Cesarean Delivery: Factors Affecting Trends

By

Yvonne Cheng

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Professor Alan E. Hubbard
Professor Sylvia Guendelman

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Abstract

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Today, nearly 1 in 3 women giving birth will undergo cesarean delivery. This is far from the 1970s when only about 1 in 20 women have cesareans. Higher frequencies of cesarean deliveries, however, do not necessarily correspond with improved perinatal outcomes. In fact, neonatal outcomes have not improved in the past decades. It is well documented that cesarean delivery is associated with increased risk of maternal morbidity and mortality. Further, cesarean delivery can have a negative impact on perinatal outcomes of subsequent pregnancies, with higher risk of stillbirth and uterine rupture. Increasing number of repeat cesarean deliveries also correlates with increasing maternal morbidity.

Data suggest that current cesarean delivery in the U.S. could be safely lowered without increasing infant mortality. Although numerous strategies have been suggested and tried to reduce cesarean delivery, it continues to rise at a rate disproportional to the changing maternal characteristics that may be partly responsible for the increase. The goal of this research is to identify potentially modifiable physician practice factors and patient characteristics that are associated with the increased risk of cesarean delivery. Identification of these risk factors is needed to develop strategies to curtail the current upward trend in use of cesarean delivery. As a first step to address this long term goal, this dissertation several analyses to investigated obstetric characteristics and practice patterns associated with cesarean delivery in United States based on existing datasets. Additionally, I conducted a survey study and collected clinician-level data to investigate obstetric providers' potential influence on the decision to recommend cesarean delivery.

The Background chapter presents a brief history of cesarean delivery and reviews common indications of cesarean delivery. Cesarean delivery is often considered to impose some risks to the parturient, with the tradeoff of potentially

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conveying benefit to the fetus. Thus, this chapter also reviews maternal and neonatal morbidity associated with cesarean delivery, as well as potential health economic impact.

First, to explore if pregnancy intervention, particularly, induction of labor, is associated with increased risk of cesarean delivery in the U.S., I used marginal structural models (MSM) to examine this research aim. In this analysis, the relation between induction of labor at a specific gestational age (e.g., 39 weeks) was compared to expectant management (delivery at a later gestational age, i.e., 40, 41 or 42 weeks, by either entering spontaneous labor or subsequently induction of labor for various medical/obstetric indications) and associated maternal/neonatal outcomes. This analytic approach is in contrast to traditional multivariable regression approaches that are pervasive in the obstetric literature. As multivariable regression analyses estimate the effect of association conditional on confounding covariates, it does not address specifically the risk of outcome for each subject under both exposed and unexposed conditions. Based on the concept of counterfactuals, MSM compares outcome frequency under different exposure distributions (exposed and non-exposed) in the same sample population and estimates the effect of exposure across the entire population. By applying causal inference framework through the use of MSM, this analysis estimated the population-level, marginal effect of induction on cesarean delivery and other perinatal outcomes that correspond to hypothetical interventions. Based on the MSM analysis, I show that induction of labor was associated with a decreased risk of cesarean delivery compared to expectant management.

Next, I examined the association between advanced maternal age and cesarean delivery in the U.S. Delayed childbearing has become increasingly common in the U.S. Increase in maternal age has been associated with higher risk of adverse pregnancy outcomes. Thus, I used the population intervention models to estimate the population attributable fraction of advanced maternal age (age >35 years at estimated date of delivery) on cesarean delivery. More specifically, population intervention models build upon the causal inference literature to model the difference of an effect between the distribution of a population in an observed environment (the actual study population) and a counterfactual treatment-specific population distribution (the population outcome that would have been observed under "intervention" such that the exposure would be at some target, optimal level). In this analysis, I used the population intervention models to estimate the potential changes in the distribution of cesarean delivery in low-risk population of nulliparous women who gave live births in the U.S. While maternal age cannot be easily "intervened" on, I chose to use population intervention models to gain insights into the potential changes in the distribution of cesarean delivery, focusing on the population prevalence of advanced maternal age as a risk factor. Through this analysis, I observed that advanced maternal age was a risk factor of cesarean delivery.

While patient characteristics may influence the decision to undergo cesarean delivery, clinicians may also play an important role. However, few studies have been

published regarding this topic. Thus, I conducted a cross-sectional survey study to explore provider characteristics that might be associated with increased likelihood of recommending cesarean delivery. I used multivariable logistic regression analysis fit by maximum likelihood to assess provider factors associated with an increased likelihood of recommending cesarean delivery. Further, I also used the Deletion/Substitution/Addition (DSA) algorithm to independently assess clinician factors associated with an increased likelihood to recommend cesarean. As multivariable logistic regression analysis was based on conditional probability to estimate the effect of the exposure-outcome association, this was in contrast to the DSA algorithm that used polynomial basis functions to identify predictors for the exposure-outcomes of interest based on cross-validation and the L2 loss function.

As the current rise in cesarean delivery has profound impact on maternal and child health, there are also social and economic repercussions associated with rise in cesareans that are not yet well understood. This dissertation examined several increasingly common factors, including induction of labor, and advanced maternal age that might be associated with increased risk or increased likelihood of cesarean delivery. This work was achieved through the application of causal inference framework and analytical methods such as marginal structural models and population intervention models and the usage of nationwide birth data. Additionally, provider characteristics and experience information were collected via a cross-sectional survey to explore clinician-level information to identify factors driving the increase in cesarean delivery. These analyses serve as a first step towards the understanding of why cesarean delivery continues to increase in the U.S. and worldwide, but much work remains to be done.

Dedication

This dissertation is dedicated to my loving, supportive family:

    Ying Min and Mei-eh Cheng,
    Michael, Elly, Jason, and Anna Hepfer

without whom none of this would be possible, and to my brother, George Cheng, whom I wish were here to share this moment.

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Chapter 1: Background

1.1. Introduction

Cesarean delivery in the U.S. has increased more than 50% during the past decade. Cesarean deliveries are most often performed with the stated goal of improving maternal or neonatal health; yet, there is little data to suggest that the observed excess cesarean deliveries have contributed to improved perinatal outcomes. In contrast, there is evidence for increased maternal and neonatal morbidity and mortality associated with cesarean delivery for both current and future pregnancies. Not only is the annual incidence rates of total cesarean deliveries on the rise, the number of primary cesarean deliveries are also increasing.

This upward trend of cesarean is seen across all maternal age categories and in all racial/ethnic subgroups. Some have attributed this increase to changing maternal demographics (delayed childbearing, increase medical conditions including obesity, more multiple gestations) as well as changing obstetric practice factors such as diminishing vaginal breech deliveries and threat of legal/malpractice suits. Nonetheless, these factors appear to explain relatively little of the observed temporal trends. Further, geographic differences in cesarean delivery exist across the U.S., and little is known regarding factors underlying these differences. Some studies suggest clinicians may play an important role; however, such literature remains scant and most were conducted outside of the U.S.

In order to curtail the current continual increase in cesarean delivery, a more comprehensive understanding of the factors responsible is required. Analysis of existing nationwide and statewide data on patient-level information and well-designed prospective studies focusing on non-patient characteristics can shed light on the factors that underlie the increase in cesarean delivery. These are the first steps toward building strategies for effective intervention, with the ultimate goal of improving maternal and child health.

1.2. Historic perspective on cesarean delivery

The first cesarean was believed to have been performed in 320BC, under the circumstance that the pregnant women had died and her abdomen was cut open to deliver and, thus, save the baby's life. Historically, cesarean delivery resulted in the death of the mother and was performed when the mother has already deceased or just prior to her death. It was not until the 1500s that the first woman was recorded to have survived undergoing a cesarean delivery. Even during the nineteenth century the mortality from cesarean delivery was greater than 85%.[1]

By the early decades of the twentieth century, several important innovations in surgical care began to reduce maternal mortality of women undergoing cesarean delivery. These included adaptations to the principles of asepsis, introduction of uterine suturing, application of a low-transverse uterine incision, advances in anesthesia, blood transfusion, and antibiotics use.[2]

1.3.   Cesarean delivery during the nineteenth century

With the decrease in related maternal mortality and morbidity, cesarean delivery became a reasonable alternative for vaginal delivery.[3] In 1950, a study reported that 1,000 consecutive cesarean deliveries were preformed in the U.S. between 1942 and 1946 without any maternal death.[4] This was considered a remarkable achievement. Before then, cesarean delivery was primarily performed for maternal medical or obstetric indications such as placenta previa, failed induction of labor for severe preeclampsia, or repeat cesarean delivery, where the ongoing risk of labor was believed to potentially outweigh the risk of undergoing a major abdominal surgery.[5] Since the 1960s, cesarean delivery became increasingly more commonly performed for fetal or obstetric indications, such as arrest in progress of labor and fetal intolerance of labor, or fetal distress; this was the case particularly with the emergence of fetal heart rate rhythm monitoring technology.[6]

Even with increasingly widened application of cesarean delivery, the annual incidence rate of cesarean delivery comprised fewer than 5/100 (5%) of live births during the 1960s and 1970s. However, cesarean deliveries have increased rapidly during the 1980s such that in 1988 the annual incidence rate of cesarean delivery in the U.S. was 23.5/100 person-years, the highest among developed countries during that time.[7,8] Particularly, repeat cesareans accounted for an increasing proportion of all cesarean deliveries: in 1985 one in three cesareans performed was a repeat.[9] This phenomenon was due largely to the predominant practice that followed the dictum of "once a cesarean, always a cesarean," which was first put forth in 1916 by Crogin.[10] Indeed, the option of attempting vaginal delivery after previous cesarean delivery (VBAC) was not commonly accepted or adapted: less than 3% of women who had prior cesarean delivery had VBACs in the 1970s.[11]

The below figure demonstrate the trends in cesarean delivery from 1970 to 1993; total and primary cesarean deliveries are expressed as number of cesarean per 100 live births per given year; VBACs are expressed as number of vaginal birth after previous cesarean per 100 live births to women with a history of prior cesarean deliveries per given year:

Figure 1: Trends in cesarean delivery and vaginal birth after previous cesarean (VBAC) rates, 1970 to 1993: total and primary cesareans are expressed as number of cesarean per 100 live births; VBAC is expressed as number of vaginal birth after previous cesarean per 100 live births to women with a previous cesarean delivery [11]
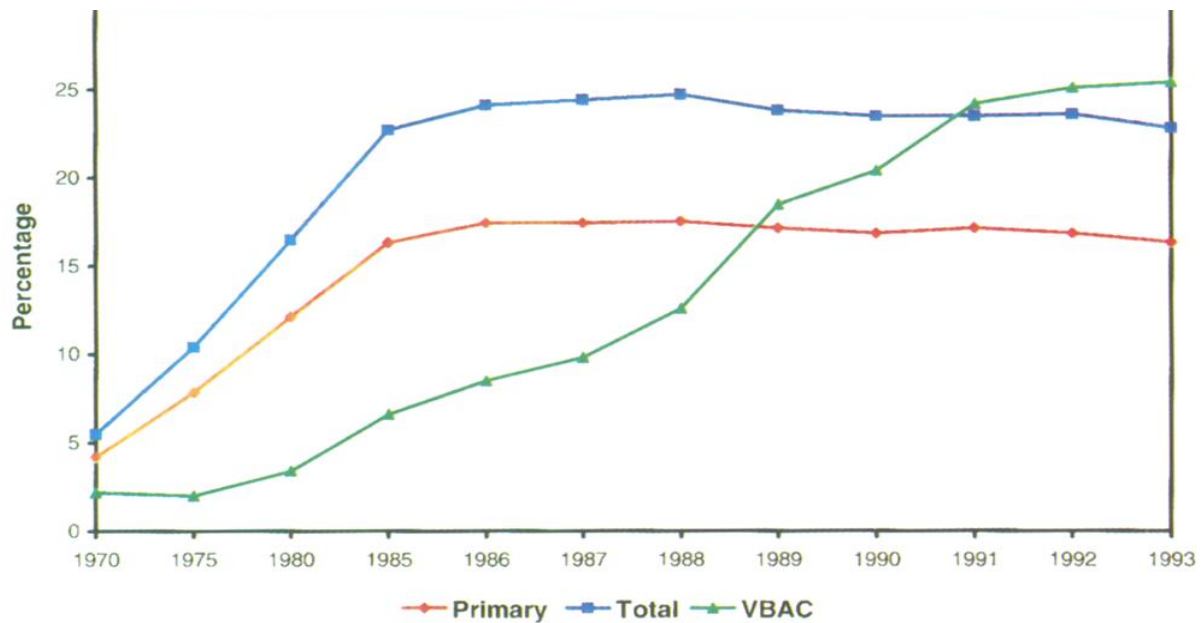
While the increase in total number of cesarean delivery during this time period can be partially attributed to the large proportion of repeat cesarean deliveries performed, there was also a concurrent increase in primary cesarean delivery that cannot be accounted for by increase in repeat cesareans (Figure 1). Many investigators in the late 1980s had noted that this increase in cesarean was observed across all reproductive age groups and within all geographical regions in the U.S.[12,13]

1.4.   Effort in decrease cesarean delivery during the 1980s-90s

The concern for rising cesarean delivery has led to consensus conferences held by both the National Institute of Health (NIH) and the World Health Organization in the 1980s.[14,15] These conferences concluded that the cesarean delivery rates were too high. Thus, there was a strong push for decreasing cesarean delivery during this time period. Given that most women who had previous cesarean delivery undergo repeat cesareans, there was particular push for trial of labor/vaginal birth after previous cesarean (VBAC) as an acceptable method for reducing cesarean deliveries.[14,15]

Although neither elective repeat cesarean delivery (ERCD) nor trial of labor after previous cesarean (TOLAC) is without risk of perinatal morbidity/mortality, clinicians

were encouraged by the relatively high success frequency (60-80%) of VBACs that could be achieved among diverse groups of pregnant women, and in various hospital settings, and practicing clinicians.[16,17,18] Additionally, one of the Healthy People 2000 national health objectives at that time aimed to reduce the overall annual incidence rate of cesarean delivery to less than or equal to 15.0/100 deliveries,[19] a level that was last observed in 1978.[20] Since the release of this agenda in 1990,[14] and with efforts to encourage TOLAC by professional organizations and consensus, total cesarean deliveries in the U.S. declined and reached a nadir in 1996 to 20.7 per 100 live births.

This decrescendo trend of cesarean was short lived. With increasing number of women with previous cesarean deliveries attempting VBACs, there were also reports of uterine scar dehiscence or rupture which can lead to compromised maternal or neonatal outcomes. Although the overall estimated risk of uterine dehiscence or rupture remains low (2.7/1000) in women with prior cesarean undergoing TOLAC and there were no differences in risk of maternal death or need for hysterectomy among women who had a trial of labor after cesarean compared to elective repeat cesarean without labor,[21,22,23,24,25] there has been a steep decline in the frequency of VBAC (28.3% in 1996; 9.2% in 2004). Concurrently, not only the total cesarean deliveries have been on the rise since the past decade, so have been primary cesarean deliveries (Figure 2).[14]

Figure 2: Total and primary cesarean delivery rate and vaginal delivery after cesarean in the U.S.: 1989-2004[14]
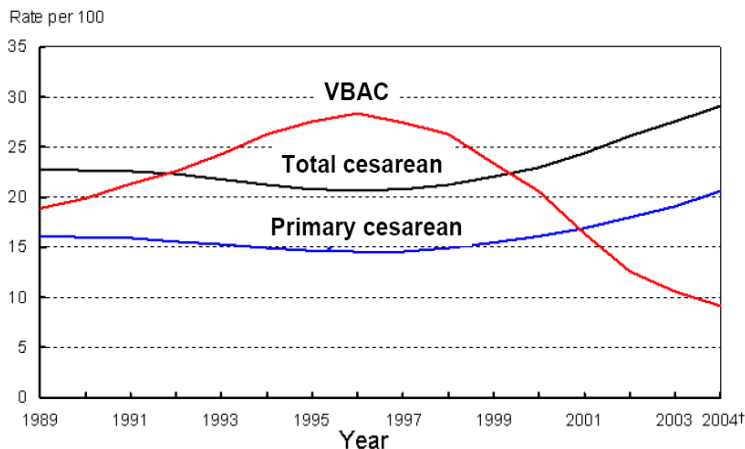
Today, nearly one in three pregnant women giving birth undergoes cesarean delivery.[26] This represents an over 50% increase in cesarean delivery during the past decade.[27,28] Although one of the aims of Healthy People 2010 objective was to reduce cesarean deliveries, with the goal of 15% (or 15/100 person-year) for primary cesarean among low-risk (full term, singleton, vertex presentation) women and 63% (or 63 per 100 person-year with previous cesareans) for repeat cesarean,[29] the annual incidence rate of cesarean delivery has continued to increase each and every year since 1996. As there is a lack of clear evidence to indicate that the increased cesarean delivery rate

improves maternal and perinatal health outcome, little is known regarding the "optimal" annual rate of cesarean delivery that maximizes population health benefits.

1.5. Indications of cesarean delivery

The four most frequent indications of cesarean delivery are: 1). Repeat cesarean, 2). Labor dystocia, 3). Malpresentation or breech presentation, and 4). Fetal intolerance of labor or fetal distress.[9,10,30] While these four indications have been noted to account for approximately 90% of cesarean deliveries in the U.S. in the 1980s and 1990s, a lowered threshold for these standard indications has been implicated to contribute to the trend of increase in cesarean delivery during this time period.[31,32] A number of studies also have compared trend of cesarean delivery in the U.S. to other countries worldwide and noted significant differences. One study noted that although similar proportions of cesarean delivery were performed for breech presentation and fetal distress in the U.S. compared to northern European countries such as Norway, Scotland, and Sweden, previous cesarean and labor dystocia were performed more frequently in the U.S. than others.[9]

Besides the above four common indications of cesarean, some of the other medical or obstetric indications for cesarean include: abnormal placentation such as placenta previa, placenta vasa previa, placenta abruption, maternal medical conditions such as active genital herpes outbreaks, maternal Human Immunocompromise Virus (HIV) infection with high viral load, cervical cancer, obstruction to vaginal canal, history of myomectomy or classical cesarean delivery, and fetal indications such as spinal bifida, severe hydrocephaly, multifetal gestations (twins and higher order gestations), or fetal airway obstructions requiring EXIT (ex utero intrapartum treatment) procedure. These indications combined account for approximately 10% of the primary cesarean deliveries performed.[33]

It has been reported that changes in maternal characteristics, such as age, race/ethnicity, and pre-pregnancy weight distribution can significantly affect the incidence rate of primary cesarean delivery. Older expectant mothers have higher risk of cesarean delivery, as do women with higher pre-pregnancy body mass index (BMI).[34,35,36] Racial differences in the frequency of cesarean delivery also exists, with highest rates of cesareans being among Latinas and lowest among Asians; further, this racial/ethnic variation is not entirely explained by known risk factors.[37] Particularly, one study has shown that adjustment for changes in the maternal demographic profile may account for as much as 18% of the increase in cesarean delivery in the 1980s in this analysis using administrative data from Washington State.[38]

Other factors that have been reported to influence cesarean delivery include payment source, type of practice and hospital setting. When the private payers were compared to all other payers (MediCal, government sponsored insurance, Kaiser, and other health maintenance organizations) in California, a significant increase in all categories of cesarean births existed, with some categories as much as 10 percentage

points higher.[39] Compared to hospitals with state and local government ownership, proprietary hospitals in California have higher cesarean deliveries. Wide variations also exist among private attending physicians, and this likely was related to physicians' enthusiasm for trial of labor after previous cesarean/VBAC and their role in management of labor dystocia.[40]

Although there were some differences in the effort to decrease cesarean delivery during this time period, most studies have observed an overall reduction in cesarean delivery. The decrease was thought mostly due to the widespread, increased effort of attempting and achieving VBACs. Other factors that might have contributed to the improvements included clearer guidelines for trials of labor and labor management, continual labor support, and focused attention on physician practice patterns.[41] Additionally, a decrease in the use of primary cesarean for labor dystocia was also seen at the same time.[25,42,43]

1.6.   Cesarean delivery: maternal and neonatal morbidity

Currently, cesarean delivery is generally perceived as a low-risk procedure by both the expectant mothers and the clinicians. Despite this popular perception, cesarean delivery itself is associated with higher risks of maternal morbidity and mortality when compared to vaginal delivery. The annual rate of maternal death causally related to mode of delivery was estimated in one population-based study as 0.2 per 100,000 vaginal births and 2.2 per 100,000 cesarean deliveries.[44]

While risks of morbidity and mortality of cesarean delivery are influenced by the associated medical complications in the woman undergoing cesarean, serious intraoperative complications do occur in approximately 2% of cesarean deliveries. These include: anesthesia accidents (such as problems with intubation, drug reactions, aspiration pneumonia), postpartum hemorrhage, massive hemorrhage requiring transfusion of blood/blood products or hysterectomy, injuries to bowel or bladder, and amniotic fluid or thromboembolic embolism.[45,46] Additionally, some of the maternal postpartum complications associated with cesarean delivery are: serious puerperal infections (endomyometritis, urinary track infection), surgical wound complications (e.g., infection/cellulitis, would separation or dehiscence), bowel dysfunction, and thromboembolism.[47,48,49] Significantly, puerperal deep vein thrombosis occurs in 1-2% of women delivered by cesarean and that pulmonary embolism is one of the leading cause of maternal mortality in this setting. The adjusted odds of pregnancy-related death after a cesarean delivery is 3.9 times that of a vaginal delivery.[50] Cesarean delivery requires longer hospital stay and longer recovery time than that of vaginal delivery. Further, the odds of maternal postpartum readmission is nearly two times higher in women who had cesarean compared to vaginal delivery.[51,52]

While it is clear that cesarean delivery is not without immediate risk of maternal morbidity and mortality, the long-term impact of cesarean delivery on future pregnancy can be more difficult to assess. Some of these include: need for cesarean delivery in

subsequent pregnancy, uterine scare rupture or dehiscence in future pregnancies, abnormal placentation (including placenta previa and accrete) with high risk of massive maternal hemorrhage, ectopic pregnancy, infertility, bowel obstruction resulting from intra-abdominal adhesions, decision to limit family size due to increased risk of complications from multiple repeat cesarean deliveries.[53,54,55,56]

Studies that examine the economic implications of mode of delivery not only found cesarean delivery in labor is associated with higher costs of hospital care compared to vaginal deliveries,[57] but that first cesarean in labor is associated with increased cumulative cost of care regardless of the number and type of subsequent deliveries.[58]

As cesarean delivery imposes risks of morbidity for the expecting mother, it appears to be a safe and relatively atraumatic method of delivery for the neonate. In part, the rise in cesarean delivery since the 1970s is fueled by concerns of fetal wellbeing during labor or the actual delivery process in some circumstances. Nonetheless, cesarean delivery is associated with risks of complications for the neonates as well. Some of these undesirable outcomes include: fetal asphyxia resulting from utero-placental hypoperfusion induced by anesthesia or maternal position at time of surgery, scapel lacerations, and neonatal respiratory morbidity such as transient tachypnea of the newborns.[59,60,61]

Large population study of births in the U.S. consistently reports that neonatal and infant mortality is higher when delivered by planned cesarean than by vaginal delivery, even after adjusting for demographic and medical factors.[62,63] Further, women who have a first cesarean delivery carry higher risks of maternal and neonatal morbidity and mortality in subsequent pregnancies,[64,65] including unexplained stillbirth regardless of method of delivery in subsequent pregnancies.[66] Thus, while rare, cesarean delivery is associated with serious morbidity and mortality for both the expectant mother and her offspring, and can have significant impact on the index as well as future pregnancies.

1.7. Cesarean delivery: health economic impact

Despite numerous strategies to reduce cesarean delivery,[67] it continues to rise at a rate disproportional to the changing maternal characteristics that may be partly responsible for the increase. With 4 million plus births per year, cesarean delivery is the most commonly performed in-patient surgery in the U.S. and represents in excess of 17 billion U.S. dollars in expenditure per year.[68,69] It is generally believed that the cost of cesarean delivery is higher than that of vaginal delivery or VBACs (Table 1). [70,71,72]

Table 1: Costs of Cesarean Section versus Trial of Labor (Data obtained from University Health System Consortium)[69]	Costs
Vaginal delivery without complications	$4490 (2245-6735)
Vaginal delivery with complications	$5560 (2780-8340)
C-section without complications	$6946 (3473-10,419)
C-section with complications	$8553 (4277-12,830)

However, in some circumstances, such as with VBAC, cost of elective repeat cesarean delivery without trial of labor may be lower than a failed trial of labor that results in repeat cesarean delivery.[73,74]

As cesarean delivery is associated with a longer length of hospital stay and a higher occupancy proportion of rooms for the hospital, higher occupancy rate above a certain threshold can lead to reduced patient satisfaction, increased stress on staff and resources, and increase costs to ensure safe practice.[71] Additionally, the medical impact of rising rates of cesarean delivery on both short-term and long-term maternal and neonatal outcomes, and the associated costs of associated morbidities needs to be taken into account. One recent study showed that the annual incidence rate of placenta accrete is increasing in conjunction with the rising cesarean delivery rate.[75] Abnormal placentation can add costs to the health care system since additional interventions (such as use of interventional radiology, blood transfusions, need for hysterectomy, and intensive care admissions) as well as preterm delivery are often needed to optimize outcome. [76,77] Further, preterm delivery has been well recognized as one of the primary cause of neonatal and infant morbidity and mortality, and preterm birth is a major contributor to inpatient hospital cost not only after birth but throughout childhood.[78,79,80,81]

A review of studies on economic aspects of mode of delivery revealed that most papers report only health service costs; nonetheless, cesarean delivery appears to be more costly than uncomplicated vaginal delivery.[82] Further, the true cost of cesarean delivery is likely much higher than reported, since the available estimates often do not

include direct and indirect costs related to surgical complications or opportunity and economic cost related to hours lost in work force for the patient and/or the caretakers.

Interestingly, one qualitative study that examined women's account of recovery after cesarean birth revealed that 30 of the 32 women interviewed had described difficulties following the postoperative advice they received prior to hospital discharge. Further, their physical recovery after cesarean was hindered by health issues including post-operative pain, reduced mobility, abdominal would problems, infection, vaginal bleeding, and urinary incontinence.[83]

Thus, the current rise in cesarean delivery has a profound impact on maternal and child health. Additionally, there are social and economic repercussions associated with cesarean deliveries that are not yet well understood. Experts in the field of obstetrics concur that accurate estimates of the balance between the risks and benefits of cesarean delivery are imperative to optimize perinatal care.

1.8   Increase in cesarean delivery during the recent decade

Since cesarean delivery is not without imposed risk to the parturient and the neonate, the question remains, why has the annual incidence rate of cesarean increased by more than 50 percent since 1996? A number of hypotheses exist regarding the dramatic increase in cesarean over the past decade. First, the demographics of the pregnant women have changed such that delayed childbearing is associated with complications of pregnancy such as hypertension, diabetes mellitus, placenta abruption, and placenta previa, as well as preterm births.**[84]** All of these are factors associated with increased risk of cesarean delivery.

Additionally, the obesity epidemic in the U.S.[85] has led to an increase in the proportion of pregnant women who are obese, and obesity is an independent risk factor for cesarean delivery and pregnancy complications.[86,87] Further, increasing use of assisted reproductive technology, such as ovulation stimulation, in vitro fertilization (IVF), and intracytoplasmic sperm injection (ICSI), is also associated with a higher risk of cesarean delivery in pregnancies conceived by these techniques independent of twins and higher ordered pregnancies.[88,89] As assisted reproductive technology has led to an increase in the frequency of multiple gestations (>30%),[90] a large proportion of twin pregnancies undergo cesarean delivery, and most (95%) of the triplet and higher ordered pregnancies are delivered by cesarean.[91,92,93] Some studies have also suggested an association between the risk of cesarean delivery and the level of malpractice claims faced by hospitals and physicians;[94,95,96] although some studies do not support such an association.[97,98] This topic remains controversial and awaits further elucidation.

Further, as mentioned previously, the annual incidence rate of vaginal birth after previous cesarean (VBAC) has declined more than 70% since 1996 (Figure2).[99] While the precise reason for this sharp decline remains unclear, it is likely in part due to

concerns about perinatal complications associated with uterine rupture in labor and changes in hospital policies that strictly regulate trial of VBACs.[100,101,102] Uterine rupture, defined as complete separation through the entire thickness of the uterine myometrial wall (including serosa), by itself, is an anatomic finding rather than health outcome since asymptomatic rupture can occur.[103] However, uterine rupture is potentially life-threatening and catastrophic for the expecting mother and her fetus(es), and it is the outcome associated with TOLAC that most significantly increases the risk of perinatal morbidity and mortality. This has been an area under intense scrutiny. While the absolute occurrence of uterine rupture or dehiscence remains very low regardless of intended route of delivery, and that maternal mortality is similarly very rare for both TOLAC and ERCD, the odds of perinatal/neonatal death was nearly twice that in women who had a trial of labor compared to those who undergone cesarean delivery without labor.[104,105] One study that examined temporal trends in the rates of trial of labor in low-risk pregnancies in New York state observed that there was no change in the actual success of VBAC among women who attempted trial of labor after previous cesarean, but that the decline in the rates of VBAC that have been observed nationally likely may be due to a decline in TOLAC attempts as oppose to fewer women achieving VBAC. [106]

The steep declines in trial of labor attempts and vaginal birth after cesarean deliveries suggest that there was a rapid change in the perception of optimal treatment practices for these patients by obstetricians.[109] The American College of Obstetricians and Gynecologists (ACOG) conducted a survey study in 2003 to examine obstetrician-gynecologists' practice patterns and opinions regarding VBAC. Among physicians who completed the survey, 49% of the respondents reported performing more cesarean deliveries then they were 5 years earlier and that the primary reasons for this increase were the risk of liability and patient preference for delivery methods.[107] Indeed, among all births that occurred in the U.S. in 2007, the potential proportion of births that could have a VBAC continues to increase but only 8.3% of women with a previous cesarean had a VBAC.[108] This has likely been influenced by the more stringent practice guidelines regarding trial of labor after cesarean from the ACOG and increased medico-legal pressures that have led to decrease in the number of physicians and hospitals available to provide VBACs.[109,110] Thus, it appears that the dictum of "once a cesarean, always a cesarean" again permeates the current obstetric care.

In addition to the sharp decline in TOLAC/VBACs, some data suggest that the current cesarean delivery rise is likely also fueled by an increase in the number of cesarean deliveries by maternal request (CDMR), i.e., primary cesarean deliveries performed at term to a singleton pregnancy based on maternal preference in the absence of medical or obstetric indication.[111,112] The ACOG Committee Opinion on CDMR reports that a potential benefit is decreased risk of hemorrhage for the mother; potential risks included a longer maternal hospital stay, increased risk of respiratory problems for the neonates, and greater complications in subsequent pregnancies.[113] The National Institute of Health (NIH) also held a State-of-the-Science Conference and concluded that there is insufficient evidence to fully evaluate the benefits versus risks of

CDMR compared to planned vaginal delivery and that such decision should be "carefully individualized and consistent with ethnical principles."[114]

In addition to the above changes in population characteristics and practice pattern, induction of labor may also play a role. Induction of labor is among the most common obstetric interventions. In 2008, 23.1 per 100 (23.1%) live births in the U.S. had labor induction,[115] and this represents more than a doubling of the frequency in the 1990s.[116] There exists the prevailing belief that induction of labor increases the risk of cesarean delivery. This likely stems from observational studies that compared women who had induction of labor to women with spontaneous labor at a particular gestational age.[117,118,119,120] This association, however, has not been validated by prospective trials. In fact, a systematic review of existing literature identified nine randomized controlled trials that report an overall decreased risk of cesarean in women who were induced in comparison to those who were expectantly managed, particularly at gestational age 41 weeks and beyond;[121,122,123] however, evidence is less clear prior to 41 weeks.[124] Even when labor inductions were compared to expectant management in recent observational studies, such data remain conflicted.[125,126,127] Thus, whether increase in induction of labor over the past decades contributes to the current increase in cesarean delivery remains unclear.

1.9   Provider and other non-patient factors on cesarean delivery

Clinical decision making involves patient's informed consent and this process can be complex, where the wellbeing of the parturient and her baby must be weighed. At times, the risks/benefits of management options are not aligned for the parturient and her offspring. Studies that examined women's experience in labor and their perception towards mode delivery report that most women feel involved and satisfied with the decision to undergo cesarean delivery.[128,129] However, one study reported approximately one-third felt lack of involvement in such decision.[130] Particularly, women who have had emergency cesarean deliveries felt less involved in the decision-making process.[131,132] While patient's preference and perception of their experience are important aspects of health care, little data exists regarding factors that may influence clinicians' perception of and influence on labor management and mode of delivery.

Some investigators suggest that obstetricians, compared to midwives, are the more likely to embrace technology and recommend interventions that include caesarean delivery and labor inductions; however, family physicians appear to be more heterogeneous in their attitudes towards birth and mode of delivery.[133,134] While non-patient factors may play important roles in the upward trend of cesarean delivery, there are few studies on the subject to consistently support such an association. Data for the U.S. population on this topic is particularly scant.

1.10   Study Aims

Today, nearly 1 in 3 women giving birth will undergo cesarean delivery, but higher rates of cesarean deliveries do not necessarily correspond with improved perinatal outcomes. It is well documented that cesarean delivery is associated with increased risk of maternal morbidity and mortality,[135,136] and can have a negative impact on perinatal outcomes of subsequent pregnancies, with higher risk of stillbirth and uterine rupture as well as increasing maternal morbidity.[137,138] Although data support that cesarean delivery in the U.S. could be safely lowered without increasing infant mortality,[139] and that both the World Health Organization (WHO) and Healthy People 2010 support the target of annual incidence rate of 15/100 for primary cesarean and 63/100 for repeat cesarean births,[29] the U.S. cesarean delivery has increased for the past 14 consecutive years.

While most experts in the field of obstetrics concur that accurate estimates of the balance between the risks and benefits of cesarean delivery are imperative to optimize perinatal care, investigation on this topic, however, has been inadequate. This is partly due to: 1) limited availability of data; 2) failure to use optimal methods to assess impact of risk factors; and 3) inadequate data on excess morbidity/cost attributable to unnecessary cesarean delivery. To complicate matters further, the U.S., Health Insurance Portability and Accountability Act (HIPAA) of 1996[140] restricts access to some patient-level data necessary to examine this topic in depth. Finally, there are little data on the impact of physician and practice characteristics on the frequency of cesarean delivery.

The goal of this research is to examine patient characteristics and provider factors that are associated with the increased risk of cesarean delivery. Understanding how such factors may influence the decision to recommend/perform cesarean delivery is imperative in developing strategies to curtail the current increase in cesarean delivery. As a first step to address this long term goal, this research will investigate obstetric characteristics and practice patterns associated with cesarean delivery in United States, based on existing datasets as well as a prospective survey study with clinician-level data to address and investigate provider's potential influence on the decision to recommend cesarean delivery in low-risk women.

I propose three specific aims to examine the factors contributing to current rising cesarean delivery trend in the U.S.:

Specific Aim 1: To determine the association between induction of labor, compared to expectant management, and cesarean delivery in low-risk pregnancies

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I will use U.S. natality birth certificate database to examine whether induction of labor in low-risk pregnancies (singleton, term, vertex pregnancies not complicated by existing medical or obstetric conditions) to nulliparous women who delivered in the U.S. I will compare women who had induction of labor at a given gestational age (e.g., 39 weeks)

to a later gestational age (e.g., 40, or 41 weeks) using marginal structural models (MSM).

Hypothesis 1: Induction of labor, compared to expectant management, is not associated with increased risk of cesarean delivery in low-risk population.

Specific Aim 2: **To determine patient-level factors, particularly, advanced maternal age, and its association with cesarean delivery in the U.S. over time, from 1994 to 2006**

I will use existing U.S. natality birth certificate datasets from 1994 to 2006 to examine the role of advanced maternal age on cesarean the rising trend of cesarean delivery in the U.S. I will use population intervention models to assess the impact of maternal age on cesarean delivery at a population-level. Population intervention models utilizes data driven methods (super learner) for model fitting[141] to estimate the possible impact of maternal age on cesarean delivery over time.

Hypothesis 2: Maternal age is associated with increased risk of cesarean delivery, and the magnitude of association over the study period has changed over time.

Specific Aim 3: **To characterize clinicians' practice settings and experiences that influence their likelihood to recommend a cesarean delivery in different clinical scenarios, conditional on relevant maternal and fetal risk factors for adverse pregnancy outcomes.**

I will conduct a survey study among clinicians who practice obstetrics across the U.S. The survey will collect information on clinical experience and practice setting and assess clinicians' aptitude for recommending a cesarean delivery, given various clinical scenarios.

Hypothesis 3: Provider characteristics, past clinical experience, practice setting, and patient population characteristics are independent determinants of physician preference for use of cesarean delivery, conditional of patient-level factors.

In summary, Aims 1and 2 will provide experience with the advanced clinical epidemiology methods for assessing causal associations, evaluating/identifying risk factors through the application of new biostatistics approaches (causal statistical methods) to control for potential biases arising from observational data. Aim 3 will explore provider characteristics and their association with the propensity of recommending cesarean delivery, which have not been examined previously.

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Chapter 2: Material and Methods

2.1: Study population

The demographic profile of the maternal population has changed during the past decade such that a larger proportion of pregnancies are considered high-risk. The extent to which modifiable and non-modifiable patient characteristics alter the risk of cesarean delivery is unclear as is how maternal characteristics and obstetric factors interact to alter a women's *a priori* risk of cesarean delivery.. Therefore, I propose to examine maternal and obstetric characteristics that are associated with cesarean delivery in the U.S.

The target population of this study is all women undergoing singleton live births with a gestational age ≥24 weeks who delivered in the U.S. during the period 1994 to 2006. The actual population will include women with singleton live births ≥24 weeks gestational age during the study period whose demographic, obstetric and neonatal outcome information were available for analysis. The number of cesarean deliveries performed for live births ≥24 weeks gestation in the U.S. reached a nadir in 1996 but has been increasing ever since (Table 1). Compared to 1996, there were approximately 520,000 more cesarean deliveries performed in 2006, an increase of more than 50%, which greatly outpaced the increased number of births:

Table 1: U.S. births 1994-2006	Total Live Births (≥24 weeks)	Total Cesarean (% total deliveries)	
1994	3,876,322	823,288	(21.2%)
1995	3,827,418	798,985	(20.0%)
1996	3,812,300	788,937	(20.7%)
1997	3,800,449	791,018	(20.8%)
1998	3,856,889	817,142	(21.2%)
1999	3,875,478	851,995	(22.0%)
2000	3,981,984	913,781	(22.9%)
2001	3,958,076	967,962	(24.5%)
2002	3,952,096	1,032,151	(26.1%)
2003	4,015,879	1,106,085	(27.5%)
2004	4,040,869	1,176,255	(29.1%)
2005	4,083,209	1,238,189	(30.3%)
2006	4,214,972	1,311,631	(31.1%)

The National Center for Health Statistics (NCHS) of the Center for Disease Control and Prevention (CDC) has prepared the annual U.S. natality birth files since the 1970s. The natality data include births to U.S. and non-U.S. residents which occurred in the 50 United States, the District of Columbia, the Virgin Islands and U.S. territories. Information regarding the pregnancy and birth was collected using the U.S Standard Certificate of Live Birth. Issued by the U.S. Department of Health and Human Services,

the U.S. Standard Certificate of Live Birth has served as the principal means for attaining uniformity in the content of the documents used to collect information on births in the United States; this process is revised and updated every 10-15 years.[1]

There were 2 forms of U.S. Standard Certificate of Live Birth used during the study period. The 1989 revision of U.S. Standard Certificate of Live Birth replaced the 1978 revision, and used checkboxes to obtain detailed medical and health information about the mother and child. This 1989 revision of U.S. Standard Certificate of Live Birth was used by all states between 1990 and 2002. In 2003, a revised U.S. Standard Certificate of Life Birth (2003 revision) was adopted with initial implementation of two states (Pennsylvania and Washington). Full implementation in all States was phased in over several years such that in 2004, Florida Idaho, Kentucky, New Hampshire, New York, Pennsylvania, South Carolina Tennessee, and Washington implemented the 2003 revision. In 2005, the 2003 revision was used by 12 states and representing 31% of births: Florida, Idaho, Kansas, Kentucky, Nebraska, New Hampshire, New York, Pennsylvania, South Carolina, Tennessee, Texas, Washington. In 2006, 19 states representing 49% of live births implemented the 2003 revision (California, Delaware, Florida, Idaho Kansas, Kentucky, Nebraska, New Hampshire, New York, North Dakota, Ohio Pennsylvania, South Carolina, South Dakota, Tennessee, Texas, Vermont , Washington, and Wyoming while the remaining states used the 1989 revision.

While the majority of information collected by the 1989 and 2003 versions of the birth certificate were similar, some fields reported were different. When comparable, revised data (from the 2003 revision) were combined with data from the 1989 revision. Revised data were denoted by "R"; unrevised data were denoted by "U" in the "Rev" column of the documentation. When data from the 1989 and 2003 revision of certificates were not comparable (e.g., education attainment of the mother, month when prenatal care began) revised and unrevised data were both reported, as separate fields in the data file.[1] Further, he quality of birth certificate data collection was tightly monitored by the NCHS. First, the NCHS appointed a panel of vital statistics data providers and users, the Working Group to Improve Data Quality to evaluate the 1989 and 2003 certificates.[2] Detailed specifications for electronic and paper systems were implemented to ensure data uniformity in the national databases as well as data quality.[2] Also, over 95% of births are registered electronically, which assisted in data quality surveillance and control.

2.2:   Causal inference framework

The ultimate goal of conducting epidemiological studies is to make causal inference about associations between exposure and outcomes of interest. In an ideal experiment set to assess the effect of certain treatment (exposure) on an outcome of interest, the comparison (treatment/no treatment) groups should be exactly alike except for their treatment status. Under this ideal condition, the difference in outcome is solely due to the treatment status such that same outcomes would be expected if treatment status were exchanged between the comparison groups—i.e., exchangeability.[3] Thus,

exchangeability ensures that comparison groups are comparable (or, comparability) with respect to baseline risk of outcome. Randomization, in randomized controlled trials, (RCTs) aims to achieve exchangeability and remove measured and unobservable confounding.[4,5] Exchangeability is a fundamental requirement for valid inference in epidemiologic studies set to examine the causal effect of a treatment on outcome of interest.

Yet, observational studies are often limited by inherent confounding, or bias in estimation of the effects of the exposure on outcome due to inherent difference of risk at baseline between exposed and unexposed individuals or populations.[6] The existence of inherent differences between comparison groups compromises the comparability between exposure groups, leading to lack of exchangeability and confounding bias.[7] Thus, lack of exchangeability compromises any inference about the causal nature of observed associations. As cause could be defined by "an object followed by another... where, if the first object had not been, the second never had existed" according to renowned philosopher Hume,[8] the concept of counterfactual condition is such that if A had not occurred, then B would not have either, where A and B actually did occur.[9] Under the counterfactual approach, an individual with an observed exposure status would have one corresponding observed outcome as well as other "counterfactual" exposure-outcome pair(s) where, contrary to the fact, the same exact individual were to have hypothetical outcome that would have occurred given some exposure that he/she did not. Applied to a population, the resulting counterfactual dataset would contain outcomes for each individual with all possible exposure status, thus satisfying the concept of exchangeability and comparability for causal effect estimates.

The basis of the causal inference framework explores the differences in mean outcomes between treatment (exposed) and control groups, expressed as risk differences or relative risks or hazards, and is based upon the concept of counterfactuals.[10,11] A counterfactual outcome, Y_a, is defined as the outcome 1=yes, 0=no) an individual would experience if the treatment variable, A, took on a particular value a. Since, in reality, a subject would only undergo one exposure at a given time point (A) with one corresponding outcome (Y), the counterfactual condition refers to "what would have been" or, the outcome that would have occurred if, contrary to fact, a subject had experienced some exposure which he/she had not. Thus, the counterfactual framework assumes the existence of unobserved outcomes corresponding to the theoretical unobserved exposures that complements the observed data to make up a full dataset, containing both observed, and unobserved counterfactual data.[12,13] The causal parameter estimation is derived from full dataset that contains outcomes for each subject for all possible treatment assignments.[10,11,14] While the observational data collected by researchers contain only the "observed" data, the "missing", unobserved outcome(s) can be estimated from observed data to complete the full dataset.[15]

Several statistical methods have been developed for such estimation including: inverse probability of treatment weighting (IPTW),[16] G-computation,[17] doubly robust estimates,[18,19] and targeted maximum likelihood estimates (TMLE).[20] I will describe

and discuss in specific terms some of these estimators and application of these concepts (e.g., marginal structural models, and population intervention models) of the causal inference framework to address each of the study aims in subsequent chapters which describe the subject matter analyses for this dissertation.

2.3:   Causal inference framework assumptions

The validity of the causal inference framework relies on several underlying assumptions. First, no residual/unmeasured confounding is assumed (known as sequential randomization in longitudinal analyses). While the causal inference literature usually explicitly specifies this assumption, it is not unique only to the causal inference framework. As researchers frequently use multivariable regression models to examine and control for confounding (hence referred to as "traditional" multivariable regression), the effect estimates obtained from any traditional multivariable regression analysis similarly rely on the assumption of no residual or unmeasured confounding in order to yield unbiased parameter estimates.[21]

Next, correct model specification is also assumed. In traditional multivariable regression analysis, covariates that are considered as potential confounders are usually selected based on knowledge of subject matter and existing literature. Using this approach, the regression model estimates the effect of treatment-outcome association within strata of the confounders as well as the effect of confounding variables, whose effects are not of interest. After fitting the traditional regression model of outcome Y on exposure A and confounder W, this would be the final step of the estimation process, and the coefficient for A would be presented as the exposure-outcome association, conditional on W. This is in contrast to the causal inference framework, where the effect model can be selected based on methods such as G-computation, doubly robust, or TMLE[17-20] to select the Q-model and minimize model misspecification (please see Chapter 3 and 4 Methods section for further details on G-computation and TMLE). These estimators use flexible, data-adaptive algorithms such as Deletion/Substitution/Addition (DSA) algorithm or super learner for model selection. [22,23] Further, the confounders in causal inference framework are considered to be nuisance variables, and their confounding effects are controlled at different stages in the analysis. Further, nuisance variables are modeled in nuisance models that precede the final model used to estimates the effect of treatment-outcome association. Besides the assumption of correct model specification of the effect model, in causal inference approaches, it is also assumed that the nuisance models are correctly specified.[24]

Besides the assumption of no residual confounding and correct model specification, other conditions are also explicitly stated and validated for the causal inference construct.   These include the assumption that potential measured confounders occurred prior to the exposure, which in turn occurred prior to the measured outcome (i.e., appropriate temporal ordering). Also, it is assumed that each subject's observed outcome is consistent with his/her unobserved counterfactual

outcome (consistency assumption), and that treatment assignment is independent of the outcome (i.e., coarsening at random).[25,26]

Finally, the causal inference framework relies on the validation of positivity assumption, or the experimental treatment assignment (ETA) assumption. More specifically, the positivity assumption requires that there were both exposed subjects and unexposed subjects in every stratum of the data, with strata defined conditional on the confounders. Estimation of the effect of exposure intuitively requires the comparison of exposed and non-exposed subjects on outcome of interest, and the positivity assumption formalizes this requirement across the data space. Violation of the positivity assumption, thus, compromises the identifiability of a parameter (which refers to the extent to which parameters can be estimated given a particular dataset); and failure of this assumption is equivalent to extrapolating or interpolation outside of the observed data.[27] While the assumption of positivity needs to apply to any meaningful analysis, testing for its validity is often ignored in analysis of observational data.

In summary, this work will utilize causal inference framework through the application of marginal structural models (MSM) and population intervention models to explore risk factors of cesarean delivery. These represent analytic methods that can be applied to observational data, which, under certain assumptions, can estimate the causal association of how a population mean outcome changes when the population exposure of interest changes.[28] While their application is particularly advantageous over multivariable regression analysis in accounting for time-varying confounders, causal inference framework offers causal interpretation of observational data even in the absence of time-varying confounding.[26] More specifically, traditional multivariable regression estimates the difference between the exposed and those unexposed across strata of multiple potential confounders, conditional on covariates. The effect estimates so obtained may not be representative of the population-level effect of the exposure-- the marginal, unconditional causal effect.[27] Estimation of association based the causal inference work, when meeting underlying assumptions, estimates the difference in outcome had the entire study population been unexposed, versus if the entire sample were exposed.

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Chapter 3:

A counterfactual approach to examine the association between perinatal outcome and induction of labor compared to expectant management

3.1 Abstract

Objective: To examine the association of labor induction and mode of delivery by comparing women who were induced at a given gestational to delivery at a later gestational age.

Study Design: This is a retrospective cohort study of low-risk nulliparous women who had term, singleton, vertex, live births in the U.S. in 2005. Women who had induction at a given gestational age (e.g., 39 weeks) were compared to delivery at a later gestational age (e.g., 40, 41, or 42 weeks). We used inverse probability-of-treatment weighted estimation of marginal structural models to examine the effect of induction (at 39, 40, 41 weeks) compared to expectant management. We used bootstrap with replacement to estimate standard error and 95% confidence intervals (CI).

Results: Compared to women who did not have induction of labor at 39 weeks and delivered at a later gestational age (40, 41, or 42 weeks), women who were induced had a lower risk of cesarean delivery (aOR 0.88, 95% CI [0.86-0.91]), neonatal birthweight >4000gm (aOR 0.62, [0.59-0.364), labor dystocia (aOR 0.81, [0.76-0.85]) and their neonates were less likely to have 5-minute Apgar score <7 (aOR 0.77, [0.68-0.86]), meconium aspiration syndrome (aOR 0.59, [0.44-0.80]), and admission to neonatal intensive care unit (aOR 0.75, [0.65-0.85]). Similarly, women who had induction of labor at 40 weeks had a lower risk of cesarean delivery (aOR 0.88; 95% CI 0.86-0.91) and neonatal morbidity compared to women who did not have induction and delivered at a later gestational age (41 or 42 weeks).

Conclusion: Induction of labor in low-risk women at term is not associated with increased risk of cesarean delivery compared to women who delivered at a later gestational age.

3.2   Introduction

Induction of labor is among the most common obstetric interventions. In 2008, 23.1 per 100 (23.1%) live births in the United States had labor induction.[1] This represents more than a doubling of the frequency since the 1990s.[2] The most common indication for induction is postterm pregnancy, which is known to carry increased risk of perinatal morbidity and mortality for the neonate as well as increased risk of perineal trauma, labor dystocia and cesarean delivery for the mother.[3] As perinatal morbidity increases in a continuous, not threshold, fashion in term gestations,[4] it is unclear whether induction of labor prior to 42 weeks in low-risk pregnancy may improve perinatal outcomes.

The prevailing belief that induction of labor increases the risk of cesarean delivery likely stems from observational studies that compared women who had induction of labor to women with spontaneous labor at a particular gestational age.[5,6,7,8] This association, however, has not been validated by prospective trials. A systematic review of existing literature identified nine randomized controlled trials that report an overall increased risk of cesarean in women who were expectantly managed compared to women who underwent elective induction of labor, particularly at gestational age 41 weeks and beyond;[9,10,11] evidence is less clear prior to 41 weeks.[12]

The discrepancies in findings between observational studies and prospective trials likely reside in analytical designs that do not reflect the reality of the underlying subject matter. In clinical settings, a pregnant woman can either undergo induction of labor or she can continue pregnancy and deliver later; her options are not induction of labor now, or spontaneous labor now. This comparison (i.e., induction now versus spontaneous labor now) fails to meet the criteria of an experimental condition (or "treatment") that an investigator could actually assign in a randomized controlled trial, and therefore comparing these groups in an observational study does not identify the causal effect of interest. Rather, the appropriate comparator, or the counterfactual condition, (what would have happened under conditions contrary to actual happenstance) for women who undergo labor induction at a given gestational age (e.g., 39 weeks) is women who do not have labor induction at that gestational age (i.e., who are expectantly managed) and subsequently deliver at a later gestational age (e.g., 40, 41, or 42 weeks; Figure 1).

While the ultimate goal of conducting epidemiological studies is to make causal inference about exposure (e.g. induction of labor) and outcomes of interest (e.g. perinatal outcomes), observational studies are often limited by inherent confounding bias and can assess association but not causality. Marginal structural models (MSMs) are an analytic technique that can be applied to observational data, and which under certain assumptions can estimate the causal association of how a population mean outcome changes when the population exposure of interest changes.[13] While their application is particularly advantageous over multivariable regression analysis in accounting for time-varying confounders, MSMs offer causal interpretation of observational data even in the absence of time-varying confounding.[13,14] More specifically, traditional multivariable regression analysis estimates the difference

between the exposed (women who had induction of labor) and those unexposed across strata of multiple potential confounders. The effect estimates so obtained, conditional on covariates, may not be representative of the population-level effect of the exposure--the marginal, unconditional causal effect [15]comparing the difference in outcome had the entire study population been unexposed (no induction=expectant management), versus if the entire sample were exposed (underwent induction). Much of the prior research that has analyzed induction using the appropriate comparison group has employed conditional methods that do not estimate marginal causal effects.[4,16] To our knowledge, counterfactual-based methods have not yet been applied to this counterfactual-related topic.

Given this background and a paucity of data on induction and neonatal outcomes, particularly prior to 41 weeks gestation, we aimed to examine the association between induction of labor and cesarean delivery and associated perinatal outcomes. We analyzed a large population-based cohort of nulliparous women who had singleton live births in the U.S. in 2005. Specifically, we compared low-risk women who had induction of labor at a given gestational age to women who delivered at a later gestational age (the counterfactual condition).

3.3   Material and Methods

3.3.1   Study Population

This is a retrospective study of maternal and infant data from live births delivered in the United States (US) in 2005, using the Vital Statistics Natality birth certificate registry provided by the Centers for Disease Control and Prevention. This dataset includes all live births to US and non-US residents occurring in the 50 United States, the District of Columbia, the Virgin Islands, and US territories. The 2005 birth certificate data could be collected by using the 2003 version of the US standard certificate of birth (used by 12 states and representing 31% of births: Florida, Idaho, Kansas, Kentucky, Nebraska, New Hampshire, New York, Pennsylvania, South Carolina, Tennessee, Texas, Washington and Puerto Rico) or the 1989 version of the US standard certificate of birth (used by the remainder of the states, the District of Columbia, and territories).[17]

The target population was nulliparous women with singleton, vertex live births delivered between 39 weeks and 42 weeks gestation. In both the 1989 and 2003 versions of the U.S. standard certificate of birth, gestational age was recorded as two variables, one based on obstetric/clinical estimation and one based on last menstrual period (LMP). Clinical dating has been shown previously to provide a more accurate assessment of gestational age than menstrual dating,[18] Gestational age for 5.8% of births in 2005 was determined based on obstetric/clinical data.[17] Because accurate determination of gestational age is paramount to this study analysis, only births that have the same gestational age by both LMP and clinical/obstetric dating were included in the study cohort. Gestational age at delivery was categorized as 39, 40, 41, or 42 completed weeks. Women with prior live births or total births (including index

pregnancy) greater than one were considered multiparous and excluded. Other exclusion criteria were: multifetal gestations, non-vertex presentation, and delivery prior to 39 weeks or after 42 weeks gestation. We also excluded women with medical or obstetric conditions; these included pregestational or gestational diabetes, chronic hypertension, gestational hypertension or preeclampsia/eclampsia (in the induction group), cardiac, lung, renal diseases, oligohydramnois or polyhydramnois, placenta previa, placental abruption, and intrauterine fetal demise. The definitions and diagnostic criteria of conditions and outcomes were based on definitions compiled by a committee of federal and state health statistics officials for the Association of Vital Record and Health Statistics.[19] The National Center for Health Statistics regulates the birth certificate information, checking it for completeness, validity, and consistency between items. If an irregularity is identified, steps are taken to resolve it. The data collection and coding process is reviewed on an ongoing basis for quality control.[20]

3.3.2 Analysis

To examine the effect of induction of labor (exposure of interest) and perinatal outcomes, we compared low-risk nulliparous women who had induction of labor at a given gestational age (e.g. 39 weeks; the exposed group) to women who did not have induction and continued pregnancy with delivery at 40, 41 or 42 weeks by either spontaneous labor or induction of labor (the unexposed group). To illustrate, we noted that the comparison of induction of labor to spontaneous labor at a given gestational age (Figure 1A) is inappropriate as one cannot choose to have induction now or spontaneous labor now; instead, we assigned pregnancies at 39 weeks GA that were induced as the "induction" (exposed) group; we assigned pregnancies without induction at 39 weeks that delivered at a later gestation as the "expectant" (unexposed) group (Figure 1B). This classification scheme mirrors the design of clinical trials on this topic, and corresponds to the causal parameter of interest. Of note, pregnancies designated as the "expectant" group can either undergo spontaneous labor, or induction of labor for any or new medical/obstetric indications. We made a similar analytic scheme for women who had induction of labor at 40 weeks and compared them to women who delivered at a later gestational age (41, or 42 weeks); women who had induction at 41 weeks were compared to deliveries at 42 weeks.

The hypothesized relationship between exposure, outcome of interest, and potential confounding covariates was encoded and illustrated using directed acyclic graph (DAG). Because we were interested in the marginal (unconditional) causal effect of labor induction (exposure, noted as A in Figure 2) on perinatal outcomes (e.g. cesarean delivery, noted as Y in Figure 2), we defined the counterfactuals of interest as: Y_a=outcome Y when exposure is set to value a, such that Y_1=outcome with induction and Y_0=outcome without induction. Note that the marginal causal effect of interest at individual level, Y_1-Y_0, is inherently a counterfactual construct, since at any given point in time a pregnant woman could either have induction of labor (Y_1), or expectant management (Y_0), but not both.[15]

Given this, the MSM estimates the average marginal causal effect at the population level, which can be expressed on an additive scale as:

$$\beta_1 = E(Y_1 - Y_0) = E(Y_1) - E(Y_0)$$

where $E(Y_1)$ and $E(Y_0)$ are the population mean frequency of cesarean delivery when all women in the population at a given week of gestation had induction and had expectant management, respectively. The MSM construct makes use of the concept of the "ideal experiment," a hypothetical experiment than would enable unbiased estimation of causal effect, but which is never feasible in practice. In this framework, potential confounders (W), which could influence the exposure distribution (or "treatment assignment" in the ideal experiment framework) as well as the outcome, were: maternal age (dichotomized as ≤34 or >35 years), race/ethnicity (categorized as non-Hispanic White, non-Hispanic Black, Hispanic/Latina, Asian), educational attainment (≤16 years[high school] or >16 years), cigarette smoking in pregnancy (yes/no), prenatal care visits (≤8, >8 visits), gestational weight gain (≤35 pounds, >35 pounds), as well as interaction terms for age-education and age-weight gain. All of these covariates met the assumption for confounding based on the rules of DAGs, as applied to the DAG for this study. [21,22]

We employed Inverse Probability of Treatment Weighting (IPTW) to estimate the MSM. Briefly, this estimator reweights the observed dataset based on the inverse of each observation's probability of treatment in order to simulate a dataset that is free of confounding-- i.e., where exposure/treatment is assigned randomly.[23, 24] The individual probability of treatment was modeled using multivariable logistic regression, using covariates defined above as candidate covariates. The Deletion/Substitution/Addition (DSA) algorithm was used to determine model specification (see Appendix 1). With the covariates selected from DSA algorithm, we then fit these covariates using traditional logistic regression mode. Akaike Information Criterion (AIC) was used to determine the final regression model (Appendix 2). The confidence intervals obtained by these 2-step methods would be more conservative. The model with the lowest AIC values s was selected as the treatment model which was used to obtain estimates of the MSM: $logit(Pr(Y_a=1)) = \beta_0 + \beta_1 a$. We fit a separate MSM for each gestational-age specific comparison (i.e., induction at 39, 40 or 41 weeks' gestation).

The goal of IPTW estimation is to model the probability of exposure as a function of the confounders; then to use this treatment model to create weights, the inverse of which will redistribute, theoretically, to create a "pseudo-population in which the "induction → cesarean delivery" association is unconfounded.[25] We chose to use stabilized weights, i.e., marginal probability / conditional probability, or P(A)/P(A|W), because stabilized weights provide estimates are more efficient than unstabilized weights--obtained simply as the inverse of the conditional probabilities.[19,21] Assumption of experimental treatment assignment (ETA, AKA positivity assumption) was confirmed by examining the distribution of probability of treatment (exposure) given confounders; all probabilities of exposure were between 5% and 95% for all three comparisons (39 weeks induction versus expectant management; 40 weeks induction versus expectant management; and 41 weeks induction versus expectant management). After

population/marginal effect estimates of induction on outcome (β_1) was derived using MSM, standard errors and 95% confidence intervals of the effect estimates (β_1) were calculated using bootstrap with 1,000 repetitions.

In addition to employing MSMs to examine the association between induction of labor compared to expectant management and perinatal outcomes, we also used targeted maximum likelihood estimation (TMLE) to explore such association (Appendix 3), since TMLE has been shown to provide the optimal tradeoff between bias and efficiency.[26] However, since TMLE is not yet familiar to many investigators and the effect estimates and inferences obtained from TMLE were similar to that obtained from MSMs, we chose to present effect estimates by MSMs.

The primary outcome was the frequency of caesarean delivery and operative vaginal delivery (including vacuum-assisted vaginal delivery and/or forceps delivery). Secondary outcomes included 5-minute Apgar score <7, neonatal injury (in vaginal deliveries only), meconium aspiration, and "neonatal morbidity" as a composite variable of 5-minute Apgar<7, meconium aspiration syndrome, birth injury, use of mechanical ventilation >30 minutes or >6 hours, neonatal antibiotics use, neonatal seizure, and admissions to the neonatal intensive care unit (NICU). Institutional Review Board (IRB) approval was obtained from the Committee on Human Research at the University of California, San Francisco as well as from the Committee for Protectiono of Human Subjects at the University of California, Berkeley. Analysis was performed using Stata v11.0 (College Station, TX) and R v2.12.1 (R Foundation for Statistical Computing, Vienna, Austria).

3.4   Results

There were 442,003 low-risk nulliparous women who met study criteria. The majority of women were between the age of 20-34 years (73.3%), of non-Hispanic White race/ethnicity (62.5%), had >8 years of education (80.8%), had gestational weight gain less than 35 lbs (58.2%), and had at least 8 prenatal care visits (89.8%; Table 1).

Using the analytic scheme of comparing low-risk nulliparous women who had induction at 39 weeks gestational age to their counterparts/counterfactual (women who did not have induction at 39 weeks and subsequently delivered at a later gestational age, i.e., 40, 41, or 42 weeks), the frequency of cesarean was 26.2% among those who had induction while it was 28.4% for women who delivered at a later gestational age (by either labor induction or spontaneous labor; Table 2). The association between induction (compared to expectant management/delivery later as the referent) and cesarean delivery was examined using marginal structural models to estimate the odds ratio and 95% CI calculated from standard errors obtained by bootstrapping with 1,000 repeats. Induction of labor was associated with a lower odds of cesarean (aOR=0.88, 95% CI 0.86-0.91; Table 2). Induction of labor at 39 weeks compared to expectant

management also had lowered odds of fetal macrosomia, labor dystocia, fetal intolerance of labor and chorioamnionitis as well as decreased neonatal morbidity (Table 2).

Similarly, induction of labor at 40 weeks compared to expectant management/delivery at a later gestational age (41 or 42 weeks) was associated with a lower frequency of cesarean delivery (31.0% for induction, 33.7% fa1or expectant management) and the marginal estimates of odds was consistently lower for induction: OR=0.88; 95% CI 0.86-0.91). Induction of labor at 40 weeks compared to expectant management also had lowered odds of fetal macrosomia, labor dystocia, and chorioamnionitis (Table 3). The odds of undesirable neonatal outcomes, including 5-minute Apgar score <7, meconium aspiration syndrome, ventilator use >6hours, admissions to the neonatal intensive care unit (NICU) were also lower in the induction group compared to expectant management/delivery at either 41 or 42 weeks (Table 3).

We observed similar findings when comparing induction at 41 weeks to delivery at 42 weeks for maternal outcomes. Induction, compared to delivery later, appeared to have a lower odds of 5-minute Apgar score <7 (OR 0.68, 95% CI 0.51-0.89) and composite neonatal morbidity OR=0.72; 95% CI 0.60-0.85). While there was a trend of decreased odds, other individual neonatal outcome measures (meconium aspiration syndrome, ventilator use >6hours, NICU admissions, Table 4) had 95% confidence intervals that contained unity.

3.5 Tables and Figures

Table 1: Maternal characteristics (total n= 442,003)

	Number of women	%
Age		
<=19 years	85,752	19.4
20-34 years	323,846	73.3
>=35 years	32,403	7.3
Race/Ethnicity		
Non-Hispanic White	276,350	62.5
African American	58,880	13.3
Latina/Hispanic	71,957	16.3
Asian	24,153	5.5
Other	10,683	2.4
Education		
0-8 years (less than high school)	80,307	18.1
9-12 years (some high school/grad)	116,091	26.3
13-16+ years (some college/grad+)	240,650	54.5
Not stated/unknown	4,953	1.1
Gestational weight gain		
≤ 35 lbs	278,404	58.2
> 35 lbs	199,213	41.7
Prenatal care visits		
< 8 visits	43,070	10.2
≥ 8 visits	377,918	89.8
Marital status		
Not married	186,307	42.2
Married	255,696	57.8
Gestational age at delivery		
39 weeks	181,328	41.0
40 weeks	190,578	43.1
41 weeks	65,831	14.9
42 weeks	4,266	1.0

Source: National Center for Health Statistics (2005)

Table 2: Induction of labor at 39 weeks compared to expectant management (delivery at 40, 41, or 42 weeks) and maternal/neonatal outcomes: odds ratio examined based on marginal structural models

Maternal Outcome	Frequency	OR	95% CI
Cesarean Delivery			
Induction (n=42,769)	26.2 %	0.88	0.86 – 0.91
Expectant (n=278,578)	28.4 %	Referent	
Operative vaginal delivery*			
Induction (n=31,574)	14.3 %	1.17	1.11 – 1.22
Expectant (n=199,390)	12.9 %	Referent	
Birthweight >4,000 gm			
Induction (n=42,947)	6.4 %	0.62	0.59 – 0.64
Expectant (n=279,733)	11.9 %	Referent	
Labor dystocia			
Induction (n=24,006)	5.9 %	0.81	0.76– 0.85
Expectant (n=178,413)	6.7 %	Referent	
Fetal Intolerance of labor			
Induction (n=24,006)	6.2 %	0.99	0.95– 1.03
Expectant (n-178,413)	7.1 %	Referent	
Chorioamnionitis			
Induction (n=42,936)	2.5 %	0.78	0.73 – 0.83
Expectant (n=279,706)	3.5 %	Referent	

Neonatal outcome	Frequency	OR*	95% CI
5-minute Apgar <7			
Induction (n=42,793)	0.89 %	0.77	0.68 – 0.86
Expectant (n=278,612)	1.09 %	Referent	
Meconium Aspiration			
Induction (n=23,963)	0.08 %	0.59	0.44 – 0.80
Expectant (n=177,733)	0.29 %	Referent	
Ventilator use >6hours			
Induction (n=18,890)	0.25 %	0.61	0.43 – 0.86
Expectant (n=100,892)	0.36 %	Referent	
NICU admission			
Induction (n=18,890	2.57 %	0.75	0.65 – 0.84
Expectant (n=100,892)	3.05 %	Referent	
Composite morbidity[§]			
Induction (n=42,853)	2.55 %	0.78	0.73 – 0.84
Expectant (n=278,625)	2.97 %	Referent	

*Operative vaginal delivery: examined among women who delivered vaginally
[§] Composite neonatal morbidity includes: 5-minute Apgar score <7, meconium aspiration syndrome, ventilator use >30minutes or > 6 hours, birth injury, neonatal seizure, neonatal antibiotics use, and NICU admission

Source: National Center for Health Statistics (2005)

Table 3: Induction of labor at 40 weeks compared to expectant management (delivery at 41 or 42 weeks) and maternal/neonatal outcomes: odds ratio examined based on marginal structural models

Maternal Outcome	Frequency	OR	95% CI
Cesarean Delivery			
Induction (n=52,383)	31.0 %	0.88	0.86 – 0.91
Expectant (n=74,680)	33.7 %	Referent	
Operative vaginal delivery*			
Induction (n=36,129)	15.5 %	1.17	1.12 – 1.22
Expectant (n=49,628)	13.4 %	Referent	
Birthweight >4,000 gm			
Induction (n=56,606)	11.0 %	0.62	0.59 – 0.63
Expectant (n=75,224)	16.5 %	Referent	
Labor dystocia			
Induction (n=30,331)	7.2 %	0.80	0.76 – 0.85
Expectant (n=48,727))	8.8 %	Referent	
Fetal Intolerance of labor			
Induction (n=30,331)	8.0 %	1.00	0.95 – 1.04
Expectant (n=48,727)	8.2 %	Referent	
Chorioamnionitis			
Induction (n=52,606)	3.2 %	0.78	0.73 – 0.83
Expectant (n=75,218)	4.1 %	Referent	

Neonatal outcome	Frequency	OR*	95% CI
5-minute Apgar <7			
Induction (n=52,469)	1.00 %	0.88	0.68 – 0.86
Expectant (n=74,952)	1.27 %	Referent	
Meconium Aspiration			
Induction (n=30,263)	0.20 %	0.61	0.44 – 0.79
Expectant (n=48,518)	0.39 %	Referent	
Ventilator use >6hours			
Induction (n=22,194)	0.28 %	0.59	0.43 – 0.86
Expectant (n=26,364)	0.47 %	Referent	
NICU admission			
Induction (n=22,194)	2.70 %	0.74	0.66 – 0.84
Expectant (n=26,364)	3.60 %	Referent	
Composite morbidity[§]			
Induction (n=52,457)	2.74 %	0.78	0.73 – 0.84
Expectant (n=74,882)	3.50 %	Referent	

*Operative vaginal delivery: examined among women who delivered vaginally
[§] Composite neonatal morbidity includes: 5-minute Apgar score <7, meconium aspiration syndrome, ventilator use >30minutes or > 6 hours, birth injury, neonatal seizure, neonatal antibiotics use, and NICU admission

Source: National Center for Health Statistics (2005)

Table 4: Induction of labor at 41 weeks compared to expectant management (delivery at 42 weeks) and maternal/neonatal outcomes: odds ratio examined based on marginal structural models

Maternal Outcome	Frequency	OR	95% CI
Cesarean Delivery			
Induction (n=28.425)	36.0 %	0.88	0.82 – 0.94
Expectant (n=4,744)	39.0 %	Referent	
Operative vaginal delivery*			
Induction (n=18,044)	15.7 %	1.31	1.15 – 1.39
Expectant (n=2,893)	12.0 %	Referent	
Birthweight >4,000 gm			
Induction (n=28,470)	16.7 %	0.75	0.69 – 0.82
Expectant (n=4,772)	20.2 %	Referent	
Labor dystocia			
Induction (n=17,450)	9.8 %	0.73	0.64 – 0.82
Expectant (n=2,746)	12.4 %	Referent	
Fetal Intolerance of labor			
Induction (n=17,450)	9.1 %	1.26	1.12 – 1.43
Expectant (n=2,746)	8.4 %	Referent	
Chorioamnionitis			
Induction (n=28,470)	4.5 %	1.10	0.93 – 1.30
Expectant (n=4,772)	4.3 %	Referent	

Neonatal outcome	Frequency	OR*	95% CI
5-minute Apgar <7			
Induction (n=28,381)	1.19 %	0.68	0.51 – 0.89
Expectant (n=4,729)	1.78 %	Referent	
Meconium Aspiration			
Induction (n=17,379)	0.33 %	0.96	0.43 – 2.12
Expectant (n=2,739)	0.40 %	Referent	
Ventilator use >6hours			
Induction (n=10,980)	0.56 %	1.92	0.34 – 10.8
Expectant (n=2,003)	0.35 %	Referent	
NICU admission			
Induction (n=10,980)	3.48 %	0.95	0.70 – 1.28
Expectant (n=2,003)	4.04 %	Referent	
Composite morbidity[§]			
Induction (n=28,359)	3.33 %	0.72	0.60 – 0.85
Expectant (n=4,742)	4.90 %	Referent	

*Operative vaginal delivery: examined among women who delivered vaginally
[§] Composite neonatal morbidity includes: 5-minute Apgar score <7, meconium aspiration syndrome, ventilator use >30minutes or > 6 hours, birth injury, neonatal seizure, neonatal antibiotics use, and NICU admission

Source: National Center for Health Statistics (2005)

Figure 1: This figure illustrates the study comparison groups employed in previous studies (A) and in the present study (B).

A: comparing induction of labor at a given gestational age to spontaneous labor at the same gestational age simulates the choices of "induction now or spontaneous labor now," which does not reflect the clinical reality.

B: comparing induction of labor at a given gestational age to delivery at a later gestational age by either spontaneous labor or induction simulates the choice of "induction now or continue pregnancy and delivery at a later gestation," which is the decision clinicians/patients make at any given point in time
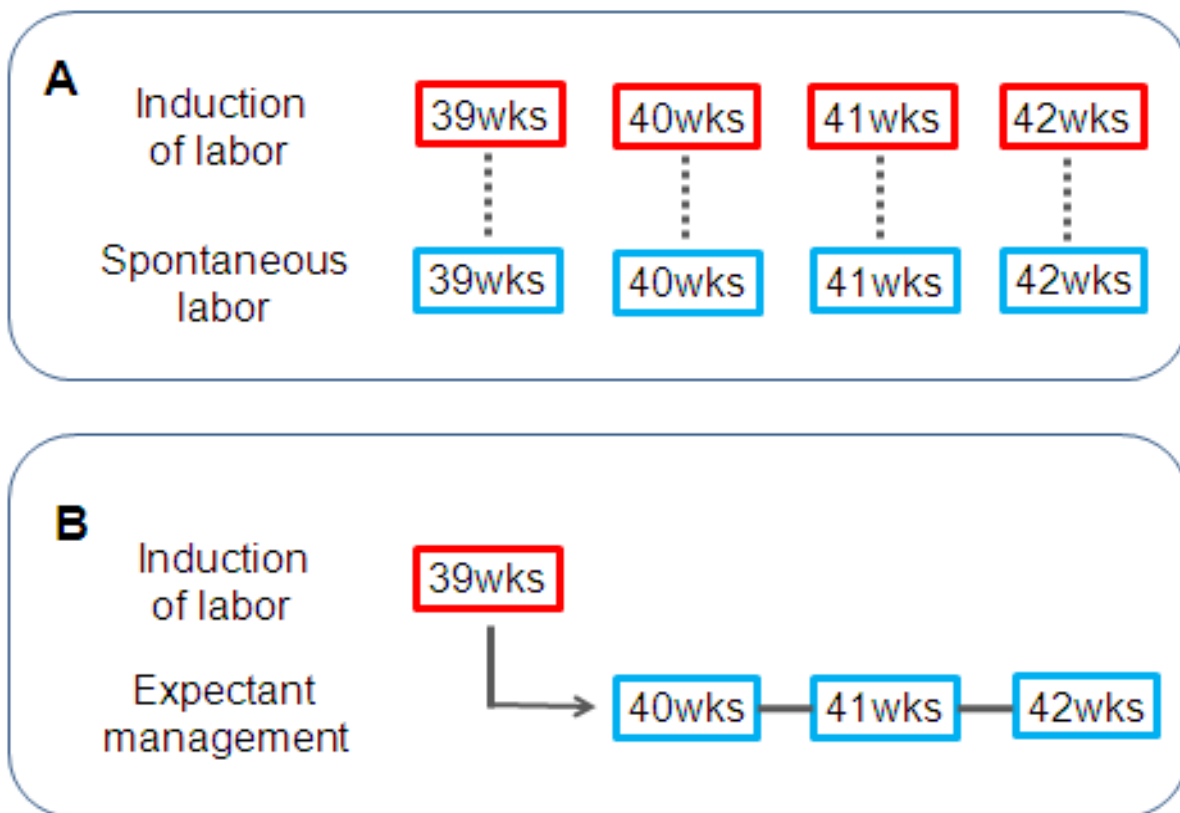
Figure 2: Directed acyclic diagram (DAG) that illustrate the association of exposure (noted as A), outcome (noted as Y) and potential confounding covariates (noted as W).

Covariates
(W): race/ethnicity, age, education, marital status, cigarette smoking, gestational weight gain, prenatal care

Exposure
(A): Induction of labor

Outcome
(Y): Cesarean delivery, maternal/neonatal outcomes
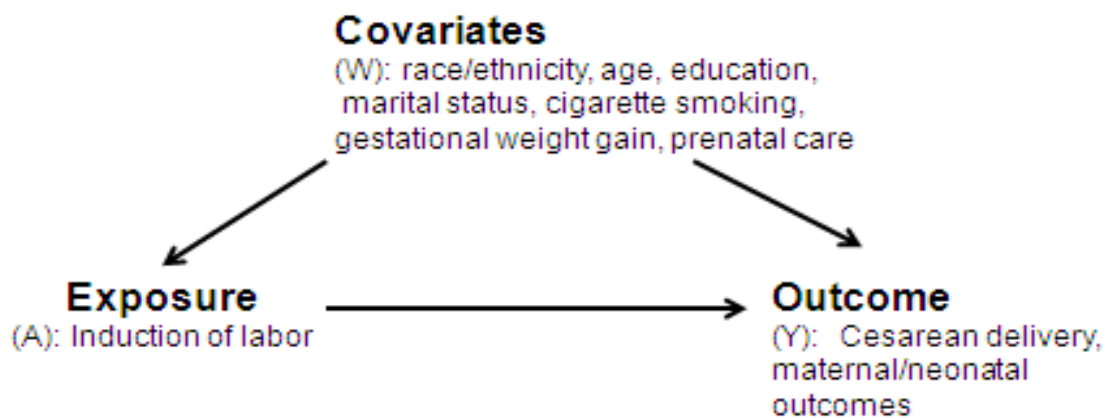
3.6   Discussion

We used marginal structural models to examine the relation between induction of labor at a specific gestational age (e.g., 39 weeks) compared to expectant management (delivery at a later gestational age, i.e., 40, 41 or 42 weeks by either entering spontaneous labor or subsequently needing induction of labor for various medical/obstetric indications) and associated maternal/neonatal outcomes. MSMs are an analytical approach to adjust for confounding in observational data based on the concept of counterfactuals. Counterfactual conditions refer to what would have happened under conditions contrary to what actually occurred. We examined induction of labor as the "exposure" at a given gestational age, the counterfactual to induction of labor was no induction of labor at that gestational age with delivery at a later gestational age.

It is important to note that while traditional multivariable logistic regressions provides an conditional estimate of the exposure-outcome association, marginal structural models compare outcome frequency under different exposure distributions (exposed and non-exposed) in the same sample population (thus, the counterfactual construct) and estimate the effect of exposure across the entire population, and not conditional on covariates. By applying such causal inference methods (i.e., MSM), our study estimates the population-level effect of induction on cesarean delivery and other perinatal outcomes that correspond to hypothetical interventions: if all were to undergo induction of labor versus if all were to have expectant management.

The use of marginal structural models required that several underlying assumptions are met in order for the effect estimates to be valid.[14,15] While the assumptions of correct model specification, and no residual/unmeasured confounding are not unique to the application of MSMs, as these criterion are also implicitly assumed for the standard epidemiologic analysis using multivariable regressions, the concept relating to the existence of counterfactuals applies to the MSM estimation but not traditional regression. Commonly the regression model specification relies on subject matter knowledge and procedures such as backward or forward stepwise regression to derive a final parsimonious model. In this analysis, we used causal graphs to express our specific hypotheses and to examine the relation between exposure, outcome and confounding covariates; we also used traditional logistic regression methods as well as DSA algorithm to determine the candidate covariates to be included in the regression model for the application of MSM.

In the analyses of induction at 39 weeks compared to delivery later, and the analyses of induction at41 weeks compared to delivery later, the regression models fitted based on covariates selected from DSA resulted in lowest AIC, which we take to be our best-fit model given the data distribution. The application of DSA algorithm has several advantages. First, the DSA algorithm is a flexible, data-adaptive machine learning model search algorithm that is based on cross-validation and the L2 loss function (which is "observed minus expected") and thus does not rely on a parametric

model assumption. Additionally, as a data-adaptive estimation procedure, DSA can fit complex polynomial forms to the dataset and allows for comparison of models based on different number of observations. Thus, it can account for informative censoring through the use of weights in each regression.[27]

Besides the assumption of correct model specification and no unmeasured confounding, additional conditions are explicitly stated and validated for the causal inference/MSM construct. For example, MSMs assumed that the potential measured confounders occurred prior to the exposure, which in turn occurred prior to the measured outcome (i.e., appropriate temporal ordering). Also, each subject's observed outcome would be consistent with his/her unobserved counterfactual outcome (consistency assumption), and that treatment assignment is independent of the outcome (i.e., coarsening at random).[14,15]

Additionally, causal inference/MSM relied on the validation of positivity assumption, or the Experimental Treatment Assignment (ETA) assumption. For this analysis, the positivity assumption required that there were both exposed (induction of labor) subjects and unexposed (no induction/expectant management) subjects in every stratum of the data, with strata defined conditional on the confounders. Estimation of the effect of exposure intuitively requires the comparison of exposed (induced) and non-exposed (no induction) subjects on outcome of interest, the positivity assumption formalizes this requirement across the data space. Violation of the positivity assumption, thus, compromises the identifiability of a parameter (which refers to the extent to which parameters can be estimated given a particular dataset); and failure of this assumption is equivalent to extrapolating or interpolation outside of the observed data.[28] While the assumption of positivity needs to apply to any meaningful analysis, testing for its validity is often ignored in analysis of observational data. We examined the probability of exposure and non-exposure of our study population and ensured that the assumption of positivity was met for our MSM analyses.

While previous observational studies compared women who had induction of labor to spontaneous labor at the same gestational age and report increased risk of cesarean, we observed a decreased risk of cesarean. The discrepant findings likely reside in difference in comparison groups: we compared induction to no induction/expectant management and not induction to spontaneous labor. We also used MSM to estimate the causal relationship between induction and perinatal outcomes and our findings are consistent with randomized, prospective studies that have examined induction of labor versus expectant management.[13] While randomized controlled trials (RCTs) are considered the gold standard for removing confounding to examine the "true" effect of exposure (treatment) on outcome of interest, trials are not always possible and can be time-consuming, expensive, or at times, unethical to carry out.

Through the counterfactual framework, we demonstrated the application of MSMs in addressing some of the challenges of observational data and interpretation of results. We do not suggest that MSMs replace the need for well-designed/conducted RCTs; however, in situations where only observational data is available, MSMs may offer insights on what might have been observed if RCTs were conducted. While we

chose to use IPTW, more sophisticated methods of analysis (e.g., TMLE) with better priorities in terms of bias and efficiency are available and will become a method of choice for analysis of observations data. Similarly, more flexible model fitting through machine learn also are available that further minimize unwarranted assumptions about the data generating distributions in observational studies.[29]

While the causal inference literature supports that MSMs are among the growing analytical methods to provide estimation of causal effects from observation data, there are limitations to our study. Through the application of MSM, our analyses offered marginal interpretation (as oppose to conditional interpretation from traditional regression analysis based on logistic regression) of the association between induction of labor in low-risk population and perinatal outcomes. Despite the counterfactual framework, MSM analyses were still based on observational data and, thus, relied on high quality of the data to enable correct model specification and minimize unmeasured confounding—these basic assumptions applicable to not just MSMs but were also assumed by traditional multivariable regression analyses. Ideally, would like to examine detailed obstetrical information, such as precise indication of induction or cervical examination on admission as potential confounding variables; however, such information were not available. Another important aspect of labor management is women's perception, preference and experience regarding the birth of their children. This study was not able to assess the impact of cost or patient preference/satisfaction, two important issues when considering labor induction.

In summary, our retrospective study examines whether induction at 39, 40, or 41 weeks gestation compared to expectant management using casual inference analytical methods and observed that induction was associated with decreased risk of caesarean delivery and decreased neonatal morbidity. As women with spontaneous labor report the highest level of satisfaction with their experience, and women undergoing induction are more likely to report dissatisfaction with the labor process,[30] one important aspect of labor management is women's perception, preference and experience regarding the birth of their children. The American College of Obstetricians and Gynecologists (ACOG) stated that, "induction of labor should take into account "maternal and fetal conditions, gestational age, cervical status, and other factors." The goal of induction of labor is to achieve a vaginal delivery when the benefits of expeditious delivery outweigh the potential risk of continuing pregnancy.[31] Providing patient-centered, evidence based care necessitates understanding the patient's needs and values in addition to assessing perinatal outcomes associated with induction of labor.

3.7   Appendix

Appendix 1: Introduction to Deletion/Substitution/Addition (DSA) algorithm

A number of methods exist to allow the data to identify the best predictors of a given outcome. Some examples include decision trees, neural networks, support vector regression, least angle regression, logic regression, and the Deletion/Substitution/Addition (DSA) algorithm.[27,32] While logic regression constructs Boolean (TRUE/FALSE) expressions of binary covariates, the DSA algorithm uses polynomial basis functions.[33] We implemented the DSA algorithm to identify confounding covariates for the exposure/outcomes of interest.

More specifically, the DSA algorithm is a flexible, data-adaptive machine learning model search algorithm that is based on cross-validation and the L2 loss function (which is "observed minus expected").[27]   DSA iteratively generates polynomial generalized linear models based on the existing terms in a current "best" model and applies the following three steps: 1) a deletion step which removes a term from the model; 2) a substitution step which replaces one term with another; and 3) an addition step which adds a term to the model. This search for the "best'" estimator starts with the base model, and the final model will minimize the empirical risk of learner sets among all estimators considered such that the final model is characterized by "optimum" size, order of interactions and set of candidate variables selected by cross-validation.[34] With each iteration, the cross-validated (CV) risk is evaluated and the final model selected by the DSA algorithm is the one that minimizes the empirical risk on the learning set. The DSA algorithm also aims to minimize the L2 Loss function.

As the search for the best estimator can be specified by 4 arguments, which we control: 1) the number of variables in the models considered (for this study, maximum size=10); 2) the maximum order of interactions for the model (maximum order of interaction=2); 3) the order of the polynomial to which the interactions of variables are raised (maximum power=3), and the set of candidate variables to be considered in each model.

Appendix 2: treatment model selection for MSM models that examined weeks at induction vs. expectant management: model with least Akaike Information Criterion (AIC) value selected

| Treatment model selection for induction at 39 weeks vs. expectant management (delivery at 40, 41, or 42 weeks)	AIC
Tx 1: race/ethnicity	215627.6
Tx 2: race/ethnicity + age	215580.7
Tx 3: race/ethnicity + age + education	215579.7
Tx 4: race/ethnicity + age + education + weight gain	215581.2
Tx 5: race/ethnicity + age + education + weight gain + prenatal care	215525.0
Tx 6: race/ethnicity + age + education + weight gain + prenatal care + smoking	215465.5
Tx 7: race/ethnicity + age + education + weight gain + prenatal care + smoking + age*education + age*weight gain	215460.8
Tx 8: DSA: Hispanic + Black + Asian + education*Hispanic + education*age + prenatal care + smoking + education*Black	186618.6

Treatment model selection for induction at 40 weeks vs. expectant management (delivery at 41 or 42 weeks)	AIC
Tx 1: race/ethnicity	125581.1
Tx 2: race/ethnicity + age	125537.4
Tx 3: race/ethnicity + age + education	125521.9
Tx 4: race/ethnicity + age + education + weight gain	125523.9
Tx 5: race/ethnicity + age + education + weight gain + prenatal care	125471.5
Tx 6: race/ethnicity + age + education + weight gain + prenatal care + smoking	125458.9
Tx 7: race/ethnicity + age + education + weight gain + prenatal care + smoking + age*education + age*weight gain	125438.3
Tx 8: DSA: Hispanic + Black + Asian + prenatal care + smoking + education*age + education*Asian + education*Hispanic + education*Black + age*Hispanic	131379.8

Treatment model selection for induction at 41 weeks vs. expectant management (delivery at 42 weeks)	AIC
Tx 1: race/ethnicity	215627.6
Tx 2: race/ethnicity + age	23185.4
Tx 3: race/ethnicity + age + education	23173.7
Tx 4: race/ethnicity + age + education + weight gain	23130.9
Tx 5: race/ethnicity + age + education + weight gain + prenatal care	23129.5
Tx 6: race/ethnicity + age + education + weight gain + prenatal care + smoking	23012.0
Tx 7: race/ethnicity + age + education + weight gain + prenatal care + smoking + age*education + age*weight gain	23005.2
Tx 8: DSA: Hispanic + education + prenatal care + smoking + education*age + education*Black + Hispanic*weight gain + education*Hispanic	20489.0

Appendix 3: Brief description of targeted maximum likelihood estimation (TMLE)

The counterfactual framework provides a basis for defining causal effects between treatment and control groups. The causal parameter is estimated from the full, unobserved, counterfactual dataset containing outcomes for each subject for all possible treatment assignments, while in practice the data observed/collected contains only one outcome value corresponding to the treatment actually observed.(Rubin 1974) Common estimators for such "missing data problem" include the inverse probability of treatment weight (IPTW) estimator,[35] G-computation estimator,[36] the double robust IPTW estimator,[37] and targeted maximum likelihood estimation (TMLE).[38,39]

More specifically, IPTW relies on estimating the probability of treatment (known as the treatment mechanism, and the "g-part" of the likelihood), and G-computation relies on estimating the outcome distribution, given exposure and covariates (as is common in conventional regression, and is called the "Q-part" of the likelihood in this context). As denoted in a heuristic DAG below, where **A** denotes exposure/treatment, **Y** denotes outcome, and **W** denotes confounder,
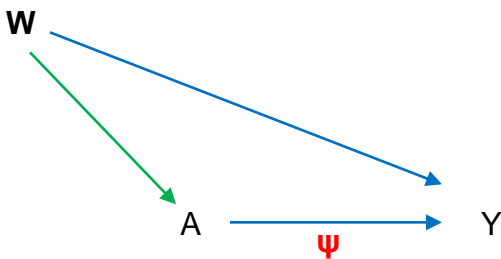
the goal of analysis is to estimate the effect (parameter) of interest with minimum bias and variance. In this case, that parameter of interest is the effect of exposure on outcome without the confounding bias introduced by *W* (this unbiased effect is represented as **ψ**). To estimate A→Y without bias, we must consider how the confounder set is associated with exposure (i.e., the "g-part" of the likelihood, P(A|W)), represented by the green arrow) and also how these confounders and the exposure predict the outcome (i.e., the "Q-part" of the likelihood, E(Y | A, W), represented by the blue arrows). Building upon these concepts, TMLE estimates both components of the likelihood (the g- and the Q-parts) to provide doubly robust estimates (i.e., unbiased effects if either of the two models is correctly specified). TMLE accomplishes this by augmenting the Q-model with a "clever covariate" based upon the g-function (see Mackey et al for further explanation).[40]

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Chapter 4:

Estimating the contribution of maternal age to risk of cesarean delivery using population intervention models analysis

4.1 Abstract

Objective: There exist numerous studies that report increase in maternal age is associated with a higher risk of cesarean delivery; however, these studies are heterogeneous in study design and population examined. Thus, we aimed to estimate the effect of maternal age on cesarean delivery in nulliparous women who gave live birth in the U.S. between 1990 and 2006.

Study Design: This is a retrospective cohort study of low-risk nulliparous women who had term (gestational age between 37weeks 0 days and 41 weeks 6 days), singleton, vertex, live births in the U.S. between 1994 and 2006. The association between maternal age, examined as a dichotomous outcome (<35 years or ≥35 years at time of birth), and cesarean delivery was examined using multivariable logistic regression and population intervention models. Bootstrap technique with 1,000 repetitions with replacement was used to estimate standard error and calculate 95% confidence intervals for the population intervention parameter estimates.

Results: There were 10,808,598 women who met study criteria who gave live births in the U.S. between 1994 and 2006. The proportion of women with advanced maternal age (AMA, defined as age ≥35 years at time of birth) increased during the study period, from 5.8% in 1994 to 6.8% in 1998 to 7.4% in 2002 and 7.5% in 2006. Concurrently, the frequency of cesarean delivery among women who were AMA also increased: from 31.0% in 1994 to 31.2% in 1998 to 38.1% in 2002 to 46.7% in 2006. Using multivariable logistic regression analysis, the odds of cesarean delivery in women with AMA was nearly twice that of women younger than 35 years and was relatively constant over the study period (aOR 2.11, 95% CI 2.08 – 2.16 in 1994; aOR 2.17 95% CI 2.13 – 2.21 in 1998; aOR 2.18, 95%CI 2.15 – 2.22 in 2002; and aOR 2.22, 95% CI 2.17 – 2.26 in 2006).

We used the population intervention models to estimate the difference between the mean observed outcome (cesarean delivery) and the mean counterfactual outcome when the exposed (i.e., women with AMA) were "intervened upon" and set to < 35 years old, based on the causal inference framework. According to the population intervention parameters, we estimated that there woud be approximately a -0.8 per100 births in reduction in the annual incidence rate of cesarean delivery in 1994, 1995, and 1996 (Table 3). In 1999, the estimated reduction of the annual incidence rate of cesarean delivery was -1.0/100 births. The impact of AMA on cesarean increased progressively such that in 2006, the population intervention parameter estimation was that if AMA were "intervened on", there would be a -1.33/100 births reduction in cesarean delivery.

[53]

Conclusion: The proportion of women who delayed childbearing increased during the study period such that there were more women with advanced maternal age in 2006 compared to one decade earlier. Using population intervention models, we estimated that the impact of AMA on cesarean also increased between 1994 and 2006.

4.2   Introduction

Over the past two decades, there has been a steady increase in birth rates (birth per 1,000 women per year) in the United States among women of age groups 30-34, 35-39, and 40-44 years.[1] More specifically, the proportion of live births among women aged 35 years and older in the U.S. increase from approximately 5% of total live birth in 1970 to approximately 13% in 2007.[2] Similar trends of delayed childbearing have been observed worldwide, particularly in the most developed countries and some developing countries.   Likely, delayed marriage, pursuit of higher education and career advancement, improved effective contraception, and advances in assisted reproductive technology (ART) are some but not all contribute to the trend of delayed childbearing for larger proportion of women today compared to decades earlier.[3,4,5]

A large body of literature exists to suggest that increasing maternal age is associated with higher risk of adverse pregnancy outcomes, such as miscarriages, birth defect and genetic/chromosomal abnormalities, stillbirth as well as obstetric complications such as preterm delivery, preeclampsia, gestational diabetes mellitus, placenta previa, placenta abruption, and cesarean delivery.[6,7,8,9,10,11,12] One study that examined inter-pregnancy interval and subsequent perinatal outcomes among women who delayed initiation of childbearing observed persistent risk of adverse outcomes into subsequent pregnancies, particularly with a short inter-pregnancy interval.[13,14] However, there are some studies that report no association between maternal age and adverse outcomes.[15,16] While systematic reviews attempted to examine this question, significant heterogeneity exists as studies differed in design, analytical comparisons, and population examined.[17,18] Further, it appeared that many women are generally unaware of the potential consequences of delayed childbearing.[19]

Although age increases in a continuous fashion, the association between maternal age and pregnancy outcomes is often examined by treating age as a binary variable. While effect estimates for binary or categorical comparisons are at times easier to interpret in the clinical setting, more likely, binary treatment of age-related risk in obstetrics stems from the observation that a number of perinatal risks associated with age, such as genetic or chromosomal abnormalities, subfertility, and miscarriage, increases more in a threshold fashion than a continuous fashion, particularly after age 35 at time of birth. Thus, advanced maternal age (AMA) is often used to describe women age 35 and older at time of estimated date of delivery (EDD).

For this study, we aimed to estimate the risk of cesarean delivery in nulliparous women associated with advanced maternal age. More specifically, we used population intervention models to estimate the population attributable fraction of AMA on primary cesarean delivery between 1994 and 2006. The population attributable fraction represents the reduction in incidence (of cesarean delivery) that would be achieved if the population had been entirely unexposed, compared with its current (observed, actual) exposure pattern. Thus, population intervention models build upon the causal inference literature to model the difference of an effect between the observed exposure distribution of a population (i.e., the actual study population) and a counterfactual exposure distribution (the population outcome that would have been observed under

[55]

"intervention" such that the exposure would be at some target, optimal level).[20,21] Developed by Hubbard and van der Laan, population intervention models propose a direct estimation equation approach to model two parameters related to a "causal" attributable risk, where these models are functions of the level at which one wishes to intervene.[22,23]

Using this analytical technique, we wished to gain insights into the potential changes in the distribution of cesarean delivery in our population of nulliparous women who gave live births in the U.S. if women with delayed childbearing were counseled regarding the contribution of advanced maternal age on cesarean delivery, thus "intervening" on age as a risk factor. Population intervention models enable the estimation of the potential effects of an intervention, or alternatively, the population-level effects of removing some adverse exposure from the population. Through this analysis, we estimate the impact of potential population changes due to maternal age on cesarean delivery.

4.2   Material and Methods

Study Population

This was a retrospective study of maternal and infant data from live births delivered in the United States (US) between 1994 and 2006, using the Vital Statistics Natality birth certificate registry provided by the Centers for Disease Control and Prevention. The U.S. Standard Certificate of Live Birth, issued by the U.S. Department of Health and Human Services, has served as the principal means for attaining uniformity in the content of the documents used to collect information on births in the United States; this process is revised and updated every 10-15 years.[24] The data collected includes all live births to US and non-US residents occurring in the 50 United States, the District of Columbia, the Virgin Islands, and US territories.

There were 2 forms of U.S. Standard Certificate of Live Birth used during the study period. The 1989 revision of U.S. Standard Certificate of Live Birth replaced the 1978 revision, and used checkboxes to obtain detailed medical and health information about the mother and child; this 1989 revision of U.S. Standard Certificate of Live Birth was used by all between 1990 and 2002. In 2003, a revised U.S. Standard Certificate of Life Birth (2003 revision) was adopted with initial implementation of two states (Pennsylvania and Washington). Full implementation in all States was phased in over several years such that in 2004, Florida Idaho, Kentucky, New Hampshire, New York, Pennsylvania, South Carolina Tennessee, and Washington implemented the 2003 revision. In 2005, the 2003 revision was used by 12 states and representing 31% of births: Florida, Idaho, Kansas, Kentucky, Nebraska, New Hampshire, New York, Pennsylvania, South Carolina, Tennessee, Texas, Washington. In 2006, 19 states representing 49% of live births implemented the 2003 revision (California, Delaware, Florida, Idaho Kansas, Kentucky, Nebraska, New Hampshire, New York, North Dakota,

Ohio Pennsylvania, South Carolina, South Dakota, Tennessee, Texas, Vermont , Washington, and Wyoming while the remaining states used the 1989 revision.[20]

We examined term births (gestational age between 37weeks 0 days and 41weeks 6 days) to nulliparous women who were residents of the U.S. Pregnancies with multiple gestations, breech presentation at time of delivery and births to foreign residents were excluded. Since many medical problems (such as hypertension, diabetes mellitus) which often occur in adulthood are thus more prevalent in women with delayed childbearing and that the presence of medical problems is associated with increased risk of cesarean delivery, we excluded women with medical or obstetric conditions to estimate the effect of AMA → primary cesarean delivery not mediated through or attributable to these known medical/obstetric conditions. Thus, women with medical or obstetric conditions such as pre-gestational or gestational diabetes, chronic hypertension, gestational hypertension or preeclampsia/eclampsia (in the induction group), cardiac, lung, renal diseases, oligohydramnois or polyhydramnois, placenta previa, and placental abruption were excluded from study analysis.

The definitions and diagnostic criteria of conditions and outcomes were based on definitions compiled by a committee of federal and state health statistics officials for the Association of Vital Record and Health Statistics.[25] We also excluded women who had missing information on age, method of delivery, and information regarding medical, obstetric problems, as well as missing information on race/ethnicity, prenatal care, education, cigarette smoking status, and marital status.

Analysis

To enable comparison between conventional methods and causal models, and to contrast relative and absolute measure of association, we conducted analyses using both logistic regression and the population intervention model. We first compared the frequency of cesarean delivery in nulliparous women age ≥35 and women age <35 meeting study inclusion/exclusion criteria using chi-square test, and estimated the association between advanced maternal age and cesarean delivery (designating age<35 as referent) using multivariable logistic regression controlling for potential confounders. In contrast with the causal inference framework, conventionally, the association between exposed and unexposed could be estimated on an additive scale by calculating:

$$E[Y \mid A = 1, W=w] - E[Y \mid A = 0, W=w]$$

where we designated maternal age ≥35 as our exposure of interest (*A*), A=1 if maternal age ≥35 or A=0 if maternal age <35 at time of delivery and (*W)* denoted the vector of confounders needed to control for unbiased estimation. This approach provides a conditional association by comparing the mean outcome among the exposed to the mean outcome among the unexposed, assuming that the two groups are exchangeable (i.e., conditional on covariates).

[57]

We were interested in examining the population-level association between advanced maternal age and cesarean delivery using the causal inference approach which provides an marginal (i.e., unconditional) estimate this association. In the context of the causal inference framework a particular parameter of interest is estimated from the theoretical full (counterfactual) data under certain assumptions.[26,27] In this study, the possible counterfactual outcomes (Y_a) for each subject of the study population are Y_1 and Y_0 under exposure (*1*) and no exposure (*0*), and Y=primary cesarean delivery for this study (the observed outcome; 1-yes, 0-other form of delivery).

There are various causal parameters that one might focus on. One such parameter, One such parameter, the individual-level effect of ($Y_1 - Y_{0)}$ cannot be simply estimated from observed data, as one of the counterfactual outcomes necessarily would be unobserved, i.e., each subject will either be exposed (age >35) with corresponding outcome Y_1, or unexposed with corresponding outcome Y_0, but not both. The outcome under the unobserved exposure leads to a "missing data problem" that is a characteristic of how causal inference construct frames questions of interest using the counterfactual framework.

The goal of analysis is to estimate the parameter of interest from the full data (include data on outcomes under the unobserved exposure).[22] In contrast to the individual-level causal parameter, one could focus on a population-level parameter, for example: $E[Y_1] - E[Y_0]$. Rather than comparing the individual-level effect of treatment *a* in an individual, this parameter compares the mean outcomes for a sample, when the entire sample's exposure is set to *a*=1 versus *a*=0. Because this parameter describes the effects of an entire sample exposure to treatment/reference conditions, it can be called the "total effects parameter."

The total effects parameter is now familiar from marginal structural model (MSM) analyses;[28] however, this parameter may not always correspond to a real-world effect of interest. Defining this parameter in reference to the present research question, the total effect parameter compares the entire study population under exposure (advanced maternal age) versus referent conditions (maternal age < 35). In the context of the current research, it would be implausible that guidelines would recommend decreasing the entire population's maternal age at delivery, so the health effect encoded in the total effects parameter is not necessarily relevant.

A causal question that maps better onto a question of real-world importance is, what would be the effect if one could have advised women of advanced maternal age to have gotten pregnant at a younger age, relative to the caesarian section frequency actually observed in the entire population understudy ? In contrast with the total effects parameter, this parameter is a called a population intervention parameter:

$$E[Y_0] - E[Y]$$

This parameter, estimated by a population intervention model, corresponds to the difference between the mean observed outcome (incidence of cesarean delivery in the entire study population) and the mean counterfactual outcome if the exposed (i.e., women with AMA) had been "intervened upon" to have gotten pregnant ≤ 35 years old.

[58]

Similar to the total effects parameter and in contrast with conventional methods, this approach does not compare outcome levels among subgroups of the observed data, but rather uses the hypothetical full data to estimate an effect across the entire sample to provide a marginal estimate of the impact of such advice.

For this study, In contrast to the conditional approach, the causal inference framework considers confounders as "nuisance" variables, and their confounding effects are controlled at different stages in the analysis. Below we describe the specific nuisance models fit for the estimators employed in these analyses. Using this approach to control for confounders, the following observed-data parameter, averaged across strata of the confounders W can be calculated:

$$E_W[E(Y \mid A=0, W=w) - E(Y \mid A=a, W=w)]$$

Under specific causal assumptions (consistency, sequential randomization, positivity), this parameter of the observed data would be an estimate of the population intervention parameter, $E[Y_0] - E[Y_1]$, a parameter of the full data that is analogous to a causal population attributable risk.[22]

The hypothesized relationship between exposure (A, maternal age), outcome of interest (Y, primary cesarean), and potential confounding covariates was encoded in a directed acyclic graph (DAG) (Figure 1). In the graph, confounders (W) were: maternal age (dichotomized as ≤34 or >35 years), race/ethnicity (categorized as non-Hispanic White, non-Hispanic Black, Hispanic/Latina, Asian), educational attainment (≤16 years [high school] or >16 years), marital status (yes/no), cigarette smoking in pregnancy (yes/no), prenatal care visits (≤8, >8 visits), gestational weight gain (≤35 pounds, >35 pounds). All of these covariates met the assumption for confounding based on the rules of DAGs, as applied to the DAG for this study.[29,30]

To carry out population intervention models to examine the population attributable fraction of AMA on cesarean delivery, we utilized the *multiPIM version 0.3-3 R*-package that is freely available through http://www.stat.berkeley.edu/users/sritter/Site/multiPIM.html. For this version of the multiPIM package, the G-computation approach was used to estimate the population intervention model. G-computation is a method for that relies on a nuisance model of the outcome regressed on the exposure and confounders (E(Y | A,W), the Q-model) to generate predicted counterfactual outcomes (Y_a) under one or more counterfactual exposures (A=a) (see Appendix 1).[22,31]

For G-computation to obtain an unbiased estimate of exposure effect, the Q-model must be correctly specified. For this study, "super learner" algorithm (utilized as part of the *multiPIM* package) was used for model selection of the Q-model in G-computation. Developed by Sinisi *et al*, the term "leaner" refers to any analytical methods used to "learn" from a dataset the best predictors for a given outcome. These candidate learners can include polynomial functions, spines, and machine learning algorithms.[32] Some examples of candidate learners include: decision trees, neural networks, support vector regression, logic regression, and Deletion/Substitution/Addition (DSA) algorithm as well as any other models that yield predictions.[32] More specifically,

the candidate learners used for this analysis included: polychotomous regression and multiple classification (polyclass),[33] penalized regression,[34] logistic regression, classification and regression trees,[35] and classification and regression with random forest.[36]

Super learner applies a user determined set of algorithms (candidate learners) to the observed data, and chooses the optimal learner for a given prediction problem based on cross-validated risk; thus, super learner itself is a prediction algorithm and has been shown to perform asymptotically as well as the "true" underlying the model.[29,37] Super learner can be superior to traditional methods for model selection in that it represents a flexible, data-adaptive, machine learning model search algorithm that is based on cross-validation and the L2 loss function and thus does not rely on a parametric model assumption and can be free of *a priori* bias regarding model specification.[32,33]

Because the relatively performance of various learners depends on the true data-generating distribution, which leaner will perform best for a given prediction problem and the dataset generally is not known *a priori*. Thus, super learner "chooses" one optimal leaner for a given prediction problem based on cross-validated risk. For our study, super learner chose "polyclass" (polychotomous regression and multiple classification) that used adaptively selected linear splines and their tensor products to model conditional class probabilities,[33] to predict the Q-model. Please see Appendix 2 for the Q-model selected by super learner in this analysis.

After determining the model specification using super learner, G-computation was implemented to predict Y_0 outcomes for each woman under the "intervention" (i.e., no advanced maternal age in the entire population). The *multiPIM* package implemented this step, which is simply the application of the Q-model (selected by super learner) to predict counterfactual outcomes for each observation, intervening to set $a=0$ universally. The process of calculating the Y_0 counterfactual outcome for each woman simulates the full dataset, and enables calculation of the simple risk difference $E[Y_0] - E[Y]$, the population intervention parameter that encodes the parameter of interest.

Once the estimates of the population-level effect were obtained using population intervention model analysis, standard error was estimated with bootstrapping technique and 95% confidence intervals were calculated based on standard error and point estimates. Resampling of the study population with replacement was performed to generate bootstrap-resampled datasets and parameter estimates. This process was repeated 1,000 times to simulate the sampling distribution from which standard error was derived.[38]

The primary outcome was the frequency of caesarean delivery. In order to examine time-trend of the effect of maternal age on cesarean delivery, our study period spanned more than 2 decades, from 1990 through 2006. We treated each year independently from previous years. Institutional Review Board (IRB) approval was obtained from the Committee on Human Research at the University of California, San

Francisco as well as from the Committee for Protectiono of Human Subjects at the University of California, Berkeley. To carry out the population intervention models, we used R v2.12.1 (R Foundation for Statistical Computing, Vienna, Austria) and Stata v11.0 (College Station, Texas) statistical softwares.

4.4   Results

There were 10,808,598 nulliparous women with singleton, live, term births in cephalic presentation who met study inclusion/exclusion criteria. We examined the frequency of cesarean delivery among women age 35 and older at time of birth and women who were less than 35 years of age from 1994 to 2006. Because the annual incidence rate of cesarean delivery reached a nadir in 1996 and had been increasing ever since, we examined the time-trend of annual cesarean delivery frequency, stratified by maternal age. During the study period, the proportion of women meeting definition for advanced maternal age (AMA) incrased from 5.8% in 1994 to 6.8% in 1998to 7.4% in 2002 and 7.5% in 2006 (Table 1). Additionally, the frequency of cesarean delivery among women AMA increased substantially from 31.0% in 1994 and 31.2% in 1998 to 38.1% in 2002 and 46.7% in 2006 (Table 1).

In contrast to observed increase in maternal age, other maternal characteristics, such as marital status, education attainment, and access to prenatal visits remained relatively stable over the study period (Table 2). The racial/ethnic make-up of the study population changed slightly such that there were a larger proportion of Hisptanic and Asian women and a slight decrease in White and Black women (Table 2).

We estimated the association between cesarean delivery and maternal age by adjusting for potential confounding factors using logsitic regression. While the incidence of cesarean delivery increased with maternal age over time, the adjusted odds ratio remained relatively stable duirng the study period (Table 1). In 1994, the odds of cesarean delivery for women 35 years or older was approximately twice that of women less than 35 years (aOR 2.12, 95% CI 2.08-2.16).   The adjusted odds ratio for similar comparisons ranged between 2.11 (in 1996) and 2.22 (in 2006) and were statistically significant (Table 1).

Next, we used population intervention models to estimate the potential impact of maternal age on cesarean delivery over time from 1994 to 2006. Again, the population intervention parameter estimated difference between the mean observed outcome and the mean counterfactual outcome when the exposed (i.e., women with AMA) were "intervened upon" and set to < 35 years old. More specifically, if AMA (maternal age ≥35 years) were "intervened" on, there woud be approximately a -0.8 per 100 births in reduction of cesarean delivery in 1994, 1995, and 1996 (Table 3). In 1999, the estimated reduction of cesarean delivery was -1.0/100 births, and the impact of AMA on maternal age increased progressively since 1999 such that in 2006, the population intervention parameter estimation was -1.33/100 births reduction in cesarean delivery if AMA were "intervened" on (Table 3). We estimated that this would correspond to

approximately 3,800 reduction in cesarean deliveries in 2006 compared to 1300 around 1994-1996 (Table 3).

4.5   Tables and Figures

Table 1: The association between maternal age and primary cesarean delivery presented as simple 2x2 table and adjusted odds ratio using multivariable logistic regression controlling for race/ethnicity, education, marital status, cigarette smoking, prenatal visits, and gestational weight gain

| Birth Year	Maternal age (years)	No Cesarean n	%	Cesarean n	%	aOR	95% CI
1994	<35 (n=910,149)	759,527	83.5	150,622	16.5	Referent	
	≥35 (n=55,785)	38,480	69.0	17,272	31.0	2.12	2.08 – 2.16
1995	<35 (n=916362)	767,089	83.7	148,925	16.3	Referent	
	≥35 (n=58,936)	40,878	69.4	18,034	30.6	2.13	2.09 – 2.17
1996	<35 (n=900,949)	756,186	84.0	144,407	16.0	Referent	
	≥35 (n=62,084)	43,325	69.8	18,730	30.2	2.11	2.07 – 2.15
1997	<35 (n=908,677)	762,777	84.0	145,592	16.0	Referent	
	≥35 (n=64,873)	45,024	69.4	19,824	30.6	2.15	2.11 – 2.18
1998	<35 (n=917,789)	767,558	83.7	149,893	16.3	Referent	
	≥35 (n-67,312)	46,253	68.7	21,027	31.3	2.17	2.13 – 2.21
1999	<35 (n=926,909)	767,910	82.9	158,702	17.1	Referent	
	≥35 (n-69,431)	46,729	67.3	22,674	32.7	2.17	2.13 – 2.20
2000	<35 (n=946,569)	776,730	82.1	169,582	17.9	Referent	
	≥35 (n=73,136)	48,174	65.9	24,946	34.1	2.19	2.16 – 2.23
2001	<35 (n=946,923)	764,966	80.8	181,753	19.2	Referent	
	≥35 (n=74,762)	47,925	64.1	26,816	35.9	2.18	2.14 – 2.21
2002	<35 (n=952,426)	756,005	79.4	196,244	20.6	Referent	
	≥35 (n=76,650)	47,458	61.9	29,175	38.1	2.18	2.15 – 2.22
2003	<35 (n=979,597)	765,147	78.1	214,450	21.9	Referent	
	≥35 (n=82,655)	49,613	60.0	33,042	40.0	2.22	2.19 – 2.26
2004	<35 (n=976,243)	749,149	76.7	227,094	23.3	Referent	
	≥35 (n=83,753)	49,018	58.5	34,735	41.5	2.18	2.15 – 2.21
2005	<35 (n=990,368)	750,062	75.7	240,306	24.3	Referent	
	≥35 (n=84,894)	48,399	57.0	36,495	43.0	2.19	2.16 – 2.22
2006	<35 (n=1,014,430)	763,082	75.2	251,348	24.8	Referent	
	≥35 (n=84,444)	47,241	55.9	37,203	44.1	2.23	2.20 – 2.27

Table 2: Maternal characteristics over study time period: 1994, 1998, 2002, and 2006

Race/ethnicity	1994 number (%)	1998 number (%)	2002 number (%)	2006 number (%)
White	613,981 (63.5%)	611,448 (62.1%)	607,491 (59.0%)	629,622 (57.3%)
Black	144,085 (14.9%)	141,502 (14.4%)	139,819 (13.6%)	155,455 (14.1%)
Hispanic	156,720 (16.2%)	173,479 (17.6%)	207,136 (20.1%)	232,915 (21.2%)
Asian	44,351 (4.6%)	50,827 (5.2%)	66,114 (6.4%)	71,441 (6.5%)
American Indian	7,162 (0.7%)	7,845 (0.8%)	8,516 (0.8%)	9,441 (0.9%)
Prenatal visit- 8 or more				
No	94,507 (10.0%)	85,374 (8.9%)	89,981 (8.9%)	113,330 (10.6%)
Yes	847,308 (90.0%)	871,717 (91.1%)	917,733 (91.1%)	955,821 (89.4%)
Marital status-married				
No	369,859 (38.3%)	387,893 (39.4%)	415,670 (40.4%)	493,575 (44.9%)
Yes	596,440 (61.7%)	597,208 (60.6%)	613,406 (59.6%)	605,299 (55.1%)
Education - more than high school (>12 years)				
No	523,218 (54.8%)	502,268 (51.7%)	501,797 (49.3%)	505,852 (46.5%)
Yes	430,965 (45.2%)	469,686 (48.3%)	515,080 (50.7%)	580,887 (53.5%)

Table 3: The association of maternal age and cesarean delivery estimated by population intervention models (PIM) and effect estimates expressed number of cesarean that would be decreased under intervention

Birth Year	Mater-nal age (years)	No Cesarean (n)	Cesarean (n)	Population Intervention Parameter $E[Y_0] - E[Y]$ (per 100 births)	Stand-ard error	95% CI	PIM Estimates of Decease in cesarean (n)
1994	<35	759,527	150,622				
	≥35	38,480	17,272	-0.79	0.0398	-0.87 – -0.71	-1,327
1995	<35	767,089	148,925				
	≥35	40,878	18,034	-0.82	0.0395	-0.90 – -0.76	-1,369
1996	<35	756,186	144,407				
	≥35	43,325	18,730	-0.83	0.0338	-0.90 – -0.76	-1,354
1997	<35	762,777	145,592				
	≥35	45,024	19,824	-0.91	0.0394	-0.99 – -0.83	-1,505
1998	<35	767,558	149,893				
	≥35	46,253	21,027	-0.80	0.0308	-0.86 – -0.74	-1,367
1999	<35	767,910	158,702				
	≥35	46,729	22,674	-1.00	0.0403	-0.92 – -1.08	-1,814
2000	<35	776,730	169,582				
	≥35	48,174	24,946	-1.08	0.0405	-1.16 – -1.00	-2,101
2001	<35	764,966	181,753				
	≥35	47,925	26,816	-1.13	0.0415	-1.21 – -1.05	-2,357
2002	<35	756,005	196,244				
	≥35	47,458	29,175	-1.20	0.0424	-1.28 – -1.12	-2,669
2003	<35	756,147	214,450				
	≥35	49,613	33,042	-1.28	0.0369	-1.35 – -1.21	-3,168
2004	<35	749,149	227,094				
	≥35	49,018	34,735	-1.24	0.0331	-1.31 – -1.18	-3,249
2005	<35	750,062	240,306				
	≥35	48,399	36,495	-1.30	0.0344	-1.37 – -1.27	-3,598
2006	<35	763,082	251,341				
	≥35	47,241	37,403	-1.33	0.0381	-1.44 – -1.25	-3,840

Figure 1: Directed acyclic diagram (DAG) that illustrate the association of exposure (noted as A), outcome (noted as Y) and potential confounding covariates (noted as W).
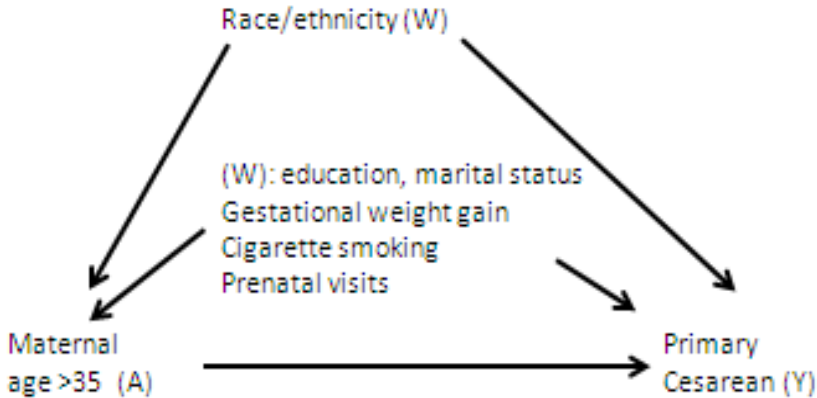
4.6. Discussion

We used population intervention models to estimate the potential impact of maternal age on cesarean delivery in nulliparous low-risk women with singleton, vertex, term, live births between 1994 and 2006 in the U.S. We observed that the proportion of women who were 35 years or older at time of birth increased during the study period. Concurrent with this increase was the rise in cesarean delivery, which has incrased more than 50% between 1996 and 2006.[39]

While it was not surprising that the annual frequency of cesaraen delivery among women with advanced maternal age increased during the same period, the observed frequency of 46.7% cesarean delivery among our population of nulliparous women who were AMA in 2006 seemed substantial, especially given that these were women considered to have a low-risk pregnancy—without a history of medical or obstetric complications. Since medical problems such diabetes (pre-pregnancy or gestational), hypertensive disorders (chronic hypertension, gestational hypertension, or preeclampsia), renal diseases and obstetric conditions such as placenta previa, abruption are known risk factors of cesarean delivery,[40,41,42] likely the frequency of cesarean delivery in women with AMA and having medical/obstetric conditions would have even higher risk of cesarean delivery than our study population.

In this analysis, we used multivariable logistic regression and population interventions models independently to examine the association beteween advanced maternal age and cesarean delivery. It was interesting to note that while the frequency of cesarean delivery increased over the study period, the adjusted odds ratio estimated from multivariable logistic regression remained relatively stable from year to year between 1994 and 2006 (2.11 – 2.22), suggesting that overall women with AMA had about twice the odds of having cesarean delivery compared to those who were not AMA regardless of time (year) of delivery. This relative association was in contrast to the effect estimates derived from population intervention models, which suggested that the absolute population-level effect of advance maternal age on cesarean delivery increased over time during the study period. Additionally, it is important to note that while multivariable logistic regression analyses provided a conditional estimate of the exposure-outcome association, population intervention models estimated the difference between the mean observed outcome and the mean counterfactual outcome when the exposed (i.e., women with AMA) were "intervened upon" and set to "low-risk" (or < 35 years old) in the study population.

Thus, in contrast with conventional multivariable regression analyses which compare outcome levels among subgroups of the observed data, conditional on covariates, the population intervention models approach uses the hypothetical full data and compared the actual exposure pattern of the population to a counterfactual population that is completely unexposed, to yield the difference between the mean observed outcome (incidence of cesarean delivery in the entire study population) and the mean counterfactual outcome if the exposed (i.e., women with AMA) had been "intervened upon.

While we recognized that maternal age, unlike other behavioral factors such as cigarette smoking or gestational weight gain that could be more susceptible to modification, could not be easily "intervened" on or modified at the individual level, we chose to use population intervention models to gain insights into the potential changes in the distribution of cesarean delivery, focusing on the population prevalence of advanced maternal age as a risk factor—one which changed over the time period of our study. In this analysis, the population intervention parameters estimated were akin to the concept of population attributable risk or population attributable fraction—the reduction in incidence that would been achieved if the population had been entirely unexposed, compared to the actual, observed exposure pattern. As delay childbearing has become more common and that women who chose to delay reproduction may not be entirely aware of the potential effect of age on pregnancy outcomes, our study results might be useful in counseling women of reproductive age contemplating pregnancy. Furthermore, the approach employed in this paper draws attention to the macro-level impact of increasing maternal age, an effect whose importance may be understated through use of relative rather than absolute measures of association.[43]

Since the population intervention models is based on the causal inference framework, there are several assumptions regarding the data structure and the nature of associations between exposure, outcome, and confounding covariates. First, population intervention models assumed no unmeasured confounding, and correct model specification. Commonly the regression model specification relies on subject matter knowledge and procedures such as backward or forward stepwise regression and testing for goodness of fit to derive a final parsimonious model. In this analysis, the Q-model was derived using super learner, which is a data-adaptive, machine learning, model search algorithm that is based on cross-validation and does not rely on a parametric model assumption and can be free of *a priori* bias regarding model selection. Additionally, the causal inference framework assumed that the potential measured confounders occurred prior to the exposure, which in turn occurred prior to the measured outcome (i.e., appropriate temporal ordering). Also, each subject's observed outcome would be consistent with his/her unobserved counterfactual outcome (consistency assumption), and that treatment assignment is independent of the outcome (i.e., coarsening at random).[44,45] While similar assumptions are often made for traditional multivariable regression analysis and epidemiological studies, they are explicitly made in the causal inference framework.

Through the application of population intervention models, our analyses offered insights regarding the population-level impact of maternal age on cesarean delivery by estimating the population intervention parameter, (as oppose to While our analysis employs the causal inference framework, it was still based on observational data, and could still prone to bias if the above assumptions were not met. Additionally, we examined maternal age as a dichotomous outcome, and thus were not able to further infer regarding the nature of the association between maternal age and cesarean delivery. Future research should examine the exposure-response relation, analyzing the potential burden associated with increase in maternal age as a continuous variable or as a categorical variable (for example, the impact of each additional one-year or 5-year maternal age increase on frequency of cesarean delivery). By excluding women with

many underlying health conditions, the present study examined the effect of maternal age on prevalence of cesarean delivery, not mediated through these conditions (e.g., pre-gestational hypertension and diabetes, which increase with maternal age and are independent risk factors for cesarean delivery). Future work could examine the total effects of maternal age (i.e., all causal pathways including those mediated through underlying health conditions), and could examine the relative contribution of these mediating variables to the total effect of maternal age.

In summary, this study examined the population-level effect of advanced maternal age on prevalence of cesarean delivery, and found a fairly consistent elevated odds of cesarean delivery over many years (an approximately twofold increase in odds associated with AMA). However, the association between AMA and prevalence of cesarean as measured on an absolute scale increased over time, as both the exposure and the outcome became more prevalent. These findings highlight the importance of the changing demographic and medical profile of women giving birth in the US, especially as it relates to the population burden of disease and obstetric intervention.

4.7   Appendix

Appendix 1: A brief introduction to G-computation

G-computation estimator is based on using a model of the outcome (Y) on the risk factor of interest (A), and the confounders (W). Under the assumption of no unmeasured confounding, then

$$E(Y \mid A = 1, W = w) = E(Y_1 \mid W = w)$$

Further, a regression of Y on A and W can be used to estimate the mean of a counterfactual (Y_1) in strata of W.[22] In this population intervention model, G-computation would provide the full data by estimating the unobserved counterfactual outcomes of the women of advanced maternal age (i.e. the outcome when, contrary to fact, their exposure status was set to maternal age <35).

The first step of G-computation was to fit a regression of the outcome on the exposure and relevant covariates using the observed dataset. This regression model, called the "Q-model", was not different from the traditional logistic regression of Y on A conditional on W. While in the traditional regression model approach such as maximum likelihood estimation, this model would be the final step of the estimation and the coefficient for A represent the exposure/outcome association, the "Q-model" so obtained from G-computation differed in that this Q-model would be treated as a nuisance model that estimates nuisance parameters in addition to the parameters of interest. Additionally, this Q-model would then be applied to estimate effects in later stage of analysis (in contrast to traditional regression where the Q-model would be the final step of effect estimation).[46]

Once the Q-model has been correctly specified, it is used to predict counterfactual outcomes for each observation under each exposure regimen. For example, to estimate the marginal effect of parameter $E[Y_1] - E[Y_0]$, both a=1 and a=0 was applied into the Q-model to obtain predicted outcomes under these two conditions and computes Y_1 and Y_0 for all subjects in the observed dataset, thus generating the hypothetical "full dataset." Having generated the full dataset with G-computation, the marginal effect of treatment could be estimated using various approaches, such as calculation of risk difference, implementation of marginal structural models (MSM), or estimation of population attributable fraction using population intervention models (PIM).

In contrast to estimating the mean outcome when a population is exposed versus unexposed (i.e., $E[Y_1] - E[Y_0]$), population intervention models compares the mean outcome under some hypothetical "intervention" (target exposure) scenario to the mean outcome under the observed exposure scenario: $E[Y] - E[Y_a]$ where Y_a denote the counterfactual outcome under the hypothetical "intervention" exposure.

Appendix 2: Q-model selected using super learner, which chose *polyclass* as the algorithm for model selection

4.056 + -1.295 (college education) + -0.919 (married marital status) + -0.800 (Asian) + 0.450 (Black)_+ 0.695 (Asian * college education) + 0.355 (Asian * married) + 0.727 (Native American) + -0.214 (prenatal visits 8 or more) + 0.186 (college education * prenatal visits 8 or more) + -0.608 (Black * married) + -0.245 (Asian * prenatal visits 8 or more) + -0.160 (Black * prenatal visits 8 or more) + -.437 (Black)

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Chapter 5:

Clinicians' experience and obstetric management: factors associated with recommending cesarean delivery

5.1   Abstract

Objective: Obstetrics is one of the most sued subspecialties in the U.S. This survey study aimed to examine clinicians' characteristics and experience associated with recommending cesarean deliveries.

Study Design: This is a convenience survey study of 1,486 clinicians who practice obstetrics in the U.S. This survey included 8 common obstetric clinical vignettes and 27 questions regarding clinicians' practice environment. The questionnaire was sent in electronic format, one-time blast without repeat reminders. Reponses to the questionnaire was also collected electronically using *SurveyMonkey*[TM]. Using the management choices of the clinical vignettes, clinicians were categorized based on their composite likelihood of recommending cesarean. Factor analysis and chi-square test were used for statistical comparison with $p<0.05$ designated as statistical significance.

Results: Of 3,646 clinicians who received and opened the survey electronically in November 2010, 1555 participated and 1,486 (94%) completed the survey. Clinicians were categorized by their propensity of recommending cesarean in 8 common obstetric scenarios: more likely (n=215), average likelihood (n=1,099), and less likely (n=168) to recommend cesarean. Among clinicians categorized as having a higher propensity of recommending cesarean delivery, a higher proportion (29.3%) were age ≥ 61 compared age categories 31-50 years or 25-30 years (13.0% and 6.9%, respectively; $p<0.001$). Further, having had law suit filed for an obstetric related case was associated with more likely to recommend cesarean compared to no history of law suit (17.2% versus 11.3%, $p=0.008$) as was self-reported frequent worry about being sued (every day, 20.3%; every week/month, 12.3%; few times a year/never, 11.4%, $p<0.001$).

Conclusion: Obstetric malpractice suit and frequent worry about suit are associated with higher propensity of recommending cesarean delivery in common obstetric settings. Additionally, increasing age/experience is not associated with a lower threshold of recommending cesarean.

5.1 Introduction

In 2009, approximately one in three live births (32.9/100) was delivered via cesarean in the United States. This represents the 13th consecutive year of increase, and compared to 1996, a 60% rise in the annual incidence rate of cesarean delivery.[1] While the exact reasons for such continual upward trend are unclear, some investigators hypothesize that delayed childbearing, increase use in assisted reproductive technology (ART), the obesity epidemics, more pregnancies complicated by medical/obstetric conditions, and decline in trial of labor after previous cesarean delivery (TOLAC) as well as cesarean delivery by maternal request (CDMR) have been contributors.[1,2,3,4,5,6,7,8,9] However, these factors likely do not account entirely for the observed 60% increase in cesarean delivery over the past decade.

Some studies suggest that clinicians may play an important role; however, few studies have been published regarding this topic matter.[10,11,] It has been observed that odds of cesarean increased with delivery on a Friday, and delivery between 6am and 6pm,[12] and that male providers were more likely than their female colleagues to perform cesarean, particularly in the academic practice setting.[13,14] The reasons behind these findings are not well understood. While non-medical variables, such as provider characteristics and hospital/system factors, may be potential explanatory factors as part of the decision-making process, there are few data on the impact of physician practice patterns, attitudes toward labor/mode of delivery, and other clinical and nonclinical factors (e.g., institutional policies, litigation suits, malpractice insurance policies, economic incentives) on the decision to perform a cesarean delivery.

Given this background, we designed a cross-section survey study of clinicians who practice obstetrics in the United States to explore provider factors that may be associated with increase in cesarean deliveries. We hypothesized that provider training experience and practice environment contribute to increase in cesarean delivery.

5.3 Material and Methods

We conducted a cross-section, convenience survey study of clinicians (general obstetrician-gynecologists, Maternal-Fetal Medicine specialists, family medicine physicians, and clinical nurse midwives) who practice obstetrics in the United States and who were registered as active members of American Medical Association (AMA). Medical students, current trainees (interns or residents) and retired clinicians were filtered and excluded from the email list obtained through the AMA. The questionnaire was sent via one-time email "blast" by *SurveyMonkey*[TM], and responses were collected through the *SurveyMonkey*[TM] website (www.surveymonkey.com). The email included a short message explaining the purpose of the survey along with link to the questionnaire (Appendix 1). The questionnaire required approximately 5-minutes to complete. One-time only email blast was sent out on November 4, 2010 and the survey was closed on January 31, 2011. Only completed surveys were included in the analysis.

The first part of the questionnaire included 8 common clinical scenarios regarding management of term pregnancy and management of first and second stages of labor. These vignettes were designed to assess clinicians' inclination to recommend cesarean delivery under various specified conditions. There were no "right" or "wrong" answers to these vignettes. Each vignettes included 4-5 management choices, ranging from low threshold for recommending cesarean delivery (i.e., more likely to recommend cesarean), to high threshold for recommending cesarean delivery (i.e., less likely to recommend cesarean). The answer choices to these clinical vignettes were arranged in random order to minimize bias in answer selection (i.e., answer A chosen more frequently because A was placed as the first choice option). We then used exploratory factor analysis to examine correlations of these 8 questions. We tested 3 models (3 factor model, 2 factor model, and 1 factor model) with the following criteria: >0.20 factor loading and <0.10 cross item loading. According to such analysis, 2 factor model with 7 items (vignettes 1, 2, 4-8) appeared to be the best model.

For each of the clinical vignettes, an *arbitrary* score from 1 to 4, or 5, depending on the number of answer choices available. The scores were assigned such that 1 represented most likely to recommend cesarean delivery and 4 (or 5) represented less likely to recommend cesarean delivery. For example, for vignette #1 below:

A 25-year-old G2P1 at 38 weeks who has a history of an uncomplicated term vaginal delivery is in clinic for routine care. You find that the fetus is in frank breech presentation. The clinical estimated fetal weight is 3,200 gm. You recommend:

1   Cesarean at 39 weeks, without attempting external cephalic version (ECV)
2   Attempt ECV; if still breech, then cesarean delivery at 39 weeks
3   Attempt ECV; if still breech then a trial of vaginal breech delivery
4   Awaiting spontaneous labor and a trial of vaginal breech delivery without ECV

a score of 1 was assigned for clinicians who chose answer option 1, cesarean delivery without attempting external cephalic version, and that a score of 4 was assigned for answer option 4. The rational for assigning a score of 1 to option #1 was that this option does not allow the possibility of potential attempt of vaginal delivery. While breech presentation is often considered an acceptable indication of cesarean delivery, the goal of attempting ECV is to achieve cephalic presentation for a trial of vaginal delivery and that vaginal breech delivery could be performed by experienced clinicians in carefully selected patients to avoid cesarean delivery for the indication of breech presentation. Thus, the answer choices above (and for the other clinical vignettes) were designed to represent a gradation of cesarean thresholds, from most likely to recommend cesarean to less likely to recommend cesarean. Similar score assignment was repeated for all the other clinical vignettes. We analyzed the results of these 7 vignettes (1, 2, 4-8) as a group and created a composite answer choice to these 7 vignettes. While the scores were assigned numerically, they did not encode a linear relationship in the threshold of recommending cesarean. Thus, we created 3 categories of cesarean threshold based

on the composite scores: "more cesarean" included those with composite scores of 10-16; "average cesarean" included those with composite scores of 17-22, and "less cesarean" included those with composite scores of 23-27. These categorical thresholds were set based on the 10th and 90th centile distributions of the composite, such that physicians with a composite score of 10-16 represented those more frequently (top 10 centiles) recommended cesarean given the clinical vignettes, and those with a composite score of 23-27 represented clinicians less frequently recommended cesarean given the clinical vignettes (the bottom 10 centiles).

In addition to the clinical vignettes, the questionnaire also collected information regarding clinicians' demographics, clinical experience, and practice environment. We examined the association between clinicians' clinical experience and practice environment and their likelihood of recommending cesarean delivery, based on the answers to the clinical vignettes and categorized based on above analytic scheme. We used chi-square tests with $p < 0.05$ to note statistical significance.

Multivariable logistic regression was also carried out to examine the association between provider characteristics and the higher likelihood of recommending cesarean delivery. Further, we used Deletion/Subtraction/Addition (DSA) algorithm to examine characteristic associated with cesarean delivery. DSA algorithm is a flexible, data-adaptive, machine learning model search algorithm that is based on cross-validation and the L2 loss function.[15] More specifically, DSA iteratively generates polynomial linear models based on the existing terms in a current "best" model and applies the following three steps: 1) a deletion step which removes a term from the model; 2) a substitution step which replaces one term with another; and 3) an addition step which adds a term to the model. This search for the "best'" estimator starts with the base model, and the final model will minimize the empirical risk of learner sets among all estimators considered such that the final model is characterized by "optimum" size, order of interactions and set of candidate variables selected by cross-validation.[15] Cross-validated (CV) risk is evaluated with each iterations of model selection such that the final model selected by the DSA algorithm is the one that minimizes the empirical risk on the learning set. For this analysis, we designated the same potential covariates as those covariates examined using the multivariable logistic regression models and we set maximum size=10, maximum sum of power=2, and maximum order of interaction = 2). Analysis was performed using Stata v11.0 (College Station, TX) and R v2.12.1 (R Foundation for Statistical Computing, Vienna, Austria).

5.4   Results

There were 28,846 email listings available through the AMA registry that met study inclusion criteria. A one-time email survey was sent out to these AMA members on November 4, 2010 at 08:00, Eastern Standard Time. There were 1,171 bounces (4.1%), resulting in 27,675 clinicians who received the mailed survey. Of these, 3,646 opened the email message, 19 opted out of the survey; 1,555 clicked on the survey link and started the survey and 1,486 (94%) completed the entire survey. We were able to

obtain demographic information on those who opened the email (including those who did and did not complete the survey). The demographic make-up between clinicians who opened the link and those who actually completed the survey appeared similar: the male:female ratio were about equal and the majority were obstetrician-gynecologists (Table 1). However, we did not have individual-level data for those who did not complete the survey to further perform analysis to examine their comparability. The mean and median age of the survey participants were 47 years, with 39 and 55 years being the 25th and 75th centiles, respectively. Geographical distribution of clinicians' primary practice was relatively even: 19.3% primarily practice in the Northeast, 22.2% in the Midwest, 30.2% in the South, and 28.3% in the West (Table 1).

The answer distributions to the clinical vignettes were presented in Figures 1 through 8. We examined clinicians' characteristics associated with the likelihood of recommending cesarean delivery. Male clinicians' were more likely to recommend cesarean delivery based on the clinical vignettes than female providers. Clinicians age 61and greater at time of survey were also more likely to recommend cesarean delivery than those who were younger (Table 2). Since there were more male clinicians who practice obstetrics in past years compared to today (thus male providers were likely to be older and more years out of training), we examined the association between age, gender and likelihood of recommend cesarean delivery using multivariable logistic regression. After controlling for age, and number of years out of training/residency, whether residency was university or community, military based, primary practice location (Midwest, south, and west compared to Northwest as referent) and practice type (academic versus HMO versus hospitalist/laborist compared to private practice) and practice setting (rural or urban compared to suburban) and litigation experience (Table 5), male providers was no longer more likely than female providers to recommend cesarean delivery (aOR 1.39, 95% CI 0.94-2.04). However, age≥61 years remained as an associated factor for more likely to recommend cesarean (aOR 1.71, 95% CI 1.05-2.77; Table 5).

Clinicians who would not attempt trial of labor after previous cesarean (TOLAC,aka VBAC: vaginal birth after previous cesarean) were more likely to recommend cesarean delivery given the clinical vignettes than those who would attempt TOLAC (Table 2). For clinicians who would not attempt TOLAC (n=286, 20% of those who completed the survey), we asked, "if no (TOLAC), please specify why not" and collected 284 written responses. The most common cited reasons for not attempting TOLAC included: inadequate staff/support (according to the American College of Obstetricians and Gynecologists [ACOG] guidelines),[16] hospital policy, increased risk of fetal morbidity, and litigation. For example, some of the comments were:

Inadequate staff/support

> *"cannot adhere to hospital/ACOG guidelines regarding immediate availability 24/7"*

> *"had previously but not now due to surgical coverage issues"*

"No in-house OBGYN or Anesthesia"

"Hospital malpractice precludes it. Community hosp. that does not have in-house peds or anesthesia"

"malpractice risk, inability for facility to meet ACOG guidelines, do 2 VBAC a year on average with spontaneous labor and normal to rapid labor"

"The O. R. situation is not compatible for covering crash c-section for 24 hr"

"not allowed in our hospital. no 24 hour in-house or staff or anesthesia"

Hospital policy:

"VBAC is not allowed in the hospital in which I work"

"VBACs not allowed in the hospital I practice at"

"Our hospital does not support VBAC"

"Our hospital does not allow a trial of labor"

"Hospital doesn't advocate VBAC."

"recently the hospital stopped vbacs!"

"The contracted hospital insurance carrier does not permit VBAC - this is NOT our MD practice's preference"

"hospital does not allow but I've snuck a few in"

Concerns for malpractice law suits/litigation:

"hospital insurance company does not allow"

"mal practice will not allow"

"lawsuits"

"Insurance driven"

"Liability"

"Liability insurance provider will not cover this, personal choice to avoid being

sued in a highly litigious state"

"Illinois is litigious and our malpractice carrier does not cover it"

"medical-legal issues, small hospital not equipped to handle vbac complications"

"got sued for bad baby VBAC delivery"

"Bad malpractice if complication occurs"

"defensive medicine"

Increased risk of morbidity:

"not worth the risk, no malpractice"

"fetal risk"

"Rupture unpredictable"

"experienced 2 uterine ruptures in our practice which resulted in both babies dying.

Decided the risks weren't worth the vaginal delivery experience. Both cases also

resulted in lawsuits which we won."

"[history] of multiple uterine ruptures with poor outcomes"

Similarly, of those who do not attempt breech extraction of the second twin, a higher proportion were more likely to recommend cesarean delivery than those who do offer/attempt breech extraction (22.4% vs. 10.2%, p<0.001); and, of those who do perform primary cesarean delivery by maternal request (CDMR), a higher proportion were more likely to recommend cesarean delivery than clinicians who would decline CDMR (Table 2). These characteristics remained statistically significant factors associated with the likelihood of recommending cesarean in multivariable logistic regression analysis (Table 5).

Since obstetrics is one of the most sued specialties in the field of medicine, we examined whether clinician's experience regarding malpractice suits/litigation would be associated likelihood of recommending cesarean delivery given the clinical vignettes. We observed that for clinicians who have had law suit filed for an obstetric-related case, more of them were more likely to recommend cesarean (17.2%) than clinicians who had not been sued (11.3%; p=0.008). Additionally, Of the 787 clinicians (55% of the survey

participants) who reported having had obstetric-related law suits, we asked if the experience of being sued changed how they practice obstetrics. Among the clinicians who had been sued, 473 (60%) reported recommending cesarean more frequently, and 290 (37%) reported more likely to refer to specialists, while 40 (5%) reported that they stopped practicing obstetrics subsequent to having had lawsuits. While a higher proportion of clinicians who frequently worry about being sued were also more likely to recommend cesarean than those who infrequently worry about law suit (20.3% vs. 11.4%, respectively; p<0.001), when this factor was examined along with others in multivariable logistic regression analysis, having had lawsuit was no longer a statistically significant factor (aOR 1.30; 95% CI 0.89-1.90).

When we inquired about malpractice insurance and its association with cesarean delivery, it appeared that clinicians with high cost of liability/malpractice insurance were not more likely to recommend cesarean than those with low cost of liability/malpractice insurance, clinicians who did not know the precise cost were less likely to recommend cesarean (Table 3). The proportion of clinicians more likely to recommend cesarean were not different between those who reported practicing in states with non-economic damages cap for professional liability and those in states without non-economic-damages cap; however, clinicians who were unaware of whether their state of primary practice had non-economic damages cap in place had the lowest proportion of likely to recommend cesarean (Table 3).

A higher proportion (21%) of clinicians whose primary practice resides in the South were more likely to recommend cesarean delivery than those who practice in other regions of the U.S. (10.9-12.5%; p<0.001, Table 4) and having primary practice in Southern states remained a significant factor associated with more likely to recommend cesarean delivery in multivariable logistic regression analysis (Table 5) as well as according to the DSA algorithm. Further, there were fewer clinicians who practice within the health maintenance organization (HMO) system that were categorized as more likely to recommend cesarean (4.8%), followed by clinicians practice in the academic setting (8.3%), and private/non-academic/solo practice (14.8%), while laborists/hospitalists had the highest proportion of being more likely to recommend cesarean (29.5%; p<0.001). When this association was further examined using multivariable logistic regression controlling for potential confounding variables including region of practice, age and gender of clinicians, training experience, the presence/absence of ever sued,, urban/rural setting, clinicians in the South remained more likely to recommend cesarean compared to Northeast (aOR 1.86, 95% CI 1.14-3.05) while there were no differences in odds for clinicians in Midwest or West (Table 5). Similarly, hospitalists/laborists had higher odds of recommend cesarean (aOR 1.93, 95% CI 1.28-2.90) compared to clinicians who practice in the academic setting while it was not different for clinicians in HMO practice or academic practice (Table 5).

Just as many clinicians report lack of anesthesia support as a reason for not offering or attempting TOLAC (Table 2), more clinicians who reported having anesthesia support only as as-needed (on-call, not always in the hospital) basis were more likely to recommend cesarean (19.9%) than those clinicians who had anesthesia in-hospital or

dedicated OB anesthesia in hospital 24-hours a day (14.9%, and 11.5%, respectively; p=0.003, Table 4). While a higher proportion of clinicians who reported that they practice in the metropolitan area (21.4%) were more likely to recommend cesarean than those who practice in rural or suburban setting (Table 4), when practice setting was examined along with other characteristics, we actually observed that clinicians who practiced in metropolitan area were less likely to recommend cesarean compared to those who practice in suburban area (aOR 0.58, 95% CI 0.38-0.90; Table 5).   Further, more clinicians who served a patient population with a higher combined annual household income were more likely to recommend cesarean delivery than those whose patient population did not have high annual income (Table 4).

We further examined factors associated with more likely to recommend cesarean delivery by using the DSA algorithm. Accordingly to this analysis, hospitalist/laborist practice setting, age greater than 60, ever being sued, primary practice in the South, and patient population with high income, or high school education were positively associated with likelihood of recommending cesarean delivery Conversely, characteristics such as offering TOLAC/VBAC, breech extraction of second twin, and providing care to patients generally with low income, and metropolitan practice setting were inversely associated with likelihood of recommending cesarean delivery. While a number of factors associated with likelihood of cesarean delivery were identified by both the multivariable logistic regression analysis and the DSA algorithm (TOLAC/VBAC, breech extraction of second twin, metropolitan practice setting, primary practice in the Southern states, and age>60), the DSA algorithm identified several characteristics that were not considered significant in the multivariable logistic regression analysis: having had obstetric-related suits, patient income, and education.

5.5 Tables and Figures

Table 1: Characteristics of providers who received/opened* and survey and those who received/answered the survey "Obstetric providers' preference toward mode of delivery"

	Characteristics of providers who received and *opened* the survey (n=3,646)		Characteristics of providers who received and *answered* the survey (n=1,486)	
	Number (n)	Percent Total (%)	Number (n)	Percent Total (%)
Gender				
Male	1,980	54.3	729	49.4
Female	1,666	45.7	747	50.6
Primary Subspecialty				
Family Physician	378	10.4	66	4.4
Obstetrician/Gynecologist	3,266	89.5	1,301	87.8
Maternal-Fetal Medicine	---	---	109	7.4
Primary care	2	0.01	6	0.4
Age at time of survey				
21 – 30 years	165	4.5	74	5.0
31 – 40 years	935	25.6	372	25.3
41 – 50 years	1,074	29.5	424	28.8
51– 60 years	939	25.8	429	29.2
≥ 61 years	533	14.6	174	11.8
Region of primary practice§				
Northeast	819	22.5	288	19.3
Midwest	748	20.5	331	22.2
South	1,180	32.3	449	30.2
West	899	24.7	421	28.3

*Individual data regarding clinicians who received and opened the survey (but did not answer the survey) were not available such that further comparison between who opened the survey and who answered the survey could not be performed

§ U.S. regions assigned according to the U.S. Census Bureau:

Northeast: CT, MA, ME, NH, NJ, NY, PA, RI, VT
Midwest: IA, IN, IL, KS, MI, MN, MO, NB, ND, OH, SD, WI
South: AL, AR, DC, DE, FL, GA, KY, LA, MD, MS, NC, OK, SC, TN, VA, WV, TX
West: AK, AZ, CA, CO, HI, ID, MT, NM, NV, OR, UT, WA, WY

Table 2: Clinicians' characteristics associated with more likely, average likelihood, or less likely to recommend cesarean delivery based on the composite responses to clinical vignettes #1, 2, 4, 5, 6, 7, and 8 (7 items).

	More Cesarean	Average Cesarean	Less Cesarean	p-value
Gender				
Male	19.3 %	70.9 %	9.8 %	<0.001
Female	9.7 %	77.4 %	12.9 %	
Age at time of survey				
25-30	6.9 %	76.4 %	16.7 %	
31-60	13.0 %	77.0 %	11.8 %	<0.001
≥61	29.3 %	72.0 %	10.8 %	
Years out of training/residency				
1 – 5 years	12.2 %	79.3 %	8.5 %	
6 – 10 years	12.6 %	77.4 %	10.0 %	0.002
11 – 20 years	12.6 %	78.5 %	8.9 %	
≥ 21 years	19.3 %	67.4 %	13.3 %	
Primary Subspecialty				
Family Physician	11.3 %	79.0 %	9.7 %	
Obstetrician/Gynecologist	15.0 %	73.9 %	11.2 %	<0.001
Maternal-Fetal Medicine	11.3 %	77.4 %	11.3 %	
Training environment				
University-based	14.9 %	72.9 %	12.2 %	
Community-based	12.6 %	75.7 %	11.7 %	0.20
Military-based	13.8 %	81.6 %	4.6 %	
Self-report deliveries per month				
≤ 9	14.6 %	70.7 %	14.7 %	0.50
10 – 19	15.2 %	73.9 %	10.9 %	
≥ 20	12.8 %	76.0 %	11.2 %	
Attempt trial of labor after cesarean (TOLAC)?				
No	32.0 %	63.9 %	4.1 %	
Yes, only spont. labor	16.1 %	76.4 %	7.4 %	<0.001
Yes, spont/induced labor	4.2 %	77.0 %	19.0 %	
Attempt breech extraction of second twin?				
No	22.4 %	68.9 %	8.7 %	<0.001
Yes	10.2 %	77.0 %	12.8 %	
Perform primary cesarean delivery by maternal request?				
No	9.2 %	76.3 %	14.5 %	<0.001
Yes	16.8 %	73.3 %	9.9 %	

Table 3: Clinicians' experience associated with more likely, average likelihood, or less likely to recommend cesarean delivery based on the composite responses to clinical vignettes #1, 2, 4, 5, 6, 7, and 8 (7 items).

	More Cesarean	Average Cesarean	Less Cesarean	p-value
Having had law suit filed for an obstetric-related case				
No	11.3 %	77.0 %	11.8 %	0.008
Yes	17.2 %	72.0 %	10.8 %	
Self-reported frequency of clinician thinking / worrying about being sued				
Every day	20.3 %	71.2 %	8.5 %	
Every week / month	12.3 %	76.4 %	11.2 %	<0.001
Few times a year / never	11.4 %	74.6 %	14.0 %	
Self-estimated cost of liability/malpractice insurance over the past year				
< $35,000	18.1 %	69.8 %	12.1 %	
$35,000 – $50,000	19.5 %	69.7 %	10.9 %	<0.001
$50,000 – $75,000	18.9 %	74.5 %	6.6 %	
$75,000 – $100,000	17.2 %	70.5 %	12.3 %	
≥ $100,000	17.1 %	72.6 %	10.3 %	
Do not know	6.9 %	76.0 %	11.2 %	
Self-reported state of primary practice with non-economic damages caps for professional liability?				
No	15.4 %	74.9 %	9.7 %	
Yes	16.3 %	72.6 %	11.1 %	0.04
Do not know	9.9 %	76.0 %	14.1 %	

Table 4: Clinicians' practice environment associated with more likely, average likelihood, or less likely to recommend cesarean delivery based on the composite responses to clinical vignettes #1, 2, 4, 5, 6, 7, and 8 (7 items).

|	More Cesarean	Average Cesarean	Less Cesarean	p-value
Region of primary practice*				
Northeast	12.5 %	77.1 %	10.4 %	
Midwest	11.6 %	73.8 %	14.7 %	<0.001
South	21.4 %	71.6 %	7.0 %	
West	10.9 %	74.8 %	14.3 %	
Nature of practice				
Academic	8.3 %	78.9 %	12.8 %	
Non-academic group/solo	14.8 %	74.6 %	10.6 %	<0.001
HMO§	4.8 %	79.6 %	15.5 %	
Laborists / Hospitalists	29.5 %	62.4 %	8.1 %	
Anesthesia support in hospital:				
On-call, not always in hospital	19.9 %	72.6 %	7.5 %	
In hospital 24-hours a day	14.9 %	74.2 %	10.8 %	0.003
Dedicated OB anesthesiologists in hospital 24-hours a day	11.5 %	75.3 %	13.2 %	
Practice setting				
Rural	12.5 %	12.5 %	12.5 %	
Suburban	11.6 %	11.6 %	11.6 %	<0.001
Metropolitan	21.4 %	21.4 %	21.4 %	
Average combined household income of the patient population				
< $35,000	12.7 %	76.5 %	10.8 %	
$35,000 to $75,000	15.7 %	72.4 %	11.9 %	0.03
> $75,000	21.3 %	68.8 %	9.9 %	
Do not know	10.2 %	77.3 %	12.8 %	

[87]

Table 5: Multivariable logistic regression estimation of the association between clinicians' characteristics associated with more likely to recommend cesarean delivery based on the composite responses to clinical vignettes #1, 2, 4, 5, 6, 7, and 8 (7 items).

| Provider Characteristics	Adjusted Odds Ratio	95% CI
Male	1.39	0.94 – 2.04
Age ≥61 years	1.71	1.05 – 2.77
Out of Residency ≥16 years	0.78	0.52 – 1.17
Obstetrician/Gynecologists	0.96	0.51 – 1.81
University-based residency	1.34	0.94 – 1.91
Offers TOLAC/VBAC	0.42	0.33 – 0.54
Offers breech extraction of second twin	0.54	0.38 – 0.76
Offers CDMR (elective cesarean)	1.65	1.08 – 2.52
Primary practice geographic region: compared to northeast		
Midwest	1.03	0.78 – 1.84
South	1.86	1.14 – 3.05
West	0.96	0.55 – 1.67
Practice type: compared to private practice	0.94	0.54 – 1.65
Academic	0.59	0.22 – 1.60
HMO	1.93	1.28 – 2.90
Hospitalist		
Practice setting: compared to suburban		
Rural	0.78	0.50 – 1.21
Urban	0.58	0.38 – 0.90
Having had obstetric-related suits	1.30	0.89 – 1.90
Frequent worry about suits	1.24	0.86 - 1.78

Figure 1: Clinical vignette #1 and answer distribution

A 25-year-old G2P1 at 38 weeks who had a prior uncomplicated, term, vaginal delivery sees you in clinic for routine care. You find that the fetus is in frank breech presentation. Your clinical estimated fetal weight (EFW) is 3,200 g. You recommend:
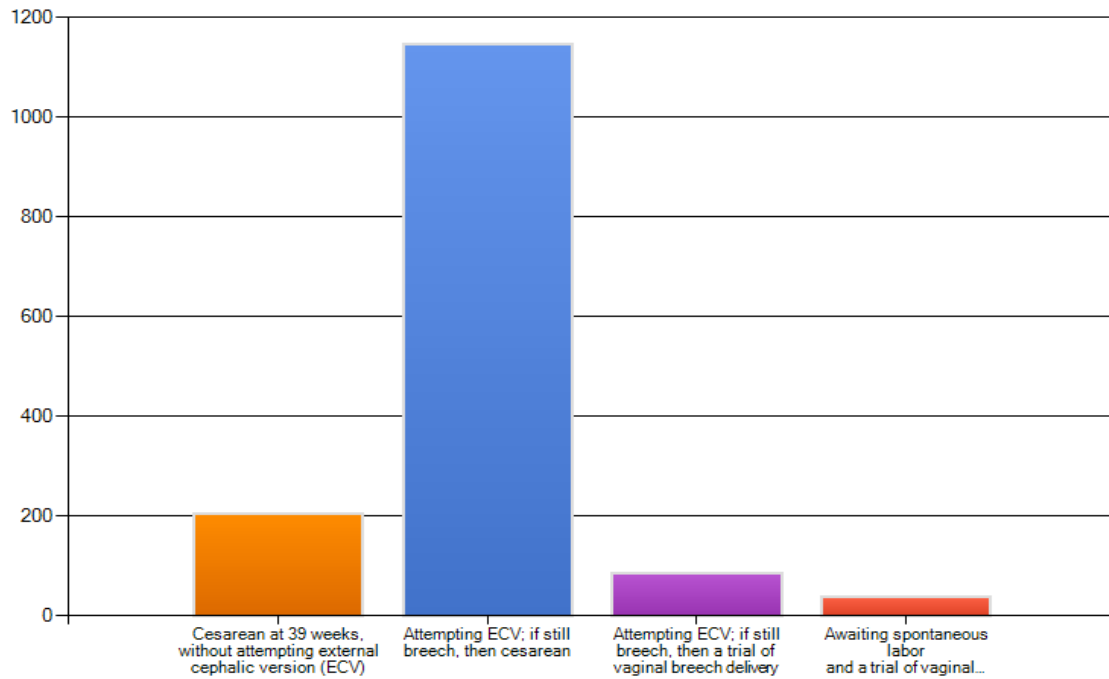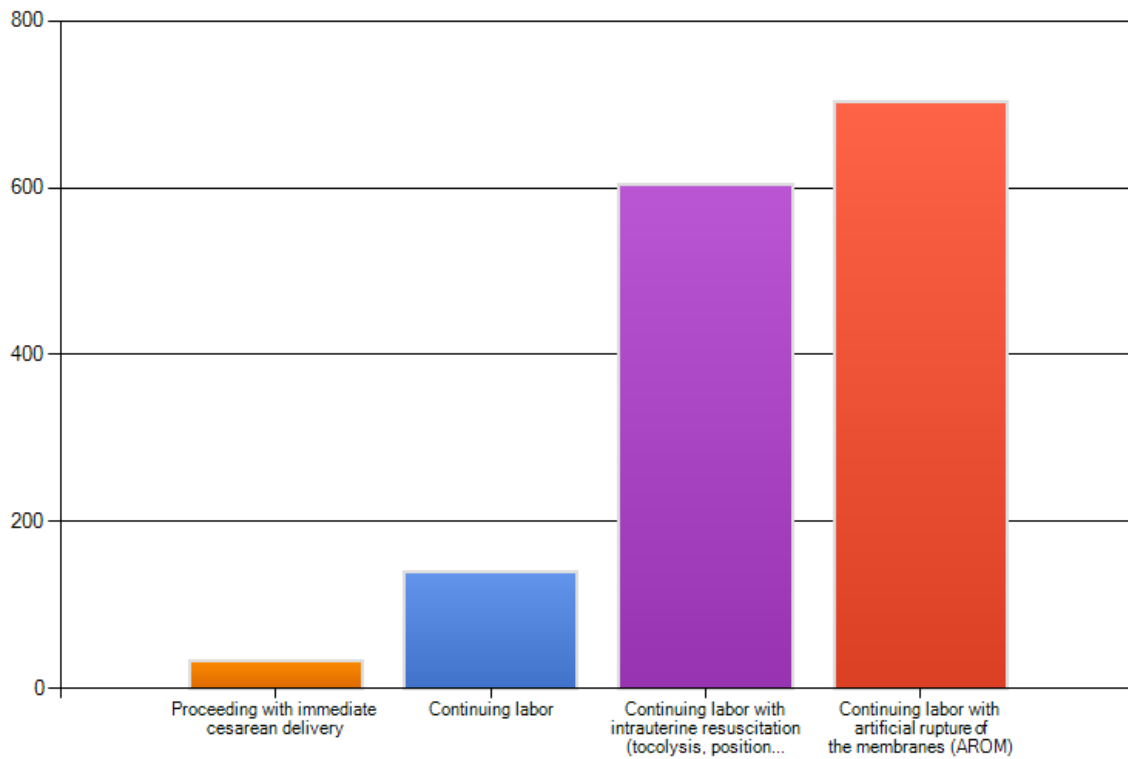
Figure 2: Clinical vignette #2 and answer distribution

A 28-year-old G2P1 at 37 weeks sees you in clinic for routine care. She has a prior low-transverse cesarean delivery for breech presentation. This pregnancy is uncomplicated and the fetus is cephalic. For her delivery plan, you recommend:
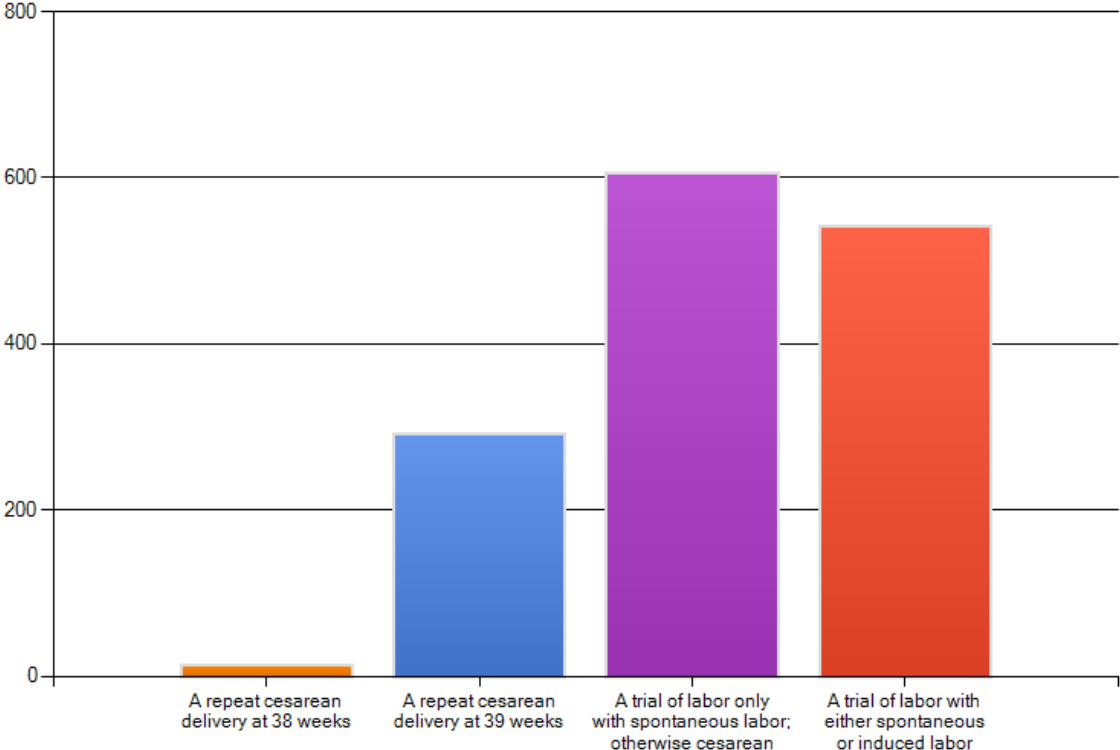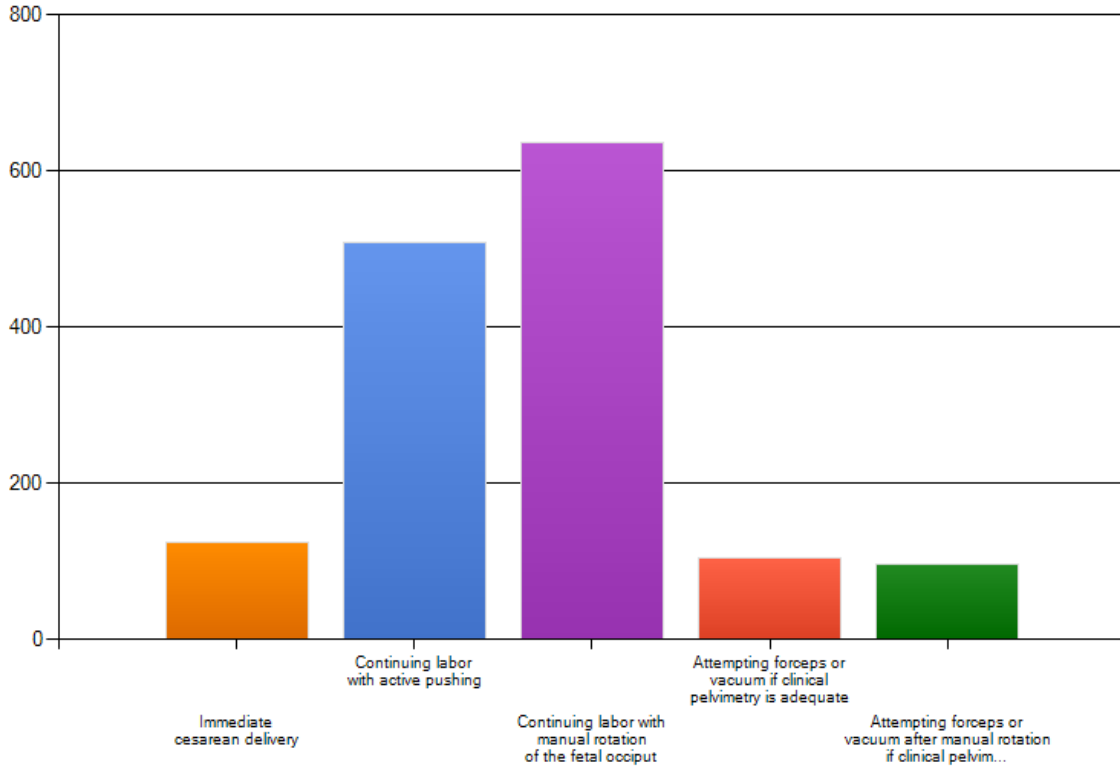
Figure 3: Clinical vignette #3 and answer distribution

A 25-year-old G1P0 at 39 weeks is in early labor: cervix is 4 cm dilated, contractions are every 2-3 minutes, and membranes are intact. Fetal monitoring shows occasional late decelerations with moderate variability. You recommend:

Figure 4: Clinical vignette #4 and answer distribution

A 25-year-old G1P0 at 39 weeks is in active labor: cervix is 6 cm dilated, contractions are every 3 minutes, and membranes are ruptured. Fetal monitoring is reassuring and EFW is 3,400 g. Two hours later, the cervix is unchanged. An intrauterine pressure catheter was placed and shows inadequate contraction forces. You recommend:
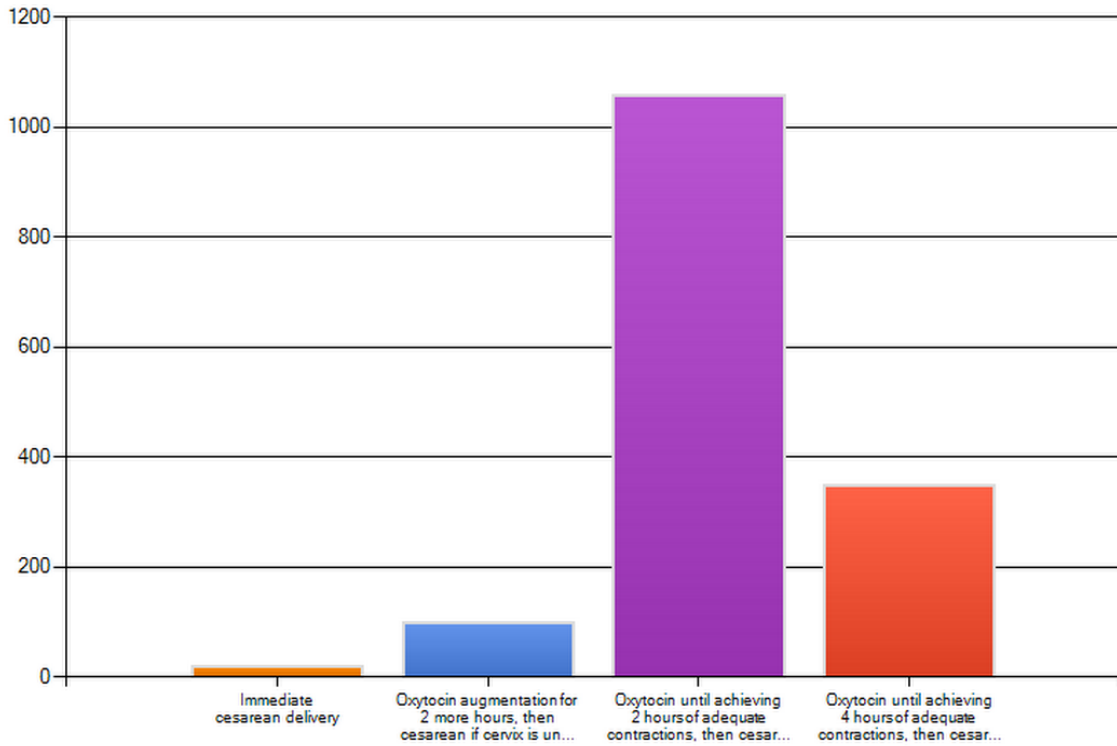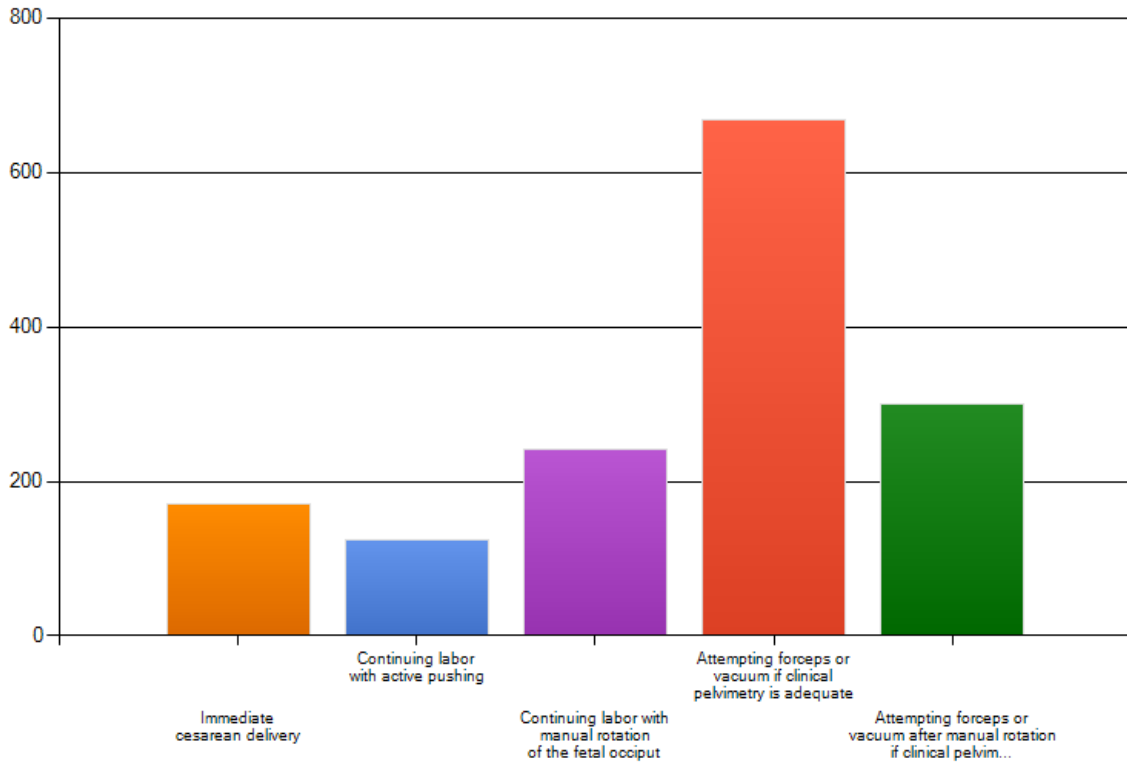
Figure 5: Clinical vignette #5 and answer distribution

A 25-year-old G2P1 at 39 weeks with a prior term vaginal delivery has been pushing for 2 hours with epidural analgesia. The occiput is at 1 station, in occiput posterior (OP) position. Fetal monitoring is reassuring and EFW is 3,600 g. You recommend:
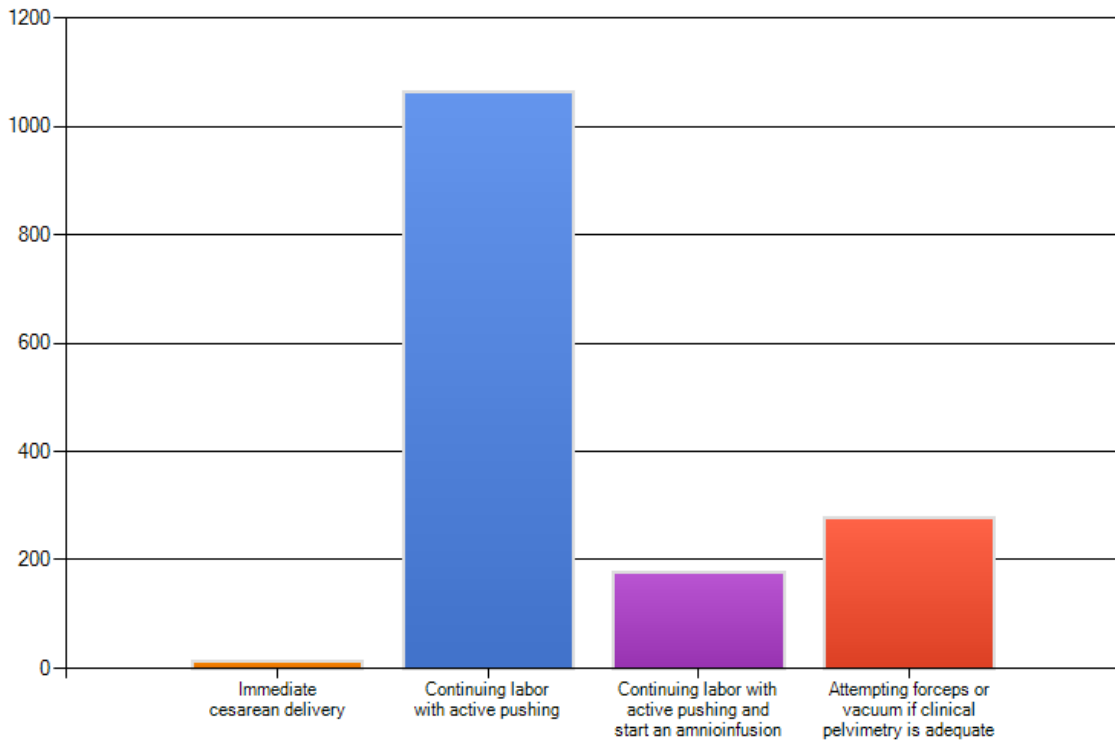
Figure 6: Clinical vignette #6 and answer distribution

A 25-year-old G1P0 at 39 weeks with epidural anesthesia has been pushing for 3 hours. The fetal occiput is at 2 station, in occiput posterior (OP) position. Fetal monitoring is reassuring; the clinical EFW is 3,400 g. You recommend:
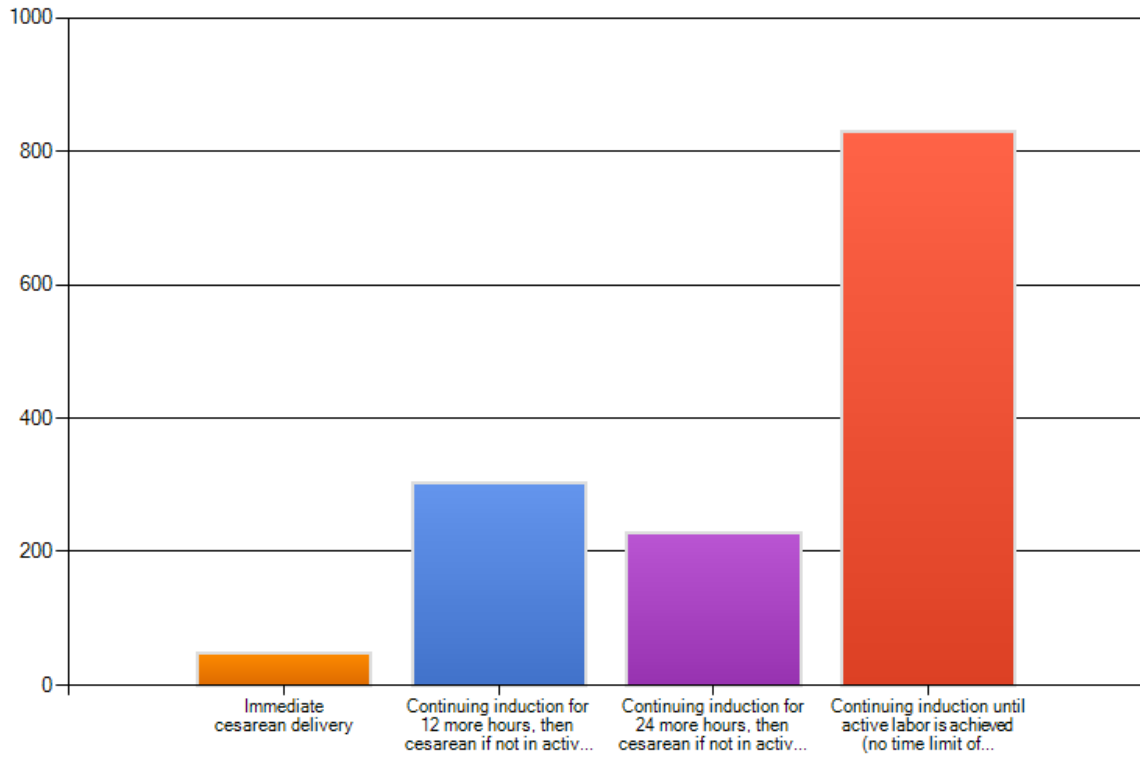
Figure 7: Clinical vignette #7 and answer distribution

A 25-year-old G1P0 at 39 weeks with epidural anesthesia has been pushing for 1 hour. The fetal occiput is at 2 station, in occiput anterior (OA) position; EFW is 3,200 g. Fetal monitoring shows frequent moderate, variable decelerations with rapid return to baseline and maintenance of moderate variability. You recommend:

Figure 8: Clinical vignette #8 and answer distribution

A 25-year old G1P0 at 37 weeks is being induced for mild preeclampsia. Fetal growth and monitoring are reassuring. After 12 hours of cervical ripening, her cervix remains unchanged: 1 cm dilated, 3 cm long. You recommend:

- Immediate cesarean delivery
- Continuing induction for 12 more hours, then cesarean if not in activ...
- Continuing induction for 24 more hours, then cesarean if not in activ...
- Continuing induction until active labor is achieved (no time limit of...)

Figure 9: Cross validation graph from DSA analysis

Interaction order 1

Interaction order 2

5.6   Discussion

While most studies on factors associated with increased risk of cesarean delivery focused on maternal/obstetric characteristics, there had been little information on clinicians' role in such decision making process: when to recommend cesarean and when would it be safe to continue labor. This cross-section, convenience survey study aimed to examine clinicians' characteristics, experience, and practice setting that may be associated with a higher likelihood of recommending cesarean delivery.

Ideally, direct observation of clinicians in the clinical setting (i.e., in out-patient and in Labor and Delivery units) would provide most accurate assessment of clinicians' role in the decision making process regarding whether to undergo cesarean delivery or continue labor. However, such endeavor can be labor-intensive, time-consuming, and usually involves small sample size. Further, clinicians under observation may practice obstetrics differently than otherwise in their natural setting. Thus, the clinical vignettes of this survey which described the commonly encountered scenarios in obstetrics, incorporating decision making in the out-patient setting as well as in-patient labor management, served as proxy to assess clinicians' threshold for recommending cesarean delivery. Another advantage of incorporating the clinical design was that the clinicians who participated in the survey were already familiar with the format because the standardized examinations such as the United States Medical Licensing Examinations (USMLE) and Counsel on Resident Education in Obstetrics and Gynecology (CREOG) who had utilized clinical vignettes as one of the primary testing format.

One of the primary objectives of this survey study was to identify clinician characteristics that may be associated with a tendency of more likely to recommend cesarean delivery in the clinical setting. We used multivariable logistic regression analysis and Deletion/Substitution/Addition (DSA) algorithm independently to assess clinician factors associated with more likely to recommend cesarean. Although both methods identified that offering trial of labor after previous cesarean delivery, offering breech exaction of second twin, and primary practice in metropolitan area were inversely associated with likely to recommend cesarean and that clinicians with primary practice in the Southern states, clinicians who practice as hospitalist/laborist, and age>60 were positively associated with likely to recommend cesarean delivery, there were several characteristics identified as associated factors by DSA but not by multivariable logistic regression analysis. These included: having had obstetric-related lawsuits, patient population with high income, patient population with higher education.

As multivariable logistic regression analysis was based on conditional probability to estimate the effect of the exposure-outcome association, this was in contrast to the DSA algorithm that used polynomial basis functions[17] to identify predictors for the exposure-outcomes of interest based on cross-validation and the L2 loss function.[15] While it appeared reassuring that most of the associated factors of likely to recommend cesarean were identified by both methods independently, DSA additionally identified several factors, including having had lawsuits, that did not reach statistical significance

in multivariable logistic regression, but not vice versa. Since we do not know the "true" predictor model of cesarean delivery, we could not objectively determine which method provided a better fit, although our survey did suggest that the experience of lawsuit to be an influencing factor in subsequent questions. It could also be possible that neither method provided the best model such that any and all the covariates observed in the models might be considered as potentially relevant.

One important finding of this study was that a larger proportion of clinicians who have had law suit filed against them for obstetric-related cases were more likely to recommend cesarean delivery than clinicians who have not had law suits. While the association between obstetricians and litigations has been recognized, whether and how litigation may lead to defensive medicine in obstetrics had not been well documented. According to this survey, a large proportion (60%) of clinicians who reported having been sued reported more likely to recommend cesarean because of litigation experience. According to the DSA algorithm, having had obstetric-related lawsuits was identified as a characteristics associated with likelihood of recommending cesarean delivery. Additionally, the majority (60%) of the responders of this survey reported having being sued and such prevalence was similar from this study compared to a larger survey by AMA. In 2007, the American Medical Association surveyed 4700 physicians and reported that 69.2% of obstetricians-gynecologists have had law suits.[18] But even more importantly, this study found that the majority of obstetricians-gynecologists had law suits even before age 40, within the first 5-10 years out of residency training.[16,19]

While being involved in malpractice litigations has been documented as one of the most stressful situations and can be psychologically devastating, being sued at the early stage of one's career can have a lasting impact on one's practice pattern for an entire career. As our study observed, having had law suits and frequent worry about being sued were both associated with a higher likelihood of recommending cesarean delivery. Likely, these experiences might have led to more defensive medicine in practice.

We hypothesized that clinicians who pay a higher annual premium for malpractice insurance and clinicians who practice in states without non-economic damages cap for liability payout might have higher prevalence and high cost of malpractice suits; and, as part of being risk averse, they were more likely to recommend cesarean delivery. We did not observe such an association. Rather, it was clinicians who reported not knowing their cost of annual malpractice insurance premium and clinicians not aware whether their state has non-economic damages cap legislation in place who had a lower likelihood of recommending cesarean delivery than clinicians with such knowledge. Perhaps, it was not about the potential cost of a malpractice suits, but that clinicians without such knowledge represent those who practice obstetrics without the bias of potential defensive medicine.

As there were geographical differences in the annual rate of cesarean delivery,[1] it has not been clear which factors were associated with such differences. One

hypothesis might be that patient characteristics such as racial/ethnic, and body mass index (BMI) differences exists between the Northeast, Midwest, South and West, and these have been identified as independent risk factors of cesarean delivery.[20,21,22,23] Additionally, we also report that clinicians who primarily practiced in the South were more likely to recommend cesarean delivery based on the clinical vignettes clinicians of other regions. This association persisted after controlling for potential confounding factors such as clinician's gender, age, litigation experience, type of clinical practice, setting of practice (rural/urban) and availability of anesthesiologists. To verify that more cesareans were indeed performed in the southern states, we examined the annual incidence rate of total cesarean delivery by states for all live births in 2007 and observed the mean cesarean delivery frequency was indeed higher for the South than others.[24] The precise reason underlying this association between clinicians who practice in the South and higher propensity of recommending cesarean observed in this study remained unclear and deserves further investigation.

Through this survey study, we observed that a higher proportion of clinicians who practice as laborists/hospitalists were more likely to recommend cesarean delivery compared to clinicians who practice in the academic, non-academic/solo, or HMO settings. This association held statistically significant after controlling for potential confounding factors such as age, gender, and litigation experience. As laborists/hospitalists represented a group of clinicians who practice solely in the in-patient setting, one might expect them to have a lower likelihood of recommending cesarean delivery as they "specialize" in labor management; yet, we observed the inverse association. Perhaps, as laborist/hospitalists, these clinicians would not have the opportunity to foster relationships with their patients through prenatal care visits, and thus have a different threshold in recommending cesarean delivery than clinicians who practice in both out-patient and in-patient settings.

There were limitations to this study. Despite a large number of email rosters was available through the AMA membership, we had a low proportion of survey recipients who opened the email. However, of those who did, approximately 40% participated in the survey with a high proportion (94%) that completed the survey. While we would love to have demographic information on all recipients of the email survey to ensure that clinicians who completed the survey were representative of the target population, this information was not available through the AMA. However, we were able to obtain some demographic information on those who opened the email and those who completed the survey and was somewhat reassured that the demographics between these two cohorts of clinicians. Potentially, repeat email reminders, paper surveys in addition to emails, or small monetary compensation for time could have increased the survey participation; however, we did not have additional resources to carry out these plans. For future studies, we might use a smaller sampling frame that is still representative of the clinicians who practice obstetrics in the U.S. and focus on strategies to increase study participation.

This study was novel in that we focused on clinicians' factors rather than patient factors that might be associated with increased cesarean delivery. While we identified a

number of factors related to clinicians' experience and practice setting that might be associated with higher likelihood of recommending cesarean, certainly, information learned from this survey study should be further examined and validated. We plan to design future studies to examine the interplay of hospital policy may influence clinicians' decision-making process, whether the presence of clinical nurse midwives may reduce obstetric interventions, and if the implementation of laborists/hospitalists may streamline obstetric care or increase cesarean delivery by field observations and in-depth interviews of clinicians, nurses, and hospital staffs that make up the obstetric care team.

5.7 Appendix

Appendix 1: e-mail message and questionnaire sent to obstetric providers in the U.S. registered with the American Medical Association (AMA) followed by link to the survey of obstetric providers' preferences towards mode of delivery conducted through *SurveyMonkey*^{TM}.

SUBJECT: UCSF STUDY ON CESAREAN DELIVERY
FROM: ChengY@obgyn.ucsf.edu
REPLY TO: ChengY@obgyn.ucsf.edu
SEND TEST EMAIL TO: ChengY@obgyn.ucsf.edu; Stephanie.handler@gmail.com
LINK TO SURVEY: https://www.surveymonkey.com/s/ucsfoppmodstudy

SAMPLE EMAIL:

[Date}

Dear Colleague:

We are interested in studying quality of care in obstetrics and identifying patterns of cesarean delivery. You have been selected at random to participate in this survey. The survey takes only approximately 10 minutes to complete. We highly appreciate your time and willingness in participating in this survey. We DO NOT collect identifiable information about you and there will be no possibility that you could be identified or that your answers be attributed to you.

The survey is designed to collect obstetric provider information, including clinicians' experience, practice environment, and patient characteristics. Eight short hypothetical clinical vignettes are included to find out what clinicians would do in clinical practice in various obstetric scenarios. There are no right or wrong answers to these vignettes.

We would like to thank you for participating in this study and greatly appreciate your valuable time and effort. Please join us in our goal to improve the health of pregnant women and their neonates.

Sincerely yours,

Yvonne Cheng, MD, MPH
Assistant Professor
University of California, San Francisco

Alan Hubbard, PhD
Assistant Professor
University of California, Berkeley

Aaron Caughey, MD, PhD
Professor and Chair
Oregon Health and Science University

Ira Tager, MD, MPH
Professor
University of California, Berkeley

Appendix 2: Sample questionnaire

CLINICAL VIGNETTES

The following 8 questions contain short descriptions of hypothetical clinical scenarios followed by potential management options. Please check the option that most represents what you would do. There are not "right and wrong" answers; this is an assessment of practice style.

1. A 25-year-old G2P1 at 38 weeks who has a history of an uncomplicated term vaginal delivery is in clinic for routine care. You find that the fetus is in frank breech presentation. The clinical estimated fetal weight is 3,200 gm. You recommend:

- ☐ Cesarean at 39 weeks, without attempting external cephalic version (ECV)
- ☐ Attempt ECV; if still breech, then cesarean delivery at 39 weeks
- ☐ Attempt ECV; if still breech, then a trial of vaginal breech delivery
- ☐ Awaiting spontaneous labor and a trial of vaginal breech delivery without ECV

2. A 28-year-old G2P1 at 37 weeks is seeing you in clinic for routine care. She has a history of a low-transverse cesarean delivery for breech presentation. This pregnancy is uncomplicated, and she asks about delivery plans. You recommend:

- ☐ A repeat cesarean delivery at 38 weeks
- ☐ A repeat cesarean delivery at 39 weeks
- ☐ A trial of labor only with spontaneous labor, otherwise cesarean
- ☐ A trial of labor with either spontaneous or induced labor

3. A 25-year-old G1P0 at 39 weeks is in early labor: cervix is 4 cm dilated, contractions are every 2-3 minutes, and membranes are intact. Fetal monitoring shows occasional late decelerations with moderate variability. You recommend:

- ☐ Proceeding with immediate cesarean delivery
- ☐ Continuing labor
- ☐ Continuing labor with intrauterine resuscitation (tocolysis, position change, O_2)
- ☐ Continuing labor with artificial rupture of the membranes (AROM)

[105]

4. A 25-year-old G1P0 at 39 weeks is in active labor: cervix is 6 cm dilated, contractions are every 3 minutes, and membranes are ruptured. Fetal monitoring is reassuring and EFW is 3,400 gm. Two hours later, the cervix is unchanged. You place an intrauterine pressure catheter, which shows inadequate contraction forces. You recommend:

- ☐ Immediate cesarean delivery
- ☐ Oxytocin augmentation for 2 more hours, then cesarean if the cervix is unchanged
- ☐ Oxytocin augmentation until achieving 2 hours of adequate contractions, then cesarean if the cervix is unchanged
- ☐ Oxytocin augmentation until achieving 4 hours of adequate contractions, then cesarean if the cervix is unchanged

5. A 25-year-old G2P1 at 39 weeks with a prior term vaginal delivery has been pushing for 2 hours with epidural anesthesia; the fetal occiput is at +1 station, in occiput posterior (OP) position. Fetal monitoring is reassuring and EFW is 3,600 gm. You recommend:

- ☐ Immediate cesarean delivery
- ☐ Continuing labor with active pushing
- ☐ Continuing labor with manual rotation of the fetal occiput
- ☐ Attempting forceps or vacuum if clinical pelvimetry is adequate
- ☐ Attempting forceps or vacuum after manual rotation if pelvimetry is adequate

6. A 25-year-old G1P0 at 39 weeks with epidural anesthesia has been pushing for 3 hours. The fetal occiput is at +2 station, in occiput posterior (OP) position. Fetal monitoring is reassuring; the clinical EFW is 3,200 gm. You recommend:

- ☐ Immediate cesarean delivery
- ☐ Continuing labor with active pushing
- ☐ Continuing labor with manual rotation of the fetal occiput
- ☐ Attempting forceps or vacuum if clinical pelvimetry is adequate
- ☐ Attempting forceps or vacuum after manual rotation if pelvimetry is adequate

7. A 25-year-old G1P0 at 39 weeks with epidural anesthesia has been pushing for 1 hour. The fetal occiput is at +2 station, in OA position; EFW is 3,200 gm. Fetal monitoring shows frequent moderate variable decelerations, with rapid return to baseline and maintenance of moderate variability. You recommend:

- ☐ Immediate cesarean delivery
- ☐ Continuing labor with active pushing
- ☐ Continuing labor with active pushing and starting an amnioinfusion
- ☐ Attempting forceps or vacuum if clinical pelvimetry is adequate

8. A 25-year old G1P0 at 37 weeks is being induced for mild preeclampsia. Fetal growth and monitoring are reassuring. After 12 hours of cervical ripening, her cervix remains unchanged: 1 cm dilated, 3 cm long. You recommend:

☐ Immediate cesarean delivery
☐ Continuing induction for 12 more hours, then cesarean if not in active labor
☐ Continuing induction for 24 more hours, then cesarean if not in active labor
☐ Continuing induction until active labor is achieved (no time limit of induction)

PROVIDER INFORMATION:

1. Your age (in years):_____

2. Gender:

☐ Male   ☐ Female

3. In which state do you primarily practice?   __ __

4. Do you deliver babies?

☐ No   ☐ Yes

5. If you do deliver babies, approximately how many deliveries did you perform per month over the last 12 months?:

☐ <5   ☐ 5-9   ☐ 10-14   ☐ 15-19   ☐ ≥20   ☐ Don't know

6. How would you best describe the nature of your practice?

☐ Academic—mainly research
☐ Academic—mainly clinical practice
☐ Academic—balanced research and clinical practice
☐ Health maintenance organization (HMO)
☐ Non-academic group practice:
     How many members are in your group? _____
☐ Solo practice
☐ Laborist / Hospitalist
☐ Other—please describe:

7. What is your specialty?
- ☐ Certified Nurse Midwifery (CNM)
- ☐ Family Physician / general practice
- ☐ Obstetrician / Gynecologist (Ob/Gyn)
- ☐ Maternal-Fetal Medicine (MFM) / perinatology
- ☐ Other—please describe:

8. In which year did you finish your clinical training/residency? __ __ __ __

9. In which state did you finish clinical training/residency? __ __ (use US Post Office Abbreviation)

10. Was your clinical training/residency university-based or community-based?
- ☐ University   ☐ Community   ☐ Military

11. If you underwent sub-specialty or fellowship training, in what area was your sub-specialty training / fellowship?
- ☐ MFM   ☐ REI   ☐ Gyn Onc   ☐ Uro Gyn
- ☐ Other—please specify: _____

12. In which year did you finish your sub-specialty training / fellowship: __ __ __ __

13. In which state did you finish your sub-specialty training / fellowship: __ __

14. What is the primary cesarean delivery rate for your hospital (estimate): __ __

15. What is your personal primary cesarean rate (estimate): __ __

16. Do you attempt trial of labor/vaginal delivery after cesarean (VBAC) in your practice?
- ☐ No   ☐ Yes

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17. Do you attempt breech extraction of second twin in your practice?

☐ No ☐ Yes

18. Do you perform cesarean delivery by maternal request (primary elective cesarean)?

☐ No ☐ Yes

PRACTICE ENVIRONMENT

19. How would you describe your practice setting?

☐ Rural ☐ urban ☐ Metropolitan

20. Please describe what kind of anesthesia support is available to you in the hospital where you deliver babies:

☐ Anesthesiologist or anesthetist available only during the day

☐ Anesthesiologist or anesthetist on-call but not always physically in hospital

☐ Anesthesiologist or anesthetist on-call in the hospital 24-hours a day

☐ Dedicated OB anesthesiologist on-call in the hospital 24-hours a day

21. What was the average cost of your professional liability insurance / malpractice insurance over the past year?

☐ < $35k ☐ $35k to 50k ☐ $50k to 75k ☐ $75k to 100k

☐ $100k to 125k ☐ $125k to 150k ☐ >$150k ☐ Don't know

22. Does the state in which you primarily practice have non-economic damages caps for professional liability insurance:

☐ No ☐ Yes ☐ Don't Know

23. On average, how often do you think or worry about being sued for malpractice:

☐ Every day ☐ Every week ☐ Every month

☐ Few times a year ☐ Every few years ☐ Never

24. Have you ever had a law suit filed against you for an OB or L&D-related case:

☐ No ☐ Yes

25. If you have had law suit(s) filed against you, has this experience influenced your management of patients:

☐ No ☐ Yes ☐ Not applicable

26. If you have ever been sued, how has it changed your practice? Please check all that apply:

☐ More likely to perform cesarean ☐ Less likely to perform cesarean

☐ More likely to perform forceps/vacuum ☐ Less likely to perform forceps/vacuum

☐ More likely to refer high-risk patients ☐ Less likely to refer high-risk patients

☐ More counseling of risks/benefits ☐ Less counseling of risks/benefits

☐ Stopped practicing obstetrics

☐ Other—Please describe:

PATIENT CHARACTERISTICS

27. How would you characterize the patient population for which you provide care?

Insurance:

☐ Mostly private ☐ Mostly HMO ☐ Mostly MediCaid ☐ Mixed

Education:

☐ Mostly less than high school ☐ Mostly high school graduates

☐ Mostly college/graduates or more ☐ Don't know

Average combined household income:

☐ < $15k ☐ $15k to 35k ☐ $35k to 50k ☐ $50k to 75k

☐ $75k to 100k ☐ $100k to 150k ☐ > $150k ☐ Don't know

5.8   References

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Chapter 6. Discussion

6.1   Summary

With 4.1 million births per year, cesarean delivery is the most commonly performed in-patient surgery in the U.S. and represents in excess of 17 billion U.S. dollars in expenditure per year, not counting the indirect cost of cesarean delivery.[1,2,3] Thus, the current rise in cesarean delivery has a profound impact on maternal and child health as well as social and economic repercussions that are not yet well understood. As part of the Healthy People 2020 objectives that are currently under development, reducing cesarean births among low-risk women remains a priority.[4] Although numerous strategies have been suggested and tried to reduce cesarean delivery, it continues to rise at a rate disproportional to the changing maternal characteristics that may be partly responsible for the increase. The goal of this research was thus to identify patient characteristics and clinician characteristics that are associated with the increased likelihood of having cesarean delivery or recommending cesarean delivery, respectively.

First, in Chapter 3 (A counterfactual approach to examine the association between perinatal outcome and induction of labor compared to expectant management) I used marginal structural models (MSM) to examine the relation between induction of labor at a specific gestational age (e.g., 39 weeks) compared to expectant management (delivery at a later gestational age, i.e., 40, 41 or 42 weeks, by either entering spontaneous labor or subsequently induction of labor for various medical/obstetric indications) and associated maternal/neonatal outcomes. This analytic scheme more accurately reflected the clinical management options: to undergo induction now or continue pregnancy (expectant management), leading to delivery at a later gestational age.[5] This was in contrast to many observational studies in the past which compared induction of labor to spontaneous labor.[6,7,8,9] Another strength of this analysis was the application of MSM to examine the association between induction of labor and cesarean delivery/perinatal outcomes. Based on the concept of counterfactuals, MSM compares outcome frequency under different exposure distributions (exposed and non-exposed) in the same sample population and estimates the effect of exposure across the entire population.[10,11,12] This is in contrast to traditional multivariable regression approaches, which, which estimate the effect of association conditional on confounding covariates and does not address specifically the risk of outcome for each subject under both exposed and unexposed conditions. It is this latter characteristic of the causal inference framework that permits inference that is more likely to have a causal interpretation. By applying causal inference framework through the use of MSM, this analysis estimated the population-level, marginal effect of induction on cesarean delivery and other perinatal outcomes that correspond to hypothetical interventions.

Based on the MSM analysis, I show that induction of labor was associated with a decreased risk of cesarean delivery compared to expectant management. Further, induction was associated with improved neonatal outcomes according to our analysis,

which an important new finding. Given neonatal morbidity is a rare event, it might be likely that my large population-based study had sufficient statistical power to examine rare outcomes, which previous studies did not.

Next, I examined the association between advanced maternal age and cesarean delivery in the U.S in Chapter 4 (Estimating the contribution of maternal age to risk of cesarean delivery using population intervention models analysis). Delayed childbearing has become increasingly common in the U.S.[13] such that the proportion of live births among women aged 35 years and older was13% in 2007 (compared to 5% in 1970's).[14] Increase in maternal age has been associated with higher risk of adverse pregnancy outcomes. These risks include: birth defect and genetic/chromosomal abnormalities, medial and obstetric complications as well as cesarean delivery.[15,16,17,18,19,20,21] Thus, I used the population intervention models to estimate the population attributable fraction of advanced maternal age (age >35 years at estimated date of delivery) on cesarean delivery. Developed by Hubbard and van der Laan, population intervention models build upon the causal inference literature to model the difference of an effect between the distribution of a population in an observed environment (the actual study population) and a counterfactual treatment-specific population distribution (the population outcome that would have been observed under "intervention" such that the exposure would be at some target, optimal level).[22,23] In this analysis, age <35 was considered the target level.

The population intervention models estimated the potential changes in the distribution of cesarean delivery in low-risk population of nulliparous women who gave live births in the U.S., if women with delayed childbearing were counseled regarding the contribution of advanced maternal age on cesarean delivery and "intervened" on age of pregnancy as a risk factor. Although maternal age, unlike other behavioral factors, could not be easily "intervened" upon or modified at the individual level, I chose to use population intervention models to gain insights into the potential changes in the distribution of cesarean delivery, focusing on the population prevalence of advanced maternal age as a risk factor. Through this analysis, I observed that advanced maternal age was a risk factor of cesarean delivery. Using the population intervention model, the number of cesareans that would have been avoided had all women become pregnant at an age covered by the intervention level (< 35 years at time of delivery) was higher in 2006 compared to that in 1994. This analysis shed light on the relative importance of advanced maternal age as a risk factor of cesarean delivery, which was smaller than expected, suggesting that other factors might be involved..

I hypothesized that while patient characteristics may influence the decision to undergo cesarean delivery, clinicians may also play an important role. However, few studies have been published regarding this topic .[24,25] Thus, I conducted a cross-sectional survey study to explore provider characteristics that might be associated with increased likelihood of recommending cesarean delivery (see Chapter 5: Clinicians' experience and obstetric management: factors associated with recommending cesarean delivery). The survey included an e-mail sent questionnaire composed of 2 parts. The first part included 8 common clinical scenarios regarding management of

term pregnancy and management of first and second stages of labor; these vignettes were designed to assess clinician's inclination to recommend cesarean delivery under various commonly encountered scenarios. The second part of survey included questions regarding clinicians' demographic information as well as their clinical experience and practice setting/environment.

I used multivariable logistic regression analysis fit by maximum likelihood and a model fit with the data-adaptive Deletion/Substitution/Addition (DSA) algorithm independently to assess clinician factors associated with an increased likelihood to recommend cesarean. This information is summarized in the Table below, where covariates included/selected in the predictive model were noted by "X" according to the methods used:

	Multivariable Logistic Regression	DSA Algorithm
Offer trial of labor after previous cesarean delivery	X	X
Offer breech extraction of second twin	X	X
Primary practice in metropolitan are	X	X
Primary practice in the Southern states*	X	X
Practice as hospitalists/laborists	X	X
Age >60 years	X	X
Having had obstetric-related lawsuit(s)		X
Patient population with high annual income (> $75,000)		X
Patient population with high education (college and more)		X

* Southern states include: AL, AR, DC, DE, FL, GA, KY, LA, MD, MS, NC, OK, SC, TN, VA, WV, TX

While both methods identified a number of covariate as associated factors for more likely to recommend cesarean delivery, there were several characteristics identified as associated factors by DSA but not by multivariable logistic regression analysis. These included having had obstetric-related lawsuits, patient population with high income, patient-population with higher education. As multivariable logistic regression analysis was based on conditional probability to estimate the effect of the exposure-outcome

[115]

association, this was in contrast to the DSA algorithm that used polynomial basis functions to identify predictors for the exposure-outcomes of interest based on cross-validation and the L2 loss function.[26,27] Since we do not know the "true" predictor model of cesarean delivery, we could not objectively determine which method provided a better fit, although our survey did suggest that the experience of lawsuit to be an influencing factor in subsequent questions.

It is imperative to identify factors associated with an increased risk of cesarean delivery to conceptualize and design interventions to achieve a more optimal rate relative to population health benefit. This research examined several increasingly common factors, including induction of labor, and advanced maternal age that might be associated with increased risk or increased likelihood of cesarean delivery. This was achieved through the application of causal inference framework and analytical methods such as marginal structural models and population intervention models and the usage of nationwide birth data. Additionally, provider characteristics and experience information were collected via a cross-sectional survey to explore clinician-level information to identify factors driving the increase in cesarean delivery.

6.2   Innovative nature of research

This body of work examined patient factors and provider characteristics associated with cesarean delivery and add to existing knowledge in a number of ways that has not been explored previously. First, the application of advanced analytical techniques, such as model fitting with the data-adaptive Deletion/Substitution/Addition (DSA) and super learner, has not been used in the obstetric literature. These methods could enhance the assessment of candidate variables as risk factors of cesarean delivery. Second, application of causal statistical methods, such as marginal structural models and population intervention models, was used to estimate the effect of potential risk factors on cesarean delivery. Finally, through the collection and examination of clinician-level information, this research explored provider factors that may influence the decision/recommendation to undergo cesarean delivery.

Currently, little information exists on system-level factors, such as clinician's practice setting, environment, and hospital policy, on cesarean delivery. This study served as a beginning to shed light on this important topic. Ultimately, the goal of this research is to inform and curtail current continual rising trend of cesarean delivery in the U.S., and to improve the health and wellbeing of the expecting mother and her children. Future research will focus on the underlying contributions of these differences, and deriving targets to potentially intervene upon and improve care.

6.3   Future Research

While this research evaluated the population attributable risk of advanced maternal age on cesarean delivery, there are other maternal risk factors that may be associated with increased risk of cesarean delivery which await evaluation. For

example, the obesity epidemic in the U.S. has led to an increase in the proportion of pregnant women who are obese,[28] and obesity is an independent risk factor for cesarean delivery and pregnancy complications; however, the magnitude of effect estimate of maternal obesity of cesarean delivery varied among studies.[29,30,31] With the availability of patient education and counseling programs that can incorporate nutrition counseling, dietary modification, and exercise regimen, maternal obesity can be a modifiable risk factor. Given this, population intervention models well suited as an analytical method to estimate the population attributable risk of maternal obesity on cesarean delivery and have properties that are more desirable than tradition algorithms for estimation of PAR. Population intervention models analysis could provide insight into the potential impact of intervention on perinatal outcome.

One area of interest is the difference in cesarean delivery among geographical regions (i.e., Northeast, Midwest, South, and West) as well as between states within these regions. Using data from one of the largest healthcare delivery system in the U.S., variations of 200-300% in rates of primary cesarean delivery were observed: 19%±5% (range 9-27%).[32] Another study also reported a four-fold variation in geographical variation between high versus low utility of cesarean delivery for birth over 2,500gm that was largely unexplained.[33] As the precise reasons for such difference have yet to be elucidated, I plan to examine factors that may be associated with such difference in the regional utility of cesarean delivery. While I speculate that this difference could be partly due to variations in maternal demographics or racial/ethnic make-up, I plan to use analytic methods such as ones presented in this work based on the causal inference framework to examine the potential exposure-outcome associations.

Further, the clinicians also might play a role. The survey study conducted through this work suggested that clinicians who primarily practice in the South were more likely to recommend cesarean delivery given the clinical scenarios described. Yet, it remains unclear what characteristics about the clinicians who practice in the South which contributes to the higher likelihood to recommend cesarean delivery. The identification of such factors might inform public health and policy making at the population level to device strategies to curtail unnecessary cesarean deliveries

Another area of research interest is the shared medical decision- making process between the patient and the obstetric provider. More specifically, I plan to explore the extent to which the observed increase in cesarean delivery might be patient-driven. For example, one speculation is that cesarean delivery by maternal request (CDMR), or primary elective cesarean delivery, contributes to the recent rise in cesarean. But the proportion of primary cesarean preformed truly without medical or obstetric indications is currently unclear. Currently, elective cesarean delivery cannot be identified directly based on International Statistical Classification of Diseases and Related Health Problems version 9 (ICD-9) codes. Thus, its precise identification can be challenging. One study has demonstrated the application of recursive partitioning algorithm to develop a hierarchy of conditions by which patients with multiple conditions could be sorted with respect to the binary outcome of labor or elective primary cesarean without

labor.[34] While this study reported 4% of deliveries underwent elective primary cesarean delivery in 1995,[34] these data were from a 15+ years earlier and prior to the current cesarean epidemic. Thus, I plan to investigate the trend of elective primary cesarean delivery in California using birth certificate data linked with hospital discharge data to explore the topic of CDMR. Additionally, as reasons for women to prefer elective cesarean delivery versus spontaneous vaginal delivery might vary widely, understanding patients' perception and preferences can help clinicians to deliver care and may guide counseling regarding risks/benefits of a trial of labor as oppose to elective surgery.

As obstetrics represents one of the most litigious medical specialties, findings from this work (through the survey study) showed that medical liability and defensive medicine is likely to be associated with increased cesarean delivery. Could the prevailing belief that "obstetricians don't get sued for doing cesarean sections; we get sued for not doing cesareans soon enough" contribute to the cesarean epidemic? I plan to investigate if and how clinicians' perception and experience of obstetric lawsuits can influence their clinical judgments and recommendations. I will also explore if the presence of non-economic damages cap as one part of tort reform may be associated with a lower likelihood to recommend cesarean. A recent survey study on clinicians who practice obstetrics in California suggests that leaders in obstetrics may potentially influence their colleagues' knowledge, attitudes, and behavior.[35] It would be interesting to investigate if continued education of providers regarding malpractice risks and defensive medicine may lead to changes in cesarean delivery.

Further, it appeared that hospital policies on practices such as attempting trial of labor after cesarean delivery can influence clinicians' delivery of care. Future studies should also examine the interplay of system infrastructure and hospital policy may influence clinicians' decision-making process. For example, would hospitals that offer obstetric care and labor management with clinical nurse midwives as part of the care delivery team have a lower likelihood of performing cesarean delivery as clinical nurse midwives have been shown to be less likely to embrace clinical interventions than obstetricians? [36,37]

Another area that desires further investigation is the association between laborists/hospitalists with increased likelihood to recommend cesarean delivery. While the implementation of laborists/hospitalists may streamline obstetric care and decrease operative interventions, it was surprising that this survey identified laborists/hospitalists as more likely to recommend cesarean delivery. As this association was not through direct observation but via hypothetical clinical scenarios, this observation should be further investigated. I propose field observations and in-depth interviews of clinicians, hospitalists, nurses, and hospital staff that make up the obstetric care team as well as the hospital administrative to identify factors and practices that may influence clinical practice and delivery of care.

6.4   Conclusion

[118]

The annual incidence rate of cesarean delivery has increased more than 60% in the past 16 year such that 1 in 3 pregnant women will deliver by cesarean today in the U.S. The current rise in cesarean delivery has a profound impact on maternal and child health as well as social and economic repercussions that are not yet well understood. Through this research, we examined how induction of labor and maternal age may play a role in cesarean delivery. Further, the decision to undergo cesarean was not limited to evolving patient demographics but that providers also played a role. This study serves as a first step towards the understanding of why cesarean delivery continues to increase in the U.S. and worldwide, but much work remains to be done. Understanding how such factors may influence the decision to recommend/perform cesarean delivery is imperative in developing strategies to curtail the current increase in cesarean delivery

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