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# Risk of Preeclampsia in Pregnancies After Assisted Reproductive Technology and Ovarian Stimulation

**Angela S. Martin**[1,2], **Michael Monsour**[2], **Jennifer F. Kawwass**[1,2], **Sheree L. Boulet**[2], **Dmitry M. Kissin**[1,2], **Denise J. Jamieson**[1,2]

[1]Department of Gynecology and Obstetrics, Emory University, 69 Jesse Hill Jr. Drive, SE, 4th Floor, Glenn Building, Atlanta, GA 30303, USA

[2]Division of Reproductive Health, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, GA 30341, USA

## Abstract

**Objective—**To compare the risk of preeclampsia among spontaneously conceived pregnancies to those after hyperestrogenic ovarian stimulation (hyperestrogenic OS) with and without assisted reproductive technology (ART), and stimulation with non-hyperestrogenic aromatase inhibitor stimulation (non-hyperestrogenic OS).

**Methods—**Live-born singleton deliveries among women 20–49 years were identified in the 2004–2012 Truven Health MarketScan Commercial Claims and Encounters Databases using ICD-9 and CPT codes. Maternal characteristics were compared using Chi squared and Fisher exact tests. We performed multilevel multivariable logistic regression, controlling for maternal age, parity, comorbid conditions, and region of delivery, and calculated adjusted odds ratios (aOR) and 95 % confidence intervals for mild and severe preeclampsia.

**Results—**1,014,526 spontaneously conceived, 6881 hyperestrogenic OS with ART, 27,516 hyperestrogenic OS without ART, and 2117 non-hyperestrogenic OS pregnancies were identified. The adjusted odds of developing preeclampsia were increased for deliveries after hyperestrogenic OS with ART (mild preeclampsia aOR 1.42, 1.24–1.62; severe preeclampsia aOR 1.83, 1.59–2.11) and without ART (mild preeclampsia aOR 1.32, 1.24–1.42; severe preeclampsia aOR 1.53, 1.41–1.66). Adjusted odds of preeclampsia were similar between spontaneously conceived and non-hyperestrogenic OS pregnancies.

**Conclusions for Practice—**Risk of preeclampsia after ART may in part be related to supraphysiologic estrogen associated with hyperestrogenic OS.

### Keywords

Aromatase inhibitors; Assisted reproductive technology; In vitro fertilization; Ovarian stimulation; Preeclampsia

✉ Angela S. Martin, amatlac@emory.edu.

Compliance with Ethical Standards

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

## Introduction

Preeclampsia, a significant cause of maternal and fetal morbidity and mortality, complicates 2–8 % of pregnancies [7]. While the precise etiology remains unknown, abnormal placental development and subsequent aberrant or inadequate uteroplacental circulation involving abnormally shallow cytotrophoblast invasion plays a central role in the pathogenesis [10, 18].

Many studies have found an association between pregnancies conceived after assisted reproductive technology (ART), such as in vitro fertilization (IVF), and increased preeclampsia risk [17, 21]. Exposure to supraphysiologic estradiol during implantation and in the first trimester has been proposed to be responsible for this association in both animal and human studies [2, 9]. Albrecht et al. found when pregnant baboons were exposed to serum estradiol levels approximately threefold above normal in early pregnancy, the mean percentage of spiral arteries/arterioles invaded by extravillous cytotrophoblasts was 75–100 % lower than in untreated baboons. In human placentas of pregnancies complicated by preeclampsia, cytotrophoblast invasion of the interstitial uterine compartment is often shallow [6], as was seen in the baboons treated with supraphysiologic estrogen. Therefore, elevated estrogen may contribute to abnormal placentation and subsequent aberrant or inadequate uteroplacental circulation that plays a central role in the pathogenesis of preeclampsia. We hypothesize that the increased risk of preeclampsia among ART pregnancies may be due to elevated estrogen levels associated with certain types of hyperestrogenic ovarian stimulation (OS).

Although this physiologic explanation seems plausible, the evidence is conflicting. While some studies show an increased risk of preeclampsia in pregnancies conceived after ART compared to spontaneous conception [13, 19, 20], others show no such risk [3, 16, 22]. Many of these studies are limited by small sample size and poor study design. Few examine women who underwent different types of OS without ART to help determine whether elevated pre-implantation sex steroid concentrations characteristic of OS may be responsible for elevated risks.

We compared preeclampsia risk among spontaneously conceived pregnancies to pregnancies after OS with medications known to cause elevated estrogen levels, such as clomiphene and exogenous gonadotropins, with and without ART (hyperestrogenic OS), and OS with only aromatase inhibitors which do not cause supraphysiologic estrogen levels (non-hyperestrogenic OS).

## Methods

We used Truven Health MarketScan Commercial Claims and Encounters Databases, which includes longitudinal, de-identified health insurance claims data from large employers and health plans across the United States to conduct a retrospective cohort study. All women aged 20–49 years who had a live birth and were continuously enrolled for at least 1 year prior to delivery were identified by International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) diagnosis and procedure codes and Current Procedural

Terminology (CPT) codes between January 1, 2004 and December 31, 2012. Deliveries were defined as any inpatient hospital admission record including a pregnancy-related diagnosis or procedure code for vaginal or cesarean delivery, identified by the ICD-9-CM codes 650, 669.7, V27, and procedure codes 72.0–72.9, 73.22, 73.59, 73.6, 74.0–74.2, 74.4, 74.99, Diagnosis Related Group (DRG) codes for vaginal or cesarean delivery, 370–375 for version 24 or earlier, or 765–768, 774, 775 for version 25 and later, and CPT codes 59409, 59612 for vaginal delivery and 59514, 59620 for cesarean delivery. We excluded deliveries with ICD-9-CM codes indicating a fetal death (656.4x) and multiple gestation (651.x, V27.2–V27.7, V91.x) due to their association with ART as well as our outcome, preeclampsia [8, 17]. Molar pregnancy (630), spontaneous abortion or termination (631, 632, 634.x–638.x, 69.01, 69.51, 74.91, 75.0, DRG 380, 381 for version 24 or earlier, 770, 779 for version 25 and later, or CPT codes 59840, 59841, 59850–59852, 59855–59857), ectopic pregnancy (633.x, DRG 378 for version 24 and earlier and 777 for version 25 and later), and pregnancies with a complication following a molar pregnancy, abortion, termination, and ectopic pregnancy (639.x) were also excluded. Because the data are de-identified, the Centers for Disease Control and Prevention deemed this study to be exempt from review by an institutional review board.

Deliveries after OS with medications known to cause supraphysiologic estrogen levels (hyperestrogenic OS) were identified if at least one of the following outpatient prescriptions was filled within 45 weeks prior to delivery: clomiphene citrate, cetrorelix acetate, chorionic gonadotropin alfa, recombinant follicle stimulating hormone, recombinant luteinizing hormone, follitropin alfa, follitropin beta, ganirelix acetate, gonadorelin acetate, gonadorelin hydrochloride, lutropin alfa, urofollitropin, histrelin acetate. We excluded any delivery with a CPT code present for thawing of a cryopreserved embryo (89352) to prevent including frozen embryo transfers when medications are usually given in doses targeting lower, more physiologic hormone levels. Deliveries were then further classified as hyperestrogenic OS with ART if a specific ICD-9-CM or CPT code was present indicating an ART visit or procedure (ICD-9-CM V26.81, CPT 58970, 58974, 58976) within 45 weeks prior to delivery. A delivery was classified as non-hyperestrogenic OS if an outpatient prescription was filled for an aromatase inhibitor, specifically anastrozole or letrozole, within 45 weeks prior to delivery, and none of the above listed hyperestrogenic medications were filled. Deliveries from the non-hyperestrogenic OS group were excluded if ICD-9-CM or CPT codes indicating ART were present. All remaining deliveries without the above listed medications, ART codes, or an ICD-9-CM or CPT code indicating an intrauterine insemination visit or procedure (ICD-9-CM V26.1, CPT 58321, 58322) were considered spontaneously conceived pregnancies. In order to prevent inclusion of misclassified non-spontaneous conceptions, we excluded women from the spontaneously conceived pregnancy group if they had a diagnosis of infertility on two or more outpatient claims at least 30 days apart or at least one inpatient claim in the 12 months prior to delivery. If a woman had more than one delivery during the study period, only the first delivery was included.

Characteristics between groups were compared using Chi squared and Fisher exact tests and included maternal age at delivery, parity, comorbid conditions, and region of delivery. These characteristics were chosen due to their potential as confounding variables based on previously published literature examining risk factors for preeclampsia [4, 12, 23].

Comorbidities were identified using ICD-9-CM or CPT codes reported within one year prior to delivery in inpatient or outpatient claims and included tobacco use (305.1, 649.0, V158.2, CPT 99406, 99407), pregestational diabetes (250–250.93 and 648.00–648.04), gestational diabetes (648.8x), chronic hypertension (401.0, 401.1, 401.9, 402.00–405.99, 642.0, 642.1, 642.2), and obesity (649.1, 278.00, 278.01, 278.03). Women were identified as having a comorbid condition based on the presence of the diagnosis or procedure code on at least one inpatient claim or two or more outpatient claims at least 30 days apart, except for tobacco use and obesity, which were present at much lower rates than expected, and were therefore included if only one or more outpatient claim was present. Due to the large number of comparisons between groups (N = 24), the Holm–Bonferroni method was applied, resulting in statistical significance for $p$ values ≤0.002.

Our primary outcomes, mild and severe preeclampsia, were identified using ICD-9-CM codes present during the inpatient delivery admission (mild preeclampsia 642.40–642.44, severe preeclampsia 642.50–642.54). Crude odds ratios (OR) with 95 % confidence intervals (CI) were obtained from a logistic regression. Adjusted odds ratios (aOR) with 95 % CI were calculated for mild and severe preeclampsia using multilevel multivariable logistic regression, adjusting for maternal age, parity, comorbid conditions (pregestational diabetes, gestational diabetes, chronic hypertension, and obesity), and region of delivery (Northeast, North-central, South, and West). Tobacco use had no effect on the odds ratios in the multivariable logistic regression model, and was therefore not included in the final model. Hyperestrogenic OS with or without ART, and non-hyperestrogenic OS pregnancies were compared to spontaneously conceived pregnancies. SAS version 9.3 was used for all analyses.

## Results

Using the first singleton delivery for each woman from January 1, 2004 through December 31, 2012, we identified 1,014,526 spontaneously conceived, 6881 hyperestrogenic OS with ART, 27,516 hyperestrogenic OS without ART, and 2117 non-hyperestrogenic OS pregnancies. Demographic characteristics in each group are shown in Table 1. Women delivering after hyperestrogenic OS with and without ART, and non-hyperestrogenic OS were significantly more likely to be 35–44, nulliparous, and have chronic hypertension, pregestational or gestational diabetes compared to women who conceived spontaneously. Obesity was similar between the spontaneous conception and hyperestrogenic OS with ART deliveries (4.7 and 4.5 % respectively) and more prevalent in hyperestrogenic OS without ART and non-hyperestrogenic OS deliveries (5.4 and 6.5 % respectively). Tobacco use was highest among spontaneous conceptions at 2.7 % compared to 0.9–1.6 % in the other groups.

Overall, mild preeclampsia was diagnosed in 2.5 % of spontaneously conceived pregnancies compared to 3.4 % of hyperestrogenic OS with ART, 3.6 % of hyperestrogenic OS without ART, and 3.2 % of non-hyperestrogenic OS deliveries. Severe preeclampsia was diagnosed in 1.6 % of spontaneously conceived pregnancies compared to 3.1 % of hyperestrogenic OS with ART, 2.5 % of hyperestrogenic OS without ART, and 2.2 % of non-hyperestrogenic OS deliveries (Table 2).

Crude and adjusted odds ratios are presented in Table 2. As compared with deliveries from spontaneous conceptions, the adjusted odds of developing preeclampsia were increased for deliveries after hyperestrogenic OS with ART (mild preeclampsia aOR 1.42, 1.24–1.62; severe preeclampsia aOR 1.83, 1.59–2.11) and hyperestrogenic OS without ART (mild preeclampsia aOR 1.32, 1.24–1.42; severe preeclampsia aOR 1.53, 1.41–1.66). Adjusted odds of preeclampsia were not significantly elevated in non-hyperestrogenic OS deliveries compared to spontaneous conceptions (mild preeclampsia aOR 1.16, CI 0.91–1.48; severe preeclampsia aOR 1.17, CI 0.87–1.57).

## Discussion

We found women exposed to OS medications known to increase serum estrogen levels, such as clomiphene and exogenous gonadotropins, have an increased risk of preeclampsia regardless of ART use. In contrast, stimulation with aromatase inhibitors that do not cause supraphysiologic estrogen levels was not associated with preeclampsia after adjusting for age, parity, and comorbid conditions. These findings support our hypothesis that increased risk of preeclampsia among ART pregnancies may be due, in part, to elevated estrogen levels associated with certain types of OS. Supraphysiologic estrogen during implantation may contribute to abnormal placentation and subsequent aberrant or inadequate uteroplacental circulation that plays a central role in the pathogenesis of preeclampsia. This hypothesis is supported by a study in baboons that found vascular invasion of uterine spiral arteries was markedly decreased after exposure to serum estradiol levels threefold above normal in the first trimester [2]. Furthermore, a recent study demonstrated women exposed to estradiol levels greater than the 90th percentile for their institution had a significant increased risk of preeclampsia (4.5 % without elevated estradiol levels vs. 18.5 % estradiol >90th percentile) [9].

Interestingly, relative to the risk of preeclampsia among spontaneously conceived pregnancies, the risk of *severe* preeclampsia was greater than the risk of *mild* preeclampsia among deliveries after hyperestrogenic OS. It has been hypothesized that preeclampsia is more than one disease characterized by distinct features in severe or early-onset preeclampsia. In particular, studies evaluating placental pathology among those with an early onset, most commonly defined as disease onset prior to 34 weeks, found an increase in vascular lesions, small placental size, and placental insufficiency, which was not seen in preeclampsia diagnosed late in the third trimester [11, 14, 15]. If supraphysiologic estrogen during ovarian stimulation does in fact cause aberrant placentation, a higher risk of severe compared to mild preeclampsia would be expected, as was seen in our study.

Results of the current study cannot exclude alternative mechanisms for increased risk of preeclampsia, such as the infertility itself. We sought to answer this question by including deliveries after OS with traditional estrogen elevating medications and after aromatase inhibitor stimulation, where estrogen levels are not supraphysiologic. Both groups would theoretically have infertility requiring some type of ovarian stimulation. We found only the former group to have elevated adjusted odds of preeclampsia, suggesting there is a mechanism other than infertility contributing to the increased risk. One could argue, however, that women using aromatase inhibitor stimulation may have less severe infertility

than those requiring traditional hyperestrogenic OS medications. In addition, we cannot rule out that ART procedures themselves are contributing to the increased risk or preeclampsia, given that the aOR for hyperestrogenic OS with ART was slightly higher than the aOR for hyperestrogenic OS without ART deliveries. In order to better address this question, including a comparison group of pregnancies conceived by ART with non-hyperestrogenic aromatase inhibitor stimulation only, or by transfer of a frozen embryo into a more physiologic hormonal environment would have been beneficial. The former group only comprised 0.2 % of ART cycles in our database and was therefore too small to include and draw meaningful conclusions from. We were only able to identity approximately 1/3 of the expected number of frozen embryo transfers among the ART cycles in our database. Given that this population was much smaller than expected, we were concerned about possible ascertainment bias and did not include them in this analysis. Further research is needed to evaluate risks of preeclampsia after unstimulated or minimally stimulated ART cycles.

The strengths of our study include a large, contemporary database with the ability to identify appropriate comparison groups for the ART population; specifically women undergoing OS without ART and those using aromatase inhibitors only. Additionally, we were able to control for important maternal characteristics such as age and parity, as well as comorbid conditions that may predispose women seeking infertility treatment to preeclampsia.

This study was subject to several limitations. First, there are inherent limitations when relying on ICD-9 codes to identify comorbidities and pregnancy related conditions. In California, however, a recent report found that sensitivity of reporting was 60–80 % or better for common pregnancy related comorbidities [24]. MarketScan is a health insurance claims database, therefore, any woman who did not file a claim for prescriptions, office visits, or procedures may have been misclassified. If ART procedures were not covered by insurance, claims would not likely be filed, and thus underreporting of ART would occur, leading to misclassification of the exposure. In IVF cycles using donor embryos, medications are administered to target physiologic hormone levels, and such pregnancies should have been excluded from our hyperestrogenic OS ART group. There are no ICD-9-CM or CPT code designating donor embryo transfer and we therefore could not exclude them. According to the National ART Surveillance System data, donor embryo transfers accounted for 12 % of ART cycles in 2011 [1]. These limitations, however, would equalize the hyperestrogenic OS with ART and spontaneous conception groups, minimizing differences found. Another limitation is our inability to include multiple gestations and stillbirths due to the small number of these pregnancies within the ART group, and therefore the inability to draw meaningful conclusions from any association found. Finally, this is an observational study that does not provide information on the pathophysiology of preeclampsia.

Preeclampsia affects up to 8 % of all pregnancies [7] and is a tremendous burden to the affected mother and her fetus. One in seven preterm births and one in ten maternal deaths are directly related to preeclampsia and eclampsia [5]. This study adds to the growing body of evidence that the potentially modifiable hormonal milieu during ovarian stimulation contributes to the risk of preeclampsia. By identifying this potentially modifiable risk factor, we can start to develop strategies to minimize risk for women undergoing ART and ovarian stimulation. In addition, understanding the etiology of preeclampsia could lead

to the development of effective preventive interventions for all women, regardless of ovarian stimulation or ART use.

## 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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## Significance

**What is already known on this subject?**

Preeclampsia is one of the leading causes of maternal and fetal morbidity and mortality in the United States. Elevated estrogen in earl pregnancy may play a role in the abnormal placentation seen in preeclampsia.

*What this study adds* we found ovarian stimulation medications known to increase serum estrogen levels increased the risk of preeclampsia. This potentially modifiable hormonal milieu during ovarian stimulation, allows for the development of strategies to minimize risk for women undergoing assisted reproductive technology and ovarian stimulation. In addition, understanding the etiology of preeclampsia could lead to the development of effective preventive interventions for all women, regardless of ovarian stimulation or assisted reproductive technology use.

**Table 1**

Demographic characteristics of the study group

| | Spontaneous conception N (%) | Hyperestrogenic OS with ART N (%) | Hyperestrogenic OS without ART[a] N (%) | Non-hyperestrogenic OS without ART[a] N (%) |
|---|---|---|---|---|
| Total | 1,014,526 | 6881 | 27,516 | 2117 |
| Age | | | | |
| <25 | 127,939 (12.6) | 54 (0.8) | 841 (3.1) | *b* |
| 25–34 | 670,721 (66.1) | 3301 (48.0) | 17,617 (64.0) | 1459 (68.9) |
| 35–44 | 213,499 (21.1) | 3459 (50.2) | 9000 (32.7) | 573 (27.1) |
| ≥45 | 2367 (0.2) | 67 (1.0) | 58 (0.2) | *b* |
| *p* value[c] | | <0.0001 | <0.0001 | <0.0001 |
| Parity | | | | |
| Multiparous | 329,539 (32.5) | 3657 (53.1) | 11,770 (42.8) | 863 (40.8) |
| Non-nulliparous | 684,987 (67.5) | 3224 (46.9) | 15,746 (57.2) | 1254 (59.2) |
| *p* value[c] | | <0.0001 | <0.0001 | <0.0001 |
| Comorbid condition | | | | |
| Tobacco use | 27,499 (2.7) | 65 (0.9) | 314 (1.1) | 34 (1.6) |
| *p* value[c] | | <0.0001 | <0.0001 | 0.001 |
| Pregestational diabetes | 21,759 (2.1) | 208 (3.0) | 891 (3.2) | 73 (3.5) |
| *p* value[c] | | <0.0001 | <0.0001 | 0.0001 |
| Gestational diabetes | 71,724 (7.1) | 707 (10.3) | 2854 (10.4) | 213 (10.1) |
| *p* value[c] | | <0.0001 | <0.0001 | <0.0001 |
| Chronic hypertension | 38,284 (3.8) | 310 (4.5) | 1159 (4.2) | 110 (5.2) |
| *p* value[c] | | 0.002 | 0.0002 | 0.001 |
| Obesity | 47,292 (4.7) | 310 (4.5) | 1492 (5.4) | 137 (6.5) |
| *p* value[c] | | 0.566 | <0.0001 | 0.0002 |
| Region of delivery | | | | |
| Northeast | 115,602 (11.4) | 1738 (25.3) | 5561 (20.2) | 101 (4.8) |
| North-central | 251,264 (24.8) | 1950 (28.3) | 8926 (32.4) | 474 (22.4) |
| South | 422,737 (41.7) | 2320 (33.7) | 8072 (29.3) | 1239 (58.5) |

| | Spontaneous conception N (%) | Hyperestrogenic OS with ART N (%) | Hyperestrogenic OS without ART[a] N (%) | Non-hyperestrogenic OS without ART[a] N (%) |
|---|---|---|---|---|
| West | 214,212 (21.1) | *b* | 4835 (17.6) | *b* |
| Unknown | 10,711 (1.0) | *b* | 122 (0.5) | *b* |
| *p* value[c] | | <0.0001 | <0.0001 | <0.0001 |

Bonferroni corrected *p* value ≤0.002 denotes statistical significance

*OS* ovarian stimulation, *ART* assisted reproductive technology

[a] Includes women who underwent ovarian stimulation only and ovarian stimulation with intrauterine insemination

[b] Not reported due to small number to protect patient confidentiality

[c] Chi-square or Fisher Exact test *p* value compared to spontaneous conception

**Table 2**

Odds of preeclampsia in pregnancies after hyperestrogenic and non-hyperestrogenic ovarian stimulation compared to spontaneous conceptions

| | Mild preeclampsia | | | Severe preeclampsia | | |
|---|---|---|---|---|---|---|
| | N (%) | OR (95 % CI) | aOR[a] (95 % CI) | N (%) | OR (95 % CI) | aOR[a] (95 % CI) |
| Spontaneous conception | 25,401 (2.5) | Reference | Reference | 16,351 (1.6) | Reference | Reference |
| Hyperestrogenic OS with ART | 236 (3.4) | 1.39 (1.22–1.58) | **1.42 (1.24–1.62)** | 210 (3.1) | 1.92 (1.67–2.21) | **1.83 (1.59–2.11)** |
| Hyperestrogenic OS without ART | 894 (3.6) | 1.31 (1.22–1.40) | **1.32 (1.24–1.42)** | 677 (2.5) | 1.54 (1.43–1.67) | **1.53 (1.41–1.66)** |
| Non-hyperestrogenic OS without ART | 68 (3.2) | 1.29 (1.02–1.65) | 1.16 (0.91–1.48) | 46 (2.2) | 1.36 (1.01–1.82) | 1.17 (0.87–1.57) |

Bold values indicate significant adjusted odds ratios

*OR* odds ratio, *CI* confidence intervals, *aOR* adjusted odds ratio, *OS* ovarian stimulation, *ART* assisted reproductive technology

[a]Adjusted for age, parity, comorbid conditions (pregestational diabetes, gestational diabetes, chronic hypertension and obesity), and region of delivery (Northeast, North-central, Midwest, South, and West) in a multilevel logistic model