HHS Public Access

Author manuscript

*Obstet Gynecol*. Author manuscript; available in PMC 2023 December 01.

Published in final edited form as:

*Obstet Gynecol*. 2022 December 01; 140(6): 939–949. doi:10.1097/AOG.0000000000004936.

# Obstetric and Neonatal Outcomes One or More Years After a Diagnosis of Breast Cancer

**Kirsten JORGENSEN, MD**,
The University of Texas MD Anderson Cancer Center, Department of Gynecologic Oncology and Reproductive Medicine, Houston, Texas

**Roni NITECKI, MD MPH**,
The University of Texas MD Anderson Cancer Center, Department of Gynecologic Oncology and Reproductive Medicine, Houston, Texas

**Hazel B. NICHOLS, PhD**,
University of North Carolina Gillings School of Global Public Health, Chapel Hill, North Carolina

**Shuangshuang FU, PhD**,
University of Texas Health Science Center at Houston, /University of Texas MD Anderson Cancer Center, Houston, Texas

**Chi-Fang WU, PhD**,
University of Texas Health Science Center at Houston, /University of Texas MD Anderson Cancer Center, Houston, Texas

**Alexander MELAMED, MD MPH**,
New York-Presbyterian /Columbia University Medical Center, Department of Obstetrics and Gynecology, Division of Gynecologic Oncology, New York, New York

**Paula BRADY, MD**,
Columbia University Irving Medical Center, Department of Obstetrics and Gynecology, Division of Reproductive Endocrinology, New York, New York

**Mariana CHAVEZ-MACGREGOR, MD MSC**,
The University of Texas MD Anderson Cancer Center, Department of Breast Oncology, Department of Health Services Research, Division of Cancer Prevention and Population Sciences, Houston, Texas

**Mark A. CLAPP, MD MPH**,
Massachusetts General Hospital, Department of Obstetrics and Gynecology, Maternal-Fetal Medicine Program, Boston, Massachusetts

**Sharon GIORDANO, MD MPH FASCO**,

**Corresponding Author:** Kirsten Jorgensen, MD, Dept. of Gynecologic Oncology and Reproductive Medicine, Dept. of Health Services Research, The University of Texas MD Anderson Cancer Center, Houston, TX, kajorgensen@mdanderson.org.

Financial Disclosure

Mark A. Clapp received payment from Delfina Care for serving on the advisory board (no relation to content of submitted work). Jose Alejandro Rauh-Hain received payment from the NIH, Guidepoint, and the Schlesinger Group. He also received payment once as a speaker for J&J. The other authors did not report any potential conflicts of interest.

Each author has confirmed compliance with the journal's requirements for authorship.

The University of Texas MD Anderson Cancer Center, Department of Breast Medical Oncology, Department of Health Services Research, Houston, Texas

**J. Alejandro RAUH-HAIN, MD, MPH**
The University of Texas MD Anderson Cancer Center, Department of Gynecologic Oncology and Reproductive Medicine

## Abstract

**Objective:** To evaluate obstetric and neonatal outcomes of the first live birth conceived one or more years following breast cancer diagnosis.

**Methods:** We performed a population-based study to compare live births between women with a history of breast cancer and matched controls with no cancer history. Cases and controls were identified using linked data from the California Cancer Registry and California Office of Statewide Health Planning and Development datasets. Cases were diagnosed with stage I-III breast cancer at ages 18-45 years between January 1, 2000, and December 31, 2012, and conceived ≥12 months after breast cancer diagnosis. Controls were covariate–matched women without a history of breast cancer who delivered during 2000-2012. The primary outcome was preterm birth <37 weeks. Secondary outcomes were preterm birth <32 weeks, small for gestational age, cesarean delivery, severe maternal morbidity, and neonatal morbidity. Subgroup analyses were used to assess time from initial treatment to conception and receipt of additional adjuvant therapy prior to pregnancy on outcomes of interest.

**Results:** Of 30,021 women age 18-45 diagnosed with stage I-III breast cancer during 2000-2012, 553 met the study inclusion criteria. Those with a history of breast cancer and matched controls had similar odds of preterm birth <37 weeks (odds ratio [OR], 1.29; 95% CI, 0.95-1.74), preterm birth <32 weeks (OR, 0.77; 95% CI, 0.34-1.79), delivering a small for gestational age neonate (<5th percentile: OR, 0.60; 95% CI, 0.35-1.03; <10th percentile: OR, 0.94; 95% CI, 0.68-1.30), and experiencing severe maternal morbidity (OR, 1.61; 95% CI, 0.74-3.50). Patients with a history of breast cancer had higher odds of undergoing a cesarean delivery (OR, 1.25; 95% CI, 1.03-1.53), however their offspring did not have increased odds of neonatal morbidity compared to controls (OR, 1.15; 95% CI, 0.81-1.62).

**Conclusion:** Breast cancer ≥1 year before conception was not strongly associated with obstetric and neonatal complications.

## Precis:

Obstetric and neonatal outcomes ≥ 1 year following breast cancer diagnosis are similar to obstetric and neonatal outcomes for individuals without a cancer history.

## Introduction

Breast cancer is the most commonly diagnosed malignancy among female adolescents and young adults, accounting for 30% of the cancers in these groups.[1] Despite increasing incidence of breast cancer in young women[1] and a growing population of premenopausal breast cancer survivors, they remain a relatively understudied population. Addressing the

unique needs of this population has emerged as a public health priority,[2,3] particularly providing guidance for patients interested in pregnancy.[4]

Retaining the ability to have children is one of the most important determinants of reproductive-age cancer survivors' quality of life after treatment,[5] and has a positive impact on the ability to cope with cancer.[4,6-8] However, while many premenopausal breast cancer survivors desire biological children,[9,10] pregnancy rates in this population are significantly lower than their age-matched peers.[11] Among the reasons for not pursuing pregnancy after breast cancer, a meta-analysis identified fear of adverse obstetric outcomes as an important barrier to parenthood.[7]

A limited number of retrospective reviews demonstrate increased rates of preterm birth,[12] growth restriction,[13,14] and cesarean delivery[15] among cancer survivors. However, most studies of pregnancy outcomes among survivors of various cancers include those who deliver ≤12 months following diagnosis and lack specificity regarding cancer type, stage, treatment, neonatal and obstetric outcomes.[16-19] The objective of this study was to compare obstetric and neonatal outcomes between breast cancer survivors and women without a history of cancer. We hypothesized that breast cancer survivors who conceive ≥12 months after diagnosis have similar rates of obstetric and neonatal complications compared to healthy controls.

## Methods

We performed a population-based analysis using an approach we have previously described,[20] with linked data from the California Cancer Registry and California Office of Statewide Health Planning and Development (OSHPD). We obtained approval for this study from the Institutional Review Board of The University of Texas MD Anderson Cancer Center, OSHPD, the California Cancer Registry, and the State of California Committee for the Protection of Human Subjects.

The California Cancer Registry is California's statewide population-based cancer surveillance system and includes data on incident cancers diagnosed among state residents.[21] The California OSHPD inpatient and ambulatory surgery discharge datasets are generated via mandated hospital reporting and contain patient-level demographic, diagnostic, treatment, disposition, and charge data for every inpatient and ambulatory surgery discharge. The California OSHPD datasets include maternal antepartum and postpartum hospital records for the 9 months before and 1 year after delivery, including information regarding the delivery, neonatal complications, and infant data. Diagnosis and procedure codes in the OSHPD datasets are based on the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9). The OSHPD datasets exclude deliveries in military facilities, homes, out-of-state facilities, and birthing centers not reporting to the California OSHPD.

California Cancer Registry records were linked to OSHPD records for patients diagnosed between January 2000 and December 2012. The data linkage was conducted by OSHPD following deterministic matching procedures using a combination of maternal date of birth,

social security number, and ZIP code. These procedures established a linked database with both oncologic characteristics and obstetric and neonatal outcomes, as previously reported.[20]

The reliability of the databases and variables utilized in this study has been previously demonstrated,[22,23] with up to 98% accurate linkage between vital statistics and maternal, neonatal and infant hospital discharge records.[24-26] Cancer case reporting to the California Cancer Registry is overall accurate, with audits confirming a 99% reporting rate.[25] The California Cancer Registry has been linked to OSHPD datasets for prior studies of pregnancy outcomes in patients with other types of cancers.[20]

Using the California Cancer Registry, we identified women ages 18-45 diagnosed with stage I-III breast cancer (according to the 8th edition of the American Joint Committee on Cancer staging manual)[27] between January 1, 2000, and December 31, 2012 (n=30,021). We then linked each eligible woman with breast cancer to the OSHPD dataset. Using a method we have previously described,[20] we identified births in this group and calculated the date of conception by subtracting the estimated gestational age at delivery from date of delivery. We defined cases as those patients who conceived at least 12 months after the diagnosis of breast cancer, rationalizing that this duration would account for time required for most adjuvant therapies.[20,28] Of the 30,021 women diagnosed with breast cancer, we excluded those who did not have a pregnancy (n=22,094), whose births were missing a delivery date (n=2,325) or showed unlikely combinations of living status and gestational age [<22 weeks or >45 weeks; (n=81)], deliveries prior to 20 weeks gestational age (n=247), those with pregnancies conceived before or within the 12 months following cancer diagnosis (n=4,673), and patients whose date of birth in the California Cancer Registry was inconsistent with the date of birth in the linked OSHPD file (n=48) (Figure 1). To focus our analyses on deliveries closest to cancer diagnosis and treatment, we included only the first post-diagnosis birth that occurred during the study period. Controls were derived from the 3,691,280 patients who delivered in California during the years 2000-2012 and who did not link to a record in the California Cancer Registry.

The primary outcome was preterm birth, defined as birth at <37 weeks because this outcome is a leading cause of obstetric morbidity in the U.S.[29,30] and has good validity in this dataset.[31] Secondary outcomes of interest were preterm birth <32 weeks[32]; small for gestational age (SGA) neonate, defined as a neonate below the fifth percentile and below the tenth percentile of birth weight for sex and gestational age;[33] cesarean delivery; fetal demise; severe maternal morbidity; and neonatal morbidity. Neonatal morbidity was defined as the presence of 1 or more of the 9 indicators of neonatal morbidity, adapted from Grobman and colleagues (Box 1).[34] Severe maternal morbidity was defined as the presence of 1 or more of the 21 indicators established by the Centers for Disease Control and Prevention algorithm (Box 1).[35]

We compared distributions of demographic and clinical data using the Pearson chi-square test or Fisher exact test when appropriate for categorical data and the Student t-test or Wilcoxon rank-sum test for continuous variables. To match controls to cases, we used greedy nearest neighbor propensity-score matching without replacement in a 1:3 ratio of cases to controls with a caliper width set to 0.2 times the standard deviation of the

propensity score. We selected a breast cancer case, and then selected as a matched subject, the control whose propensity scores was closest to that of the breast cancer case. This created a cohort of subjects who differed with respect to their history of breast cancer but were balanced on observed covariates. Covariates examined in this study (Table 1) included: age (continuous), education (<12 years, ≥12 years, or missing), insurance status (public, private, uninsured, or missing), race and ethnicity (Asian or Pacific Islander, Black, Hispanic, non-Hispanic White, or none of the above), annual income (in quartiles), year of delivery, parity (nulliparous or multiparous), trimester of entry to prenatal care, fetal number per gestation (singleton, twin, or triplet or more), and the presence of maternal comorbidities as defined by the Centers for Disease Control and Prevention, including hypertension (none, chronic, gestational, pre-eclampsia, or severe preeclampsia or eclampsia), diabetes mellitus (none, pregestational, or gestational), renal disease, and abnormal placentation. Covariates were obtained from hospital records at time of delivery. Our study investigated obstetric and neonatal outcomes that vary by the race and ethnicity of the pregnant woman, therefore, we included race and ethnicity data to account for possible confounding.[36]

To assess for outcome differences according to use of systemic chemotherapy, we conducted subgroup analyses stratifying cases by receipt of chemotherapy, as chemotherapy exposure has previously been associated with worse obstetric and neonatal outcomes.[15,20,37,38] We controlled for stage in this analysis. We also stratified the cases by months from initial date of treatment to conception (24-60 months, and >60 months, compared to <24 months),[39] as recommendations during the study period included waiting least 24 months before conception because of high risk of early tumor recurrence[40]; more than 24 months for women who are younger and those with more aggressive tumor types; and greater than 60 months for those with estrogen-receptor-positive breast cancer.[41] An analysis of primary and secondary outcomes for patients who conceived between 3 and 12 months after diagnosis is included in Appendix 1**, available online at** http://links.lww.com/xxx, for comparison purposes.

Logistic regression and Wald statistics were used to calculate the odds ratio (OR) and 95% confidence intervals (CI) for the association between breast cancer status and the various obstetric and neonatal outcomes. All statistical tests were 2-sided with thresholds for statistical significance set at $P<0.05$ and a 95% CI not inclusive of the null (1.0). Those with missing values on outcomes of interest were not included in the matching process and removed from the regression model. These analyses were implemented in SAS Enterprise Guide, version 7.11 (SAS Institute Inc.).

We performed a secondary descriptive analysis and reviewed all cases to identify the number of cases with two or more pregnancies following a diagnosis of breast cancer. We then performed descriptive statistics on outcomes of interest among this population.

We conducted sensitivity analyses to evaluate how robust the associations were to potential unmeasured confounding. We used the “E-value,”[42] a measure that makes minimal assumptions, to quantify the minimum strength of association that an unmeasured confounder must have with both the exposure (breast cancer diagnosis) and the outcome to fully explain away the measured association. We calculated E-values of our adjusted ORs

to estimate unmeasured confounding that would be required to shift a near-null association to a clinically meaningful difference (RR 2.0) and shift the lower limit of the confidence interval to exclude the null (Appendix 2**, available online at** http://links.lww.com/xxx). These analyses were implemented in Stata version 17.

## Results

Of the 30,021 women age 18-45 diagnosed with stage I-III breast cancer between January 1, 2000 and December 31, 2012, and reported to the California Cancer Registry, 553 met the study inclusion criteria (Figure 1). Using propensity scores in a 1:3 ratio, we matched 1,659 controls to the 553 breast cancer cases, for a total of 2,212 in the matched cohort. Before propensity-score matching, there were significant differences between the groups. Compared to the population controls, breast cancer patients were older, more likely to be Non-Hispanic White, more often nulliparous, more often privately insured, with lower rates of gestational diabetes, and abnormal placentation. There were no significant differences between cases and population controls in the rates of hypertensive disease, pregestational diabetes, or renal disease. After propensity-score matching, there were no differences in the distributions of observed demographic and clinical covariates between groups (Table 1).

In the propensity-matched cohort there were no statistically significant differences between breast cancer cases and controls in preterm birth <37 weeks (OR, 1.29; 95% CI, 0.95-1.74) or preterm birth <32 weeks (OR, 0.77; 95% CI, 0.34-1.79). (Figure 2) Frequencies of preterm delivery (<37 weeks) by stage are available in Appendix 3**, available online at** http://links.lww.com/xxx. Breast cancer patients and controls exhibited statistically similar odds of an SGA neonate (<5th percentile: OR, 0.60; 95% CI, 0.35-1.03; <10th percentile: OR, 0.94; 95% CI, 0.68-1.30), severe maternal morbidity (OR, 1.61; 95% CI, 0.74-3.50), and neonatal morbidity (OR, 1.15; 95% CI, 0.81-1.62). Breast cancer patients had higher odds of undergoing cesarean delivery (OR, 1.25; 95% CI, 1.03-1.53) than women without a history of cancer. There were overall only 5 instances of fetal demise in the dataset (1 among cases and 4 among controls) (OR 0.75; 95% CI 0.08-6.72), limiting interpretability of odds ratios, thus it was not included in Figure 2.

In subgroup analysis, receipt of chemotherapy among cases did not modify neonatal or obstetric outcomes (Table 2). Breast cancer history was associated with decreased odds of preterm birth <37 weeks for those who conceived 24-60 months after initiating treatment when compared to those who conceived <24 months following treatment initiation (OR 0.42; 95% CI, 0.24-0.75, $P<.01$), but not among those who conceived >60 months following treatment initiation (Table 3). The majority of preterm deliveries occurred among conceptions between 12 and 60 months of diagnosis (Table 4). Analysis of cases with more than one pregnancy following a diagnosis of breast cancer revealed 94 women accounting for 104 pregnancies that met criteria, see Appendix 4**, available online at** http://links.lww.com/xxx, for descriptive statistics.

Sensitivity analysis demonstrated an unmeasured confounder would need to be associated with both breast cancer and preterm birth <37 weeks with a risk ratio of at least 2.47 to shift the OR to 2.0 (previously specified clinically meaningful difference), and by a risk ratio

of at least 1.25 to shift the lower confidence level to exclude the null (from 0.95 to 1.01) (Appendix 6**, available online at** http://links.lww.com/xxx).

## Discussion

We observed that odds of obstetric and neonatal complications among women with a history of breast cancer were similar to those in matched population-based controls, with the exception of higher odds of cesarean delivery for those with a history of breast cancer.

Consistent with our findings, a Danish study of 695 births and a North Carolina study did not find significant associations between breast cancer diagnosis and preterm birth or low birth weight.[43, 44] In contrast, Hartnett and colleagues reported that breast cancer survivors had a higher risk of preterm birth and low birth weight than women without cancer.[45] A meta-analysis reviewing nine studies found an increased risk of preterm birth and SGA among those born to mothers with a history of breast cancer compared to the general population.[15] However, it included patients who delivered <12 months after diagnosis, and prior studies demonstrate an increased risk of preterm birth during this time.[12] Our study included only those with conception ≥12 months following diagnosis.

Prior studies of women with any cancer history suggest mixed results regarding maternal morbidity, with some demonstrating higher rates of postpartum or antepartum complications,[46,47] and others demonstrating no difference among breast cancer survivors specifically.[48] The rate of cesarean delivery in our study was 45.6%, within the upper range of cesarean delivery rates previously reported in the literature.[15] Prior studies have suggested that the risk of cesarean delivery might be increased in women with a history of breast cancer because of closer monitoring compared to the general population.[44,49,50] Sensitivity analysis demonstrated that moderate unmeasured confounders could explain away the study association, these include obesity, time of day, prior obstetric history, and delivering facility, among others.[51,52] Limitations of the datasets used in our study precluded analysis of these variables.

In subgroup analyses among breast cancer patients who received chemotherapy compared to breast cancer patients that did not receive chemotherapy, we did not find a statistically significant difference in adverse obstetrical or neonatal outcomes after controlling for stage. Our results are consistent with prior analysis from North Carolina that found no difference in preterm birth <37 weeks or SGA neonate <10th percentile among breast cancer survivors who received chemotherapy compared to population controls.[15,44]

In our study, women with a history of breast cancer who conceived 24-60 months following treatment initiation had decreased odds of preterm birth relative to those who conceived <24 months following treatment initiation. This is similar to prior studies that demonstrated higher risk of preterm birth among cancer survivors.[15] However, the difference was not significant for women who conceived >60 months following treatment initiation, suggesting attenuation of the benefit of waiting to conceive.

This study represents a large, single-study assessment of obstetric outcomes in breast cancer patients who had a successful pregnancy with conception ≥12 months following

diagnosis. The linked database used in our study was robust and allowed for assessment of a heterogeneous population, increasing generalizability. The use of a sensitivity analysis in our study provided further clarity on the impact of unmeasured confounders.

Limitations of our study include lack of random allocation, inability to verify registry data, lack of data for all possible confounding variables, and use of historical data reflecting prior management of breast cancer treatment and pregnancy. Additionally, this study was underpowered due to an overall small number of outcomes, despite being a large database cohort study. The databases are limited to administratively entered codes and are subject to possible underreporting or misclassification of variables, as well as inaccuracies in the linkage process. We were unable to control for prior preterm birth, a risk factor for subsequent preterm birth,[29] due to limitations in the datasets, though the absence of a significant association between preterm birth and breast cancer diagnosis in our study suggests that prior preterm birth is not a confounder. Lastly, we matched for risk factors for adverse obstetric outcomes, including history of pregnancy-induced hypertension, pre-eclampsia, and eclampsia, thus possibly muting an association seen in higher rates among breast cancer survivors, however, there was overall a low number of cases with these risk factors and baseline characteristics prior to matching were similar.

The results of this study may facilitate clinical decision-making for patients, oncologists, and obstetricians by informing the risks of adverse events surrounding pregnancy among breast cancer survivors. It adds to a limited number of published studies on the obstetric and neonatal outcomes after breast cancer. Using unique database linkages, such as those in our study, could strengthen the design of prospective studies and address limitations of prior prospective studies.[53]

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgments

Editorial support was provided by Stephanie Deming, ELS, of the Research Medical Library at The University of Texas MD Anderson Cancer Center. Ms. Deming’s sole compensation for this work was her salary, which is paid by The University of Texas MD Anderson Cancer Center.

### Sources of Funding:

This work was supported by grants from the National Institutes of Health, including grants from the National Cancer Institute (K08CA234333 [J. Alejandro Rauh-Hain]; P30CA016672 [Roni Nitecki, Sharon Giordano, Shuanshuang Fu, Kirsten Jorgensen, and J. Alejandro Rauh-Hain]; and T32CA101642 [Roni Nitecki and Kirsten Jorgensen], and the National Center for Advancing Translational Sciences (KL2TR001874 [Alexander Melamed]. Sharon Giordano is supported by CPRIT RP160675 and Komen SAC150061. The funding sources were not involved in development of the research hypothesis; study design; data collection, analysis, or interpretation; manuscript writing; or the decision to submit the article for publication.

## References

1. Cathcart-Rake EJ, Ruddy KJ, Bleyer A, Johnson RH. Breast cancer in adolescent and young adult women under the age of 40 years. JCO Oncol Pract. Published online January 15, 2021. doi:10.1200/OP.20.00793

2. Smith AW, Seibel NL, Lewis DR, Albritton KH, Blair DG, Blanke CD, et al. Next steps for adolescent and young adult oncology workshop: an update on progress and recommendations for the future. Cancer. 2016;122(7):988–999. doi:10.1002/cncr.29870 [PubMed: 26849003]

3. Nass SJ, Beaupin LK, Demark-Wahnefried W, Fasciano K, Ganz PA, Hayes-Lattin B, et al. Identifying and addressing the needs of adolescents and young adults with cancer: summary of an institute of medicine workshop. Oncologist. 2015;20(2):186–195. doi:10.1634/theoncologist.2014-0265 [PubMed: 25568146]

4. Deshpande NA, Braun IM, Meyer FL. Impact of fertility preservation counseling and treatment on psychological outcomes among women with cancer: a systematic review. Cancer. 2015;121(22):3938–3947. doi:10.1002/cncr.29637 [PubMed: 26264701]

5. Letourneau JM, Ebbel EE, Katz PP, Ai WZ, Chien AJ, Melisko ME, et al. Pre-treatment fertility counseling and fertility preservation improve quality of life in reproductive age women with cancer. Cancer. 2012;118(6):1710–1717. doi:10.1002/cncr.26459 [PubMed: 21887678]

6. Peate M, Meiser B, Friedlander M, Zorbas H, Rovelli S, Sansom-Daly U, et al. It's now or never: fertility-related knowledge, decision-making preferences, and treatment intentions in young women with breast cancer—an Australian fertility decision aid collaborative group study. J Clin Oncol. Published online March 28, 2011. doi:10.1200/JCO.2010.31.2462

7. Peate M, Meiser B, Hickey M, Friedlander M. The fertility-related concerns, needs and preferences of younger women with breast cancer: a systematic review. Breast Cancer Res Treat. 2009;116(2):215–223. doi:10.1007/s10549-009-0401-6 [PubMed: 19390962]

8. Chan JL, Letourneau J, Salem W, Cil AP, Chan SW, Chen LM, et al. Regret around fertility choices is decreased with pre-treatment counseling in gynecologic cancer patients. J Cancer Surviv. 2017;11(1):58–63. doi:10.1007/s11764-016-0563-2 [PubMed: 27480882]

9. Edge B, Holmes D, Makin G. Sperm banking in adolescent cancer patients. Arch Dis Child. 2006;91(2):149–152. doi:10.1136/adc.2005.075242 [PubMed: 16174641]

10. Soliman H, Agresta SV. Current issues in adolescent and young adult cancer survivorship. Cancer Control. 2008;15(1):55–62. doi:10.1177/107327480801500107 [PubMed: 18094661]

11. Stensheim H, Cvancarova M, Møller B, Fosså SD. Pregnancy after adolescent and adult cancer: a population-based matched cohort study. Int J Cancer. 2011;129(5):1225–1236. doi:10.1002/ijc.26045 [PubMed: 21387311]

12. Hartnett KP, Mertens AC, Kramer MR, Lash TL, Spencer JB, Ward K, et al. Pregnancy after cancer: does timing of conception affect infant health? Cancer. 2018;124(22):4401–4407. doi:10.1002/cncr.31732 [PubMed: 30403424]

13. Madanat-Harjuoja LM, Malila N, Lähteenmäki P, Boice JD, Gissler M, Dyba T. Preterm delivery among female survivors of childhood, adolescent and young adulthood cancer. Int J Cancer. 2010;127(7):1669–1679. doi:10.1002/ijc.25157 [PubMed: 20054856]

14. Stensheim H, Klungsøyr K, Skjærven R, Grotmol T, Fosså SD. Birth outcomes among offspring of adult cancer survivors: a population-based study. Int J Cancer. 2013;133(11):2696–2705. doi:10.1002/ijc.28292 [PubMed: 23729011]

15. Lambertini M, Blondeaux E, Bruzzone M, Parachino M, Anderson RA, de Azambuja E, et al. Pregnancy after breast cancer: a systematic review and meta-analysis. J Clin Oncol. 2021;39(29):3293–3305. doi:10.1200/JCO.21.00535 [PubMed: 34197218]

16. Gunderson CC, Fader AN, Carson KA, Bristow RE. Oncologic and reproductive outcomes with progestin therapy in women with endometrial hyperplasia and grade 1 adenocarcinoma: a systematic review. Gynecol Oncol. 2012;125(2):477–482. doi:10.1016/j.ygyno.2012.01.003 [PubMed: 22245711]

17. Eskander RN, Randall LM, Berman ML, Tewari KS, Disaia PJ, Bristow RE. Fertility preserving options in patients with gynecologic malignancies. Am J Obstet Gynecol. 2011;205(2):103–110. doi:10.1016/j.ajog.2011.01.025 [PubMed: 21411052]

18. Plante M. Vaginal radical trachelectomy: an update. Gynecol Oncol. 2008;111(2 Suppl):S105–S110. doi:doi:10.1016/j.ygyno.2008.07.020 [PubMed: 18755501]

19. Satoh T, Hatae M, Watanabe Y, Yaegashi N, Ishiko O, Kodama S, et al. Outcomes of fertility-sparing surgery for stage I epithelial ovarian cancer: a proposal for patient selection. J Clin Oncol. 2010;28(10):1727–1732. doi:10.1200/JCO.2009.24.8617 [PubMed: 20194858]

20. Nitecki RM, Clapp MAM, Fu S, Lamiman K, Brady PC, Kaimal A, et al. Outcomes of the first pregnancy after fertility-sparing surgery for early-stage ovarian cancer. Obstet Gynecol. 2021;137(6):1109–1118. doi:10.1097/AOG.0000000000004394 [PubMed: 33957660]
21. Pfaendler KS, Chang J, Ziogas A, Bristow RE, Penner KR. Disparities in adherence to National Comprehensive Cancer Network treatment guidelines and survival for stage IB-IIA cervical cancer in california. Obstet Gynecol. 2018;131(5):899–908. doi:10.1097/AOG.0000000000002591 [PubMed: 29630020]
22. Schmitt SK, Sneed L, Phibbs CS. Costs of newborn care in California: a population-based study. Pediatrics. 2006;117(1):154–160. doi:10.1542/peds.2005-0484 [PubMed: 16396873]
23. Main EK, McCain CL, Morton CH, Holtby S, Lawton ES. Pregnancy-related mortality in California: causes, characteristics, and improvement opportunities. Obstet Gynecol. 2015;125(4):938–947. doi:10.1097/AOG.0000000000000746 [PubMed: 25751214]
24. Gilbert WM, Nesbitt TS, Danielsen B. Childbearing beyond age 40: pregnancy outcome in 24,032 cases. Obstet Gynecol. 1999;93(1):9–14. doi:10.1016/s0029-7844(98)00382-2 [PubMed: 9916947]
25. Leiserowitz GS, Xing G, Cress R, Brahmbhatt B, Dalrymple JL, Smith LH. Adnexal masses in pregnancy: How often are they malignant? Gynecologic Oncology. 2006;101(2):315–321. doi:10.1016/j.ygyno.2005.10.022 [PubMed: 16310839]
26. Herrchen B, Gould J, Nesbitt T. Vital statistics linked birth/infant death and hospital discharge record linkage for epidemiological studies. Comput Biomed Res. 1997;30:290–305. doi:10.1006/cbmr.1997.1448 [PubMed: 9339323]
27. Amin MB, Gress DM, Vega LRM, Edge SB. AJCC Cancer Staging Manual. 8th edition. (Greene FL, Byrd DR, Brookland RK, Washington MK, Compton CC, eds.). Springer; 2017.
28. Nitecki R, Woodard T, Rauh-Hain JA. Fertility-sparing treatment for early-stage cervical, ovarian, and endometrial malignancies. Obstetrics & Gynecology. 2020;136(6):1157–1169. doi:10.1097/AOG.0000000000004163 [PubMed: 33156194]
29. ACOG. Prediction and Prevention of Spontaneous Preterm Birth: ACOG Practice Bulletin, Number 234. Obstet Gynecol. 2021;138(2):e65. doi:10.1097/AOG.0000000000004479 [PubMed: 34293771]
30. Martin JA, Hamilton BE, Osterman MJK, Driscoll AK. Births: Final Data for 2018. National Vital Statistics Reports. 2019;68(13):47.
31. Yasmeen S, Romano PS, Schembri ME, Keyzer JM, Gilbert WM. Accuracy of obstetric diagnoses and procedures in hospital discharge data. Am J Obstet Gynecol. 2006;194(4):992–1001. doi:10.1016/j.ajog.2005.08.058 [PubMed: 16580288]
32. World Health Organization. Preterm birth. Accessed October 14, 2021. https://www.who.int/news-room/fact-sheets/detail/preterm-birth
33. Aris IM, Kleinman KP, Belfort MB, Kaimal A, Oken E. A 2017 US reference for singleton birth weight percentiles using obstetric estimates of gestation. Pediatrics. 2019;144(1):e20190076. doi:10.1542/peds.2019-0076 [PubMed: 31201230]
34. Grobman WA, Rice MM, Reddy UM, Tita A, Silver RM, Mallett G, et al. Labor induction versus expectant management in low-risk nulliparous women. N Engl J Med. 2018;379(6):513–523. doi:10.1056/NEJMoa1800566 [PubMed: 30089070]
35. Centers for Disease Control and Prevention. How Does CDC Identify Severe Maternal Morbidity? Accessed October 13, 2021. https://www.cdc.gov/reproductivehealth/maternalinfanthealth/smm/severe-morbidity-ICD.htm
36. Bryant AS, Worjoloh A, Caughey AB, Washington AE. Racial/Ethnic Disparities in Obstetrical Outcomes and Care: Prevalence and Determinants. Am J Obstet Gynecol. 2010;202(4):335–343. doi:10.1016/j.ajog.2009.10.864 [PubMed: 20060513]
37. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Breast Cancer. Published online September 13, 2021. https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf
38. Blackburn BE, Ganz PA, Rowe K, Snyder J, Wan Y, Deshmukh V, et al. Reproductive and gynecological complication risks among thyroid cancer survivors. J Cancer Surviv. 2018;12(5):702–711. doi:10.1007/s11764-018-0707-7 [PubMed: 30128858]

39. Raphael J, Trudeau ME, Chan K. Outcome of patients with pregnancy during or after breast cancer: a review of the recent literature. Curr Oncol. 2015;22(Suppl 1):S8–S18. doi:10.3747/co.22.2338 [PubMed: 25848342]
40. Pagani O, Price KN, Gelber RD, Gastiglione-Gertsch M, Holmberg SB, Lindtner J, et al. Patterns of recurrence of early breast cancer according to estrogen receptor status: a therapeutic target for a quarter of a century. Breast Cancer Res Treat. 2009;117(2):319–324. doi:10.1007/s10549-008-0282-0 [PubMed: 19137426]
41. Pagani O, Partridge A, Korde L, Badve S, Bartlett J, Albain K, et al. Pregnancy after breast cancer: if you wish, ma'am. Breast Cancer Res Treat. 2011;129(2):309–317. doi:10.1007/s10549-011-1643-7 [PubMed: 21698406]
42. VanderWeele TJ, Ding P. Sensitivity analysis in observational research: introducing the E-value. Ann Intern Med. 2017;167(4):268–274. doi:10.7326/M16-2607 [PubMed: 28693043]
43. Langagergaard V, Gislum M, Skriver MV, Nørgård B, Lash TL, Rothman KJ, et al. Birth outcome in women with breast cancer. Br J Cancer. 2006;94(1):142–146. doi:10.1038/sj.bjc.6602878 [PubMed: 16306874]
44. Anderson C, Engel SM, Anders CK, Nichols HB. Live birth outcomes after adolescent and young adult breast cancer. Int J Cancer. 2018;142(10):1994–2002. doi:10.1002/ijc.31227 [PubMed: 29266267]
45. Hartnett KP, Ward KC, Kramer MR, Lash TL, Mertens AC, Spencer JB, et al. The risk of preterm birth and growth restriction in pregnancy after cancer. Int J Cancer. 2017;141(11):2187–2196. doi:10.1002/ijc.30914 [PubMed: 28836277]
46. Clark H, Kurinczuk JJ, Lee AJ, Bhattacharya S. Obstetric outcomes in cancer survivors. Obstet Gynecol. 2007;110(4):849–854. doi:10.1097/01.AOG.0000284458.53303.1c [PubMed: 17906019]
47. Haggar FA, Pereira G, Preen D, Holman CD, Einarsdottir K. Adverse obstetric and perinatal outcomes following treatment of adolescent and young adult cancer: a population-based cohort study. PLoS One. 2014;9(12):e113292. doi:10.1371/journal.pone.0113292 [PubMed: 25485774]
48. Sabeti Rad Z, Friberg B, Henic E, Rylander L, Ståhl O, Källén B, et al. Deliveries after malignant disease before pregnancy: maternal characteristics, pregnancy, and delivery complications. J Adolesc Young Adult Oncol. 2016;5(3):240–247. doi:10.1089/jayao.2016.0008 [PubMed: 27111543]
49. Dalberg K, Eriksson J, Holmberg L. Birth outcome in women with previously treated breast cancer--a population-based cohort study from Sweden. PLoS Med. 2006;3(9):e336. doi:10.1371/journal.pmed.0030336 [PubMed: 16968117]
50. Nichols HB, Schoemaker MJ, Cai J, Xu J, Wright LB, Brook MN, et al. Breast cancer risk after recent childbirth: a pooled analysis of 15 prospective studies. Ann Intern Med. 2019;170(1):22–30. doi:10.7326/M18-1323 [PubMed: 30534999]
51. Cáceres IA, Arcaya M, Declercq E, Belanoff CM, Janakiraman V, Cohen B, et al. Hospital differences in cesarean deliveries in Massachusetts (US) 2004–2006: the case against case-mix artifact. PLoS One. 2013;8(3):e57817. doi:10.1371/journal.pone.0057817 [PubMed: 23526952]
52. Declercq E, MacDorman M, Osterman M, Belanoff C, Iverson R. Prepregnancy obesity and primary cesareans among otherwise low-risk mothers in 38 U.S. states in 2012. Birth. 2015;42(4):309–318. doi:10.1111/birt.12201 [PubMed: 26489891]
53. Lee HM, Kim BW, Park S, Park S, Lee JE, et al. Childbirth in young Korean women with previously treated breast cancer: the SMARTSHIP study. Breast Cancer Res Treat. 2019;176(2):419–427. doi:10.1007/s10549-019-05244-6 [PubMed: 31020470]

**Box 1. Indicators used to define neonatal and severe maternal morbidity ***

**Indicators of neonatal morbidity**

- Respiratory support within 72 hours after birth
- Hypoxic-ischemic encephalopathy
- Seizure
- Infection (sepsis or pneumonia within 30 days of birth)
- Meconium aspiration syndrome
- Birth trauma
- Intracranial or subgaleal hemorrhage
- Apgar score of 3 or less at 5 minutes
- Hypotension requiring vasopressor support

**Indicators of severe maternal morbidity**

- Acute myocardial infarction
- Aneurysm
- Acute renal failure
- Adult respiratory distress syndrome
- Amniotic fluid embolism
- Cardiac arrest or ventricular fibrillation
- Conversion of cardiac rhythm
- Disseminated intravascular coagulation
- Eclampsia
- Heart failure or arrest during surgery or procedure
- Puerperal cerebrovascular disorders
- Pulmonary edema or acute heart failure
- Severe anesthesia complications
- Sepsis
- Shock
- Sickle cell disease with crisis
- Air and thrombotic embolism
- Blood products transfusion
- Hysterectomy

- Temporary tracheostomy
- Ventilation

*Neonatal morbidity indicators were adapted from Grobman and colleagues,[34] and severe maternal morbidity indicators are from the Centers for Disease Control and Prevention algorithm.[35]

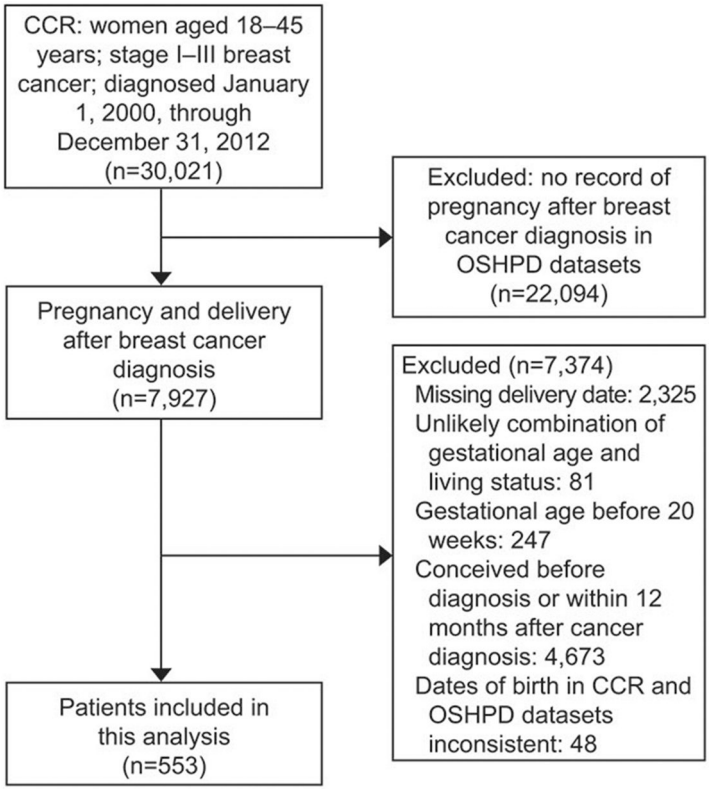


**Figure 1:**

Selection of cases. CCR, California Cancer Registry; OSHPD, California Office of Statewide Health Planning and Development.

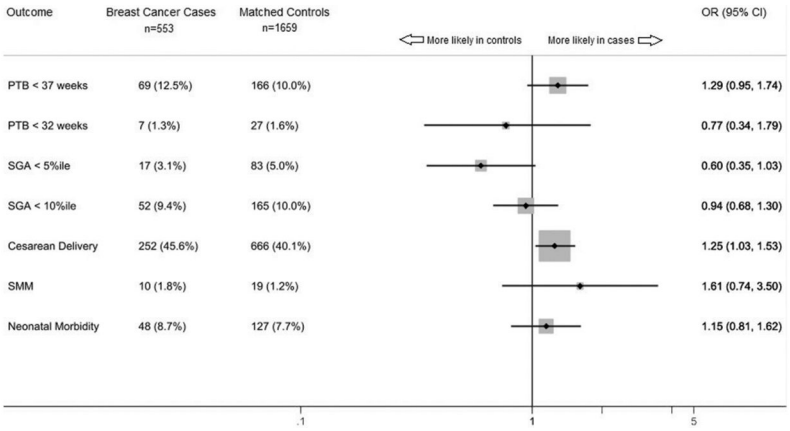


**Figure 2:**

Obstetric and neonatal outcomes of patients with breast cancer and matched controls, adjusted for age. See Appendix 5, available online at http://links.lww.com/xxx, for unadjusted forest plot. *Diamonds and lines* represent odds ratios and 95% CIs, respectively. The *size of the gray boxes* indicates the number of patients (n) included in the assessment, with larger gray boxes indicating more data points. *Odds ratios (ORs) greater than 1* indicate a higher risk in breast cancer cases. The vertical line is centered at the null (1.0). PTB, preterm birth; SGA, small for gestational age based on curves by Oken and colleagues[33]; SMM, severe maternal morbidity based on the Centers for Disease Control and Prevention algorithm.[35]

**Table 1.**

Covariates in breast cancer patients and population and matched controls *

| Covariate | Breast cancer patients (n=553) | Population Controls (n=3,691,280) | *P* value | Matched controls (n=1659) | *P* Value |
|---|---|---|---|---|---|
| Age at delivery, median (IQR), years | 36 (33-39) | 31 (27-34) | <.001 | 36 (33-39) | 0.89 |
| Education | | | <.001 | | 0.82 |
| <12 years | 118 (21.3) | 1,288,268 (34.9) | | 360 (21.7) | |
| ≥12 years | 417 (75.4) | 2,309,909 (62.6) | | 1236 (74.5) | |
| Missing | 18 (3.3) | 93,103 (2.5) | | 63 (3.8) | |
| Insurance | | | <.001 | | 0.97 |
| Missing | 1 (0.2) | 17,672 (0.5) | | 4 (0.2) | |
| Private | 460 (83.2) | 2,612,634 (70.8) | | 1376 (82.9) | |
| Public | 85 (15.4) | 1,019,089 (27.6) | | 261 (15.7) | |
| Uninsured | 7 (1.3) | 41,885 (1.1) | | 18 (1.1) | |
| Race and Ethnicity | | | .001 | | 0.97 |
| Asian or Pacific Islander | 18 (3.3) | 120,116 (3.3) | | 58 (3.5) | |
| Black | 33 (6.0) | 206,269 (5.6) | | 89 (5.4) | |
| Hispanic | 132 (23.9) | 1,176,905 (31.9) | | 382 (23.0) | |
| Non-Hispanic White | 280 (50.6) | 1,596,524 (43.3) | | 855 (51.5) | |
| None of the above | 90 (16.3) | 591,466 (16.0) | | 275 (16.6) | |
| Annual income (US dollars, quartile) | | | .018 | | 1 |
| 0-38,999 | 199 (36.0) | 1,438,185 (39.0) | | 594 (35.8) | |
| 39,000-47,999 | 80 (14.5) | 668,313 (18.1) | | 240 (14.5) | |
| 48,000-62,999 | 172 (31.1) | 1,019,121 (27.6) | | 519 (31.3) | |
| 63,000+ | 100 (18.1) | 547,524 (14.8) | | 300 (18.1) | |
| Missing | 2 (0.4) | 18,137 (0.5) | | 6 (0.4) | |
| Delivery year | | | <.001 | | 1 |
| 2000 | 0 (0.0) | 282,382 (7.6) | | - | |
| 2001 | 1 (0.2) | 275,998 (7.5) | | 3 (0.2) | |
| 2002 | 11 (2.0) | 275,298 (7.5) | | 32 (1.9) | |
| 2003 | 23 (4.2) | 283,129 (7.7) | | 72 (4.3) | |
| 2004 | 35 (6.3) | 283,253 (7.7) | | 111 (6.7) | |
| 2005 | 46 (8.3) | 288,821 (7.8) | | 141 (8.5) | |
| 2006 | 53 (9.6) | 292,695 (7.9) | | 148 (8.9) | |
| 2007 | 56 (10.1) | 292,509 (7.9) | | 152 (9.2) | |
| 2008 | 63 (11.4) | 288,959 (7.8) | | 206 (12.4) | |
| 2009 | 64 (11.6) | 282,379 (7.6) | | 202 (12.2) | |
| 2010 | 70 (12.7) | 279,102 (7.6) | | 207 (12.5) | |
| 2011 | 67 (12.1) | 282,765 (7.7) | | 194 (11.7) | |

| Covariate | Breast cancer patients (n=553) | Population Controls (n=3,691,280) | *P* value | Matched controls (n=1659) | *P* Value |
|---|---|---|---|---|---|
| 2012 | 64 (11.6) | 283,990 (7.7) | | 191 (11.5) | |
| Parity | | | <.001 | | 1 |
| Nulliparous | 265 (47.9) | 1,204,245 (32.6) | | 795 (47.9) | |
| Multiparous | 287 (51.9) | 248,6029 (67.3) | | 861 (51.9) | |
| Missing | 1 (0.2) | 1006 (0.0) | | 3 (0.2) | |
| Trimester of entry to prenatal care | | | .14 | | 0.85 |
| First | 506 (91.5) | 3,279,113 (88.8) | | 1533 (92.4) | |
| Second | 39 (7.1) | 32,3357 (8.8) | | 108 (6.5) | |
| Third | 3 (0.5) | 53,893 (1.5) | | 8 (0.5) | |
| Missing | 5 (0.9) | 34,917 (0.9) | | 10 (0.6) | |
| Fetal number per gestation | | | .41 | | 1 |
| Singleton | 527 (95.3) | 3,551,461 (96.2) | | 1581 (95.3) | |
| Twin | 24 (4.3) | 132,940 (3.6) | | 72 (4.3) | |
| Triplet or more | 2 (0.4) | 6879 (0.2) | | 6 (0.4) | |
| Chronic hypertension | | | .65 | | 1 |
| No | 542 (98.0) | 3,627,170 (98.3) | | 1626 (98.0) | |
| Yes | 11 (2.0) | 64,110 (1.7) | | 33 (2.0) | |
| Pregnancy-induced hypertension | | | .06 | | 0.14 |
| No | 517 (93.5) | 3,484,342 (94.4) | | 1591 (95.9) | |
| Gestational hypertension | 9 (1.6) | 82,128 (2.2) | | 18 (1.1) | |
| Pre-eclampsia | 15 (2.7) | 85,328 (2.3) | | 29 (1.7) | |
| Severe pre-eclampsia or eclampsia | 12 (2.2) | 39,482 (1.1) | | 21 (1.3) | |
| Pregestational diabetes | | | .88 | | 0.12 |
| No | 547 (98.9) | 3,648,607 (98.8) | | 1651 (99.5) | |
| Yes | 6 (1.1) | 42,673 (1.2) | | 8 (0.5) | |
| Gestational diabetes | | | .002 | | 0.97 |
| No | 490 (88.6) | 3,403,676 (92.2) | | 1471 (88.7) | |
| Yes | 63 (11.4) | 287,604 (7.8) | | 188 (11.3) | |
| Renal disease | | | .06 | | 0.10 |
| No | 549 (99.3) | 3,680,397 (99.7) | | 1655 (99.8) | |
| Yes | 4 (0.7) | 10,883 (0.3) | | 4 (0.2) | |
| Abnormal placentation | | | .01 | | 0.79 |
| No | 541 (97.8) | 3,655,275 (99.0) | | 1626 (98.0) | |
| Yes | 12 (2.2) | 34,422 (0.9) | | 33 (2.0) | |

IQR, interquartile range.

*Values in table are number of patients (percentage) unless otherwise indicated. Percentages may not add to 100% due to rounding.

**Table 2.**

Subgroup analyses of obstetric and neonatal complications among cases who received chemotherapy compared to cases that did not receive chemotherapy

| Outcomes | n | OR (95% CI) |
|---|---|---|
| PTB <32 weeks | 7 | 0.34 (0.07–1.80) |
| PTB <37 weeks | 69 | 1.16 (0.64–2.08) |
| SGA <5th %ile | 17 | 0.47 (0.16–1.40) |
| SGA <10th %ile | 52 | 0.60 (0.32–1.13) |
| Cesarean section | 252 | 1.22 (0.83–1.80) |
| Severe maternal morbidity | 10 | 0.47 (0.11–2.08) |
| Neonatal morbidity | 48 | 1.08 (0.56–2.11) |

Total number of cases: 553. One instance of fetal demise among those who received chemotherapy; OR and CI not calculated. Outcomes controlled for stage.

Abbreviations: OR, odds ratio; CI, confidence interval; PTB, preterm birth; SGA, small for gestational age, %ile, percentile.

**Table 3.**

Subgroup analyses of obstetric and neonatal complications by timing from treatment initiation to conception compared to conceptions within 24 months of treatment initiation

| | | 24-60 months | >60 months |
|---|---|---|---|
| **Outcomes** | **n** | **OR (95% CI)** | **OR (95 % CI)** |
| PTB <32 weeks | 7 | 0.14 (0.02–1.23) | 0.88 (0.16–4.99) |
| PTB <37 weeks | 69 | 0.42 (0.24–0.75) | 0.65 (0.32–1.31) |
| SGA <5th %ile | 17 | 1.08 (0.32–3.69) | 2.44 (0.63–9.52) |
| SGA <10th %ile | 51 | 0.90 (0.46–1.75) | 0.97 (0.41–2.31) |
| Cesarean section | 250 | 1.23 (0.83–1.82) | 1.34 (0.80–2.21) |
| Severe maternal morbidity | 10 | 0.60 (0.13–2.81) | 1.86 (0.35–9.91) |
| Neonatal morbidity | 47 | 0.61 (0.31–1.21) | 1.06 (0.47–2.39) |

Total of 550 cases with complete data for review when controlling for stage. One fetal demise occurred, no OR or CI calculated. Abbreviations: OR, odds ratio; CI, confidence interval; PTB, preterm birth; SGA, small for gestational age; %ile, percentile.

**Table 4:**

Frequency of preterm delivery (<37 weeks) by time from diagnosis to conception among 553 cases*

| Time from diagnosis to conception (months) | Preterm Birth <37 weeks n=69 | No Preterm Birth <37 weeks n=484 | Total n=553 |
|---|---|---|---|
| 12 to <24 | 29 (42.0) | 125 (25.8) | 154 (27.9) |
| 24 to <60 | 26 (37.7) | 268 (55.4) | 294 (53.1) |
| ≥60 | 14 (20.3) | 91 (18.8) | 105 (19.0) |

*Values in table are number of patients (column percentage)