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ASSISTED REPRODUCTION TECHNOLOGIES

Hypertensive disorders of pregnancy and infertility treatment: a population-based survey among United States women

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Abstract

Purpose To explore associations between infertility treatment and hypertensive disorders of pregnancy.

Methods We collated multi-year as well as multi-state data from a national representative survey examining the association between self-reported infertility treatment (i.e., medication, intrauterine insemination, or assisted reproductive technology) and hypertensive disorders of pregnancy (i.e., high blood pressure, pregnancy-induced hypertension (PIH), preeclampsia, and toxemia). Data were analyzed using logistic regression. A total of 21,884 women in the United States (U.S.), from the Centers for Disease Control and Prevention's (CDC) Pregnancy Risk Assessment Monitoring System (PRAMS) survey (2009–2015), participated in the study.

Results In our analysis, 12.91% women reported a history of infertility treatment and 15.19% reported a history of hypertensive disorder of pregnancy. Compared with women who had never had infertility treatment, women who reported infertility treatment had 1.18 (adjusted OR, 95% confidence interval (CI) 1.05, 1.33) higher odds of reporting hypertensive disorder of pregnancy. Neither types of infertility treatment nor proximity of treatment to pregnancy were independently associated with hypertensive disorder of pregnancy.

Conclusions Our results suggest that among U.S. women, the treatment of infertility may be associated with hypertension disorder of pregnancy regardless of type of treatment.

Keywords Infertility · Cardiovascular disease · Hypertension · Reproductive health · PRAMS

Introduction

In the United States (U.S.), approximately 11–16% percent of U.S. women report impaired fecundity [1, 2]. Infertility, defined as the failure to achieve a successful pregnancy after 12 months of unprotected intercourse, is a public health issue associated with chronic diseases including cancer, diabetes, and cardiovascular disease [3–7]. In addition, while data are limited, infertility status and infertility treatment may function independently as risk factors for hypertensive disorders of pregnancy (HDP) [8]. Infertility treatment itself has also been linked to HDP including preeclampsia, a leading cause of maternal and fetal morbidity worldwide [8, 9].

In patients undergoing infertility treatment, it has been previously reported that the increased risk is mostly due to the higher frequency of multifetal gestation [10]. However, risk remains increased even in singleton gestations for those undergoing in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI), especially in women aged 40 years and older [10–14]. While animal models and studies in human tissue provide plausible mechanisms for this association, there is not a clear consensus on pathophysiology [8].

Recently, studies using large population databases including data from the Framingham Heart Study, the Nurses' Health Study II, the National Health and Nutrition Examination Survey (NHANES), and a nationwide report

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of U.S. insurance claims have captured an increase in both the presence of cardiovascular risk factors and the incidence of chronic disease in infertile women [4, 6, 15, 16]. Notably, there are fewer of these large population studies investigating pregnancy-specific health outcomes. A systematic review and subsequent meta-analysis of assisted reproductive technology (ART) and HDP included heterogeneous studies, many of which were smaller and without sufficient control for maternal age, parity, BMI, and multiple gestation [17, 18]. Additionally, many of these studies were restricted to singleton vs nonsingleton pregnancies or invasive vs non-invasive assisted reproductive technologies [17, 18]. Since HDP functions as a risk factor for later cardiovascular health, a leading cause of mortality, identifying risk factors is crucial for individual and public health [19, 20]. In this study, we examined the association of self-reported HDP and infertility treatment using a population-based survey with a national representative sample of women controlling for important confounders inclusive of all gestational orders and types of infertility treatments.

Material and methods

Patients

We analyzed data from 2009 to 2015 Centers for Disease Control and Prevention's (CDC) Pregnancy Risk Assessment Monitoring System (PRAMS) survey, which utilizes a core questionnaire in all states to identify high-risk groups of women and infants. Surveillance represents approximately 83% of all U.S. births. States with a 65% (2009–2011), 60% (2012–2014), and 55% (2015) response rate were included in the analysis [21]. Additional data from 2016 and 2017 are available from the CDC; however, the Phase 8 (2016 and beyond) revised questionnaire had substantive changes that were too dissimilar to be combined. Analysis weights were derived to account for nonresponse, sampling, and non-coverage issues with data collection in an effort to ensure the sample that reflects the targeted population [22]. States can also utilize a standard questionnaire to include specific yet uniform questions of further interest regarding topics affecting women in their state. In particular, 38 states included questions regarding HDP while ten states included questions regarding history of infertility treatment. Our analytic sample included women who completed the core questionnaire including hypertension-related questions as well as the additional infertility-related questions. Data were representative across nine states including Delaware, Illinois, Massachusetts, Maryland, Michigan, Missouri, Nebraska, New York, and Utah.

Outcomes

Respondents were determined to have a hypertensive disorder of pregnancy if they responded "Yes" to "high blood pressure, hypertension (including pregnancy-induced hypertension [PIH]), preeclampsia, or toxemia" in response to the following question, "Did you have any of the following problems during *your most recent* pregnancy?" If they responded "No," they were considered to not have the outcome of hypertensive disorder of pregnancy.

Infertility treatment was defined based on how women responded to the question, "Did you take any fertility drugs or receive any medical procedures from a doctor, nurse, or other health care worker to help you get pregnant with your new baby? This may include infertility treatments such as fertility-enhancing drugs or assisted reproductive technology." If they answered "Yes," they were coded as recipients of infertility treatment; otherwise, they were considered non-recipients of infertility treatment prior to this most recent pregnancy if they responded "No."

Covariates were considered based on known associations of behavior and health variables with infertility and cardiovascular health based on prior literature [23]. Chronic hypertension, a known risk factor for HDP, could not be controlled for due to the wording of the survey questionnaire. Age was stratified as < 20, 20–29, 30–34, 35–39, and 40+ years. Races and ethnicities were categorized in PRAMS as non-Hispanic white, non-Hispanic black, Hispanic, or other. Maternal education achievement was defined in three groups: greater than 12 years, less than 12 years, or 12 years. Household income was defined as less than or greater than $52,000. For insurance type, respondents reported having private insurance, Medicaid or another governmental insurance (including Medicare, military health insurance, state-sponsored, Indian Health Service, other government, single-service health plan), or no health insurance. A diagnosis of diabetes prior to pregnancy (including Type 1 or Type 2) was a binary variable. Obstetric history including number of previous live births (0, 1, 2, 3, or more) and plurality (singleton, twin gestation, or other) were also grouped, accordingly.

We examined smoking history and BMI. Smoking status was binary, wherein respondents were considered ever smokers if they responded yes to any consumption prior to most recent pregnancy. BMI was calculated by dividing weight (kg) by squared height (m^2), and coded into four categories: < 18.5, 18.5–24.9, 25–29.9, and greater than 30 kg/m^2.

This project underwent review and was approved by CDC's Institutional Review Board. The study procedures were exempt from review and thus no additional approval was required from Institutional Review Board (IRB) at authors' respective institutions.

Statistics

We conducted all analyses in SAS version 9.4, using survey commands and survey weights developed by CDC PRAMS to account for nonresponse, non-coverage, and sampling differences within the sample.

Two logistic regression models were fit to assess the association between infertility treatment and reported hypertension in pregnancy: an unadjusted model and an adjusted model, which included reported use of fertility treatment prior to pregnancy, maternal age, maternal race/ethnicity, maternal education achievement, pre-pregnancy BMI, insurance type prior to pregnancy, parity, birth plurality, and tobacco use prior to pregnancy.

Given that studies have postulated that the association with infertility and hypertensive disorders of pregnancy is primarily conferred with the use of IVF/ICSI, we conducted a sensitivity analysis to determine if the type of infertility treatment differentially contributed to the association with hypertension in pregnancy [11, 24]. Since use of fertility treatment during the month preceding pregnancy may confer different risks for hypertension compared with general use of infertility treatment, we conducted a sensitivity analysis to determine if the association with HDP differed depending on when treated. We also conducted additional sensitivity analyses evaluating only low-risk women (e.g., normal BMI, singleton gestation). Finally, backwards selection was performed with all variables included in the model and the effects removed successfully until the most parsimonious model was created.

Results

By collating multi-year as well as multi-state data, the analytic sample included 21,884 respondents who had a recent live birth, weighted to be representative of the U.S. population (Table 1). Women who used fertility services (12.91% of respondents) were more likely to be older, non-Hispanic white, and nonsmokers. They were more likely to have higher educational attainment, higher household income, private insurance, lower parity, lower BMI, and a history of recent multifetal gestation.

Approximately 15% of respondents reported a history of hypertensive disorder of pregnancy. Women who reported age ≥ 35 years, non-Hispanic black ethnicity, greater years of education, higher pre-pregnancy BMI, no insurance prior to pregnancy, nulliparity, tobacco use 3 months prior to pregnancy, and increased birth plurality reported higher rates of hypertension disorders of pregnancy. There was no difference in hypertension based on income or in those with a history of type 2 diabetes mellitus. Women with a history of infertility treatment were more likely to report a hypertensive disorder of pregnancy ($n = 595$; 21.23%) than those that did not ($n = 2540$; 13.49%; unadjusted OR 1.73, 95% CI 1.56–1.91).

After adjustment for potential confounders (maternal age, maternal race/ethnicity, maternal education achievement, pre-pregnancy BMI, insurance type prior to pregnancy, parity, birth plurality, and tobacco use prior to pregnancy), women reporting use of infertility treatment for their most recent pregnancy were more likely to report a hypertensive disorder during their most recent pregnancy as shown in Table 2 (adjusted OR 1.18, 95% CI 1.05–1.33). Types of infertility treatment used (medication, intrauterine insemination, assisted reproductive technology, or other) were not independently associated with a hypertensive disorder of pregnancy ($p = 0.3623$). Additionally, the subset of patients who reported needing infertility treatment but ultimately conceived spontaneously ($n = 122$) were analyzed (8.79% vs 7.94% in the HDP group). Specifically, whether fertility treatment was used at any time prior to the recent pregnancy versus being used the month just prior to pregnancy was not independently associated with a hypertension disorder of pregnancy ($p = 0.6351$).

In data not shown, we completed a sensitivity analysis excluding all women who did not fall within the 20–29-year age group. We found that among this age group, women who reported use of infertility treatment remained more likely to report a hypertensive disorder of pregnancy (aOR 1.27, 95% CI 1.03–1.57). We also conducted additional sensitivity analyses evaluating only low-risk women (e.g., normal BMI, singleton gestation) without any changes in our demonstrated associations between HDP and infertility treatment (e.g., normal BMI (aOR 1.36, 95% CI 1.12–1.64), singleton gestation (aOR 1.22, 95% CI 1.07–1.39). When looking among purely nulliparous women, the relationship is blunted but still present (aOR 1.17, 95% CI 1.00–1.37). Notably, utilizing backwards selection to create a parsimonious model, all variables except for insurance status remained in the model.

Discussion

At a recent collaborative workshop with the CDC and the National Institute of Child Health and Human Development, experts discussed the need for continued research investigating the association of reproductive health with overall health [7]. Specifically, they identified fertility status as an early biomarker for future health and highlighted the need to utilize existing databases to examine the association of infertility with chronic disease [7].

In this study, we utilized a large, nationally representative survey and found that women who reported a history of infertility treatment were significantly more likely to report HDP. While the OR demonstrated in the present study is modest, we believe that the borderline statistical significance still has important clinical implications. Given the possible relationship

Table 1 Characteristics of U.S. women with a recent live birth, who reported use of infertility treatment ($n = 2826$), Pregnancy Risk Assessment Monitoring System (PRAMS) survey, 2009–2015

Characteristic	History of infertility treatment *N* (%)	No history of fertility treatment *N* (%)	Chi-squared associated *p* value
Total	2826 (12.91)	19,058 (87.09)	
Maternal characteristics			
Age (year)			< 0.0001
< 20	9 (0.32)	602 (3.16)	
20–29	764 (27.03)	8896 (46.68)	
30–34	935 (33.09)	5922 (31.08)	
35–39	811 (28.70)	3105 (16.29)	
40+	307 (10.86)	532 (2.79)	
Race/ethnicity			< 0.0001
Non-Hispanic white	2015 (71.35)	11,874 (62.47)	
Non-Hispanic black	272 (9.63)	2156 (11.34)	
Hispanic	217 (7.68)	2785 (14.65)	
Other	320 (11.33)	2192 (11.53)	
Maternal education achievement			< 0.0001
< 12 years	94 (3.35)	2217 (11.73)	
12 years	256 (9.12)	3276 (17.33)	
> 12 years	2456 (87.53)	13,412 (70.94)	
Pre-pregnancy BMI			< 0.0001
< 18.5	84 (3.05)	735 (4.07)	
18.5–24.9	1411 (51.23)	9515 (52.69)	
25–29.9	624 (22.66)	4363 (24.16)	
30+	635 (23.06)	3446 (19.08)	
Household income (total)			< 0.0001
≤ $52,000	590 (30.33)	8390 (58.82)	
> $52,000	1355 (69.97)	5873 (41.18)	
Health insurance prior to pregnancy			< 0.0001
Private	2427 (88.51)	11,956 (65.41)	
Medicaid or other	215 (7.84)	3771 (20.63)	
None	100 (3.65)	2552 (13.96)	
Diagnosis of diabetes prior to pregnancy			0.3839
Yes	72 (2.56)	434 (2.29)	
No	2746 (97.44)	18,517 (97.71)	
Obstetric history			
Number of previous live births			< 0.0001
0	1477 (52.71)	7699 (40.61)	
1	901 (32.16)	6828 (36.01)	
2	304 (10.85)	2788 (14.70)	
3+	120 (4.28)	1645 (8.68)	
Most recent birth plurality			< 0.0001
Single	2056 (72.75)	18,456 (96.84)	
Twin	715 (25.30)	588 (3.09)	
Other	55 (1.95)	14 (0.07)	
Social history			
History of tobacco use prior to pregnancy			< 0.0001
Yes	223 (7.95)	2931 (15.54)	
No	2583 (92.05)	15,928 (84.46)	
History of alcohol use prior to pregnancy			0.6342
Yes	1474 (52.91)	8946 (47.57)	
No	1312 (47.09)	9858 (52.43)	
Hypertensive disorder of pregnancy			< 0.0001
Yes	595 (21.23)	2540 (13.49)	
No	2208 (78.77)	16,295 (86.51)	

between infertility treatment and HDP, consultation with an infertility specialist provides a preconception opportunity to counsel a highly motivated population to optimize lifestyle/health, which may mitigate the negative sequela associated with cardiovascular disease. There was neither an association of type infertility treatment nor of timing proximity of treatment to the pregnancy.

Not only is preeclampsia a leading cause of maternal mortality worldwide, HDP may further predict those at risk of future cardiovascular disease (CVD), a leading cause of mortality for the population-at-large [19, 20]. Approximately, 40% of women with HDP will go on to develop chronic hypertension postpartum [20]. Risk of CVD has been reported to be 2 times higher in women with pregnancies complicated by

Table 2 Adjusted odds ratios and confidence intervals for the association between infertility treatment and self-report of hypertension disorder of pregnancy, Pregnancy Risk Assessment Monitoring System (PRAMS) survey, 2009–2015

	Adjusted OR (95% confidence interval)	Chi-squared associated *p* value
Age (year)		< 0.0001
< 20	1.02 (0.78–1.32)	
20–29	Reference	
30–34	1.00 (0.90–1.10)	
35–39	1.32 (1.17–1.49)	
40+	1.58 (1.29–1.93)	
Race/ethnicity		
Non-Hispanic white	Reference	< 0.0001
Non-Hispanic black	1.15 (1.02–1.30)	
Hispanic	0.61 (0.52–0.72)	
Other	0.70 (0.60–0.81)	
Maternal education achievement		< 0.0001
< 12 years	1.05 (0.88–1.26)	
12 years	1.29 (1.15–1.45)	
> 12 years	Reference	
Pre-pregnancy BMI		< 0.0001
< 18.5	0.77 (0.58–1.02)	
18.5–24.9	Reference	
25–29.9	1.88 (1.70–2.08)	
30+	3.27 (2.96–3.61)	
Health insurance prior to pregnancy		0.0143
Private	Reference	
Medicaid or other	1.14 (1.01–1.29)	
None	0.91 (0.78–1.06)	
History of fertility treatment		0.0071
Yes	1.18 (1.05–1.33)	
No	Reference	
Number of previous live births		< 0.0001
0	Reference	
1	0.50 (0.45–0.55)	
2	0.46 (0.40–0.52)	
3+	0.44 (0.37–0.52)	
Most recent birth plurality		< 0.0001
Single	Reference	
Twin	2.08 (1.78–2.42)	
Other	2.98 (1.73–5.14)	
Tobacco consumption prior to pregnancy		0.0006
Yes	1.22 (1.09–1.36)	
No	Reference	

preeclampsia [20]. A recent report supported by the American Heart Association highlighted the risks associated with HDP and stressed the importance of identifying high-risk patients in order to implement preventive measures [20]. Additionally, patients pursuing infertility treatment are often designated as advanced maternal age (AMA) which also predisposes an increased risk to HDP [25]. Interestingly, a recent study in the murine model compared older and younger mice, finding elevated systolic blood pressures particularly in later gestation due to increasing age [26]. These potential risk factors for HDP underscore the importance for future studies which address obstetric risks in older women as delaying childbearing becomes more common. Furthermore, given that patients typically undergo infertility treatment prior to onset of CVD, consultation with

reproductive endocrinologists also provides an ideal time to counsel patients and possibly provide risk-reducing interventions to optimize long-term cardiovascular health [20].

In a prior study, attempts were made to elucidate the effect of infertility diagnosis vs infertility treatment by comparing those who reported infertility and received treatment to those who did not; however, the authors were focused on long-term and not pregnancy-specific risks [27]. While it is still unknown whether it is infertility status or infertility treatment that confers increased risk of hypertensive disorders, there are a few hypotheses that could explain the link. Specifically, a recent review highlighted comorbid relationships of infertility and other pathologies that shared genes and molecular pathways [25]. Additional research is needed to elucidate these molecular mechanisms and to determine if infertility treatment is an independent risk factor separate from infertility status for HDP.

This investigation of HDP's association of infertility includes one of the largest samples of women in the infertility treatment group of any study. Not only are our findings consistent with emerging evidence of the link between cardiovascular disease, infertility, and infertility treatment but this study also focuses on pregnancy-specific outcomes [4, 10, 11]. While HDP are traditionally thought of as a more acute, short-term health concern; it has been well demonstrated to confer long-term increased risk of cardiovascular disease [20]. Similar to other studies using national data, we found a statistically significant association of infertility treatment with cardiovascular risk, specifically HDP [4, 10, 14–17]. Unlike prior studies of self-reported cardiovascular disease and hypertension diagnosis in a homogenous population or focused only on coronary heart disease, we found an association of infertility treatment and HDP [27, 28]. Notably, we controlled for important confounders and were inclusive of all gestational orders and infertility treatments.

Infertility treatment itself could also predispose women to HDP. Recently, there has been a specific focus on IVF pregnancies and the impact of supraphysiologic estrogen in fresh cycles on placentation and obstetric outcomes. There appears to be a higher risk of HDP following fresh transfers in IVF cycles, as compared with frozen transfers [29], and in IVF cycles with higher estradiol level [30], potentially due to abnormal placentation and ultimately uteroplacental vascular insufficiency. Animal studies point to potential defects in vascular invasion of uterine spiral arteries with supraphysiologic levels of estrogen [31].

There have been multiple studies finding increased risk of HDP when using donor oocyte or donor sperm for conception, potentially due to an immunologically foreign fetus [24, 32–35]. Importantly, we could not specifically focus on the use of donor gametes in this study. It is possible that some of our identified risk is attributed to a donor gamete source.

Limitations of this study include the use of retrospective data from a self-reported survey that is susceptible to recall bias and possible underreporting of events. Additional data from 2016 and 2017 are available from the CDC. Due to revisions to the questionnaire format after 2016 (Phase 8), we were unable to compare HDP across all years, but do not suspect this inclusion would change the strength of association given the current size of the study sample. The prevalence of self-reported HDP was 15%, which is slightly higher than previous estimates [36]. Dietz et al. reviewed the sensitivity, specificity, and positive predictive value (PPV) of hypertension during pregnancy in two PRAMS sites, New York and Vermont, compared with abstracted hospital records, which served as the gold standard. Questions on HDP were found to have high specificity, moderate sensitivity, and low PPV. Low PPV for HDP is likely due to overreporting as identified as demonstrated in prior studies [23, 36, 37]. It is possible that women undergoing infertility treatment may be more likely to attend doctor's visits and thus more likely to be diagnosed with HDP. Additionally, we were unable to assess hypertension as a clinical spectrum (chronic hypertension, gestational hypertension, preeclampsia vs eclampsia). By survey design only patients who report a live birth are represented and therefore not all who have susceptibility to HDP are captured. Lastly, the survey classifications of type of treatment (medication/IUI, ART, none, and other) are poorly defined and would include a variety of different medications, regimens, and techniques that may have unique risk profiles.

There are numerous strengths to the study, including its national reach and large number of women sampled. The prevalence of reported infertility treatment in our study is similar to national estimates by the National Survey of Family Growth [38], indicating a likely national representative population. In terms of the exposure specifically explored in this study, PRAMS made substantial revisions to the infertility questions between Phase 4 to Phase 5 with estimates now closer to National ART Surveillance System (NASS) data. While there may still be overreporting of ART use among women over age 40 and nulliparous women, there was no significant difference between PRAMS and NASS counts in 2004. Given PRAMS infertility questions have not changed since 2004, our researchers still feel PRAMS represents a useful questionnaire given its inclusion of questions relating to infertility as well as other maternal and child health indicators [39]. In addition, in our analysis, the effect of known risk factors of hypertensive disorders is similar to those described previously in the literature [23]. Additionally, in our analysis, the effect of known risk factors of hypertensive disorders is similar to those described previously in the literature [23]. As discussed, we conducted several sensitivity analyses including women of younger age, multiparous, of normal BMI, and with a singleton gestation with preservation of the association between infertility treatment and HDP. Utilizing backwards selection to create a parsimonious model, all variables except for insurance status remained in the model. This provides further support for our findings that use of infertility treatment likely confers an independent yet significant

risk for HDP. Our sample is also more heterogeneous than in prior studies due to oversampling as well as adjustment for populations less likely to respond to the survey, such as those who are unmarried or have less education.

In conclusion, this study further supports a link between the use of infertility treatment and HDP. Given this relationship, the consultation for infertility treatment provides an opportunity to counsel a highly motivated population to optimize lifestyle/health in order to mitigate the negative sequela associated with cardiovascular disease [7, 40]. It is important to continue to track maternal morbidity outcomes as patients transition care from their reproductive endocrinology practices to obstetric perinatal and postpartum care. Future research utilizing preconception cohort studies could help delineate whether risk is conferred from infertility status or infertility treatment and whether that risk is modified by specific therapeutic interventions. As an increasing proportion of the population utilizes assisted reproductive technologies, data collection on specific treatment regimens may provide unique insights to subgroups at increased risk for chronic diseases.

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Compliance with ethical standards This project underwent review and was approved by CDC's Institutional Review Board. The study procedures were exempt from review and thus no additional approval was required from Institutional Review Board (IRB) at authors' respective institutions.

Conflict of interest The authors declare that they have no conflict of interest.

Disclaimer The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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