The Optimal Control of Child Delivery for Women with Hypertensive Disorders of Pregnancy

by

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ABSTRACT

Hypertensive disorders of pregnancy (HDP) affect up to 5%-15% of pregnancies around the globe, and form a leading cause of maternal and neonatal morbidity and mortality. HDP are progressive disorders for which the only cure is to deliver the baby. An increasing trend in the prevalence of HDP has been observed in the recent years. This trend is anticipated to continue due to the rise in the prevalence of diseases that strongly influence hypertension such as obesity and metabolic syndrome. In order to lessen the adverse outcomes due to HDP, we need to study (1) the natural progression of HDP, (2) the risks of adverse outcomes associated with these disorders, and (3) the optimal timing of delivery for women with HDP.

In the first study, the natural progression of HDP in the third trimester of pregnancy is modeled with a discrete-time Markov chain (DTMC). The transition probabilities of the DTMC are estimated using clinical data with an order restricted inference model that maximizes the likelihood function subject to a set of order restrictions between the transition probabilities. The results provide useful insights on the progression of HDP, and the estimated transition probabilities are used to parametrize the decision models in the third study.

In the second study, the risks of maternal and neonatal adverse outcomes for women with HDP are quantified with a composite measure of childbirth morbidity, and the estimated risks are compared with respect to type of HDP at delivery, gestational age at delivery, and type of delivery in a retrospective cohort study. Furthermore, the safety of child delivery with respect to the same variables is assessed with a provider survey and technique for order performance by similarity to ideal solution (TOPSIS). The methods and results of this study are used to parametrize the decision models in the third study.

In the third study, the decision problem of timing of delivery for women with HDP is formulated as a discrete-time Markov decision process (MDP) model that minimizes the risks of maternal and neonatal adverse outcomes. We additionally formulate a robust MDP model that gives the worst-case optimal policy when transition probabilities are allowed to vary within their confidence intervals. The results of the decision models are assessed within a probabilistic sensitivity analysis (PSA) that considers the uncertainty in the estimated risk values. In our PSA, the performance of candidate delivery policies is evaluated using a large number of problem instances that are constructed according to the orders between model parameters to incorporate physicians' intuition.

In memory of my beloved grandfather Ali Usta.

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Chapter 1

INTRODUCTION

Hypertensive disorders of pregnancy (HDP) are a set of medical complications associated with high blood pressure and proteinuria. Proteinuria is a condition in which the urine contains protein at an abnormally high level. Hypertension with proteinuria is defined as preeclampsia. It is a hypertensive disease with multi-system involvement that happens only during pregnancy. It usually occurs after 20 weeks of gestation and typically near term. HDP are progressive disorders, and the only cure is to deliver the baby (Barton *et al.*, 2001; Duley, 2009; Haddad *et al.*, 2007; Kuklina *et al.*, 2009; Foo *et al.*, 2015; Magee *et al.*, 2016). HDP impact up to 5% to 15% of pregnancies globally (ACOG, 2013b; Bazzano *et al.*, 2016). Therefore, they are considered a common complication, and a primary cause of maternal (of or relating to a mother) and neonatal (of or relating to a newborn) mortality and morbidity in the world (ACOG, 2013b; Gillon *et al.*, 2014).

It is estimated that preeclampsia causes about 50,000-60,000 deaths per year around the globe (Duley, 1992; Van Lerberghe *et al.*, 2005; ACOG, 2013b). The number of women who endure life threating complications due to preeclampsia is about 50-100 times higher than the preeclampsia caused deaths in the U.S. according to the recent estimates (Callaghan *et al.*, 2008; Kuklina *et al.*, 2009; ACOG, 2013b). Women with preeclampsia have an increased risk of severe complications such as abruptio placentae, thrombocytopenia, disseminated intravascular coagulation, pulmonary edema, and aspiration pneumonia. In addition, blood transfusion and mechanical ventilation are required much more frequently in these patients (Zhang *et al.*, 2003).

HDP form a major factor for prematurity, which brings significant risks of death and lifelong problems to infants (ACOG, 2013b). Preeclampsia is the cause of 25-43% of all medically indicated preterm (i.e., less than 37 weeks of gestation) births. Babies born from pregnancies complicated with preeclampsia are more likely to have health problems such as chronic hypertension, stroke, insulin resistance, mental and neurological disorders (Tranquilli *et al.*, 2012).

In a typical case of HDP, a pregnant woman is first diagnosed with hypertension; then hypertension may lead to preeclampsia (with or without severe features). The longer the pregnancy is, the higher the risks are for the mother to develop pregnancy-related complications, and for such complications to worsen. For the baby, delivery before the full term (37-40 weeks of gestation) is not desirable due to severe complications that prematurity may bring. The fact that delivery is the only cure for HDP makes the timing of delivery a challenging decision (Barton *et al.*, 2001; Magee *et al.*, 2016). If the mother is diagnosed with preeclampsia too early, the decision of delivery becomes even more challenging. In that case, the baby needs time to grow and mature, and on the other hand, the mother should be protected from the risk of serious complications that HDP may bring on.

For a complicated pregnancy, the timing of delivery is determined by a sequence of vital medical decisions. In each week of gestation, the possible actions to choose are waiting for labor, inducing labor, or delivering with cesarean delivery. Inducing labor and cesarean delivery are the two types of interventions to deliver the baby at a time decided by the physicians and the pregnant woman. Cesarean delivery is an intervention that involves a major abdominal surgery to deliver the baby. Induction of labor involves inducing the labor with induction medications and methods when the spontaneous labor is not present.

A delivery is typically classified according to the route that the baby is delivered. The route of delivery can be either vaginal delivery or cesarean delivery. Vaginal delivery happens naturally in the presence of spontaneous labor. In the absence of spontaneous labor, the labor can be induced to deliver the baby vaginally. Whether it is induced or not, having labor may result in either a vaginal delivery or an emergency cesarean delivery. Emergency cesarean delivery may be required due to a variety of reasons such as non-progressive labor and fetal distress.

1.1 Classification of Hypertensive Disorders

HDP is classified into four categories: (1) gestational (pregnancy-induced) hypertension, (2) preeclampsia, (3) chronic hypertension, and (4) chronic hypertension with superimposed preeclampsia (ACOG, 2013b; Bazzano *et al.*, 2016). Gestational hypertension is usually diagnosed by new-onset elevations of blood pressure observed after 20 weeks of gestation (often near term) (ACOG, 2013b). Some women experience blood pressure elevations so severely that the health outcomes may be comparable to preeclampsia (Buchbinder *et al.*, 2002). Besides, many of the women with gestational hypertension may develop preeclampsia before proteinuria. As a result, gestational hypertension demands enhanced surveillance even when the blood pressure elevations are mild (ACOG, 2013b).

Preeclampsia, the disease in the second category, is the most common type of HDP. It is mostly diagnosed by new-onset hypertension and new-onset proteinuria. Although proteinuria is often present in the cases of preeclampsia, it is certainly not necessary for the diagnosis of preeclampsia. When combined with pregnancy-induced hypertension, factors such as impaired liver function, renal insufficiency, visual or cerebral disturbances may also lead to the diagnosis of preeclampsia with severe features (ACOG, 2013b; Magee *et al.*, 2016). Eclampsia is considered as one of the

most severe manifestations of preeclampsia that involves convulsions (ACOG, 2013b), and is also included in this category.

In this study, our focus is on gestational hypertension and preeclampsia. There are two forms of preeclampsia, namely, mild preeclampsia (preeclampsia without severe features) and severe preeclampsia (preeclampsia with severe features). By convention, the terms *mild* and *severe* are used to classify the severity of preeclampsia. This classification should not be misleading for the reader since the risks of morbidity and mortality significantly increase even in the cases of mild preeclampsia, i.e., preeclampsia without severe features (ACOG, 2013b).

Chronic hypertension, the disease in the third category, is defined as high blood pressure diagnosed before the beginning of pregnancy or 20 weeks of gestation (ACOG, 2013b). Preeclampsia may complicate this hypertensive disorder, and become chronic hypertension with superimposed preeclampsia, which is the disease in the fourth category. Since the diagnosis of preeclampsia for women with chronic hypertension is difficult and introduces significant risk of misclassification bias, we do not consider the patients with chronic hypertension in this study.

1.2 National Guidelines for the Management of HDP

Task Force on Hypertension in Pregnancy of American College of Obstetricians and Gynecologists (ACOG) published a comprehensive report in 2013 that includes evidence-based clinical practice recommendations in the management of HDP. According to these recommendations, women with gestational hypertension and mild preeclampsia should be closely monitored with serial assessment of maternal symptoms and fetal movement. For these women, blood pressure should be measured at least twice weekly, and platelet counts and liver enzymes should be assessed once in a week. Strict bed rest is not suggested for the women without severe features of

preeclampsia. Expectant management, i.e., waiting for spontaneous labor without an intervention to deliver the baby, is the recommended action before the 37^{th} week of gestation. At or after that week of gestation, delivery instead of continued close monitoring is recommended (ACOG, 2013b).

For women with severe preeclampsia, expectant management is recommended before the 34^{th} week of gestation with close observation if the maternal and fetal conditions are stable. Delivery is recommended at and after the 34^{th} week of gestation, and if the maternal or fetal conditions are unstable at any gestational age. The care for a woman with severe preeclampsia should be undertaken in a facility with maternal and neonatal intensive care resources. The mode of delivery does not need to be cesarean delivery for women with mild or severe preeclampsia. It should be decided based on gestational age, presentation of the fetus in the uterine, cervical status, and maternal and fetal conditions (ACOG, 2013b).

1.3 Contributions of the Dissertation

In addition to close monitoring of the pregnant woman, the optimal management of HDP involves delivery at the optimal time for the well being of both the mother and the baby ACOG (2013b). Clinical practice guidelines fail to establish a consensus on the recommended time of delivery for HDP, and there are noteworthy inconsistencies in the timing of delivery for pregnancies complicated with preeclampsia (Gillon *et al.*, 2014). The decision of timing of delivery is still a challenge for clinicians, since early delivery which increases the risks for the fetus is the only definitive cure for preeclampsia (Kuklina *et al.*, 2009). Especially for gestational ages of 34-36 weeks, the guidelines of major institutions such as ACOG (US) and National Institute of Health and Care Excellence (UK) are inconclusive in the timing of delivery for preeclampsia (Bazzano *et al.*, 2016). Substandard care of patients with preeclampsia and other

forms of HDP play a part in maternal and neonatal adverse outcomes including death that might have been preventable (Van Dillen *et al.*, 2010; ACOG, 2013b; Gillon *et al.*, 2014). As a result, we are in urgent need of new best practice recommendations to guide obstetricians in the care of women with HDP, and future research focusing on the optimal timing of delivery (ACOG, 2013b; Gillon *et al.*, 2014).

The purpose of this dissertation is to address the optimal timing of delivery for women with HDP with an objective of minimizing the maternal and neonatal adverse outcomes due to childbirth. The work for this dissertation can be grouped under three studies as follows:

1. The natural history modeling of HDP progression in a retrospective observational cohort study (Chapter 2),

2. The assessment of the risks of maternal and neonatal adverse outcomes in HDP using patient data, and the assessment of childbirth safety in HDP using a provider survey (Chapter 3), and

3. The study of the optimal timing of delivery for women with HDP using a Markov Decision Process (MDP) model and a robust MDP (RMDP) model (Chapter 4).

In Chapter 2, we model the natural progression of HDP with a discrete time Markov chain, and estimate the probabilities of HDP progression. In Chapter 3, we first estimate the risk of childbirth morbidity for the mother and the newborn using patient data. In this chapter, we secondly measure the safety of childbirth complicated with HDP that is perceived by providers using a survey. We use technique for order performance by similarity to ideal solution (TOPSIS) to evaluate the survey results. The results and methods of Chapters 2 and 3 are used to parametrize the MDP and the RMDP models in Chapter 4.

In Chapter 4, we build an MDP model of the decision problem of the optimal timing of delivery for women with HDP. We evaluate the results of this model using a probabilistic sensitivity analysis to guard against the estimation errors in the risks of adverse outcomes. In addition, we study the same problem with a robust MDP model that provides the optimal timing of delivery that is robust to estimation errors in transition probabilities. We also evaluate the results of the RMDP model using our probabilistic sensitivity analysis framework that involves generation of problem instances by imposing a set of order restrictions between the risk values. Finally, in Chapter 5, we summarize the contributions of the dissertation and directions for future research.

This research is conducted in collaboration with Dr. Dean Coonrod, Chair of Department of Obstetrics and Gynecology at Maricopa Integrated Health System (MIHS). MIHS is the source of all clinical data used in this study. The institutional review board of MIHS approved the study and the use of patient data.

Chapter 2

THE NATURAL HISTORY OF HYPERTENSIVE DISORDERS OF PREGNANCY

2.1 Introduction

Although the prevalence of hypertensive disorders of pregnancy (HDP) has increased, our understanding of how HDP progresses throughout pregnancy is not complete. We need models of HDP progression that are easy to communicate with physicians, and able to provide meaningful results. As such, the objectives of this study are (1) to model the natural progression of HDP by retrospectively observing a large cohort during the third trimester of pregnancy, and (2) to estimate the probabilities of a pregnant woman to develop hypertensive disorders and go into spontaneous labor as the pregnancy progresses in each week of gestation in the third trimester.

The estimated probabilities show how the risks of developing gestational hypertension and preeclampsia change with gestational age. The estimations are obtained using HDP diagnosis data collected during the prenatal care, and the delivery outcome data collected during the delivery hospitalization. The estimated probabilities are used to construct the transition probability matrix (TPM) under the action of waiting, i.e., when the decision is to take no intervention in our Markov decision process (MDP) model described in Chapter 4.

To the best of our knowledge, no study in the medical literature estimates the probabilities to develop hypertensive disorders as a function of gestational age. However, there are medical studies on the overall risk of developing hypertensive disorders at any time during pregnancy. One study focuses on the predictability of hypertensive

disorders with blood pressure tracking in pregnancy, and demonstrated that blood pressure changes from the second to the third trimester increase the risks of gestational hypertension and preeclampsia (Gaillard *et al.*, 2011). Another study measures the rate of progression from mild gestational hypertension (for a singleton pregnancy between 24 and 35 weeks of gestation) to preeclampsia (Barton *et al.*, 2001). In addition, a number of studies investigate the impact of nutrition and physical activity on the risk of developing gestational hypertension and preeclampsia as compared to control groups (Levine *et al.*, 1997; Saftlas *et al.*, 2004; Rumbold *et al.*, 2006; Roberts *et al.*, 2010). Moreover, a recent study reviews the physiological processes in the progression of hypertensive disorders such as placental factors in the development of preeclampsia (Foo *et al.*, 2015).

We model the natural progression of HDP as a discrete-time Markov chain (DTMC). Beck and Pauker (1983) introduce the use of DTMCs in medical prognosis by proposing a general purpose model for the progression of a chronic disease that has particular health states. Since then, Markov modeling has been employed in modeling the natural progression of a variety of diseases including diabetic retinopathy, systemic inflammatory response syndrome, Crohn's disease, Parkinson's disease, human papillomavirus infection and cervical carcinogenesis (Dasbach *et al.*, 1991; Frausto *et al.*, 1998; Silverstein *et al.*, 1999; Myers *et al.*, 2000; Costin and Geman, 2013).

The research goal of this study is to address the lack of understanding in the natural history of HDP and how it progresses during the third trimester of pregnancy by building a mathematical representation of the development and progression of the disease that is parametrized using clinical data. Our DTMC model is easy to communicate and understand, and produces reliable estimations based on patient data from a large cohort and validated trends in disease progression. This model can set a foundation in natural history modeling of HDP by producing data-driven

estimations of risks of disease progression. The estimations of risks will be informative for the care decisions including the timing of delivery faced by clinicians in the care of patients with HDP.

The organization of this chapter is as follows. In Section 2.2, we present the methods in modeling the natural history of HDP. In Section 2.3, we describe the cohort under study, and present the results. Finally, in Section 2.4, we discuss the outcome of this study.

2.2 Methods

In this retrospective observational cohort study, we model the natural progression of HDP with a DTMC, and estimate the transition probabilities based on patient data. The patient data is provided by Maricopa Integrated Health System (MIHS) which is a public healthcare system in Maricopa County of Arizona. Our data includes HDP diagnoses during the prenatal care, and all delivery related diagnoses (including HDP) during the delivery hospitalization. Our cohort includes the pregnant women who sought care at MIHS over the course of prenatal to postpartum period, and gave birth between March 2012 and December 2015. The institutional review board of MIHS approved the study and the use of patient data.

We consider the development of gestational hypertension (GH) and its possible progression into preeclampsia until spontaneous labor arrives during the third trimester of pregnancy that spans 28 weeks of gestation to delivery. We consider two types of preeclampsia differing in severity, namely mild preeclampsia (mPE, preeclampsia without severe features), and severe preeclampsia (sPE, preeclampsia with severe features). This convention is also consistent with the diagnosis coding in the patient data under study. In cases of deliveries with induced labor and cesarean

deliveries prior to labor that are observed in the data, we include the duration of pregnancies only until the gestational age of the intervention into our estimations.

Our cohort includes the women who delivered at a gestational age greater than or equal to 28 weeks. We do not include the women who delivered at gestational ages earlier than 28 weeks, since there were only a few number of such women. We exclude the women that have multiple pregnancy, stillbirth, and missing information on the type and gestational age of delivery. Since the diagnosis of preeclampsia for women with chronic hypertension is difficult and introduces significant risk of misclassification bias, we additionally exclude the women diagnosed with chronic (essential) hypertension (with or without superimposed preeclampsia). As a result, we focus on gestational hypertension together with its progress into preeclampsia. Moreover, we also exclude women diagnosed with secondary hypertension caused mainly by another medical condition such as renal disease, since such conditions are expected to strongly influence blood pressure and the progression of HDP. If a woman has more than one delivery during the time period of the data, we randomly select one of her deliveries to include in our estimations.

Maternal factors such as maternal age and body mass index (BMI) are also considered as candidate inclusion-exclusion criteria. Studies show that the risk of HDP is not significantly affected by advanced maternal age (Sibai *et al.*, 1997; Jacobsson *et al.*, 2004). Besides, less than 4% of the women in our cohort have maternal ages greater than 40. Therefore, we do not exclude women with advanced maternal age. On the other hand, the risk of HDP may be affected by BMI of the mother. However, there is no reliable data on maternal BMI at the beginning of pregnancy to include in our study.

2.2.1 Discrete Time Markov Chain Model

We define the state of the DTMC as the triplet $\boldsymbol{s} = (h, t, d)$. The first dimension h is the maternal health, and $h \in \mathcal{H}$ where $\mathcal{H}$ includes (1) severe preeclampsia (sPE), (2) mild preeclampsia (mPE), (3) gestational hypertension (GH), and (4) no diagnosis of HDP (N). We order maternal health from the most severe (sPE) to the least severe (N), and number them from 1 (=sPE) to 4 (=N). The second dimension t is the gestational age, and $t \in \mathcal{T}$ where $\mathcal{T} = \{28, 29, \ldots, T\}$ and $T = 42$. We include t as a state variable (instead of modeling it as the stage of the Markov chain) so that the DTMC represents natural history with stationary transition probabilities.

We use the third dimension of the state to differentiate between the continuation and the end of pregnancy. As a result, we have $d \in \{P, S\}$ where P denotes being pregnant and S denotes delivering with spontaneous labor. To sum up, we define the state space as follows: $\mathcal{S}^{\text{DTMC}} = \{\boldsymbol{s} = (h, t, d) : h \in \mathcal{H}, t \in \mathcal{T}, d \in \{P, S\}\}$. We refer to the states with $d = P$ and $d = S$ as "pregnancy states" and "labor states", respectively. Here, it should be noted that the state definition is extended in the MDP model presented in Chapter 4 to include the modes of delivery that are only possible with interventions to deliver the baby.

The state space $\mathcal{S}^{\text{DTMC}}$ is composed of transient states representing the progression of pregnancy (pregnancy states), and absorbing states representing the end of pregnancy with spontaneous labor (labor states). The only exception to this is for the pregnancy states at the end of post-term pregnancy, i.e., the 42^{nd} week. We treat these states as absorbing states for the completeness of the Markov model, and do not calculate the probabilities of going further from these states since it would be very unlikely to go beyond 42 weeks of gestation. As a result, the set of absorbing states is defined as $\widehat{\mathcal{S}}^{\text{DTMC}} = \{\boldsymbol{s} = (h, t, d) : h \in \mathcal{H}, t \in \mathcal{T}, d = S\} \bigcup \{\boldsymbol{s} = (h, t, d) : h \in \mathcal{H}, t = T, d = P\}$.

Accordingly, the set of transient states is defined as $\mathcal{S}^{\text{DTMC}} \setminus \widehat{\mathcal{S}}^{\text{DTMC}} = \{\boldsymbol{s} = (h, t, d) : h \in \mathcal{H}, t \in \mathcal{T} \setminus \{T\}, d = P\}$.

Figure 2.1 depicts the transitions from a pregnancy state $\boldsymbol{s} = (h, t, P)$ as gestational age proceeds from week t to week t^+ where $t^+ = t+1$. If there is no spontaneous labor at pregnancy state $\boldsymbol{s} = (h, t, P)$, the pregnancy continues with the same or a worse maternal health at gestational age $t + 1$, and the chain reaches a pregnancy state (h', t^+, P) with $h' \leq h$. If spontaneous labor arrives by the end of week t, the pregnancy ends with the same or worse maternal health, and the chain moves to a labor state (h', t^+, S) with $h' \leq h$. Since labor states are absorbing, there is a self-loop from/to the state (h', t^+, S) which occurs with probability one.

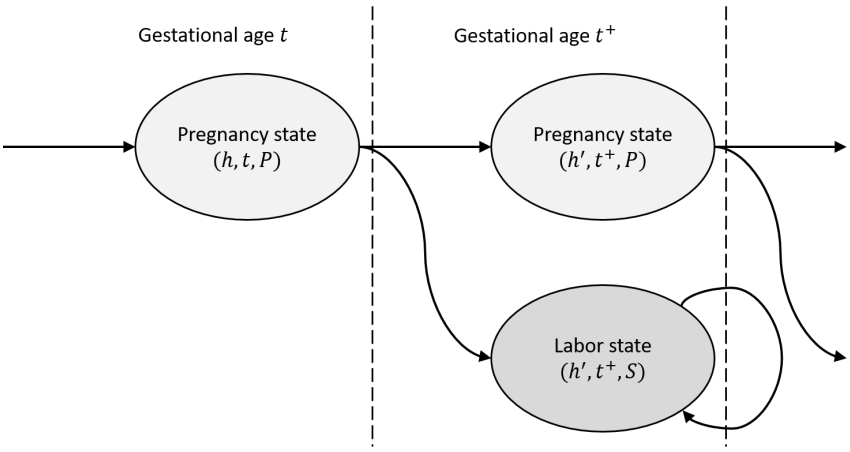

Figure 2.1: Transitions Between the States of DTMC as Gestational Age Increases from Week t to Week $t + 1$

We denote the transition probability from state $\boldsymbol{s} = (h, t, d)$ to $\boldsymbol{s'} = (h', t', d')$ where $\boldsymbol{s}, \boldsymbol{s'} \in \mathcal{S}^{\text{DTMC}}$ with $\mathcal{P}(\boldsymbol{s'}|\boldsymbol{s})$ (or, equivalently $\mathcal{P}(h', t', d'|h, t, d)$). The transitions with a non-zero probability from a pregnancy state only include moving to another pregnancy state or a labor state with the same or a worse maternal health in the next gestational age. Since HDP are progressive disorders, our DTMC does not make transitions to a state with better maternal health in terms of HDP.

As a result, we have $\mathcal{P}(h', t^+, P|h, t, P) = 0$ and $\mathcal{P}(h', t^+, S|h, t, P) = 0$ for all $(h, t, P), (h', t^+, P), (h', t^+, S) \in \mathcal{S}^{\text{DTMC}}$ such that $h' > h$ and $t < 42$. Additionally, we do not allow transitions from week t to any other week than week $t + 1$. For all absorbing states $\boldsymbol{s} \in \widehat{\mathcal{S}}^{\text{DTMC}}$, we have $\mathcal{P}(\boldsymbol{s}|\boldsymbol{s}) = 1$.

2.2.2 The Estimation of Transition Probabilities

The construction of transition probability matrix includes the estimation of conditional probabilities of going from transient pregnancy states $\boldsymbol{s} = (h, t, P)$ to the other pregnancy states $\boldsymbol{s'} = (h', t^+, P)$, or to labor states $\boldsymbol{s'} = (h', t^+, S)$ for $h' \leq h$ and $t < 42$ where $t^+ = t + 1$. To estimate these probabilities, we first construct the path of disease progression for each pregnancy in the cohort under study. At this step, we assume that the maternal health stays as healthy (i.e., $h = \text{N}$) until an HDP diagnosis is made, changes at the time of the diagnosis, and stays the same until a diagnosis of worse maternal health is made.

The diagnosis codes of gestational hypertension, mild and severe preeclampsia are grouped into maternal health according to the state definition of our DTMC. The diagnoses of elevated blood pressure are not taken into account, since blood pressure readings are not sufficient to make an HDP diagnosis. The date of diagnosis is taken as the date of admission, and it is translated into the gestational age of diagnosis (in weeks) by using the gestational age at the time of delivery (in weeks) and the date of delivery in the data. After constructing the paths of disease progression, we count the frequencies of transitions between the states of DTMC in the constructed paths. Finally, we calculate the maximum likelihood estimates and confidence intervals (CIs) of transition probabilities using these frequencies.

We denote $n(\boldsymbol{s}, \boldsymbol{s'})$ as the number of occurrences that a transition happens from state $\boldsymbol{s}$ to state $\boldsymbol{s'}$ in the constructed paths of disease progression for the entire cohort

under study. Then, the maximum likelihood estimate of the probability $\mathcal{P}(\boldsymbol{s'}|\boldsymbol{s})$ is given by Equation (2.1).

$$\widehat{\mathcal{P}}(\boldsymbol{s'}|\boldsymbol{s}) = \frac{n(\boldsymbol{s}, \boldsymbol{s'})}{\sum_{\boldsymbol{s'} \in \mathcal{S}^{\mathrm{DTMC}}} n(\boldsymbol{s}, \boldsymbol{s'})} \tag{2.1}$$

The denominator of the right-hand side of Equation (2.1) is equal to the number of transitions from state $\boldsymbol{s}$ to all other states in $\mathcal{S}^{DTMC}$. Craig and Sendi (2002) describe a similar method of estimation of transition probabilities for the cases in which the observation intervals are the same with the duration of transitions in a Markov model. For the estimate of the probability $\mathcal{P}(\boldsymbol{s'}|\boldsymbol{s})$, we calculate 95% CIs with the adjusted Wald method (Agresti, 1996; Wilson, 1927). In this method, the CI limits are derived by adjusting Wald's formula by adding the squared z-critical value to the denominator, and half of the squared z-critical value to the numerator of the proportion estimate. This method is shown to provide good coverage probabilities when the sample size is not large (Agresti and Coull, 1998; Sauro and Lewis, 2005; Lewis and Sauro, 2006). All calculations are performed using Python programming language.

The HDP diagnoses data set provides the required information to mark the changes in maternal health in paths of disease progression. The maternal outcome data set is used to determine the gestational age of the delivery and the presence of spontaneous labor. The presence of spontaneous labor is determined for each delivery as follows. If it is a vaginal delivery, and there is no element of induced labor (such as dinoprostone) used in the delivery, it is considered as a delivery with spontaneous labor. A cesarean delivery is also considered as a delivery with spontaneous labor, if there is an element of labor augmentation such as artificial rupture of membranes, or a diagnosis code indicating the presence of spontaneous labor. A validated algorithm

to identify laboring women provides the diagnoses codes (Henry *et al.*, 1995; Korst *et al.*, 2004).

Although we have reasonable sample sizes to estimate the probabilities of transitions from pregnancy states with GH and N, instances of data on transitions from pregnancy states with mPE and sPE are quite scarce. Table 2.1 presents the number of observations used in the estimation of probabilities of transitions from the pregnancy state $\boldsymbol{s} = (h, t, P)$ to the pregnancy states $\boldsymbol{s'} = (h', t^+, P)$, or to the labor states (h', t^+, S) with $h' \leq h$. That is, it shows the denominator of Equation (2.1), which can be expanded as follows for all $\boldsymbol{s} = (h, t, P)$ with $t \leq 41$.

$$\sum_{\boldsymbol{s'} \in \mathcal{S}^{\mathrm{DTMC}}} n(\boldsymbol{s}, \boldsymbol{s'}) = \sum_{h' \leq h} \left[n(h', t^+, P|h, t, P) + n(h', t^+, S|h, t, P) \right] \tag{2.2}$$

According to Table 2.1, the sample sizes for pregnancy states with mPE and sPE vary between 0 and 21. For four particular pregnancy states (i.e., $(\mathrm{sPE}, 28, P)$, $(\mathrm{sPE}, 29, P)$, $(\mathrm{sPE}, 41, P)$, $(\mathrm{mPE}, 41, P)$), there are no more than two observations. On the other hand, the sample sizes for pregnancy states with GH and N vary between 28 and 98, and between 2,631 and 8,154 (for $t \leq 40$), respectively (see GH and N columns of Table 2.1). There is an imbalance in the sample sizes of estimations, and the estimations with low sample size adversely impact the accuracy of natural history model built with our DTMC. As a result, we build and solve an order restricted inference model to improve the estimations with small sample size with the help of the estimations with larger sample size and the order relations between both types of estimates. The order relations are established with the observed trends in the data and clinical experience. We include the observations at gestational week 27 into the calculations since they help in the estimations of following weeks through order relations.

Gestational age	Number of observations			
	sPE	mPE	GH	N
27	1	2	27	8,270
28	2	4	28	8,258
29	1	4	35	8,244
30	4	5	36	8,230
31	4	7	46	8,199
32	6	8	53	8,154
33	6	13	57	8,101
34	6	19	74	7,991
35	12	16	81	7,836
36	12	21	98	7,476
37	9	19	98	6,726
38	7	6	91	5,308
39	13	5	50	2,631
40	5	5	26	768
41	0	1	3	57

Table 2.1: The Number of Observations at Pregnancy States Used in the Estimations of Transition Probabilities

2.2.3 Order Restricted Inference Model

Maximum likelihood estimation of ordered multinomial parameters are obtained with order restricted inference (ORI) models which maximize the likelihood function subject to the constraints imposing order restrictions by treating multinomial probabilities as variables (Jewell and Kalbfleisch, 2004; Lim *et al.*, 2009). We build an optimization model (ORI-TPM model) to obtain maximum likelihood estimates of transition probabilities that satisfy the order restrictions. Our goal is to incorporate the observed trends in the data and the clinical experience in the estimation process, and improve the estimations of transition probabilities with low sample size. In this model, we treat transition probabilities as variables allowed to vary within their CIs calculated with the available data.

Although some of the estimations are based on small samples, we are able to observe trends in the estimated transition probabilities with respect to maternal health and gestational age. We have validated these trends with a medical expert with more than 25 years of experience in obstetrics, and confirmed that they can be added as order restrictions in ORI-TPM model. We include the validated trends as constraints that represent order restrictions in the ORI-TPM model. As a result, the ORI-TPM model improves the estimates for transitions with low sample size using the other estimates obtained using higher sample size by considering the medically established order relations.

The decision variables of ORI-TPM model are as follows. $X_{hh't}$ and $Y_{hh't}$ are the estimates of $\mathcal{P}(h', t^+, P|h, t, P)$ and $\mathcal{P}(h', t^+, S|h, t, P)$ for all $h, h' \in \mathcal{H}$, $t \in \mathcal{T}$ and $t \leq T-1$ where $t^+ = t+1$, respectively. That is, $X_{hh't}$ is the estimate of the probability of maternal health to change from h to h' at gestational age t as pregnancy continues by one week, and $Y_{hh't}$ is the estimate of the probability of having spontaneous labor with the same or different maternal health at gestational age t.

As input parameters, ORI-TPM model requires upper and lower bounds of CIs, and the number of observed transitions from state (h, t, P) to state (h', t^+, P), or to state (h', t^+, S). The notation used for the parameters are as follows.

$m_{hh't}$: The number of observed transitions from state (h, t, P) to state (h', t^+, P)

$n_{hh't}$: The number of observed transitions from state (h, t, P) to state (h', t^+, S)

$L^X_{hh't}$: Lower bound of the CI for estimate of $\mathcal{P}(h', t^+, P|h, t, P)$

$U^X_{hh't}$: Upper bound of the CI for estimate of $\mathcal{P}(h', t^+, P|h, t, P)$

$L^Y_{hh't}$: Lower bound of the CI for estimate of $\mathcal{P}(h', t^+, S|h, t, P)$

$U^Y_{hh't}$: Upper bound of the CI for estimate of $\mathcal{P}(h', t^+, S|h, t, P)$

The objective is to maximize the likelihood function given in Equation (2.3). Equivalently, we maximize the logarithm of this likelihood function which is given in Equation (2.4).

$$\text{Maximize } \mathcal{L} = \prod_{h\in\mathcal{H}} \prod_{h'\in\mathcal{H}} \prod_{t<T} (X_{hh't})^{m_{hh't}} \times (Y_{hh't})^{n_{hh't}} \tag{2.3}$$

$$\text{Maximize } \log \mathcal{L} = \sum_{h\in\mathcal{H}} \sum_{h'\in\mathcal{H}} \sum_{t<T} m_{hh't} \log(X_{hh't}) + \sum_{h\in\mathcal{H}} \sum_{h'\in\mathcal{H}} \sum_{t<T} n_{hh't} \log(Y_{hh't}) \tag{2.4}$$

The constraints of the model are enumerated as follows.

1. The estimates should be within the given lower and upper bounds.

   $L^X_{hh't} \leq X_{hh't} \leq U^X_{hh't}$ for $h, h' \in \mathcal{H}$, $t \in \mathcal{T}$, and $t \leq T-1$

   $L^Y_{hh't} \leq Y_{hh't} \leq U^Y_{hh't}$ for $h, h' \in \mathcal{H}$, $t \in \mathcal{T}$, and $t \leq T-1$

2. The probability of maternal health to get better as gestational age increases is zero.

   $X_{hh't} = 0$ for $h, h' \in \mathcal{H}$, $h < h'$, $t \in \mathcal{T}$, and $t \leq T-1$

   $Y_{hh't} = 0$ for $h, h' \in \mathcal{H}$, $h < h'$, $t \in \mathcal{T}$, and $t \leq T-1$

3. The sum of transition probabilities from a pregnancy state is equal to one.

   $\sum_{h'\in\mathcal{H}} \{X_{hh't} + Y_{hh't}\} = 1$ for $h \in \mathcal{H}$, $t \in \mathcal{T}$, and $t \leq T-1$

4. The worse the maternal health h is at a given gestational age t, the more likely that the maternal health will become even worse. For instance, the probability for a woman with GH to develop mPE (or sPE) is higher than the same for

a woman with no hypertensive problems. Similarly, the probability for a woman with mPE to develop sPE is higher than the same for a woman with GH.

$X_{41t} + Y_{41t} \leq X_{31t} + Y_{31t}$ for $t \in \mathcal{T}$, $t \leq T-1$

$X_{42t} + Y_{42t} \leq X_{32t} + Y_{32t}$ for $t \in \mathcal{T}$, $t \leq T-1$

$X_{31t} + Y_{31t} \leq X_{21t} + Y_{21t}$ for $t \in \mathcal{T}$, $t \leq T-1$

5. The probability for a woman with no HDP to develop a type of HDP (GH, mPE, or sPE) increases as gestational age increases.

$X_{43t} + Y_{43t} \leq X_{43t^+} + Y_{43t^+}$ for $t \in \mathcal{T}$, $t \leq T-2$

$X_{42t} + Y_{42t} \leq X_{42t^+} + Y_{42t^+}$ for $t \in \mathcal{T}$, $t \leq T-2$

$X_{41t} + Y_{41t} \leq X_{41t^+} + Y_{41t^+}$ for $t \in \mathcal{T}$, $t \leq T-2$

6. The probability for a woman with GH to develop mPE (or sPE) increases as gestational age increases.

$X_{31t} + Y_{31t} \leq X_{31t^+} + Y_{31t^+}$ for $t \in \mathcal{T}$, $t \leq T-2$

$X_{32t} + Y_{32t} \leq X_{32t^+} + Y_{32t^+}$ for $t \in \mathcal{T}$, $t \leq T-2$

7. The probability for a woman with mPE to develop sPE increases as gestational age increases.

$X_{21t} + Y_{21t} \leq X_{21t^+} + Y_{21t^+}$ for $t \in \mathcal{T}$, $t \leq T-2$

8. The probability of spontaneous labor increases as gestational age increases.

$Y_{44t} + Y_{43t} + Y_{42t} + Y_{41t} \leq Y_{44t^+} + Y_{43t^+} + Y_{42t^+} + Y_{41t^+}$ for $t \in \mathcal{T}$, $t \leq T-2$

$Y_{33t} + Y_{32t} + Y_{31t} \leq Y_{33t^+} + Y_{32t^+} + Y_{31t^+}$ for $t \in \mathcal{T}$, $t \leq T-2$

$Y_{22t} + Y_{21t} \leq Y_{22t^+} + Y_{21t^+}$ for $t \in \mathcal{T}$, $t \leq T-2$

$Y_{11t} \leq Y_{11t^+}$ for $t \in \mathcal{T}$, $t \leq T-2$

9. The probability of spontaneous labor increases with deteriorating maternal health at a given gestational age t.

$$Y_{44t} + Y_{43t} + Y_{42t} + Y_{41t} \leq Y_{33t} + Y_{32t} + Y_{31t} \quad \text{for } t \in \mathcal{T},\ t \leq T-1$$

$$Y_{33t} + Y_{32t} + Y_{31t} \leq Y_{22t} + Y_{21t} \quad \text{for } t \in \mathcal{T},\ t \leq T-1$$

$$Y_{22t} + Y_{21t} \leq Y_{11t} \quad \text{for } t \in \mathcal{T},\ t \leq T-1$$

10. Non-negativity constraints.

$$X_{hh't},\ Y_{hh't} \geq 0 \quad \text{for } h, h' \in \mathcal{H},\ t \in \mathcal{T}, \text{ and } t \leq T-1$$

We implement the ORI-TPM model in AMPL (A Modeling Language for Mathematical Programming), and solve it with one of AMPL's nonlinear solvers (Knitro). The output of the ORI-TPM model is the order restricted estimation of transition probabilities of the DTMC model.

We validate the ORI-TPM model by simulating the disease progression with the transition probabilities estimated using the ORI-TPM model. We build a simulation model in which we superimpose the decision of intervention to deliver the baby prior to spontaneous labor with the goal of reflecting what is happening in practice. We run the simulation model 1,000 times with 8,300 women (total number of women in the data included in probability estimations), and construct the CIs of numbers of women observed at each pregnancy state. The ORI-TPM model is validated by confirming that the numbers of women observed at pregnancy states in the patient data generally fall within the CIs constructed with the simulations.

Figure 2.2 shows the plots drawn for the validation of the ORI-TPM model. Each plot is drawn for the number of women observed at pregnancy states with a given maternal health (N, GH, mPE, and sPE). In these plots, solid lines show the number of women observed in the data, and dashed lines show the average number of women

observed in the simulations. Gray vertical lines are the error bars depicting the CIs of numbers of women observed at each pregnancy state that are built with simulations. The error bars at the top plot are very small due to high sample sizes, and as a result, they are not visible. According to the plots of Figure 2.2, the numbers of women observed at pregnancy states in the patient data generally fall within the CIs built with the simulations.

2.3 Results

The patient data under study has HDP diagnosis and delivery outcome information on 10,248 pregnancies. After the exclusions given in Figure 2.3, the number of pregnancies included in the calculations is 8,300. Out of 8,300 women, 1,231 (14.8%) women developed gestational hypertension and/or preeclampsia. Table 2.2 demonstrates the demographics of the study population under study. The study population mostly includes Hispanic or Latina women regarding race and ethnicity, and mostly Medicaid-paid births since the data source is a safety-net institution in the Southwest of U.S.

Using the estimated transition probabilities of DTMC, we calculate the risks of worsening maternal health (in terms of HDP) as gestational age proceeds by one week. Figure 2.4 shows the estimated probabilities for a woman with no HDP (i.e., $h = \text{N}$ at gestational age t) to develop GH, mPE, or sPE ($h = \text{GH, mPE, or sPE}$ at gestational age $t^+ = t + 1$) in each gestational age. In this figure, the probability of developing GH is calculated with the sum $\mathcal{P}(\text{GH}, t^+, P|\text{N}, t, P) + \mathcal{P}(\text{GH}, t^+, S|\text{N}, t, P)$ for a given gestational age t ($t \leq 41$). That is, it is calculated as the sum of the probability of developing GH as pregnancy continues at gestational week t, and the probability of developing GH and having spontaneous labor within gestational week t. The probabilities of developing mPE and sPE are calculated similarly.

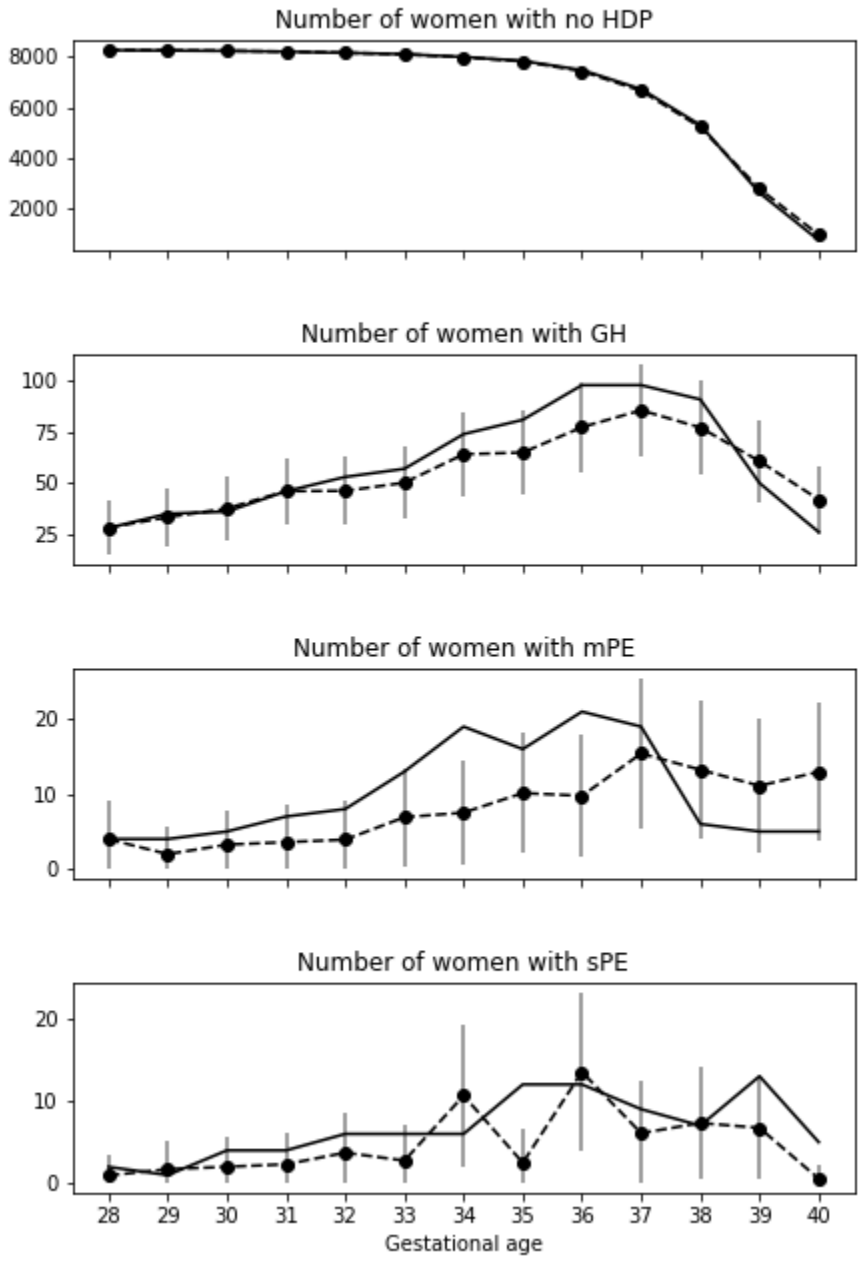

Figure 2.2: The Number of Women Observed in the Data (Solid Black Lines), and Average Number of Women Observed in the Simulations (Dashed Black Lines) Together with Their CIs (Vertical Gray Lines)

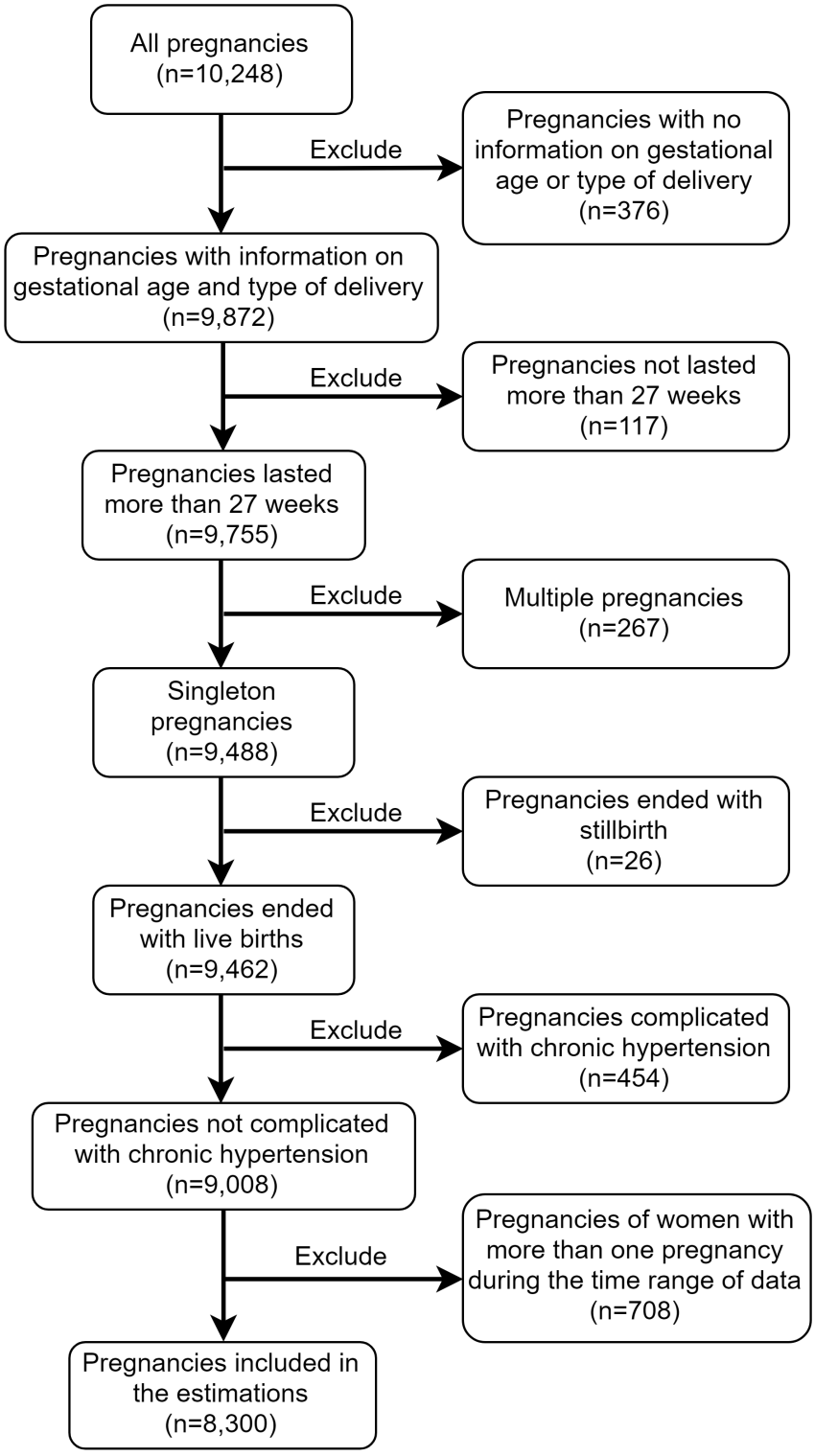

Figure 2.3: Summary of the Application of Exclusion Criteria

Variable	Number of observations (%)
Maternal Age	
<20	745 (9.0%)
20-24	1,839 (22.2%)
25-29	2,041 (24.6%)
30-34	1,981 (23.9%)
≥35	1,689 (20.3%)
Unknown	5 (0.1%)
Race and Ethnicity	
Asian	199 (2.4%)
Black or African American	722 (8.7%)
White/Caucasian	680 (8.2%)
Hispanic/Latino	6,390 (77.0%)
Other	119 (1.4%)
Unknown	190 (2.3%)
Smoking	
Smoker	388 (4.7%)
Non-smoker	7,912 (95.3%)
Insurance Status	
Private insurance/government payer	424 (5.1%)
Medicaid	6,743 (81.2%)
Self-pay	1,128 (13.6%)
Unknown	5 (0.1%)
Marital Status	
Married	3,494 (42.1%)
Not married	4,733 (57.0%)
Unknown	73 (0.9%)

Table 2.2: Demographics of the Study Population

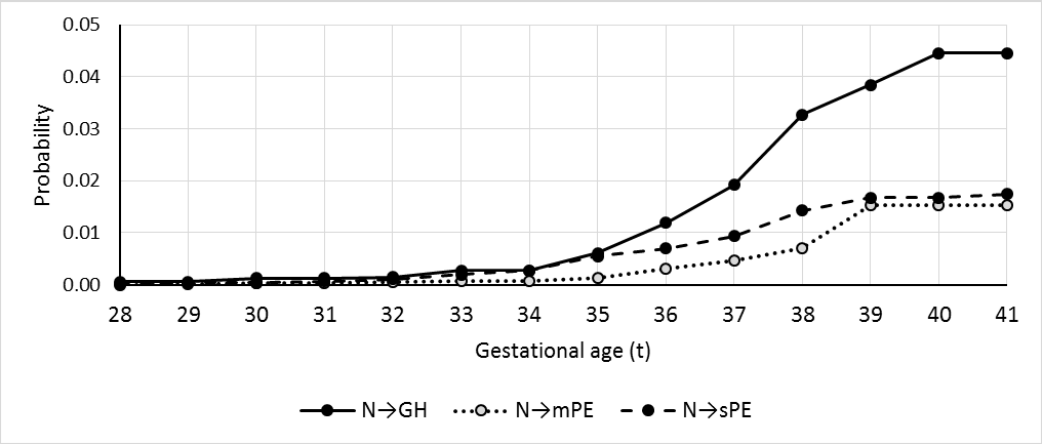

Figure 2.4: The Estimated Probabilities of Developing HDP for a Woman with No HDP

"N $\rightarrow$ GH" denotes the event of developing GH when there is no diagnosis of hypertensive disorders. "N $\rightarrow$ mPE" and "N $\rightarrow$ sPE" denote the same for mPE and sPE, respectively.

Additionally, we calculate the risk of developing preeclampsia for a woman with GH as the gestational age advances by one week. Figure 2.5 demonstrates the estimated probabilities for a woman with GH to develop preeclampsia. In this figure, the probability of developing mPE is calculated with the sum $\mathcal{P}(\text{mPE}, t^+, P|\text{GH}, t, P) + \mathcal{P}(\text{mPE}, t^+, S|\text{GH}, t, P)$ for a given gestational age t ($t \leq 41$). That is, it is calculated as the sum of the probability of developing mPE from GH as pregnancy continues at gestational week t, and the probability of developing mPE from GH and having spontaneous labor within gestational week t. The probabilities of developing sPE are calculated similarly. The probability of developing preeclampsia is calculated by adding the probabilities of developing mPE or sPE with or without spontaneous labor. As a result, each point corresponds to the sum $\mathcal{P}(\text{mPE}, t^+, P|\text{GH}, t, P) + \mathcal{P}(\text{sPE}, t^+, P|\text{GH}, t, P) + \mathcal{P}(\text{mPE}, t^+, S|\text{GH}, t, P) + \mathcal{P}(\text{sPE}, t^+, S|\text{GH}, t, P)$ for a given gestational age t.

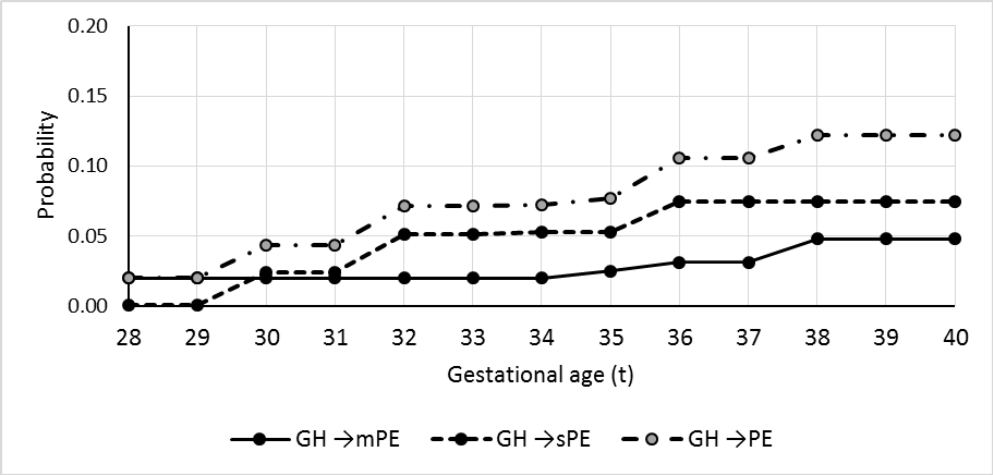

Figure 2.5: The Estimated Probabilities of Developing Preeclampsia for a Woman With GH.

"GH → mPE" denotes the event of developing mPE when there is a diagnosis of GH. "GH → sPE" and "GH → PE" denote the same for sPE and preeclampsia (PE), respectively.

Finally, we calculate the probabilities of having spontaneous labor to explore the impact of HDP on the chances of spontaneous labor. Figure 2.6 shows the estimated probabilities of having spontaneous labor as gestational age proceeds by one week when a woman has N, GH, mPE, or sPE. The probability of spontaneous labor is calculated by summing up the probabilities of going into spontaneous labor with or without deteriorating maternal health. For instance, the probability of having spontaneous labor with GH is calculated with the sum $\mathcal{P}(\text{GH}, t^+, S|\text{GH}, t, P) + \mathcal{P}(\text{mPE}, t^+, S|\text{GH}, t, P) + \mathcal{P}(\text{sPE}, t^+, S|\text{GH}, t, P)$. That is, it is calculated as the sum of the probability of continuing GH and having spontaneous labor within gestational week t, and the probability of developing mild or severe preeclampsia from GH and having spontaneous labor within gestational week t.

Figure 2.4 shows how the risks of developing GH, mPE and sPE increase with gestational age for a normotensive woman as imposed by the order restrictions. Ac-

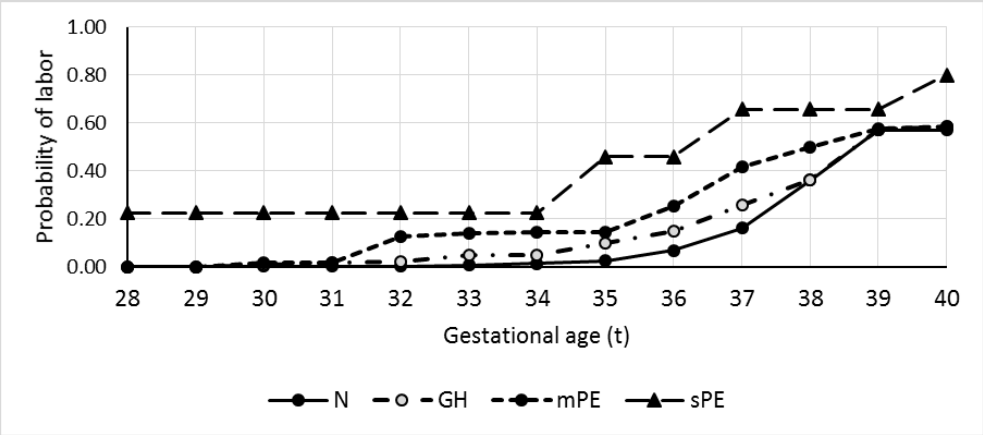

Figure 2.6: The Estimated Probabilities of Having Spontaneous Labor When the Maternal Health Is N, GH, mPE, or sPE

cording to these estimations, the risks increase more rapidly between 35 and 38 weeks of gestation. Additionally, the estimated risk of developing GH is higher than the same of sPE and mPE at any gestational age, which is not included as an order restriction. Figure 2.5 depicts how the risks of developing mPE and sPE increase with gestational age for a woman with GH as imposed by the order restrictions. In this figure, the estimated risk of developing sPE is mostly higher than the same of mPE, which is not included as an order restriction. Figure 2.6 demonstrates how the presence of a type of HDP increases the risk of preterm labor.

Figures 2.7-2.9 show the risks calculated with the maximum likelihood estimates of DTMC's transition probabilities without order restrictions. It is worthwhile to note that the results depicted in Figures 2.8 and 2.9 show significant fluctuations due to the limited number of observations. The ORI model helps us improve the estimations by removing excessive noise and fluctuations that make it hard to come up with meaningful conclusions.

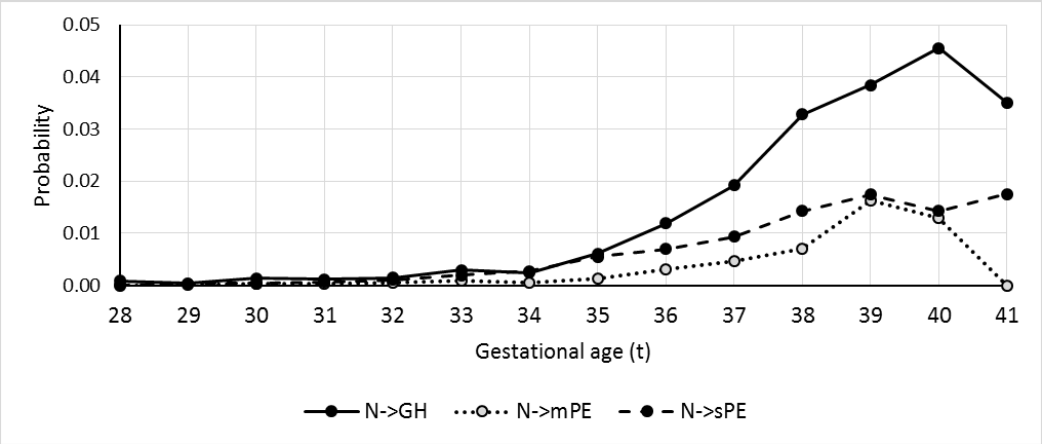

Figure 2.7: The Estimated Probabilities of Developing HDP for a Woman with No HDP Without Order Restrictions

"N → GH" denotes the event of developing GH when there is no diagnosis of hypertensive disorders. "N → mPE" and "N → sPE" denote the same for mPE and sPE, respectively.

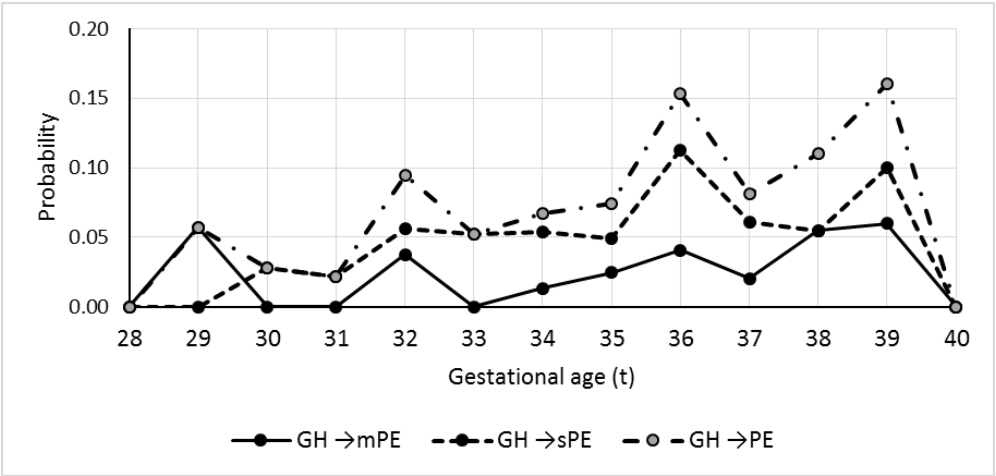

Figure 2.8: The Estimated Probabilities of Developing Preeclampsia for a Woman With GH Without Order Restrictions

"GH → mPE" denotes the event of developing mPE when there is a diagnosis of GH. "GH → sPE" and "GH → PE" denote the same for sPE and PE, respectively.

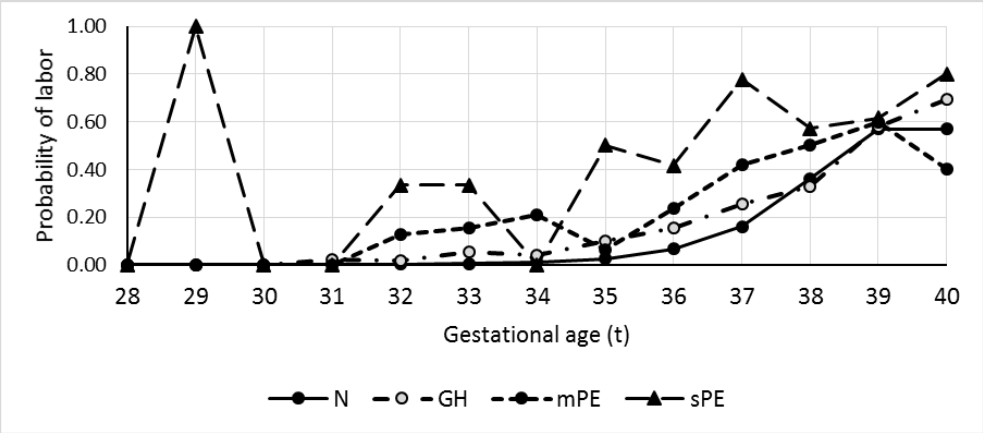

Figure 2.9: The Estimated Probabilities of Having Spontaneous Labor When the Maternal Health Is N, GH, mPE, or SPE Without Order Restrictions

2.4 Conclusions

In this study, we model the natural progression of HDP in the third trimester of pregnancy with a DTMC, and estimate its transition probabilities with an ORI model that maximizes the likelihood function subject to a set of order restrictions between the transition probabilities. In the estimation of these probabilities, we use data on HDP diagnosis collected during prenatal care spanning 28 weeks of gestation to delivery, and data on delivery admission. The estimated transition probabilities are used to calculate (1) the risk of developing gestational hypertension or preeclampsia for a woman with no HDP, (2) the risk of worsening health by developing preeclampsia for a woman with gestational hypertension, and (3) the probability of developing labor when there is a type of HDP. We present the trends in these risks with respect to gestational age (see Figures 2.4-2.6).

One strength of the study is the use of reasonable population size in the estimations. In addition, the data is obtained from one institution, which limits the bias that may happen due to variations in the diagnosis of HDP. On the other hand, the

limitations of the study include the lack of BMI data, which does not allow us to use BMI in exclusion criteria. Besides, we could not model entire duration of the pregnancy due to limited data on HDP prior to 28 weeks of gestation. Moreover, these results are from a study population that is mostly Hispanic or Latina that sought care with Medicaid, and they may not be generalizable. Studies using data from a wide range of institutions would provide better results regarding generalizability.

Markov chain models are considered as a natural approach to adopt in modeling the natural history of a disease that has a sequence of health states (Welton and Ades, 2005). These models have advantages in healthcare applications such as being simple to develop and communicate. However, the Markovian property can be very limiting for modeling disease progression since it requires transition probabilities to be independent of the factors such as time spent in the current state and the history of past states. These factors are likely to be significant in determining the course of a disease and may allow for further refinement of risk determination. In that case, they can be incorporated into the Markov model by creating additional variables, which can potentially amplify the model size and make the model difficult to parametrize (Siebert *et al.*, 2012). Due to the limited size of our cohort, we could not address this issue. It should be addressed with a larger population study, since an increase in model size would require an increase in total sample size required for probability estimations.

The estimations show how the risk of developing a type of HDP for a woman with no HDP and the risk of developing mild or severe preeclampsia for a woman with gestational hypertension increase with gestational age. Additionally, the estimations demonstrate the magnitude of elevation in the risk of preterm labor due to the presence of gestational hypertension and preeclampsia. The study can be replicated using study populations with different demographics, and the trends in risk estimations can

be used to counsel patients and manage patient care in determining the intensity of follow-up appointments and the timing of possible interventions.

Chapter 3

ASSESSING THE RISKS OF MATERNAL AND NEONATAL MORBIDITY IN HYPERTENSIVE DISORDERS OF PREGNANCY

3.1 Introduction

For making informed decisions in the care of women with hypertensive disorders of pregnancy (HDP), it is essential to shed light on the risks of maternal and neonatal adverse outcomes of childbirth, and how these risks change with respect to gestational age. Such an understanding of the associated risks can help us uncover various trade-offs involved in the decisions of timing and mode of delivery. In this chapter, we assess the risks of maternal and neonatal adverse outcomes of childbirth with respect to gestational age at delivery in two different studies.

In the first study, we estimate the risks of significant morbidities with a composite measure of childbirth morbidity by retrospectively observing a cohort of patients. The measure that we use is childbirth composite morbidity (CCM) rate which is recently introduced by Korst *et al.* (2014). In the second study, we use a provider survey and technique for order performance by similarity to ideal solution (TOPSIS) to assess the safety of child delivery in terms of adverse health outcomes. In this provider survey, the physicians are asked to rate the safety of child delivery with respect to maternal and neonatal adverse outcomes in the cases of different HDP diagnoses, timings and modes of delivery. We evaluate the responses to provider survey with TOPSIS which is a multi-criteria decision-making tool.

The goal of this chapter is to compare either the risk of adverse outcomes of childbirth or the safety of childbirth for the mother and the baby with respect to

the presence of HDP at the time of delivery, gestational age at delivery, and mode of delivery. Therefore, in both studies, the calculations are performed as functions of maternal health (in terms of HDP), gestational age at delivery, and mode of delivery. The methods and results of this chapter are used in parameterizing the Markov decision process (MDP) and the robust MDP models, and supporting the assumptions made to generate results in Chapter 4.

The organization of this chapter is as follows. In Section 3.2, we present the assessment of the risks of maternal and neonatal adverse outcomes with CCM rate. In Section 3.3, we describe and discuss the assessment of childbirth safety with the provider survey. In Section 3.4, we discuss the results and implications of both studies.

3.2 Assessment of the Risks of Childbirth Composite Morbidity

In this retrospective cohort study, our objectives are to quantify the risks of maternal and neonatal adverse outcomes for women diagnosed with HDP with a composite measure of childbirth morbidity, and to compare these risks with respect to the type of HDP at the time of delivery, gestational age, and mode of delivery. The estimated risks of maternal and neonatal adverse outcomes can be used to guide physicians in the decisions of timing and mode of delivery for women diagnosed with HDP. The measure that we adopt in this study is the CCM rate introduced by Korst *et al.* (2014).

3.2.1 Background

There are wide varieties of maternal and neonatal adverse outcomes that may happen due to childbirth. Maternal adverse outcomes of childbirth include but not limited to extended length of postpartum stay, postpartum hemorrhage, postpartum depression, admission to intensive care unit (ICU), perineal tear, need for blood transfu-

sion, placental abruption, uterine rupture, convulsions, pulmonary edema, acute renal failure, acute liver failure, acute respiratory distress, oliguria, liver hemorrhage, disseminated intravascular coagulopathy, HELLP syndrome, neurologic complications, and stroke (Mann *et al.*, 2006; Gregory *et al.*, 2009; Walker *et al.*, 2010; Korst *et al.*, 2014). Neonatal adverse outcomes of childbirth include but not limited to admission to neonatal intensive care unit (NICU), small-for-gestational-age (SGA) infant, puerperal infection, prematurity, low Apgar score, birth trauma, cerebral palsy, neonatal seizures, neonatal sepsis, respiratory distress syndrome, bronchopulmonary dysplasia, transient tachypnea, intracranial hemorrhage, periventricular leukomalacia, retinopathy of prematurity, need for respiratory support, hypoglycemia, and necrotizing enterocolitis (Mann *et al.*, 2006; Gregory *et al.*, 2009; Walker *et al.*, 2010; Howell *et al.*, 2014; Korst *et al.*, 2014).

In obstetrical care, it has been difficult to identify measures to assess the care quality in terms of childbirth morbidity. This difficulty is due to the challenges that there is a wide range of adverse outcomes of childbirth that are rare, and the data availability is often limited (Janakiraman and Ecker, 2010; Boulkedid *et al.*, 2013a). Besides, childbirth hospitalization is unique among other types of hospitalizations, since it includes at least two patients, the mother and the baby (or babies), and trade-offs may arise in the care of both parties (Howell *et al.*, 2014; Korst *et al.*, 2014). To overcome these challenges, Mann *et al.* (2006), Gregory *et al.* (2009), and Korst *et al.* (2014) propose composite measures that can be used to assess, control and compare the quality of obstetrical care within and between hospitals regarding maternal and neonatal health outcomes.

Mann *et al.* (2006) develop three obstetrical quality measures, namely the adverse outcome index (AOI), the weighted adverse outcome index (WAOI), and the severity index (SI) with the help of two consensus development conferences. AOI is defined

as the percentage of deliveries with at least one adverse outcome from a set of six maternal (i.e., maternal death, uterine rupture, ICU admission, return to operating or delivery room, blood transfusion, and perineal tear) and four neonatal (i.e., intrapartum or neonatal death, birth trauma, NICU admission, and low Apgar score) adverse outcomes. WAOI is the weighted AOI, which is calculated by dividing the sum of adverse outcome scores (as weights) of all deliveries by the total number of deliveries. SI is WAOI calculated after excluding the deliveries without an adverse outcome from the set of chosen outcomes. It is calculated by dividing the sum of adverse outcome scores of all deliveries by the number of deliveries with at least one adverse outcome.

Gregory *et al.* (2009) present a list of significant maternal and neonatal childbirth complications, and define an *ideal delivery* as a delivery without any of the complications given in that list. Ideal delivery (ID) rate, the proportion of deliveries without a complication, is proposed as a composite measure of quality in obstetrical care that is easy to use and interpret. Korst *et al.* (2014) expand the list of childbirth complications given by Gregory *et al.* (2009), and improve the notion of composite childbirth morbidity, the presence of any significant maternal or neonatal morbidity during childbirth, by incorporating additional maternal and neonatal complications.

The measure proposed by Korst *et al.* (2014) is the CCM rate which is the proportion of deliveries with at least one significant maternal or neonatal complication. The CCM rate can be interpreted as the reverse of the ID rate. The expanded list of adverse outcomes includes a variety of maternal morbidities such as uterine rupture, high degree perineal laceration, liver failure, kidney failure, postpartum hemorrhage, anesthesia and wound complications, and a variety of neonatal morbidities such as birth trauma and injuries, shock, renal failure, neurological and respiratory complications. Moreover, Korst *et al.* (2014) provide a detailed list of conditions to determine

high-risk deliveries such as malpresentation, maternal kidney and liver disorders, diabetes, heart disease, antepartum bleeding, substance use, fetal intrauterine growth restriction, and fetal congenital anomalies.

There are also other studies that investigate quality measures in obstetrics. Simpson (2005) explores *failure to rescue*, a quality measure of care for surgical patients, as a method to assess quality of care during delivery and improve patient safety in cases of common obstetric complications including eclampsia. This measure is proposed to assess *rescue* processes that include monitoring the patients, timely identification of the complications, appropriateness of the interventions, and role of care team members. Since *failure to rescue* does not measure quality in terms of morbidities, and it includes care factors that is beyond our scope such as role of team members, it is not considered as a candidate measure in our study.

Say *et al.* (2009) propose a set of criteria to identify *maternal near miss* (MNM) (a woman who survives a life-threatening condition), and the use of MNM incidence ratio (the ratio of the number of MNM cases to total number of live births) as a quality indicator in obstetrical care. The criteria to identify MNM cases include clinical and laboratory-based criteria such as respiratory rate and blood creatinine levels. We do not consider MNM incidence ratio as a candidate measure in our study, since it is not possible to calculate it with the available diagnosis data.

In addition to composite measures described before, there are other common obstetric quality measures such as the number of elective deliveries before 39 completed weeks of gestation, and the number of pregnancies without risk factors delivered with cesarean section (Janakiraman and Ecker, 2010). We choose not to discuss these measures in detail since they are not suitable for assessing and comparing the risk of childbirth morbidity for women with risk factors such as HDP. However, we refer interested readers to Janakiraman and Ecker (2010) and Boulkedid *et al.* (2013a) for

detailed discussions of obstetrical quality measures, and to Boulkedid *et al.* (2013b) and Sibanda *et al.* (2013) for the latest efforts on reaching a consensus on the use of quality indicators in obstetrical care.

3.2.2 Methods

In this study, our focus is on gestational (pregnancy induced) hypertension (GH) as well as its possible progression into preeclampsia. There are two forms of preeclampsia; namely, mild preeclampsia (mPE, preeclampsia without severe features), and severe preeclampsia (sPE, preeclampsia with severe features). As a convention, we use the terms mild and severe to classify the severity of preeclampsia, which is in line with the medical diagnosis coding in the patient data we use in this study.

The source of our clinical data is Maricopa Integrated Health System (MIHS). MIHS is a public healthcare system serving as a safety net for the underserved population from diverse cultures in Maricopa County of Arizona. The data under study include pregnant women who received care from prenatal to postpartum period, and gave birth at MIHS between March 2012 and August 2015. The electronic medical records at MIHS are initiated in March 2012. We do not use the data after August 2015, since MIHS started to use ICD-10 coding system after that month, and the measure we adopt is based on ICD-9 codes. This study is approved by the institutional review board of MIHS. The data sets and their contents are as follows:

- *HDP diagnoses data set* includes the diagnoses related to HDP from the prenatal to the postpartum period. It contains the dates (both admission and discharge) and codes of all HDP related diagnoses.

- *Maternal outcome data set* includes maternal discharge and encounter diagnoses of visits and admissions from prenatal to postpartum period. It also contains

information on the type and gestational age of deliveries, and the administration of medications and procedures for induction and augmentation of labor.

- *Neonatal outcome data set* includes discharge and encounter diagnoses made for the neonates since their birth. It also includes information on Apgar scores, neonatal demise, and stillbirth.

- *Blood transfusion data set* includes maternal blood transfusion events during the delivery admission. It also provides information on the date and amount of blood transfusions.

- *ICU admissions data set* includes maternal admissions to ICU during the delivery admission. It contains information on the diagnoses of admissions, and the dates of admission and discharge.

- *NICU admissions data set* includes admissions to NICU following the delivery. It contains information on the diagnoses of admissions, and the dates of admission and discharge.

The data sets are linked together through mother and baby identifiers. Figure 3.1 summarizes the exclusion criteria used in our study. The deliveries with missing information on gestational age or type of delivery are excluded from the study. In addition, we exclude the deliveries with gestational age less than or equal to 32 weeks, since the sample sizes are too small to provide reliable estimates. Multiple deliveries and deliveries with stillbirth are also excluded, and as a result, only live singleton deliveries are included. Moreover, we exclude the deliveries of pregnant women diagnosed with chronic hypertension to reduce misclassification bias. If a woman has given birth more than once during the time range of data, we randomly choose one of her deliveries, and include that delivery in our study.

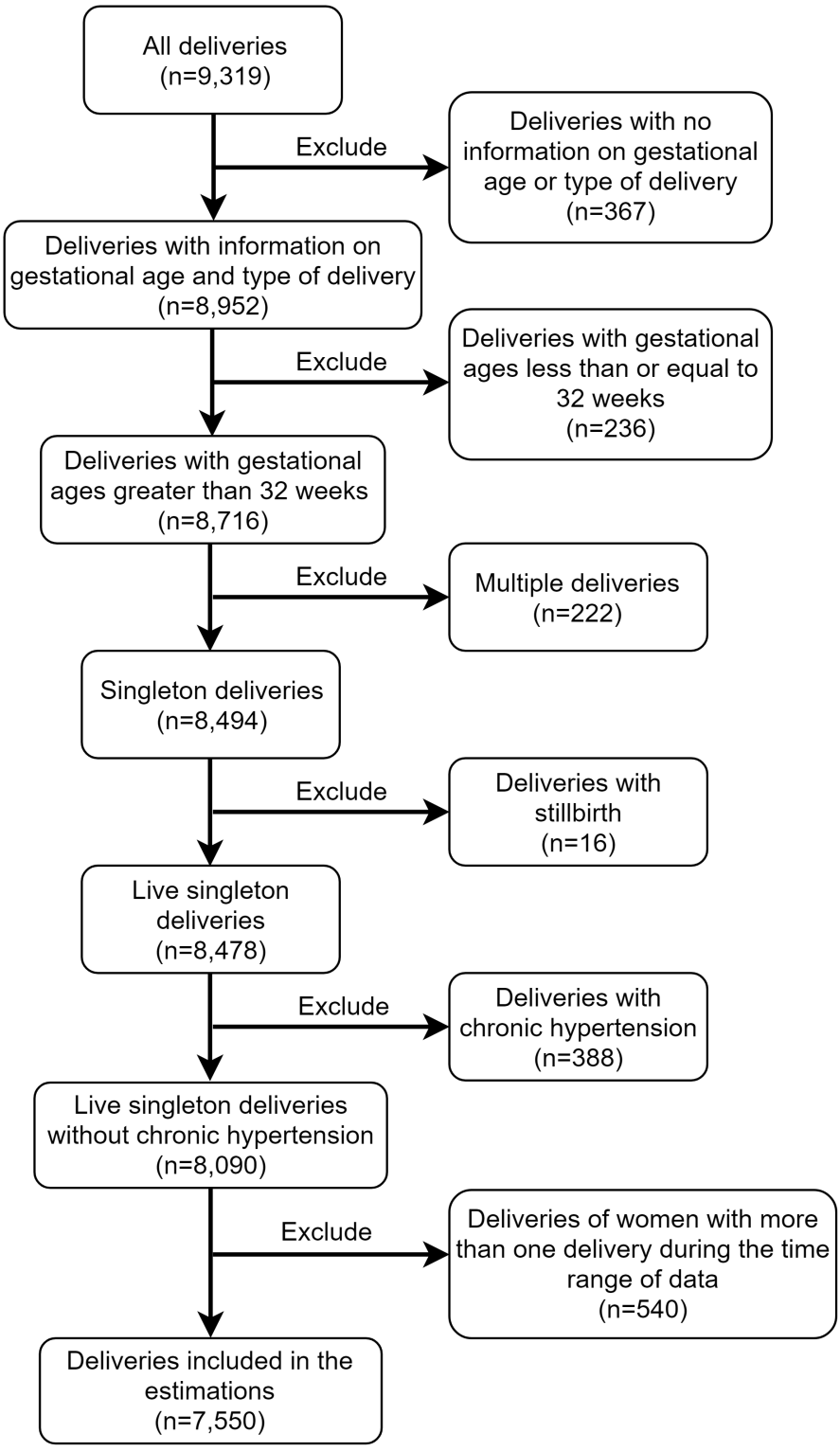

Figure 3.1: Summary of the Application of Exclusion Criteria

The deliveries are grouped into three categories as follows: (i) delivery following spontaneous labor, (ii) delivery following induced labor, and (iii) cesarean delivery with no labor. The motivation behind such a grouping is to assess the difference in risks of morbidity produced by the delivery decision of waiting for spontaneous labor, inducing labor, or delivering with cesarean delivery prior to labor. This grouping is implemented by determining the presence and the type of labor with the use of the variables type of delivery (vaginal or cesarean delivery), element(s) of induced labor, and element(s) of labor augmentation in the maternal outcome data set, and ICD-9 diagnosis codes in the maternal and neonatal outcome data sets. The diagnosis codes are obtained from a validated algorithm to determine patients who labored (Henry *et al.*, 1995; Korst *et al.*, 2004).

Figure 3.2 summarizes how the available data is used for grouping deliveries. If at least one element of induced labor is used in a delivery (e.g., dinoprostone, and oxytocin for induction), it is included in the group "delivery following induced labor" whether or not it is a vaginal or a cesarean delivery. A delivery is included in the group "delivery following spontaneous labor" if it is a vaginal delivery without induced labor. It is also included in the group "delivery following spontaneous labor," if it is a cesarean delivery in which at least one element of labor augmentation (e.g., artificial rupture of membranes, and oxytocin for augmentation) is used, or if it is a cesarean delivery with at least one diagnosis code indicating labor. A delivery is included in the group "cesarean delivery with no labor," if it is a cesarean delivery, and there is no indication for induced or spontaneous labor.

Korst *et al.* (2014) define a composite outcome as the occurrence of any significant morbidity or mortality for mother or neonate due to childbirth. Accordingly, the CCM rate is calculated as the percentage of deliveries with a composite outcome. We disaggregate the definition of composite outcome to be able to estimate the risks of

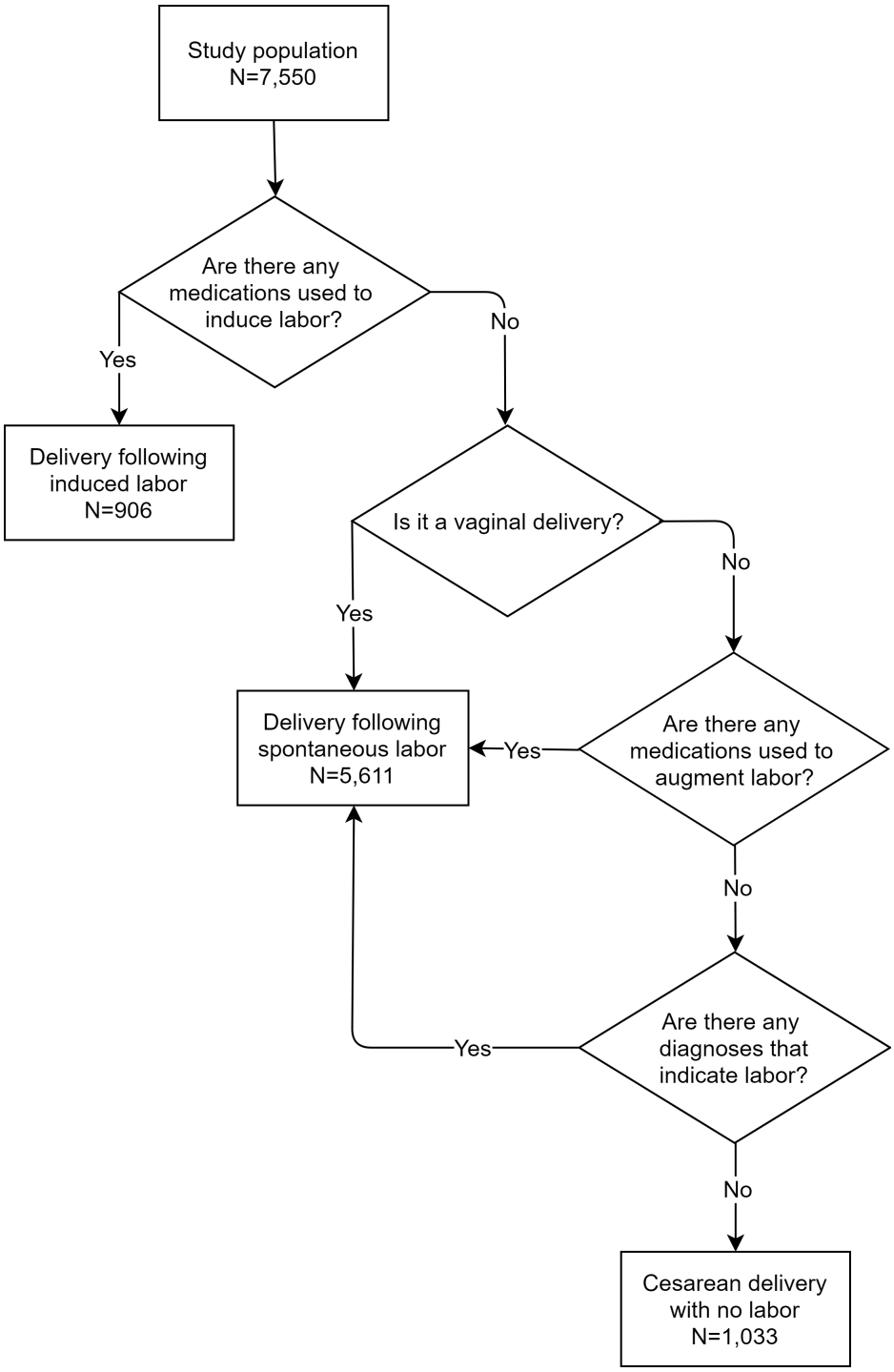

Figure 3.2: Flow Algorithm for the Classification of Delivery Groups

adverse outcomes separately for the mother and the neonate. We define *maternal composite outcome* as the occurrence of any significant morbidity or mortality to mother due to childbirth. Similarly, we define *neonatal composite outcome* as the occurrence of any significant morbidity or mortality to neonate due to childbirth. The maternal (neonatal) CCM rate is calculated as the fraction of deliveries with a maternal (neonatal) composite outcome.

Korst *et al.* (2014) provide tables of maternal and neonatal morbidities included in the calculation of CCM rate together with their ICD-9 diagnosis codes. The deliveries with at least one diagnosis of significant maternal morbidity are identified using the provided diagnosis codes, and maternal outcome data set. The same procedure is repeated with the diagnosis codes provided for neonatal morbidities, and neonatal outcome data set. Korst *et al.* (2014) additionally provide procedure codes that indicate maternal blood transfusion, maternal ICU admission (e.g., mechanical ventilation and circulatory monitoring), and NICU admission (e.g., arterial catheterization and gavage feeding) in the calculation of CCM rate. The available data sets in this study do not include such procedure codes. However, we include the records in the data sets of maternal blood transfusion events, ICU admissions, and NICU admissions in our calculation of maternal and neonatal composite outcomes in place of procedure codes.

The presence of maternal and neonatal composite outcomes is determined separately for each delivery. A delivery has a maternal composite outcome if the mother is diagnosed with at least one of the significant maternal morbidities listed by Korst *et al.* (2014), is admitted to ICU, has a blood transfusion, or dies due to delivery. Maternal mortality is not included in our calculations, since there is no such case during the time period of the data. Similarly, a delivery has a neonatal composite outcome if the neonate is diagnosed with at least one of the significant neonatal mor-

bidities listed by Korst *et al.* (2014), the neonate is admitted to NICU, or it is a case of neonatal demise.

We divide the cohort under study into subgroups with respect to the type of HDP at delivery (i.e., no HDP, GH, mPE, and sPE), gestational age at delivery, and delivery group. We gather gestational ages greater than 32 weeks into five non-overlapping groups (i.e., 33-34, 35-36, 37-38, 39-40, and 41-42 weeks) to increase the sample size in each estimation. We calculate maternal and neonatal CCM rates for each subgroup.

Each calculated maternal (neonatal) CCM rate is treated as an individual binomial proportion for which the success probability is the probability of having a maternal (neonatal) composite outcome. As a result, we are able to construct 95% confidence intervals (CIs) around the probability of having these outcomes. Adjusted Wald method is adopted in the construction of CIs, since it provides good coverage probabilities for small samples (Agresti and Coull, 1998; Sauro and Lewis, 2005; Lewis and Sauro, 2006).

Wilson's estimates, the midpoints of adjusted Wald intervals, are also calculated as better point estimates for small samples (Lewis and Sauro, 2006). The formulas of Wilson's estimate ($\hat{p}_w$, or $\hat{p}'_w$) and $100(1-\alpha)\%$ adjusted Wald interval (Wilson, 1927; Agresti, 1996) for a sample size of $n > 0$ are given in Equations (3.1) and (3.2) when the constructed CIs fall within the natural limits of [0,1], and in Equations (3.3) and (3.4) when the case is otherwise. In these equations, x denotes the number of successes, and z denotes the z-score of standard normal distribution.

$$\hat{p}_w = \frac{x + z^2_{\alpha/2}/2}{n + z^2_{\alpha/2}} \tag{3.1}$$

$$CI = \left(\hat{p}_w - z_{\alpha/2} \sqrt{\frac{\hat{p}_w(1-\hat{p}_w)}{n + z^2_{\alpha/2}}}, \hat{p}_w + z_{\alpha/2} \sqrt{\frac{\hat{p}_w(1-\hat{p}_w)}{n + z^2_{\alpha/2}}} \right) \tag{3.2}$$

$$\hat{p}'_w = \frac{x + z^2_\alpha/2}{n + z^2_\alpha} \tag{3.3}$$

$$CI = \left(0, \hat{p}'_w + z_\alpha \sqrt{\frac{\hat{p}'_w(1-\hat{p}'_w)}{n + z^2_\alpha}} \right), \text{ or } CI = \left(\hat{p}'_w - z_\alpha \sqrt{\frac{\hat{p}'_w(1-\hat{p}'_w)}{n + z^2_\alpha}}, 1 \right) \tag{3.4}$$

In an additional analysis, we construct two multivariable logistic regression models with outcome variables of maternal and neonatal composite outcomes. In both models, the predictor variables are the type of HDP at delivery (i.e., no HDP, GH, mPE, and sPE), gestational age at delivery (i.e., 33-34, 35-36, 37-38, 39-40, and 41-42 weeks), and the delivery group (delivery following spontaneous labor, delivery following induced labor, cesarean delivery with no labor). The base values for the predictor variables are taken as no HDP, 39-40 weeks of gestation, and delivery following spontaneous labor. We use JMP 12 statistical software for the construction of these models, and report the results as odds ratios (ORs) with their 95% CIs. JMP 12 calculates CIs on ORs as likelihood ratio based.

3.2.3 Results

In total, we have data on 7,550 live singleton births after the exclusions depicted in Figure 3.1. Our cohort has 370, 170, and 575 women who had sPE, mPE, and GH at the time of delivery, respectively. In total, 1,115 deliveries from a total of 7,550 deliveries have a diagnosis of HDP. As a result, 14.8% of deliveries are used to estimate the CCM rates with HDP. Table 3.1 gives demographics of our cohort which mostly includes Hispanic or Latina women who receive care with Medicaid.

Variable	Number of observations (%)
Maternal Age	
<20	680 (9.0%)
20-24	1,673 (22.2%)
25-29	1,850 (24.5%)
30-34	1,788 (23.7%)
≥35	1,554 (20.6%)
Unknown	5 (0.1%)
Race and Ethnicity	
Asian	184 (2.4%)
Black or African American	657 (8.7%)
White/Caucasian	605 (8.0%)
Hispanic/Latino	5,836 (77.3%)
Other	96 (1.3%)
Unknown	172 (2.3%)
Smoking	
Smoker	355 (4.7%)
Non-smoker	7,195 (95.3%)
Insurance Status	
Private insurance/government payer	347 (4.6%)
Medicaid	6,193 (82.0%)
Self-pay	1,006 (13.3%)
Unknown	4 (0.1%)
Marital Status	
Married	3,202 (42.4%)
Not married	4,288 (56.8%)
Unknown	60 (0.8%)

Table 3.1: Demographics of the Study Population

Tables 3.2 and 3.3 demonstrate how our cohort is distributed among the subgroups determined with the type of HDP at delivery, gestational age at delivery, and delivery group.

Tables 3.4-3.6 and 3.7-3.9 show the values of Wilson's estimates together with adjusted Wald 95% CIs of the maternal and the neonatal CCM rates calculated for the subgroups of the cohort under study, respectively. The maternal and neonatal

Maternal health	The number of deliveries					
	Wk 33-34	Wk 35-36	Wk 37-38	Wk 39-40	Wk 41-42	Total
sPE	30 (24.0%)[a]	69 (15.6%)	134 (6.6%)	118 (2.8%)	19 (2.6%)	370 (4.9%)
mPE	4 (3.2%)	10 (2.3%)	63 (3.1%)	82 (1.9%)	11 (1.5%)	170 (2.3%)
GH	6 (4.8%)	29 (6.5%)	188 (9.3%)	294 (6.9%)	58 (8.0%)	575 (7.6%)
No HDP	85 (68.0%)	335 (75.6%)	1,632 (80.9%)	3,742 (88.3%)	641 (87.9%)	6,435 (85.2%)
Total	125	443	2,017	4,236	729	7,550

Table 3.2: The Number of Deliveries with Respect to Maternal Health and Gestational Age at Delivery

[a] The percentages of deliveries with a type of HDP among all deliveries with the same gestational age.

CCM rates should be interpreted as the risks of significant maternal and neonatal morbidity, respectively. Tables 3.4-3.6 demonstrate a larger effect of HDP on maternal CCM rates than gestational age, and overall lower maternal CCM rates in those with induced labor than the other delivery groups. Tables 3.7-3.9 show the importance of gestational age on neonatal CCM rates. These trends are tested by the multivariable logistic regression models.

Tables 3.10 and 3.11 present the results obtained with the logistic regression models. The odds ratios for maternal CCM demonstrate that HDP plays a more important role than gestational age in higher occurrence of maternal composite outcome. GH

Delivery group	The number of deliveries		
	Vaginal delivery	Cesarean delivery	Total
Delivery following spontaneous labor	5,136 (91.5%)	475 (8.5%)	5,611
Delivery following induced labor	742 (81.9%)	164 (18.1%)	906
Cesarean delivery with no labor	-	1,033 (100%)	1,033
Total	5,878 (77.9%)	1,672 (22.1%)	7,550

Table 3.3: The Number of Deliveries with Respect to Our Delivery Classification (Delivery Groups) and Type of Delivery

Maternal health	Wilson's estimates and adjusted Wald 95% CIs				
	Wk 33-34	Wk 35-36	Wk 37-38	Wk 39-40	Wk 41-42
sPE	0.40 (0.15-0.65)	0.33 (0.17-0.49)	0.35 (0.23-0.46)	0.32 (0.22-0.42)	0.42 (0.13-0.70)
mPE	0.43 (0.06-0.80)	0.45 (0.16-0.75)	0.33 (0.19-0.48)	0.24 (0.13-0.35)	0.36 (0.08-0.65)
GH	0.18 (0.00-0.40)	0.24 (0.05-0.42)	0.31 (0.23-0.39)	0.28 (0.22-0.35)	0.32 (0.17-0.46)
No HDP	0.15 (0.06-0.24)	0.15 (0.10-0.19)	0.15 (0.13-0.17)	0.19 (0.17-0.20)	0.20 (0.16-0.24)

Table 3.4: Wilson's Estimates and Adjusted Wald 95% CIs of Maternal CCM Rates in the Subgroups with Delivery Following Spontaneous Labor

Maternal health	Wilson's estimates and adjusted Wald 95% CIs				
	Wk 33-34	Wk 35-36	Wk 37-38	Wk 39-40	Wk 41-42
sPE	0.26 (0.04-0.49)	0.24 (0.08-0.40)	0.25 (0.13-0.37)	0.30 (0.15-0.46)	33 (0.06-0.60)
mPE	-	0.37 (0.00-0.78)	0.23 (0.05-0.40)	0.27 (0.08-0.46)	0.24 (0.00-0.53)
GH	-	0.18 (0.00-0.40)	0.17 (0.05-0.28)	0.22 (0.11-0.33)	0.23 (0.05-0.40)
No HDP	0.30 (0.01-0.58)	0.16 (0.03-0.30)	0.10 (0.04-0.15)	0.14 (0.10-0.18)	0.16 (0.11-0.21)

Table 3.5: Wilson's Estimates and Adjusted Wald 95% CIs of Maternal CCM Rates in the Subgroups with Delivery Following Induced Labor

Maternal health	Wilson's estimates and adjusted Wald 95% CIs				
	Wk 33-34	Wk 35-36	Wk 37-38	Wk 39-40	Wk 41-42
sPE	0.50 (0.22-0.78)	0.42 (0.20-0.64)	0.35 (0.16-0.53)	0.42 (0.13-0.70)	0.37 (0.00-0.78)
mPE	0.63 (0.22-1.00)	0.50 (0.09-0.91)	0.14 (0.00-0.32)	0.40 (0.09-0.70)	0.37 (0.00-0.78)
GH	0.37 (0.00-0.78)	0.45 (0.16-0.75)	0.15 (0.03-0.26)	0.30 (0.16-0.44)	0.24 (0.00-0.53)
No HDP	0.37 (0.19-0.55)	0.20 (0.11-0.29)	0.16 (0.11-0.21)	0.15 (0.12-0.18)	0.16 (0.04-0.27)

Table 3.6: Wilson's Estimates and Adjusted Wald 95% CIs of Maternal CCM Rates in the Subgroups with Cesarean Delivery with No Labor

Maternal health	Wilson's estimates and adjusted Wald 95% CIs				
	Wk 33-34	Wk 35-36	Wk 37-38	Wk 39-40	Wk 41-42
sPE	0.10 (0.00-0.23)	0.24 (0.09-0.39)	0.10 (0.03-0.17)	0.12 (0.05-0.19)	0.25 (0.00-0.49)
mPE	0.24 (0.00-0.53)	0.36 (0.08-0.65)	0.09 (0.01-0.18)	0.08 (0.01-0.15)	0.27 (0.01-0.53)
GH	0.33 (0.02-0.64)	0.19 (0.02-0.36)	0.08 (0.03-0.13)	0.08 (0.04-0.12)	0.12 (0.02-0.22)
No HDP	0.22 (0.11-0.32)	0.21 (0.16-0.27)	0.07 (0.05-0.08)	0.06 (0.05-0.07)	0.07 (0.04-0.09)

Table 3.7: Wilson's Estimates and Adjusted Wald 95% CIs of Neonatal CCM Rates in the Subgroups with Delivery Following Spontaneous Labor

Maternal health	Wilson's estimates and adjusted Wald 95% CIs				
	Wk 33-34	Wk 35-36	Wk 37-38	Wk 39-40	Wk 41-42
sPE	0.47 (0.21-0.72)	0.34 (0.17-0.52)	0.23 (0.12-0.35)	0.21 (0.07-0.35)	33 (0.06-0.60)
mPE	-	0.63 (0.22-1.00)	0.23 (0.05-0.40)	0.11 (0.00-0.23)	0.24 (0.00-0.53)
GH	-	0.56 (0.23-0.88)	0.24 (0.11-0.37)	0.22 (0.11-0.33)	0.23 (0.05-0.40)
No HDP	0.50 (0.19-0.81)	0.47 (0.29-0.65)	0.17 (0.10-0.23)	0.13 (0.09-0.16)	0.09 (0.05-0.12)

Table 3.8: Wilson's Estimates and Adjusted Wald 95% CIs of Neonatal CCM Rates in the Subgroups with Delivery Following Induced Labor

Maternal health	Wilson's estimates and adjusted Wald 95% CIs				
	Wk 33-34	Wk 35-36	Wk 37-38	Wk 39-40	Wk 41-42
sPE	0.42 (0.13-0.70)	0.26 (0.06-0.46)	0.27 (0.10-0.44)	0.25 (0.00-0.49)	0.37 (0.00-0.78)
mPE	0.63 (0.22-1.00)	0.71 (0.37-1.00)	0.27 (0.01-0.53)	0.16 (0.00-0.36)	0.37 (0.00-0.78)
GH	0.63 (0.22-1.00)	0.36 (0.08-0.65)	0.12 (0.01-0.22)	0.15 (0.04-0.26)	0.24 (0.00-0.53)
No HDP	0.26 (0.09-0.42)	0.23 (0.14-0.32)	0.15 (0.10-0.20)	0.12 (0.09-0.15)	0.21 (0.08-0.34)

Table 3.9: Wilson's Estimates and Adjusted Wald 95% CIs of Neonatal CCM Rates in the Subgroups with Cesarean Delivery with No Labor

and mPE have very close odds ratios (OR=1.74 for GH, and OR=1.77 for mPE) that are both significant, which indicates that gestational hypertension may lead to maternal adverse outcomes as often as mild preeclampsia. For the occurrence of neonatal composite outcome, HDP is not a significant factor, and earlier gestational ages have the highest significant impact (OR=3.41 for 33-34 weeks, and OR=3.59 for 35-36 weeks).

The comparisons with respect to delivery groups reveal some interesting results. Although induced labor has a significantly lower occurrence of maternal composite outcome than spontaneous labor (OR=0.62), it has a significantly higher risk in terms of neonatal composite outcome (OR=2.39). Cesarean delivery (with no labor) has a lower risk of maternal morbidity (OR=0.87), and a significantly higher risk of neonatal morbidity (OR=1.95) when compared to the delivery following spontaneous labor.

Variable		Maternal	
		OR[a] (95% CI)	P-value[b]
HDP	sPE	2.50 (1.95-3.18)	<.0001
	mPE	1.77 (1.23-2.51)	0.0027
	GH	1.74 (1.41-2.12)	<.0001
	No HDP	Referent	-
Gestational age (weeks)	33-34	1.06 (0.67-1.62)	0.80
	35-36	0.86 (0.66-1.11)	0.26
	37-38	0.82 (0.71-0.94)	0.0057
	39-40	Referent	-
	41-42	1.09 (0.89-1.34)	0.40
Delivery group	Delivery following spontaneous labor	Referent	-
	Delivery following induced labor	0.62 (0.51-0.76)	<.0001
	Cesarean delivery with no labor	0.87 (0.73-1.04)	0.13

Table 3.10: Odds Ratios and P-Values of Predictor Variables in Logistic Regression Model for Maternal Morbidity

[a] ORs are adjusted for all variables (HDP, gestational age and delivery group) included in the model. [b] P-values are based on chi-squared test for nominal variables.

Variable		Neonatal	
		OR[a] (95% CI)	P-value[b]
HDP	sPE	1.28 (0.93-1.74)	0.13
	mPE	1.05 (0.60-1.72)	0.85
	GH	1.23 (0.92-1.62)	0.16
	No HDP	Referent	-
Gestational age (weeks)	33-34	3.41 (2.16-5.24)	<.0001
	35-36	3.59 (2.78-4.62)	<.0001
	37-38	1.17 (0.96-1.43)	0.11
	39-40	Referent	-
	41-42	0.94 (0.69-1.26)	0.69
Delivery group	Delivery following spontaneous labor	Referent	-
	Delivery following induced labor	2.39 (1.92-2.97)	<.0001
	Cesarean delivery with no labor	1.95 (1.58-2.40)	<.0001

Table 3.11: Odds Ratios and P-Values of Predictor Variables in Logistic Regression Model for Neonatal Morbidity

[a] ORs are adjusted for all variables (HDP, gestational age and delivery group) included in the model. [b] P-values are based on chi-squared test for nominal variables.

3.2.4 Conclusions

We examine 7,550 live singleton births with gestational ages 33 to 42 weeks in a retrospective cohort study with the goal of estimating the risks of maternal and neonatal morbidity based on clinical data. We estimate the risks of maternal and neonatal morbidity for the deliveries of women with HDP with a composite measure of childbirth morbidity with respect to the type of HDP at delivery, gestational age at delivery, and delivery group. From these factors, we show the significant contributors to the risks of maternal and neonatal morbidity. The results of this study are for a population that is mostly Hispanic and Medicaid patients.

Our motivations behind using the CCM rate can be summarized as follows. First, it is the most comprehensive composite measure in terms of the variety of adverse outcomes incorporated into the calculation. Secondly, when calculated separately for the mother and the baby, it allows for a natural comparison between the well-being of two parties without any need for adjustments since it is a binary score. Thirdly, the composite outcome can be modeled as a binomial proportion where the success probability is defined as the probability of having such an outcome. Finally, it is easy to interpret and can be calculated with the available data.

Although the CCM rate is found to be the best for this study among available measures, it has shortcomings. The CCM rate accounts for significant morbidities without including the relative severities. In addition, it does not consider comorbidities, i.e., the occurrence of multiple morbidities simultaneously. Since it takes a high number of morbidities into account, it requires more detailed discharge diagnoses data, and it may be more prone to being impacted by coding errors.

The maternal and neonatal CCM rates exhibit mostly expected trends such as being higher for the deliveries with HDP. However, we also have interesting observa-

tions that are not anticipated prior to our study. The CCM rates of mild preeclampsia and gestational hypertension are either close or very close, which points out that gestational hypertension can have manifestations as severe as mild preeclampsia. This observation supports other medical studies such as Buchbinder *et al.* (2002) that call attention to the possible risks of gestational hypertension. It also supports the ACOG Task Force's recommendation to manage gestational hypertension and preeclampsia without severe features similarly ACOG (2013b).

Another interesting observation is that the maternal CCM rates of induced labor are mostly less than the same of cesarean delivery with no labor. They are also mostly less than the same of spontaneous labor for mothers. As a result, induction of labor should be considered as an important option for delivering the baby in the presence of HDP while considering the neonatal impact. Our method may help physicians in the process of deciding timing and mode of delivery by making the trade-offs between maternal and neonatal morbidity more overt.

The results should be interpreted by considering strengths and limitations of our study. We examine a relatively large sample of deliveries in a single institution, which decreases the heterogeneity of clinical practice, and limits the heterogeneity of diagnosis coding on which our results depend. MIHS includes a single practice group, which further decreases the former effect. Moreover, we consider delivery groups that depend not only on the route of delivery but delivery decisions. As a result, we reflect the impact of delivery decisions on the comparisons of risk values. On the other hand, our results may not be generalizable, since our cohort is from one hospital with a population that may not be typical of other institutions. Besides, our study uses composite maternal morbidity and delivery groups, which makes comparisons to other studies that examine cesarean delivery as a maternal outcome of interest challenging.

Our study is one of the few studies which have considered decisions of timing and mode of delivery for maternal and fetal well-being. One early randomized trial has found that induction of labor leads to lower cesarean delivery rates with equivalent neonatal outcomes for post-term pregnancies as opposed to expectant management (Hannah *et al.*, 1992). That study has led to the concept of preventive induction of labor for maternal and fetal considerations. Other studies of expectant management versus induction of labor have reinforced this concept; however, the randomized data was limited to one study (Darney *et al.*, 2013; Nicholson *et al.*, 2015). Parallel to this, there has been an examination of the effect of elective induction prior to 39 weeks of gestation on the increased risk of neonatal morbidity, and as a result, this has become an unacceptable practice (ACOG, 2013a).

HDP are a set of disorders for which non-elective delivery is indicated prior to 39 weeks (ACOG, 2013b), and for which there are randomized trial studies (Koopmans *et al.*, 2009; Broekhuijsen *et al.*, 2015). Our study is largely confirming the results of these recommendations and the studies indicating that mild preeclampsia and gestational hypertension should not undergo delivery prior to 37 weeks due to resulting neonatal morbidity. In line with the preventive induction concept, it may be of interest to assess whether expectant management for those with rises in blood pressure below diagnostic thresholds might benefit from early induction prior to term. Such a study would require comparisons of expectant management versus early delivery as has been suggested by a number of authors (Darney *et al.*, 2013; Zhang *et al.*, 2016).

3.3 Assessment of Childbirth Safety with Provider Survey

In this study, we have conducted a provider survey at MIHS to reveal clinicians' perception of the safety of a child delivery as a function of the presence of HDP at delivery, gestational age at delivery, and mode of delivery. The survey is created in

a way that TOPSIS can be used to quantify the safety of childbirth with respect to maternal and neonatal health outcomes. TOPSIS is a method of multi-criteria decision making that aims to find the best alternative using the distance of alternatives from the *positive ideal solution* (best possible solution) and *negative ideal solution* (worst possible solution) with respect to multiple factors.

3.3.1 Background

First created by Ching-Lai and Yoon (1981), TOPSIS is extended for group decision making in fuzzy environments by Chen (2000) to incorporate human judgments that cannot be estimated exactly with numerical values. In this extension, the importance weights of decision criteria and the ratings of alternative decisions are assessed with linguistic variables instead of exact numerical values by each decision maker. We use this extension of TOPSIS with the goal of comparing and ranking the safety of childbirth under different states of maternal health (in terms of HDP), gestational age at delivery, and mode of delivery with respect to maternal and neonatal health outcomes.

In the preparation phase of the survey, samples of candidate survey questions were given to Dr. Dean Coonrod and Dr. James Balducci who are obstetricians with more than 25 years of experience. The final survey questions are shaped according to their feedback. The safety of childbirth instead of the risk of adverse outcomes is chosen for quantification in the survey, since the concept of safety is found to be easier to communicate with future respondents. The survey is composed of three main parts in which the participants are asked to do the following tasks: (1) determine the importance of different maternal and neonatal health outcomes, (2) indicate the safety of different delivery groups with respect to health outcomes in the cases of types of

HDP and gestational ages at delivery, and (3) Provide general information about themselves and their practice.

3.3.2 Methods

In the first part of the survey, the participants are asked to choose the importance of health outcomes on a scale of 1 to 10 where 1 and 10 designate *not important* and *extremely important*, respectively. This task corresponds to determining the importance weights of health outcomes which are the decision criteria in the framework of TOPSIS. The health outcomes included in the survey are maternal mortality, major maternal morbidities, minor maternal morbidities, perinatal/neonatal mortality, major neonatal morbidities, and minor neonatal morbidities.

Minor maternal morbidities include morbidities such as postpartum depression, postpartum hemorrhage, urinary tract infection, and anemia. Major maternal morbidities include morbidities such as abruptio placentae, blood transfusion, pulmonary edema, uterine rupture, stroke, HELLP syndrome, acute renal failure, acute liver failure, acute respiratory distress, convulsions, disseminated intravascular coagulopathy, neurologic complications, ICU admission, and oliguria. Minor neonatal morbidities include morbidities such as low Apgar score, SGA infant, transient birth injury, puerperal infection, suspected sepsis, and hyperbilirubinemia. Finally, major neonatal morbidities include morbidities such as bronchopulmonary dysplasia, cerebral palsy, hyaline membrane disease/respiratory distress syndrome, hypoglycemia, intracranial hemorrhage, neonatal seizures, neonatal sepsis, necrotizing enterocolitis, periventricular leukomalacia, retinopathy of prematurity, and need for respiratory support. This description of health outcomes is provided to the respondents in the instructions of the survey.

In the second part of the survey, the participants are asked to consider only one type of health outcome at a time, and rate the safety of delivery states with respect to a given health outcome. This task corresponds to rating the alternatives (delivery states) with respect to decision criteria (health outcomes) in TOPSIS. The linguistic rating scale includes *very safe*, *safe*, *neither safe nor unsafe*, *unsafe* and *very unsafe*.

Each delivery state is treated as an alternative, where a delivery state is defined as a combination of three variables which are maternal health (in terms of HDP) at delivery, gestational age at delivery, and delivery group. This definition is similar to how the state of the DTMC is defined in Section 3.2. Maternal health states are sPE, mPE, GH, and no diagnosis of HDP. Gestational ages are divided into four time buckets (24-28, 29-32, 33-36 and 37-42 weeks) to have a reasonable number of questions in the survey. Delivery groups are delivery with spontaneous labor, delivery with induced labor, and delivery with no labor as defined in Section 3.2.2. In total, we have 48 delivery states.

The participants are instructed to consider that spontaneous labor and induced labor may result in vaginal delivery, assisted vaginal delivery, or emergency cesarean delivery, and respond the questions in the second part accordingly. In the instructions of the survey, we also asked participants to assume that

- The fetus is stable on admission, and there is no reasonable chance of spontaneous labor in the next 24 hours, and
- The women do not have any medical conditions that strongly influence hypertension and/or route of delivery such as chronic hypertension, preexisting renal disease, preexisting cardiac problems, preexisting diabetes, placenta previa, prior cesarean delivery, obesity, and other conditions.

Finally, in the third part, the participants are asked to provide information about themselves and their practice to determine the level of credibility of their answers. The information that we would like to find out in this part of the survey are as follows:

- Average number of deliveries the respondent performs in a month (less than 10, 10-19, 20-29, 30-39, 40-49, or greater than or equal to 50, not applicable),
- What portion of the respondent's practice is obstetrics (less than 25%, 25%-50%, 50%-75%, 75%-100%),
- The description of the respondent's job practice (resident, general obstetrics and gynecology, nurse midwife or practitioner, maternal-fetal medicine, and other), and
- The experience of the respondent in terms of how many years he/she had practiced obstetrics.

The survey is distributed in an educational resident meeting at MIHS on 10/3/2014. In total, we had 48 respondents who were given a paper copy of the survey. We exclude the surveys filled out by medical students and physicians with less than three years of obstetrics experience. We also exclude the surveys that were not completely filled out. After exclusions, the total number of respondents included in calculations is 23.

The respondents included in calculations have 14.1 years of obstetrics experience on average. 70% of included respondents perform more than 20 deliveries in a month. For 18 out of 23 respondents, more than 50% of their practice is obstetrics. The distribution of job practice together with obstetrics experience among the included respondents is as follows:

Rating of health outcomes	Triangular fuzzy number
1 *(Not important)*	$(0.00, 0.00, 0.10)$
2	$(0.05, 0.15, 0.25)$
3	$(0.15, 0.25, 0.35)$
4	$(0.25, 0.35, 0.45)$
5	$(0.35, 0.45, 0.55)$
6	$(0.45, 0.55, 0.65)$
7	$(0.55, 0.65, 0.75)$
8	$(0.65, 0.75, 0.85)$
9	$(0.75, 0.85, 0.95)$
10 *(Extremely important)*	$(0.90, 1.00, 1.00)$

Table 3.12: Linguistic Rating of Health Outcomes and the Corresponding Triangular Fuzzy Numbers

- 8 respondents are residents with an average of 3.5 years of obstetrics experience,
- 14 respondents are physicians in general obstetrics and gynecology with an average of 19.4 years of obstetrics experience, and
- 1 respondent is a physician in maternal and fetal medicine with 25 years of experience.

After obtaining the linguistic ratings from the respondents on health outcomes and delivery states, the next step is the translation of *linguistics variables* into *triangular fuzzy numbers* that can be used in calculations. A *linguistic variable* is defined as a variable with a value in linguistic terms, and a *triangular fuzzy number* $\tilde{n}$ is defined as a triplet (n_1, n_2, n_3) by Chen (2000). Tables 3.12 and 3.13 present the triangular fuzzy numbers that corresponds to the linguistic variables that are used to rate health outcomes and delivery states in the survey.

Rating of delivery states	Triangular fuzzy numbers
Very safe (VS)	$(0.90, 1.00, 1.00)$
Safe (S)	$(0.60, 0.75, 0.90)$
Neither safe or unsafe (N)	$(0.35, 0.50, 0.65)$
Unsafe (U)	$(0.10, 0.25, 0.40)$
Very unsafe (VU)	$(0.00, 0.00, 0.10)$

Table 3.13: Linguistic Rating of Delivery States and the Corresponding Triangular Fuzzy Numbers

In summary, the remaining steps in our application of TOPSIS are as follows:

1. The ratings given by respondents on each health outcome are aggregated to obtain the aggregated fuzzy weight of each health outcome.

2. The ratings given by respondents on each delivery state with respect to a given health outcome are aggregated to obtain the aggregated fuzzy rating of each delivery state with respect to that health outcome. This step is repeated for all health outcomes. As a result, we obtain aggregated ratings $\tilde{x}_{ij}$ for all delivery states $i \in \{1, 2, \ldots, 48\}$ and health outcomes $j \in \{1, 2, \ldots, 6\}$.

3. The fuzzy decision matrices are constructed separately for maternal and neonatal health outcomes. The maternal fuzzy decision matrix, $\tilde{D}_M$, consists of aggregated ratings $\tilde{x}_{ij}$ with $j = \{1, 2, 3\}$. Similarly, the neonatal fuzzy decision matrix, $\tilde{D}_N$, consists of aggregated ratings $\tilde{x}_{ij}$ with $j \in \{4, 5, 6\}$.

4. The weighted fuzzy decision matrices are constructed by incorporating the aggregated weights into the fuzzy decision matrices. Since all fuzzy numbers are already defined in $[0, 1]$, there is no need for normalization at this step.

5. Fuzzy positive ideal solution (FPIS) and fuzzy negative ideal solution (FNIS) are defined as (1,1,1) and (0,0,0), respectively.

6. The distance of each delivery state from FPIS and FNIS are calculated. We denote the distance from FPIS and FNIS with respect to maternal (neonatal) health outcomes with d_i^{M*} and d_i^{M-} (d_i^{N*} and d_i^{N-}), respectively. Equation (3.5) shows the calculation of distance between triangular fuzzy numbers $\tilde{m} = (m_1, m_2, m_3)$ and $\tilde{n} = (n_1, n_2, n_3)$.

$$d(\tilde{m}, \tilde{n}) = \sqrt{\frac{1}{3}\left[(m_1 - n_1)^2 + (m_2 - n_2)^2 + (m_3 - n_3)^2\right]} \tag{3.5}$$

7. The closeness coefficients of each delivery state are calculated for maternal (CC_i^M) and neonatal (CC_i^N) health outcomes with Equations (3.6) and (3.7).

$$CC_i^M = \frac{d_i^{M-}}{d_i^{M*} + d_i^{M-}} \tag{3.6}$$

$$CC_i^N = \frac{d_i^{N-}}{d_i^{N*} + d_i^{N-}} \tag{3.7}$$

The closeness coefficients, CC^M and CC^N, that are calculated at the 7^{th} step constitute measures of safety of delivery states in terms of maternal and neonatal health outcomes, respectively. We use these two measures of safety to compare and rank the delivery states with respect to maternal health, gestational age, and delivery group. All calculations are performed using Python programming language.

3.3.3 Results

Tables 3.14 and 3.15 show the closeness coefficients of delivery states calculated for maternal and neonatal health outcomes, respectively. According to the results shown in these tables, the safety of childbirth decreases as maternal health gets worse for

Delivery group	Maternal health	Maternal closeness coefficients			
		Wk 24-28	Wk 29-32	Wk 33-36	Wk 37-42
Delivery with spontaneous labor	sPE	0.34	0.36	0.46	0.46
	mPE	0.52	0.52	0.63	0.64
	GH	0.55	0.56	0.65	0.69
	No HDP	0.62	0.63	0.67	0.75
Delivery with induced labor	sPE	0.22	0.23	0.38	0.40
	mPE	0.39	0.41	0.52	0.60
	GH	0.46	0.45	0.52	0.64
	No HDP	0.50	0.54	0.61	0.71
Cesarean delivery with no labor	sPE	0.32	0.32	0.40	0.42
	mPE	0.40	0.42	0.54	0.59
	GH	0.43	0.46	0.53	0.60
	No HDP	0.46	0.48	0.58	0.66

Table 3.14: Maternal Closeness Coefficients Calculated with TOPSIS

both the mother and the neonate as expected. However, the extent of decrease is not the same for the mother and the neonate. When we compare the safety of childbirth with no HDP (with a given gestational age and delivery group) to the same with sPE, we see that the average decrease in safety is 40.5% for the mother and 17.2% for the neonate. In addition, the safety of childbirth decreases as gestational age decreases for both parties. Similar to what we observe for maternal health, the extent of decrease is not close for both parties. The average decrease in safety between a term birth at 37-42 weeks of gestation and a preterm birth at 24-28 weeks of gestation is 28.4% for the mother and 69.7% for the neonate. Interestingly, the safety of childbirth with induced labor and no labor are generally very close.

Delivery group	Maternal health	Neonatal closeness coefficients			
		Wk 24-28	Wk 29-32	Wk 33-36	Wk 37-42
Delivery with spontaneous labor	sPE	0.19	0.30	0.43	0.62
	mPE	0.27	0.34	0.53	0.72
	GH	0.29	0.37	0.54	0.72
	No HDP	0.29	0.39	0.58	0.74
Delivery with induced labor	sPE	0.17	0.27	0.44	0.63
	mPE	0.18	0.27	0.50	0.72
	GH	0.19	0.29	0.50	0.72
	No HDP	0.21	0.31	0.54	0.74
Cesarean delivery with no labor	sPE	0.18	0.28	0.45	0.62
	mPE	0.19	0.27	0.50	0.70
	GH	0.18	0.27	0.51	0.71
	No HDP	0.20	0.29	0.54	0.73

Table 3.15: Neonatal Closeness Coefficients Calculated with TOPSIS

3.3.4 Conclusions

In this study, our goal is to measure the safety of childbirth as a function of the type of HDP at delivery, gestational age at delivery, and delivery group with respect to maternal and neonatal health outcomes. We conduct a provider survey, and evaluate its results with the TOPSIS extended to fuzzy environment. In our provider survey, participants rate the safety of childbirth in different delivery states with linguistic variables ranging from very safe to very unsafe. We define delivery states with maternal health at delivery, gestational age at delivery, and delivery group (i.e., delivery with spontaneous labor, delivery with induced labor, and cesarean delivery with no labor). We use the closeness coefficients of TOPSIS calculated with maternal (neonatal) health outcomes as measures of childbirth safety for the mother (the neonate).

In summary, the results show that the safety of childbirth decreases as maternal health worsens in terms of HDP, and if the delivery happens earlier than full term for both the mother and the neonate. The type of HDP at delivery is the main determinant of childbirth safety in terms of maternal health outcomes, and gestational age plays a similar role in neonatal health outcomes. The closeness coefficients of gestational hypertension and mild preeclampsia are either close or very close. As a final remark in this section, it is worthwhile to note that these conclusions are based on the safety perceived by providers, and as a result, they may not perfectly reflect the reality.

3.4 Discussion

In this chapter, we assess the risks of maternal and neonatal adverse outcomes of childbirth with respect to gestational age at delivery in two different studies. In the first study, we examine the clinical data on 8225 live singleton births with gestational ages of 33-42 weeks. We quantify the risks of maternal and neonatal childbirth morbidities with a composite measure within the patient subgroups determined with respect to the type of HDP at delivery, gestational age at delivery and delivery group (i.e., delivery with spontaneous labor, delivery with induced labor, and cesarean delivery with no labor). In the second study, we use a provider survey and TOPSIS to assess the safety of child delivery with respect to maternal and neonatal adverse outcomes. In this provider survey, the physicians are asked to rate the safety of child delivery with respect to maternal and neonatal adverse outcomes in the cases of different types of HDP at delivery, timings of delivery, and delivery groups.

Both studies agree on the conclusion that the main determinants of maternal and neonatal morbidities are maternal health (in terms of HDP) and gestational age (at delivery), respectively. Therefore, the physicians' perception of the factors that

mainly derive maternal and neonatal morbidities seems to be accurate. Both the CCM rates in the first study and the safety values in the second study calculated for mild preeclampsia and gestational hypertension are either close or very close, which indicates that gestational hypertension can be as critical as mild preeclampsia. This observation supports earlier medical studies such as Buchbinder *et al.* (2002) which emphasizes the severity of outcomes that gestational hypertension may bring about. It also strengthens the ACOG Task Force's recommendation to manage gestational hypertension and preeclampsia without severe features similarly (ACOG, 2013b).

The methods and results of both studies presented in this chapter are used in parameterizing the MDP and the RMDP models in Chapter 4, and establishing the assumptions made to generate results. The method of the first study is used to calculate the CCM rates for each week of gestation in the third trimester of pregnancy. These CCM rates are used as values assigned to delivery states, each of which represents a delivery with given maternal health, gestational age, and delivery group, in the value function of the MDP and the RMDP models.

Chapter 4

THE OPTIMAL TIMING OF CHILD DELIVERY FOR WOMEN WITH HYPERTENSIVE DISORDERS OF PREGNANCY

4.1 Introduction

In this chapter, we model the decision problem of timing of delivery in cases of hypertensive disorders of pregnancy (HDP) as a Markov Decision Process (MDP) by including the conflicting objectives of both the mother and the neonate. Our research objective is to find the optimal timing of delivery in cases of HDP that minimizes the risks of maternal and neonatal adverse outcomes that may happen due to childbirth. We formulate a discrete-time, infinite-horizon MDP model that minimizes the risks of maternal and neonatal adverse outcomes. The formulated MDP model provides the optimal delivery strategies with two sets of input parameters estimated with patient data: (1) transition probabilities (estimated in Chapter 2), (2) the risks of maternal and neonatal adverse outcomes (estimated using childbirth composite morbidity (CCM) rates as outlined in Chapter 3).

To shield the model results against uncertainty in the estimates of model parameters and the sensitivity of results to these estimates, first we use a robust MDP (RMDP) model. In this model, we allow transition probabilities to change within an uncertainty set defined by the confidence intervals (CIs) of transition probabilities calculated with patient data. The goal is to find the worst-case optimal policy when the transition probabilities are allowed to be determined by nature within their CIs with the objective of maximizing the risk of adverse outcomes. Secondly, we evaluate the results of MDP model in a probabilistic sensitivity analysis framework in which

the risks of adverse outcomes are sampled according to the predetermined order restrictions. Thirdly, we include the RMDP model within the probabilistic sensitivity analysis, and adopt nature's transition probabilities in the evaluation of policies. We gather the results of all analyses, and comment on the best structured policies and how the recommended timing of delivery changes as we vary the weight given to maternal (or neonatal) health outcomes.

The remainder of this chapter is organized as follows. In Section 4.2, we present an overview of the medical literature relevant to our problem, the operations research literature studying medical decision problems with MDPs, and the literature on RMDPs. In Section 4.3, we describe our MDP and RMDP models, and provide the structural properties of the models' outputs under certain conditions. Section 4.4 presents the estimation of model parameters, and the results of numerical study including a probabilistic sensitivity analysis with its robust counterpart. Finally, we present the conclusions of our study, and discuss future research directions in Section 4.5.

4.2 Literature

To the best of our knowledge, there is no operations research literature on the decision problem of the timing of child delivery for women with HDP. However, there is an extensive number of clinical studies that investigate care and delivery policies in the management of HDP. Several clinical studies focus on expectant management before 34 weeks of gestation for women with severe preeclampsia (sPE), and discuss the adverse outcomes that expectant management may lead to based on retrospective or prospective studies (Belghiti *et al.*, 2011; Haddad *et al.*, 2004; Hall *et al.*, 2001b, 2000; Vigil-De Gracia *et al.*, 2003). Another set of clinical studies address the same issue of expectant management for women with sPE to provide recommendations on

how to select patients for expectant monitoring (Hall *et al.*, 2006; Sibai and Barton, 2007; Chammas *et al.*, 2000; Shear *et al.*, 2005). There are also clinical studies that compare expectant management with interventionist care for women with HDP for the gestational ages either less than 34 weeks or greater than 36 weeks (Magee *et al.*, 2009; Koopmans *et al.*, 2007; Sibai, 2011). Finally, a number of studies compare cesarean delivery against induction of labor in terms of maternal and/or neonatal outcomes for the cases of sPE before 34 weeks of gestation (Hall *et al.*, 2001a; Alanis *et al.*, 2008; Coppage and Polzin, 2002).

Medical studies focus on either a type of patient, a course of pregnancy or a limited set of adverse outcomes, and mostly discuss descriptive results. Most of them treat cesarean delivery as an adverse outcome, although it is generally considered to be a mode of delivery that can be chosen by pregnant women even when there is no medical indication. As a result, medical studies fail to handle the problem comprehensively, and they do not provide instructive results that can guide clinicians in the decision-making process. The trade-offs such as competing objectives of the mother and the baby that prevail in the problem should be handled simultaneously to provide meaningful medical guidelines.

The optimal control of the timing of child delivery is a sequential decision-making problem under the uncertainty of disease progression and adverse outcomes. The framework of MDPs fits well to this problem by capturing its fundamental features such as the option of intervening at discrete time points as well as stochastic nature of disease progression and spontaneous labor. Alagoz *et al.* (2010) state that MDPs are powerful tools for probabilistic sequential decision-making that are underutilized in medical decision-making compared to industrial and manufacturing applications. Still, there are only a handful of studies that employ MDP in medical decision-making especially for disease progression and intervention decisions.

Shechter *et al.* (2008) study the optimal time to initiate HIV therapy with an MDP model of HIV progression and treatment. Chhatwal *et al.* (2010) consider the decision of biopsy based on mammographic features and demographic factors of a woman when there is a suspicion of breast cancer according to mammogram results. An MDP model is used to generate biopsy policies that are based on clinical data, and perform better than the ones in use. He *et al.* (2010) study dosage decisions by considering the trade-off between the risk of ovarian hyperstimulation syndrome and the rate of pregnancy using an MDP model of the controlled ovarian hyperstimulation cycle of the in vitro fertilization-embryo transfer therapy.

Denton *et al.* (2009) and Kurt *et al.* (2011) model the decision problem of optimal timing of initiating statin therapy for patients with type 2 diabetes with an MDP model by taking a societal perspective and the patient's perspective, respectively. Mason *et al.* (2012) study the impact of adherence on the optimal timing of initiating statin therapy with an MDP model. Additionally for type 2 diabetes patients, Mason *et al.* (2014) study the optimal timing of blood pressure and cholesterol medications.

Alagoz *et al.* (2004) study the optimal timing of living-donor liver transplant that maximizes total reward of the patient. The single dimensional state of the MDP model is patient's health modeled by distinct levels. Alagoz *et al.* (2007a) consider a similar problem of organ transplantation for patients with end-stage liver disease with an available living donor. An MDP model is used to decide the timing of transplantation, and the use of a cadaveric or a living-donor liver in case of a transplantation decision. The state of the MDP model is described with the patient state and organ quality. Alagoz *et al.* (2007b) address the organ accept or reject decision for patients with the same disease on a waiting list of cadaveric liver transplantation. Patient state and organ quality are included in the state of the process to determine if an offered organ should be accepted or not. Sandıkçı *et al.* (2008) consider the same

problem with a more inclusive state definition that additionally contains a measure of patient's ranking on the waiting list. An MDP model is used to find out patient's price of privacy, which is defined as the loss of expected lifetime because of incomplete information on the waiting list.

Iyengar (2005) and Nilim and El Ghaoui (2005) independently propose robust dynamic programming that includes a robust variant of Bellman recursion with the mutual goal of dealing with the ambiguity in the transition probabilities due to estimation errors. Robust MDPs have been applied to problems such as aircraft routing (Nilim *et al.*, 2002) and secure power control in cognitive radio networks (Xiao *et al.*, 2012) to find solutions robust to estimation errors in transition probabilities. In medical decision-making, the only application of robust MDPs is the study of Zhang and Denton (2016) to the best of our knowledge. In this study, a general robust MDP model with transition probability matrices in a controllable uncertainty set is developed for medical treatment decisions, and the developed model is used to find optimal treatment decisions for patients with type 2 diabetes by optimizing the sequence and timing of medications for glycemic control.

The available studies on medical decision-making problems with MDP modeling either do not include any analysis on the sensitivity of model parameters, or apply deterministic sensitivity analysis by changing a subset of the model parameters within predetermined ranges. However, the results of MDP models are often sensitive to parameter estimates. The parameters are usually estimated based on clinical data which may be limited in size and include errors. As a result, sensitivity analysis should be regarded as crucial in MDP modeling. To the best of our knowledge, our study is the first to incorporate probabilistic sensitivity analysis with order restrictions between parameters, and combine robustness with respect to transition probabilities within a probabilistic sensitivity analysis framework.

4.3 Model Formulation

The decision problem under study is the timing of delivery in cases of pregnancies with gestational hypertension and preeclampsia. As noted earlier, we consider both maternal and neonatal health outcomes which often create conflicting objectives. Maternal health and gestational age are the two main factors that are considered by physicians to decide the timing of delivery when the fetus is medically stable, and there is no reasonable chance of spontaneous labor in the next few days so that a decision for an intervention would be meaningful.

We consider a pregnant woman in her third trimester of pregnancy receiving prenatal care and visiting her doctor or midwife periodically. The typical frequency for prenatal visits is once in two to three weeks starting from the 28^{th} to the 36^{th} week, and once-a-week after the 36^{th} week. Prenatal visits are expected to be more frequent if there is any sign or diagnosis of complications. A routine part of prenatal visits is measuring blood pressure. Observation of blood pressure during the prenatal visits is the initial step in the diagnosis of HDP. In case of a suspicious blood pressure elevation, the pregnant woman is monitored closely for the probable presence of HDP. As a result, physicians typically have timely and perfect information regarding the presence of any type of HDP for a woman in prenatal care during the third trimester of pregnancy.

We formulate a discrete-time, infinite-horizon MDP model in which the objective is to minimize the weighted risk of maternal and neonatal adverse outcomes[1]. We denote the weight given to the maternal (neonatal) health outcome by α $(1-\alpha)$,

[1]We focus on health outcomes, and exclude financial costs associated with delivery or treatments in case of adverse outcomes. However, the overall financial cost is expected to decrease with fewer adverse outcomes.

where $0 \leq \alpha \leq 1$. The state of the patient is denoted by $\boldsymbol{s} = (h, t, d)$, where h is the maternal health, t is the gestational age, and d is the status of being pregnant or the type of delivery if delivery has already happened.

The decision process is modeled for an infinite horizon using a multi-dimensional state space in which the gestational age is one of the dimensions. Modeling the gestational age as one of the state dimensions enables us to incorporate the dependency of model parameters on gestational age, and avoid having non-stationary parameters that would change with respect to gestational age as decision stages advance. As a result, it also allows us to obtain optimal delivery strategies that are stationary.

The state space is defined as $\mathcal{S} = \{\boldsymbol{s} = (h, t, d) : h \in \mathcal{H}, t \in \mathcal{T}, d \in \mathcal{D}\}$. The elements of the set $\mathcal{H}$ from the most severe to the least severe (with their rankings) are (1) sPE (severe preeclampsia), (2) mPE (mild preeclampsia), (3) GH (gestational hypertension) and (4) N (normotensive). The set $\mathcal{T}$ includes gestational ages from the 33^{rd} ($t = 33$) week to the 42^{nd} week ($t = T = 42$). The elements of set $\mathcal{D}$ are P (continuing pregnancy), S (delivery with spontaneous labor), and I (delivery with intervention).

A delivery with intervention is either a delivery with induced labor, or a (non-emergent) cesarean delivery prior to labor. A delivery with spontaneous or induced labor is either a vaginal delivery or a (emergency) cesarean delivery. Although deliveries are mostly grouped with respect to the actual route of delivery (i.e., vaginal delivery and cesarean delivery) in the medical literature, we group deliveries according to the intended route of delivery to obtain states representing the outcomes of delivery decisions.

The state space $\mathcal{S}$ is composed of transient states representing the progression of pregnancy (called pregnancy states) and absorbing states representing the termination of pregnancy (called delivery states). Transient and absorbing states differ by their

third state variable, d. The set of absorbing states is defined as $\hat{\mathcal{S}} = \{\boldsymbol{s} = (h, t, d) : h \in \mathcal{H}, t \in \mathcal{T}, d \in \mathcal{D} \setminus \{P\}\}$, and the set of transient states is defined as $\mathcal{S} \setminus \hat{\mathcal{S}} = \{\boldsymbol{s} = (h, t, d) : h \in \mathcal{H}, t \in \mathcal{T}, d = P\}$.

The possible actions to choose in a state of pregnancy $\boldsymbol{s} \in \mathcal{S} \setminus \hat{\mathcal{S}}$ are (1) $\mathtt{W}$: waiting, i.e., doing nothing until the next decision epoch, (2) $\mathtt{I}$: intervening to deliver. The only exception is for the states of still being pregnant at the end of post-term pregnancy, which corresponds to the 42^{nd} week ($t = T = 42$). In that week, waiting is no longer an option, since a pregnancy continuing beyond the 42^{nd} week is undesirable for the well being of both the mother or the baby. As a result, the set of admissible actions is $\mathcal{A}_s = \{\mathtt{W}, \mathtt{I}\}$ for all $\boldsymbol{s} = (h, t, P)$ such that $h \in \mathcal{H}$, $t \leq T - 1$, and $\mathcal{A}_s = \{\mathtt{I}\}$ for all $\boldsymbol{s} = (h, T, P)$ such that $h \in \mathcal{H}$. The set of actions is denoted with $\mathcal{A}$, and $\mathcal{A} = \bigcup_{\boldsymbol{s}} \mathcal{A}_{\boldsymbol{s}} = \{\mathtt{W}, \mathtt{I}\}$. The actions are taken at the beginning of each gestational week starting from the 33^{rd} week ($t = 33$), and the decision process terminates when a delivery state is reached.

The probability of going from state $\boldsymbol{s} = (h, t, d)$ to $\boldsymbol{s'} = (h', t', d')$ where $\boldsymbol{s}, \boldsymbol{s'} \in \mathcal{S}$ under action $\mathtt{a} \in \mathcal{A}$ is denoted with $\mathcal{P}(\boldsymbol{s'}|\boldsymbol{s}; \mathtt{a})$, or equivalently $\mathcal{P}(h', t', d'|h, t, d; \mathtt{a})$. The transition probabilities and the resulting transition probability matrices under each action $\mathtt{a} \in \mathcal{A}$ are stationary, since the gestational age is included in the state definition. If the chosen action is to wait in a pregnancy state $\boldsymbol{s} = (h, t, P) \in \mathcal{S} \setminus \hat{\mathcal{S}}$ with $t \leq T - 1$, the possibilities include moving to a pregnancy state with the same or a worse[1] maternal health in the next gestational week. It is also possible that the wait action results in spontaneous labor, and hence, ending the pregnancy at a delivery state with $d = S$. Therefore, we have $\mathcal{P}(h', t^+, P|h, t, P; \mathtt{W}) > 0$ and

[1]We assume that it is not possible for maternal health to get better as gestational age advances, since delivery is the only treatment of HDP, and there is no pharmacological cure (Duley, 2009; Foo *et al.*, 2015; Haddad *et al.*, 2007). We revisit this as an assumption in Section 4.3.1.

$\mathcal{P}(h', t^+, S|h, t, P; \mathtt{W}) > 0$ for all $h, h' \in \mathcal{H}$ such that $h' \leq h$ and $t \leq T-1$ where $t^+ = t+1$. Moreover, we have $\mathcal{P}(h', t', P|h, t, P; \mathtt{W}) = 0$ and $\mathcal{P}(h', t', S|h, t, P; \mathtt{W}) = 0$ for any t' such that $t' \neq t+1$. If the chosen action at a pregnancy state $\boldsymbol{s} \in \mathcal{S} \setminus \hat{\mathcal{S}}$ is not to wait (i.e., intervening via inducing labor or cesarean delivery), then the pregnancy is terminated and the patient moves to a delivery state $\boldsymbol{s} \in \hat{\mathcal{S}}$ with the same maternal health and gestational age. Therefore, we have $\mathcal{P}(h, t, I|h, t, P; \mathtt{I}) = 1$ for all $h \in \mathcal{H}$ and $t \in \mathcal{T}$.

Once the pregnancy ends with delivery, the decision process terminates by reaching a delivery state for which the value of adverse health outcomes is assumed to be known. The value of adverse health outcomes at delivery states are associated with the maternal health and the gestational age at the time of delivery, as well as the type of delivery. The goal is to take actions to move patients to the best delivery states in the light of the known value of adverse health outcomes associated with the delivery states. For simplicity, we refer the value of adverse health outcomes as *costs* in the rest of the dissertation.

We denote the maternal and the neonatal costs of delivery states $\boldsymbol{s} \in \hat{\mathcal{S}}$ by $\eta^M(\boldsymbol{s})$ and $\eta^N(\boldsymbol{s})$, respectively. Moreover, we have $\eta(\boldsymbol{s}) = \alpha\eta^M(\boldsymbol{s}) + (1-\alpha)\eta^N(\boldsymbol{s})$ for all $\boldsymbol{s} \in \hat{\mathcal{S}}$ as the weighted total cost of a delivery state where $\alpha \in [0, 1]$. Bellman's equation is given in Equation (4.1) in which $\upsilon(h, t, d)$ denotes the value of state $\boldsymbol{s}$ where $\boldsymbol{s} = (h, t, d) \in \mathcal{S}$. We use $\eta(\boldsymbol{s})$ (or, equivalently $\eta(h, t, d)$) as the value of delivery state $\boldsymbol{s} \in \hat{\mathcal{S}}$ in Bellman's equation. The value of pregnancy state $\boldsymbol{s} = (h, t, P)$ for all $h \in \mathcal{H}$ and $t \leq T-1$ is the minimum of the expected cost-to-go calculated for the waiting action and the cost of intervention. At gestational age $T = 42$, the value of pregnancy state $\boldsymbol{s} = (h, T, P)$ for all $h \in \mathcal{H}$ is equal to the cost of intervention (i.e., $\eta(h, T, I)$) since waiting is not an option at $t = T$.

Under the action of waiting at a pregnancy state (h, t, P) with $t \leq T-1$, either (1) the pregnancy continues with the same or a worse maternal health (i.e., the process reaches the pregnancy state (h', t^+, P) with $h' \leq h$ by the next decision epoch), or (2) the pregnancy terminates with spontaneous labor at gestational age t with the same or a worse maternal health (i.e., the process reaches the delivery state (h', t^+, S) with $h' \leq h$ by the next decision epoch), and receives the cost of delivery state (h', t, S). The expected cost-to-go for the action of waiting at a pregnancy state with $t \leq T-1$ is calculated using these two possibilities. There is no immediate cost attached to choosing an action in any state, since there is no accumulation in costs.

$$\upsilon(\boldsymbol{s}) = \begin{cases} \min \Big\{ \sum_{h' \leq h} \mathcal{P}(h', t^+, P | h, t, P; \mathtt{W}) \upsilon(h', t^+, P) \\ \qquad + \sum_{h' \leq h} \mathcal{P}(h', t^+, S | h, t, P; \mathtt{W}) \eta(h', t, S), \\ \qquad \eta(h, t, I) \Big\} & \text{if } h \in \mathcal{H},\ t < T,\ d = P \\ \eta(h, T, I) & \text{if } h \in \mathcal{H},\ t = T,\ d = P \\ \eta(h, t, d) & \text{if } h \in \mathcal{H},\ t \in \mathcal{T},\ d \in \{S, I\} \end{cases} \tag{4.1}$$

The MDP model can be solved using a value iteration algorithm, and is able to produce the optimal decisions at pregnancy states with two sets of inputs: transition probabilities under waiting action and the costs of delivery states. The solution provides a set of optimal actions for the pregnancy states, i.e, $\mathtt{a}^*(h, t)$ such that $h \in \mathcal{H}$ and $t \in \mathcal{T}$. The optimal policy and the resulting decision rules are stationary. We do not need to use discounted or an average cost criterion in the value function unlike the majority of infinite horizon MDP models in the literature. The reason is that the process ends up with a delivery state regardless of the state that it is

initiated, and each delivery state is given a finite value in the value function without adding a cost that accumulates through decision epochs.

In our problem, the transition probabilities under the action of waiting (i.e., $\mathcal{P}(h', t^+, P|h, t, P; \mathtt{W})$ and $\mathcal{P}(h', t^+, S|h, t, P; \mathtt{W})$ for all $h,\ h' \in \mathcal{H},\ h' \leq h$, and $t \leq T-1$) are maximum likelihood estimates (MLEs) from a set of patient data as described in Chapter 2, and as a result, they are subject to estimation errors. Besides, they do not include the variation that may stem from heterogeneity between individual patients (Zhang and Denton, 2016). We use an RMDP formulation to deal with the potential issue of uncertainty of transition probabilities with the goal of obtaining optimal delivery strategies that are robust to estimation errors in these probabilities.

The approach in RMDP modeling leads to a game between the decision maker and the nature. While the decision maker chooses between actions to minimize the cost, the nature picks transition probabilities to achieve the exact opposite (Iyengar, 2005). As a result, it gives the worst-case optimal policy (Iyengar, 2005; Nilim and El Ghaoui, 2005). We define $\mathcal{Q}_{\boldsymbol{s}}$ as the stationary uncertainty set of the row of transition probability matrix under waiting action that corresponds to the pregnancy state $\boldsymbol{s} \in \mathcal{S} \setminus \hat{\mathcal{S}}$. $\mathcal{Q}_{\boldsymbol{s}}$ (or, equivalently $\mathcal{Q}_{(h,t,d)}$) is defined in Equation (4.2) according to the interval matrix model given by Nilim and El Ghaoui (2005). In this equation, $\mathcal{P}^l(\boldsymbol{s'}|\boldsymbol{s}, \mathtt{W})$ and $\mathcal{P}^u(\boldsymbol{s'}|\boldsymbol{s}, \mathtt{W})$ denote the lower and the upper bounds of $\mathcal{P}(\boldsymbol{s'}|\boldsymbol{s}, \mathtt{W})$, respectively. The uncertainty set $\mathcal{Q}$ is defined as $\mathcal{Q} = \prod_{\boldsymbol{s} \in \mathcal{S} \setminus \hat{\mathcal{S}}} \mathcal{Q}_{\boldsymbol{s}}$, and has the rectangular uncertainty property by definition. The decision of transition probabilities at state $\boldsymbol{s}$ is independent of the decision of transition probabilities at state $\boldsymbol{s'}$ where $\boldsymbol{s'} \neq \boldsymbol{s}$ with this property.

$$\mathcal{Q}_{\boldsymbol{s}} = \left\{ \boldsymbol{\mathcal{P}} \in \mathbb{R}_{+}^{|\mathcal{S}|} : \sum_{\boldsymbol{s'} \in \mathcal{S}} \mathcal{P}(\boldsymbol{s'}|\boldsymbol{s}, \mathtt{W}) = 1,\ \mathcal{P}^{l}(\boldsymbol{s'}|\boldsymbol{s}, \mathtt{W}) \leq \mathcal{P}(\boldsymbol{s'}|\boldsymbol{s}, \mathtt{W}) \leq \mathcal{P}^{u}(\boldsymbol{s'}|\boldsymbol{s}, \mathtt{W}) \right\}$$

$$\forall \boldsymbol{s} = (h, t, P) :\ h \in \mathcal{H},\ , t \in \mathcal{T},\ t \leq T - 1 \quad (4.2)$$

Bellman's equation of the RMDP model is given in Equation (4.3) in which $v^R(h, t, d)$ denotes the robust value of state $\boldsymbol{s}$ where $\boldsymbol{s} = (h, t, d) \in \mathcal{S}$. It is similar to the Bellman's equation of the MDP model with one crucial difference in the calculation of the expected cost-to-go calculated for the waiting action at pregnancy states with $t \leq T - 1$. In this calculation, the nature decides on the transition probabilities within $\mathcal{Q}_{\boldsymbol{s}}$ to maximize the expected cost of waiting at pregnancy states $\boldsymbol{s} = (h, t, P)$ with $t \leq T - 1$. According to Nilim and El Ghaoui (2005), we can assume that the control and nature policies are stationary in the infinite horizon problem without loss of generality. As a result, the nature picks a transition probability matrix which is stationary in our problem. The RMDP model can be solved with robust dynamic programming.

$$v^R(\boldsymbol{s}) = \begin{cases} \min \left\{ \max\limits_{\substack{\mathcal{P}(h', t^+, d'|h, t, P; \mathtt{W}) \\ \in \mathcal{Q}_{(h,t,P)}}} \left\{ \begin{array}{l} \sum_{h' \leq h} \mathcal{P}(h', t^+, P|h, t, P; \mathtt{W}) v^R(h', t^+, P) \\ + \sum_{h' \leq h} \mathcal{P}(h', t^+, S|h, t, P; \mathtt{W}) \eta(h', t, S) \end{array} \right\}, \right. \\ \qquad \left. \eta(h, t, I) \right\} \qquad \text{if } h \in \mathcal{H},\ t \leq T - 1,\ d = P \\ \eta(h, T, I) \qquad \text{if } h \in \mathcal{H},\ t = T,\ d = P \\ \eta(h, t, d) \qquad \text{if } h \in \mathcal{H},\ t \in \mathcal{T},\ d \in \{S, I\} \end{cases} \quad (4.3)$$

4.3.1 Structural Properties

In this section, we present the structural properties of our MDP and RMDP models. These structural properties shed light on how certain parameter characteristics provide desirable properties of the optimal actions and delivery policies. The insights of this section are used to generate candidate policies in our numerical study. All proofs are given in Appendix A.1. We use t^+ and t^- (similarly h^+ and h^-) to be equal to $t+1$ and $t-1$ ($h+1$ and $h-1$), respectively. We start with defining functions $f(h,t)$ and $f^R(h,t)$ to be the expected cost and the expected robust cost of being in a pregnancy state $\boldsymbol{s}=(h,t,P)$ with a policy of waiting ($a=\mathtt{W}$) for one week and intervening to deliver ($a=\mathtt{I}$) the following week (if the delivery does not happen with spontaneous labor in that one week), respectively.

$f(h,t)$ and $f^R(h,t)$ are defined with Equations (4.4) and (4.5), respectively. They are defined for all $h\in\mathcal{H}$ and $t\leq T-1$, since waiting is an option until week $T-1$. The first term in Equation (4.4) is the expected cost of waiting for one week at the pregnancy state of (h,t,P) and intervening to deliver in the following week if the pregnancy continues without spontaneous labor from gestational age t to t^+. Similarly, the second term is the expected cost of waiting at the pregnancy state of (h,t,P) and having delivery with spontaneous labor before the pregnancy reaches the gestational age t^+. We define function $f^R(h,t)$ to be similar to the function $f(h,t)$ with the difference that the nature decides on the transition probabilities in $f^R(h,t)$. As a result, $f^R(h,t)$ is the maximum that $f(h,t)$ can take when the transition probabilities are picked from the uncertainty set $\mathcal{Q}_{(h,t,P)}$.

$$f(h,t)=\sum_{h'\leq h}\mathcal{P}(h',t^+,P|h,t,P;\mathtt{W})\eta(h',t^+,I)+\sum_{h'\leq h}\mathcal{P}(h',t^+,S|h,t,P;\mathtt{W})\eta(h',t,S) \tag{4.4}$$

$$f^R(h,t) = \max_{\substack{\mathcal{P}(h',t^+,d'|h,t,P;\mathtt{W}) \\ \in \mathcal{Q}_{(h,t,P)}}} \Bigg\{ \sum_{h' \leq h} \mathcal{P}(h', t^+, P|h, t, P; \mathtt{W}) \eta(h', t^+, I) + \sum_{h' \leq h} \mathcal{P}(h', t^+, S|h, t, P; \mathtt{W}) \eta(h', t, S) \Bigg\}$$

$$= \max_{\substack{\mathcal{P}(h',t^+,d'|h,t,P;\mathtt{W}) \\ \in \mathcal{Q}_{(h,t,P)}}} \big\{ f(h,t) \big\} \tag{4.5}$$

Lemma 4.1 provides a sufficient condition for waiting to be uniquely optimal for a given state of pregnancy in our MDP and RMDP models. In words, the sufficient condition is the cost of delivering with an intervention at that state to be greater than the expected cost of waiting for one week, and delivering with an intervention in the absence of spontaneous labor in the following week. The difference between the left-hand side and the right-hand side of the conditions in parts (a) and (b) for a pregnancy state provides the expected decrease in the risk of adverse outcomes by choosing waiting instead of intervening at that pregnancy state, and as a result, gives us an indication on how confidently we can recommend the action of waiting.

Lemma 4.1. [Sufficient Condition for the Optimality of Waiting] For a given $\alpha \in [0,1]$, $h \in \mathcal{H}$, and $t \leq T-1$,

(a) In the MDP model, if $\eta(h,t,I) > f(h,t)$ then $a^*(h,t,P) = \mathtt{W}$, uniquely, and

(b) In the RMDP model, if $\eta(h,t,I) > f^R(h,t)$ then $a^*(h,t,P) = \mathtt{W}$, uniquely.

Example 4.1. Consider the pregnancy states $\boldsymbol{s}_1 = (\text{sPE}, 33, P)$ and $\boldsymbol{s}_2 = (\text{GH}, 38, P)$. Table 4.1 gives the values of $\eta(h,t,I) - f(h,t)$ for these two particular pregnancy states with different α values. The expected decreases in the risk of adverse outcomes by choosing the action of waiting for one week instead of intervening at $\boldsymbol{s}_1$ are 0.25 and 0.01 when α is equal to 0.00 and 0.75, respectively. According to Lemma 4.1, the

State	$\alpha = 0.00$	$\alpha = 0.25$	$\alpha = 0.50$	$\alpha = 0.75$	$\alpha = 1.00$
$\boldsymbol{s}_1 = (\text{sPE}, 33, P)$	0.25	0.17	0.09	0.01	-0.07
$\boldsymbol{s}_2 = (\text{GH}, 38, P)$	0.02	-0.01	-0.04	-0.08	-0.11

Table 4.1: The Difference Between $\eta(h, t, I)$ and $f(h, t)$ for the States Given in Example 4.1

optimal action at $\boldsymbol{s}_1$ in both cases is waiting. However, we can be more confident about the optimality of the waiting action when $\alpha = 0.00$ considering the fact that both the costs of delivery states and transition probabilities are subject to estimation errors. We can make a similar comparison between the expected decreases in the risk of adverse outcomes at $\boldsymbol{s}_1$ and $\boldsymbol{s}_2$ (0.25 and 0.02, respectively) when $\alpha = 0.00$.

Lemma 4.2 gives an overview of relations between the optimality of actions in the MDP and the RMDP models. Since the nature maximizes the cost of waiting in the RMDP model, the cost of waiting at a pregnancy state in the MDP model cannot be higher than the same in the RMDP model. Therefore, if the optimal action is intervening in the MDP model (at a given pregnancy state), it is also optimal to intervene in the RMDP model. Similarly, if the optimal action is waiting in the RMDP model (at a given pregnancy state), it is also optimal to wait in the MDP model.

Lemma 4.2. [Optimality of actions in MDP and RMDP models] For a given $\alpha \in [0, 1]$, $h \in \mathcal{H}$, and $t \leq T - 1$,

(a) If $a^*(h, t, P) = \texttt{I}$ in the MDP model, then $a^*(h, t, P) = \texttt{I}$ in the RMDP model, and

(b) If $a^*(h, t, P) = \texttt{W}$ in the RMDP model, then $a^*(h, t, P) = \texttt{W}$ in the MDP model.

Since HDP are a set of progressive diseases in which the maternal health is not expected to improve, the probability of going to a state with better maternal health as the gestational age advances is zero. This is formalized in Assumption 4.1. This assumption is used to limit the transitions to happen only from one state to another state with the same or a worse maternal health. As a result, we are able to derive (1) the conditions for the optimality of the action intervening to deliver in a subset of states determined by a given maternal health and gestational age, and (2) the conditions for the optimality of a switching curve policy.

Assumption 4.1.

$$\mathcal{P}(h', t^+, P|h, t, P; \mathtt{W}) = 0, \quad \forall h,\ h' \in \mathcal{H},\ h' > h,\ t \leq T-1 \tag{4.6}$$

Proposition 4.1 gives the necessary and sufficient conditions for intervening to be the optimal action in a subset of the pregnancy states defined by $h \leq \check{h}$ and $t \geq \check{t}$ for a given $\check{h}$ and a given $\check{t}$ where $h,\ \check{h} \in \mathcal{H},\ t,\ \check{t} \in \mathcal{T}$, and $\check{t} \leq T-1$. The subset of the pregnancy states is depicted by boundaries on maternal health $\check{h}$ and gestational age $\check{t}$ in Figure 4.1. This figure illustrates the optimal actions at pregnancy states $\boldsymbol{s} = (h, t, P)$ with $t \leq T-1$. The optimal action is to intervene in the darker area, if and only if, the condition of Proposition 4.1 holds for all pregnancy states that correspond to that area (i.e., pregnancy states with $h \leq \check{h}$ and $t \geq \check{t}$). For the MDP model (the RMDP model), the condition given by Equation (4.7) (Equation (4.8)) requires that the cost of intervention to be less than or equal to the cost (the robust cost) of the policy in which the decision maker chooses to wait for one week and deliver the baby in the absence of spontaneous labor with an intervention in the following week.

Proposition 4.1. [Optimality Conditions] Under Assumption 4.1 and for a given $\alpha \in [0, 1]$, $\check{h} \in \mathcal{H}$, and $\check{t} \leq T-1$, $a^*(h, t, P) = \mathtt{I}$ for all $h \leq \check{h}$ and $t \geq \check{t}$ if and only if,

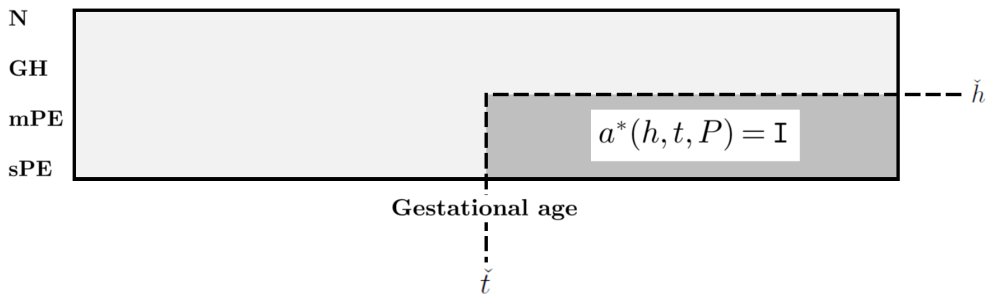

Figure 4.1: The Structure of Actions as Proposed by Proposition 4.1

(a) The following statement holds in the MDP model:

$$\eta(h,t,I) \leq f(h,t) \quad \forall h \leq \check{h},\ t \geq \check{t},\ t \neq T. \tag{4.7}$$

(b) The following statement holds in the RMDP model:

$$\eta(h,t,I) \leq f^R(h,t) \quad \forall h \leq \check{h},\ t \geq \check{t},\ t \neq T. \tag{4.8}$$

Example 4.2. Consider the case when $\alpha = 1.00$. Figure 4.2 gives the values of $\eta(h,t,I) - f(h,t)$ for all pregnancy states with $t \leq T-1$. According to the values shown in this figure, $\eta(h,t,I) - f(h,t) \leq 0$ (i.e., $\eta(h,t,I) \leq f(h,t)$) for all pregnancy states in the subsets defined by $\check{h}_1 = N$ and $\check{t}_1 = 38$, and $\check{h}_2 = GH$ and $\check{t}_2 = 36$. As a result, we can conclude that the optimal action is to intervene at the states in the darker area shown in Figure 4.2 without solving for the optimal actions with value iteration algorithm.

A *switching curve policy* is characterized by critical indices (thresholds) on gestational age (for each maternal health $h \in \mathcal{H}$) after which the optimal action is to intervene. Under certain conditions, such a policy is optimal and it is monotone in maternal health as depicted in Figure 4.3. In this policy, the critical indices on gestational age are non-decreasing in maternal health. We propose Conditions (1) and

	33	34	35	36	37	38	39	40	41
N	0.00	0.04	0.00	0.00	0.02	-0.03	-0.04	-0.04	-0.06
GH	-0.01	0.00	0.12	-0.01	-0.03	-0.11	-0.03	-0.05	-0.05
mPE	0.00	0.00	0.15	-0.03	-0.07	-0.11	-0.05	-0.06	-0.09
sPE	-0.07	0.00	0.06	-0.03	-0.03	-0.05	-0.04	-0.06	-0.07

Figure 4.2: The Difference Between $\eta(h,t,I)$ and $f(h,t)$ for All Pregnancy States with $t \leq T-1$ When $\alpha = 1.00$

(2) (Conditions (3) and (4)) to show the existence of monotone switching curves in a delivery policy provided by the MDP model (the RMDP model). For a given $h \in \mathcal{H}$, the critical indice $t^*(h)$ is the lowest gestational age t that satisfies the conditions of Proposition 4.1 in the subset of states defined with $\check{h} = h$ and $\check{t} = t$.

Condition 1 $f(h^+,t) - f(h,t) \leq \eta(h^+,t,I) - \eta(h,t,I)$

Condition 2 $f(h,t^-) - f(h,t) \leq \eta(h,t^-,I) - \eta(h,t,I)$

Condition 3 $f^R(h^+,t) - f^R(h,t) \leq \eta(h^+,t,I) - \eta(h,t,I)$

Condition 4 $f^R(h,t^-) - f^R(h,t) \leq \eta(h,t^-,I) - \eta(h,t,I)$

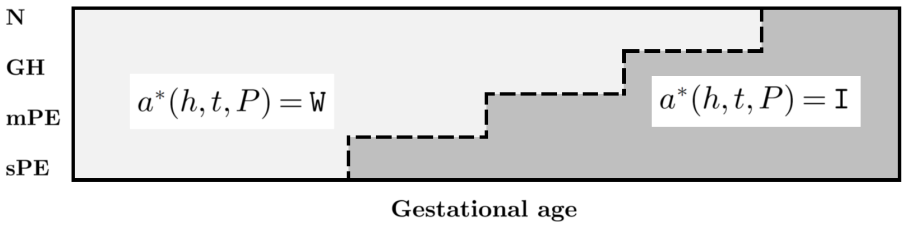

Figure 4.3: The Structure of Optimal Delivery Policy as Proposed by Proposition 4.2

Condition (1) suggests that there is more benefit of an intervention than waiting when maternal health worsens. This has intuitive appeal since intervention becomes more crucial as maternal health deteriorates both for the mother and the neonate. Similarly, Condition (2) implies that there is more benefit of an intervention as gestational age proceeds. This also intuitively sounds reasonable since delivery becomes riskier for the mother as the baby grows in size. Hence, an intervention should have more benefit at a later gestational age compared to an earlier one for the mother. For neonates, the baby requires more time to fully grow at an earlier gestational age. Hence, an intervention should have less benefit at an earlier gestational age compared to a later one.

Under Conditions (1) and (2), the optimal delivery policy belongs to the class of monotone switching-curve policies in the MDP model as suggested by Proposition 4.2. Similarly, we have Conditions (3) and (4) for the same goal in the RMDP model.

Proposition 4.2. [Switching-Curve Policy] Under Conditions (1) and (2), the following statements hold for $\alpha \in [0, 1]$ in the MDP model:

(a) For states $\boldsymbol{s} = (h, t, P) \in \mathcal{S} \setminus \hat{\mathcal{S}}$, there exists a critical index $t^*(h)$ such that waiting is preferred if, and only if, $t \leq t^*(h)$,

(b) Critical indices $t^*(h)$ form a non-decreasing sequence: $h_1 \geq h_2 \Rightarrow t^*(h_1) \geq t^*(h_2)$,

Under Conditions (3) and (4), the following statements hold for $\alpha \in [0, 1]$ in the RMDP model:

(c) For states $\boldsymbol{s} = (h, t, P) \in \mathcal{S} \setminus \hat{\mathcal{S}}$, there exists a critical index $t_R^*(h)$ such that waiting is preferred if, and only if, $t \leq t_R^*(h)$,

(d) Critical indices $t_R^*(h)$ form a non-decreasing sequence: $h_1 \geq h_2 \Rightarrow t_R^*(h_1) \geq t_R^*(h_2)$.

In the RMDP model, the nature picks the transition probabilities to maximize the expected cost of waiting, and waiting becomes more costly as opposed to intervening when compared to the MDP model. Therefore, we expect the critical indices $t_R^*(h)$ to be not greater than the critical indices $t^*(h)$ under Conditions (1)-(4). Figure 4.4 illustrates how the switching curve policies in the MDP and the RMDP models may look like. Under Conditions (1)-(4), we show the order between the critical indices of switching curve policies in the MDP and the RMDP models in Proposition 4.3. We use Proposition 4.1 in the proof of Proposition 4.3 as given in Appendix A.1.

Proposition 4.3. [Order in Critical Indices] Under Conditions (1)-(4) and for $\alpha \in [0,1]$, $t_R^*(h) \leq t^*(h)$ for $h \in \mathcal{H}$.

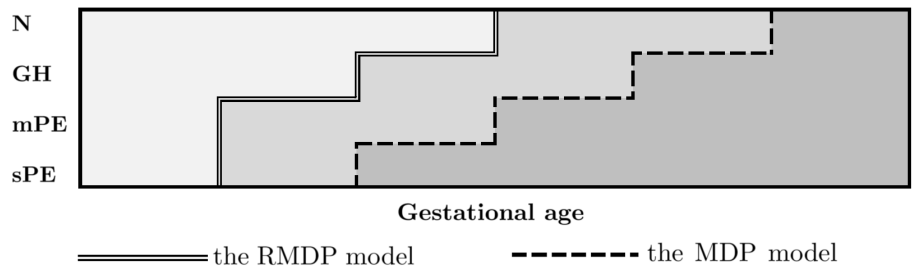

Figure 4.4: The Structure of Optimal Delivery Policies as Proposed by Proposition 4.3

4.4 Numerical Study

We estimate the parameters of our MDP model with clinical data. The source of clinical data is Maricopa Integrated Health system (MIHS), a teaching hospital and healthcare system in Maricopa County of Arizona. Our cohort contains women who received care throughout their pregnancy, and gave birth at MIHS between March 2012 and December 2015. The data used in the parameter estimations include the

singleton pregnancies, and excludes the ones that ended with a stillbirth. It also excludes the pregnancies complicated with chronic hypertension that is diagnosed prior to pregnancy, since the focus of our study is pregnancy-induced hypertension. If a woman gave birth more than once during the time period of the data, only one of her pregnancies is randomly selected and included in the study.

We present the estimation of parameters (as an overview of estimations in Chapters 2 and 3) together with the imputation of missing ones in Section 4.4.1. We discuss the results of our MDP and RMDP models gathered with the estimated parameters in Section 4.4.2. In Section 4.4.3, we describe the probabilistic sensitivity analysis of our MDP and RMDP models on the costs of delivery states, and present the policy recommendations. In Section 4.4.4, we discuss the implications of the results of our numerical study.

4.4.1 Estimation and Imputation of the Model Parameters

The MDP and the RMDP models require the estimation of transition probabilities and the costs of delivery states together with their CIs as parameters. For the estimation of transition probabilities, we use the results of ORI-TPM model presented in Chapter 2. We calculate the CIs of transition probabilities with the adjusted Wald method. For the estimation of the costs of delivery states, we calculate maternal and neonatal CCM rates at each gestational age $t \in \mathcal{T}$ as outlined in Section 3.2.2.

Since $\eta^M(h,t,d)$ is estimated with the maternal CCM rate, it is the risk of maternal composite outcome occurring due to childbirth. Therefore, it can be considered as a binomial proportion for which the success probability is the probability of having a maternal composite outcome. This is the same for $\eta^N(h,t,d)$ and neonatal CCM rate. Although we have a large sample size in total, some of the delivery states have few observations due to the high number of delivery states, and uneven distribution

of observations among these states. For instance, the sample size is smaller than 10 for 36% (29 out of 80) of the delivery states, and there are no observations for 5% (4 out of 80) of the delivery states.

As point estimates of $\eta^M(h,t,d)$ and $\eta^N(h,t,d)$, we use Wilson's estimates (Wilson, 1927), which are shown to outperform MLEs for binomial proportions in case of small sample sizes (Lewis and Sauro, 2006). Similarly, we employ the adjusted Wald method to construct 95% CIs of $\eta^M(h,t,d)$ and $\eta^N(h,t,d)$ for all $\boldsymbol{s} = (h,t,d) \in \hat{\mathcal{S}}$, since this method gives good coverage probabilities when the number of observations is small (Agresti and Coull, 1998; Sauro and Lewis, 2005; Lewis and Sauro, 2006).

In the estimation of the costs of delivery states, we use two different methods to impute the missing values, and improve the estimates with small samples. The first method is maximum likelihood estimation under order restrictions with respect to maternal health, gestational age, and type of delivery. This method involves constructing a nonlinear optimization model in which the objective is to maximize the likelihood function subject to the constraints that impose the order restrictions. The model is named as the order restricted inference of the costs of delivery states (ORI-CDS), and it is given in Appendix A.2. We gather a collection of estimations with ORI-CDS by including order restrictions with respect to different sets of dimensions of the delivery states. The order restrictions are explained in detail in Section 4.4.3. We interpolate the costs of delivery states with no observations using the costs of the nearest delivery states in terms of gestational age.

The second method is multiple imputation by chained equations (MICE) that uses a random forest algorithm to impute the missing values (Raghunathan *et al.*, 2001; Van Buuren, 2007; Buuren and Groothuis-Oudshoorn, 2011; White *et al.*, 2011). Although we have observations to estimate the costs of 95% of the delivery states, a significant portion of these states have low sample sizes. We treat these delivery states

as states with missing values, and impute their estimations as well. We iteratively enlarge the portion of the delivery states that we treat their costs as missing values to impute, and gather different sets of estimations.

We determine the delivery states to include in the imputations based on the range of the adjusted Wald CIs of cost estimations. In total, we gather five sets of costs by imputing the costs of delivery states with CIs having ranges larger than 0.6, 0.5, 0.4, 0.3, and 0.2 in addition to the costs of delivery states with no observations. To gather each set, we run MICE 100 times with the R package mice (Buuren and Groothuis-Oudshoorn, 2011), and average the imputations over all runs for each delivery state. We use Wilson's estimates for the costs that are not imputed with MICE.

4.4.2 The Optimal Delivery Policies

We obtain the optimal actions at the pregnancy states by solving the MDP model using a value iteration algorithm with transition probabilities estimated using the ORI-TPM model and different sets of costs of delivery states. The sets of costs of delivery states include MLEs, Wilson's estimates, and the estimates found with ORI-CDS model and MICE as discussed in Section 4.4.1. We calculate the costs of delivery states for all $\alpha \in \{0.00,\ 0.25,\ 0.50,\ 0.75,\ 1.00\}$. The costs with $\alpha = 1.00$ and $\alpha = 0.00$ correspond to the maternal and the neonatal policies, respectively. Additionally, we gather the worst-case optimal policies by solving the RMDP model with robust dynamic programming with the same set of α values. In these solutions, we use the 95% CIs of transition probabilities to define the uncertainty set given in Equation (4.2). The optimal actions found with different α values and the costs of delivery states are provided in Appendix A.3. We make the following observations on the optimal actions based on the results gathered with the MDP and the RMDP models.

Observation 1 Optimal actions and resulting delivery policies are highly sensitive to the costs of delivery states.

Observation 2 When the objectives of mother and neonate are combined with a given $\alpha \in (0, 1)$, the optimal actions mostly do not form switching curve policies.

Observation 1 is not unexpected, since MDPs have the potential to be sensitive to model parameters (Steimle and Denton, 2017). Since MDPs are sequential decision models, a change in the cost of a delivery state is likely to impact the decisions preceding its gestational age like a "domino effect", as discussed by Chen *et al.* (2017). The sensitivity of the optimal actions to the costs of delivery states makes it difficult to determine delivery policies to recommend for clinical practice. Besides, the structure of the recommended optimal policies is of critical importance in its implementation in clinical practice (Puterman, 1994; Steimle and Denton, 2017). As Observation 2 indicates, the optimal actions do not constitute a policy with a certain structure especially for $\alpha \in (0, 1)$. For the MDP model (the RMDP model), conditions (1) and (2) (conditions (3) and (4)) of Proposition 4.2 mostly do not hold, and therefore the optimal actions do not form a switching curve policy.

Observations 1 and 2 motivate us to employ a probabilistic sensitivity analysis (PSA) approach as presented in Section 4.4.3. Our goals in adopting a PSA approach are twofold. We first use PSA to explore the best switching-curve policy (or policies) that can be recommended for use in practice under the light of the available data, and established clinical information on the order of the model parameters. Secondly, PSA is adopted to evaluate the sensitivity and confidence in the recommended structured policies. The main motivation behind these two goals is the fact that we estimate the costs of delivery states using a data set with limited sample size for a significant portion of delivery states.

Similar issues with limited or missing data can be seen in other medical decision problems that involve diseases that are of critical importance but not seen widely in population, or problems for which there is not an organized data collection effort. Our PSA approach may lower the barrier of the need for ample data in sequential medical decision-making problems, and be useful in solving the decision models that would not be studied due to the lack of sufficient data to estimate all parameters.

4.4.3 Probabilistic Sensitivity Analysis

In this section, we examine the performance of a set of delivery policies (called candidate policies) by probabilistically sampling the maternal and neonatal costs of delivery states within their CIs constructed with the available patient data. We incorporate the order restrictions between the costs in terms of maternal health, gestational age, and type of delivery into their probabilistic sampling. These order restrictions are deduced based on the clinical information established in the medical literature and observed in our data.

In a problem instance, first we sample maternal and neonatal costs of all delivery states. Then, we calculate the optimality gaps between the optimal policy for that particular problem instance and the candidate delivery policies. The output of this analysis is the optimality gap averaged over all problem instances for each candidate delivery policy under study. The average optimality gap for a candidate delivery policy is a measure of policy acceptability when the joint uncertainty of cost of delivery states is taken into account.

The studies modeling medical decision-making problems with MDPs typically either use deterministic sensitivity analyses in which they change the value of parameters within scenario analyses, or solve the MDP models only with point estimate of parameters without evaluating the sensitivity of solutions to these parameters (Alagoz

et al., 2004; Sandıkçı *et al.*, 2008; Shechter *et al.*, 2008; Chhatwal *et al.*, 2010; Kurt *et al.*, 2011; Chen *et al.*, 2017). However, these approaches fail to provide sufficient information to evaluate the confidence in the recommendations produced with the MDP models, and to translate the model outputs into clinical insights (Chen *et al.*, 2017).

PSA is a recommended approach by The ISPOR-SMDM Modeling Good Research Practices Task Force in addition to a deterministic sensitivity analysis to assess the impact of parameter uncertainty on model results (Briggs *et al.*, 2012). Chen *et al.* (2017) propose a probabilistic approach to conduct sensitivity analysis in sequential decision problems that are solved with MDPs. The framework of our PSA approach is different than the one proposed by Chen *et al.* (2017) in two ways. First, we impose order restrictions between parameters in the process of probabilistic sampling. Secondly, we compare a set of candidate policies with respect to their optimality gap instead of building the analysis on a single base case policy.

One way of generating a problem instance is sampling maternal and neonatal costs for all delivery states with uniform distribution from their CIs. If the generated problem instance satisfies the order restrictions between all delivery states, it is included in the set of problem instances. Otherwise, it is discarded, and a new instance is generated. Our initial experiments demonstrate that it is computationally ineffective to collect a set of problem instances with this straightforward approach, since it is required to sample a large number of problem instances to find one instance that satisfies all order restrictions. Therefore, we first adjust the bounds of CIs according to the order restrictions as outlined in Algorithm 1 prior to the generation of problem instances. We continue adjusting the bounds as costs are sampled in a problem instance. The goal is to efficiently create problem instances that would be plausible by satisfying the order restrictions between delivery states.

Algorithm 1 Adjust lower and upper bounds of $\eta^M(\boldsymbol{s})$

Inputs:
$l^M(\boldsymbol{s})$, $u^M(\boldsymbol{s})$ Lower and upper bounds of CIs of $\eta^M(\boldsymbol{s})$ for $\boldsymbol{s} \in \hat{\mathcal{S}}$
while $\exists$ bounds of $\eta^M(\boldsymbol{s})$ to update, **do**
  for each delivery state $\boldsymbol{s}_1 \in \hat{\mathcal{S}}$ **do**
    for each delivery state $\boldsymbol{s}_2 \in \hat{\mathcal{S}}$ **do**
      if $\boldsymbol{s}_1 <_M \boldsymbol{s}_2$ **then**
        if $l^M(\boldsymbol{s}_1) < l^M(\boldsymbol{s}_2)$ **then**
          $l^M(\boldsymbol{s}_1) \leftarrow l^M(\boldsymbol{s}_2)$
        end if
        if $u^M(\boldsymbol{s}_1) < u^M(\boldsymbol{s}_2)$ **then**
          $u^M(\boldsymbol{s}_2) \leftarrow u^M(\boldsymbol{s}_1)$
        end if
      end if
    end for
  end for
end while

We define the relations $\overset{h}{<}_M$, $\overset{t}{<}_M$ and $\overset{d}{<}_M$ ($\overset{h}{<}_N$, $\overset{t}{<}_N$ and $\overset{d}{<}_N$) to formulate the order restrictions between two delivery states in terms of maternal (neonatal) cost with respect to the state dimensions h, t, and d, respectively. For instance, $\boldsymbol{s}_1 \overset{h}{<}_M \boldsymbol{s}_2$ ($\boldsymbol{s}_1 \overset{h}{<}_N \boldsymbol{s}_2$) indicates that $\boldsymbol{s}_1$ is worse than $\boldsymbol{s}_2$ (or, equivalently $\boldsymbol{s}_2$ is better than $\boldsymbol{s}_1$) in terms of h with respect to the risk of maternal (neonatal) adverse outcomes. We have the order restriction $\boldsymbol{s}_1 <_M \boldsymbol{s}_2$ if we have $\boldsymbol{s}_1 \overset{h}{<}_M \boldsymbol{s}_2$, or $\boldsymbol{s}_1 \overset{t}{<}_M \boldsymbol{s}_2$, or $\boldsymbol{s}_1 \overset{d}{<}_M \boldsymbol{s}_2$. The order restriction $<_N$ is defined similarly with the relations $\overset{h}{<}_N$, $\overset{t}{<}_N$ and $\overset{d}{<}_N$. The order restrictions $<_M$ and $<_N$ are used in the probabilistic sampling of the maternal and neonatal costs of delivery states.

Table 4.2 presents how each relation is translated into order restrictions for any given two states $\boldsymbol{s}_1 = (h_1, t_1, d_1)$ and $\boldsymbol{s}_2 = (h_2, t_2, d_2)$ where $\boldsymbol{s}_1, \boldsymbol{s}_2 \in \hat{\mathcal{S}}$. As expected, both maternal and neonatal costs of delivery states increases with decreasing h, i.e., deteriorating maternal health (Barton *et al.*, 2001; Habli *et al.*, 2007; Kuklina *et al.*, 2009; Bazzano *et al.*, 2016). Maternal cost of delivery states decreases as gestational age advances until the end of early term (37-38 weeks), and increases after the start of

Relation	Order in h	Order in t	Order in d
$\boldsymbol{s}_1 \overset{h}{<}_M \boldsymbol{s}_2$	$h_1 < h_2$	$t_1 = t_2$	$d_1 = d_2$
$\boldsymbol{s}_1 \overset{t}{<}_M \boldsymbol{s}_2$	$h_1 = h_2$	$t_1 < t_2$ and $t_1, t_2 \leq 38$; or $t_1 > t_2$ and $t_1, t_2 \geq 39$	$d_1 = d_2$
$\boldsymbol{s}_1 \overset{d}{<}_M \boldsymbol{s}_2$	$h_1 = h_2$	$t_1 = t_2$	$d_1 = S$, $d_2 = I$
$\boldsymbol{s}_1 \overset{h}{<}_N \boldsymbol{s}_2$	$h_1 < h_2$	$t_1 = t_2$	$d_1 = d_2$
$\boldsymbol{s}_1 \overset{t}{<}_N \boldsymbol{s}_2$	$h_1 = h_2$	$t_1 < t_2$ and $t_1, t_2 \leq 41$	$d_1 = d_2$
$\boldsymbol{s}_1 \overset{d}{<}_N \boldsymbol{s}_2$	$h_1 = h_2$	$t_1 = t_2$	$d_1 = I$, $d_2 = S$

Table 4.2: The Order Restrictions Implied by the Defined Relations

the full term (39-40 weeks) (Von Dadelszen *et al.*, 2011). On the other hand, neonatal cost decreases as the pregnancy prolongs since the fetus have more time to reach full maturation in utero (Hutcheon *et al.*, 2011; Auger *et al.*, 2016; Magee *et al.*, 2016). Maternal and neonatal costs demonstrate opposite trends in terms of type of delivery in our patient data. While maternal costs are higher in deliveries with spontaneous labor, neonatal costs are less in the presence of spontaneous labor (Habli *et al.*, 2007).

Before sampling the costs of delivery states, our PSA procedure starts with adjusting the lower and upper bounds of CIs according to order restrictions "$\cdot <_M \cdot$" and "$\cdot <_N \cdot$". We denote lower (upper) bounds of $\eta^M(\boldsymbol{s})$ and $\eta^N(\boldsymbol{s})$ with $l^M(\boldsymbol{s})$ and $l^N(\boldsymbol{s})$ ($u^M(\boldsymbol{s})$ and $u^N(\boldsymbol{s})$), respectively. The bounds are adjusted by making comparisons between two states at a time. For instance, if we have $\boldsymbol{s}_1 \in [0.14, 0.45]$, $\boldsymbol{s}_2 \in [0.19, 0.23]$ and $\boldsymbol{s}_1 <_M \boldsymbol{s}_2$, we assume that $\eta^M(\boldsymbol{s}_1)$ cannot be smaller than the lowest value that $\eta^M(\boldsymbol{s}_2)$ may have, and we adjust $l^M(\boldsymbol{s}_1)$ to be equal to $l^M(\boldsymbol{s}_2)$. Similarly, if we have $\boldsymbol{s}_1 \in [0.21, 0.25]$, $\boldsymbol{s}_2 \in [0.14, 0.36]$, and $\boldsymbol{s}_1 <_M \boldsymbol{s}_2$, then we assume that $\eta^M(\boldsymbol{s}_2)$ cannot be greater than the highest value that $\eta^M(\boldsymbol{s}_1)$ may have, and we adjust $u^M(\boldsymbol{s}_2)$ to be

Statistics	CI range of $\eta^M(\boldsymbol{s})$ values		CI range of $\eta^N(\boldsymbol{s})$ values	
	Before	After	Before	After
Average	0.42	0.24	0.38	0.21
Median	0.37	0.22	0.32	0.13
Standard deviation	0.25	0.16	0.26	0.19

Table 4.3: The Statistics of CI Ranges Over All Delivery States Before and After Adjusting Bounds

equal to $u^M(\boldsymbol{s}_1)$. The bounds of $\eta^M(\boldsymbol{s})$ and $\eta^N(\boldsymbol{s})$ are adjusted separately until there are no possible adjustments left between any two delivery states.

Algorithm 1 formalizes the steps followed for the procedure of adjusting bounds of maternal cost of delivery states. The same procedure is followed for the bounds of neonatal cost of delivery states. On average, the CI ranges reduced approximately by half after adjusting the bounds according to the order restrictions prior to probabilistic sampling of costs. Table 4.3 presents the statistics of the CI ranges over all delivery states before and after adjusting the bounds of maternal and neonatal costs of delivery states. In our computations, the bounds of both $\eta^M(\boldsymbol{s})$ and $\eta^N(\boldsymbol{s})$ are adjusted by visiting the while loop at line (2) of Algorithm 1 three times.

In PSA, new values of $\eta^M(\boldsymbol{s})$ and $\eta^N(\boldsymbol{s})$ are sampled for all delivery states $\boldsymbol{s} \in \hat{\mathcal{S}}$ in each problem instance, and $\mathring{N}$ problem instances are generated in total. Algorithm 2 shows the steps to follow for sampling of maternal cost of delivery states ($\eta^M(\boldsymbol{s})$) in the generation of problem instances. The same steps are followed for the sampling of neonatal cost of delivery states ($\eta^N(\boldsymbol{s})$) with inputs $l^N(\boldsymbol{s})$ and $u^N(\boldsymbol{s})$, and order restriction "$\cdot <_N \cdot$". In a problem instance, Algorithm 2 samples the cost of one delivery state at a time until sampling is completed for all delivery states. We use

Algorithm 2 Generate problem instances

1: **Inputs**:
   $\mathring{N}$ The number of problem instances to generate
   $l^M(\boldsymbol{s})$, $u^M(\boldsymbol{s})$ Adjusted lower and upper bounds of $\eta^M(\boldsymbol{s})$ for all $\boldsymbol{s} \in \hat{\mathcal{S}}$
2: Sort delivery states $\boldsymbol{s} \in \hat{\mathcal{S}}$ with respect to $u^M(\boldsymbol{s}) - l^M(\boldsymbol{s})$ in ascending order
3: **for** $i = 1..\mathring{N}$ **do**
4: **input**: $l^M(\boldsymbol{s})$, $u^M(\boldsymbol{s})$ for all $\boldsymbol{s} \in \hat{\mathcal{S}}$
5: **for** $\check{\boldsymbol{s}}_1 = 1..|\hat{\mathcal{S}}|$ **do**
6: **for** $\check{\boldsymbol{s}}_2 = 1..(\check{\boldsymbol{s}}_1 - 1)$ **do**
7: **if** $\boldsymbol{s}_1 <_M \boldsymbol{s}_2$ **do**
8: **if** $l^M(\boldsymbol{s}_1) < \eta^M(\boldsymbol{s}_2) < u^M(\boldsymbol{s}_1)$ **do**
9: $l^M(\boldsymbol{s}_1) \leftarrow \eta^M(\boldsymbol{s}_2)$
10: **end if**
11: **if** $\eta^M(\boldsymbol{s}_2) > u^M(\boldsymbol{s}_1)$ **do**
12: $c \leftarrow c + 1$
13: **end if**
14: **end if**
15: **if** $\boldsymbol{s}_2 <_M \boldsymbol{s}_1$ **do**
16: **if** $l^M(\boldsymbol{s}_1) < \eta^M(\boldsymbol{s}_2) < u^M(\boldsymbol{s}_1)$ **do**
17: $u^M(\boldsymbol{s}_1) \leftarrow \eta^M(\boldsymbol{s}_2)$
18: **end if**
19: **if** $\eta^M(\boldsymbol{s}_2) < l^M(\boldsymbol{s}_1)$ **do**
20: $c \leftarrow c + 1$
21: **end if**
22: **end if**
23: **end for**
24: Generate uniform random variable a in $[0, 1]$
25: $\eta^M(\boldsymbol{s}_1) \leftarrow l^M(\boldsymbol{s}_1) + a \times \left(u^M(\boldsymbol{s}_1) - l^M(\boldsymbol{s}_1)\right)$
26: **end for**
27: **end for**

$\check{\boldsymbol{s}}$ (see lines (5)-(6) of Algorithm 2) to denote the order of delivery state $\boldsymbol{s}$ within all delivery states in the sampling process.

Before sampling the cost of delivery state $\boldsymbol{s}_1$ with the order $\check{\boldsymbol{s}}_1$, its bounds are adjusted with respect to the costs sampled (of delivery states $\boldsymbol{s}_2$ with $\check{\boldsymbol{s}}_2 \in \{1, ..., \check{\boldsymbol{s}} - 1\}$) before that particular state. The rationale behind the adjustment scheme is similar with that of Algorithm 1. For a pair of states $\boldsymbol{s}_1$ and $\boldsymbol{s}_2$ where the maternal cost of $\boldsymbol{s}_2$ is already sampled, if we have $\boldsymbol{s}_1 <_M \boldsymbol{s}_2$ and $l^M(\boldsymbol{s}_1) < \eta^M(\boldsymbol{s}_2) < u^M(\boldsymbol{s}_1)$, we adjust $l^M(\boldsymbol{s}_1)$ to be equal to $\eta^M(\boldsymbol{s}_2)$. Similarly, if we have $\boldsymbol{s}_2 <_M \boldsymbol{s}_1$ and

$l^M(\boldsymbol{s}_1) < \eta^M(\boldsymbol{s}_2) < u^M(\boldsymbol{s}_1)$, we adjust $u^M(\boldsymbol{s}_1)$ to be equal to $\eta^M(\boldsymbol{s}_2)$. The maternal cost of $\boldsymbol{s}_1$ is sampled after all possible adjustments are completed, and the procedure moves to the next delivery state with the order $\check{\boldsymbol{s}}_1 + 1$. After maternal costs of all delivery states are sampled within a problem instance, the procedure starts the sampling of next problem instance until $\mathring{N}$ problem instances are generated. Before the generation of each problem instance, the lower and upper bounds are set to their original adjusted values in line (4) of Algorithm 2.

Although they are rare, it is possible to have violations of order restrictions between pairs of states with Algorithm 2. For a pair of states $\boldsymbol{s}_1$ and $\boldsymbol{s}_2$ where the maternal cost of $\boldsymbol{s}_2$ is already sampled, we have a violation if we have $\boldsymbol{s}_1 <_M \boldsymbol{s}_2$ and $\eta^M(\boldsymbol{s}_2) > u^M(\boldsymbol{s}_1)$, or $\boldsymbol{s}_2 <_M \boldsymbol{s}_1$ and $\eta^M(\boldsymbol{s}_2) < l^M(\boldsymbol{s}_1)$. The variable c counts the number of violations within a created problem instance in lines (12) and (20) of Algorithm 2. The sampling process starts with sorting the delivery states with respect to their CI ranges in ascending order (line (2) of Algorithm 2) in an effort to minimize the count of violations. The average counts of violations are 1.7 and 0.2 over 1000 problem instances when the delivery states are sorted with respect to their CI ranges in the sampling of $\eta^M(\boldsymbol{s})$ and $\eta^N(\boldsymbol{s})$, respectively. The same average counts are 7.0 and 8.3 when the costs are sampled in orders randomized in each problem instance. If we do not adjust the bounds as outlined in Algorithm 1, and use this randomized ordering, the average counts of violations are 40.3 and 42.7 in the sampling of $\eta^M(\boldsymbol{s})$ and $\eta^N(\boldsymbol{s})$, respectively.

Similar to the notation used in Chen *et al.* (2017), we use π^j and π^i_α to denote the j^{th} candidate delivery policy and the optimal delivery policy found with α for the i^{th} problem instance, respectively. $V^i_\alpha(\pi^j, \boldsymbol{s})$ denotes the expected cost of candidate policy π^j with α for the i^{th} problem instance for pregnancy state $\boldsymbol{s} \in \mathcal{S} \setminus \hat{\mathcal{S}}$. $\upsilon^i_\alpha(\boldsymbol{s})$ is the expected cost of pregnancy state $\boldsymbol{s} \in \mathcal{S} \setminus \hat{\mathcal{S}}$ with the optimal delivery policy π^i_α

Algorithm 3 Probabilistic sensitivity analysis

Inputs:

α	The weight given to the maternal health outcomes, $\alpha \in [0, 1]$
$\mathring{N}$	The number of problem instances to generate
Π	Set of candidate delivery policies
$\mathcal{P}(\boldsymbol{s}'\|\boldsymbol{s}, \mathtt{W})$	Transition probabilities under the action of waiting
$l^M(\boldsymbol{s}), u^M(\boldsymbol{s})$	Lower and upper bounds of CIs of $\eta^M(\boldsymbol{s})$ for $\boldsymbol{s} \in \hat{\mathcal{S}}$
$l^N(\boldsymbol{s}), u^N(\boldsymbol{s})$	Lower and upper bounds of CIs of $\eta^N(\boldsymbol{s})$ for $\boldsymbol{s} \in \hat{\mathcal{S}}$

Adjust $l^M(\boldsymbol{s}), u^M(\boldsymbol{s}), l^N(\boldsymbol{s})$, and $u^N(\boldsymbol{s})$ with Algorithm 1
Generate $\mathring{N}$ problem instances with Algorithm 2
for $i = 1..\mathring{N}$ **do**
    Compute $v^i_\alpha(\boldsymbol{s})$ for all pregnancy states $\boldsymbol{s} \in \mathcal{S} \setminus \hat{\mathcal{S}}$ with value iteration
end for
for $j = 1..|\mathcal{J}|$ **do**
    for $i = 1..\mathring{N}$ **do**
        Compute $V^i_\alpha(\pi^j, \boldsymbol{s})$ for all pregnancy states $\boldsymbol{s} \in \mathcal{S} \setminus \hat{\mathcal{S}}$
    end for
end for
Calculate $\delta_\alpha(\pi^j, \boldsymbol{s})$ for all $\pi^j \in \Pi$ and $\boldsymbol{s} \in \mathcal{S} \setminus \hat{\mathcal{S}}$
Calculate $\Delta_\alpha(\pi^j)$ for all $\pi^j \in \Pi$

for the i^{th} problem instance. Then, the optimality gap of the j^{th} candidate policy at pregnancy state $\boldsymbol{s}$ is defined as follows:

$$\delta_\alpha(\pi^j, \boldsymbol{s}) = \frac{\sum_{i=1}^{\mathring{N}} \left(V^i_\alpha(\pi^j, \boldsymbol{s}) - v^i_\alpha(\boldsymbol{s}) \right)}{\mathring{N}}. \tag{4.9}$$

The numerator of Equation (4.9) is defined as the *absolute gap* by Chen *et al.* (2017). We measure the performance of each candidate policy with respect to the maximum difference between its optimality gap and the minimum optimality gap (attained by any candidate policy) at a pregnancy state. We denote this measure as $\Delta_\alpha(\pi^j)$ for candidate policy π^j, and define it with Equation (4.10). Algorithm 3 summarizes the procedure of PSA. Its output is the maximum optimality gap $\Delta_\alpha(\pi^j)$ of each candidate policy included in set $\Pi = \{\pi^1, \pi^2, \ldots, \pi^J\}$ over $\mathring{N}$ problem instances.

$$\Delta_\alpha(\pi^j) = \max_{\boldsymbol{s} \in \mathcal{S} \setminus \hat{\mathcal{S}}} \left\{ \delta_\alpha(\pi^j, \boldsymbol{s}) - \min_{\pi^k \in \Pi} \left\{ \delta_\alpha(\pi^k, \boldsymbol{s}) \right\} \right\}. \tag{4.10}$$

In this decision problem, the number of possible decision sequences is 2^{36}, which is about 70 billion with 36 pregnancy states with $\mathcal{A}_{\boldsymbol{s}} = \{\mathtt{W}, \mathtt{I}\}$. Since it is not possible to check all possible decision sequences, a small subset of these policies are included in the set of candidate policies. The main goal is to include reasonable policies that can be adopted in practice. As a result, these policies should be in line with the policies discussed in clinical practice guidelines. These guidelines discuss delivery policies based on a recommended gestational age for delivery with respect to the type of HDP that the mother has (ACOG, 2013b; Magee *et al.*, 2016).

The candidate delivery policies to be included in PSA are constructed as follows. All policies are set to deliver after 40^{th} week of pregnancy when the mother has no HDP. Therefore, a candidate policy is denoted with three gestational ages (t_1, t_2, t_3) each denoting the minimum gestational age at which the action is to intervene in cases of GH, mPE, and sPE, respectively. Only policies with a structure such that $t_1 \geq t_2 \geq t_3$ are included, and t_1, t_2 and t_3 are chosen as even numbers to have a reasonable number of candidate policies. In summary, the set of candidate delivery policies is defined as $\Pi = \{\pi = (t_1, t_2, t_3) : t_1 \geq t_2 \geq t_3;\ \text{and } t_i \leq 40, t_i \in \mathcal{T}, t_i \in 2\mathbb{Z}\ \forall i \in \{1, 2, 3\}\}$, and its size is 20.

We run PSA for $\alpha \in \{0.00, 0.25, 0.50, 0.75, 1.00\}$ with the same $\mathring{N} = 1000$ problem instances. We use the output of ORI-TPM model as estimates of transition probabilities. Table 4.4 presents the results with the order restrictions on maternal health, gestational age, and type of delivery given in Table 4.2. The smallest values of $\Delta_\alpha(\pi^j)$ over all candidate policies in Π are underlined in Table 4.4 for each α value. Since the order restrictions with respect to delivery group have less evidence both for maternal and neonatal cost of delivery states, we additionally run PSA analysis without these order restrictions. Although the values of $\Delta_\alpha(\pi^j)$ are different, the candidate deliveries giving the smallest of those values do not differ significantly.

Policy	$\alpha = 0.00$	$\alpha = 0.25$	$\alpha = 0.50$	$\alpha = 0.75$	$\alpha = 1.00$
(34,34,34)	0.375	0.287	0.201	0.149	0.113
(36,34,34)	0.375	0.287	0.201	0.149	0.113
(36,36,34)	0.375	0.287	0.201	0.144	0.094
(36,36,36)	0.216	0.143	0.078	0.035	**0.009**
(38,34,34)	0.375	0.287	0.201	0.149	0.113
(38,36,34)	0.375	0.287	0.201	0.144	0.094
(38,36,36)	0.216	0.143	0.078	**0.026**	0.013
(38,38,34)	0.375	0.287	0.201	0.144	0.094
(38,38,36)	0.197	0.106	0.022	0.029	0.072
(38,38,38)	0.091	0.038	**0.000**	0.061	0.142
(40,34,34)	0.375	0.287	0.201	0.149	0.113
(40,36,34)	0.375	0.287	0.201	0.144	0.094
(40,36,36)	0.216	0.143	0.078	0.043	0.083
(40,38,34)	0.375	0.287	0.201	0.144	0.094
(40,38,36)	0.197	0.106	0.022	0.043	0.083
(40,38,38)	0.091	0.036	0.014	0.061	0.142
(40,40,34)	0.375	0.287	0.201	0.144	0.123
(40,40,36)	0.197	0.106	0.022	0.059	0.123
(40,40,38)	0.091	0.036	0.018	0.061	0.142
(40,40,40)	**0.000**	**0.000**	0.020	0.075	0.166

Table 4.4: The Optimality Gaps of Candidate Policies Found with PSA

According to Table 4.4, the time to intervene is 40 weeks regardless of the maternal health at α values favoring the neonatal health outcomes (i.e., $\alpha = \{0.00, 0.25\}$). At α values giving more weight to the maternal health outcomes (i.e.,$\alpha = \{0.75, 1.00\}$), the time to intervene is between 36 to 38 weeks, and it decreases with worse maternal health. The time to intervene is 38 weeks when $\alpha = 0.50$ which gives equal weights to maternal and neonatal health outcomes.

We incorporate the RMDP model in PSA to additionally consider the impact of uncertainty in transition probabilities on optimal delivery policies. In this approach, we use lower and upper bounds of transition probabilities under the action of waiting instead of their point estimates. In each problem instance, first we solve for the

Algorithm 4 Probabilistic sensitivity analysis with nature's transition probabilities (rPSA)

Inputs:

α	The weight given to the maternal health outcomes
$\mathring{N}$	The number of problem instances to generate
$\mathcal{P}^l(\boldsymbol{s}'\|\boldsymbol{s},\mathtt{W}),\ \mathcal{P}^u(\boldsymbol{s}'\|\boldsymbol{s},\mathtt{W})$	Lower and upper bounds of CIs of transition probabilities for all $\boldsymbol{s},\boldsymbol{s}' \in \mathcal{S}$
$l^M(\boldsymbol{s}),\ u^M(\boldsymbol{s})$	Lower and upper bounds of CIs of $\eta^M(\boldsymbol{s})$ for $\boldsymbol{s} \in \hat{\mathcal{S}}$
$l^N(\boldsymbol{s}),\ u^N(\boldsymbol{s})$	Lower and upper bounds of CIs of $\eta^N(\boldsymbol{s})$ for $\boldsymbol{s} \in \hat{\mathcal{S}}$
$\{\pi^1, \pi^2, \ldots, \pi^J\}$	Set of candidate delivery policies

Adjust $l^M(\boldsymbol{s}), u^M(\boldsymbol{s}), l^N(\boldsymbol{s})$, and $u^N(\boldsymbol{s})$ with Algorithm 1
Generate $\mathring{N}$ problem instances with Algorithm 2
for $i = 1..\mathring{N}$ **do**
    Compute $\upsilon_\alpha^{R,i}(\boldsymbol{s})$ and $\mathcal{P}^{R,i}(\boldsymbol{s}'|\boldsymbol{s},\mathtt{W})$ for all pregnancy states $\boldsymbol{s} \in \mathcal{S} \setminus \hat{\mathcal{S}}$ with robust dynamic programming
end for
for $j = 1..|\mathcal{J}|$ **do**
    for $i = 1..\mathring{N}$ **do**
        Compute $V_\alpha^i(\pi^j, \boldsymbol{s})$ with $\mathcal{P}^{R,i}(\boldsymbol{s}'|\boldsymbol{s},\mathtt{W})$ for all pregnancy states $\boldsymbol{s} \in \mathcal{S} \setminus \hat{\mathcal{S}}$
    end for
end for
Calculate $\delta_\alpha(\pi^j, \boldsymbol{s})$ for all $\pi^j \in \Pi$ and $\boldsymbol{s} \in \mathcal{S} \setminus \hat{\mathcal{S}}$
Calculate $\Delta_\alpha(\pi^j)$ for all $\pi^j \in \Pi$

optimal value with the robust value function given in Equation (4.3). Outputs are the optimal robust values at pregnancy states (denoted as $\upsilon_\alpha^{R,i}(\boldsymbol{s})$), and the nature's transition probabilities (denoted as $\mathcal{P}^{R,i}(\boldsymbol{s}'|\boldsymbol{s},\mathtt{W})$) in each problem instance. For each candidate policy, we calculate $V_\alpha^i(\pi^j, \boldsymbol{s})$ and the optimality gap $\delta_\alpha(\pi^j, \boldsymbol{s})$ with $\upsilon_\alpha^{R,i}(\boldsymbol{s})$. Algorithm 4 outlines the steps in PSA with nature's transition probabilities (referred as rPSA).

Table 4.5 presents $\Delta_\alpha(\pi^j)$ values for all $\pi^j \in \Pi$ calculated with Algorithm 4 under the order restrictions on maternal health, gestational age, and type of delivery given in Table 4.2. The smallest values of $\Delta_\alpha(\pi^j)$ over all candidate policies in Π are underlined for each α value.

Policy	$\alpha = 0.00$	$\alpha = 0.25$	$\alpha = 0.50$	$\alpha = 0.75$	$\alpha = 1.00$
(34,34,34)	0.363	0.270	0.177	0.100	**0.022**
(36,34,34)	0.363	0.270	0.177	0.100	**0.022**
(36,36,34)	0.363	0.270	0.177	0.100	0.028
(36,36,36)	0.190	0.109	0.039	**0.000**	0.050
(38,34,34)	0.363	0.270	0.177	0.100	0.055
(38,36,34)	0.363	0.270	0.177	0.100	0.055
(38,36,36)	0.190	0.109	0.039	0.008	0.055
(38,38,34)	0.363	0.270	0.177	0.100	0.132
(38,38,36)	0.190	0.093	**0.013**	0.072	0.132
(38,38,38)	0.082	**0.027**	**0.013**	0.099	0.195
(40,34,34)	0.363	0.270	0.177	0.100	0.114
(40,36,34)	0.363	0.270	0.177	0.100	0.114
(40,36,36)	0.190	0.109	0.040	0.071	0.114
(40,38,34)	0.363	0.270	0.177	0.100	0.132
(40,38,36)	0.190	0.093	0.040	0.072	0.132
(40,38,38)	0.082	**0.027**	0.040	0.099	0.195
(40,40,34)	0.363	0.270	0.177	0.101	0.172
(40,40,36)	0.190	0.093	0.073	0.101	0.172
(40,40,38)	0.082	0.046	0.073	0.101	0.195
(40,40,40)	**0.021**	0.046	0.073	0.106	0.198

Table 4.5: The Optimality Gaps of Candidate Policies Found with rPSA

According to Table 4.5, the time to intervene is 40 weeks regardless of the maternal health when only the neonatal health outcomes are considered (i.e., $\alpha = 0.00$). When $\alpha = 0.25$, the time to intervene decreases to 38 weeks for both mPE and sPE. At α values giving more weight to the maternal health outcomes (i.e., $\alpha = \{0.75, 1.00\}$), the time to intervene is between 34 to 36 weeks, and it does not change with respect to maternal health for a given α value. Similar to the PSA results, the time to intervene is 38 weeks when $\alpha = 0.50$.

Maternal	PSA					rPSA				
health	0.00	0.25	0.50	0.75	1.00	0.00	0.25	0.50	0.75	1.00
GH	40	40	38	38	36	40	38-40	38	36	34-36
mPE	40	40	38	36	36	40	38	38	36	34
sPE	40	40	38	36	36	40	38	36-38	36	34

Table 4.6: Time to Intervene with Different α Values

4.4.4 Discussion of Numerical Results

Table 4.6 shows the time to intervene under different α values found with PSA and rPSA. The time to intervene found with rPSA is mostly earlier than the one found in PSA as it can be seen in this table. The only exception is seen when α is zero, i.e., when only the baby is considered. The difference between the results of PSA and rPSA increases as α increases from 0 to 1, since the nature increases the probabilities of reaching worse maternal health states, and maternal health outcomes is more dependent on maternal health state.

When we compare the time to intervene for GH, mPE and sPE found using our PSA (given in the PSA columns of Table 4.6) to the same found by solving the MDP model with the costs of delivery states estimated using the ORI-CDS model (given in Figure A.4), we see that the results mostly agree with each other. For $\alpha \in \{0.00, 0.25\}$, the time to intervene is the 40^{th} week according to both methods for all $h \in \{\text{GH}, \text{mPE}, \text{sPE}\}$. When only the maternal health outcomes are considered with $\alpha = 1.00$, both methods suggests that the time to intervene should be the 36^{th} week for all types of HDP. For $\alpha = 0.50$, the optimal actions given by the MDP model do not form a policy with a structure that can be compared to other α values, and the time to intervene for sPE is beyond the 40^{th} week which is not plausible.

However, the results with PSA clearly show the relation between the weight given to the maternal health outcomes and the time to intervene.

We also compare the time to intervene for GH, mPE, and sPE found using rPSA (given in the rPSA columns of Table 4.6) to the same found by solving the RMDP model with the costs of delivery states estimated using the ORI-CDS model (given in Figure A.13). Unlike the results of the MDP model and the PSA, the results of the RMDP model and the rPSA are mostly quite different from each other for all $\alpha \in \{0.00, 0.25, 0.50, 0.75, 1.00\}$. The optimal actions found with the RMDP model suggest that the time to intervene for sPE should be later than the same of GH and mPE for all $\alpha \in \{0.00, 0.25, 0.50, 0.75\}$, which is not realistic. Therefore, the results of the RMDP model cannot be recommended for use in practice without the insights gathered with our rPSA.

4.5 Conclusions

We develop an MDP model to discover the optimal gestational week to deliver under a choice of weights given to maternal and neonatal health outcomes. In the MDP model, the delivery states representing childbirth are assigned values with respect to maternal health, gestational age (in weeks), and type of delivery in terms of maternal and neonatal adverse outcomes. These values are referred as the costs of delivery states, and quantified separately for the mother and the baby with a composite outcome measure that includes a variety of serious morbidities and mortality. We derive the structural properties of the MDP model, and propose conditions under which the model produces switching curve policies. We solve the MDP model using a value iteration algorithm with two sets of inputs estimated with patient data. These input sets are transition probabilities and the costs (maternal and neonatal) of delivery states.

We estimate transition probabilities and the costs of delivery states with two separate order restricted inference models. In these models, the objective is to maximize the likelihood function subject to the assumed orders between the values of parameters. Since the available patient data is limited and not able to provide ample sample size to estimate the costs of all delivery states, we additionally estimate these costs with MICE method. The results gathered with value iteration algorithm show the sensitivity of model outputs to the estimation of costs of delivery states. Therefore, we develop a PSA framework which considers the joint uncertainty in the costs of delivery states in its search for the best switching curve delivery policies which minimize the maximum optimality gap over all pregnancy states. We additionally consider the uncertainty in transition probabilities with our RMDP model and rPSA approach.

As discussed, there are inconsistencies and gaps in the recommendations for timing of delivery in clinical practice guidelines, and the decision of when to deliver is still a challenge for clinicians (Kuklina *et al.*, 2009; Gillon *et al.*, 2014; Bazzano *et al.*, 2016). As a result, optimal timing of delivery for pregnancies with HDP should be addressed with appropriate decision models. In this study, we consider this decision problem, and model it as an MDP and a robust MDP. MDP modeling is a well-established approach to capture the stochastic nature of disease progression in this problem similar to other problems in previous MDP studies on medical decision-making such as Alagoz *et al.* (2004); Shechter *et al.* (2008), and Sandıkçı *et al.* (2008). Unlike other medical decision problems previously formulated with MDPs, this problem involves two parties, the mother and the baby (or babies), that have conflicting objectives.

Our results demonstrate the impact of timing of delivery on the maternal and neonatal health outcomes, and how the weight given to the maternal (or, neonatal) health outcomes can influence the decision on timing of delivery. Overall, they emphasize the value of expectant management and pregnancy prolongation to improve

neonatal health outcomes. The data under study mostly include Hispanic and Latina patients who received care with Medicaid. As a result, the results of this study may not be generalizable to wider populations.

Major clinical practice guidelines agree on recommending delivery after 37 weeks in case of gestational hypertension and preeclampsia. Our results with $\alpha \geq 0.5$ support this recommendation. On the other hand, immediate delivery is recommended in case for severe preeclampsia regardless of the gestational age in the guidelines. Our results with different α values show the trade-off between maternal and neonatal outcomes in this recommendation. The guidelines do not agree on a recommendation for gestational hypertension and preeclampsia at gestational age of 34-36 weeks. Our results show how the risks for serious morbidities change during these weeks with respect to timing of delivery. We refer interested readers to Bazzano *et al.* (2016) for a discussion of recommendations of major HDP guidelines on timing of delivery.

One of the key challenges in this study lies in obtaining the patient data that allows for connecting the information between mother and baby. National databases in the United States such as The Nationwide Inpatient Sample (NIS) of the Healthcare Cost and Utilization Project are de-identified, and as a result, it is not possible to associate the neonatal health outcomes with maternal health. Another key challenge is in the complexity of measuring the health outcomes in obstetrics. The problem involves a variety of health outcomes with varying severity that are often rare, and the composite measures developed to combine these outcomes are not widely used due to difficulties in their interpretation. We refer interested readers to Ross (2007) for a discussion on the use of composite measures in obstetrics research. We have found CCM measure (Korst *et al.*, 2014) to be the most suitable one to adopt in this study, since it is the most comprehensive measure in the obstetrics literature that includes a wide variety of serious morbidities. However, it can be only used with ICD-9-CM

diagnosis coding, and the translation to next revision of diagnosis coding (ICD-10) is not straightforward.

In summary, we address the decision problem of optimal timing of delivery for women with HDP in this study. We develop an MDP model that considers the uncertainty in the progression of hypertensive disorders in the course of a pregnancy. This is the first study that handles this problem as a sequential and stochastic decision problem in which the uncertainty and dynamism of disease progression are taken into account. In addition, this study pioneers in considering the conflicting objectives of the mother and the baby, and combining them in the same decision model.

Chapter 5

CONCLUSIONS

In this chapter, we summarize the contributions of this dissertation, and outline the directions for future research. The most important contribution of this dissertation is to study the optimal timing of delivery in the cases of hypertensive disorders of pregnancy (HDP) that minimize the adverse outcomes due to childbirth by considering both the mother and the baby. Below is the summary of all contributions together with the chapters that they are included in.

We model the natural history of HDP progression in a retrospective observational cohort study in Chapter 2. We build a discrete-time Markov chain (DTMC) model that includes maternal health (presence and type of HDP), gestational age, and state of being pregnant or having spontaneous labor in the state definition. We estimate the transition probabilities of the DTMC for the third trimester of pregnancy based on patient data using an order restricted inference model. Using the estimated transition probabilities, we show the trends in the risks of developing HDP and going into spontaneous labor with respect to maternal health and gestational age.

We assess the risks of maternal and neonatal adverse outcomes that may happen due to childbirth in Chapter 3. In this part of the dissertation, we review current obstetrical quality measures and evaluate their use in a medical decision making framework. We estimate the risk of significant childbirth morbidities with respect to maternal health (presence and type of HDP) at delivery, gestational age at delivery, and mode of delivery separately for the mother and the newborn based on patient data using a composite obstetrical measure. Additionally, we estimate the safety of childbirth for the mother and the newborn with respect to the same variables with

a provider survey and technique for order performance by similarity to ideal solution (TOPSIS).

In Chapter 4, we study of the optimal timing of delivery for pregnancies complicated with HDP. First, we build a Markov decision process (MDP) model that provides the optimal timing of delivery with two sets of inputs: (1) transition probabilities of HDP progression and going into spontaneous labor, (2) the risks of significant maternal and neonatal morbidities due to childbirth stratified by maternal health, gestational age and mode of delivery. Secondly, we build a robust MDP (RMDP) model that gives the worst-case timing of delivery by taking the uncertainty in the estimation of transition probabilities into account. We analytically explore the structural properties of the MDP and the RMDP models to show how a certain structure on the input may provide a certain structure on the optimal solution such as *monotone switching curve policies*.

In Chapter 4, we solve our MDP and RMDP models to obtain the optimal timing of delivery in cases of HDP with different weights given to maternal and neonatal health outcomes. We analyze the results of both the MDP and the RMDP models within a probabilistic sensitivity analysis (PSA) framework to consider the joint uncertainty in the estimations of the risks of maternal and neonatal adverse outcomes. In our PSA, we include the order restrictions between the risk estimates in the generation of problem instances to avoid having unrealistic instances. Since the outputs of MDP models are often sensitive to parameter estimates which are usually obtained using patient data which may be limited in size and include errors, the results of MDP models should be evaluated with a sensitivity analysis. To the best of our knowledge, our study is the first that incorporates PSA with order restrictions between parameters, and combine robustness with respect to transition probabilities within a PSA framework.

In future research, our decision model can be extended by including the blood pressure values in the state definition to consider the impact of blood pressure elevations in the disease progression. In a broader perspective, the decision of timing of delivery is also vital in other maternal complications such as diabetes and chronic hypertension. This study can lead the way to the adaptation of stochastic modeling for other obstetric complications that makes timing of delivery challenging.

In addition to the timing of delivery, the type of intervention (induction of labor vs. cesarean delivery) may be also crucial when the pregnant woman has a type of HDP. Even for healthy pregnant women, the interventions of induction of labor and cesarean delivery are still topics of debate and should be resolved based on evidence on risks and benefits (Anderson, 2004). In this dissertation, we could not address the optimal type of intervention due to the limited sample sizes to estimate the risks of adverse outcomes (especially for induction of labor) in our patient data. However, this issue should be addressed in the future by extending our MDP models with the addition of delivery states representing different types of interventions.

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APPENDIX A

APPENDICES OF CHAPTER 4

A.1 Proofs of Chapter 4

For Lemma 1 and Proposition 1, we demonstrate the proofs of only the parts on the robust Markov decision process (RMDP) model. The parts on the Markov decision process (MDP) model are proved when $\mathcal{Q}$ is considered as a singleton set with one point estimate of transition probabilities.

Proof of Lemma 4.1. If $\eta(h,t,I) > f^R(h,t)$ for some $\boldsymbol{s} = (h,t,P)$ where $h \in \mathcal{H}$ and $t \leq T-1$, then the following inequalities hold:

$$\begin{aligned}\eta(h,t,I) &> \max_{\substack{\mathcal{P}(h',t^+,d'|h,t,P;\mathtt{W}) \\ \in \mathcal{Q}_{(h,t,P)}}} \Bigg\{ \sum_{h' \leq h} \mathcal{P}(h',t^+,P|h,t,P;\mathtt{W})\eta(h',t^+,I) \\ &\qquad + \sum_{h' \leq h} \mathcal{P}(h',t^+,S|h,t,P;\mathtt{W})\eta(h',t,S) \Bigg\} \\ &\geq \max_{\substack{\mathcal{P}(h',t^+,d'|h,t,P;\mathtt{W}) \\ \in \mathcal{Q}_{(h,t,P)}}} \Bigg\{ \sum_{h' \leq h} \mathcal{P}(h',t^+,P|h,t,P;\mathtt{W})\upsilon^R(h',t^+,P) \\ &\qquad + \sum_{h' \leq h} \mathcal{P}(h',t^+,S|h,t,P;\mathtt{W})\eta(h',t,S) \Bigg\}. \quad \text{(A.1)}\end{aligned}$$

The first inequality in Equation (A.1) is due to the definition of the function $f^R(h,t)$. As a result of Bellman's equation, we have $\upsilon^R(h,t,P) \leq \eta(h,t,I)$ for all $h \in \mathcal{H}$ and $t \in \mathcal{T}$. The first inequality can be preserved by replacing $\eta(h,t,I)$ with $\upsilon^R(h,t,P)$. The second inequality implies that the cost of intervention is greater that the expected robust cost of waiting. Therefore, $a^*(h,t,P) = \mathtt{W}$, uniquely. □

Proof of Lemma 4.2. Let $c(h,t,P)$ and $c^R(h,t,P)$ denote the cost of waiting at pregnancy state $\boldsymbol{s} = (h,t,P)$ in the MDP and the RMDP models, respectively. We define the functions $c(h,t,P)$ and $c^R(h,t,P)$ with Equations (A.2) and (A.3) as follows for $t \leq T-1$.

$$c(h,t,P) = \sum_{h' \leq h} \mathcal{P}(h',t^+,P|h,t,P;\mathtt{W})\upsilon(h',t^+,P) + \sum_{h' \leq h} \mathcal{P}(h',t^+,S|h,t,P;\mathtt{W})\eta(h',t,S) \quad \text{(A.2)}$$

$$c^R(h,t,P) = \max_{\mathcal{P}(h',t^+,d'|h,t,P;\mathtt{W})\in\mathcal{Q}_{(h,t,P)}} \Bigg\{ \sum_{h'\le h} \mathcal{P}(h',t^+,P|h,t,P;\mathtt{W})\upsilon^R(h',t^+,P) + \sum_{h'\le h} \mathcal{P}(h',t^+,S|h,t,P;\mathtt{W})\eta(h',t,S) \Bigg\} \quad \text{(A.3)}$$

Once we show that $c^R(h,t,P) \ge c(h,t,P)$ for all pregnancy states $\boldsymbol{s} = (h,t,P) \in \mathcal{S} \setminus \hat{\mathcal{S}}$, then the proof of Lemma 2 is straightforward. At gestational age $T-1$, we have $c^R(h,T-1,P) \ge c(h,T-1,P)$ for all $h \in \mathcal{H}$. We show that $c^R(h,t,P) \ge c(h,t,P)$ holds for week t by supposing that it holds for t^+ (i.e., $c^R(h,t^+,P) \ge c(h,t^+,P)$) for all $h \in \mathcal{H}$ and $t \le T-2$. At gestational age t^+, if $c^R(h,t^+,P) \ge c(h,t^+,P)$, then we have $\upsilon^R(h,t^+,P) \ge \upsilon(h,t^+,P)$, and the inequalities shown below.

$$\begin{aligned}
c^R(h,t,P) &= \max_{\mathcal{P}(h',t^+,d'|h,t,P;\mathtt{W})\in\mathcal{Q}_{(h,t,P)}} \Bigg\{ \sum_{h'\le h} \mathcal{P}(h',t^+,P|h,t,P;\mathtt{W})\upsilon^R(h',t^+,P) + \sum_{h'\le h} \mathcal{P}(h',t^+,S|h,t,P;\mathtt{W})\eta(h',t,S) \Bigg\} \\
&\ge \max_{\mathcal{P}(h',t^+,d'|h,t,P;\mathtt{W})\in\mathcal{Q}_{(h,t,P)}} \Bigg\{ \sum_{h'\le h} \mathcal{P}(h',t^+,P|h,t,P;\mathtt{W})\upsilon(h',t^+,P) + \sum_{h'\le h} \mathcal{P}(h',t^+,S|h,t,P;\mathtt{W})\eta(h',t,S) \Bigg\} \\
&\ge \sum_{h'\le h} \mathcal{P}(h',t^+,P|h,t,P;\mathtt{W})\upsilon(h',t^+,P) + \sum_{h'\le h} \mathcal{P}(h',t^+,S|h,t,P;\mathtt{W})\eta(h',t,S) \\
&= c(h,t,P) \qquad \text{(A.4)}
\end{aligned}$$

□

Proof of Proposition 4.1. For a given $\alpha \in [0,1]$, first suppose that $a^*(h,t,P) = \mathtt{I}$ for all $h \le \check{h}$ and $t \ge \check{t}$ where $h, \check{h} \in \mathcal{H}$, $t, \check{t} \in \mathcal{T}$, and $\check{t} \le T-1$. As a result, we have $\upsilon^R(h,t,P) = \eta(h,t,I)$ for all $h \le \check{h}$ and $t \ge \check{t}$. We also know that $\upsilon^R(h,t,P)$

satisfies Bellman's equation of RMDP which can be written as follows under Assumption 4.1 for all $h \leq \check{h}, t \geq \check{t}, t \leq T-1$:

$$\upsilon^R(h,t,P) = \min\Bigg\{ \max_{\mathcal{P}(h',t^+,d'|h,t,P;\mathtt{W})\in\mathcal{Q}} \Bigg\{ \sum_{h'\leq h} \mathcal{P}(h',t^+,P|h,t,P;\mathtt{W})\upsilon(h',t^+,P) + \sum_{h'\leq h} \mathcal{P}(h',t^+,S|h,t,P;\mathtt{W})\eta(h',t,S)\Bigg\},\ \eta(h,t,I)\Bigg\}$$

Additionally, we have $\upsilon(h,t,P) = \eta(h,t,I)$ for all $h \in \mathcal{H}$ and $t = T$. Having $\upsilon(h,t,P) = \eta(h,t,I)$ for all $h \leq \check{h}$ and $t \geq \check{t}$ implies the following inequalities.

$$\begin{aligned}\eta(h,t,I) &\leq \max_{\mathcal{P}(h',t^+,d'|h,t,P;\mathtt{W})\in\mathcal{Q}} \Bigg\{ \sum_{h'\leq h} \mathcal{P}(h',t^+,P|h,t,P;\mathtt{W})\upsilon(h',t^+,P) + \sum_{h'\leq h} \mathcal{P}(h',t^+,S|h,t,P;\mathtt{W})\eta(h',t,S)\Bigg\} \\ &= \max_{\mathcal{P}(h',t^+,d'|h,t,P;\mathtt{W})\in\mathcal{Q}} \Bigg\{ \sum_{h'\leq h} \mathcal{P}(h',t^+,P|h,t,P;\mathtt{W})\eta(h',t^+,I) + \sum_{h'\leq h} \mathcal{P}(h',t^+,S|h,t,P;\mathtt{W})\eta(h',t,S)\Bigg\} \\ &= f(h,t), \quad \forall h \leq \check{h}, t \geq \check{t}, t \neq T.\end{aligned}$$

The first inequality is an outcome of the minimum operator in the definition of the value function for transient states $\boldsymbol{s} = (h,t,P) \in \mathcal{S} \setminus \hat{\mathcal{S}}$. The equality following that is derived from that by replacing $\upsilon^R(h',t^+,P)$ with $\eta(h',t^+,I)$ which are equal since $a^*(h,t,P) = \mathtt{I}$ for all $h \leq \check{h}$ and $t \geq \check{t}$. The last equality is due to the definition of the function $f^R(h,t)$ given by Equation (4.5) under Assumption 4.1. The first and final lines correspond to the conditions given in the proposition.

For a given $\alpha \in [0,1]$, secondly suppose that $\eta(h,t,I) \leq f^R(h,t)$ for all $h \leq \check{h}, t \geq \check{t}, t \neq T$. Bellman's equation is satisfied for the transient states with $h \leq \check{h}$ and $t \geq \check{t}$ when we let $\upsilon^R(h,t,P) = \eta(h,t,I)$ for all $h \leq \check{h}$ and $t \geq \check{t}$ as it is demonstrated

below. We start with writing Bellman's equation under Assumption 4.1 and continue with simplifying by using $\upsilon^R(h,t,P) = \eta(h,t,I)$ separately for all $h \leq \check{h}, t \geq \check{t}, t \neq T$ and $h \leq \check{h}, t = T$.

$$\upsilon^R(h,t,P) = \min\Bigg\{ \max_{\mathcal{P}(h',t^+,d'|h,t,P;\mathtt{W})\in\mathcal{Q}} \Bigg\{ \sum_{h'\leq h} \mathcal{P}(h',t^+,P|h,t,P;\mathtt{W})\upsilon(h',t^+,P) + \sum_{h'\leq h} \mathcal{P}(h',t^+,S|h,t,P;\mathtt{W})\eta(h',t,S)\Bigg\},\ \eta(h,t,I)\Bigg\}$$

Replacing $\upsilon^R(h',t^+,P)$ with $\eta(h',t^+,I)$, and simplifying by using the function $f^R(h,t)$ give us the following equalities. The last equality is due to the condition $\eta(h,t,I) \leq f^R(h,t)$ for all $h \leq \check{h}, t \geq \check{t}, t \neq T$.

$$\upsilon^R(h,t,P) = \min\big\{f^R(h,t), \eta(h,t,I)\big\} = \eta(h,t,I) \quad \forall h \leq \check{h}, t \geq \check{t}, t \neq T$$

Similarly, for $h \leq \check{h}, t = T$, we have $\upsilon^R(h,t,P) = \eta(h,t,I)$ due to Bellman's equation. As a result, $a^*(h,t,P) = \mathtt{I}$ for all $h \leq \check{h}$ and $t \geq \check{t}$ since $\upsilon^R(h,t,P) = \eta(h,t,I)$. $\square$

Proof of Proposition 4.2. In this proof, we show that there exists a monotone switching curve that separates the action of waiting from the action of intervention under Conditions (1)-(2) in the MDP model. In order to do this, we prove that $a^*(h,t,P) = \mathtt{W} \Rightarrow a^*(h^+,t,P) = \mathtt{W}$, and $a^*(h,t,P) = \mathtt{W} \Rightarrow a^*(h,t^-,P) = \mathtt{W}$. The proof is similar for the RMDP model with Conditions (3)-(4).

For $t = T$, $a(h,t,P) = \mathtt{I}$; as a result $h^*(T)$ does not exist. So, consider $t = T-1$ which is the largest t that has $\mathtt{W} \in \mathcal{A}_{\boldsymbol{s}}$ where $\boldsymbol{s} = (h, T-1, P)$. Let $\tilde{h}$ be the smallest h such that $a^*(h,T-1,P) = \mathtt{W}$. If there is no such $\tilde{h}$, we continue with $t = T-2$ or the largest t which has waiting as the optimal action for any h.

By Assumption 4.1 and $a^*(\tilde{h},T-1,P) = \mathtt{W}$, we have:

$$\sum_{h'\leq\tilde{h}} \mathcal{P}(h',T,P|\tilde{h},T-1,P;\mathtt{W})\upsilon(h',T,P) + \sum_{h'\leq\tilde{h}} \mathcal{P}(h',T,S|\tilde{h},T-1,P;\mathtt{W})\eta(h',T-1,S) < \eta(\tilde{h},T-1,I)$$

We know that $\upsilon(h,T,P) = \eta(h,T,I)$ since $a(h,T,P) = \texttt{I}$. Adding this to the above inequality gives:

$$\sum_{h' \leq \tilde{h}} \mathcal{P}(h',T,P|\tilde{h},T-1,P;\texttt{W})\eta(h',T,I) + \sum_{h' \leq \tilde{h}} \mathcal{P}(h',T,S|\tilde{h},T-1,P;\texttt{W})\eta(h',T-1,S) < \eta(\tilde{h},T-1,I).$$

Due to the definition of the function $f(h,t)$ given by Equation (4.4), it follows that

$$f(\tilde{h},T-1) < \eta(\tilde{h},T-1,I). \tag{A.5}$$

Adding $f(\tilde{h}^+,T-1) - f(\tilde{h},T-1)$ (the left-hand side of Condition (1.1)) to the left-hand side and $\eta(\tilde{h}^+,T-1,I) - \eta(\tilde{h},T-1,I)$ (the right-hand side of Condition (1.1)) to the right-hand side in Inequality (A.5) provide:

$$f(\tilde{h}^+,T-1) < \eta(\tilde{h}^+,T-1,I).$$

As a result, we show that if the inequality given in Equation (A.5) holds for $\tilde{h}$, it holds for $\tilde{h}^+$ under Condition (1.1). Therefore, we have $f(\tilde{h},T-1) < \eta(\tilde{h},T-1,I)$ for all $h \geq \tilde{h}$.

Similarly, adding $f(\tilde{h},T-2) - f(\tilde{h},T-1)$ (the left-hand side of Condition (1.2)) to the left-hand side and $\eta(\tilde{h},T-2,I) - \eta(\tilde{h},T-1,I)$ (the right-hand side of Condition (1.2)) to the right-hand side in Inequality (A.5) provide:

$$f(\tilde{h},T-2) < \eta(\tilde{h},T-2,I).$$

As a result, we show that if the inequality given in Equation (A.5) holds for $\boldsymbol{s} = (\tilde{h},T-1,P)$, it holds for $\boldsymbol{s} = (h,t,P)$ where $h \geq \tilde{h}, t \leq T-1$ due to Conditions (1.1) and (1.2). Therefore, we have $f(h,t) < \eta(h,t,I)$ for all $h \geq \tilde{h}$ and $t \leq T-1$.

Due to above statements and the definition of $f(h,t)$, the cost of waiting in state (h,t,P) and taking the optimal action for all possible next states cannot be worse

than the cost of $f(h,t)$. As a result, $v^*(h,t,P) < \eta(h,t,I)$ for all $h \geq \tilde{h}$ and $t \leq T-1$. As a result, $a^*(h,t,P) = \texttt{W}$ for all $h \geq h'$ and $t \leq T-1$.

Next, consider $t = T-2$ where $\tilde{h}'$ is the smallest h such that $a^*(h,T-2,P) = \texttt{W}$. By a similar reasoning, we have $a^*(h,t,P) = \texttt{W}$ for all $h \geq \tilde{h}'$ and $t \leq T-2$. Proceeding with a similar fashion for other gestational ages, proves the parts (a) and (b) of the proposition. □

Proof of Proposition 4.3. Under conditions (1)-(4), we know that there exists a switching curve policy separately for the MDP and the RMDP models. Suppose that we have $t^*(\check{h}) = \check{t}$ for a given $\check{h} \in \mathcal{H}$ in the MDP model. To prove Proposition 4.3.1, we show that $t_R^*(\check{h}) \leq \check{t}$ for any $\check{h} \in \mathcal{H}$ in the RMDP model.

Since $t^*(\check{h}) = \check{t}$, then the following condition holds due to Proposition 1,

$$\eta(h,t,I) \leq f(h,t), \quad \forall h \leq \check{h},\ t \geq \check{T},\ t \leq T-1. \tag{A.6}$$

We also know that $f(h,t) \leq f^R(h,t)$ for all $h \leq \check{h}$, $t \geq \check{T}$, and $t \leq T-1$ due to the maximization operator in the definition of $f^R(h,t)$. As a result, we have,

$$\eta(h,t,I) \leq f(h,t) \leq f^R(h,t), \quad \forall h \leq \check{h},\ t \geq \check{T},\ t \leq T-1. \tag{A.7}$$

By Propositon 1, we can conclude that $a^*(h,t) = \texttt{I}$ for all states with $h \leq \check{h}$ and $t \geq \check{T}$. As a result, we have $t_R^*(\check{h}) \leq \check{t} = t^*(\check{h})$.

□

A.2 Order Restricted Inference Model of the Costs of Delivery States

We denote the order restricted inference model of the costs of delivery states (CDS) with ORI-CDS. The decision variables of the ORI-CDS model are as follows:

M_{htd}**:** The estimate of $\eta^M(h,t,d)$ for all $h \in \mathcal{H}$, $t \in \mathcal{T}$ and $d \in \{S,I\}$,

N_{htd}**:** The estimate of $\eta^N(h,t,d)$ for all $h \in \mathcal{H}$, $t \in \mathcal{T}$ and $d \in \{S,I\}$.

The parameters of the ORI-CDS model are as follows. The confidence intervals (CIs) are calculated with the adjusted Wald method.

n_{htd} : The number of child deliveries observed at state (h, t, d)

c^M_{htd} : The number of maternal composite outcomes observed at state (h, t, d)

c^N_{htd} : The number of neonatal composite outcomes observed at state (h, t, d)

L^M_{htd} : Lower bound of the CI for estimate of $\eta^M(h, t, d)$

L^N_{htd} : Lower bound of the CI for estimate of $\eta^N(h, t, d)$

U^M_{htd} : Upper bound of the CI for estimate of $\eta^M(h, t, d)$

U^N_{htd} : Upper bound of the CI for estimate of $\eta^N(h, t, d)$

The objective function is to maximize the likelihood function that includes the estimations of $\eta^M(h, t, d)$ and $\eta^N(h, t, d)$ for all $h \in \mathcal{H}$, $t \in \mathcal{T}$ and $d \in \{S, I\}$ as given in Equation (A.8). Equivalently, we maximize the logarithm of this objective function which is given in Equation (A.9).

$$\text{Maximize } \mathcal{L} = \prod_{h\in\mathcal{H}} \prod_{t\in\mathcal{T}} \prod_{d\in S,I} \left((M_{htd})^{c^M_{htd}} (1 - M_{htd})^{\left(n_{htd} - c^M_{htd}\right)} \right) \times \left((N_{htd})^{c^N_{htd}} (1 - N_{htd})^{\left(n_{htd} - c^N_{htd}\right)} \right) \tag{A.8}$$

$$\begin{aligned} \text{Maximize } \log \mathcal{L} = & \sum_{h\in\mathcal{H}} \sum_{t\in\mathcal{T}} \sum_{d\in S,I} \left(c^M_{htd} \log M_{htd} + (n_{htd} - c^M_{htd}) \log (1 - M_{htd}) \right) \\ & + \sum_{h\in\mathcal{H}} \sum_{t\in\mathcal{T}} \sum_{d\in S,I} \left(c^N_{htd} \log N_{htd} + (n_{htd} - c^N_{htd}) \log (1 - N_{htd}) \right) \end{aligned} \tag{A.9}$$

The constraints of the model are enumerated as follows. Below, we have $h^+ = h+1$, and $t^+ = t + 1$.

1. The estimates should be within the given lower and upper bounds.

   $L^M_{htd} \leq M_{htd} \leq U^M_{htd}$ for $h \in \mathcal{H}$, $t \in \mathcal{T}$, and $d \in \{S, I\}$

   $L^N_{htd} \leq N_{htd} \leq U^N_{htd}$ for $h \in \mathcal{H}$, $t \in \mathcal{T}$, and $d \in \{S, I\}$

2. The risk of maternal composite outcome increases with deteriorating maternal health.

   $M_{htd} \leq M_{h^+td}$ for $h, h^+ \in \mathcal{H}$, $t \in \mathcal{T}$, and $d \in \{S, I\}$

3. The risk of maternal composite outcome decreases with gestational age until 38^{th} week, and increases after that week.

   (a) $M_{htd} \geq M_{ht^+d}$ for $h, h^+ \in \mathcal{H}$, $t < 38$, and $d \in \{S, I\}$

   (b) $M_{htd} \leq M_{ht^+d}$ for $h, h^+ \in \mathcal{H}$, $t \geq 38$, and $d \in \{S, I\}$

4. The risk of maternal composite outcome is greater for delivery with spontaneous labor than delivery with intervention.

   $M_{htS} \geq M_{htI}$ for $h \in \mathcal{H}$, and $t \in \mathcal{T}$

5. The risk of neonatal composite outcome increases with deteriorating maternal health.

   $N_{htd} \leq N_{h^+td}$ for $h, h^+ \in \mathcal{H}$, $t \in \mathcal{T}$, and $d \in \{S, I\}$

6. The risk of neonatal composite outcome decreases with gestational age.

   $N_{htd} \geq N_{ht^+d}$ for $h, h^+ \in \mathcal{H}$, $t < 41$, and $d \in \{S, I\}$

7. The risk of neonatal composite outcome is greater for delivery with intervention than delivery with spontaneous labor.

   $N_{htS} \leq N_{htI}$ for $h \in \mathcal{H}$, and $t \in \mathcal{T}$

8. Non-negativity constraints.

   M_{htd}, $N_{htd} \geq 0$ for $h \in \mathcal{H}$, $t \in \mathcal{T}$, and $d \in \{S, I\}$

A.3 The Optimal Delivery Policies

Figures A.1-A.9 and Figures A.10-A.18 show the optimal delivery policies found with different sets of the CDS and α values using the MDP and the RMDP models, respectively.

α = 0.00

Maternal	Gestational age								
health	33	34	35	36	37	38	39	40	41
N	W	W	W	W	W	W	W	W	W
GH	W	W	I	W	W	W	W	W	W
mPE	W	W	W	W	W	W	I	W	I
sPE	W	W	W	W	W	W	W	W	I

α = 0.75

Maternal	Gestational age								
health	33	34	35	36	37	38	39	40	41
N	W	W	W	W	W	I	I	W	I
GH	W	W	W	W	I	I	W	I	W
mPE	W	W	W	W	I	I	W	I	I
sPE	W	W	W	I	W	I	I	W	I

α = 0.25

Maternal	Gestational age								
health	33	34	35	36	37	38	39	40	41
N	W	W	W	W	W	W	W	W	I
GH	W	W	I	W	W	W	W	W	W
mPE	W	W	W	W	W	I	W	W	I
sPE	W	W	W	W	W	W	W	W	I

α = 1.00

Maternal	Gestational age								
health	33	34	35	36	37	38	39	40	41
N	W	W	W	W	W	I	I	I	I
GH	I	W	W	W	I	I	I	I	I
mPE	W	W	W	I	I	I	W	I	I
sPE	I	W	W	I	W	I	I	W	I

α = 0.50

Maternal	Gestational age								
health	33	34	35	36	37	38	39	40	41
N	W	W	W	W	W	W	W	W	I
GH	W	W	W	W	I	I	W	W	W
mPE	W	W	W	W	W	I	W	I	I
sPE	W	W	W	I	W	I	I	I	I

Figure A.1: The Optimal Policy Found with Maximum Likelihood Estimates of the CDS

α = 0.00									
Maternal	Gestational age								
health	33	34	35	36	37	38	39	40	41
N	W	W	W	W	W	W	W	W	I
GH	W	W	W	W	W	W	W	W	W
mPE	W	W	W	W	W	W	I	W	I
sPE	W	W	W	W	W	W	W	W	I

α = 0.75									
Maternal	Gestational age								
health	33	34	35	36	37	38	39	40	41
N	W	W	W	W	W	I	I	I	I
GH	W	W	W	W	W	I	W	I	I
mPE	W	W	W	W	I	I	W	I	I
sPE	W	W	W	I	W	I	W	W	I

α = 0.25									
Maternal	Gestational age								
health	33	34	35	36	37	38	39	40	41
N	W	W	W	W	W	W	W	W	I
GH	W	W	W	W	W	W	W	W	I
mPE	W	W	W	W	W	I	W	I	I
sPE	W	W	W	W	W	W	W	W	I

α = 1.00									
Maternal	Gestational age								
health	33	34	35	36	37	38	39	40	41
N	W	W	W	W	W	I	I	I	I
GH	W	W	W	W	I	I	I	I	I
mPE	W	W	W	W	I	I	W	I	I
sPE	I	W	W	I	W	I	I	W	I

α = 0.50									
Maternal	Gestational age								
health	33	34	35	36	37	38	39	40	41
N	W	W	W	W	W	W	I	W	I
GH	W	W	W	W	W	I	W	I	I
mPE	W	W	W	W	W	I	W	I	I
sPE	W	W	W	I	W	I	W	W	I

Figure A.2: The Optimal Policy Found with Wilson's Estimates of the CDS

α = 0.00									
Maternal	Gestational age								
health	33	34	35	36	37	38	39	40	41
N	W	W	W	W	W	W	W	W	W
GH	W	W	W	W	W	W	W	W	W
mPE	W	W	W	W	W	W	W	W	W
sPE	W	W	W	W	W	W	W	W	W

α = 0.75									
Maternal	Gestational age								
health	33	34	35	36	37	38	39	40	41
N	W	W	W	W	W	I	I	I	I
GH	W	W	W	W	I	I	I	I	I
mPE	W	W	W	W	I	I	I	I	I
sPE	W	W	W	W	W	I	I	I	I

α = 0.25									
Maternal	Gestational age								
health	33	34	35	36	37	38	39	40	41
N	W	W	W	W	W	W	W	W	W
GH	W	W	W	W	W	W	W	W	W
mPE	W	W	W	W	W	W	W	W	W
sPE	W	W	W	W	W	W	W	W	W

α = 1.00									
Maternal	Gestational age								
health	33	34	35	36	37	38	39	40	41
N	W	W	W	W	W	I	I	I	I
GH	W	W	W	I	I	I	I	I	I
mPE	W	W	W	I	I	I	I	I	I
sPE	I	W	W	I	I	I	I	I	I

α = 0.50									
Maternal	Gestational age								
health	33	34	35	36	37	38	39	40	41
N	W	W	W	W	W	W	I	W	I
GH	W	W	W	W	W	I	W	I	W
mPE	W	W	W	W	W	I	I	I	I
sPE	W	W	W	W	W	W	W	W	W

Figure A.3: The Optimal Policy Found with the Estimates of ORI-CDS Model Including the Order Restrictions on Maternal Health and Gestational Age

α = 0.00

Maternal health	Gestational age 33	34	35	36	37	38	39	40	41
N	W	W	W	W	W	W	W	W	W
GH	W	W	W	W	W	W	W	W	W
mPE	W	W	W	W	W	W	W	W	W
sPE	W	W	W	W	W	W	W	W	W

α = 0.75

Maternal health	Gestational age 33	34	35	36	37	38	39	40	41
N	W	W	W	W	W	I	I	I	I
GH	W	W	W	W	I	I	I	I	I
mPE	W	W	W	W	I	I	I	I	I
sPE	W	W	W	W	W	I	I	I	I

α = 0.25

Maternal health	Gestational age 33	34	35	36	37	38	39	40	41
N	W	W	W	W	W	W	W	W	W
GH	W	W	W	W	W	W	W	W	W
mPE	W	W	W	W	W	W	W	W	W
sPE	W	W	W	W	W	W	W	W	W

α = 1.00

Maternal health	Gestational age 33	34	35	36	37	38	39	40	41
N	W	W	W	W	W	I	I	I	I
GH	W	W	W	I	I	I	I	I	I
mPE	W	W	W	I	I	I	I	I	I
sPE	I	W	W	I	I	I	I	I	I

α = 0.50

Maternal health	Gestational age 33	34	35	36	37	38	39	40	41
N	W	W	W	W	W	W	I	W	I
GH	W	W	W	W	W	I	W	I	W
mPE	W	W	W	W	W	I	I	I	I
sPE	W	W	W	W	W	W	W	W	W

Figure A.4: The Optimal Policy Found with the Estimates of ORI-CDS Model Including All Order Restrictions

α = 0.00

Maternal health	Gestational age 33	34	35	36	37	38	39	40	41
N	I	I	W	I	I	I	W	W	W
GH	I	I	W	W	W	W	W	I	I
mPE	I	I	W	W	W	W	I	I	I
sPE	I	I	W	W	W	W	W	W	I

α = 0.75

Maternal health	Gestational age 33	34	35	36	37	38	39	40	41
N	W	W	W	W	W	I	I	I	I
GH	I	W	W	W	W	I	I	I	I
mPE	I	I	W	W	I	I	I	I	I
sPE	I	I	W	I	I	I	I	I	I

α = 0.25

Maternal health	Gestational age 33	34	35	36	37	38	39	40	41
N	I	W	W	W	W	I	I	I	I
GH	I	I	W	W	W	I	I	I	I
mPE	I	I	W	W	W	W	I	I	I
sPE	I	I	W	W	I	W	I	I	I

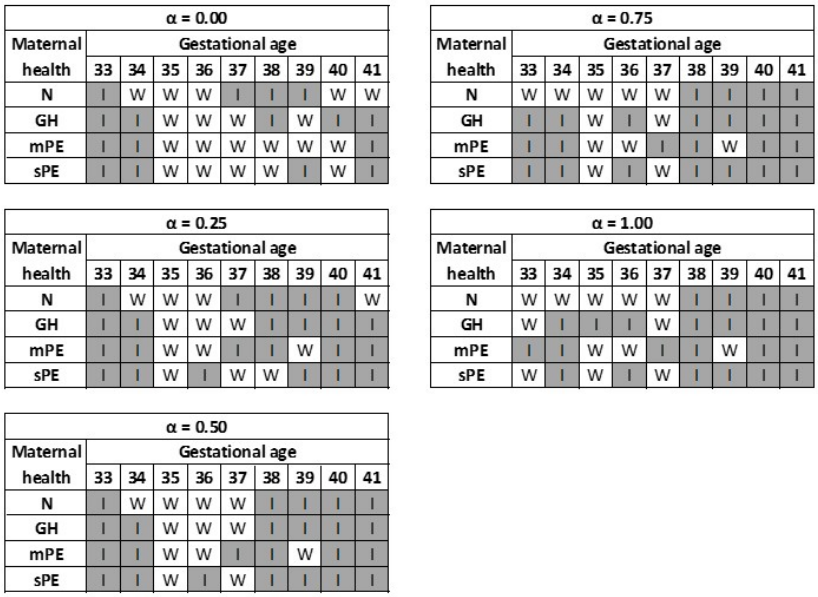
α = 1.00

Maternal health	Gestational age 33	34	35	36	37	38	39	40	41
N	W	W	W	W	W	I	I	I	I
GH	W	W	W	W	W	I	I	I	I
mPE	I	I	I	W	I	I	I	I	I
sPE	I	I	I	I	I	I	I	I	I

α = 0.50

Maternal health	Gestational age 33	34	35	36	37	38	39	40	41
N	I	W	W	W	W	I	I	I	I
GH	I	I	W	W	W	I	I	I	I
mPE	I	I	W	W	W	W	I	I	I
sPE	I	I	W	W	I	I	I	I	I

Figure A.5: The Optimal Policy Found by Imputing the CDS with CI Ranges Larger Than 0.2



α = 0.00

Maternal health	Gestational age								
	33	34	35	36	37	38	39	40	41
N	I	W	W	W	I	I	I	W	W
GH	I	I	W	W	W	I	W	I	I
mPE	I	I	W	W	W	W	W	W	I
sPE	I	I	W	W	W	W	I	W	I

α = 0.75

Maternal health	Gestational age								
	33	34	35	36	37	38	39	40	41
N	W	W	W	W	W	I	I	I	I
GH	I	I	W	I	W	I	I	I	I
mPE	I	I	W	W	I	I	W	I	I
sPE	I	I	W	I	W	I	I	I	I

α = 0.25

Maternal health	Gestational age								
	33	34	35	36	37	38	39	40	41
N	I	W	W	W	I	I	I	I	W
GH	I	I	W	W	W	I	I	I	I
mPE	I	I	W	W	I	I	W	I	I
sPE	I	I	W	I	W	W	I	I	I

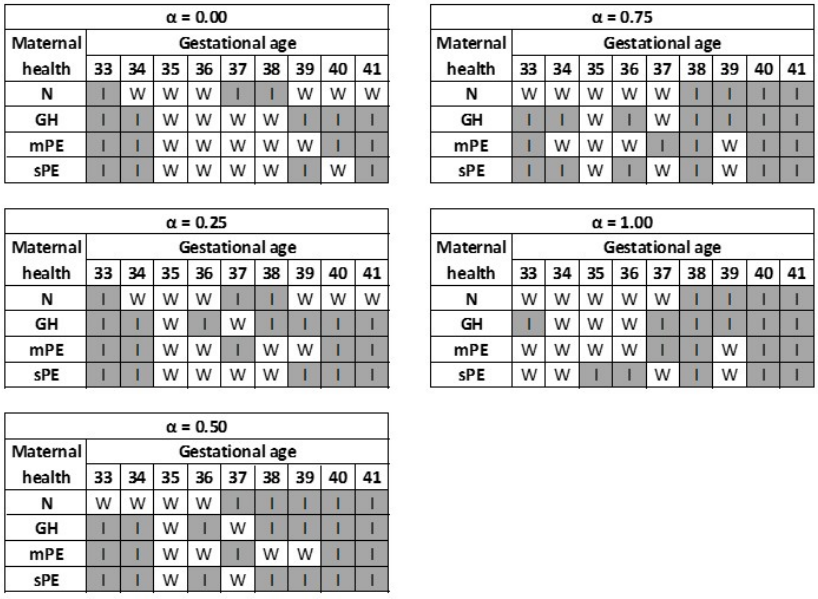
α = 1.00

Maternal health	Gestational age								
	33	34	35	36	37	38	39	40	41
N	W	W	W	W	W	I	I	I	I
GH	W	I	I	I	W	I	I	I	I
mPE	I	I	W	W	I	I	W	I	I
sPE	W	I	W	I	W	I	I	I	I

α = 0.50

Maternal health	Gestational age								
	33	34	35	36	37	38	39	40	41
N	I	W	W	W	W	I	I	I	I
GH	I	I	W	W	W	I	I	I	I
mPE	I	I	W	W	I	I	W	I	I
sPE	I	I	W	I	W	I	I	I	I

Figure A.6: The Optimal Policy Found by Imputing the CDS with CI Ranges Larger Than 0.3



α = 0.00

Maternal health	Gestational age								
	33	34	35	36	37	38	39	40	41
N	I	W	W	W	I	I	W	W	W
GH	I	I	W	W	W	W	I	I	I
mPE	I	I	W	W	W	W	W	I	I
sPE	I	I	W	W	W	W	I	W	I

α = 0.75

Maternal health	Gestational age								
	33	34	35	36	37	38	39	40	41
N	W	W	W	W	W	I	I	I	I
GH	I	I	W	I	W	I	I	I	I
mPE	I	W	W	W	I	I	W	I	I
sPE	I	I	W	I	W	I	W	I	I

α = 0.25

Maternal health	Gestational age								
	33	34	35	36	37	38	39	40	41
N	I	W	W	W	I	I	W	W	W
GH	I	I	W	I	W	I	I	I	I
mPE	I	I	W	W	I	W	W	I	I
sPE	I	I	W	W	W	W	I	I	I

α = 1.00

Maternal health	Gestational age								
	33	34	35	36	37	38	39	40	41
N	W	W	W	W	W	I	I	I	I
GH	I	W	W	W	I	I	I	I	I
mPE	W	W	W	W	I	I	W	I	I
sPE	W	W	I	I	W	I	W	I	I

α = 0.50

Maternal health	Gestational age								
	33	34	35	36	37	38	39	40	41
N	W	W	W	W	I	I	I	I	I
GH	I	I	W	I	W	I	I	I	I
mPE	I	I	W	W	I	W	W	I	I
sPE	I	I	W	I	W	I	I	I	I

Figure A.7: The Optimal Policy Found by Imputing the CDS with CI Ranges Larger Than 0.4

α = 0.00

Maternal health	Gestational age								
	33	34	35	36	37	38	39	40	41
N	I	W	W	W	I	I	W	W	W
GH	I	I	W	W	W	W	I	I	I
mPE	I	I	W	W	W	W	W	I	W
sPE	I	I	W	W	W	W	I	W	I

α = 0.75

Maternal health	Gestational age								
	33	34	35	36	37	38	39	40	41
N	W	W	W	W	W	I	I	W	I
GH	I	W	W	W	I	I	I	I	I
mPE	I	W	W	W	I	I	W	I	I
sPE	I	W	W	I	I	I	I	W	I

α = 0.25

Maternal health	Gestational age								
	33	34	35	36	37	38	39	40	41
N	I	W	W	W	I	I	I	W	W
GH	I	I	W	I	W	W	I	I	I
mPE	I	I	W	W	I	W	W	I	W
sPE	I	W	W	W	W	W	I	W	I

α = 1.00

Maternal health	Gestational age								
	33	34	35	36	37	38	39	40	41
N	W	W	W	W	W	I	I	I	I
GH	W	W	W	W	I	I	I	I	I
mPE	W	W	W	W	I	I	W	I	I
sPE	I	W	W	I	W	I	I	W	I

α = 0.50

Maternal health	Gestational age								
	33	34	35	36	37	38	39	40	41
N	I	W	W	W	I	I	I	W	I
GH	I	I	W	W	I	W	I	I	I
mPE	I	I	W	W	I	W	W	I	W
sPE	I	W	W	I	I	I	I	W	I

Figure A.8: The Optimal Policy Found by Imputing the CDS with CI Ranges Larger Than 0.5

α = 0.00

Maternal health	Gestational age								
	33	34	35	36	37	38	39	40	41
N	I	I	W	W	I	I	I	W	W
GH	I	I	W	W	W	W	W	I	I
mPE	I	I	W	W	W	W	W	I	W
sPE	I	I	W	W	W	W	I	W	I

α = 0.75

Maternal health	Gestational age								
	33	34	35	36	37	38	39	40	41
N	W	W	W	W	I	I	I	W	I
GH	I	I	W	W	I	I	W	I	I
mPE	W	I	W	W	I	I	W	I	I
sPE	W	W	W	I	W	I	I	W	I

α = 0.25

Maternal health	Gestational age								
	33	34	35	36	37	38	39	40	41
N	I	W	W	W	I	I	I	W	W
GH	I	I	W	W	I	W	W	I	I
mPE	I	I	W	W	I	W	W	I	W
sPE	I	I	W	W	W	W	I	W	I

α = 1.00

Maternal health	Gestational age								
	33	34	35	36	37	38	39	40	41
N	W	W	W	W	W	I	I	I	I
GH	W	W	W	W	I	I	I	I	I
mPE	W	W	W	W	I	I	W	I	I
sPE	W	W	W	I	W	I	I	W	I

α = 0.50

Maternal health	Gestational age								
	33	34	35	36	37	38	39	40	41
N	W	W	W	W	I	I	I	W	I
GH	I	I	W	W	I	I	W	I	I
mPE	I	I	W	W	I	W	W	I	I
sPE	I	W	W	I	W	I	I	W	I

Figure A.9: The Optimal Policy Found by Imputing the CDS with CI Ranges Larger Than 0.6

α = 0.00									
Maternal health	Gestational age								
	33	34	35	36	37	38	39	40	41
N	W	W	W	W	W	W	W	W	I
GH	W	W	I	W	W	W	W	W	I
mPE	W	W	W	W	W	I	I	W	I
sPE	W	W	W	I	W	W	I	W	I

α = 0.75									
Maternal health	Gestational age								
	33	34	35	36	37	38	39	40	41
N	W	W	W	W	W	I	I	I	I
GH	I	W	W	W	I	I	W	I	I
mPE	W	W	W	W	I	I	W	I	I
sPE	I	W	W	I	W	I	I	W	I

α = 0.25									
Maternal health	Gestational age								
	33	34	35	36	37	38	39	40	41
N	W	W	W	W	W	W	W	W	I
GH	W	W	I	W	W	I	W	W	I
mPE	W	W	W	W	W	I	I	I	I
sPE	W	W	W	I	W	W	W	W	I

α = 1.00									
Maternal health	Gestational age								
	33	34	35	36	37	38	39	40	41
N	W	W	W	W	W	I	I	I	I
GH	I	W	W	W	I	I	I	I	I
mPE	W	W	W	I	I	I	W	I	I
sPE	I	W	W	I	I	I	I	I	I

α = 0.50									
Maternal health	Gestational age								
	33	34	35	36	37	38	39	40	41
N	W	W	W	W	W	W	I	W	I
GH	W	W	W	W	I	I	W	I	I
mPE	W	W	W	W	W	I	W	I	I
sPE	W	W	W	I	W	I	I	W	I

Figure A.10: The Optimal Robust Policy Found with Maximum Likelihood Estimates of the CDS

α = 0.00									
Maternal health	Gestational age								
	33	34	35	36	37	38	39	40	41
N	W	W	W	W	W	W	W	W	I
GH	W	W	W	W	W	W	W	W	I
mPE	W	W	W	W	W	I	I	I	I
sPE	W	W	W	I	W	W	I	W	I

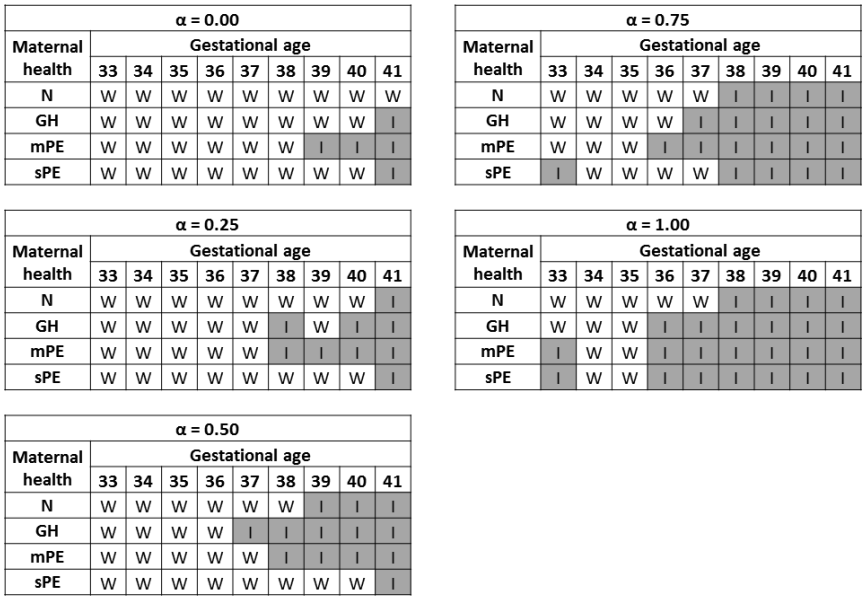
α = 0.75									
Maternal health	Gestational age								
	33	34	35	36	37	38	39	40	41
N	W	W	W	W	W	I	I	I	I
GH	W	W	W	W	I	I	W	I	I
mPE	W	W	W	W	I	I	W	I	I
sPE	I	W	W	I	W	I	I	W	I

α = 0.25									
Maternal health	Gestational age								
	33	34	35	36	37	38	39	40	41
N	W	W	W	W	W	W	W	W	I
GH	W	W	W	W	W	I	W	W	I
mPE	W	W	W	W	W	I	I	I	I
sPE	W	W	W	I	W	W	I	W	I

α = 1.00									
Maternal health	Gestational age								
	33	34	35	36	37	38	39	40	41
N	W	W	W	W	W	I	I	I	I
GH	W	W	W	W	I	I	I	I	I
mPE	W	W	W	W	I	I	W	I	I
sPE	I	W	W	I	I	I	I	W	I

α = 0.50									
Maternal health	Gestational age								
	33	34	35	36	37	38	39	40	41
N	W	W	W	W	W	W	I	W	I
GH	W	W	W	W	W	I	W	I	I
mPE	W	W	W	W	W	I	W	I	I
sPE	W	W	W	I	W	I	I	W	I

Figure A.11: The Optimal Robust Policy Found with Wilson's Estimates of the CDS



α = 0.00									
Maternal health	Gestational age								
	33	34	35	36	37	38	39	40	41
N	W	W	W	W	W	W	W	W	W
GH	W	W	W	W	W	W	W	W	I
mPE	W	W	W	W	W	W	I	I	I
sPE	W	W	W	W	W	W	W	W	I

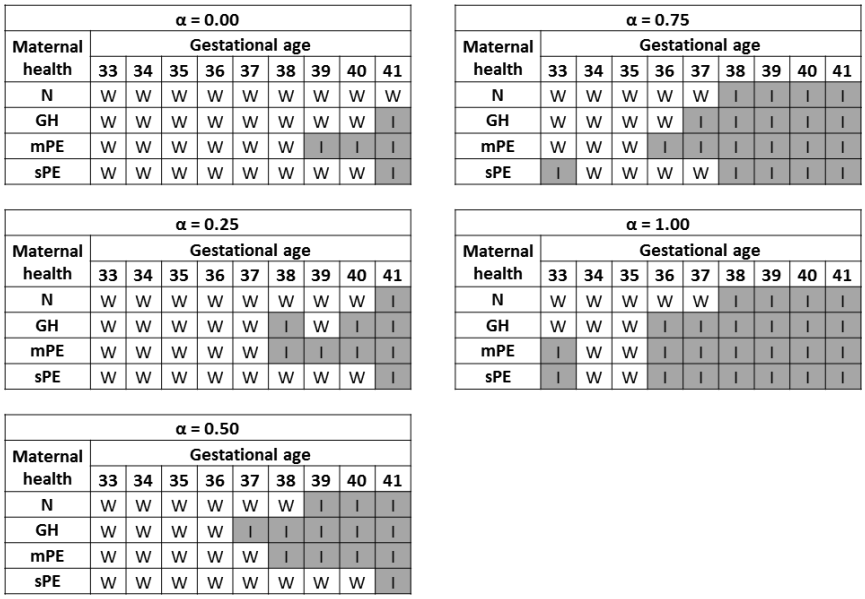
α = 0.75									
Maternal health	Gestational age								
	33	34	35	36	37	38	39	40	41
N	W	W	W	W	W	I	I	I	I
GH	W	W	W	W	I	I	I	I	I
mPE	W	W	W	I	I	I	I	I	I
sPE	I	W	W	W	W	I	I	I	I

α = 0.25									
Maternal health	Gestational age								
	33	34	35	36	37	38	39	40	41
N	W	W	W	W	W	W	W	W	I
GH	W	W	W	W	W	I	W	I	I
mPE	W	W	W	W	W	I	I	I	I
sPE	W	W	W	W	W	W	W	W	I

α = 1.00									
Maternal health	Gestational age								
	33	34	35	36	37	38	39	40	41
N	W	W	W	W	W	I	I	I	I
GH	W	W	W	I	I	I	I	I	I
mPE	I	W	W	I	I	I	I	I	I
sPE	I	W	W	I	I	I	I	I	I

α = 0.50									
Maternal health	Gestational age								
	33	34	35	36	37	38	39	40	41
N	W	W	W	W	W	W	I	I	I
GH	W	W	W	W	I	I	I	I	I
mPE	W	W	W	W	W	I	I	I	I
sPE	W	W	W	W	W	W	W	W	I

Figure A.12: The Optimal Robust Policy Found with the Estimates of ORI-CDS Model Including the Order Restrictions on Maternal Health and Gestational Age



α = 0.00									
Maternal health	Gestational age								
	33	34	35	36	37	38	39	40	41
N	W	W	W	W	W	W	W	W	W
GH	W	W	W	W	W	W	W	W	I
mPE	W	W	W	W	W	W	I	I	I
sPE	W	W	W	W	W	W	W	W	I

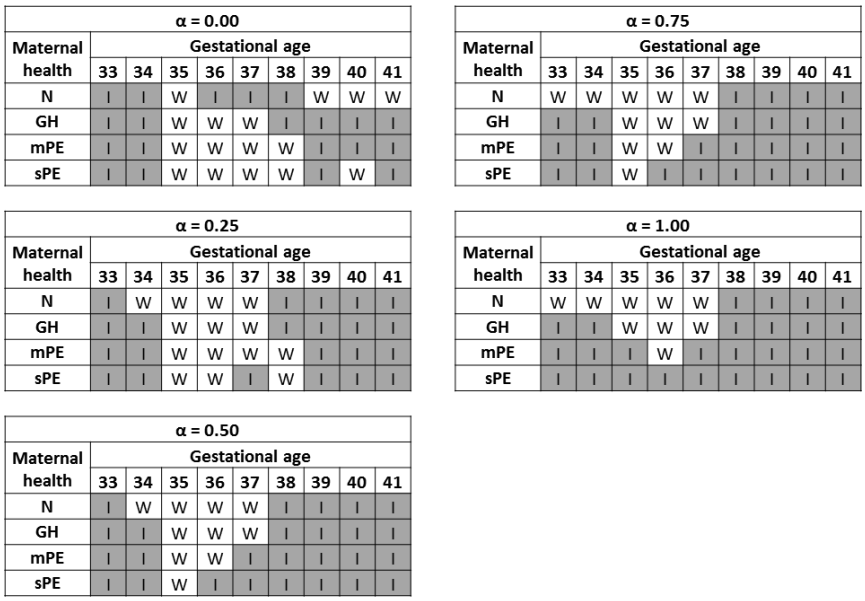
α = 0.75									
Maternal health	Gestational age								
	33	34	35	36	37	38	39	40	41
N	W	W	W	W	W	I	I	I	I
GH	W	W	W	W	I	I	I	I	I
mPE	W	W	W	I	I	I	I	I	I
sPE	I	W	W	W	W	I	I	I	I

α = 0.25									
Maternal health	Gestational age								
	33	34	35	36	37	38	39	40	41
N	W	W	W	W	W	W	W	W	I
GH	W	W	W	W	W	I	W	I	I
mPE	W	W	W	W	W	I	I	I	I
sPE	W	W	W	W	W	W	W	W	I

α = 1.00									
Maternal health	Gestational age								
	33	34	35	36	37	38	39	40	41
N	W	W	W	W	W	I	I	I	I
GH	W	W	W	I	I	I	I	I	I
mPE	I	W	W	I	I	I	I	I	I
sPE	I	W	W	I	I	I	I	I	I

α = 0.50									
Maternal health	Gestational age								
	33	34	35	36	37	38	39	40	41
N	W	W	W	W	W	W	I	I	I
GH	W	W	W	W	I	I	I	I	I
mPE	W	W	W	W	W	I	I	I	I
sPE	W	W	W	W	W	W	W	W	I

Figure A.13: The Optimal Robust Policy Found with the Estimates of ORI-CDS Model Including All Order Restrictions



α = 0.00

Maternal health	Gestational age								
	33	34	35	36	37	38	39	40	41
N	I	I	W	I	I	I	W	W	W
GH	I	I	W	W	W	I	I	I	I
mPE	I	I	W	W	W	W	I	I	I
sPE	I	I	W	W	W	W	I	W	I

α = 0.75

Maternal health	Gestational age								
	33	34	35	36	37	38	39	40	41
N	W	W	W	W	W	I	I	I	I
GH	I	I	W	W	W	I	I	I	I
mPE	I	I	W	W	I	I	I	I	I
sPE	I	I	W	I	I	I	I	I	I

α = 0.25

Maternal health	Gestational age								
	33	34	35	36	37	38	39	40	41
N	I	W	W	W	W	I	I	I	I
GH	I	I	W	W	W	I	I	I	I
mPE	I	I	W	W	W	W	I	I	I
sPE	I	I	W	W	I	W	I	I	I

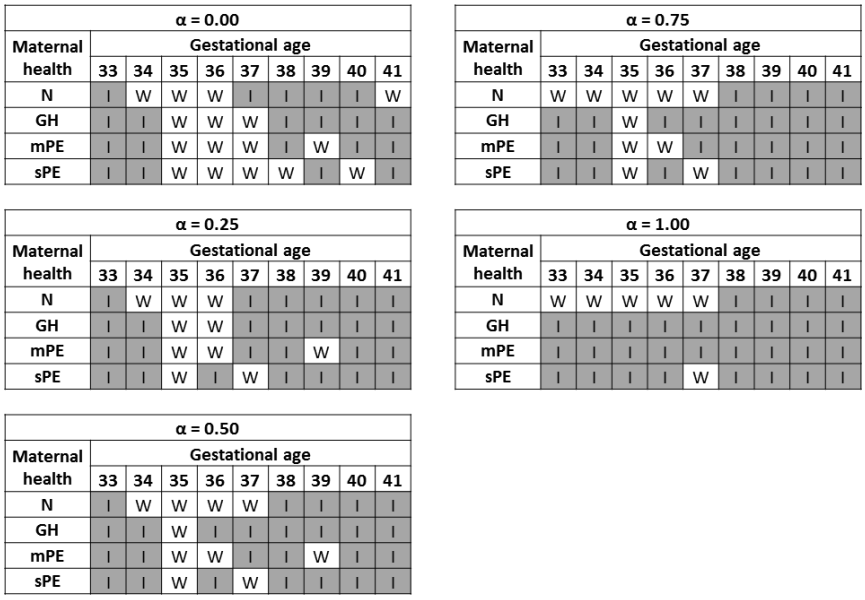
α = 1.00

Maternal health	Gestational age								
	33	34	35	36	37	38	39	40	41
N	W	W	W	W	W	I	I	I	I
GH	I	I	W	W	W	I	I	I	I
mPE	I	I	I	W	I	I	I	I	I
sPE	I	I	I	I	I	I	I	I	I

α = 0.50

Maternal health	Gestational age								
	33	34	35	36	37	38	39	40	41
N	I	W	W	W	W	I	I	I	I
GH	I	I	W	W	W	I	I	I	I
mPE	I	I	W	W	I	I	I	I	I
sPE	I	I	W	I	I	I	I	I	I

Figure A.14: The Optimal Robust Policy Found by Imputing the CDS with CI Ranges Larger Than 0.2



α = 0.00

Maternal health	Gestational age								
	33	34	35	36	37	38	39	40	41
N	I	W	W	W	I	I	I	I	W
GH	I	I	W	W	W	I	I	I	I
mPE	I	I	W	W	W	I	W	I	I
sPE	I	I	W	W	W	W	I	W	I

α = 0.75

Maternal health	Gestational age								
	33	34	35	36	37	38	39	40	41
N	W	W	W	W	W	I	I	I	I
GH	I	I	W	I	I	I	I	I	I
mPE	I	I	W	W	I	I	I	I	I
sPE	I	I	W	I	W	I	I	I	I

α = 0.25

Maternal health	Gestational age								
	33	34	35	36	37	38	39	40	41
N	I	W	W	W	I	I	I	I	I
GH	I	I	W	W	I	I	I	I	I
mPE	I	I	W	W	I	I	W	I	I
sPE	I	I	W	I	W	I	I	I	I

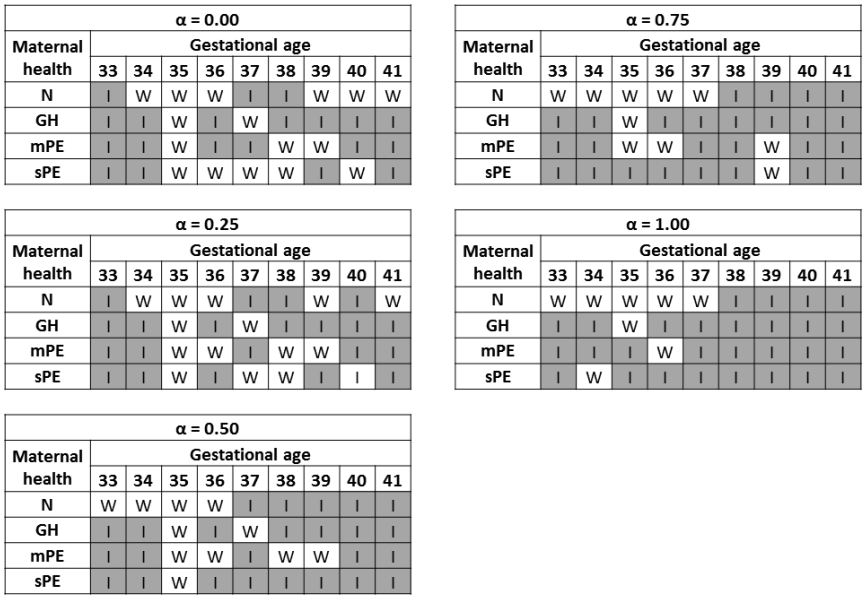
α = 1.00

Maternal health	Gestational age								
	33	34	35	36	37	38	39	40	41
N	W	W	W	W	W	I	I	I	I
GH	I	I	I	I	I	I	I	I	I
mPE	I	I	I	I	I	I	I	I	I
sPE	I	I	I	I	W	I	I	I	I

α = 0.50

Maternal health	Gestational age								
	33	34	35	36	37	38	39	40	41
N	I	W	W	W	W	I	I	I	I
GH	I	I	W	I	I	I	I	I	I
mPE	I	I	W	W	I	I	W	I	I
sPE	I	I	W	I	W	I	I	I	I

Figure A.15: The Optimal Robust Policy Found by Imputing the CDS with CI Ranges Larger Than 0.3



α = 0.00									
Maternal health	Gestational age								
	33	34	35	36	37	38	39	40	41
N	I	W	W	W	I	I	W	W	W
GH	I	I	W	I	W	I	I	I	I
mPE	I	I	W	I	I	W	W	I	I
sPE	I	I	W	W	W	W	I	W	I

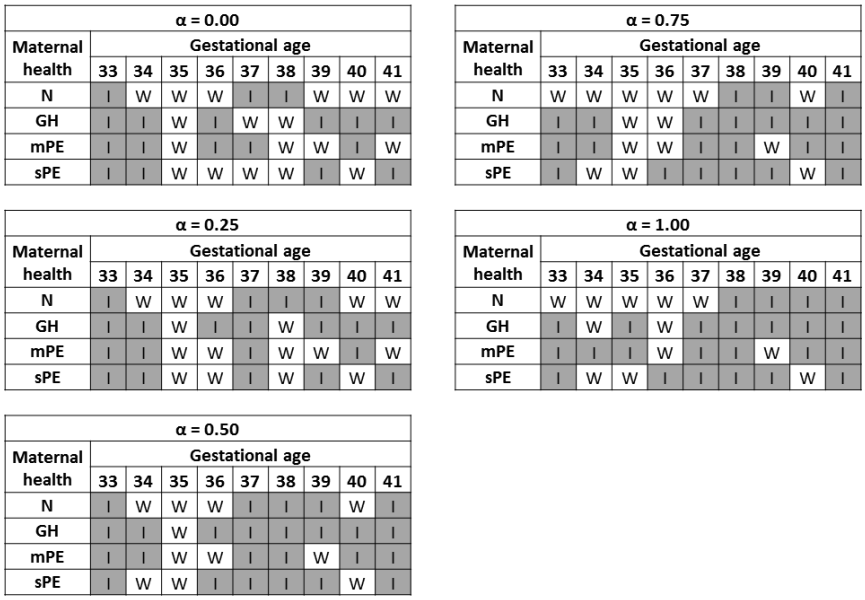
α = 0.75									
Maternal health	Gestational age								
	33	34	35	36	37	38	39	40	41
N	W	W	W	W	W	I	I	I	I
GH	I	I	W	I	I	I	I	I	I
mPE	I	I	W	W	I	I	W	I	I
sPE	I	I	I	I	I	I	W	I	I

α = 0.25									
Maternal health	Gestational age								
	33	34	35	36	37	38	39	40	41
N	I	W	W	W	I	I	W	I	W
GH	I	I	W	I	W	I	I	I	I
mPE	I	I	W	W	I	W	W	I	I
sPE	I	I	W	I	W	W	I	I	I

α = 1.00									
Maternal health	Gestational age								
	33	34	35	36	37	38	39	40	41
N	W	W	W	W	W	I	I	I	I
GH	I	I	W	I	I	I	I	I	I
mPE	I	I	I	W	I	I	I	I	I
sPE	I	W	I	I	I	I	I	I	I

α = 0.50									
Maternal health	Gestational age								
	33	34	35	36	37	38	39	40	41
N	W	W	W	W	I	I	I	I	I
GH	I	I	W	I	W	I	I	I	I
mPE	I	I	W	W	I	W	W	I	I
sPE	I	I	W	I	I	I	I	I	I

Figure A.16: The Optimal Robust Policy Found by Imputing the CDS with CI Ranges Larger Than 0.4



α = 0.00									
Maternal health	Gestational age								
	33	34	35	36	37	38	39	40	41
N	I	W	W	W	I	I	W	W	W
GH	I	I	W	I	W	W	I	I	I
mPE	I	I	W	I	I	W	W	I	W
sPE	I	I	W	W	W	W	I	W	I

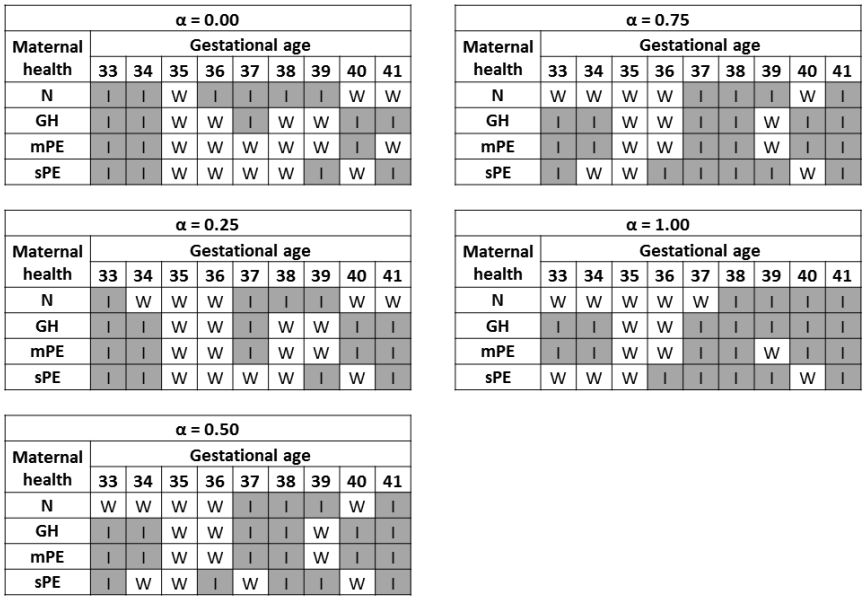
α = 0.75									
Maternal health	Gestational age								
	33	34	35	36	37	38	39	40	41
N	W	W	W	W	W	I	I	W	I
GH	I	I	W	W	I	I	I	I	I
mPE	I	I	W	W	I	I	W	I	I
sPE	I	W	W	I	I	I	I	W	I

α = 0.25									
Maternal health	Gestational age								
	33	34	35	36	37	38	39	40	41
N	I	W	W	W	I	I	I	W	W
GH	I	I	W	I	I	W	I	I	I
mPE	I	I	W	W	I	W	W	I	W
sPE	I	I	W	W	I	W	I	W	I

α = 1.00									
Maternal health	Gestational age								
	33	34	35	36	37	38	39	40	41
N	W	W	W	W	W	I	I	I	I
GH	I	W	I	W	I	I	I	I	I
mPE	I	I	I	W	I	I	W	I	I
sPE	I	W	W	I	I	I	I	W	I

α = 0.50									
Maternal health	Gestational age								
	33	34	35	36	37	38	39	40	41
N	I	W	W	W	I	I	I	W	I
GH	I	I	W	I	I	I	I	I	I
mPE	I	I	W	W	I	I	W	I	I
sPE	I	W	W	I	I	I	I	W	I

Figure A.17: The Optimal Robust Policy Found by Imputing the CDS with CI Ranges Larger Than 0.5



α = 0.00

Maternal health	Gestational age								
	33	34	35	36	37	38	39	40	41
N	I	I	W	I	I	I	I	W	W
GH	I	I	W	W	I	W	W	I	I
mPE	I	I	W	W	W	W	W	I	W
sPE	I	I	W	W	W	W	I	W	I

α = 0.75

Maternal health	Gestational age								
	33	34	35	36	37	38	39	40	41
N	W	W	W	W	I	I	I	W	I
GH	I	I	W	W	I	I	W	I	I
mPE	I	I	W	W	I	I	W	I	I
sPE	I	W	W	I	I	I	I	W	I

α = 0.25

Maternal health	Gestational age								
	33	34	35	36	37	38	39	40	41
N	I	W	W	W	I	I	I	W	W
GH	I	I	W	W	I	W	W	I	I
mPE	I	I	W	W	I	W	W	I	I
sPE	I	I	W	W	W	W	I	W	I

α = 1.00

Maternal health	Gestational age								
	33	34	35	36	37	38	39	40	41
N	W	W	W	W	W	I	I	I	I
GH	I	I	W	W	I	I	I	I	I
mPE	I	I	W	W	I	I	W	I	I
sPE	W	W	W	I	I	I	I	W	I

α = 0.50

Maternal health	Gestational age								
	33	34	35	36	37	38	39	40	41
N	W	W	W	W	I	I	I	W	I
GH	I	I	W	W	I	I	W	I	I
mPE	I	I	W	W	I	I	W	I	I
sPE	I	W	W	I	W	I	I	W	I

Figure A.18: The Optimal Robust Policy Found by Imputing the CDS with CI Ranges Larger Than 0.6