly in this paper, also plays a major role in the induction and sustaining labor.

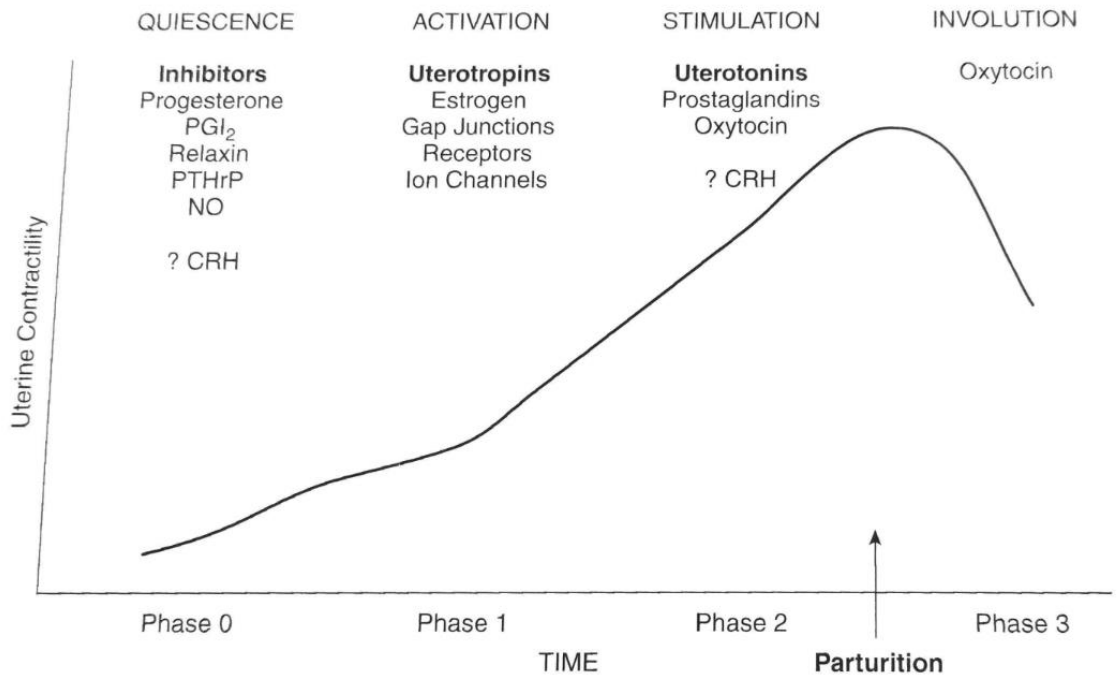

***Figure 5**: The relationship of major hormones and regulators in relation to uterine contractility and parturition. CRH, corticotropin-releasing hormone; NO, nitric oxide; PGI_2, prostacyclin, PTHrP, parathyroid hormone-related peptide. Adapted from Challis, J.R.G. (1999). Characteristics of parturition. In R.K. Creasy & R. Resnik (eds.). Maternal-fetal medicine (4th ed.). Philadelphia, Saunders.*

An Overview of Methods for Labor Induction

The labor process, both in duration and onset, greatly varies across individuals. Preterm labor, classified as parturition prior to 37 weeks of gestation, may cause fetal distress. Similarly, post-term labor, classified as parturition after 40 weeks, poses a risk to fetal wellbeing due to insufficient nutrition derived from the placenta. In cases of fetal distress, maternal distress, or postdate pregnancy, providers often employ a range of different methods to induce labor. The first step in labor induction revolves around ripening the cervix. Promoting the cervix to absorb water and become more malleable increases the chances for successful vaginal delivery. Mechanical approaches such as inserting a balloon catheter to apply direct pressure on the cervix may be used to ripen the cervix (Tenore, 2003). The primary pharmacological method for induction of labor involves cervical ripening by misoprostol (Cytotec) and promotion of uterine contraction via Pitocin, a synthetic version of oxytocin. Alternative methods, particularly herbal methods indicated in inducing labor includes blue cohosh, raspberry leaf, evening primrose, and castor oil. Comparing the mechanism and the possible interactions of both the pharmacological method and alternative methods elucidates on the importance of using scientifically backed methods to ensure the safety of the expectant mother and the baby.

Herbal Supplements as Labor Inducers

Many different herbal medications and preparations have been used by women to aid or induce labor. Of these, blue cohosh, red raspberry leaf, castor oil, and evening primrose make up the most common herbal supplements used for cervical ripening, induction, and augmentation of labor. The mechanism for both evening primrose and raspberry leaf remains relatively unknown. Little to no clinical research exists to help elucidate both the safety and efficacy of these two herbal medications. Only a handful clinical studies suggest that raspberry is a safe and effective method to induce labor, however, many of these trials are small with no statistically significant data (Hall et.al., 2012). Caretakers still debate over the efficacy and safety of both evening primrose and red raspberry leaf. Due to a lack of research, pregnant women are often discouraged from taking these supplements.

Castor oil (*Oleum Palmae Christi*) is an ancient herbal medication derived from the seeds of *Ricinus communis*. Historically used to promote bowel movements and to treat inflammation, Castor oil has also been documented as a labor inducer in women at term. Ricinoleic acid, a hydroxylated unsaturated fatty acid, constitutes the main pharmacological mechanism of castor oil. Ricinoleic acid is a selective agonist of EP_3, a prostaglandin receptor presents in both the small intestine and the myometrium. Consumption of castor oil and subsequently ricinoleic acid activates EP_3 receptors on

smooth muscle cells in the uterus, thus initiating symptoms associated with labor (Tunaru et. al., 2012).

Blue Cohosh (*Caulophyllum thalictroides*) is derived from a perennial plant with large blueberries. In the late 1990s, up to 64% of practicing midwives prescribed Blue Cohosh to induce labor and help speed up the process of delivery. However, several case reports suggest that Blue Cohosh may be associated with myocardial infarction, hypoxic injury, and cardiovascular birth defects (Dugoua et.al., 2008; Xia et al., 2014). The preparation of Blue Cohosh yields several important active constituents such as alkaloids and triterpene saponins. While these components show biological activity in anti-inflammatory and analgesic effects, the exact mechanism for the induction of labor remains unknown (Xia et al., 2014). Blue Cohosh was shown to enhance estradiol binding to its receptors to increase the effect of estrogen, which may help initiate the birth process (Mills et.al., 2006).

Interestingly, Cytotec shares a similar mechanism with castor oil, yet they wildly differ in terms of their regulation and standards. Both either directly or indirectly influences the expression and activity of prostaglandin, changing the motility of the uterus. Generally, castor oil and other herbal preparations remain grossly under-regulated by the FDA despite their pharmacologically active mechanisms. Comparison of Cytotec and other herbal alternatives yields somewhat of a paradox. Despite patchy empirical data, the FDA remains essentially quiet on herbal supplement regulations – adopting little

regulation requirements and quality standards. Conversely, despite ample clinical data suggesting the efficacy and safety of Cytotec as a labor inducer, the FDA has yet to officially approve the use to this drug for that indication. Despite consumer perception, both pharmacological and alternative methods operate under similar mechanisms, and thus, should be held to the same standards.

Interactions Associated with Non-pharmacological Approaches

As with the case of herbal supplement raspberry leaf and evening primrose, because the main active constituents and pharmacological mechanism remain unknown, the potential for interactions with other compounds also remains unknown (Holst et.al., 2009). Recently, studies on Blue Cohosh shows a whole slew of interactions and adverse side effects. Studies indicate that Blue Cohosh might constrict coronary arteries and a decrease in oxygen flow to the heart, thus, interacting with cardiovascular drugs such as nitroglycerin, that cause vasodilation (Mills et al., 2006). These symptoms and interactions remain relatively unexplored by researchers. In some ways, the increased potential for interactions with other medications and alternative methods makes these herbal medications more dangerous compared to other preparations and pharmacological drugs. Without even a foundation of knowledge about functionality, taking these herbal supplements in tandem with other drugs increases the change for severe interactions.

Misoprostol (Cytotec): A Pharmacological Drug to Induce Labor

As mentioned above, prostaglandins are a group of compounds that have a major effect on the labor process among other physiological processes. Misoprostol is a synthetic analog that induces many of the same effects. Cervical ripening can be induced by administering misoprostol orally or intravaginally. Prostaglandin administration induces collagenase activation, which breaks down collagen in the cervix causing the amount of collagen to be dispersed, resulting in a softer cervix. Application of misoprostol also induces extracellular matrix remodeling and promotes uterine contractions by sensitizing the myometrium to oxytocin. The use of this drug has been linked to uterine tachysystole or excessive uterine contractions and changes in fetal heart rate. Thus, proper monitoring of both maternal and fetal wellbeing remains an important part of labor management. Interestingly, misoprostol in the U.S. is only approved by the FDA for ulcer treatment. For the past 30 years, this drug has been used off label for labor induction and cervical ripening, and despite years of empirical data supporting the use of misoprostol in this role, no current FDA approval for this obstetrical indication exist. The American College of Obstetricians and Gynecologists (ACOG) endorses the use of misoprostol for induction, citing a large body of clinical evidence for its safety and efficacy (Stephenson & Wing, 2015). Pitocin, a synthetic form of oxytocin, may be titrated after cervical ripening to induce uterine contractions by increasing the intracellular concentration of calcium. Both Cytotec and Pitocin dosage needs to be stringently regulated to prevent polysystole and fetal tachycardia (Arias, 2000).

Interactions Associated with Pharmacological Approaches

The conversion of Misoprostol into its pharmacologically active constituents occurs in the stomach, thus the intake of food may alter its bioavailability. Thus, dosage of Misoprostol should be altered to account for its variable metabolism. Despite studies evaluating interactions between Misoprostol and NSAIDs (aspirin or ibuprofen) and other classes of drugs, no clinically significant or relevant interactions were reported. The use of misoprostol or Cytotec has no known drug interactions. Moreover, this pharmacological therapy does not interact with the CY P450 enzymatic system often indicated in drug metabolism and absorption (Davies et.al., 2001; Goldberg et.al., 2001).

The Gap Between Pharmacological drugs and Herbal Supplements

In this chapter, many different herbal supplements were examined for both safety and efficacy with variable and inconsistent results. Ginger, one of the most studied herbal supplements, yields promising results for usage during pregnancy. However, many of the other herbal supplements such as valerian root and blue cohosh yielded little data and potentially detrimental effects on both maternal and fetal systems. In comparison, the pharmacological counterparts provided providers and patients with extensive research on potential side effects for usage during pregnancy as well as efficacy. Despite containing a whole mixture of pharmacologically active ingredients, herbal supplements remain largely underregulated.

A clear discrepancy in knowledge for the mechanism of action directly stems from the difference in FDA regulation between pharmacological therapies and herbal remedies. While drugs are required to pass premarket benchmarks, herbal supplements adhere to no standardization or premarket regulations or tests. However, this is almost like a double edge sword. Stringent testing on safety and efficacy aims to protect patients from adverse side effects, public misconceptions on data and research may deter progress in treatment.

The litigation and history of Bendectin, now marketed as Diclegis serves as a prime example of how proper scientific and clinical research corresponds with public misconceptions. After obtaining FDA approval in the 1950s, the doxylamine-pyridoxine combination became widely prescribed. At the peak of use, almost 25% of women reported taking this drug to manage NVP. However, coinciding with the Thalidomide tragedy, the safety of Bendectin came under scrutiny by a skeptical public in the late 1960s and into the 1970s. Eventually, a slew of lawsuits came in claiming that Bendectin as a teratogen, causing multitudes of birth defects in infants across the country. The pharmaceutical company elected to remove Bendectin from the market, based on weak claims unbacked by scientific studies. Shortly after, independent studies dispelled the claims that the doxylamine-pyridoxine caused fetal deformities, affirming the effectiveness and safety of Bendectin. However, this combination was only recently introduced back into the pharmaceutical market. A 30-year gap between the removal and

reintroduction of this highly effective drug left obstetric care with no FDA approved medication to mediate NVP (Slaughter et. al., 2014).

Between the case studies with herbal supplements and pharmacological drugs, clearly, there is an inconsistency in the effectiveness of FDA regulation. On one hand, most herbal supplements remain largely underregulated and hence understudied. With increasing popularity and usage, this potentially leads to different drug-herb interactions and adverse side effects. On the other hand, stringent regulations on pharmacological drugs limit the ability for the development of new techniques. Another major component in regulation involved the public's perception and understanding of the mechanisms and effects of both pharmacological therapies and herbal therapies alike. Perhaps the notion that herbal supplements are natural deters patients from investigating their mechanism and side effects while pharmacological drugs are often viewed as unnatural and associated with teratogenic effects. These preconceptions change the way the general public interprets the data and regulations set by the FDA. An effective regulatory system for both herbal supplements and pharmacological therapies should involve premarket approval, disclosure of all physiological effects, and standardization while considering the perspective of the general population.

Chapter 4.1: The Complexity of Postpartum: Pharmacological and Herbal Therapies in Treating Postpartum Depression (PPD)

Hormonal Changes Associated with PPD

In the days and weeks following childbirth, a woman's body undergoes significant physiological changes. Due to a dramatic decrease in weight, changes in social and family dynamics, and hormone fluxes, women typically experience a wide range of emotions, which can include a persistent depressive mood. One of the most expensive diseases to treat in America is depression, with over 14.8 million adults suffering from at least one major depressive episode in any given year (DBSA, 2016). PPD exists as a subset of depression affecting women anytime within the first four weeks of the postartum period to 8 weeks postpartum, affecting anywhere from 7% to 20% of all women who gave birth (Schiller, Meltzer-Brody, & Rubinow, 2015). Some of the most common symptoms of PPD include a persistent depressed mood, a decrease in interest of leisure activities, and disturbances in appetite or sleep (Solomon & Bauer, 2018). Research shows that the development of PPD is multifactorial, relying on a combination of social and biological factors (McCoy, Beal, Miller Shipman, Payton, & Watson, 2006). After giving birth, a woman's body undergoes drastic biochemical changes in the form of gonadal hormones, thyroid hormones, and pituitary hormones fluxes, causing a whole array of varying symptoms. Changes in these the biochemical processes combined with environmental stressors such as lack of support or marital conflict may lead to the development of PPD.

With such a high prevalence and increasing occurrence of PPD in routine OB/Gyn care, PPD is a major health concern affecting the patient and their immediate social groups. PDD, like major depressive disorder, can be treated using a combination of intervention by medical personnel and medication. Understanding the biochemical changes will help us elucidate out how herbal supplements and pharmaceuticals can influence the signaling pathways.

Gonadal Hormones Changes

Hormones such as estrogen, progesterone, follicle stimulating hormone (FSH), and luteinizing hormone (LH) play a large role in maintaining homeostasis and reproductive function. On a more general level, these hormones also play a large role in the regulation of emotion, arousal, and motivation. During pregnancy, estrogen and progesterone levels are elevated, largely because of placental production and contribution.

Estrogen exists as two main biologically active compounds: estradiol and estriol, which increase in pregnancy from basal levels by 100-fold and 1,000-fold respectively. However, estrogen levels crash after birth, returning to preconception levels by day five of postpartum (Hendrick, Altshuler, & Suri, 1998). This sudden change in levels correlates to the development of PPD and its associated symptoms both directly and indirectly. Because of its role in controlling emotion, the sudden decrease in estrogen correlates to the development of a persistent depressed mood that is also influenced by

psychological and social risk factors. Estradiol (E2), an active form of the hormone estrogen plays an interesting role in the regulation of different biological systems and pathways in the body. The presence of estradiol directly correlates with the function of the serotonin, a potent neurotransmitter implicated in the regulation of euphoria. E2 increases the production of tryptophan hydroxylase, an important enzyme in catalyzing the formation of serotonin from tryptophan. During the sharp decline in estrogen levels, the levels of serotonin also decrease. In addition, E2 inhibits the expression for the gene responsible for the reuptake of serotonin, allowing the neurotransmitter to increase its activity in the synapses. The decrease in the E2 levels after birth increases the reuptake of serotonin immediately after birth. Reuptake decreases the activity of these neurotransmitters, leading to both mental and physiological symptoms such as fatigue and a decrease in enjoyment of activities (McCoy et al., 2006; Rybaczyk et al., 2005).

Progesterone, another prominent gonadal hormone implicated in reproductive function, also experiences significant fluctuations throughout the pregnancy and the postpartum period. Following successful implantation of the zygote in the uterus, the levels of progesterone remain high throughout the duration of the pregnancy both through maternal and fetal contributions. This steroid hormone suppresses the maternal immune system against fetal antigens and maintains the proper environment during embryo-development. On a more global scale, progesterone increases the activity of GABA receptors, which are ion channels that govern the flow of ions into the cell. Increased activity of GABA receptors decreases the excitation of the neuron, which can help

decrease and modulate feelings of anxiety or fear. After the delivery of the placenta, the levels of progesterone sharply decline during the postpartum period. Progesterone withdrawal during the postpartum period can contribute to the anxiety symptoms seen in PPD (McCoy et al., 2006; Tuckey, 2005).

Thyroid Hormones Changes

Interestingly, studies indicate that in the 6 months following delivery, new mothers experience a higher incidence rate of thyroid dysfunction at around 7% compared to the general population, whose incidence rate lies at around 3% to 4% (Hendrick et al., 1998). The thyroid secretes differing levels of thyroid hormones to regulate metabolism, temperature, heart rate, and the production of energy in the form of ATP (Gnocchi, Steffensen, Bruscalupi, & Parini, 2016). Scientists hypothesize that abnormalities in thyroid hormone concentration may serve as an indicator for the development of major depression as thyroid dysfunction is often accompanied by depression (Schiller et al., 2015). While the development of PPD isn't directly correlated with the presence of thyroid hormone abnormalities in most women, it appears to be a significant factor for a certain subset of mothers (Hendrick et al., 1998).

Changes in thyroid hormones during pregnancy and levels of estrogen interacts via biochemical flux. During pregnancy, as mentioned before, the levels of estrogen remain elevated due to fetal contributions. This substantial gonadal hormone increase also causes an elevation in the levels of thyroxine-binding globulin (TBG) and

consequently, leading to a surge in circulating T_4 levels, which is the inactive form of the TH (Schiller et al., 2015). In addition, a placental contribution in producing excess thyroid stimulating factors and an overall iodine deficiency may also contribute to a net increase in T_3/T_4. In the case of diminished thyroid function, often referred to as hypothyroidism, studies indicate a decrease in the amount of serotonin activity (Engelsen, Fern, Ireland, Harris, & Silver, 2015; Hendrick et al., 1998).

Pituitary Hormones Changes

During the pregnancy and the birthing process, the increased levels of stress cause a substantial elevation in levels of corticotropin-releasing hormone (CRH) and adrenocorticotropic hormone (ACTH), leading to hyperactivation of the HPA axis. The HPA axis or the hypothalamus-pituitary-adrenal axis is one of the major endocrine pathways that influence our stress hormones. Activation of this pathway leads to a response in by the sympathetic nervous system, activating our fight or flight response by increasing the amount of cortisol released. The levels of cortisol, a hormone involved in activating the stress response in the body, sees a significant drop approximately our days after delivery. Yet, the HPA axis takes approximately 12 weeks postpartum to return to normal function. This dysfunction in the regulation of cortisol may link hormonal imbalance immediately following birth to the development of PPD (Schiller et al., 2015). The stress hormone fluctuation is hypothesized to contribute to clinical symptoms observed in PPD.

Treatment of PPD: An Overview of Common Pharmacological Drugs and Herbal Supplements

PPD and depression, in general, can usually be treated using a combination of psychotherapy and medications, such as selective serotonin reuptake inhibitor (SSRI). These drugs work by decreasing the activity of molecules that remove serotonin, which is a neurotransmitter linked to the feelings of euphoria, from the area between a synapse. This allows for a prolonged increase in the levels of serotonin in the brain, which can help increase its activity and alleviate symptoms typically observed in depression (Schafer, 1999). Many of the SSRI's available, such as fluoxetine or Nefazodone, have been clinically approved for use during the postpartum period (Weier & Beal, 2004). However, there is still a lack of research on the effects these antidepressant medicines have during prolonged usage in mothers who elect to breastfeed. Most of the antidepressant medications are excreted out via the breast milk, and while only a few reports indicate a maladaptive effect on the infant, there is a lack of research on the exact effect of the effect on the medication transmitted through the breast milk. Due to these perceived effects, there seems to be an increasing number of women turning toward alternative modes of treatment. Herbal supplements present as a potential alternative treatment for postpartum depression. St. John's Wort emerges as a common herbal medication used in the postpartum period to treat PPD. However, on top of the holes in the FDA regulations of herbal supplements, the efficacy and safety of St. John's Wort may pose a health risk to both the mother and the baby. A comparison between the

mechanism and the potential interactions of St. John's Wort and Prozac (fluoxetine) can help us elucidate a proper way to regulate their usage.

Non-Pharmacological Therapies for PPD

St. John's wort (SJW) is a common herb often used to treat mild to moderate depression, in place of other pharmaceutical medications such as SSRI's. Some women opt to take SJW rather than a pharmaceutical drug in the postpartum period, citing that the use of this supplement may be safer because it is thought not to affect the breast milk as much. *In vivo* studies indicate that extracts of *Hypericum perforatum*, what is commercially known as SJW, serves as an effective treatment for symptoms associated with mild. However, the pharmacological mechanism for SJW is unknown, due to a complex mixture of compounds in this supplement and the variability in its purity across brands(Butterweck & Schmidt, 2007; Linde, 2009).

Initially, the mechanism of this herbal supplement was hypothesized to induce the inhibition of both type A and B monoamine oxidase (MAO), which are responsible for the catabolism of biogenic amines. However, while MAO inhibitors are present, this has been proven to be a minor effect and it doesn't constitute the whole mechanism employed by SJW (Butterweck, 2003; Butterweck & Schmidt, 2007).

The leading theory now suggests that *Hyperforin*, a major active constituent of SJW, unselectively inhibits the reuptake of neurotransmitters such as serotonin and dopamine. While the exact mechanism remains unclear, SJW is hypothesized to indirectly decrease the reuptake of neurotransmitters by changing the permeability of the

Na+/H+ channels to increase intracellular Na+ levels. Normally, in a neuron, which is a specialized nerve cell in the body, there is a net negative charge in the membrane potential. For this cell to transmit a signal, a flow of different ions, such as Na^+, K^+, and Ca^{2+}, fluctuates to flip the charge from an overall negative charge to a positive charge. The ability of a neuron cell to create this change allows for the cell to function and rely that message on to other cells. The reuptake system of serotonin is inhibited by the influx of sodium, thus, hyperforin non-selectively inhibits this system, which is a mechanism similar to that of SSRI's. (Butterweck & Schmidt, 2007; Carlo, Borrelli, Ernst, & Izzo, 2001; Linde, 2009; Singer, Wonnemann, & Muller, 1999). While Hyperforin currently remains as the main mechanism for the effects of SJW, there could be additive effects from the other active constituents.

Pharmacological Therapies for PPD

In terms of pharmacological methods, pp to 35% of women use psychotropic medications during pregnancy and in the postpartum period. One of the most commonly prescribed psychotropic medicine during pregnancy is Prozac, drug apart of the larger family of SSRI's. The widespread usage of these medications Prozac and other SSRI's readily passes through the placental barrier during pregnancy and diffuses into the breastmilk because of their relatively hydrophobic structures. This leads to discussions about the safety of these medications not only for maternal health but also how these drugs can affect infant neurobehavior or induce potential teratogenic effects in utero.

Prozac, like most SSRI's, inhibit the molecules responsible for the reuptake of neurotransmitters such as serotonin, leading to an increase in concentrations of these molecules at the synaptic cleft (Zeskind & Stephens, 2004).

Despite different chemical compositions, SJW and Prozac employ similar mechanisms to modulate the symptoms of PPD. Hyperforin, the major active component in SJW, and Prozac, which is classified as an SSRI, modifies the levels of neurotransmitters such as serotonin by altering the activity of the enzymes responsible for the reuptake of these molecules. The etiology of PPD, similar to other mood disorders, draws from multiple variables including hormonal and biochemical changes within the body and social environments. The use of medications such as SJW and Prozac helps curb the clinical symptoms on a biological level.

Risks/Interactions Associated with Nonpharmacological Methods

Due to several active components, SJW may interact with different herbal supplements and pharmaceutical drugs when taken in tandem. There are two main types of drug-drug or herb-drug interactions: pharmacokinetic interactions, which refers to drug absorption, distribution, metabolism, and excretion and pharmacodynamic interactions, which refers to the relation between the concentration of the substance and its effect (Pharmacokinetics, 1985). One of the most pertinent interactions revolves around pharmacokinetic interactions with Cytochrome P450 (CYP), a superfamily of enzymes crucial for the metabolism of drugs and detoxification of chemicals. SJW is a known

inducer of CYP enzymes. (Lin & Lu, 1998; Thompson, 1839). Many different drugs and compounds interact with the mechanism of CYP enzymes within the body and because SJW alters the activity of these enzymes, it can modulate the effects of other drugs. For example, SJW significantly reduces the pharmacological effects of Warfarin, a common blood thinner because the induction of the CYP enzymes leads to increased clearance of the drug. This leads to serious health risks because it increases the likelihood of developing blood clots that leads to DVT or stroke. Similarly, studies indicate that SJW changes the levels of other drugs such as anti-HIV drugs, antiepileptic drugs, hypoglycemic drugs, benzodiazepines, among other classes of drugs (Borrelli & Izzo, 2009; Thompson, 1839).

Interestingly, CYP enzymes also play a major role in the formation and metabolism of estrogen within the body. Aromatase, a specific CYP enzyme, mediates the synthesis of estrogen and the management of the oxidative states of estrogen relies on another set of CYP enzymes. Drugs that induce CYP enzymes may affect increase the hydroxylation of estradiol, hence changing the activity of estrogen in the body. These changes increase the risk for the development and the persistence of PPD in mothers. While this area remains less studied, SJW, due to its influence on CYP enzymes may change the symptoms of PPD by altering the levels of estradiol (Martucci & Fishman, 1993).

Risks/Interactions Associated with Pharmacological Methods

Prozac also exhibits inhibitory action against multiple isoforms of the CYP enzymes. The inhibition of these enzymes leads to pharmacokinetic features such as a decrease in clearance of secondary drugs, precipitation of more severe side effects, and an increase in the likelihood of toxicity. Prozac, when taken in tandem with other SSRI's or other antidepressants, can cause a significant surge in serotonin levels, leading to serotonin syndrome. The inhibition of CYP also alters the metabolism of larger classes of drugs including cardiovascular drugs and other SSRI's. On the other hand, Prozac has also been shown to blocking the conversion of drugs into their active components. This specific SSRI prevents the conversion of codeine and tramadol, two common analgesic drugs, into their active components. This significantly reduces the efficacy of analgesic drugs, causing patients to experience increased pain (Gillman, 2005).

In addition to maternal effects, the ability of Prozac to diffuse across the placental barrier and the breastmilk exposes infants to these same effects. Exposed infants experience an elevation in levels of serotonin, which can cause a wide variety of physiological symptoms such as more generalized erratic motor activity and tremors (Zeskind & Stephens, 2004). The potent interactions between Prozac with other SSRI's and substances warrants careful regulation by the FDA.

While proven to be relatively effective, these medications are not without significant risks. Due to their similar mechanisms, SJW and Prozac alter the clearance of other drugs by influencing the activity of CYP, leading to impaired function or an exacerbation of symptoms. It remains imperative to report usage of both pharmaceutical

drugs, but also herbal medications to healthcare providers. This allows physicians to modulate possible interactions with other medications.

Comparing the Preparation and Regulation of SJW and Prozac

Despite their similarities in function and effect, these SJW and Prozac drastically differ in terms of their preparation methods and regulation. Prozac falls under the umbrella of pharmaceutical drugs, which requires much stricter regulations on the concentrations of the active component present. In contrast, SJW and other herbal medications operate under lax regulations. The concentrations of components in SJW are not regulated, varying depending on the preparation style. Typically, air-dried H. *perforatum L*. flowers and buds are soaked in 60%-80% methanol for approximately 30 minutes to extract out the lipophilic components found in the flower. The identified components in the final product of SJW fall under several categories: naphthodianthrones, flavonoids, hyperforin, and water-soluble components. The concentration and proportions of each constituent vary depending on the duration, harvesting, a light exposure environment (Butterweck & Schmidt, 2007), hence leading to great variability in products with a lack of FDA oversight. Different brands of SJW can contain different substituents, which can alter the effect of other drugs and increase the risk for unforeseen interactions. With so many prominent similarities, the regulation of both substances should be altered to mirror each other, thus decreasing the associated risks of interactions with other medications.

Chapter 4.2: The Complexity of Lactation: Pharmacological and Herbal Therapies to Treat Insufficient Milk Supply

Biochemical Changes Involved in Lactation

A major component of the postpartum period revolves around breastfeeding. Studies indicate that breastfeeding is the optimal form of nutrition for infants, providing both short term and long-term benefits to the baby. These benefits include immunological effects and decreased risks for diseases such as gastroenteritis, obesity, and type I and II diabetes. Breastfeeding also shows signs of enhancing the maternal-fetal emotional bond. Overall, breastfeeding provides significant benefits to the mother and provides the best health, psychological, and developmental outcomes for the infant. However, the duration of exclusive breastfeeding and lactation by the mother remains varied due to many different circumstances (Conover & Buehler, 2004; Mannion & Mansell, 2012). The development and secretion of milk by the mother relies on biochemical changes in the body.

Mammary glands, which are essentially modified sweat glands modulated by the endocrine system, plays a major role in both lactation and secretion. Lactocytes, milk-producing cells, line the alveoli of the mammary gland, located within the breast and serve as the main site of milk production. The blood capillaries that surround the alveoli of the gland provides a system for substrates such as vitamins and glucose to diffuse across the cell membrane of the lactocytes to be integrated into milk components. Interestingly, while the same basic components of the milk remain constant, diet plays a

huge role in dictating the energy content of the milk as well as the vitamin and mineral content (Hoehn & Marieb, 2016; Kent, 2007). While the vascularization of this area allows for easy diffusion of milk components and vitamins, it also makes the diffusion of lipid-soluble substances such as herbal supplements easier.

Lactogenesis I and II

Lactogenesis or the production of milk secretions is mediated primarily by prolactin, a hormone secreted by the anterior pituitary gland. The main steps in lactogenesis can be summed up into two main stages lactogenesis I and lactogenesis II. The first stage typically begins between weeks 16 and 22. During this phase, the mammary glands begin development (Kent, 2007; Zapantis, Steinberg, & Schilit, 2012).

The second stage, or lactogenesis II, typically occurs immediately after birth. Characteristic of significant milk production and secretion, this phase typically relies on fluctuations in the concentrations of certain pituitary hormones. A significant increase in prolactin, insulin, and adrenal cortisol in combination with a progesterone withdrawal in the postpartum period allow for the activation of copious milk secretions (Kent, 2007). This change is typically noted by a sudden feeling of fullness in the breasts.

Biochemical Changes Involved with Secretion

Another prominent hormone apart of this system involves oxytocin, which also causes uterine contractions to initiate and propagate the birthing process. In a process referred to as “let down,” a spike in oxytocin influences the expulsion of milk from the

breast. Suckling or stimulation of the nipple area activates sensory afferent neurons, sending a signal that prorogates to the anterior pituitary gland. The stimulation of this gland causes the release of oxytocin. Once this hormone reaches the mammary gland, via the bloodstream, oxytocin acts on the contractile cells surrounding the alveoli causing the release of breast milk. While direct stimulation via sucking by the infant remains the primary trigger for this response, schedule of feeding or even merely the sight of the baby can cause this reflex to activate. Thus, hormonal imbalance, especially in the levels of oxytocin may result in alterations of the release of the milk (Hoehn & Marieb, 2016; Newton & Newton, 1950).

Herbal Supplement Usage during Lactation

A common problem during the breastfeeding stage, which can last over a year postpartum, revolves around perceived insignificant milk supply. Most often, this issue results from improper breastfeeding techniques, but can also be the product of maternal hormone imbalance or deficiency in the breast tissues. If breastfeeding techniques, such as latching, are ruled out, the use of galactagogues can be used to increase the production or flow of milk. Galactagogues can include foods, herbal medications, and pharmaceutical drugs (Hoehn & Marieb, 2016; Westfall, 2003; Zapantis et al., 2012). Hundreds of plant species have been used to increase milk production, however, despite centuries of usage by women worldwide, most of these substances remain unproven in a lab or clinical setting.

***Table 4**: Common herbal medications used during the lactation period.[1] (Yildirim, Desdicioglu, Kara, & Yavuz Avsar, 2016), (Mannion & Mansell, 2012) [2] (Westfall, 2003), (Mannion & Mansell, 2012), [3,4] (Mannion & Mansell, 2012).*

Herbal Supplement	Reason for Use	Benefits	Associated Risk	Interactions
Fenugreek [1] 	To stimulate the development of breast milk	Stimulates oxytocin secretion to help induce labor	Hypoglycemic effects, hepatoxicity, diarrhea	Potential interactions with anticoagulant medication and antidiabetic medicine
Fennel [2] 	Expectorant, Upper respiratory tract infection, antispasmodic, galactagogue	Digestive aid, mild estrogenic properties	Seizures, nausea, pulmonary edema	Can interact with anticonvulsant medications
Blessed Thistle [3] 	Stimulates menstruation, antidiarrheal, expectorant, galactagogue		Nausea, vomiting, diarrhea, contact dermatitis	May interfere with antacids, H2 antagonists, proton pump inhibitors, insulin
Anise [4] 	Expectorant, antispasmodic, antiseptic, antiflatulence		Seizures	Interactions with anticoagulants, MAO inhibitors, and oral contraceptives

Out of the hundreds of herbal galactagogues, the most commonly used one is Fenugreek. Historically, this plant, originating from India and Northern Africa has been used to treat a range of aliments from induction of labor to digestion to cough (Ulbricht et al., 2007). The preparation of this herbal supplement typically includes the addition of saponin, alkaloids, amino acids, coumarin, among other ingredients (Abebe, 2002). Due to minimal regulation by the FDA, the concentrations of these components vary, altering the efficacy and safety of fenugreek supplements.

The main mechanism of Fenugreek remains unknown and poorly documented, moreover, the active ingredients have not been identified. Scant clinical trials have yet to establish the safety of efficacy of Fenugreek usage during pregnancy or the lactation period. It is hypothesized that Fenugreek stimulates sweat production, which may affect the function of the mammary glands, which are essentially just modified sweat glands. Fenugreek might also contain estrogenic activity. This herbal supplement contains estrogen-like compounds that can increase the levels of phytoestrogens, dietary estrogens that can potentially bind to estrogen receptors, altering the functionality of the endocrine system (Gabay, 2002; Mortel & Mehta, 2013).

Risks and Interactions Associated with Nonpharmacological Methods

Typically, Fenugreek is well tolerated with no serious side effects. However, when taken with some pharmaceutical drugs, this herbal supplement may exacerbate the effect of medications when taken in tandem. Fenugreek may interfere with hormone

therapy, due to its estrogen like-components. Moreover, studies have shown that Fenugreek may interfere with the function of diabetic drugs such as insulin as well as corticosteroids. 4-hydroxyisoleucine, one of the active components in Fenugreek, may directly stimulate insulin release, which complicates the metabolism of patients with diabetes and their insulin dosage (Mills et.al., 2006).

Pharmaceutical Drugs for Milk Production

Metoclopramide and domperidone constitute the main drug therapies currently available for the stimulation of milk production. Both of these substances act by acting as a dopamine antagonist, which subsequently increases prolactin release. A surge in prolactin signals for increasing production of milk, however, this method only addresses underlying hormone imbalance that may cause a decrease in milk production. Once other factors, particularly poor latching techniques, are addressed, physicians can prescribe a regiment with metoclopramide and domperidone to promote milk production. (Gabay, 2002; Osadchy et.al., 2012; Westfall, 2003; Zapantis et al., 2012). Case studies indicate that the usage of metoclopramide shows an increase in a decrease in milk sodium concentration, but more prominently, a significant increase in both prolactin levels in the blood and a prominent increase in daily milk production (Gabay, 2002).

In comparison, Domperidone utilizes a similar mechanism as a dopamine antagonist, this increasing the prolactin levels in the blood. However, rather than having central pharmacologic effects, Domperidone has a larger effect on the periphery

dopamine release system. Due to lower lipid solubility and a larger molecular structure, Domperidone exhibits a decreased ability to cross the blood-brain barrier. With a lower diffusion rate, this drug seems to exhibit less influence on motor neuron function compared to Metoclopramide and less overall diffusion into the breast milk. While domperidone is typically intended for use as an antiemetic to treat reflux disease, this medication is often used as a galactagogue without the presence of serious side effects (Gabay, 2002; Mannion & Mansell, 2012).

Risks/Interactions Associated with Pharmacological Methods

In 2004, the FDA issued a warning against the usage of Domperidone as a galactagogue. Citing reports of arrhythmia, QT prolongation, and hypokalemia, the U.S. bans the usage of this drug for milk enhancement. Domperidone remains available internationally and is embraced by other countries as an effective therapy for milk production (Osadchy et al., 2012). Domperidone has been shown to be a weak inhibitor of CYP3A, a specific enzyme apart of the CYP superfamily important in the clearance of certain drugs. Thus, Domperidone may increase the exposure to drugs cleared by CYP3A (Chang et.al., 2010).

Metoclopramide, a central dopamine antagonist, may cause drowsiness, fatigue, insomnia, depression, and pseudo-Parkinsonism. Due to its ability to pass into the breast milk, prolonged clearance of this drug into infants result in high serum levels, increasing

the risk for methemoglobinemia (increased methemoglobin levels in the blood) (Mannion & Mansell, 2012).

Comparison Between Pharmacological Drugs and Herbal Supplements

In comparison to pharmacological therapies, fenugreek along with many other galactagogues presents with questionable efficacy for stimulating the production of breastmilk. With little clinical evidence, the usage of herbal galactagogues propagates through individual accounts and case studies. Moreover, most of these herbal products operate using an unknown mechanism. In contrast, pharmaceutical drugs, mainly Domperidone and metoclopramide, presents strong clinical and mechanistic evidence for efficacy in stimulating milk production. Despite their differences, active components in both herbal and pharmaceutical galactagogues can directly conflict with other medications to cause adverse side effects. However, similar to the situation between the regulation of herbal supplements and pharmaceutical drugs to treat PPD, the regulation between substances used for stimulation of milk production also shows distinct discrepancies. Herbal supplements require no premarket approval, empirical support, nor do they require a prescription to obtain. In contrast, pharmacological drugs are required to complete several rounds of clinical trials before being approved for distribution. These drugs are also required to adhere to rigid production standards and labeling requirements. As mentioned earlier in this chapter, herbal supplements and pharmacological can induce a whole host of biochemical interactions, leading to physiological symptoms.

Chapter 5: Empowering Women to make the Best Treatment Choice During Pregnancy, Birth, and Beyond

While there seems to be a social distinction between herbal supplements and pharmacological treatments, I hope that through this thesis, I effectively challenge this notion. Scientific data suggests that herbal supplements can employ a similar physiological effect and induce interactions with other substances, just like any pharmacological drug. Yet, the lack of government regulation and the skewed media presentation of herbal supplements buries the associated risks and effects.

After stepping through how the hormonal fluctuations impart a multitude of symptoms and how medications, both pharmacological and herbal, influence hormonal and biological homeostasis, the overarching question is should herbal supplements be used or even recommended. In other words, do the benefits of herbal supplements outweigh the risks? I argue that in most cases, the risks actually outweigh the benefits. There is a lack of reliable information and the risks of taking these supplements remain widely unknown. Especially for women who must balance their own health with their baby's health, this poses a huge health dilemma. Researchers and providers alike should work to close the gaps in knowledge and provide women with a solid scientific foundation to make informed decisions on medication regiments.

While I cannot offer definitive answers or methods to solve this issue, I believe that there are two main directions we can take to advocate for change in the regulation and perception of herbal medications. This shift needs to be initiated by health care

professionals in the examination room. Healthcare providers need a higher and more global understanding of women's current perspective on using alternative medicine. With a more holistic point of view, physicians can change the culture around herbal medicine by creating a safe space for patients to voice questions or concerns. In many ways, this reflects the Jesuit mission of *Cura Personalis*, a Latin term that translates to "care for the entire person." Extending on the Hippocratic oath of "do no harm", under Cura personalis, doctors are responsible for not only harm reduction but also acknowledging and treating all aspects of the person. Alternative and herbal medicine is deeply ingrained in many different cultures and thus plays an important part in a patient's choices and views.

The second avenue that can change the perception of alternative medicine lies within scientific communication, particularly the media portrayal of these substances. A quick Google search yields thousands of results, with most of the top hits consisting of a number of blog posts with personal stories on the success of herbal supplements curing different diseases or symptoms. Often times, these anecdotal stories portray herbal supplements as completely harmless. While there are proven merits to certain herbal supplements, many of them, as denoted earlier have serious side effects. Scientists can take on a larger role in educating the general public. Publishing empirically supported articles in different magazines and journals help provide a more accurate portrayal of herbal supplements and can help raise awareness of the lack of information on their mechanism.

The use of herbal medicine and alternative medicine in the U.S. bisects both physiology and biochemistry with cultural influences such as tradition. The dialect and communication between researchers, health care providers, and patients are critical in navigating the different paths possible. We shouldn't shy away from herbal supplements and alternative medicine, but rather, we should encourage conversation about them. I hope that this thesis serves as a tool to spark the conversation.

List of Abbreviations

ACOG	American College of Obstetricians and Gynecologists
ACTH	Adrenal corticotropic hormone
CAM	Complementary alternative medicine
CL	Corpus luteum
CRH	Corticotropin-releasing hormone
CYP	Cytochrome P450
DSHEA	Dietary Supplement Health Education Act of 1994
DVT	Deep vein thrombosis
E2	Estradiol
FDA	Food and Drug Administration
FDCA	Food, Drug, and Cosmetic Act
FSH	Follicle stimulating hormone
GABA	gamma-Aminobutyric acid
hCG	Human chorionic gonadotropin hormone
HPA	Hypothalamus-pituitary-adrenal axis

hPL	Human placental lactogen
IRCH	International Regulatory Cooperation for Herbal Medication
LH	Luteinizing hormone
NSAIDS	Nonsteroidal Anti-inflammatory Drugs
NVP	Nausea and vomiting of pregnancy
OTC	Over the Counter
PPD	Postpartum Depression
REM	Rapid eye movement sleep
SJW	St. John's Wort
SSRI	Selective Serotonin Reuptake Inhibitor
TBG	Thyroxine-binding globulin
TH	Thyroid hormone
UTI	Urinary tract infection
WHO	World Health Organization

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