STUDY PROTOCOL

.

Title: **Comparative Effectiveness of Treatment Options for Genital Herpes Infection in Pregnant Women to Reduce Adverse Pregnancy Outcomes**

Short Title: PCORI HSV

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ABSTRACT

Preterm delivery (PTD), together with low birthweight (LBW), is the leading cause of infant death and illness, affecting 500,000 births in the U.S. each year and presenting a significant burden to families and society with annual medical costs of more than $26 billion. Reproductive tract infections can trigger early onset of labor. Recent research has shown genital herpes infection is associated with increased risks of PTD and LBW. More importantly, treating genital herpes infection, including infection with no symptoms, using currently readily available antiviral medications can be effective in removing the risk due to the infection. Thus, early identification and treatment of genital herpes infection in pregnant women could be an effective way to prevent PTD and LBW. Currently, many pregnant women with genital herpes infection, especially those with no symptoms, choose not to treat due to (a) a lack of demonstrated benefit of the treatment and (b) general hesitance to use medications during pregnancy because of concerns of safety for the fetus. Emerging evidence of an increased risk of PTD and LBW associated with genital herpes infection, if untreated, and treatment effectiveness by anti-herpes medications has significantly changed current treatment paradigms on genital herpes infection among pregnant women. This evidence also provides new hope that effectively treating the infection among pregnant women, especially before the 3rd trimester, could lead to a new method to reduce PTD and LBW and reduce racial/ethnic disparities in the risk of PTD and LBW due to the high rate of the infection in minority groups. To further examine the effectiveness of treating genital herpes in pregnant women to reduce adverse pregnancy outcomes, we propose to conduct a prospective cohort study with a two-stage design combining the large pregnant women population (90,000) in Stage I identified through KPNC electronic medical records, with a Stage II sample to collect detailed information on history and other characteristics of genital herpes infection, compliance with prescribed treatments, and additional factors that might muddle our understanding of this issue**.**   This study will address the following: (1) Does treating genital herpes infection in pregnant women reduce the risk of PTD or LBW? (2) Does the *timing* of the treatment during pregnancy influence treatment effectiveness? (3) Do other factors influence treatment effectiveness? and (4) Does genital herpes infection in pregnancy, *if untreated*, increase the risk of PTD and LBW, compared to no genital herpes infection?   Answers to these questions will be valuable to pregnant women and clinicians, and directly address their concerns when making treatment decisions.

Figure 1. Study Population and Two-Stage Design
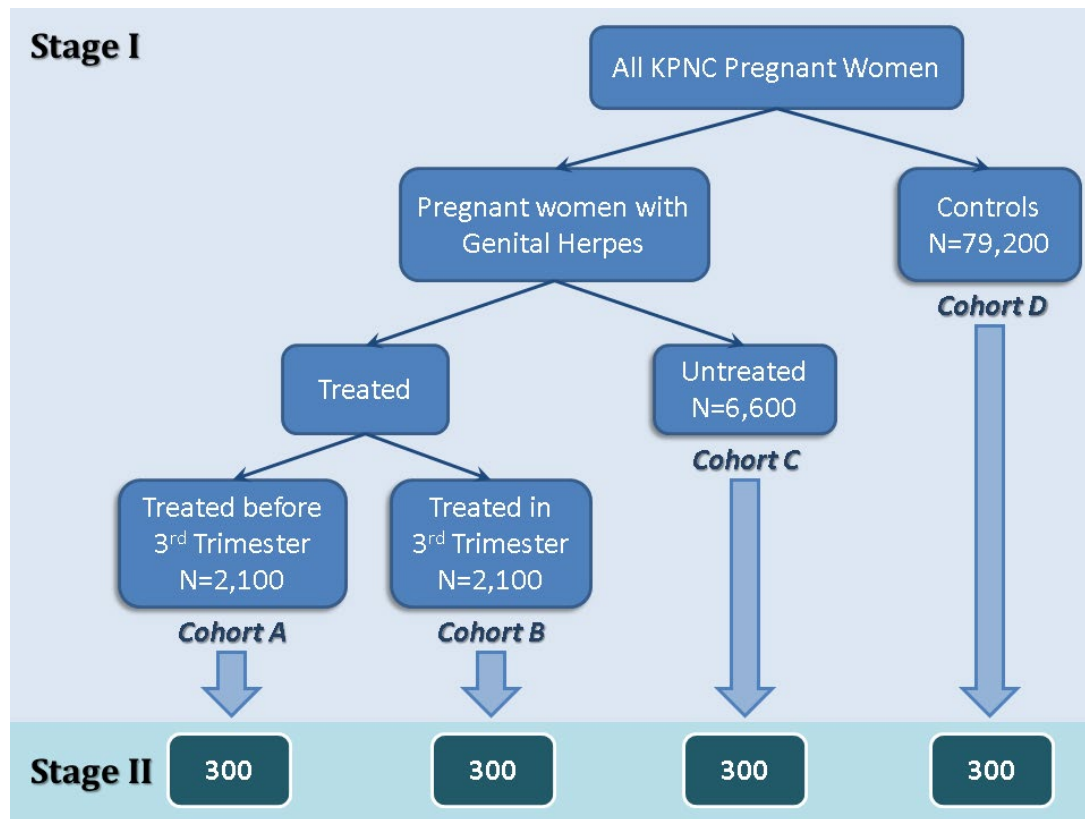
Cohort A: pregnant women with genital herpes who are treated *before* the 3rd trimester

Cohort B: pregnant women with genital herpes who are treated *after* the 3rd trimester

Cohort C: pregnant women with genital herpes, but untreated

Cohort D: pregnant women with neither genital herpes nor receiving anti-herpes medications

1   BACKGROUND INFORMATION AND RATIONALE

A.1.   Impact of preterm delivery (PTD) and low birthweight (LBW) on patients and society

PTD, defined as birth before 37 completed weeks of gestation, together with LBW, is the *leading cause* of perinatal mortality and morbidity. It accounts for about 30% of early neonatal deaths worldwide[1,2]. It is also the leading cause of congenital neurological disabilities including cerebral palsy, blindness and deafness, and learning disability in the U.S. and most developed countries[3,4]. In addition, PTD is the major cause of admission to the neonatal intensive care unit (NICU) and a significant contributor to medical expenditure for infants. In the U.S. alone, the costs associated with PTD amount to more than *$26 billion* each year, and continue to rise[5-7]. Such impact on infant health and on staggering medical and economic costs makes PTD one of the most serious challenges for clinicians and biomedical researchers today and it has become a global crisis. Leading international and national organizations including the World Health Organization (WHO), Institute of Medicine (IOM), and March of Dimes all have listed prevention and reduction of PTD as a top research priority[8-10]. One of the key reasons why PTD is a top research concern is that, despite decades of effort, there is a lack of progress in identifying modifiable risk factors, and thereby a lack of strategies to develop effective interventions to reduce PTD[10]. Consequently, the incidence of PTD has not been reduced. Currently, in the U.S., about 12% of all births (about *half a million births*) are the result of PTD each year, and many are admitted to NICUs. Such impact on patients and the staggering costs also make PTD (together with LBW) one of the top research priorities of **PCORI and AHRQ** [11].

A.2.   Genital herpes infection in relation to adverse pregnancy outcomes

Genital tract infections, including genital herpes infection, have long been suspected to be important risk factors for PTD and LBW [12-22]. The emerging literature linking placental inflammation as a common culprit and pathway triggering early labor onset resulting in PTD and LBW has provided a further supporting mechanism for genital tract infection as an important risk factors for adverse pregnancy outcomes [12-16]. Among the infectious agents, genital herpes infection has emerged as an important modifiable risk factor for adverse pregnancy outcomes, both (1) because genital herpes infection is quite prevalent among pregnant women, and (2) because treating genital herpes infection in pregnant women has been effective [23] and emerging evidence has demonstrated that treating pregnant women with genital herpes infection may lead to significant reduction of PTD and LBW [21].

Genital herpes, a sexually transmitted disease due to infection by the herpes simplex virus (HSV) [24], is prevalent among pregnant women. The prevalence based on seropositivity is estimated at around 10-15% in the U.S. although a large of proportion of those may be asymptomatic [24-30]. Genital herpes infection, if untreated during pregnancy, has been associated with increased risk of adverse pregnancy outcomes including PTD, LBW and miscarriage both for symptomatic and asymptomatic genital herpes infection [17-22,31-35]. Our preliminary results have provided additional evidence that genital herpes infection, if not treated before the 3rd trimester, is associated with a more than two-fold increased risk of **PTD** (odds ratio (OR)=**2.23**, 95% confidence interval (CI)=1.80-2.76) and a 45% increased risk of **LBW** independent of PTD: OR=**1.45**, 95%CI=1.07-1.97 (Table 1). Thus, genital herpes infection is an important contributor to adverse pregnancy outcomes due to its prevalence in pregnant women, and likely to have been overlooked in the search for risk factors and prevention strategies to reduce PTD and LBW to improve pregnancy outcomes and newborn health [21,35].

While many pregnant women who are seropositive do not have noticeable symptoms during pregnancy, the herpes virus remains in one's body (often in the nerves) _permanently_ (i.e. latent infection). Latent genital herpes infection can continue to <u>shed the virus</u> (be infectious) and <u>cause underlying inflammation</u> of the reproductive tract [36-38]. The virus can be reactivated by stress, hormonal changes and weakened immunity. These triggers are all common features of pregnancy, which provide biological plausibility for the observed association between _untreated genital herpes_ infection and an increased risk of adverse pregnancy outcomes [24,39-41]. This association between untreated genital herpes infection in pregnant women and the risk of adverse pregnancy outcomes makes genital herpes a far more serious threat to pregnancy and fetal health than the threat of vertical transmission to newborns. While vertical transmission of maternal genital herpes infection to newborns is the current clinical focus, due to a very low occurrence, there are only estimated 1,500-2,000 births per year with such vertical transmission. In contrast, there are **450,000-500,000** preterm births (and 315,000 newborns with LBW) per year in the United States, and about **68,000-76,000** PTDs could potentially be due to genital herpes infection. Most importantly, the current existing medication treatment of genital herpes is effective [23,24] and has been shown to largely mitigate the increased risk of PTD and LBW associated with genital herpes infection in pregnant women [21,35], as also presented in our preliminary results in Table 2. Thus, if these preliminary findings can be further confirmed with additional evidence from a better designed study with a two-stage design (see below), a new treatment guideline could be developed and implemented and a significant proportion of PTD and LBW (up to 76,000 per year) could be potentially prevented through effective treatment (see below).

A.3.   <u>Effective treatment of genital herpes to reduce adverse pregnancy outcomes</u>

Treating pregnant women is unique in that it impacts _both_ the mother and her developing fetus. CDC has highlighted a new initiative called "**Treating for Two**" and advocated research into medication use during pregnancy to take into account the effectiveness and risk-benefit profiles for both pregnant women and the developing fetus (http://www.cdc.gov/pregnancy/meds/treatingfortwo/) [42]. Currently, symptomatic genital herpes infection in pregnancy, usually considered more severe than asymptomatic genital herpes, is mostly treated with anti-herpes medications, such as acyclovir, that are effective in suppressing viral shedding and symptoms [23]. Acyclovir is also recommended for treating genital herpes after 36 weeks of gestation to prevent vertical transmission of maternal herpes infection to the newborn[23,24]. On the other hand, asymptomatic genital herpes before 36 weeks of gestation is often left untreated because of a lack of recognized benefits for fetal outcomes (e.g., reducing PTD and LBW). Thus, many women with mild or asymptomatic genital herpes are left untreated, and, consequently, at increased risk of PTD and LBW[17,19-22]. Untreated genital herpes infection was associated with more than twice the risk of PTD and more than 40% of increased risk of LBW, compared to controls as described above. More importantly, if treated with acyclovir, women with genital herpes had a more than 50% reduced risk of PTD (OR=**0.49,** 95%CI=0.36-0.68), and 40% reduced risk of LBW (OR=**0.60**, 95%CI=0.37-0.98) than women who were not treated (Tables 2). Our preliminary results showed that the currently recommended treatment of herpes infection with acyclovir, if expanded to treat pregnant women with genital herpes before the 3rd trimester, could largely mitigate the risk of PTD and LBW associated with genital herpes infection. This treatment effectiveness was also consistent across subtypes of PTDs.

A lack of consistency in treating genital herpes infection in pregnant women is largely due to the knowledge gap regarding (1) increased risk of PTD and LBW associated with untreated

genital herpes infection in pregnant women, and (2) evidence of treatment effectiveness in reducing PTD and LBW, in addition to preventing mother-newborn vertical transmission of herpes infection [17,19-21,35].

A.4. **Existing knowledge gaps**

Current barriers to the effective treatment of genital herpes infection in pregnant women to reduce adverse pregnancy outcomes are largely due to three important knowledge gaps: (1) the current narrow focus on the adverse effect of genital herpes infection on maternal-newborn vertical transmission only and a lack of attention to the adverse effect on other more significant outcomes such as PTD and LBW, (2) a lack of solid evidence demonstrating a significant benefit of treating genital herpes infection in pregnancy to mitigate the adverse effect, and (3) a lack of solid evidence demonstrating the benefit of treating pregnant women with asymptomatic as well as symptomatic genital herpes.

These knowledge gaps have resulted in a lack of consideration of the benefit of treating genital herpes infection in reducing the risk of PTD and LBW when treatment decisions are being made by pregnant women and their physicians. Similarly, because of the singular focus on vertical transmission to newborns and a lack of consideration of other fetal risks (e.g., PTD or LBW) in assessing treatment effectiveness, a knowledge gap also exists in understanding the effect of treatment timing, despite existing evidence that treating genital herpes infection before the 3rd trimester is more effective in reducing PTD and LBW. Thus, the current knowledge gaps in understanding the risk of untreated genital herpes and demonstrating the effectiveness of treating genital herpes infection to improve pregnancy outcomes have prevented implementing a potentially effective intervention strategy to reduce PTD and LBW through treating genital herpes infection in pregnancy. **The proposed study will provide much needed data and evidence to fill the current knowledge gaps, allowing pregnant women and their health care providers to make informed decisions on whether to treat genital herpes infection by considering the impact of both treating and <u>not</u> treating genital herpes infection in pregnancy on the health of their fetus as well as on their own health.**

B. **Significance**
B.1. **Current treatment decisional dilemma**

Treating genital herpes during pregnancy presents a unique dilemma. The decision to treat genital herpes during pregnancy is usually not only based on the risks and benefits for the pregnant woman, but more importantly, based on the risk-benefit profile for the developing fetus. While treatment for genital herpes infection during pregnancy is decided by both clinicians and pregnant women, pregnant women are predominantly concerned about their developing fetus when making treatment decisions. Because of this concern, pregnant women frequently refrain from taking medication in order to avoid perceived risk to the fetus. Thus, in comparing treatment effectiveness, the risk of choosing no treatment should be examined as one of the treatment choices or an important comparator, given that it is frequently the preferred "treatment choice" of pregnant women. <u>More than 50%</u> of women with genital herpes infection chose not to treat, based on our study population. However, opting to forego treatment could inadvertently result in harmful effects to the fetus[21]. Given the unique complexity of decision-making by pregnant women and clinicians regarding treatment in pregnancy, CDC has promoted the "**Treating for Two**" concept

to highlight the unique dilemma and consideration pregnant women face regarding treatment during pregnancy [42].

Currently, the effectiveness of treating genital herpes infection on reducing PTD or LBW has not been well understood. Thus, both pregnant women and clinicians face uncertainty about risk-benefit profiles when making decisions about treatments and their timing. Given the potential risk of PTD and LBW if genital herpes is not treated, and the significant benefit of treatment, *especially before the current recommendations of treatment during the 3rd trimester (established to reduce the risk of vertical transmission)*, a continued lack of solid evidence on treatment effectiveness would miss a valuable opportunity to reduce PTD and LBW by treating genital herpes before the 3rd trimester, leading to improved newborn health and reduction in medical costs ($26 billion each year).

This uncertainty among both pregnant women and their physicians, due to a lack of evidence-based treatment guidelines that take into account the risk-benefit balance (e.g., reducing PTD and LBW risks), is similar to the dilemma faced by pregnant women and their physicians in the context of *treating depression during pregnancy*. Like genital herpes infection, depression during pregnancy, if untreated, has been associated with increased risk of PTD and LBW. However, also like genital herpes infection, the effectiveness of treating prenatal depression on reducing adverse pregnancy outcomes has not been well documented. Thus, many women choose not to treat depression due to their aversion to taking medications in pregnancy. The proposed study is a direct analogue to the comparative effectiveness research on depression and its treatment during pregnancy in relation to PTD and LBW recently supported by PCORI.

B.2   Potential to improve decision making and clinical practice

Our proposed comparative effectiveness study will answer the following questions for pregnant women and clinicians: (1) Is there any benefit to my fetus from treating genital herpes in pregnancy? (2) Is there any risk to my fetus from not treating genital herpes, given that I have the infection? And (3) Is the treatment benefit more pronounced when starting the treatment before the 3rd trimester? Answers to these questions will allow for evidence-based decision making by pregnant women and clinicians, and also provide a scientific foundation for other stakeholders including *CDC* and the *U.S. Preventive Services Task Force* to develop recommendations and treatment guidelines for screening and treating genital herpes infection in pregnant women to be integrated into clinical practice.

B.3   Benefit to patients and their clinicians

As stated above, our proposed study will provide answers to important questions that are significant challenges faced by both pregnant women and their clinicians. When making treatment decision during pregnancy, pregnant women and their physicians face the complexity of needing to consider "Treating for Two".   The results of our study will provide important evidence to allow pregnant women and their physicians to make informed decisions based on the findings of (1) the risk of PTD and LBW if not treating genital herpes infection during pregnancy; (2) the benefit of treating the infection in reducing the risk of PTD and LBW; (3) the best timing of receiving the treatment (e.g., before the 3rd trimester).   Answers to those questions will be valuable to pregnant women and clinicians, and directly address their concerns when making treatment decisions.

B.4. <u>**Implications for reducing racial disparities in adverse pregnancy outcomes**</u>

It has long been recognized that racial disparities exists in parallel for both genital herpes infection and PTD: pregnant African-American women have almost **four times** of the prevalence of genital herpes (42% vs. 11% in Whites) and a **60%** higher PTD rate (17.1% vs. 10.8%)[43]. Thus, treating genital herpes in pregnancy could reduce the racial disparity in PTD rates, which has been very difficult to achieve due to a lack of clear understanding of the factors contributing to the racial disparity. Racial disparity in PTD may be partially explained by the difference in genital herpes infection rates.

2 STUDY OBJECTIVES

<u>**Specific Aims:**</u> In the U.S., 12% of livebirths are PTD and 8-10% are LBW, resulting in more than *$26 billion* in medical costs *annually*[10]. The impact on infant health and the staggering costs makes PTD one of the top research priorities of **PCORI, AHRQ**[11], the Institute of Medicine (**IOM)** and the World Health Organization (**WHO**)[8-10].

Genital herpes infection is prevalent, with a recent WHO estimation of 500 million people worldwide infected[44]. Treating pregnant women with genital herpes infection, especially before the 3rd trimester, has been shown to reduce the risk of PTD and LBW[21,35], thus it can be an effective intervention to reduce PTD/LBW. However, the effectiveness and benefit of treating genital herpes to reduce PTD and LBW needs to be further demonstrated in order to be incorporated into the development of treatment guidelines and clinical practice. Currently, many pregnant women choose <u>not to treat</u> genital herpes due to a general aversion to taking medications during pregnancy for the safety of their fetuses, and a lack of evidence of benefits. Paradoxically, the choice of no treatment for genital herpes may adversely impact fetal health, leading to PTD and LBW[17-22,35]. Given that pregnant women frequently prefer no treatment, studies are urgently needed to establish the risk-benefit profile between treatment and no treatment for genital herpes infection in the context of improving fetal health, including the timing of treatment (before the 3rd trimester). This study is designed to provide clear evidence of treatment effectiveness in real-world clinical practice, and risk-benefit profiles to inform both treatment decisions by pregnant women and clinicians, and evidence-based policy recommendations by CDC and the U.S. Preventive Services Task Force. ***This proposed comparative effectiveness study will address the following questions***:

1. Does treating genital herpes infection in pregnant women reduce the risk of adverse pregnancy outcomes including PTD or LBW? (<u>treated vs. untreated</u>)
2. Does the *timing* of the treatment during pregnancy influence the treatment effectiveness on reducing adverse pregnancy outcomes (PTD and LBW)? (<u>head-to-head</u> comparison of treatment timing: *before* the 3rd trimester vs. *during* the 3rd trimester)**.**
3. Do other treatment metrics, including treatment duration, dosage, and compliance, impact treatment effectiveness in reducing the risk of PTD and LBW?
4. Does treatment effectiveness vary depending on the *type* (or severity) of underlying genital herpes infection? (e.g., treating *symptomatic* genital herpes infection vs. treating *latent/asymptomatic* genital herpes)
5. Does genital herpes infection in pregnancy, *if untreated*, increase the risk of PTD and LBW, compared to no genital herpes infection? (<u>untreated vs. controls without genital herpes</u>)

In addition, this study is especially relevant in **addressing racial disparities**, given that minority pregnant women have higher rates of **both** genital herpes infection and PTD: 3 times the infection rate and 150% higher PTD rate among African-Americans compared to Whites. Thus, demonstrating the effectiveness of treating genital herpes in reducing PTD could lead to a reduction in the existing racial disparity in PTD rates.

3   STUDY PROCEDURES

3.1   Study Design

Overview of the Study Design and Approaches

We will conduct a prospective cohort study with a ***two-stage design*** based on more than 90,000 pregnant KPNC members ***in real-world clinical practice***. Due to the increased fetal risk of untreated genital herpes infection, randomizing pregnant women with the infection into treated and untreated groups presents ethical problems, thus is not feasible. Our innovative two-stage prospective cohort design, leveraging our large membership and comprehensive electronic medical record (EMR) data, is a robust alternative option for examining the comparative effectiveness of treating genital herpes infection in pregnant women to reduce PTD and LBW. This study has several unique strengths:

First, **we will conduct a KPNC member *population-based* prospective cohort study with an efficient two-stage design**. This study design is uniquely suited for KPNC's available infrastructure: an advanced and comprehensive EMR system (not claims data) and universal genital herpes screening effort during prenatal visits which provide information on the exposures (genital herpes infection and its treatment) and the outcomes (PTD and LBW) for all KPNC pregnant women and births (about *36,000 mother-birth dyads* each year). The study, which is based on the entire member population, is greatly preferable to studying hospital-based patients who are subject to selection bias due to referrals and self-selection. In addition to including all KPNC pregnant women, thereby avoiding selection bias (internal validity), Table 3 shows that KPNC members, which consist of 28-30% of the local population in the Northern California service area, are quite representative of the underlying population (i.e., providing external validity and generalizability). A *prospective cohort study* is generally a preferred study design to retrospective studies which are more subject to biases including recall bias. Finally, our unique *two-stage design* takes advantage of KPNC's comprehensive EMR system that captures exposures (genital herpes infection and anti-herpes medication use) and outcome (PTD), as well as important potential confounders for the entire pregnant women population. This EMR system allows us to have a large

| Table 3. Comparison of Characteristics for Newborns between KPNC and the General Population in the KPNC Service Regions		
Characteristics	KPNC Births (%)	All births in the KPNC Service Regions (%)
Maternal age		
< 20	12	10
20-29	43	52
30+	45	38
Maternal race/ethnicity		
Asian	15	16
African-American	10	10
Hispanic	20	25
Other	2	1
White	51	48
Unknown	2	<1
Parity		
1	41	42
2	32	31
3+	22	26
Unknown	5	<1

Stage I sample (N > 90,000 pregnant women and their births) during the study period in a cost-effective way. Using Stage II sub-samples randomly selected from each comparator in Stage I, we will be able to ascertain additional detailed characteristics of genital herpes infection and women's compliance with prescribed medications as well as additional confounders. This information will allow us to assess whether treatment effectiveness depends on differences in the characteristics of genital herpes infection, and whether any non-compliance with the prescribed treatment leads to under-estimation of the treatment effectiveness.

Second, genital herpes, especially latent/asymptomatic herpes infection, is significantly underdiagnosed in pregnant women. Thus, without a universal screening program, it is difficult to conduct a comparative effectiveness study, because a large proportion of pregnant women with genital herpes infection would go un-recognized, leading to misclassification of infection status. For example, currently, in most clinical settings only 3-5% of pregnant women are diagnosed as having genital herpes even though 10-15% is expected to have the condition. KPNC's existing *universal screening program for sexually transmitted diseases (STDs) including genital herpes,* integrated with our EMR system, make us uniquely positioned to carry out the proposed study, as we are currently able to identify 12-13% of KPNC pregnant women as having genital herpes through the screening, a more complete ascertainment.

Finally, **our selection of correct comparators will allow us to control for *confounding by indication* (genital herpes)**. Our EMR contains extensive questions on risk factors, including lifestyle factors, for all 90,000 mother-birth dyads. Through our unique two-stage study design, we will collect additional information, through interviews, on a subsample of women that will further allow us to control for additional confounders. Multiple statistical methodologies, in accordance with PCORI's methodology standards, will be employed in the analytic plan (e.g., propensity scores and instrumental variable methods) to ensure compatibility between comparison groups.

Using the KPNC EMRs, we will identify, among an expected 90,000 mother-birth dyads during the study period, those who have had genital herpes infection through various EMR databases including ICD codes (ICD9 054.1x and ICD10 A60.x), laboratory testing and viral culture, prenatal screening intake for the history of genital herpes, and medical history recorded by physicians at departments other than OBGYN departments. Currently, our preliminary data suggest that using these methods, we were able to identify about 12% pregnant women with genital herpes including asymptomatic and latent infections. This is within the expected range of the infection (10-15%) as reported in the literature. Thus, through comprehensive data sources in the KPNC EMR, we will be able to more completely identify pregnant women with genital herpes infection, a significant improvement over previous studies. Among these women with genital herpes infection, through the KPNC pharmacy

Figure 1. Study Population and Two-Stage Design
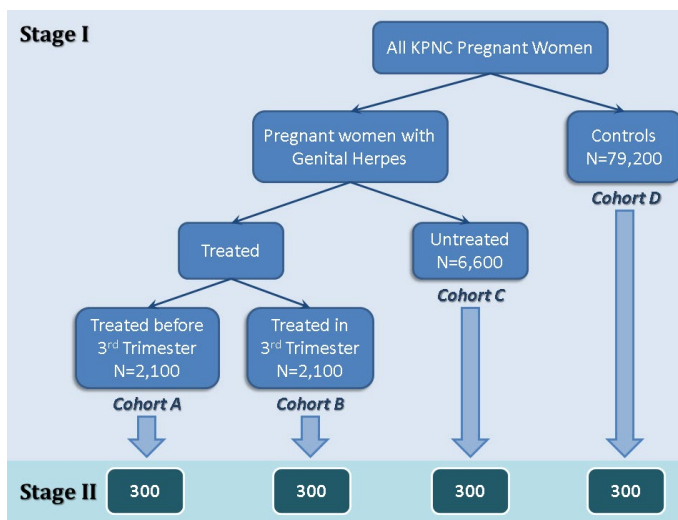
database, we will identify those who are treated with anti-herpes medications (e.g., acyclovir). Thus, four comparators in Stage I samples of all mother-birth dyads (N=90,000) will be established based on the information on genital herpes infection and its treatment and timing of the treatment (see **Figure 1**): pregnant women with genital herpes who are treated *before* the 3rd trimester (Cohort A), pregnant women with genital herpes who are treated *after* the 3rd trimester (Cohort B), women with genital herpes, but untreated (Cohort C), and women with neither genital herpes nor receiving anti-herpes medications (Cohort D). We will also randomly select 300 pregnant women from each of the four cohorts for Stage II sampling to conduct telephone interviews to ascertain more detailed medical history of genital herpes infections (for Cohorts A, B & C), compliance with prescribed medication treatment during pregnancy (Cohorts A & B), and potential confounders including risk factors for PTD and LBW (for all Cohorts). The questions in the Specific Aims will be addressed using the Cox proportional hazards regression model in analyses of PTD analysis, accommodating delayed entry into the cohort and time-dependent covariates[45-47], and logistic regression in analyses of LBW. The analysis will incorporate the large sample size from Stage I (all 90,000 births) and rich information on additional confounders and compliance from Stage II interviews. The schematic description of the two-stage study design and cohorts is presented in Figure 1.

3.2 Study Duration, Enrollment and Sites

The proposed study will be completed within three years and will include pregnant women from all KP facilities in the Northern California Region. Start-up will occur during the first three months and will involve obtaining IRB approval, hiring staff, training, conducting focus group interviews, testing data collection materials, developing and revising interview instruments (including the questionnaire) for stage-two data collection of information on confounders, establishing mechanisms for identification of eligible subjects through the EMR. Data collection (including data linkage, recruitment and conducting interviews) will be ongoing from month 4 through month 30. Ascertainment of diagnosis and treatment of genital herpes and pregnancy outcomes will continue from month 4 through month 35. Data cleaning and analysis as well as report writing will be carried out during the last 4 months. The timeline for activities involved in the study is as follows:

Months 1-3 Obtain IRB approval.
      Hire staff.
      Train interviewers.
      Set-up tracking database.
      Develop algorithm for identifying eligible participants.
      Create interview instruments including questionnaire and instructions,
      operations manual, and pilot test questionnaire.
      Conduct focus group interviews.

Months 4-30 Identify and include eligible pregnant women for the stage-one sample.
      Conduct data linkages
      Classify 90,000 women from stage-one sample into treatment categories based
      on their genital herpes infection status and treatment.
      Select a random sample of 300 from each category to form the stage-two
      subsample.
      Conduct telephone interviews with stage-two subsamples.

Months 4-35   Ascertain outcomes of interest.

Months 33-35   Clean data, conduct and complete data analyses, and prepare final report.

Months 35-36   Create materials for dissemination of the findings.
Dissemination of the findings, which will continue beyond month 36.

3.3   Study Population

3.3.1   Inclusion Criteria

1) Females $\geq$ age 18

2) Kaiser members

3) Pregnant beyond 20 weeks of gestation during the recruitment period

4) Cohort A: pregnant women with genital herpes who are treated _before_ the 3rd trimester

Cohort B: pregnant women with genital herpes who are treated _after_ the 3rd trimester

Cohort C: pregnant women with genital herpes, but untreated

Cohort D: pregnant women with neither genital herpes nor receiving anti-herpes medications

3.3.2   Exclusion Criteria

1) <18 years old

2) Not Kaiser Permanente members

3) Not pregnant.

4) Not meeting the definition for the 4 cohorts (pregnancy and HSV/treatment status).

Subjects that do not meet all of the enrollment criteria may not be enrolled.

3.3.3 Populations

Stage I population

All KPNC women aged 18 years (the minimum age required by our KPNC IRB) or older who are pregnant beyond 20 weeks of gestation during the recruitment period will be included to form the Stage I population, estimated at 90,000. These women will be assigned to one of the four cohorts based on diagnosis and treatment of genital herpes infection. Identification of genital herpes will be based on information from multiple databases captured by KPNC EMR including clinical diagnosis, laboratory testing and viral culture, prenatal screening inventory, and medical history. Treatment will be determined through prescription and dispensing of anti-herpes medications from the pharmacy data. Based on the combination of infection and treatment as well as the specific aims, we expect to establish four cohort groups.   information currently available information, we expect a total of 2,100 women with genital herpes receiving treatment before the 3rd trimester (Cohort A), 2,100 women with genital herpes receiving treatment after the 3rd trimester (Cohort B), 6,600 women with untreated genital herpes (Cohort C), and 79,200 controls with neither genital herpes nor treatment (Cohort D), as shown in Figure 1. A small adjustment may need to be made at the end of pregnancy, if the status of the infection and/or treatment has changed since the initial assignment to each comparator (e.g., from untreated to treated). Through the KPNC EMR, we will have information on genital herpes infection and treatment during pregnancy (the exposure variables), and PTD and LBW (the outcome variables) (Table 4) as well as many potential confounders (Table 5) for all 90,000 pregnant women. This large Stage I population will provide a large powerful study population to examine comparative effectiveness of genital herpes treatment in reducing adverse pregnancy outcomes, addressing the questions listed in the specific aims.

Stage II samples

A sample of 300 pregnant women from each of the four cohorts described above (Figure 1) will be randomly selected to form Stage II samples. The random selection will be spread evenly throughout the study period so that all of the estimated 90,000 participants in Stage I will have an equal chance of being selected. They will be selected after their inclusion in Stage I with known status of infection and treatment, mostly before the 3rd trimester to avoid interviewing after delivery to reduce participation and recall biases. Infection status will largely be known in the 1st or early 2nd trimester after the universal STD screening. Any change in exposure status (infection and treatment) after initial assignment will be rectified and finalized during analyses, as we have done in other similar studies with two-stage design (with different exposures in pregnancy).

Participants in Stage II samples will be interviewed to obtain more detailed information on characteristics of genital herpes infection, including history of the infection (e.g., age at initial infection, history of recurrence and treatment), whether it is a primary or latent infection, symptomatic or asymptomatic, etc. While our EMR has information on some of these characteristics of the infection, especially those ascertained through the prenatal screening tool, this Stage II interview will provide us additional characteristics of the infection to allow for assessment and thus to examine whether the treatment effectiveness varies depending on those infection characteristics (e.g., more effective for recent vs. past infection, and age at onset of initial infection, etc.).

The Stage II samples will also allow for direct ascertainment of compliance with prescribed medications. Studies based on pharmacy data alone usually have to make an assumption of 100% compliance with dispensed medications. In this study, we can directly examine the compliance and assess its potential impact on treatment effectiveness. This will be an important strength for this pharmacoepidemiologic study.

In the Stage II samples, we will conduct structured interviews to ascertain detailed information on the history of genital herpes, detailed characteristics of the infection including age at initial infection, history of recurrence and treatment, primary or latent infection, symptomatic or asymptomatic, and severity. This in-depth collection of additional information will allow for further examination of the comparability of underlying infection between treated and untreated groups, and more accurate assessment of treatment effectiveness after more thorough control for the impact of these differences in underlying infections. In addition, it will allow us to assess factors (e.g., infection characteristics) that may impact the treatment effectiveness.

Through the interview, we will also directly ascertain compliance to prescribed medications for treating genital herpes. We will make appropriate adjustment for compliance ratio in data analysis to more accurately estimate the treatment effectiveness after taking into account of non-compliance. In addition, we will also ascertain additional confounders including multivitamin intake during pregnancy and physical activity.

Informed consent will be obtained before the interview. All contact procedures will follow the standard contact and recruitment procedures as required by KPNC's IRB. All participating women will be reimbursed $40 their time and out of pocket expenses. Based on our experience with similar studies among KPNC pregnant women, a participation rate of 70-75% among eligible pregnant women can be expected. The recruitment will continue until 300 subjects from each of the four cohort groups have completed the interview.

3.4   *Comparators*

Three comparisons will be made:

1. When assessing treatment effectiveness, women with the infection who choose not to receive treatment will serve as the comparator (*untreated*). This comparator is a frequently preferred treatment option chosen by pregnant women due to their reluctance to use medications during pregnancy, based on their predominant concerns for the safety of their developing fetus as well as a lack of evidence that treating genital herpes infection is beneficial to their fetus. This comparator will also make the comparison groups more comparable by controlling for *confounding by indication*.
2. When assessing the *timing of treatment effectiveness* (before vs. after the start of the 3rd trimester), those who receive treatment after the start of (during) the 3rd trimester will be used as the comparator. This comparator group will be comparable to those who receive treatment before the 3rd trimester, except for the timing of their treatment. Using this comparator will allow a *head-to-head comparison between the timing of the treatment (before vs. during the 3rd trimester)*
3. When assessing the effect of choosing not to treat during pregnancy, women without an underlying genital herpes infection or receipt of any treatment will serve as the comparator (*normal controls*). This comparison will provide evidence of the increased risk of PTD and

LBW if genital herpes infection is <u>not</u> treated during pregnancy and will allow for a comprehensive assessment of comparative effectiveness of treating genital herpes.

4 STATISTICAL METHODS

4.1 General Approach

The study design can be characterized as two-stage, with the first stage sample consisting of 90,000 pregnant women, each of whom will be classified into the four primary exposure categories defined by genital herpes and treatment status (Figure 1). In addition to exposure status, extensive potential confounders as described above (Table 5) will also be measured on the Stage I sample of 90,000 subjects. At the second stage, a random sample of 300 women will be selected within each of the four exposure categories (total N=1,200), for detailed history and characteristics of genital herpes infection, compliance to prescribed medications, and additional confounder/effect modifier assessment prior to delivery. Unlike typical applications of two-stage sampling in epidemiologic studies, where the Stage II sample is selected on the basis of both exposure (or exposure surrogate) and outcome (i.e. two stage case-control sampling), only exposure status will be known at the time of Stage II sampling to keep the nature of a cohort study design (*covariate assessment prior to pregnancy outcome assessment*). However, pregnancy outcomes of interest will eventually be measured on all 90,000 Stage I units, and *we will utilize all available information in both Stage I and Stage II samples in estimation of associations of interest.* Study Aims will be addressed using logistic regression (LBW) and Cox proportional hazards regression models (PTD) [48,49].

4.2 Estimation

Regression parameter estimates and associated standard errors will be obtained via semiparametric maximum likelihood (SMLE) [50] utilizing exposure, outcome, and confounder measurements on all 90,000 Stage I units in addition to the additional confounder/effect modifier measurements on the subset sample at Stage II. Thus, our study design can be characterized as a missing data problem, with Stage II covariates only assessed on a subset of the full cohort. Scott and Wild presented a unified method for fitting arbitrary regression models to a large class of missing data and/or response selective sampling problems. These applications are generally characterized as: 1) a set of easily-obtainable variables are measured on a sample of N individuals (Stage I); one or more of these variables are to be used as explanatory in the regression model (e.g. herpes and treatment status), or are informative surrogates for "expensive" variables to be measured on a subsample; 2) the response variable is obtained for all N individuals (e.g. LBW and PTD status) or a subset; and, 3) a set of "expensive" explanatory variables (e.g. details in genital herpes history and characteristic, compliance to treatment, and potential confounders/effect modifiers) are measured on a subsample (Stage II). Parameter estimation is by maximizing the profile likelihood (R software available from the authors), with the estimator shown to be consistent and have full semiparametric efficiency[50] .

Aim 1. Does treating genital herpes infection in pregnant women reduce the risk of adverse pregnancy outcomes including PTD or LBW? (treated vs. untreated)

Point and interval estimates of the hazard ratio for PTD associated with treated genital herpes vs. not treated infection, will be calculated as described above, using Cox regression (Cohort A + B vs. C). In determining potential confounders in our regression models, we will first examine

risk factors that may be plausibly linked to infection and PTD. Inclusion or exclusion of potential confounding factors in our final regression models will be evaluated based on comparison of the regression coefficient associated with the contrast of interest (treated vs. untreated) both adjusted and unadjusted for the potential confounder under consideration (i.e. inclusion if regression coefficient changes by 10% or more). The change-in-estimate approach to confounder selection performs well with regard to power, bias, mean squared error and confidence interval coverage for the primary factor of interest[45]. Continuous potential confounders will first be categorized either as quartiles, or into clinically relevant categories (e.g. BMI classification, amount of cigarette smoked or alcohol intake). The shape of the association/pattern of regression coefficients across increasing levels of the categorized covariate, of interest in their own right, will serve as a guide in the approach to modeling the variable as a continuous independent variable. A simple linear term may be appropriate, but higher order polynomial terms may be necessary to capture any non-linearity in association. Departures from model assumptions will be assessed via diagnostic plots of weighted residuals and tests for interaction between exposure and time (gestational age).

*Analyses of LBW as the outcome will parallel those described above for PTD, but logistic regression techniques will be used rather than Cox regression, in **Aims 1 – 5.***

Aim 2. Does the timing of the treatment during pregnancy influence the treatment effectiveness on reducing adverse pregnancy outcomes (PTD and LBW)? (A head-to-head comparison of treatment timing: before the 3rd trimester vs. during the 3rd trimester).

Point and interval estimates of the relative hazards of PTD associated with first treatment during pregnancy before and first treatment during the 3rd trimester will be obtained (Cohort A vs. B) by extending the Aim 1 regression model to capture treatment timing.   Parameter estimation, the approach to inclusion of potential confounders, modeling of continuous covariates, and model diagnostics are as described above for Aim 1 analyses. Treatment will be handled as a time-varying covariate for proper classification of exposure status in each risk set for the Cox regression (three levels: no treatment, first treatment < 3rd trimester, treatment in 3rd trimester).   Significance of the difference between strength of association across the two treatment timing categories will be assessed via a Wald test.

Aim 3. Do other treatment metrics, including treatment duration, dosage, and compliance, impact treatment effectiveness in reducing PTD and LBW risk?

Metrics of treatment exposure of interest will be treated as time-dependent covariates in Cox regression analyses to account for changes in exposure status during follow-up, including cumulative duration (categorized as no use, 1-5 days, 6-10 days, 11-30 days, and > 30 days) based on clinical prescription patterns, and cumulative dose (categorized as no use, 1-4,800mg, 4,801-12,000mg, and >12,000 mg) also based on current clinical prescription patterns. In addition to examining these metrics in relation to pregnancy outcomes during the entire pregnancy, we will also assess trimester-specific measures of treatment duration and dose.

Aim 4. Does treatment effectiveness vary depending on the type (or severity) of underlying genital herpes infection? (e.g. treating symptomatic genital herpes infection vs. treating latent/asymptomatic genital herpes)

Analyses will examine potential heterogeneity in association between treatment and PTD across infection characteristics via the inclusion of appropriate cross-product terms and a likelihood ratio test, and point and interval estimates of association at each level of the effect modifier will be obtained via appropriate transformed linear combinations of regression parameter estimates.

Aim 5. Does genital herpes infection in pregnancy, if untreated, increase the risk of PTD and LBW, compared to no genital herpes infection? (untreated vs. controls without genital herpes) .
Point and interval estimates of the hazard ratio for PTD associated with untreated genital herpes, vs. no infection, will be calculated as described above, using Cox regression (Cohort C vs. D). The approach to inclusion of potential confounders, modeling continuous covariates, and model diagnostics is as described above.

4.3 Propensity Score (PS) Analysis

In addition to the conventional analyses outlined above, we will next apply the PS analysis method to reduce or correct for any selection bias and measured confounders. PS analysis uses information about all measured covariates to balance unobserved factors between treatment groups. Propensity score analysis can reduce over 90% of selection bias associated with unobserved factors[46]. Multivariable logistic regression for dichotomous outcomes will be used to calculate a propensity score, i.e., the probability of receiving treatment vs no treatment, as a function of all known factors that might affect the treatment outcome. The resulting probabilities (propensity scores) will be used to analyze the extent of overlap on all covariates, using graphical methods and frequency distributions. We will next employ a PS analysis using stratified Cox proportional hazards models in analyses of PTD, and conditional logistic regression in analyses of LBW, with stratification on deciles of propensity score, in the examination of each exposure metric with respect to pregnancy outcomes[47,51]. We anticipate that results from the PS and the conventional analyses will be similar given our prior experience from similar analyses of large databases, and because of our ability to account for most of the important known confounders in our conventional models. However, if we find that results differ, we will report the PS analysis results as our main findings due to the correction for selection bias in our measured characteristics.

4.4 Instrumental Variable Analysis

We will also use instrumental variable analysis (IVA) methods to assess the sensitivity of our results to unmeasured confounders. IVA is an alternative method for reducing selection bias that addresses both the effects of unobservable characteristics and the issue of dual causality between the choice of a treatment and the health outcome [52-54]. IVA methodology uses an indirect attribute that is closely associated with the type of treatment a patient receives, recreating randomized treatment assignment from a trial. This type of analysis requires identifying at least one factor that significantly affects treatment choice but is unrelated to the health outcome. IVA can be used to measure treatment effects independent of selection bias, which helps inform broad policy decisions, but it is limited in guiding clinical decisions for specific population subgroups [55]. We will initially consider physician specific prescribing preference, as measured in the KPNC pharmacy database, as the instrument [56]. It is necessary to consider how the characteristics of patients vary with respect to the instrument used when interpreting results of an IVA [52]. Our access to a rich amount of data will permit a thorough evaluation of the validity of our candidate instruments. If our selected instrument appears to be valid, and we find that IVA yields different results compared with PS analysis, we will have confirmed the likelihood of unmeasured confounding in our PS analysis. Given the extensive control for confounding using our clinical data, and the large sample sizes, we anticipate PS analysis and IVA to yield similar results. However, if IVA yields results that vary from PS results, and our instruments are reasonably valid, it suggests the presence of unmeasured confounders in our treatment comparisons in the PS and traditional analyses. Thus, it

will inform in the interpretation of findings with respect to possible impact of unmeasured confounders.

While we expect no or very little missing data on treatment exposure, pregnancy outcomes and potential confounders, we will assess all variables under study for missingness. If necessary, we will utilize multiple imputation techniques using multivariate sequential regression [57].

4.5 Sample Size and Statistical Power

Given the lack of established methods for power calculations for the SMLE in our two-stage sampling scheme, we provided minimum detectable effect estimates using the results from a simulation study that we have conducted. The study provides information on the expected efficiency gains of the two-stage SMLE, relative to a standard regression analysis of the Stage II sub-sample only (with complete data on all confounders in addition to exposure and PTD/LBW status). For the purposes of our simulation study, we made a few simplifying assumptions. We assumed three exposure categories: no infection, infection with treatment, infection without treatment, with population prevalence set at 87%, 8% and 5% (similar to preliminary data), and outcome relative risks of 1.0 (ref), 1.5 and 2.0, respectively. We assumed one binary confounder measured in the Stage II sub-sample with varying prevalence across exposure categories and strength of association with outcome. The pregnancy outcome incidence was assumed at 8% (among those unexposed to infection). The Stage I sample size was 90,000, with random selection of 300 in each of the two infection/treatment categories. Relative efficiencies [i.e. Var(Stage II MLE) / Var(SMLE)] ranged from 4 to 82 across the scenarios, demonstrating substantial gains by utilizing exposure and outcome information in the full sample of 90,000.

As an approximation to the impact of utilizing exposure and outcome information on 90,000 Stage I women in combination with the Stage II sub-sample of 1200 women, we took an "effective sample size" approach, and assumed the worst case among the simulation scenarios considered, where the relative efficiency of the SMLE was approximately 4.0. Thus, rather than basing power calculations on the Stage II sample size of 600 (300 in each group, for a two-group contrast), we based them on 2400 (i.e. 4.0 * 300; 1,200 in each cohort category). We acknowledge that estimated gains in efficiency are based on results from a simulation study and may vary in actual analysis.

Power calculations are based on the likelihood ratio test in the context of a Cox proportional hazards regression analysis for PTD, and a logistic regression analysis for LBW, as presented by Self [58] and as implemented in the software package EGRET[59]. Given previous experience[60-63], we expect negligible loss to follow-up (< 0.20%), a rate of PTD ranging from 8% - 12%[64], and LBW ranging from 8% to 10% [65]. Each primary contrast of interest in analyses addressing **Aims 1, 2 and 5** can be characterized as a comparison of two groups of women with respect to risk of PTD and LBW. Minimum (maximum, for protective effects) detectable associations are of modest to moderate strength (Table 6)*. The proposed study will have more than sufficient power to detect the associations observed in our preliminary studies. Relevant to **Aim 3**, we present the maximum (protective effects assumed) detectable pattern of hazard ratios (HR) across cumulative treatment duration categories (no treatment, 1 – 10 days (45% among treated), > 10 days (55% among treated)). For the purpose of detectable effect calculations, we assume a graded, linear trend in (log) hazard/odds ratios across duration categories, a two-sided test for trend and a significance level of .05. We have sufficient power (.80) to detect a pattern of PTD HRs of 1.0 (ref), .82, and .67 associated with no treatment, 1-10 days and >10 days, respectively, assuming the worst case

scenario of expected 8% PTD rate. Similarly, we have sufficient power (.80) to detect a pattern of

Table 6. Minimum (maximum for protective scenarios) detectable hazard ratios (HR) for preterm delivery and detectable odds ratios (OR) for low birthweight in pair-wise comparisons of genital herpes exposure/treatment categories; two-sided test, significance level (α) = .05, power (1-β) =.80.				
	Preterm Delivery (HR)		Low Birthweight (OR)	
Contrast	Rate = 8%	Rate = 11%	Rate = 8%	Rate = 10%
Treated infection vs. untreated infection (**Aim 1**; A+ B vs. C)	.71	.75	.70	.72
Treated < 3rd trimester vs.3rd trimester (**Aim 2**, A vs. B)	.66	.71	.65	.68
Untreated infection vs. no infection (**Aim 5**, C vs. D)	1.51	1.40	1.54	1.47

odds ratios ORs of 1.0 (ref), .81, and .66 associated with no treatment, 1-10 days and >10 days, respectively, assuming the worst case scenario of expected 8% LBW rate.

5. STUDY ADMINISTRATION

5.1 Data Collection and Management

5.1.1. Data sources

KPNC EMRs and other clinical databases will be used to identify all women who meet our recruitment criteria and to include them in the study. Approximately 90,000 pregnant KPNC members who are 18 years or older, will be identified and recruited to the study. All eligible pregnant women will be classified into one of the categories based on the diagnosis and treatment of their genital herpes infection during pregnancy. For each of these four categories, 300 women (for a total of 1,200) will be randomly selected and recruited to conduct telephone interviews to collect information on confounders and effect modifiers.

Birth outcomes for all participants will be ascertained through the KPNC EMR and other clinical databases

5.2 Confidentiality

All standard procedures following HIPAA requirements will be implemented for this study. Names and other identifying information on study subjects will be obtained for record-keeping purposes only, and no individuals will be identified in any reports from this study. Only persons directly involved in the study will have access to data identifying individual subjects. Records and forms with identifying information will be kept in locked drawers when not in use. Access to computerized information will require simultaneous knowledge of the database, language, file names, and multiple passwords.

5.3 Risks and Benefits

5.3.1 Potential and anticipated risks to research participants.

For participants in the telephone interview (stage-two study) and the focus groups, the risk of participating in this study is minimal. Women who had adverse pregnancy outcomes in the past may become upset when recalling these events. All interviewers will be trained on how to appropriately handle these situations in case they arise. Our experience also indicates that some women find it therapeutic to discuss these events.

5.3.2 Risk Minimization

No invasive procedures are involved in the study protocol, only interviews.   All interviewers have had experience interviewing pregnant women and are specifically trained for these types of studies. All of the women contacted for a telephone interview will have received a letter informing them about the study.

5.3.3. Benefits to participants and to society

No direct benefit is expected to participants resulting from participation in the study. Findings from the study in a publishable format will be made available to all participants who request them. The potential benefit to society is to enhance the understanding of the risk-benefit profiles of various treatment options for genital herpes infection during pregnancy to prevent preterm delivery and low birthweight.   Because of the prevalence of genital herpes among pregnant women, findings from the proposed study will have a significant public health impact. Correct treatment choices may lead to reduction of PTD and LBW which remain top public health challenges globally.

5.3.4. How potential risks are justified by potential benefits

There is only minimal risk to participants. Potential benefits to society described above can be significant.

5.4 Recruitment Strategy

The chiefs and other obstetricians in the departments of Obstetrics and Gynecology at participating KPNC facilities will be informed of the nature of the study and permission to contact their patients (if selected) in stage-two will be obtained from those departments. Informational posters will be sent to all OBGYN departments for display and OBGYNS will inform all pregnant women about our study during their prenatal visits. For stage-two samples, after they are identified, a letter explaining the study and requesting their participation will be sent to women. A postage-paid and self-addressed refusal card will be included in the letter for participants who choose to refuse. For those who do not return refusal postcards, interviewers will contact women to answer their questions and ascertain their willingness to participate in the study.

5.5 Informed Consent and HIPAA Authorization

5.5.1 Waiver of Consent FOR STAGE ONE SAMPLE

A waiver of consent has been granted for the stage-one sample, since the stage-one sample involves data only, there are no risks associated with recruiting subjects, although there is always a small chance of the loss of confidentiality during data analyses. Since there is no direct contact of patients, we do not anticipate an adverse effect on their rights or welfare.

5.5.2 Waiver of Consent FOR STAGE TWO SAMPLE

A waiver of the requirement for participants to sign a written consent form has been granted for the stage-two telephone interviews. As has been used in other studies of telephone interviews, for those who will be contacted by telephone for an interview, the consent process will be conducted over the phone. Verbal Informed consent will be obtained before each interview and no interviews will be conducted without consent for participation. Interviewers who are employees of Division of Research and who have had extensive experience conducting such interviews will obtain the consent. There is no more than minimal risk to participants and there are no other procedures involved beyond an interview.

5.5.3 Waiver of HIPAA Authorization

A waiver of HIPAA Authorization has been granted for both stages of the study. The stage-one sample will be data only. There will be no direct contact with participants. For the stage-one sample of 90,000 women, we will need to access PHI to identify maternal pregnancy and infection status. The medical record number will be used to link the mother-infant pairs and other datasets on pregnancy, maternal, and birth outcomes. Stage-two will involve telephone interviews for which we are requesting a waiver of written consent for participation (verbal consent will be obtained).

Data with identifiable information will be password protected by the programmer. An additional dataset will be created and used by the programmer which will not include any PHI. Data will not be shared outside of KPNC.

No PHI data will be disclosed to outside investigators. We will provide assurance of the confidentiality and proper procedures for protecting PHI as set forth by the KPNC IRB.

Personal identifiers will be destroyed at the end of study according to IRB requirements.

5.6 Payment to Subjects

After the interview, a thank-you letter with a check for $40 will be sent to each participant for their time and out-of-pocket expenses.

6. DISSEMINATION

There is great potential for dissemination of the results of our research in other settings. Our Stakeholder Advisory Board (SAB) members will be valuable facilitators in our dissemination and implementation of study findings. Our collaboration with American Sexual Health Association (ASHA) and The National Coalition of STD Directors (NCSD) will enable us to disseminate study findings to a broader audience through the use of their extensive national networks.

The ASHA specializes in communications outreach to the public, patients, press, providers, and policy makers by developing and delivering sensitive health information. They have a long history of providing national leadership in disseminating research findings and developing tools and education resources to help providers meet the sexual health needs of their patients. They provide providers with continuing education (CME/CE), screening guidelines for sexually transmitted infections including herpes and resources for patient education. In addition to providing education, ASHA has alliances with multiple other national organizations including the National Coalition of Sexual Health charged with encouraging and enabling health care providers and patients to have conversations about sexual health including sexually transmitted diseases (STDs), and to utilize evidence-based sexual health services including treatment for STDs. ASHA also has a policy initiative and has been successful in obtaining bipartisan support for sexually transmitted infection (STI) programs and continues to educate policy makers about the economic, social, and public health benefits of appropriate STI policy.

Situated in the nation's capital, the NCSD works toward the development of systemic change and promotion of national awareness in the policies that govern STDs including preventing STDs and reducing their adverse consequences such as adverse pregnancy outcomes among women with genital herpes infection. As the only national organization with a constituency that provides frontline STD programs and services, NCSD uses its experiences to enhance reform in the policy making process. NCSD proactively seeks to increase resources for core STD programs and services. NCSD also responds swiftly to efforts to curtail access to services and sexual health information. Their objectives of creating a full partnership among STD project areas directly funded by the Centers for Disease Control and Prevention, state and local public health agencies, the Federal Government and private agencies to effectively prevent and control STDs in the US and its territories; providing a conduit of communication and technology transfer among and between STD Directors nationally; providing a forum for technical assistance and dissemination of information about effective STD prevention and control programs among members of the Coalition; educating federal, state and local policy makers about issues relevant to the control and prevention of STDs; networking or affiliating with appropriate organizations working toward comparable goals; and promoting adequate and efficient allocation of resources to the prevention and control of STDs will all be valuable in dissemination of our study results.

There is also great potential for the implementation of the findings of this research in other settings. If antiviral medications are found to decrease the risk of PTD associated with genital herpes, ascertainment of a woman's history of STIs by a practitioner and prescribing antiviral medications during pregnancy is a relatively easy intervention to implement in any perinatal health care setting.

Drs. Flanagan (OBGYN) and Garzaro (Infectious Disease) as leaders in their respective specialties at KPNC, will work with KPNC leadership to implement the findings from this study into practice throughout the Kaiser Permanente Northern California Region. They will also work with

health care providers and educators to disseminate the findings among both providers and patients, and encourage providing genital herpes treatment among pregnant women based on findings from this study.

Possible barriers to disseminating and implementing the results of this research in other settings.

Our SAB members, the ASHA and NCSD, have been very successful at disseminating evidence-based findings to healthcare providers. They are experienced in the creation of continuing education programs for physicians to the development of resources such as toolkits, videos and apps geared toward providers to ensure that providers can offer the best sexual health care to their patients. Thus, we don't foresee any specific barriers in the dissemination. If unanticipated barriers arise, we will work with our SAB that includes providers, patients and the ASHA and NCSD to brainstorm additional methods for disseminating our study results to other providers and research settings.

We will also work with Stakeholders including Drs. Flanagan and Garzaro and directors and staff members from the ASHA and NCSD to identify and resolve any potential barriers. Important findings from this study that are to be published, especially in a high impact journal, will likely lead to revision of recommendations regarding genital herpes screening and treatment in pregnant women by policy makers (e.g., CDC) and professional societies (e.g., American College of Obstetrics and Gynecology), which will further facilitate dissemination of our findings.

Making study results available to study participants after completion of analyses.

We will work with ASHA and NCSD to develop a brief summary of the results from our study for the general public, including our participants. Both of these organizations have a long-history of developing educational materials for patients and the general public and we will use their expertise to guide development of the materials for dissemination to our study participants. The summary will then be sent to our participants according to their preference (US postal service, email, link to their websites (http://www.ncsddc.org, ashasexualhealth.org, iwannaknow.org).

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