*Original Research*

# Risk of Preeclampsia in Human Immunodeficiency Virus–Infected Pregnant Women

*Matilde Sansone, MD, Laura Sarno, MD, Gabriele Saccone, MD, Vincenzo Berghella, MD, Giuseppe Maria Maruotti, MD, Annalisa Migliucci, MD, Angela Capone, MD, and Pasquale Martinelli, MD*

**OBJECTIVE:** To evaluate the risk of preeclampsia in pregnant women with human immunodeficiency virus (HIV).

**METHODS:** This is a 26-year population-based retrospective cohort study. Human immunodeficiency virus–infected pregnant women were compared with a HIV-negative comparison group. The primary outcome was the incidence of preeclampsia. We planned subgroup analysis according to antiretroviral therapy.

**RESULTS:** A total of 84,725 women were included in the analysis, of whom 453 were HIV-infected and 84,272 HIV-negative. Of the 453 HIV-infected women, 301 (66.4%) received highly active antiretroviral therapy (HAART group) during pregnancy, whereas 152 (33.6%) did not. After adjusting for confounders, we found that HIV-infected women had a significantly higher risk of preeclampsia (10.2% compared with 4.1%; adjusted odds ratio [OR] 2.68, 95% confidence interval [CI] 1.96–3.64), preeclampsia with severe features (4.0% compared with 2.0%; adjusted OR 2.03, 95% CI 1.26–3.28), early-onset (3.5% compared with 1.4%; adjusted OR 2.50, 95% CI 1.51–4.15) and late-onset preeclampsia (6.6% compared with 2.6%; adjusted OR 2.64, 95% CI 1.82–3.85), and preterm birth at less than 37 weeks of gestation (11.0% compared with 4.7%; adjusted OR 2.50, 95% CI 1.86–3.37) compared with the comparison group. Human immunodeficiency virus–infected women who received HAART had a significantly higher risk of preeclampsia compared with women without HIV (13.0% compared with 4.1%; adjusted OR 3.52, 95% CI 2.51–4.94) and compared with the non-HAART group (13.0% compared with 4.6%; adjusted OR 3.08, 95% CI 1.34–5.07). The non-HAART group had a similar risk compared with women without HIV (4.6% compared with 4.1%; adjusted OR 1.14, 95% CI 0.53–2.44).

**CONCLUSION:** Human immunodeficiency virus–infected women had an increased risk of preeclampsia. Some of this risk seems to be linked to HAART.

*(Obstet Gynecol 2016;127:1027–32)*
*DOI: 10.1097/AOG.0000000000001424*

Preeclampsia is a pregnancy-related condition that affects approximately 3–7% of all pregnancies.[1] It is a major cause of maternal and perinatal morbidity and mortality.[2] The pathogenesis of preeclampsia remains largely unknown; however, vascular and immunologic factors seem to be involved in development of preeclampsia.[2]

The human immunodeficiency virus (HIV) is a lentivirus that causes HIV infection and acquired immunodeficiency syndrome.[3] Before 1994, when the use of antiretroviral therapy (ART) was found to prevent perinatal transmission, women with HIV were often discouraged from getting pregnant and, in many cases, encouraged to undergo sterilization.[4,5] Since that time, combination ART has decreased both vertical and sexual transmission dramatically. The development and widespread use of potent ART such as highly active ART (HAART), with the concomitant use of at least three antiretroviral drugs, has transformed HIV infection from a near certain death sentence to a chronic manageable condition, whereby patients who adhere fully to their medication regimen can have an almost normal lifespan.[6] However, some studies showed that

*From the Department of Neuroscience, Reproductive Sciences and Dentistry, School of Medicine, University of Naples Federico II, Naples, Italy; and the Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, Sidney Kimmel Medical College of Thomas Jefferson University, Philadelphia, Pennsylvania.*

*Corresponding author: Pasquale Martinelli, MD, Department of Neuroscience, Reproductive Sciences and Dentistry, School of Medicine, University of Naples Federico II, via pansini, 5, Naples 80128, Italy; e-mail: martinel@unina.it.*

***Financial Disclosure***
*The authors did not report any potential conflicts of interest.*


ISSN: 0029-7844/16

preeclampsia and fetal death have increased sharply in HIV-infected pregnant women receiving HAART.[7]

The aim of this study was to evaluate the risk of preeclampsia in HIV-infected pregnant women, including those receiving HAART.

## MATERIALS AND METHODS

This is a 26-year population-based observational retrospective cohort study. Clinical records of women who were referred to the Department of Reproductive Science, University of Naples Federico II (Naples, Italy) from January 1989 to August 2015 were collected prospectively in a dedicated database. All charts recorded in the database were carefully reviewed by three authors (M.S., L.S., G.S.). All variables reported were collected on all of the patients included in this study. Missing data were retrieved by search of the women's clinical records. Only women who delivered at our Division were included in the analysis.

The study was approved by the local institutional review board, which also checked the quality of the data set. Data were anonymized before analysis. Every pregnant woman received standard medical care and underwent laboratory testing every trimester, including complete blood count and urine dipstick for protein and glucose. Routine screening for HIV in every pregnant woman with unknown serostatus was carried out. Beginning in December 1996, HAART was offered to all HIV-positive women during pregnancy. All HIV-infected pregnant women were included in the analysis and were compared with a comparison group (pregnant women without HIV).

Primary and secondary outcomes were designated a priori. The primary outcome was the incidence of preeclampsia. Secondary outcomes included incidence of preeclampsia with severe features, early-onset (preeclampsia requiring delivery before 34 weeks of gestation) and late-onset preeclampsia (preeclampsia requiring delivery at or after 34 weeks of gestation), and incidence of preterm birth at less than 37 weeks of gestation. We planned to assess the primary outcome (incidence of preeclampsia) in subgroup analysis according to ART status (HAART or non-HAART). Highly active ART was defined as the concomitant use of at least three antiretroviral drugs, consisting of a combination of two nucleoside reverse transcriptase inhibitors and either a protease inhibitor or a non-nucleoside reverse transcriptase inhibitor. Non–highly active ART included either no ART or suboptimal therapy. Suboptimal (or nonsuppressive) therapy was defined as concomitant use of fewer than three antiretroviral drugs, such as monotherapy (zidovudine monotherapy) or dual ART (zidovudine plus lamivudine). We also planned to compare the risk of the primary outcome (incidence of preeclampsia) in HIV-infected pregnant women who received HAART during pregnancy with those who did not (the non-HAART group). We also assessed the primary outcome in the subset of women without chronic hypertension and in the subset of women with singleton gestations.

Diagnosis and management of preeclampsia and preeclampsia with severe features were based on American College of Obstetricians and Gynecologists guidelines.[8] Preeclampsia (ie, preeclampsia without severe features) was defined as a blood pressure elevation (140/90 mm Hg or greater on two occasions 4 hours apart or 160/110 mm Hg or greater once) after 20 weeks of gestation with proteinuria (300 mg or greater on 24-hour protein or greater than 0.3 protein:creatinine ratio) or any of the following if proteinuria is not present: platelets less than 100,000/μL, serum creatinine greater than 1.1 mg/dL (or doubling of creatinine in the absence of other renal disease), or aspartate aminotransferase or alanine aminotransferase at least twice the upper limit of normal.[8] Preeclampsia with severe features was defined as preeclampsia with any of the following: blood pressure 160/110 mm Hg or greater 4 hours apart on bed rest (unless on antihypertensive medication), platelets less than 100,000/μL, doubling of aspartate aminotransferase or alanine aminotransferase, serum creatinine greater than 1.1 mg/dL (or doubling of serum creatinine in the absence of other renal disease), pulmonary edema, or new cerebral or visual disturbances.[8] Our data were collected prospectively in a dedicated database from January 1989, but we retrospectively classified preeclampsia and preeclampsia with severe features based on the new American College of Obstetricians and Gynecologists guidelines.[8]

Statistical analysis was performed using SPSS 19.0. Categorical variables were compared using the $\chi^2$ or Fisher exact test. Within-group comparison was undertaken using Wilcoxon and Mann-Whitney tests. $P$ value $<.05$ was considered statistically significant. The risk of preeclampsia was estimated with multivariate analyses through logistic regression models. Logistic regression, presented as adjusted odds ratio (OR) with the 95% of confidence interval (CI), was performed to correct data for those variables significantly different between groups.

The study was performed following the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guidelines.[9]

## RESULTS

From January 1989 to August 2015, 84,725 pregnant women were included, of whom 453 (1.1%) were

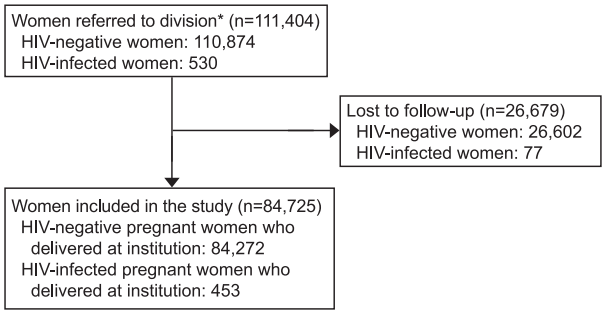


**Fig. 1.** Study algorithm. HIV, human immunodeficiency virus. *Division of Maternal-Fetal Medicine, Department of Reproductive Science, School of Medicine, University of Naples Federico II, Naples, Italy.

*Sansone. Risk of Preeclampsia in HIV-Infected Women. Obstet Gynecol 2016.*

HIV-infected and 84,272 were not HIV-infected (comparison group) (Fig. 1; Table 1). Out of the 453 HIV-infected women, 301 (66.4%) received HAART during the pregnancy and 152 (33.6%) did not (non-HAART group; Table 2). Of the 152 included in the non-HAART group, 52 received no therapy and 100 suboptimal therapy, including zidovudine monotherapy (80/100) and zidovudine plus lamivudine dual ART (20/100). Most of the HIV-infected pregnant women included in the non-HAART group (142/152) delivered before HAART was available at our division (ie, before December 1996).

After adjusting for confounders statistically proven (ethnicity and level of education), we found that HIV-infected women had a significantly higher risk of preeclampsia (10.2% compared with 4.1%; adjusted OR 2.68, 95% CI 1.96–3.64), preeclampsia with severe features (4.0% compared with 2.0%; adjusted OR 2.03, 95% CI 1.26–3.28), early-onset (3.5% compared with 1.4%; adjusted OR 2.50, 95% CI 1.51–4.15) and late-onset preeclampsia (6.6% compared with 2.6%; adjusted OR 2.64, 95% CI 1.82–3.85), and preterm birth at less than 37 weeks of gestation (11.0% compared with 4.7%; adjusted OR 2.50, 95% CI 1.86–3.37) compared with the comparison group (Table 3). Human immunodeficiency virus–infected women without chronic hypertension had a significantly higher risk of preeclampsia (10.3% compared with 3.8%; adjusted OR 2.69, 95% CI 1.99–3.64) as did HIV-infected women with singleton gestations (10.0% compared with 4.0%; adjusted OR 2.49, 95% CI 1.87–3.32).

Human immunodeficiency virus–infected women who received HAART had a significantly higher risk of preeclampsia compared with women without HIV (13.0% compared with 4.1%; adjusted OR 3.52, 95% CI 2.51–4.94) and compared with the non-HAART group (13.0% compared with 4.6%; adjusted OR 3.08, 95% CI 1.34–5.07). The non-HAART group had a similar risk compared with women without HIV (4.6% compared with 4.1%; adjusted OR 1.14, 95% CI 0.53–2.44) (Fig. 2). Notably, the incidence of preeclampsia among

**Table 1. Characteristics of the Included Women**

| Variable | HIV-Infected (n=453) | Comparison Group (n=84,272) | *P* |
|---|---|---|---|
| Age (y) | 29.1±5.7 | 29.5±11.4 | .14 |
| Ethnicity | | | **<.001** |
| Caucasian | 296 (65.3) | 67,416 (79.9) | |
| Non-Caucasian* | 157 (34.7) | 16,856 (20.1) | |
| Nulliparous | 107 (23.6) | 20,009 (23.7) | .59 |
| Multiparous | 346 (76.4) | 64,263 (76.3) | .59 |
| Prepregnancy BMI (kg/m$^2$) | 25.9±14.9 | 25.8±12.7 | .89 |
| Greater than 30 | 73 (16.1) | 15,168 (18.0) | .30 |
| Smoking | 99 (21.9) | 20,224 (24.0) | .29 |
| Chronic hypertension | 83 (18.3) | 9,057 (21.5) | .10 |
| Diabetes mellitus (including GDM) | 52 (11.5) | 10,204 (12.1) | .68 |
| Family history of hypertension† | 147 (32.5) | 24,856 (29.5) | .17 |
| Prior preeclampsia | 6 (1.3) | 1,201 (1.4) | .86 |
| Level of education (y) | | | |
| Less than 12 | 51 (11.3) | 5,899 (7.0) | **.04** |
| 12–16 | 271 (59.8) | 52,663 (62.5) | .24 |
| 17 or greater | 131 (28.9) | 25,710 (30.5) | .46 |
| No. of fetuses | | | .49 |
| Singleton | 431 (95.1) | 79,544 (94.4) | |
| Multiple | 22 (4.9) | 4,728 (5.6) | |
| ART during pregnancy | | | — |
| No therapy | 52 (11.5) | — | |
| Suboptimal | 100 (22.1) | — | |
| Non-HAART | 152 (33.6) | — | |
| HAART | 301 (66.4) | — | |

BMI, body mass index; GDM, gestational diabetes mellitus; ART, antiretroviral therapy; HAART, highly active antiretroviral therapy.

Data are mean±standard deviation or n (%) unless otherwise specified.

Bold indicates statistical significance.

HAART, the concomitant use of at least three antiretroviral drugs (a combination of two nucleoside reverse transcriptase inhibitors and either a protease inhibitor or a nonnucleoside reverse transcriptase inhibitor).

Non-HAART, either no therapy or suboptimal therapy.

Suboptimal therapy, concomitant use of fewer than three antiretroviral drugs, including monotherapy (zidovudine monotherapy) or dual therapy (zidovudine plus lamivudine).

* Non-Caucasian ethnicity, including Hispanic, Asian, black African.

† First-degree family history of hypertension.

**Table 2. Characteristics of the Included Human Immunodeficiency Virus–Infected Pregnant Women**

| Variable | HAART (n=301) | Non-HAART (n=152) | *P* |
|---|---|---|---|
| Age (y) | 28.2±4.7 | 29.3±8.4 | .33 |
| Ethnicity | | | .09 |
| Caucasian | 210 (69.8) | 86 (56.6) | |
| Non-Caucasian* | 91 (30.2) | 66 (43.4) | |
| Nulliparous | 75 (24.9) | 32 (21.1) | .37 |
| Multiparous | 226 (75.1) | 120 (78.9) | .37 |
| Prepregnancy BMI (kg/m$^2$) | 25.9±12.7 | 25.8±13.4 | |
| Greater than 30 | | | |
| Smoking | 48 (15.9) | 25 (16.4) | .71 |
| Chronic hypertension | 54 (17.9) | 29 (19.1) | .21 |
| Diabetes mellitus (including GDM) | 30 (10.0) | 12 (7.9) | .11 |
| Family history of hypertension† | 91 (30.2) | 56 (36.8) | .12 |
| Prior preeclampsia | 4 (1.3) | 2 (1.3) | .92 |
| Level of education (y) | | | |
| Less than 12 | 33 (11.0) | 18 (11.8) | .41 |
| 12–16 | 180 (59.8) | 91 (59.9) | .87 |
| 17 or greater | 87 (28.9) | 44 (28.9) | .94 |
| No. of fetuses | | | .24 |
| Singleton | 285 (94.7) | 146 (96.1) | |
| Multiple | 15 (5.3) | 7 (3.9) | |
| Transaminase elevation‡ | | | |
| CD4+ count (microliters)§ | | | |
| 500 or greater | 129 (42.9) | 65 (42.8) | .74 |
| 200–499 | 144 (47.8) | 72 (47.4) | .84 |
| Less than 200 | 28 (9.3) | 15 (9.9) | .86 |
| Plasma viral load (copies/mL)§ | | | |
| Less than 50 | 69 (22.9) | 34 (22.4) | |
| 50–399 | 171 (56.8) | 89 (58.6) | |
| 400–999 | 18 (6.0) | 15 (9.9) | |
| 1,000–9,999 | 24 (8.0) | 13 (8.6) | |
| 10,000 or greater | 19 (6.3) | 1 (0.7) | |

HAART, highly active antiretroviral therapy; BMI, body mass index; GDM, gestational diabetes mellitus.
Data are mean±standard deviation or n (%) unless otherwise specified.
Bold indicates statistical significance.
HAART, the concomitant use of at least three antiretroviral drugs (a combination of two nucleoside reverse transcriptase inhibitors and either a protease inhibitor or a nonnucleoside reverse transcriptase inhibitor).
Non-HAART, either no therapy or suboptimal therapy.
Suboptimal therapy, concomitant use of fewer than three antiretroviral drugs, including monotherapy (zidovudine monotherapy) or dual therapy (zidovudine plus lamivudine).
* Non-Caucasian ethnicity, including Hispanic, Asian, black African.
† First-degree family history of hypertension.
‡ Transaminase elevation, doubled of aspartate aminotransferase or alanine aminotransferase.
§ Measurement closest to delivery during the third trimester.

HIV-infected pregnant women started to increase in 1997 (ie, after the introduction of the HAART; Fig. 3).

## DISCUSSION

This population-based study showed that HIV-infected women had a significantly higher risk of preeclampsia compared with women without HIV. The risk was increased only among those HIV-infected women who received HAART therapy.

Our study has several strengths. This is a large 26-year population-based study. The number of the included women was very high. Human immunodeficiency virus–infected and non–infected women were similar in terms of maternal demographics. Subgroup analyses were established a priori. All of these elements enhance the reliability of a study.[10,11]

The most important limitation of our study is that this is a retrospective, nonrandomized comparison. We acknowledge that the subgroup analyses according to the ART were underpowered; however, this is indeed an uncommon cohort of women. Human immunodeficiency virus-positive women may be more likely to be diagnosed with preeclampsia as a result of the heightened antenatal surveillance or closer monitoring in labor. We were not able to collect data on neonatal outcomes and this is a major limitation of the study. The study period spans 26 years and this raises the question of practice changes over that time period, including the management of the women with preeclampsia. We did not distinguish between spontaneous and indicated preterm birth. However, the increased risk for preterm delivery among HIV-infected women may be explained by their increased risk for early-onset preeclampsia. Human immunodeficiency virus-positive women who received at least three antiretroviral drugs, consisting of a combination of two nucleoside reverse transcriptase inhibitors and either a protease inhibitor or a nonnucleoside reverse transcriptase inhibitor, were classified as receiving HAART in our database. Therefore, comparing a protease inhibitor with a nonnucleoside reverse transcriptase inhibitor was not feasible. Similarly, we did not compare between women with new-start HAART and those continuing the therapy. Highly active ART may cause clinical and laboratory alterations (eg, proteinuria, thrombocytopenia, transaminase, or creatinine elevations), complicating the diagnosis of preeclampsia; this could have the effect of falsely elevating their risk of preeclampsia. The incidence of preeclampsia in the comparison group was low (approximately 4%) and this could be the result of ascertainment bias.

Increased access to HAART has substantially reduced the risk of mother-to-child transmission among HIV-infected pregnant women worldwide.[3–6] Despite this significant effect, there are some concerns about

**Table 3. Primary and Secondary Outcomes in the Overall Analysis**

| Variables | HIV-Infected (n=453) | Comparison Group (n=84,272) | Crude OR (95% CI) | Adjusted OR (95% CI) |
|---|---|---|---|---|
| Preeclampsia | 46 (10.2) | 3,416 (4.1) | **3.01 (2.21–3.57)** | **2.68 (1.96–3.64)** |
| Preeclampsia with severe features | 18 (4.0) | 1,680 (2.0) | **2.57 (1.31–3.05)** | **2.03 (1.26–3.28)** |
| Early-onset preeclampsia | 16 (3.5) | 1,214 (1.4) | **2.87 (1.66–4.07)** | **2.50 (1.51–4.15)** |
| Late-onset preeclampsia | 30 (6.6) | 2.202 (2.6) | **2.77 (1.91–3.94)** | **2.64 (1.82–3.85)** |
| Preterm birth at less than 37 wk of gestation | 50 (11.0) | 3,982 (4.7) | **2.81 (1.94–3.44)** | **2.50 (1.86–3.37)** |

HIV, human immunodeficiency virus; OR, odds ratio; CI, confidence interval.
Data are n (%) unless otherwise specified.
Bold indicates statistical significance.

the long-term use of HAART on fetal, neonatal, and maternal outcomes.[12–14] In 2002 Wimalasundera et al reported that the incidence of preeclampsia was lower in HIV-infected women who received no ART compared with those who received ART.[12,13]

The biological plausibility to explain our findings, that is, the higher risk of preeclampsia in women with HIV, is not completely clear. One hypothesis is that HAART causes preeclampsia by a direct toxic effect on the liver and on the kidney.[12,13] It is known that the hepatotoxic and the nephrotoxic effects of antiretroviral may mimic preeclampsia.[14,15] The physiopathology of preeclampsia seems to be linked to vascular, immunologic, and genetic factors as well as to multiple-organ injury, including liver and kidney.[2,16–18] Moreover, the administration of HAART is reported to enhance maternal immune reconstitution by reestablishing the mother's immune response to fetal antigens and consequently making the HIV-women susceptible to the development of preeclampsia.[12,13,16] Therefore, the higher rate of preeclampsia in the HIV-infected women HAART-treated might be the result of immune reconstitution induced by triple ART or an overlap in the clinical manifestations of the adverse effects of HAART and preeclampsia, or both. Our findings were at odds with another study, which showed no significant association between HIV positivity and preeclampsia; however, this study did not stratify its data according to ART.[19]

Our study adds to the literature new data helpful to identify women at risk of preeclampsia. Identification of pregnant women at risk of hypertensive disorders, including preeclampsia, could potentially improve pregnancy outcomes and is also important for future research investigating the potential role of interventions to reduce the prevalence of the disease.[20–22]

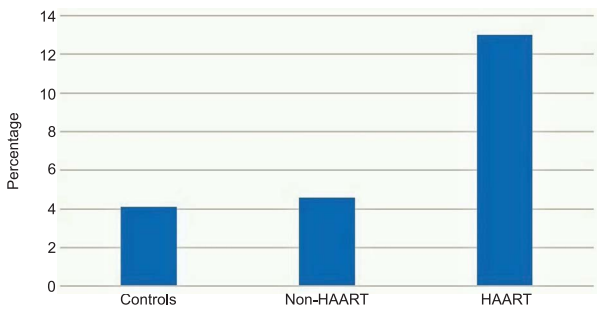


**Fig. 2.** Incidence of preeclampsia in HIV-negative pregnant women (4.1%; n=84,272) and in HIV-infected pregnant women stratified by therapy in the non-HAART (highly active antiretroviral therapy) group (4.6%; n=152) and in the HAART group (13.0%; n=301). HIV, human immunodeficiency virus.

*Sansone. Risk of Preeclampsia in HIV-Infected Women. Obstet Gynecol 2016.*

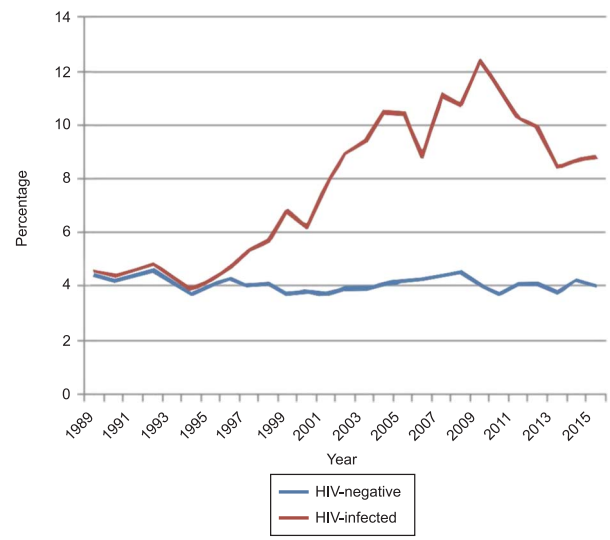


**Fig. 3.** Incidence of preeclampsia at University of Naples Federico II from 1989 to 2015. HIV, human immunodeficiency virus.

*Sansone. Risk of Preeclampsia in HIV-Infected Women. Obstet Gynecol 2016.*

In summary, HIV-infected pregnant women had an increased risk of preeclampsia. This risk seems to be linked at least in part to HAART.

## REFERENCES


1. World Health Organization. Make every mother and child count. Geneva (Switzerland): World Health Report; 2010.
2. Steegers EA, von Dadelszen P, Duvekot JJ, Pijnenborg R. Pre-eclampsia. Lancet 2010;376:631–44.
3. Douek DC, Roederer M, Koup RA. Emerging concepts in the immunopathogenesis of AIDS. Annu Rev Med 2009;60:471–84.
4. Aaron E, Cohan D, Weber S. The changing landscape for HIV-serodifferent couples desiring a child. Am J Obstet Gynecol 2015;213:746.
5. Chen JL, Philips KA, Kanouse DE, Collins RL, Miu A. Fertility desires and intensions of HIV-positive men and women. Fam Plann Perspect 2001;33:144–52, 165.
6. Saag MS. Preventing HIV in women–still trying to find their VOICE. N Engl J Med 2015;372:564–6.
7. Suy A, Martinez E, Coll O, Lonca M, Palacio M, de Lazzari E, et al. Increased risk of preeclampsia and fetal death in HIV-infected pregnant women receiving highly active antiretroviral therapy. AIDS 2006;20:59–66.
8. Executive summary: hypertension in pregnancy. American College of Obstetricians and Gynecologists. Obstet Gynecol 2013;122:1122–31.
9. on Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP, et al. The Strengthening the Reporting of the Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet 2007;370:1453–7.
10. Peterson AM, Nau DP, Cramer JA, Benner J, Gwadry-Sridhar F, Nichol M. A checklist for medication compliance and persistence studies using retrospective database. Value Health 2007;10:3–12.
11. Smith AH, Bates MN. Confidence limit analyses should replace power calculation in the interpretation of epidemiologic studies. Epidemiology 1992;3:449–52.
12. Mawson AR. Effects of antiretroviral therapy on occurrence of pre-eclampsia. Lancet 2003;361:347–8.
13. Wimalasundera TC, Larbalestier N, Smith JH, de Ruiter A, McG Thom SA, Hughes AD, et al. Pre-eclampsia, antiretroviral therapy, and immune reconstitution. Lancet 2002;360:1152–4.
14. Royal College of Obstetricians and Gynaecologists. Management of HIV in pregnancy. Green-top Guideline No. 39. Available at: https://www.rcog.org.uk/en/guidelines-research-services/guidelines/gtg39/. Retrieved April 7, 2016.
15. Maynard S, Epstein FH, Karumanchi SA. Preeclampsia and angiogenic imbalance. Annu Rev Med 2008;59:61–78.
16. Mol BW, Roberts CT, Thangaratinam S, Magee LA, de Groot CJ, Hofmeyr GJ. Pre-eclampsia. Lancet 2016;387:999–1011.
17. Zeisler H, Llurba E, Chantraine F, Vatish M, Staff AC, Sennström M, et al. Predictive value of the sFlt-1:PIGF ratio in women with suspected preeclampsia. N Engl J Med 2016; 374:13–22.
18. Paré E, Parry S, McElrath TF, Pucci D, Newton A, Lim KH. Clinical risk factors for preeclampsia in the 21st century. Obstet Gynecol 2014;124:763–70.
19. Browne JL, Schrier VJ, Grobbee DE, Peters SA, Klipstein-Grobusch K. HIV, antiretroviral therapy, and hypertensive disorders in pregnancy: a systematic review and meta-analysis. J Acquir Immune Defic Syndr 2015;70:91–8.
20. O'Gorman N, Wright D, Syngelaki A, Akolekar R, Wright A, Poon LC, et al. Competing risks model in screening for preeclampsia by maternal factors and biomarkers at 11-13 weeks gestation. Am J Obstet Gynecol 2015;214:103.e1–12.
21. Poon LC, Nicolaides KH. Early prediction of preeclampsia. Obstet Gynecol Int 2014;2014:297397.
22. Nicolaides KH. Turning the pyramid of prenatal care. Fetal Diagn Ther 2011;29:183–96.