University of Utah
UNDERGRADUATE RESEARCH JOURNAL

DRUGS AND PREGNANCY: CLINICAL MANAGEMENT WITH A CYSTIC FIBROSIS FOCUS

Micah Ballif (Kathleen Job, PhD)
Department of Chemistry

ABSTRACT

Despite the large number of women who become pregnant and use a medication during their pregnancy, there is very little information about the safety of the majority of medications. Most drugs approved by the FDA have undetermined teratogenic risk, but their use is prevalent in the management of disease during pregnancy. Physicians are faced with the daunting challenge of prescribing a dose that will have the intended therapeutic effect without putting the mother and fetus at risk, should they choose to prescribe at all.

Section 1 describes trends and practices of medication use among pregnant women. As many as 90% of pregnant women take at least one medication during their pregnancy to manage other morbidities. Research into perinatal medicine has been extremely neglected and the majority of FDA drug classifications for pregnant women conclude that there is insufficient information and human data to make any conclusive statement about the drug's safety. It is an extremely precarious challenge to prescribe a dose that is neither so low that it is ineffective or so high that it is toxic and harmful. Often, a doctor or pharmacist will simply recommend stopping the medication during pregnancy, if possible. In other instances, continued use of the medication during pregnancy is inevitable, despite the risks.

Section 2 is a literature review that examines the prevalence of common morbidities during pregnancy and common medications used as treatments, the respective drug's FDA pregnancy ranking, and consequences to the mother and fetus if the disease is left untreated. An average of 11.87% (± 1.83%) of pregnant women have at least one of the examined conditions, and an average of 82.75% (± 17.0%) of each disease's treatment options have unknown risk. The most common consequences of untreated disease in the mother are worsening of symptoms, preeclampsia, and risk of future disease, while those in the fetus are premature birth, miscarriage, and low birth weight. The results illustrate the need for both established treatment options during pregnancy as well as further research into this vulnerable population.

Section 3 is a retrospective chart review of pregnant cystic fibrosis patients at the University of Utah Hospital. The goal of the review is to understand what antibiotics pharmacists are prescribing and in what dosages in order to illuminate any prescribing patterns despite the lack of guidelines. Data collected includes demographics, antibiotic information, and pulmonary function as a measure of health. The University of Utah Hospital's database contained records for 32 patients for a total of 44 pregnancies. Analysis showed that most pregnancies showed up to a 199% higher usage of antibiotics outside of pregnancy, though some patients' usage was over 1000% greater. An average of 5.63 (± 5.93) antibiotic dosages were prescribed for use during pregnancy, and 50% of those drugs were prescribed for use the day the pregnancy ended. These elucidated trends point to areas of future research to understand the informal guidelines or physician discretion behind them.

Introduction

Each year, approximately four million women become pregnant and give birth in the United States. Many of these women have a pre-existing health condition or chronic illness they must continue to manage with medication during pregnancy. As many as 90% of pregnant women take at least one medication during their pregnancy to manage these morbidities[1].

Despite the frequency of both pregnant women becoming sick and sick women becoming pregnant, research into perinatal medicine has been extremely neglected. The vast majority of FDA drug classifications for use during pregnancy communicate there is insufficient information and human data to make any conclusive statement about perinatal drug safety. It is an extremely precarious challenge to prescribe a dose that is neither so low that it is ineffective or so high that it is toxic and harmful. Often, a doctor or pharmacist may simply recommend stopping the medication during pregnancy, if possible. In other instances, continued use of the medication during pregnancy is inevitable, despite the risks. Neither situation is completely safe, or one in which a physician or pregnant woman can rest confidently. It is essential that ethical research is conducted on drug use in pregnant women in order to eliminate a dangerous and harmful gap of knowledge.

In this thesis, I will examine the current management of various morbidities during pregnancy and create an overview of recommendations about medication usage. In Section 1 I will review literature to understand the situation regarding current medication usage and the status of clinical research involving pregnant women. Specifically, I will examine the available data to serve as the basis for prescribing decisions, describe the ethical dilemma of research on pregnant women, summarize consequences of unmanaged maternal illness, and point to directions of future research. In Section 2, I will create an overview of illness in pregnancy in order to examine what morbidities are common among pregnant women, what medications are regularly used to manage the disease or condition, and the respective drug's FDA status for use during pregnancy. I will compile a list of consequences to both mother and fetus when the condition is not managed. In Section 3, with my research group in clinical pharmacology at the University of Utah, I will examine one specific disease, cystic fibrosis (CF) in depth, as it is an illustrative and important example of a disease that must be managed by medication, even during pregnancy.

CF is unique because the disease requires a host of medications to ensure health. The use of medication, especially antibiotics, has increased the life expectancy of those with CF to a point that women are able to become pregnant. Antibiotics combat bacterial infections, one of the most prevalent and detrimental issues common to CF. Stopping those medications presents an extremely high risk to the mother as well as the fetus.

A wealth of information is included in the University of Utah Hospital's Electronic Data Warehouse (EDW), which gathers data on individuals treated at the hospital. The research group wishes to use the information available in the EDW to understand medication usage, hospital management, outcomes, and demographic characteristics of pregnant women with CF. A retrospective chart review will be performed to collect the necessary data. Subjects will include women with CF who have at some point become pregnant, ages 18-65. Data collected will include demographics, antibiotic information, pulmonary function, and type of infection. This in depth study aims to understand antibiotic prescribing patterns and outcomes associated with treatment of pregnant women.

SECTION 1-THERAPEUTIC ORPHANS: NEED FOR MEDICATION STUDIES WITH PREGNANT WOMEN

Millions of women give birth every year, and medication usage during those pregnancies is far from rare. More than 90% of women use one or more medications during the course of their pregnancies, as many as 80% during the first trimester alone[1].Overall, this high usage rate is only continuing to increase. Over the last four decades, medication use increased 68%, and nearly half of pregnant women use at least four medications over the course of their pregnancy[1].

There are several explanations for the recent increase in medication usage. Primarily, the demographic of women who are becoming pregnant has shifted to a later age[1-3]. Women are choosing to start families and become pregnant at later stages in life. Generally, women in older age demographics use more medicines to manage their health. Additionally, women are developing both chronic and acute conditions at younger ages, which overlap with pregnancy. Several studies specify chronic conditions, including diabetes, depression, hypertension, and acute obstetric complications, including nausea and cholestasis, that have increased in prevalence in younger populations in recent years[4-7]. Those conditions, among many others, require treatment with medication. Thus, as the prevalence of such diseases and conditions in younger demographics grows larger, so does the use of their respective medications in those age groups. Women of childbearing age are a significant part of such a demographic.

Two illustrative examples of increased disease prevalence among pregnant women are that of diabetes and hypertension. In a study of United States pregnancies, the CDC reported a 56% increase in gestational diabetes and a 37% increase in pre-pregnancy type I and type II diabetes[8]. Similarly, in 2005 antihypertensive medications were prescribed at nearly twice the rate of 1996 [9-11]. It is also interesting to note the case of depression-an illness which has not only increased in prevalence but one for which the practice of medication management has become more common. Currently, it is estimated that 10.5% of pregnant women are prescribed a psychotropic medicine- a drastic increase from less than 1% decades earlier[9]. In addition to antidepressants, nearly 2% of pregnant women are also prescribed another psychotropic medicine, typically an anxiolytic[12].

The aforementioned use of medication is informed and intentional, as women continue to manage acute and chronic conditions that existed prior to pregnancy or that developed during gestation. However, some medication use is a result of unintentional exposure which may or may not be realized. Several studies report high numbers of pregnant women who are exposed to drugs over the course of pregnancy. The largest exposures are to FDA class B and C drugs at a combined 78%, which have unknown teratogenic risk[.6, 14] Exposure to classes D and X drugs occurs at 3.4% and 1.1%, respectively[5]. Both classifications indicate known risk of harm to the fetus and are more dangerous for pregnant women and fetuses.

An especially important scenario to note is that of exposure during the early first trimester before the mother is aware of the pregnancy. If a mother is unaware that she is pregnant, it is entirely possible that she would not modify or avoid potentially harmful behaviors during that time period. After a pregnancy is confirmed at approximately eight weeks, the mother would have already experienced the developmental stage corresponding to the largest risk of malformation[15]. Intentional medication use or accidental exposure during this time could have severe consequences, so it is important to have data on medication safety in the time period prior to pregnancy as well.

The frequency of both exposure and intentional usage is clearly significant. However, such usage is concerning when one considers the small percentage of drug studies and clinical trials that include data for use during pregnancy. Pregnant women have been described as

"therapeutic orphans" due to the void of information regarding drug metabolism and safety during pregnancy. An overwhelming majority, 99%, of pharmacokinetic studies completed in recent years do not include drug metabolism data for pregnant women[16]. Lack of studies have a severe and immediate consequence-the inability to understand safety, risks, and proper dosages during pregnancy. An investigation with the Teratogen Information System showed that among 172 medications which were approved by the FDA from 2000 to 2010, a mere 2% of had been sufficiently studied in order to reveal teratogenic risk, and more than 70% of the drugs were devoid of any pregnancy data at all[17]. However, despite the stark lack of safety, risk-benefit analysis, and dosing studies for pregnant women, this knowledge gap has been filled in ways that hinder proper treatment of illness during pregnancy.

Currently, most dosing practices and treatment guidelines for pregnant women, where they do exist, are created with standard adult doses in mind. These practices and guidelines were developed using safety and efficacy data from healthy, majority male populations[18]. Neither of those characteristics are representative of pregnant women with an illness. As such, there is no evidence that such results are applicable to pregnant women[19]. Even studies among women are not relevant to pregnant women. Conducting drug pharmacokinetic studies with female individuals who aren't pregnant is insufficient because the risks and benefits of a drug are different for pregnant women than non-pregnant women due to physiological and pharmacokinetic differences of pregnant individuals[19]. None of these dosing guidelines can guarantee the intended therapeutic effect of the medicine. In rare instances, pharmacokinetic trials are created for pregnant women, but examination of such studies revealed that rather than focusing on risk to mother and fetus during pregnancy, the trials focused on labor and delivery[16]. Ultimately, there are very few clinical sources of information for both physicians and mothers that adequately describe safety, efficacy and dosing information for pregnant women.

Some information does exist, however, and is often "low-hanging fruit" that is simple to collect. Some of these more illustrative instances of drug use in pregnancy occur in random and uncontrolled settings. The FDA has recognized the practice of collecting data in a post-marketing setting, primarily from exposure registries or observational studies, in which an individual may elect to continue the use of certain drug during gestation, despite possible risks[20]. Such examples may provide glimpses of successful drug use during pregnancy and illuminate possibilities for future research. These instances, however, are far too rare and uncontrolled to provide adequate data or serve as the basis for comprehensive guidelines regarding safety and dosage information for pregnant patients.

Despite the many challenges surrounding the discovery and implementation of proper medication use in pregnant women, the motivations to do so are clear. Above all else, women need effective and safe medications and treatment while they are pregnant. Failure to elucidate and develop such therapy may negatively affect the health of both mother and fetus. Therefore, the lack of dosing and safety data for pregnant women must be treated as a public health issue, and a recent statement by the FDA recognizes it as such[21].

Pregnant women may experience many of the same chronic and acute conditions that their non-pregnant counterparts do, but these illnesses pose different risks to pregnant patients as well as their fetuses. Some of the most common conditions in both populations include diabetes, depression, asthma, and cardiovascular and renal diseases[22]. These conditions are not only a detriment to the mother's quality of life, but can also be extremely dangerous if uncontrolled. Maternal illnesses, whether pre-existing or developed during pregnancy, have been identified as the leading cause of death among pregnant women[23]. For example, depression in women who stop antidepressant medication completely can result in increased morbidity and hospitalization

and ultimately lead to maternal death[24]. Investigation of treatment options to avoid such severe and even fatal consequences is essential.

It is also necessary to consider the outcome of the fetus when treating illness during pregnancy. Many medications used to treat various maternal conditions can be harmful to the fetus, but leaving the condition unmanaged in the mother is not necessarily a safer option. For example, if a mother with type 1 or 2 diabetes experiences high blood sugar near conception, the fetus has an increased risk of being stillborn or premature and developing birth defects[25]. Mental illnesses such as depression also carry severe consequences for the fetus if left untreated, including spontaneous pregnancy loss and low birth weight[24]. Ultimately, action and inaction both have potentially fatal consequences for the fetus and mother, and neither physician nor pregnant patient can make most decisions about medication therapy with confidence.

Pregnant women and physicians are left to navigate pregnancy without a sufficient knowledge base of information. Attempts at standardization have been made, however, for the sake of communication and accessibility. One of the most complete sources of data concerning safety and risks of drug use while pregnant is that of the Food and Drug Administration (FDA) drug ranking system. Until 2015, a simple letter classification was used exclusively, in which each drug was assigned an "A," "B," "C," "D," or "X" rating, which represents a specific level of safety and knowledge about use and risk. Though this system is gradually being replaced with a more comprehensive, in depth description of each drug to better equip physicians and patients alike, it will still be described in this thesis due to the common knowledge of the system, the gradual phasing out of the system for drugs approved before the new system was implemented, and the continued reference to the previous system by many reputable sources of information directed at pregnant women. Description of the previous system also serves to elucidate the lack of knowledge of teratogenic risk from an official, regulated standpoint.

In the previous system, each letter ranking corresponds to a certain level of risk involved with taking the drug during pregnancy as well as the level of research done to investigate teratogenic risk. "A" corresponds to adequate research that has failed to show that the medication poses a risk to the fetus during the first trimester of pregnancy, and there is no evidence of harm during the rest of gestation. "D" and "X" both correspond to positive evidence of risk to the fetus, but the benefits that a "D" medication provides may warrant its use during pregnancy. The same is not true for "X," where the risk of using the medication significantly outweigh possible benefits and should therefore be avoided at all costs. "B" and "C" communicate the ambiguity of the vast majority of medications approved by the FDA. Both correspond to a lack of sufficient research in a human population to validate its use. "B" also lacks evidence from animal studies of harm to the fetus, while a "C" ranking does show evidence of risk from animal studies. "B" and "C" rankings essentially embody the FDA's lack of data and knowledge about the teratogenic risk of those drugs.

Though the simplicity of such a ranking system appears useful and accessible by many, it is also evident that the lack of conclusiveness presented by the rankings is a detriment to both pregnant women and their caregivers. Of all drugs approved by the FDA from 1980 to 2010, over 90% had unknown teratogenic risk[17]. Less than 10% of the medications have a definitive "A," "D," or "X" ranking, while the vast majority have an inconclusive "B" or "C" ranking. Moreover, the simplicity of such rankings fails to properly describe important subtleties of each medication, including the effects of dosages and timing during specific trimesters. For example, a drug may be especially risky during the first trimester, but far safer for use one the time associated with high risk of fetal malformation has passed. The FDA letter categories fail to impart this important information. One study notes how blanket references to the categories alone in complex situations can create unnecessary risk and improperly convey necessary

information[26]. Thus, even when teratogenic data is known, it is not represented correctly or at all in the FDA category system. Additionally, it is important to note that while implementation of the new system provides patients and physicians with descriptions of more specific areas of concern and more thoroughly compiles known information, the vast majority of medications still have undetermined teratogenic risks and are insufficiently studied. The task of properly understanding the use of medication in pregnant women remains daunting.

Ultimately, when physicians consider prescribing a medication during pregnancy, the resources available to them do not properly communicate data regarding safety, dosage, and timing. Often, physicians prescribe medications to pregnant women without knowledge of the dosage necessary to obtain the intended therapeutic effect[27]. As a result, medicinal therapy during pregnancy exists on a fine line. The physician faces the precarious challenge of prescribing a dose high enough that it is therapeutically effective while still low enough that it is not harmful to either mother or baby, and that is if the physician chooses to prescribe at all. In any other therapeutic setting, uncertainty on this scale is intolerable. Specifics of this fine line are detailed further in Section 2.

This dire situation may lead to prescribing decisions that lead to serious consequences. For example, in many instances asthma is well managed by proper medication, but more than 25% of surveyed doctors would lower the dosage or completely stop the prescription of the medication for a pregnant patient, in spite of well-known potential consequences of uncontrolled asthma to the fetus[28].

There are many factors that contribute to the lack of knowledge surrounding drug use in pregnancy and the fine line of prescription decisions. However, many are preventable, and doing so could significantly elevate the situation of pregnant women from the last remaining "therapeutic orphans" of drug metabolism studies. One of the primary sources of the lack of information about drug use in pregnant women is the simple lack of motivation for drug studies. There is no governmental incentive or mandate for pharmaceutical companies to pay for clinical trials that study pregnant women or include them as participants in a separate study. Less than 9% of studies that do consider pregnant women were sponsored by the pharmaceutical industry[16]. However, government incentives, funding, and mandates could significantly improve this number and lessen the burden of taking on such research. Several studies point to evidence of success of such programs and call for these incentives and mandates to be put into effect[29, 30]. A higher percentage of drug studies including pregnant women is key to creating a larger knowledge base for physicians to properly understand medication use among their pregnant patients.

Another contributing factor to the hesitation to treat pregnant patients with medication is significant ethical concern about enrolling pregnant patients in clinical trials and the possibility of putting the fetus at risk. This concern is largely responsible for pregnancy historically being an exclusion criterion in the vast majority of clinical trials. However, as the consequences of such exclusion are coming to light, ethicists are now arguing the opposite-it is unjust to exclude pregnant women from clinical trials because of the detrimental knowledge gap it creates[31]. In fact, exclusion harms the very population that drug companies and ethicists alike initially sought to protect. Individual bioethicists and physicians are not alone in the argument for ethical inclusion of pregnant women in studies. The Food and Drug Administration, European Medicines Agency, and US Institute of Medicine all formally recognize the damage done by exclusion of pregnant women from clinical trials and call for more adequate and well-controlled studies among this population[32-35]. Ethical analysis is an important part of addressing the insufficient treatment and knowledge of pregnant women, as the ultimate goal of healthcare and research is to improve one's health and wellbeing.

Finally, a significant factor in whether or not a medication is used to manage a condition during pregnancy is the mother's own hesitation due to lack of knowledge about correct use and uncertainty of harmful perinatal outcomes. The majority of women state that unknown or conflicting information about risks to the fetus would prevent them from taking medication[36]. Even women with health conditions predating their pregnancies often stop medication usage, particularly during the early stages of gestation[37, 38]. Notably, non-adherence rates are much higher among pregnant women than among a general adult population[37, 39]. It is logical that a mother's desire and natural instinct is to protect her baby and make the best health decisions possible for her fetus. However, this concern in combination with the lack of definite information regarding medication safety can cause pregnant patients to overestimate the risk caused by usage and exposure[40]. Overestimation of risk ultimately may lead to a loss of opportunity to properly manage a condition during pregnancy, which could result in better maternal and fetal outcomes.

Overall, lack of research involving medication use among pregnant women and its resultant prescribing practices have consequences that research is just now illuminating. There are compelling reasons and areas of potential for future work. Primarily, far more pregnant women and their fetuses are put at risk by medication exposure during pregnancy than those who would undergo drug development clinical trials in well-controlled studies[41]. There is less risk and far more benefit to be had by conducting a rigorous study than relying on uncontrolled data and largely refraining from including pregnant women in clinical trials.

New studies may have an extremely large impact and redefine the way in which research involving pregnant women is completed by focusing on the following:

1. Compilation of evidence to support clinical prescribing practices based on research.
2. Existing data and current studies that may be used to answer new research questions.
3. Development of studies to address pressing questions with large implications for pregnant women and their fetuses.
4. Repurposing already-approved drugs for use in pregnancy.
5. Investigation into far-reaching effects of drug use during pregnancy for both mother and child.
6. Better diagnostic tools for faster detection of other diseases during pregnancy.
7. Implementation of government incentives for pharmaceutical industry-funded trials.
8. Mandatory reports of unlicensed drug use among pregnant women in order to reduce *ad hoc* random reporting.
9. Better control of drug regulation and intellectual property pathways in order to facilitate future investigations[19, 42].

Research is everyone's concern, including pregnant women and their fetuses. Prioritization of these studies can ultimately improve outcomes for both mother and fetus by allowing physicians to successfully manage morbidities during pregnancy with minimal risk and increased confidence.

SECTION 2: COMMON CONDITIONS DURING PREGNANCY AND THEIR THERAPEUTIC OPTIONS

Introduction

There are many notable conditions with high prevalence both among women of childbearing age and their pregnant counterparts. As discussed in *Section 1*, such illnesses, both acute and chronic, are becoming increasingly common and occurring and younger ages than in recent decades. As this prevalence increases, so does the practice of managing the condition with medicinal therapeutics. In order to more fully understand this practice, this section presents an analysis of the most common morbidities among pregnant women, what medications are regularly used to manage the disease or condition, and the respective drug's FDA status for use during pregnancy. Additionally, a list of consequences to both mother and fetus when the condition is not managed is presented. All information was compiled into a single table.

Methods

The table is not intended to be a comprehensive collection of conditions, medications, and consequences. Rather, it is intended to illustrate through specific and common examples both the lack of knowledge surrounding use of medication during pregnancy as well as possible outcomes of common morbidities during pregnancy if left unmanaged.

Selected Conditions

The included diseases were selected for their significant prevalence and frequency of discussion in literature examined for this paper. Diseases that are exceedingly rare, affect men only, or generally are prevalent among populations of women that are not of childbearing age were excluded in order to present the most common treatment scenarios that pregnant patients and their physicians encounter. Due to the excessive number of cancers that plague the world's population, the unique drugs and specifics actions that are often required as treatments, and the additional harm that chemotherapy and radiation can bring to pregnancy, cancer and its respective treatments are not included in this chart. All sources are denoted within the chart.

Medications

Lists of medications for treatment were obtained from consumer information publications from the FDA. If the FDA did not have a comprehensive list published, alternate reputable sources such as the Mayo Clinic were used. If, within the publication, medications were described as "less commonly used," "rare," "used less frequently," "secondary treatment options," or "alternative," they were excluded from the list in order to better present the most common scenarios which pregnant patients and physicians encounter. Some medications in the list are used to treat multiple diseases. In these instances, the medication is listed under each disease for which it is a therapy in order to present a more complete picture of treatment options available for each condition. However, duplicates were eliminated in the calculation of statistics (see "Statistics" below.) All sources are denoted within the chart.

Consequences if Left Untreated

Consequences to mother and fetus if left untreated were obtained from peer-reviewed literature published in various obstetrics, gynecology, and pharmacology journals. All sources are denoted within the chart.

Statistics

Numerical variables were summarized by means (+/- SD). Binary and categorical variables were summarized by frequency (in %). Transformed numerical variables were used if their original variables were found to be a departure of Gaussian distribution assumptions before formal analyses were performed.

For each disease, the percentage of each drug classification was determined for the drugs included as treatment options. In order to understand the relative treatment safety for the different diseases, the following descriptions were used: “low risk” describes conditions for which 0-50% of the medication options have an undetermined risk, “moderate risk” describes conditions for which 50-89% of the medication options have an undetermined risk and “high risk” describes conditions for which 90-100% of the medication have an undetermined risk. Undetermined risk is defined as FDA categories “B”, “C”, or “not assigned”. Additionally, each FDA category’s overall percentage was determined for all medications examined in order to obtain a description of medication management during pregnancy as a whole. For this calculation, duplicate medications in the table were excluded. For both consequences to the mother and to the fetus if the disease is left unmanaged, the frequency of consequences for all conditions were tabulated in order to elucidate any common outcomes when conditions during pregnancy are left unmanaged.

Results and Discussion

The complete table of all medications, FDA pregnancy rankings, and consequences to mother and fetus when the condition is left unmanaged is presented in Appendix A, along with all references, and not included here due to its large size. Below is a summary of the findings.

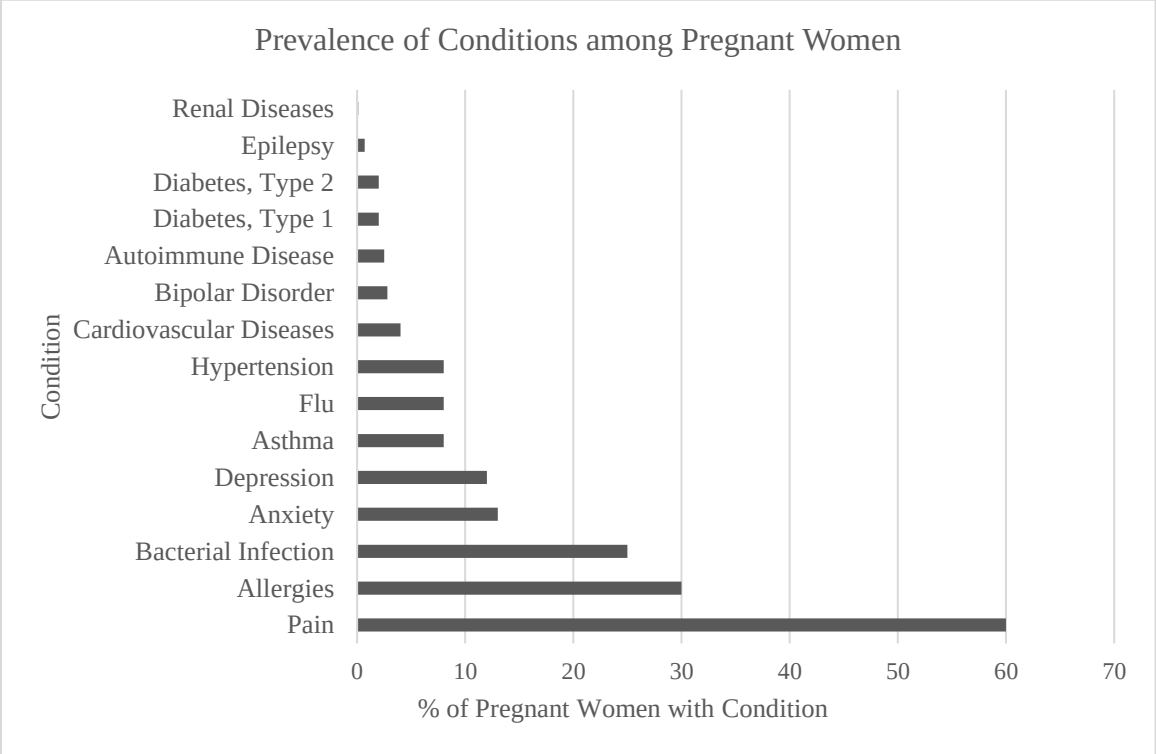

Figure 1. The percentage of all pregnant patients with the respective condition, who may or may not require medicinal treatment for it[51,55,64,66,71,75,79,82,83,89,93,98,103,108,112].

On average, 11.87% (±1.83%) of pregnant women have at least one of the examined fifteen diseases during their pregnancy. If approximately four million women become pregnant every year in the United States, this corresponds to an average of 474,800 women who have at least one of the diseases listed in Figure 1. The most common condition, pain, is experienced by 60% of all pregnant patients, or 2,400,000 women. The least common, renal disease, is experienced by 0.12% of all pregnant patients, or 4,800 women. Even the least common of the fifteen conditions examined results in a significant population that must choose either medication management with unknown levels of risk to the fetus or face potentially severe consequences of uncontrolled disease.

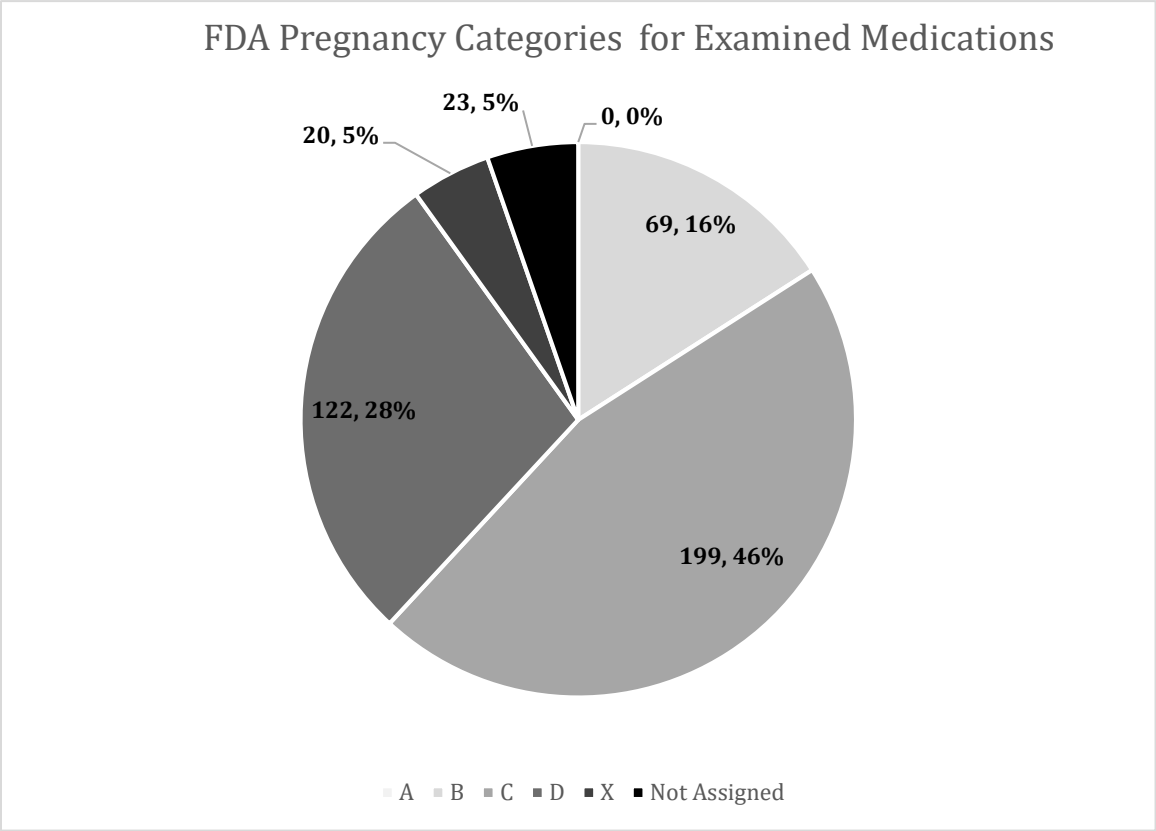

Figure 2. In the chart, the raw number of medications for the respective category is listed first, out of a total of 433, followed by the percentage of the total medications for the respective category. Because there are no category "A" medications, there is not a corresponding section of the chart[52,56,64,67,72,76,80,84-85,90,94-95,99,104,109,113].

A total of 433 medications were examined as treatment options for fifteen conditions or diseases that commonly occur during pregnancy. No condition had a medication with an "A" pregnancy category, the only ranking that conveys safety during pregnancy. The largest category, "C," contain nearly half of all medications examined at 46%. The overall percentage of medications with unknown risk, composed of categories "B," "C," and "Not Assigned," was found to be 67%-a clear majority. This is lower than the 90% value reported by Adam, Polifka, and Friedman, however, though this is likely due to the specific selection of diseases that are common during pregnancy instead of considering every single medication approved by the FDA[17] for a wide range of diseases.

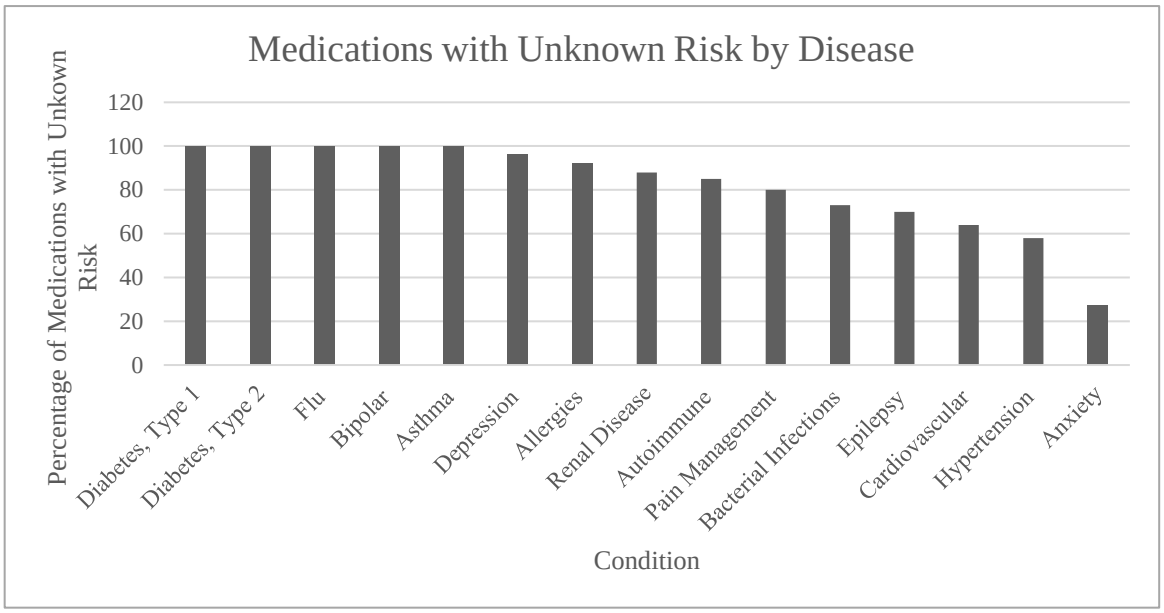

Figure 3. Overall percentage of unknown risk for each disease shown by decreasing prevalence[52,56,64,67,72,76,80,84-85,90,94-95,99,104,109,113].

On average, 82.75% (±17%) of each condition's respective medications had unknown risk. This value is much closer to Adam, Polifka, and Friedman's value of 90%[17]. Of the fifteen diseases examined, seven were high risk, specifically type 1 and type 2 diabetes, depression, asthma, allergies, flu, and bipolar disorder. In fact, 100% of the medications examined for type 1 and type 2 diabetes, flu, bipolar disorder, asthma had undetermined teratogenic risk. Epilepsy, hypertension, bacterial infection, pain, cardiovascular disease, autoimmune disease, and renal disease were all moderate risk. There was only one low risk condition-anxiety. However, even though only 27% of anxiety medications examined had unknown teratogenic risk, 73% were proven to be harmful, meaning those medications are still unsafe for use during pregnancy. Consequently, pregnant patients with anxiety may still be unable to manage the condition and may potentially face severe consequences, including loss of pregnancy even though the risk is known.

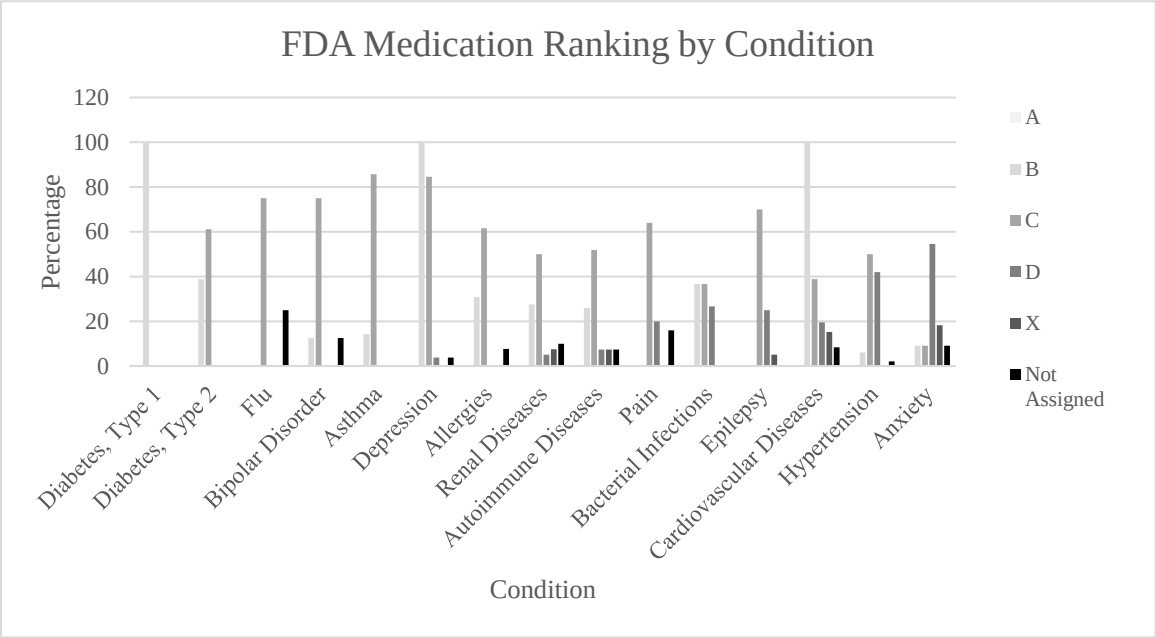

Figure 4. Each medication's respective therapeutic options shown as FDA pregnancy categories[52,56,64,67,72,76,80,84-85,90,94-95,99,104,109,113].

By visual inspection of the graph, it is evident that a majority of medication options for each disease are category "C." There is only one disease, type 1 diabetes, for which there are more category "B" medicines than category "C". This indicates that if a medication has undetermined teratogenic risk, is more likely to be category "C" than "B" or "Not Assigned." Allergies, asthma, type 1 diabetes, type 2 diabetes, and flu have no medication treatments with definitive teratogenic risk. Anxiety, autoimmune diseases, cardiovascular diseases, epilepsy, and renal diseases are the only diseases with category "X" rankings. The medications for anxiety, autoimmune diseases, cardiovascular diseases and renal diseases have the most diverse treatment options in terms of FDA categories.

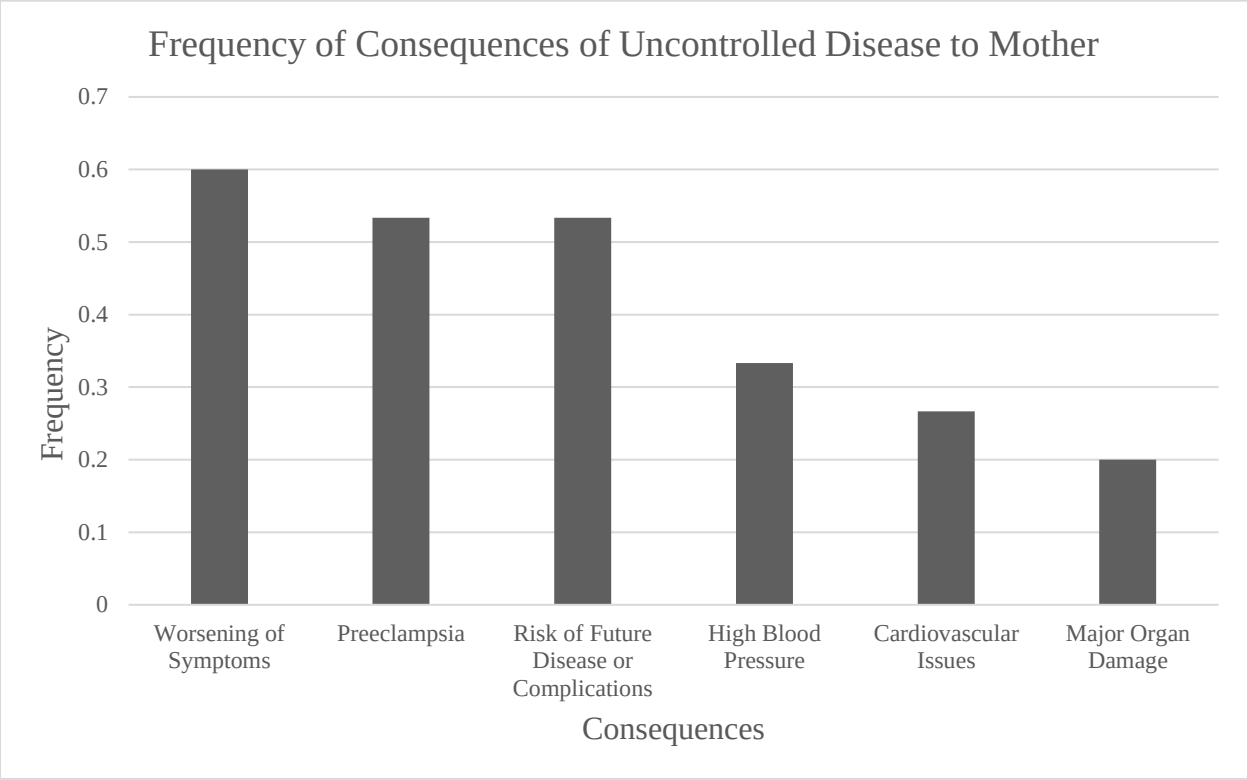

Figure 5. Consequences of uncontrolled disease to mother shown by decreasing prevalence[51,53-55,57-62,65,73,77-78,81,86-87,89,96,100-103,105-106,110-112,114].

When examining consequences to the mother if the condition is left unmanaged, several consequences appeared frequently. The most prevalent consequence was worsening symptoms of the condition, which was noted for 60% of the diseases, specifically diabetes, depression, asthma, anxiety, epilepsy, pain, allergies, autoimmune diseases, and bipolar disorder. Many of these symptoms correspond to increased pain, physical strain on the body, and worsening mental health. Preeclampsia and risk of future disease or complications were the second most common consequences, a risk for 53% of the diseases examined. Other frequently occurring consequences are high blood pressure, cardiovascular issues, and major organ damage.

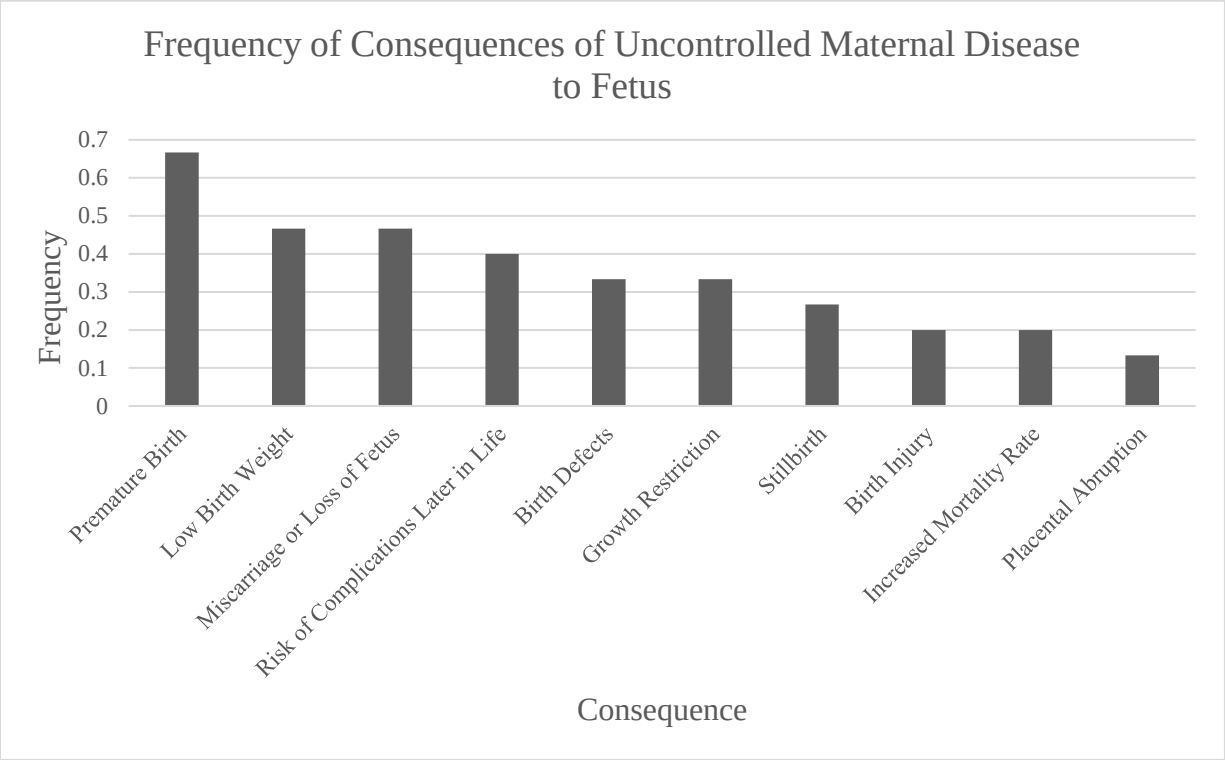

Figure 6. Consequences to fetus of uncontrolled disease in mother shown by decreasing prevalence [51,53-55,58-63,65,68-70,74,77-78,81,86,88,81-92,97,100-101,105,107,110-112,114].

The most common health consequence for the baby when the mother's disease goes unmanaged is premature birth, which is observed for 67% of the diseases examined, including depression, epilepsy, hypertension, bacterial infection, allergies, flu, autoimmune diseases, bipolar disorder, and renal disease. Miscarriage and low birth weight were the second most common consequences and occurred for 47% of all diseases examined. Birth defects and growth restriction occurred for one third of diseases. Other severe consequences, including stillbirth, birth injury, increased mortality rate, and placental abruption were observed for multiple diseases.

It is evident that for fourteen of the fifteen conditions examined, the physician and mother must choose between using medications, a majority of which have unknown risk to the fetus, and facing potentially severe and sometimes fatal consequences of uncontrolled disease for both the mother and infant. For the one remaining disease, anxiety, the physician and mother choose between similarly severe consequences of the uncontrolled disease and therapeutic options where most of the medications are proven to be harmful.

Conclusion

Even in instances when there is definitive information about the safety of a medication, it is that there is proven risk to the fetus and it is not a safe option for managing the illness during pregnancy. As a result, the mother and fetus still face potentially severe consequences from uncontrolled disease whether or not the risk of the disease's medications is established. It is essential that ethical research is conducted on drug use in pregnant women in order to eliminate a dangerous and harmful gap of knowledge and provide safe and effective treatments for illness during pregnancy.

SECTION 3: PREGNANCY, MEDICATIONS AND CYSTIC FIBROSIS

Introduction

Cystic fibrosis (CF) is the most common life-shortening Mendelian recessive genetic disorder, especially prevalent among Caucasians in North America, Europe, and Australia. The source of the disease is a gene mutation that codes for the CF transmembrane conductance regulator. This transmembrane channel is responsible for chloride anion and bicarbonate transportation and airway mucociliary clearance. CFTR dysfunction largely affects epithelial cells, resulting in airway mucus retention, persistent infection, and airway inflammation, all detrimental to lung function[43].

In 1950, shortly after the disease was identified, patients with CF had a life expectancy of mere months. However, over the course of the last sixty years, the median life expectancy has increased dramatically and is now greater than forty years in developed nations[44, 45]. This increase in age has created the potential for women with CF to be mothers, and it is reasonable to believe many women will elect to do so.

Multiple studies have found that the disease itself has no effect on maternal pregnancy survival, with similar clinical outcomes for non-pregnant CF counterparts[46, 47]. However, smaller single-center studies have shown that despite aggressive modern pre- and post-natal care's sufficient support for CF women, unusual negative circumstances surrounded those births, including lower birth weight, nutritional failure at conception, and increased rates of early gestational births[48, 49]. These negative effects were proportional to the severity of the CF, and healthier women with CF consistently had healthier pregnancies[47]. Furthermore, there is some concern that the mother's lung function may be negatively affected by pregnancy[49].

Medications are vital for the management of CF, even when pregnant. Bacterial infections, particularly chronic cases, are one of the most common problems present in CF patients. These infections are normally treated with antibiotics, and such management is essential for good health. If an infection isn't treated properly or is especially severe, it is possible that a CF patient's lung function may never return to previous levels. For CF the drugs of choice are often aminoglycosides, penicillins, fluoroquinolones, cephalosporins, and tetracyclines. Because of the large amount of antibiotics required to manage the disease, antibiotic resistance is a significant concern in CF that physicians must consider when prescribing. Understanding dosage and prescribing patterns are primary treatment concerns for drugs with potentially significant side effects and are important for obtaining positive patient outcomes[50]. During pregnancy, these outcomes are also important to the fetus' health.

These antibiotics that have allowed for a longer life span for those with CF have not been sufficiently tested for safe use in pregnant women, making pregnancy management and infant care highly difficult. Prescription of antibiotics and other medications and treatments with regards to dose alteration or discontinuation is not well understood due to the current lack of pregnancy-related data in this area. Due to the lack of understanding regarding this population possibility of risk to the fetus, many pregnant women with CF may be not be obtaining optimal treatment, putting both the fetus and mother at risk.

This study is a simple retrospective chart review of pregnant women with CF, which will generate a de-identified data set from the University of Utah Hospital. Necessary data regarding treatment and outcomes related to pregnancy in women with CF will be collected on these women before, during, and after pregnancy. The primary objective of this study is to describe

current pregnancy trends and treatment practices in patients with CF, specifically relating to antibiotic usage, and to characterize outcomes before, during, and after pregnancy.

Methods

Inclusion Criteria

The inclusion criteria for the study is as follows: all women who are pregnant or have had a pregnancy as reported to the University of Utah Hospital, diagnosed with CF, and 18-65 years of age (inclusive). There were no exclusion criteria.

Data

The data for the study comes from a retrospective chart review of pregnant patients with CF. Patients were identified by searching the University of Utah Hospital's Electronic Data Warehouse (EDW) for patients meeting the inclusionary criteria. Participants were not contacted directly. The primary investigator, Dr. Kathleen Job, worked with the EDW at the University Hospital. The data collection included data from up to ten years before pregnancy, during pregnancy, and two years after pregnancy. Data was collected from 32 patients and included:

1. Demographics: Age (year), Sex, Weight, Height, Ethnicity, Race, BMI
2. Antibiotic Information: drug information, dosing information (frequency, route, and dose), number of doses received
3. Pulmonary Function: FVC, FEV_1, FEF 25-75

Institution Review Board and Data Safety

The study protocol was submitted to the University of Utah's Institutional Review Board and is included in Appendix B. There was no patient interaction in this trial and there was no PHI disclosed. The collection of information about participants was limited to the amount necessary to achieve the aims of the research, so that no unneeded information is being collected. This research posed only minimal risk to study participants. Data collected was de-identified by the University Hospital research personnel before it was received. All data was stored on password-protected computers. The primary investigator ensured that data storage and handling was consistent with University of Utah IRB standards.

Statistical Methods

Numerical variables were summarized by means (+/- SD). Binary and categorical variables were summarized by frequency (in %). Transformed numerical variables were used if their original variables were found to be a departure of Gaussian distribution assumptions before formal analyses were performed.

Results and Discussion

The query of the University of Utah Hospital's EDW contained 32 patients that fit the inclusion criteria. 7 of these patients had multiple pregnancies on record for a total of 44 pregnancies that were examined in this study. A total of 39 medications were found as treatment options for at least one of the 44 pregnancies, and dosages for each patient were separated into those prescribed during pregnancy and those prescribed outside of pregnancy. Analysis revealed that some medications were never prescribed during pregnancy and others were only used when the patient was pregnant. This information is tabulated in Table 1 and Table 2 on the following pages.

	Number of Antibiotics	Percentage of Total
Total Treatment Options	39	-
Never Used During Pregnancy	14	35.9%
Used Only in Pregnancy	2	5.12%

Table 1. Medications never used during pregnancy and those used only during pregnancy as percentages of the total number of antibiotics, 39.

Slightly more than a third of the total number of antibiotics prescribed were given to CF patients only if they were not pregnant. Conversely, a very small portion of the total medications were used exclusively when the patient was pregnant. A future study could examine the reason for this selectivity in order to determine if the 14 antibiotics never used during pregnancy are especially harmful, if the 2 used only in pregnancy are somewhat safer but not as effective for infection treatment, and if there are guidelines established for either care scenario.

Antibiotic Treatment Options	
Aminoglycosides	**Nitrofuran**
Gentamicin	*Nitrofurantoin*
Tobramycin	**Nitromidazole**
Beta-lactam	*Metronidazole*
Aztreonam	**Oxazolidinone**
Carbapenem	*Linezolid**
Meropenem	*Tedizolid**
*Ertapenem***	**Penicillin**
*Imipenem-Cilastatin**	*Amoxicillin*
Cephalosporin	*Ampicillin*
Cefazolin	*Penicillin*
Cefepime	*Piperacillin*
Cefoxitin	*Dicloxacillin**
Ceftazidime	*Ticarcillin**
Ceftriaxone	*Zosyn (Piperacillin + Tazobactam)**
Cephalexin	**Polymixin**
*Cefdinir**	*Colistimethate**
Fluoroquinolone	**Quinolone**
Ciprofloxacin	*Moxifloxacin**
Levofloxacin	**Sulfonamide**
Glycopeptide	*Bactrim (Sulfamethoxzole + Trimethoprim)*
Vancomycin	*Sulfamethoxazole**
Lincomycin	**Tetracycline**
Clindamycin	*Doxycycline*
Macrolide	*Minocycline**
Azithromycin	*Tigecycline**
*Erythromycin***	

*Table 2. Antibiotics that were prescribed for at least one of the 39 pregnancy cases listed by antibiotic class. * Drug was never prescribed during pregnancy. ** Drug was used exclusively during pregnancy.*

The treatment options used at the University of Utah Hospital are a diverse collection of aminoglycosides, penicillins, fluoroquinolones, cephalosporins, and tetracyclines among others, as are the smaller segment that were never used during pregnancy. The two medications that were used exclusively during pregnancy are a carbapenem and a macrolide, respectively.

In order to understand how each medication was used for treatment during and outside of pregnancy, the number of dosages prescribed was compared to the total number of dosages received for each pregnancy case. Next, this number was averaged across all pregnancy cases to describe treatment of pregnant CF patients at the University of Utah Hospital as a whole. This

number was computed separately for treatment during pregnancy and before and after pregnancy in order to understand difference in prescription patterns. These average frequencies for antibiotics prescribed during pregnancy are illustrated in Figure 7.

By visual inspection, it is obvious that azithromycin, cefazolin, nitrofurantoin, and penicillin are the most frequently used antibiotic options prescribed during pregnancy. Together, those four options are 45.97% of the prescribed options. Other notable options include aztreonam, ceftriaxone, and vancomycin. There are obvious gaps in treatment options left by medications that were never prescribed during any patient's pregnancy, showing more limited treatment options.

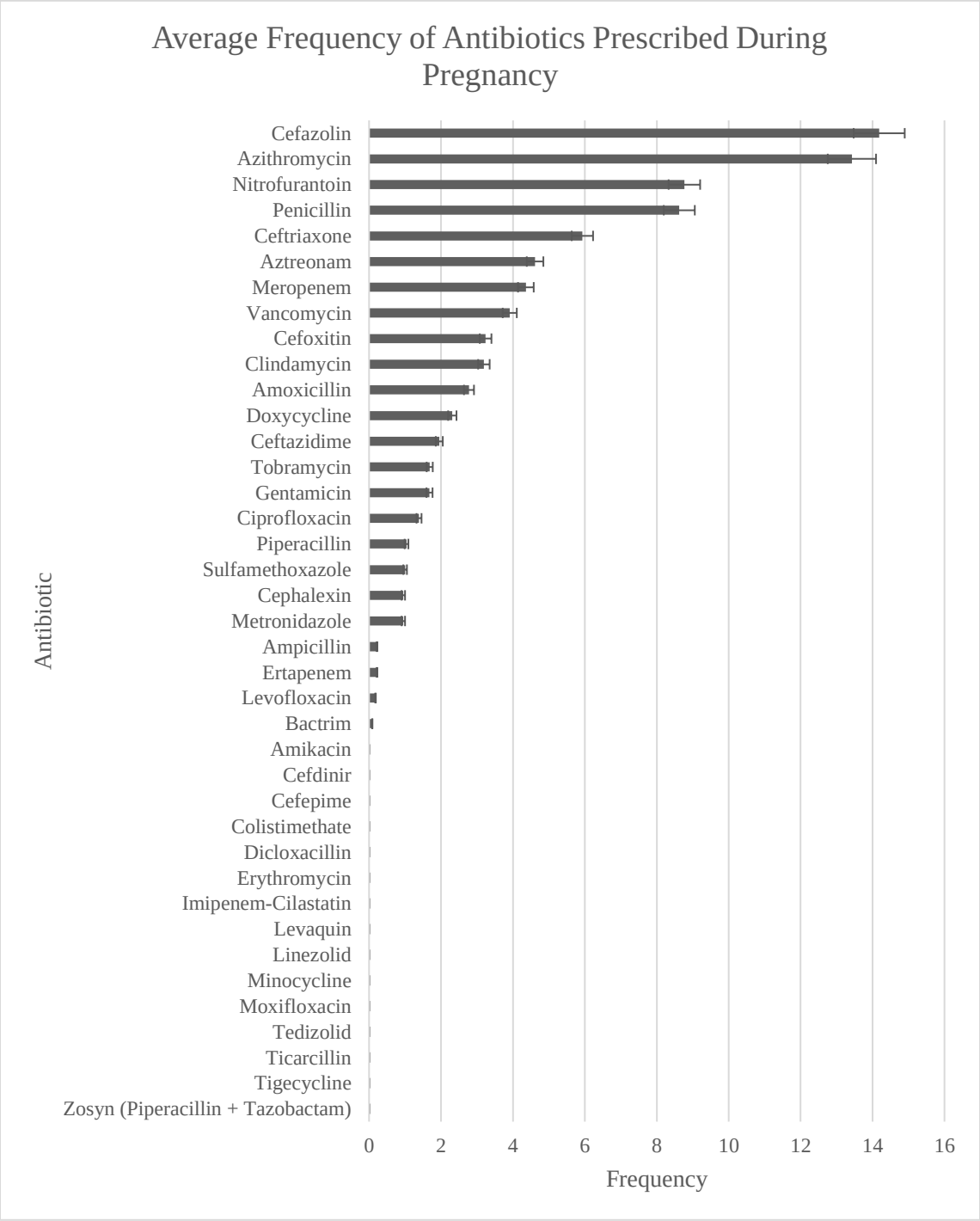

Figure 7. The frequency of usage of each antibiotic during pregnancy care averaged across all pregnancy cases. See Appendix C for numerical table.

These frequencies during pregnancy are also valuable when compared to those for non-pregnant care, which are illustrated in Figure 8.

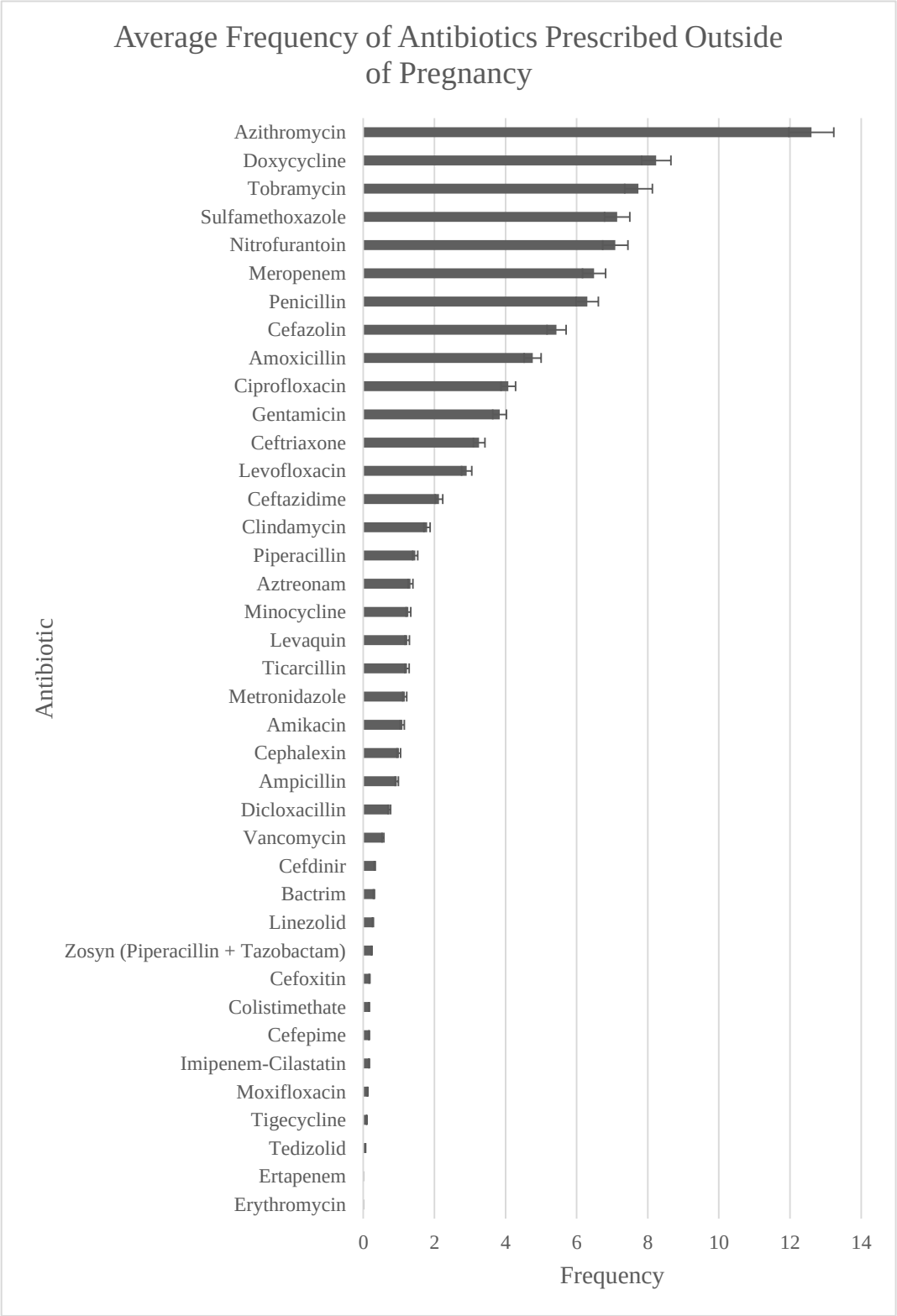

Figure 8. The frequency of usage of each antibiotic during non-pregnancy care averaged across all pregnancy cases. See Appendix C for numerical table.

In the case of non-pregnancy prescriptions, there is only one option that clearly dominates-azithromycin. A dosage of the next six antibiotics-doxycycline, meropenem, nitrofurantoin, penicillin, sulfamethoxazole, and tobramycin-are prescribed approximately 7-8%

of the time. These options compose 55.59% of the total treatment options during non-pregnant care. By visual inspection, it is obvious that many of the antibiotics which had low frequency usage during pregnancy are more frequently prescribed to non-pregnant patients. This is observed for amikacin, ampicillin, cefedinir, cefepime, levaquin, levofloxacin, linezolid, moxifloxacin, tedizolid, ticarcillin, tigecycline, and Zosyn.

These trends raise questions of why azithromycin, cefazolin, nitrofurantoin, and penicillin are the most frequently prescribed antibiotics during pregnancy, while most others are used approximately 4% of the time or less. Similarly, the increase in the usage of these medications when the patient is not should be investigated in order to elucidate a reason for such prescription patterns.

It is also illuminating to compare the diversity of treatment options prescribed in pregnant and non-pregnant care. The number of different antibiotics prescribed during pregnancy was compared to the number of different antibiotics prescribed when the patient was not pregnant. The histogram in Figure 9 shows the percent difference of these values as the bins and the frequency describes the number of pregnancy cases out of 44 for which that percent difference was observed.

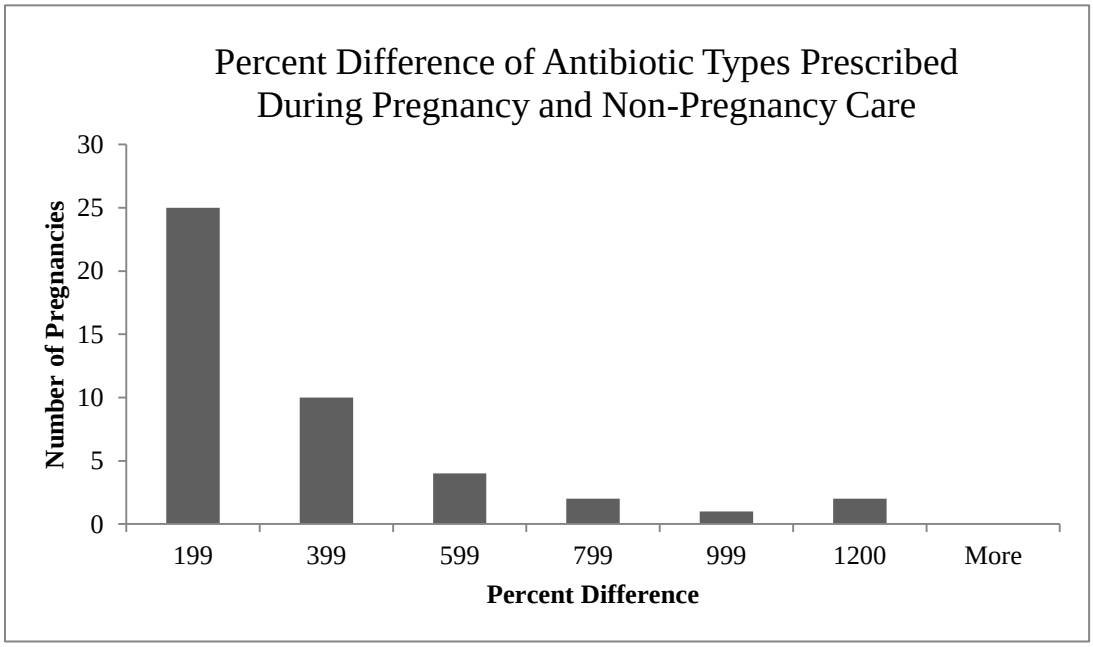

Figure 9. The number of pregnancies with a certain percent difference between the number of different antibiotics prescribed during pregnancy and the different antibiotics prescribed outside of pregnancy.

All but three pregnancy cases had more types of antibiotics prescribed during non-pregnancy care than during pregnancy. Even the smallest percent difference between antibiotic types prescribed during pregnancy and the types prescribed outside of pregnancy is still as great as 199%. 43% of pregnancy cases had a percent difference between pregnant and non-pregnant care of 200% or greater. Overall, 93% of pregnancy cases had a more diverse range of antibiotics prescribed when the patient was not pregnant. This may be indicative of physicians and patients

alike choosing less aggressive treatment options or prescribing guidelines when the patient is pregnant, which is grounds for future research.

It is revealing to examine the simple raw number of antibiotic dosages prescribed during pregnancy, as all were prescribed during same amount of time. Because the data from the University of Utah Hospital included the date of prescription dosages as well as the start and end dates of the pregnancy, it was possible to identify significant prescriptions that were given on the day of the birth and the days immediately prior and after. Table 3 includes these values.

Pregnancy Case	Patient	# of Antibiotic Dosages Prescribed During the Pregnancy	# of Prescribed Antibiotic Dosages on Day of Birth	Percentage Prescribed on Day of Birth
1	A	11	11	100
2	B	9	1	11
3	C	0	0	N/A
4	D	4	4	100
5	E	7	4	57
6	F	33	6	18
7	G	26	2	8
8	G	20	1	5
9	H	0	0	N/A
10	I	15	5	33
11	J	16	12	75
12	K	14	3	21
13	L	0	0	N/A
14	L	0	0	N/A
15	L	0	0	N/A
16	L	18	17	94
17	L	1	1	100
18	M	39	2	5
19	N	6	3	50
20	O	1	0	0
21	P	5	2	40
22	Q	8	4	50
23	R	31	11	35
24	R	25	9	36
25	S	6	3	50
26	T	6	0	0
27	U	0	0	N/A
28	U	2	0	0
29	U	0	0	N/A
30	V	1	1	100

Pregnancy Case (cont'd.)	Patient (cont'd.)	# of Antibiotic Dosages Prescribed During the Pregnancy (cont'd.)	# of Prescribed Antibiotic Dosages on Day of Birth (cont'd.)	Percentage Prescribed on Day of Birth (cont'd.)
31	W	5	5	100
32	X	1	1	100
34	Z	2	2	100
35	Z	1	0	0
36	AA	1	0	0
37	AB	6	2	33
38	AB	0	0	N/A
39	AB	2	0	0
40	AC	2	2	100
41	AC	1	1	100
42	AD	1	1	100
43	AE	5	2	40
44	AF	3	2	67
Average:		5.63 (± 5.93)	2.46 (± 3.79)	50.61% (±19.5%)

Table 3. The number of antibiotic dosages prescribed during the pregnancy, the number of dosages prescribed on the day of birth, and the percentage of those medications prescribed on the day of birth listed per each pregnancy and patient. Grouped shading helps indicate multiple pregnancies from the same patient.

Notably, there were 8 pregnancies (18.18%) examined which did not receive any prescribed antibiotics during the entire gestational period. Two women account for five of these pregnancies-three and two, respectively. This indicates that such prescribing patterns are due to the individual patient's health. The largest number of dosages prescribed during a pregnancy was 39, and there were others with similarly high values of 25, 26, 31, and 33. These strikingly different values may be indicative of the relative health of the mothers and their medicinal needs. In 10 of the pregnancies, 100% of the dosages prescribed were prescribed on the day of the birth. On average, half of the medications prescribed during pregnancy were prescribed on that final day of pregnancy. These spikes in prescription rates raise questions of the mother's health throughout the duration of the pregnancy, which may have been impacted by lower or less frequent than normal dosages and required immediate therapeutic attention after a successful birth.

Generally, the results are what one may expect for medication usage during a pregnancy: lower usage rates during pregnancy than non-pregnancy, a wider variety of treatment options when the patient is not pregnant. There are notable trends, including a sharp increase in prescription rates immediately after the pregnancy ends, several core treatment options when the patient was pregnant, and several pregnancies without any antibiotic usage at all. Ultimately, these trends raise questions of whether these patterns arise from informal guidelines or prescribing practice or at the physician's discretion. Antibiotic dosages and measures of the mother's health by trimester could provide insight into the number and timing of dosages as they correspond to the mother's need.

Ultimately, this thesis illuminates the overwhelming lack of knowledge about medication usage during pregnancy and the challenge physicians face prescribing a dose that is neither so low that it's ineffective or so high that it's harmful to the mother and fetus, should there be a prescription at all. The basic treatments for common morbidities are generally not viable during pregnancy due to lack of knowledge of the teratogenic risk of most medications, but the consequences of uncontrolled disease to mother and fetus are severe and often fatal. For CF, some mediations are vital for good health, particularly antibiotics, and are often the reason the women live long enough to reach childbearing age. It is clear that the disease is managed with much less medication during pregnancy than the non-pregnant counterpart, but reasons for the elucidated prescribing patterns remain unclear.

Conclusion

It is alarming how much medication is prescribed to pregnant women, especially when the lack of knowledge surrounding its risk is considered. More attention and resources must be dedicated to understanding available, viable, and safe treatment options for the millions of women who become pregnant each year, as well as establishing outcome-based and research-driven guidelines to serve as the basis for prescribing practices. *Section 1* describes general future research that would benefit all pregnant women and investigate medication usage in a wide variety of pregnancies. However, this CF research would also benefit from investigation into themes observed in *Section 3*. For pregnancy in CF patients, future research is comprised of pairing these antibiotic prescription patters with maternal outcomes and health during pregnancy as described by pulmonary function, specifically FVC, FEV_1, and FEF 25-75. In this way, trends seen in Section 3 may be better understood in terms of outcomes as they are related to specific dug usage and prescribing patterns.

References

1. AA Mitchell, S. G.-D. (2011). Medication use during pregnancy, with particular focus on prescription drugs. *Journal of Obstetrics and Gynecology*, 51-58.
2. Lupattelli A, S. O. (2014). Medication use in pregnancy: a cross-sectional, multinational web-based study. *British Medical Journal*, 43-65.
3. Ventura SJ, C. S. (2012). *Estimated pregnancy rates and rates of pregnancy outcomes for the United States, 1990-2008.* National Vital Statistics Report. Atlanta: Center for Disease Control and Prevention.
4. Andrade SE, R. M. (2006). Use of prescription medications among women. *Pharmacoepidemiology and Drug Safety* , 546-554.
5. Li-Ting Kao, Y.-H. C.-C.-D. (2014, February 28). Prescriptions for category D and X drugs during pregnancy in Taiwan: a population based study. *Pharmaxoepidemiology and Drug Safety, 23*(10), 1029-1034.
6. Bell R, B. K.-B. (2008). Trends in prevalence and outcomes of pregnancy in women with pre-existing type I and type II diabetes. *British Journal of Gynecology*, 445-452.
7. Center for Disease Control and Prevention. (2018, July 2). *Diabetes During Pregnancy*. Retrieved from Reproductive Health: https://www.cdc.gov/reproductivehealth/maternalinfanthealth/diabetes-during-pregnancy.htm
8. Andrade SE, R. M. (2008). Outpatient use of cardiovascular drugs during pregnancy. *Pharmacoepidemiology and Drug Safety*, 240-247.
9. Andrade SE, R. M. (2008). Use of antidepressant medications during pregnancy: a multisite study. . *American Journal of Obstetrics and Gynecology*, 194.
10. van den Bosch AE, R. T.-H. (2015). Use and impact of cardiac medication during pregnancy. *Future Cardiology*, 89-100.
11. Andrade SE, G. J. (2004). Prescription drug use in pregnancy. *American Journal of Obstetrics and Gynecology*, 398-407.
12. Soriano LC, B. B.-D. (2014). Prescription of antihypertensive medications during pregnacy in the UK. *Pharmacoepidemiology and Drug Safety*, 1051-1058.
13. Hanley GE, M. B. (2014). Patterns of psychotropic medicine use in pregnancy in the United States from 2006 to 2011 among women with private insurance. *BMC Pregnancy and Childbirth*, 242.
14. Pasternak B, H. A. (2010). Use of proton-pump inhibitors in early pregnancy and the risk of birth defects. *New England Journal of Medicine*, 2114-2123.
15. George, J. (2011). Optimising medication use during pregnancy: the potential role of pharmacists. *International Journal of Pharmacy Practice*, 81-83.

16. McCormack, S. A., & Best, B. M. (2014). Obstetric pharmacokinetic dosing studies are urgently needed. *Frontiers in Pediatrics*, 9.

17. Adam, M., Polifka, J. E., & Friedman, J. M. (2011). Evolving knowledge of the teratogenicity of medications in human pregnancy. *American Journal of Medical Genetics*, 175-82.

18. Thomas, S., & Yates, L. (2012). Prescribing without evidence-pregnancy. *British Journal of Clinical Pharmacology*, 691-697.

19. Blehar, M. C., Spong, C., Grady, C., Goldkind, S. F., Sahin, L., & Clayton, J. A. (2013). Enrolling Pregnant Women: Issues in Clinical Research. *Women's Health Issues*, 39-45.

20. Food and Drug Administration. (2018). *Pregnant Women: Scientific and Ethical Considerations for Inclusion in Clinical Trials.* White Oak: U.S. Department of Health and Human Services.

21. FDA Center for Drug Evaluation and Research. (2018). *Pregnant Women: Scientific and Ethical Considerations for Inclusion in Clinical Trials.* U.S. Department of Health and Human Services.

22. Wyszynski, D., & Shields, K. (2016). Frequency and type of medications and vaccines used during pregnancy. *Obstetric Medicine*, 21-27.

23. Knight, M., Kenyon, S., Brocklehurst, P., Neilson, J., Shakespeare, J., & Kurinczuk, J. (2012). *Saving live, improving mothers' care: lessons learned to inform future maternity care from the UK and Ireland confidential enquiries I to maternal deaths and morbidity 2009-2012.* Oxford: National Perinatal Epidemiology Unit, University of Oxford.

24. Koren, G., & Norden, H. (2012). Antidepressant use during pregnancy: the benefit-risk ratio. *American Journal of Obstetrics and Gynecology*, 157-163.

25. Centers for Disease Control and Prevention. (2018). *Diabetes during Pregnancy.* Centers for Disease Control and Prevention.

26. Grzeskowiak, L. E. (2015). Role of pharmacists in optimizing medication management during pregnancy and lactation. *Journal of Pharmacy Practice and Research*, 64-71.

27. Andrew, M., Easterling, T., Carr, D., Shen, D., Buchanan, M., Rutherford, T., . . . Herbert, M. (2007). Amoxicillin pharmacokinetics in pregnant women: modeling and simulations of dosage strategies. *Clinical Pharmacology and Therapeutics*, 547-556.

28. Lim, A., Stewart, K., Abramson, M., & George, J. (2011). Management of asthma in pregnant women by general practitioners: a cross sectional survey. *BMC Family Practice*, 121.

29. Rodriguez, W., & Roberts, R. M. (2003). Current regulatory policies regarding pediartric indications and exclusivity. . *Journal of Pediatrics, Gastroenterology, and Nutrition*.

30. Ward, R., & Kauffman, R. (2007). Future of pediatric therapeutics: reauthorization of BPCA and PREA. *Clinical Pharmacology and Therapeutics*, 477-479.

31. Lyerly, M., Little, M., & Faden, R. (2009). The second wave: toward responsible inclusion of pregnant women in clinical research. *International Journal of Feminist Approaches to Bioethics*, 5-22.

32. Food and Drug Administration (FDA). (2015). *Pregnancy and lactation labeling (drugs) final rule.* FDA.

33. European Medicines Agency (EMA). (2005). *Guideline on the exposure to medicinal products during pregnancy: need for post-authorization data.* European Medicines Agency.

34. Saint-Raymond, A., & de Vries, C. (2016). Medicine safety in pregnancy and ambitions for the EU medicine regulatory framework. *Clinical Pharmacology and Therapeutics*, 21-23.

35. Mastroianna AC, F. R. (1994). *Women and health research: ethical and legal issues of including women in clinical studies: volume I.* Washington DC: National Academies Press.

36. Wiley, K., Cooper, S., Wood, N., & Leask, J. (2015). Understanding pregnant women's attitudes and behavior toward influenza and pertussis vaccination. *Qualitative Health Research*, 360-370.

37. Sawicki, K., K, S., S, W., Leung, L., & George, J. (2009). Adherence to prescribed medicines during pregnancy: a survey of outpatients. *International Journal of Pharmacy Practice*, 78-79.

38. Matsui, D. (2012). Adherence with drug therapy in pregnancy. *Obstetrics and Gynecology International* .

39. Sawicki, E., Stewart, K., Wong, S., Paul, E., Leung, I., & George, J. (2012). Managment of asthma in pregnant women attending an Australian maternity hospital. *Australia and New Zealand Journal of Obstetrics and Gynecology*, 183-188.

40. Nordeng, H., Ystrom, E., & Finarson, A. (2010). Perception of risk regarding the use of medications and other exposures during pregnancy. *European Journal of Clinical Pharmacology*, 207-214.

41. McCullough, L., Coverdale, J., & Chervenak, F. (2005). A comprehensive ethical framework for responsibly designing and conducting pharmacologic research that involves pregnant women. *American Journal of Obstetrics and Gynecology*, 901-907.

42. David, A., Thornton, S., & Sutcliffe, A. (2017). *Developing New Pharmaceutical Treatments for Obstetric Conditions.* London: Royal College of Obstetricians and Gynecologists.

43. 43. Elborn, J. (2016). Cystic fibrosis. *The Lancet*, 2519-2531.

44. PR Burgel, G. (2015). Future trends in cystic fibrosis demography in 34 European countries. *European Respiratory Journal*, 133-141.

45. Elborn, J. (1991). Cystic fibrosis: current survival and population estimated to the year 2000. *Thorax*, 881-885.

46. Gilljam, A. M. (2000). Pregnancy in cystic fibrosis-fetal and maternal outcome. *Chest*, 85-91.

47. Goss, C. (2003). The Effect of Pregnancy on Survival in Women with Cystic Fibrosis. *Chest*, 1460-1468.

48. Cheng, E. (2006). Aggressive prenatal care results in successful fetal outcomes in CF women. *Journal of Cystic Fibrosis*, 85-91.

49. Thorpe-Beeston, J. (2013). The outcome of pregnancies in women iwth custic fibrosis-single centre experience 1998-2011. *British Journal of Obstetrics and Gynaecology*, 354-61.

50. Edmonson, C., & J.C., D. (2016). Current and future treatment options for cystic fibrosis lung disease: latest evidence and clinical mplications. *Therapeutic Advances in Chronic Disease*, 170-183

51. Centers for Disease Control and Prevention. (2018, June 1). *Pregnancy*. Retrieved from Problems of Diabetes in Pregnancy: https://www.cdc.gov/pregnancy/diabetes-types.html

52. Centers for Disease Control and Prevention. (2018, June 12). *Maternal Infant Health: Reproductive Health*. Retrieved from Diabetes During Pregnancy: https://www.cdc.gov/reproductivehealth/maternalinfanthealth/diabetes-during-pregnancy.htm

53. Mayo Clinic. (2017, April 28). *Patient Care and Health Information*. Retrieved from Gestational Diabetes: https://www.mayoclinic.org/diseases-conditions/gestational-diabetes/symptoms-causes/syc-20355339

54. Stanford Children's Health. (n.d.). *Infant of Diabetic Mother*. Retrieved from Infant of Diabetic Mother: https://www.stanfordchildrens.org/en/topic/default?id=infant-of-diabetic-mother-90-P02354

55. Bennett, H. A., Einarson, A., Taddio, A., Koren, G., & Einarson, T. R. (2004). Prevalence of depression during pregnancy: systematic review. *Obstetrics and Gynecology*, 698-709.

56. Food and Drug Administration. (2017, April 28). *Consumer Updates*. Retrieved from Depression: FDA-approved medications may help: https://www.fda.gov/forconsumers/consumerupdates/ucm095980.htm

57. Stein, A., Pearson, R. M., Goodman, S. H., Rapa, E., Rahman, A., McCallum, M., . . . Pariante, C. M. (2014). Effect of perinatal mental disorders on the fetus and child . *The Lancet*, 1800-1819.

58. Bennett, H. A., Einarson, A., Taddio, A., Koren, G., & Einarson, T. R. (2004). Depression during pregnancy: overview of clinical factors. *Clinical Drug Investigation*, 157-179.

59. Andersson, L., Sundstrom-Poromaa, I., Wulff, M., Astrom, M., & Bixo, M. (2004). Implication of antenatal depression and anxiety for obstetric outcome. *Obstetrics and Gynecology*, 467-476.

60. Andersson, L., Sundstrom-Poromaa, I., Wulff, M., Astrom, M., & Bixo, M. (2004). Neonatal outcome following maternal antenatal depression and anxiety; a population-based study. *American Journal of Epidemiology*, 872-881.

61. Bonari, L., Pinto, N., Einarson, A., Steiner, M., & Koren, G. (2004). Perinatal risks of untreated depression during prenancy. *Canadian Journal of Psychiatry*, 726-735.

62. Chan, J., Natekar, A., Einarson, A., & Koren, G. (2014). Risks of untreated depression in pregnancy. *Canadian Family Physician*, 242-243.

63. Dayan, J., Creveuil, C., Herlicoviez, M., Herbel, C., Baranger, E., Savoye, C., & Thouin, A. (2002). Role of anxiety and depression in the onset of spontaneous preterm labor. *American Journal of Epidemiology*, 293-301.

64. Kwon, H., Triche, E. W., Belanger, K., & Bracken, M. (2006). The epidemiology of asthma during pregnancy: prevalence, diagnosis, and symptoms. *Immunology and Allergy Clinics of North America*, 29-62.

65. Informed Health Online. (2008, Jan 14). *Cologne, Germany: Institue for Quality and Efficiency in Health Care*. Retrieved from Asthma in pregnancy : https://www.ncbi.nlm.nih.gov/books/NBK492985/

66. Howard, L., Molyneaux, E., Dennis, C., Rochat, T., Stein, A., & Milgrom, J. (2014). Non-psychotic mental disorders in the perinatal period. *Lancet*, 1276-1279.

67. Anxiety and Depression Association of America. (2009, December). *ADAA.* Retrieved from Medications: https://adaa.org/sites/default/files/Medications-Chart_updated-1209.pdf

68. Glover, V. (2014). Maternal depression, anxiety, and stress durin gpregnancy and child outcome; what needs to be done. *Best Practice and Research Clinical Obstetrics and Gynaecology*, 25-35.

69. Ding, X., Wu, Y., Xu, S., Zhu, R., Jia, X., Zhang, S., . . . Tao, F. (2014). Maternal anxiety during pregnancy and adverse birth outcomes: a systematic review and meta-analyis of prospective cohort studies. *Journal of Affective Disorders*, 103-110.

70. Tarabulsy, G., Pearson, J., Vaillancourt-Morel, M., Bussieres, E., Madigan, S., Lemelin, J., . . . Royer, F. (2014). Meta-analytic findings of the relation between maternal prenatal stress and anxiety and child cognitive outcome. *Journal of Developmental and Behavioral Pediatrics*, 38-43.

71. Tomson, T., & Vilho, H. (2007). Epilepsy in Pregnancy. *BMJ*, 769-773.

72. Goldenberg, M. M. (2010). Overview of drugs used for epilepsy and seizures. *Pharmacy and Therapeutics*, 932-415.

73. Vajda, F., Graham, J., O'Brien, T., Lander, C., & Eadie, M. (2015). The outcomes of pregnancy in women with untreated epilepsy. *Seizure*, 77-81.

74. Mayo Clinic. (2017, July 13). *Pregnancy week by week*. Retrieved from Epilepsy and pregnancy: what you need to know: https://www.mayoclinic.org/healthy-lifestyle/pregnancy-week-by-week/in-depth/pregnancy/art-20048417

75. Centers for Disease Control and Prevention. (2018, May 16). *High blood pressure.* Retrieved from High blood pressure during pregnancy fact sheet: https://www.cdc.gov/bloodpressure/pregnancy.htm

76. Food and Drug Administration. (2011, May). *Medcines to Help You.* Retrieved from High Blood Pressure: https://www.fda.gov/downloads/forconsumers/byaudience/forwomen/freepublications/ucm282311.pdf

77. Mayo Clinic. (2018, February 14). *Pregnancy week by week*. Retrieved from High blood pressure and pregnancy: know the facts: https://www.mayoclinic.org/healthy-lifestyle/pregnancy-week-by-week/in-depth/pregnancy/art-20046098

78. Anthony, J., Damasceno, A., & Ojjii, D. (2016). Hypertensive disorders of pregnancy: what the physician needs to know. *Cardiovascular Journal of Africa,* 104-110.

79. Bookstaver, P., Bland, C., Griffin, B., Stover, K., Eiland, L., & McLaughlin, M. (2015). A review of anitbiotic use in pregnancy. *Pharmacotherapy,* 1052-1062.

80. Anderson, L. (2016, August 23). *Drugs*. Retrieved from Antibiotics Guide: https://www.drugs.com/article/antibiotics.html

81. National Institue of Child Health and Human Development. (2017, January 31). *Health*. Retrieved from What infections can affect pregnancy?: https://www.nichd.nih.gov/health/topics/pregnancy/conditioninfo/infections

82. Shah, S., Banh, E., Koury, K., Bhatia, G., Nandi, R., & Gulur, P. (2015). Pain management in pregnancy: multimodal approaches. *Pain Research and Treatment*.

83. Kennedy, D. (2011). Analgesics and pain relief in pregnancy and breastfeeding. *Australian Prescriber,* 8-10.

84. Food and Drug Administration. (2015, July 9). *Drugs*. Retrieved from FDA drug safety communication: FDA strengthens warning that non-aspirin nonsteroidal anti-inflammatory drugs (NSAIDs) can cause heart attacks or strokes: https://www.fda.gov/drugs/drugsafety/ucm451800.htm

85. Food and Drug Administration. (2018, December 20). *For Consumers.* Retrieved from A Guide to Safe Use of Pain Medicine: https://www.fda.gov/ForConsumers/ConsumerUpdates/ucm095673.htm

86. Shah, L. (2017). *Can opioids be used for pain relief during pregnancy?* London: UK Medicines Information.

87. Duenas, M., Ojeda, B., Salazar, A., Mico, J., & Failde, I. (2016). A review of chronic pain impact on patients, their social environment and health care system. *Journal of Pain Research*, 457-467.

88. UK Teratology Information Service. (2016). *Pain relief in pregnancy.* London: UK Teratology Information Service.

89. Oykhman, P., Kim, H. L., & Ellis, A. K. (2015). Allergen Immunoherapy in pregnancy. *Allergy, Asthma, and Clinical Immunology*, 11-31.

90. Mayo Clinic. (2017, June 6). *Patient Care and Health Information*. Retrieved from Allergy medications: know your options: https://www.mayoclinic.org/diseases-conditions/allergies/in-depth/allergy-medications/art-20047403

91. American College of Allergy, Asthma, and Immunotherapy. (2018, April 17). *Who Has Allergies and Why*. Retrieved from Pregnancy and Allergies: https://acaai.org/allergies/who-has-allergies-and-why/pregnancy-and-allergies

92. Pongdee, T. (n.d.). *American Academy of Allergy, Asthma & Immunology*. Retrieved from Asthma, Allergies and Pregnancy: https://www.aaaai.org/conditions-and-treatments/library/asthma-library/asthma-allergies-and-pregnancy

93. Henry, A., & Crowther, C. (2000). Patterns of medication use during and prior to pregnancy: the MAP study. *Australian and New Zealand Journal of Obstetrics and Gynaecology*, 165-172.

94. Drugs.com Staff. (n.d.). *Medications for Cold Symptoms*. Retrieved from Drugs used to treat cold symptoms: https://www.drugs.com/condition/cold-symptoms.html?category_id=&only_generics=true&submitted=true

95. Food and Drug Administration. (September , 11 2018). *Drugs*. Retrieved from Influenza (flu) antiviral drugs and related information: https://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm100228.htm

96. de Bellefonds, C. (2018, May 10). *Your Health*. Retrieved from Flu during pregnancy: what you need to know to stay safe: https://www.whattoexpect.com/pregnancy/pregnancy-health/flu-during-pregnancy/

97. Jasni, F. (n.d.). *Pregnancy*. Retrieved from Flu & fever during pregnancy: complications and treatment: https://www.healthxchange.sg/women/pregnancy/flu-fever-pregnancy-complications-treatment

98. Khashan, A., Kenny, L., Lauresen, T., Mahmood, U., Moretensen, P., Henriksen, T. B., & O'Donoghue, K. (2011). Pregnancy and the risk of autoimmune disease. *PLos One*, 1-7.

99. Li, P., Cheng, Y., & Chen, X. (2017). Drugs for autoimmune inflammatory diseases: from small molecule compounds to anti-TNF. *Frontiers in Pharmacology*, 1-12.

100. NYU Lagone Health. (n.d.). Types of Autoimmune Diseases. Retrieved from Types of Autoimmune Diseases in Pregnancy: https://nyulangone.org/conditions/autoimmune-diseases-in-pregnancy/types

101. NYU Langone Health. (n.d.). *Medications*. Retrieved from Medications for pregnancy complications of autoimmune diseases: https://nyulangone.org/conditions/autoimmune-diseases-in-pregnancy/treatments/medications-for-pregnancy-complications-of-autoimmune-diseases

102. Waldorf, K., & Nelson, J. L. (2008). Autoimmune disease during pregnancy and the microcimerism legacy of pregnancy. *Immunological Investigations*, 631-644.

103. Regitz-Zagrosek, V., Lundquist, C. B., Borghi, C., Cifkova, R., Ferreira, R., Foidart, J., . . . Presbitero, P. (2011). ESC guidelines on the management of cardiovacular diseases during pregnancy. *European Heart Journal*, 3147-3197.

104. CenterWatch. (n.d.). *Drug Information*. Retrieved from FDA approved drugs for cardiology/vascular diseases: https://www.centerwatch.com/drug-information/fda-approved-drugs/therapeutic-area/1/cardiology-vascular-diseases

105. Franklin, W., Benton, M. K., & Parekh, D. (2011). Cardiac disease in pregnancy. *Texas Heart Institute Journal*, 151-153.

106. Silversides, C. K., Grewal, J., Mason, J., Sermer, M., Kiess, M., Rychel, V., . . . Siu, S. (2018). Pregnancy outcomes in women with heart diseases. *Journal of the American College of Cardiology*, 2419-2430.

107. Horn, J., Tanz, L., Markovitz, A., Skurnik, G., Rimm, E., Missmer, S., & Rich-Edwards, J. (2018). Early or late pregnancy loss and development of clinical cardiovascular disease risk factors: a prospective cohort study. *BJOG*, 33-42.

108. Vesga-Lopez, O. B., Keyes, K., Olfson, M., Grant, B., & Hasin, D. (2008). Psychiatric disorders in pregnant and postpartum women in the United States. *Archives of General Psychiatry*, 805-815.

109. McIntyre, R., Cha, D., Kim, R., & Mansur, R. (2013). A review of FDA-approved treatment options in bipolar depression. *CNS Spectrum*, 4-20.

110. Scrandis, D. (2017). Bipolar disorder in pregnancy: a review of pregnancy outcomes. *Journal of Midwifery & Women's Health*, 673-683.

111. Nguyen, N., Gorman, M., Kent III, E., & Caughey, A. (2014). Pregnancy outcomes in women with bipolar disorder: a retrospective cohort study. *American Journal of Obstetrics*, S323.

112. Edipidis, K. (2011). Pregnancy in women with renal disease. Yes or no? *Hippokratia*, 8-12.

113. CenterWatch. (n.d.). *Drug Information*. Retrieved from FDA approved drugs for nephrology: https://www.centerwatch.com/drug-information/fda-approved-drugs/therapeutic-area/9/nephrology

114. Williams, D., & Davison, J. (2008). Chronic kidney disease in pregnancy. *BMJ*, 211-215.

APPENDIX A: SECTION 2 MEDICATIONS CHART

Disease/Condition: % of Pregnant Women with Condition *Type of Drug	**Drug**	**FDA Classification**	**Consequences to Mother if Left Untreated**	**Consequences to Fetus if Left Untreated**
Diabetes, Type 1: 1-2% [51]			life threatening low blood glucose, ketoacidosis, high blood pressure and preeclampsia, future type 2 diabetes[51, 53, 54]	birth defects, some resulting in fetal death, that affect the heart and connecting blood vessels, brain, spine, urinary and kidney systems, and the digestive tract; stillbirth; macrosomia; birth injury; hypoglycemia; respiratory distress; higher risk of type 2 diabetes and obesity later in life[51, 53, 54]
*insulin	insulin regular	B		
	insulin aspart	B		
	insulin detemir	B		
	insulin lispro[52]	B		
Diabetes, Type 2: 1-2% [51]			life threatening low blood glucose, ketoacidosis, high blood pressure and preeclampsia, future type 2 diabetes[51, 53, 54]	birth defects, some resulting in fetal death, that affect the heart and connecting blood vessels, brain, spine, urinary and kidney systems, and the digestive tract; stillbirth; macrosomia; birth injury; hypoglycemia; respiratory distress; higher risk of type 2 diabetes and obesity later in life [51, 53, 54]
*Alpha-glucosidase inhibitors	acarbose	B		
	miglitol	B		
*Biguanide	metformin	B		
*DPP-4 inhibitors	alogliptin	B		
	linagliptin	B		
	saxagliptin	B		
	sitagliptin	B		
*SLGT 2 inhibitors	dapagliflozin	C		
	canagliflozin	C		
	empagliflozin	C		
* Sulfonylureas	glimepiride	C		
	glipizide	C		
	glyburide	C		
	chlorpropamide	C		
	olazamide	C		
	tolbutamide	C		
*Thiazolidinediones	rosiglitazone	C		
	Pioglitazone [52]	C		

Depression: 12% [55]			postpartum depression; suicidality; pregnancy complications including preeclampsia; tendency toward high-risk behaviors, including smoking, substance and alcohol abuse, poor nutrition[55, 57-62]	prematurity; low birth weight; intrauterine growth restriction; childhood development issues, including emotional, behavioral, cognitive, social, and impulse problems[55. 58-63]
* selective serotonin reuptake inhibitors (SSRIs)	fluoxetine	C		
	citalopram	C		
	escitalopram	C		
	fluvoxamine	C		
	sertraline	C		
	paroxetine	D		
*serotonin norepinephrine reuptake inhibitors (SNRIs)	venlafaxine	C		
	desvenlafaxine	C		
	duloxetine	C		
*tricyclic antidepressants	amitriptyline	C		
	imipramine	C		
	doxepin	C		
	clomiprimine	C		
	maprotiline	B		
	desipramine	C		
	trimipramine	C		
	protriptyline	C		
	nortriptyline	C		
monoamine oxidase inhibitors	phenelzine	C		
	isocarboxazid	C		
	tranylcypromine	NOT ASSIGNED		
*others	mirtazapine	C		
	bupropion	B		
	venlafaxine	C		
	duloxetine	C		
	trazodone [56]	C		
Asthma: 8% [64]			severe asthma attacks[65]	preterm birth; preeclampsia; reduced growth and low birth weight[65]
*bronchodilator	aclidinium bromide	C		
	albuterol sulfate	C		
	formoterol	C		
	levalbuterol sulfate	C		
	salmeterol	C		
	olodaterol	C		
	ipratropium bromide	B		
	arformoterol tartrate	C		
*corticosteroid	beclomethasone dipropionate	C		
	budesonide	B		
	ciclesonide[64]	C		
	flunisolide	C		

	fluticasone	C		
	mometasone furoate[64]	C		
Anxiety: 13% [66]			maternal psychological distress, panic symptoms depression, heightened anxiety symptoms caused by hormone changes, postnatal depression[59]	loss of fetus during first trimester; decrease in birth weight; increase in activity of the hypothalamus-hypophysis-adrenal axis; decrease in adult fertility rate; social, behavioral, emotional, cognitive issues; hyperactivity disorder[68-70]
*azapirone	busipirone	B		
*benzodiazepine	lorazepam	D		
	flurazepam	C		
	clonazepam	D		
	triazolam	X		
	chlordiazeperoxide	D		
	temazepam	X		
	oxazepam	NOT ASSIGNED		
	clorazepate	D		
	diazepam	D		
	alprazolam [67]	D		
Epilepsy: 0.7 %[71]			increased seizures, lack of seizure control[73]	A seizure during pregnancy can cause slowing of the heartrate, decreased oxygen supply to the fetus, birth injury, placental abruption, trauma-induced miscarriage, preterm labor, premature birth[74]
	valproate	X		
	lamotrigine	C		
	topiramate	D		
	carbamazepine	D		
	phenytoin	D		
	oxcarbazepine	C		
	ethosuximide	C		
	zonisamide	C		
	phenobarbital	D		
	primidone	D		
	felbamate	C		
	levetiracetam	C		
	tiagabine	C		
	zonisamide	C		
	gabapentin	C		
	eslicarbazepine	C		
	vigabatrin	C		
	lacosamide	C		
	pregabalin	C		
	rufinamide[72]	C		
Hypertension: 8%[75]				
*ACE inhibitors	perindopril	D		
	quinapril	D		
	ramipril	D		
	captopril	D		
	benazepril	D		
	trandolapril	D		

	fosinopril	D	preeclampsia; injury to major organs including brain, lungs, heart, kidneys, and liver; higher risk for cardiovascular disease; risk of heart attacks and strokes; cerebrovascular hemorrhage; subcapsular hematoma[77-78]	placental abruption, intrauterine growth restriction, premature delivery[77-78]
	lisinopril	D		
	moexipril	D		
	enalapril	D		
	enalaprilat	D		
*Beta Blockers	nebivolol	NOT ASSIGNED		
	timolol	C		
	carvedilol	C		
	nadolol	C		
	propranolol	C		
	betaxolol	C		
	penbutolol	C		
	metoprolol	C		
	acebutolol	B		
	atenolol	D		
	labetalol	C		
	pindolol	B		
	bisoprolol	C		
*calcium channel blockers	amlodipine	C		
	clevidipine	C		
	diltiazem	D		
	felodipine	C		
	isradipine	C		
	nicardipine	C		
	nifedipine	C		
	nimodipine	C		
	nisoldipine	C		
	verapamil	C		
*peripherally acting alpha-adrenergic blockers	doxazosin	C		
	phenoxybenzamine	C		
	prazosin	C		
	terazosin	C		
*vasodilators	hydralazine	C		
	minoxidil	C		
*angiotensin II antagonists	candesartan	D		
	irbesartan	D		
	olmesartan	D		
	losartan	D		
	valsartan	D		
	azilsartan	D		
	telmisartan	D		
	eprosartan	D		

*centrally-acting alpha adrenergics	clonidine	C		
	guanfacine[76]	B		
Bacterial Infections: 25%[79]			organ failure, difficult labor, increased demand on heart[81]	preterm labor, premature birth, lower birth weight, spread of infection from mother, birth abnormalities, miscarriage, pneumonia, intellectual disabilities, blindness[81]
*penicillins/beta-lactams	penicillin	B		
	amoxicillin	B		
*tetracyclines	doxycycline	D		
	tetracycline	D		
	minocycline	D		
*cephalosporins	cefuroxime	B		
	ceftriaxone	B		
	cefdinir	B		
*quinolones	ciprofloxacin	C		
	levofloxacin	C		
	moxifloxacin	C		
*lincomycin	clindamycin	B		
	lincomycin	C		
*macrolides	azithromycin	B		
	clarithromycin	C		
	erythromycin	B		
*sulfonamides	sulfamethoxazole-trimethoprim	D		
	sulfasalazine	B		
	sulfisoxazole	C		
*glycopeptides	dalbavancin	C		
	oritavancin	C		
	telavancin	C		
	vancomycin	C		
*aminoglycosides	gentamicin	C		
	tobramycin	D		
	kanamycin	D		
	streptomycin	D		
	amikacin	D		
*carbapenem	meropenem	B		
	Invanz[80]	B		
Pain: 60% (analgesics)/ 6% (opiates)[82-83]			hypertension; occurrences of fear, anxiety, and depression; injury; trauma; infection; nerve damage; exacerbation of pain by pregnancy hormones[86-87]	adverse effects from other conditions that the mother develops as a result of pain, especially those that affect the mother's cardiovascular system[86,88]
*OTC acetaminophen	acetaminophen	C		
*OTC non-steroidal anti-inflammatory drugs	aspirin	D		
	naproxen	C		
	ibuprofen	C		
	celecoxib	D		
	diclofenac	D		
	diflunisal	C		
	etodolac	C		

	fenoprofen	D		
	flurbiprofen	NOT ASSIGNED		
	indomethacin	C		
	ketoprofen	C		
	ketorolac	C		
	mefenamic acid	C		
	meloxicam	D		
	nabumetone	C		
	oxaprozin	C		
	piroxicam	C		
	sulindac	C		
	tolmetin	C		
*opioid	morphine	NOT ASSIGNED		
	oxycodone	NOT ASSIGNED		
	codeine	C		
	hydrocodone	NOT ASSIGNED		
	Hydromorphone[84-85]	C		
Allergies: 30%[89]			anaphylactic shock, worsened asthma, predisposition to sinusitis[89]	decreased oxygen supply; consequences of maternal asthma including preterm birth, preeclampsia, and low birth weight[91-92]
*antihistamines	diphenhydramine	B		
	chlorpheniramine	B		
	cetirizine	B		
	desloratdaine	C		
	fexofenadine	C		
	loratadine	B		
	levocetirizine	B		
	azelastine	C		
	olopatadine	C		
	emedastine	B		
	ketotifen	C		
	pheniramine	NOT ASSIGNED		
*decongestant	pseudoephedrine	NOT ASSIGNED		
	oxymetazoline	C		
	tetrahydrozoline	C		
*corticosteroids	budesonide	B		
	fluticasone furoate	C		
	fluticasone propionate	C		
	mometasone furoate	C		
	triamcinolone	C		
	beclomethasone	C		
	ciclesonide	C		
	prednisolone	C		

	methylprednisolone	C		
	hydrocortisone	C		
*leukotriene inhibitors	montelukast[90]	B		
Flu: 8%[93]			bronchitis, pneumonia, fever, myocarditis[96]	preterm labor, premature birth, miscarriage[97]
*antivirals	peramivir	C		
	zanamivir	C		
	oseltamivir phosphate	C		
	baloxavir[94-95]	NOT ASSIGNED		
Autoimmune Diseases: 2.5%[98]			disease flare-ups and exacerbation, preeclampsia, worsening organ function, blood clots[100-102]	miscarriage, low birth weight, preterm birth, still birth, birth defects, congenital heart block[100-101]
*NSAIDs	aspirin	D		
	diflunisal	C		
	sulfasalazine	B		
	acetaminophen	C		
	mefenamic acid	C		
	meclofenamate	C		
	ibuprofen	C		
	naproxen	C		
	fenoprofen	D		
	ketoprofen	C		
	flurbiprofen	NOT ASSIGNED		
	oxaprozin	C		
	piroxicam	C		
	tenoxicam	C		
*glucocorticoids	prednisolone	C		
	methylprednisolone	C		
	dexamethasone	C		
	betamethasone	C		
*DMARDs	methotrexate	X		
	leflunomide	X		
	hydroxychloroquine	NOT ASSIGNED		
	sulfasalazine	B		
*anti-TNF biologics	infliximab	B		
	adalimumab	B		
	etanercept	B		
	golimumamb	B		
	certolizumab pepol[99]	B		
Cardiovascular Diseases: 4%[103]			heart strain, blood clotting, endocarditis, myocardial infarction, increased mortality rate, preeclampsia,	increased mortality rate, miscarriage, stillbirth[105,107]
*anticoagulant	betrixaban	NOT ASSIGNED		
	tinzaparin	B		
*beta blocker	nebivolol	C		
	metoprolol	C		

*angiotensin receptor blocker	valsartan	D	arrhythmia, heart failure, pulmonary edema, gestational diabetes[103,105-106]	
	sacubitril	D		
	olmesartan	D		
	azilsartan medoxomil	D		
	telmisartan	D		
	eprosartan	D		
	candesartan	D		
*NSAID	aspirin	D		
*proton pump inhibitor	omeprazole	C		
*channel blocker	ivabradine	D		
	amlodipine besylate	C		
	clevidipine	C		
	nimodipine	C		
	verapamil	C		
	procainamide	C		
	diltiazem	D		
*enzyme	sebelipase alfa	NOT ASSIGNED		
*$P2Y_{12}$ inhibitor	cangrelor	C		
	ticagrelor	C		
*PSCK9 inhibitor	alirocumab	NOT ASSIGNED		
	evolocumab	NOT ASSIGNED		
*ACE inhibitor	perindopril arginine	D		
	enalapril	D		
	lisinopril	NOT ASSIGNED		
	trandolapril	D		
*Xa inhibitor	edoxaban	C		
	apixaban	B		
	rivaroxaban	C		
*receptor antagonist	selexipag	NOT ASSIGNED		
	vorapaxar	B		
	ambrisentan	X		
	eplerenone	B		
	macitentan	X		
*antilipemic agent	omega-3-carboxylic acids	C		
	lomitapide	X		
	icosapent	C		
*sGC stimulator	riociguat	X		
*oligonucleotide inhibitor	mipomersen sodium	B		
*statin	atorvastatin	X		
	pitavastatin	X		
	fluvastatin	X		

	cerivastatin	X		
	pravastatin	X		
	lovastatin	X		
*cholesterol absorption inhibitor	ezetimibe	C		
*sclerosing agent	polidocanol	C		
*renin inhibitor	aliskiren	D		
*diuretic	hydrochlorothiazide	B		
*thrombin inhibitor	dabigatran	C		
	bivalirudin	B		
*PDE5 inhibitor	tadalafil	B		
*anti-platelet	prasugrel	B		
	clopidogrel	B		
*anti-arrhythmic	dronedarone	X		
	ibutilide	C		
*vasodilator	treprostinil	B		
	nesiritide	C		
	rosuvastatin	X		
*fibrate	fenofibric acid	C		
*monoclonal antibody	eculizumab	C		
*anti-anginal	ranolazine	C		
*nitrate	isosorbide dinitrate	C		
	nitroglycerin	C		
*anti-hypertensive	hydralazine hydrochloride	C		
*platelet-reducing agent	anagrelide	C		
*alpha-adrenergic agonist	midodrine	C		
*thrombolytic	reteplase	C		
*radiopaque	Iodixanol[104]	B		
Bipolar Disorder: 2.8%[108]			increased risk of illness episodes, preeclampsia, hypertension[110-111]	preterm birth, placenta previa, antepartum hemorrhage, congenital abnormalities, low birth weight, intrauterine fetal demise, infant death[110-111]
*antipsychotic, atypical	quetiapine	C		
	olanzapine	C		
	lurasidone	B		
*anesthetic	ketamine	NOT ASSIGNED		
*eugeroic	modafinil	C		
	armodafinil	C		
*anticonvulsant	lamotrigine	C		
*antipsychotic, atypical + SSRI	olanzapine-fluoxetine[109]	C		
Renal Disease: 0.12%[112]			preeclampsia, increased cesarean delivery rate, decline in renal function, hypertension, anemia[112,114]	preterm birth; miscarriage; growth restriction; decrease in infant survival rate, particularly
*receptor antagonist	tolvaptan	C		
*calcimimetic	etelcalcetide	NOT ASSIGNED		
	cinacalcet	C		
*tyrosine kinase inhibitor	cabozantinib	D		

	lenvatinib	NOT ASSIGNED		when mother undergoes dialysis[112,114]
	pazopanib	D		
*vitamin D analog	calcifediol	C		
	doxercalciferol	B		
*monoclonal antibody	nivolumab	NOT ASSIGNED		
*selective uric acid reabsorption inhibitor	lesinurad	NOT ASSIGNED		
*phosphate binder	ferric citrate	B		
	sevelamer carbonate	C		
	eculizumab	C		
	lanthanum carbonate	C		
*HCV inhibitor	ledipasvir	B		
	ombitasvir	B		
	sofosbuvir	X		
	paritaprevir	B		
	ritonavir	B		
	dasabuvir	B		
*iron replacement	ferric carboxymaltose	C		
	iron sucrose	B		
	ferumoxytol	C		
*cystine depleting agent	cysteamine bitartrate	C		
*beta-3 adrenergic agonist	mirabegron	C		
*hematopoietic growth factor	peginesatide	C		
*phosphodiesterase inhibitor	avanafil	C		
*antispasmodic	oxybutynin	B		
	trospium chloride	C		
*enzyme activator	carglumic acid	C		
*muscarinic receptor antagonist	fesoterodine fumarate	C		
*erythropoiesis stimulating agent	methoxy polyethylene glycol-epoetin beta	C		
*non-peptide vasopressin inhibitor	conivaptan	C		
*antimuscarinic	solifenacin	C		
*enzyme	agalsidase beta	B		
*GnRH agonist	leuprolide acetate	X		
	triptorelin pamoate	X		
*cholinergic receptor blocker	tolterodine tartrate	C		
*anticoagulant	pentosan ploysulfate sodium	B		
*vitamin B analog	cyanocobalamin[113]	C		

APPENDIX B: IRB PROTOCOL

Protocol Summary
Version: January 2, 2019

Trends in the Use of Medications and Outcomes in Pregnant Women with Cystic Fibrosis

Principal Investigator
Kathleen Job, PhD, FCP
University of Utah Health
Clinical Pharmacology
295 Chipeta Way, S100
Salt Lake City, Utah, 84108, USA
801.213.3972
Kate.Job@hsc.utah.edu

Sub-Investigator(s)
Micah Ballif
Clinical Pharmacology
295 Chipeta Way, S100
801.213.3972
Micah.Ballif@hsc.utah.edu

Background and Introduction

Cystic fibrosis is the most common life-shortening Mendelian recessive genetic disorder, especially prevalent among Caucasians in North America, Europe, and Australia. The source of the disease is a gene mutation that codes for the cystic fibrosis transmembrane conductance regulator (CFTR). This transmembrane channel is responsible for chloride anion and bicarbonate transportation and airway mucociliary clearance. CFTR dysfunction largely affects epithelial cells, resulting in airway mucus retention, persistent infection, and airway inflammation, all detrimental to lung function[1].

In 1950, shortly after the disease was identified, patients with cystic fibrosis had a life expectancy of mere months. Their deaths were a result of malnutrition following pancreatic malabsorption and meconium ileus[2]. However, over the course of the last sixty years, the median life expectancy has increased dramatically and is now greater than forty years in developed nations[3,4]. This increase in age has created the potential for women with cystic fibrosis to be mothers, and it is reasonable to believe many women will elect to do so.

Multiple studies have found that the disease itself has no effect on maternal pregnancy survival, with similar clinical outcomes for non-pregnant cystic fibrosis counterparts[6,7]. However, smaller single-center studies have shown that despite aggressive modern pre- and post-natal care's sufficient support for cystic fibrosis women, unusual negative circumstances surrounded those births, including lower birth weight, nutritional failure at conception, and increased rates of early gestational births[8, 9]. These negative effects were proportional to the severity of the cystic fibrosis, and healthier women with cystic fibrosis consistently had healthier pregnancies[7]. Furthermore, there is some concern that lung function may be negatively affected by pregnancy[8].

Medications are vital for the management of cystic fibrosis, even when pregnant. Conventional cystic fibrosis treatments have focused on the symptoms of the disease, specifically mucus plugging and chronic infection, or on organs affected by cystic fibrosis, including the pancreas and liver. For example, bacterial infections are one of the most common problems present in cystic fibrosis patients. These infections are normally treated with antibiotics, and such management is vital for good health. Understanding dosage and prescribing patterns, and drug clearance is vital of drugs with potentially significant side effects, such as aminoglycosides (e.g. including amikacin, gentamicin, kanamycin, etc.), are important for obtaining positive patient outcomes.[2]

Prescription of antibiotics and other medications and treatments with regards to dose alteration or discontinuation is not well understood due to the current lack of pregnancy-related data in this area. These novel therapies and antibiotics that have allowed for a longer life span for those with cystic fibrosis have not been sufficiently tested for safe use in pregnant women, making pregnancy management care challenging. Due to the lack of understanding regarding this population possibility of risk to the fetus, many pregnant women with CF may be not be obtaining optimal treatment, putting both the fetus and mother at risk.

Study Purpose and Objectives

This study is a simple retrospective chart review of pregnant women with CF, which will generate a de-identified data set. Necessary data regarding treatment and outcomes related to pregnancy in women with CF will be collected on these women 120 days prior to conception, during pregnancy, and 60 days after estimated delivery date. Data collected will include demographics, antibiotic information, pulmonary function, and type of infection. This study aims to understand antibiotic prescribing patterns and outcomes associated with treatment of pregnant

women. The primary objective of this study is to describe current pregnancy trends and treatment practices in patients with cystic fibrosis, specifically relating to antibiotic usage. The secondary objective is to characterize the changes in treatment patterns before, during, and after pregnancy.

Participant Selection Criteria

Expected Sample Size: 70

Inclusion:

1. All women who are pregnant or have had a pregnancy as reported to the University of Utah Hospital.
2. Diagnosed with Cystic Fibrosis
3. 18-65 years of age (inclusive)

Exclusion:

1. None

Design

Descriptive study; retrospective review.

Study Procedures

This is a retrospective chart review of pregnant patients with CF. Patients will be identified by searching the University of Utah Hospital for patients meeting the inclusionary criteria. Participants will not be contacted directly. The PI will work with the data warehouse at the University Hospital. Data collection may include data from 90 days before the pregnancy reported pregnancy, during the year of pregnancy, and two years after the reported pregnancy year. Data collected will include:

1. Demographics: Age (year), Sex, Weight, Height, Ethnicity, Race, BMI.
2. Antibiotic Information: drug information, dosing information (frequency, route, and dose), number of doses received.
3. Pulmonary Function: FVC, FEV_1, FEF 25-75.
4.

Informed Consent-Requested Waiver

This is a retrospective chart review study and we plan to review approximately 70 individual charts based on estimates available. There will be no patient interaction in this trial and there will be no PHI disclosed. The collection of information about participants is limited to the amount necessary to achieve the aims of the research, so that no unneeded information is being collected.

Data Safety and Monitoring

This research will pose only minimal risk to study participants. Data collected will be de-identified by the University Hospital research personnel before it is received. All data will be stored on password-protected computers. The primary investigator will ensure that data storage and handling is consistent with University of Utah IRB standards.

Statistical Methods, Analyses, and Interpretation

The number of participants (sample size) will depend on the number of patients that meets the inclusion criteria as opposed to a predetermined number. Based on numbers reported from an

initial query of the University of Utah EDW, we hope to obtain data from 70 total individuals, but are unsure if we will reach that goal.

Numerical variables will be summarized by means (+/- SD). Binary and categorical variables will be summarized by frequency (in %). Parametric models will be considered primary statistical tools for the study. Transformed numerical variables will be used if their original variables are found to be a departure of Gaussian distribution assumptions before formal analyses are performed.

References (IRB Protocol)

1. Elborn JS. Cystic fibrosis. *Lancet.* 2016;388(10059):2519-2531.

2. Edmondson C, Davies JC. Current and future treatment options for cystic fibrosis lung disease: latest evidence and clinical implications. *Ther Adv Chronic Dis.* 2016;7(3):170-183.

3. Burgel PR, Bellis G, Olesen HV, et al. Future trends in cystic fibrosis demography in 34 European countries. *Eur Respir J.* 2015;46(1):133-141.

4. Davis PB. Cystic fibrosis since 1938. *Am J Respir Crit Care Med.* 2006;173(5):475-482.

5. Quon BS, Rowe SM. New and emerging targeted therapies for cystic fibrosis. *BMJ.* 2016;352:i859.

6. Gilljam M, Antoniou M, Shin J, Dupuis A, Corey M, Tullis DE. Pregnancy in cystic fibrosis. Fetal and maternal outcome. *Chest.* 2000;118(1):85-91.

7. Goss CH, Rubenfeld GD, Otto K, Aitken ML. The effect of pregnancy on survival in women with cystic fibrosis. *Chest.* 2003;124(4):1460-1468.

8. Thorpe-Beeston JG, Madge S, Gyi K, Hodson M, Bilton D. The outcome of pregnancies in women with cystic fibrosis--single centre experience 1998-2011. *BJOG : an international journal of obstetrics and gynaecology.* 2013;120(3):354-361.

APPENDIX C: AVERAGE FREQUENCY OF MEDICATIONS PRESCRIBED IN PREGNANCY AND NON-PREGNANCY CARE

	Average % of Each Med Prescribed During Pregnancy	Standard Deviation ±	Average % of Each Med Prescribed Outside of Pregnancy	Standard Dev ±
Amoxicillin	2.78	0.45	4.77	0.44
Amikacin	0.00	0.00	1.10	0.03
Ampicillin	0.22	0.02	0.94	0.03
Azithromycin	13.43	2.85	12.60	1.55
Aztreonam	4.62	0.46	1.33	0.03
Bactrim	0.09	0.00	0.30	0.00
Cefazolin	14.19	4.07	5.44	0.41
Cefdinir	0.00	0.00	0.33	0.01
Cefepime	0.00	0.00	0.16	0.00
Cefoxitin	3.24	0.53	0.17	0.00
Ceftazidime	1.95	0.15	2.13	0.09
Ceftriaxone	6.56	0.99	3.26	0.25
Cephalexin	0.95	0.05	1.00	0.04
Ciprofloxacin	1.39	0.11	4.08	0.28
Clindamycin	3.19	0.53	1.79	0.07
Colistimethate	0.00	0.00	0.17	0.00
Dicloxacillin	0.00	0.00	0.74	0.02
Doxycycline	2.31	0.20	8.24	1.12
Ertapenem	0.22	0.00	0.00	0.00
Erythromycin	0.00	0.00	0.00	0.00
Gentamicin	1.68	0.16	3.84	0.36
Imipenem-Cilastatin	0.00	0.00	0.16	0.00
Levaquin	0.00	0.00	1.24	0.06
Levofloxacin	0.18	0.00	2.91	0.14
Linezolid	0.00	0.00	0.27	0.00
Meropenem	4.36	0.64	6.49	0.55
Metronidazole	0.95	0.05	1.17	0.05
Minocycline	0.00	0.00	1.27	0.03
Moxifloxacin	0.00	0.00	0.12	0.00
Nitrofurantoin	9.74	2.26	7.09	0.70
Penicillin	8.63	1.75	6.30	1.14
Piperacillin	1.04	0.04	1.46	0.04
Sulfamethoxazole	1.00	0.04	7.14	0.65
Tedizolid	0.00	0.00	0.06	0.00
Ticarcillin	0.00	0.00	1.23	0.03

Tigecycline	0.00	0.00	0.10	0.00
Tobramycin	1.69	0.08	7.74	0.69
Vancomycin	3.91	0.66	0.56	0.01
Zosyn (Piperacillin + Tazobactam)	0.00	0.00	0.23	0.00