Received: 15 September 2022 | Revised: 12 December 2022 | Accepted: 25 January 2023

DOI: 10.1111/aogs.14530

AOGS Acta Obstetricia et Gynecologica Scandinavica

ORIGINAL RESEARCH ARTICLE

Pregnancy-associated gynecological cancer in New South Wales, Australia 1994–2013: A population-based historical cohort study

Penelope Fotheringham[1,2] | Nadom Safi[1,2] | Zhouyang Li[1,2] | Antoinette Anazodo[3] | Marc Remond[1,2] | Andrew Hayen[4] | David Currow[5] | David Roder[6] | Nada Hamad[7] | Michael Nicholl[8] | Adrienne Gordon[8] | Jane Frawley[4] | Elizabeth A. Sullivan[1,2]

[1]College of Health, Medicine and Wellbeing, University of Newcastle, Callaghan, New South Wales, Australia

[2]Hunter Medical Research Institute, New South Wales, Australia

[3]Nelune Comprehensive Cancer Centre, Prince of Wales Hospital, Randwick, New South Wales, Australia

[4]School of Public Health, University of Technology Sydney, Ultimo, New South Wales, Australia

[5]Faculty of Science, Medicine and Health, University of Wollongong, Wollongong, New South Wales, Australia

[6]Population Health, Beat Cancer Project, University of South Australia, Adelaide, South Australia, Australia

[7]The Kinghorn Cancer Centre, Darlinghurst, New South Wales, Australia

[8]Faculty of Medicine and Health, The University of Sydney, Camperdown, New South Wales, Australia

Correspondence
Elizabeth A. Sullivan, College of Health, Medicine and Wellbeing, University of Newcastle, University Drive, Callaghan, New South Wales 2308, Australia.
Email: e.sullivan@newcastle.edu.au

Funding information
Cancer Council NSW, Grant/Award Number: reference RG 18-02

Abstract

Introduction: Pregnancy-associated gynecological cancer (PAGC) refers to cancers of the ovary, uterus, fallopian tube, cervix, vagina, and vulva diagnosed during pregnancy or within 12 months postpartum. We aimed to describe the incidence of, and perinatal outcomes associated with, invasive pregnancy-associated gynecological cancer.

Material and methods: We conducted a population-based historical cohort study using linked data from New South Wales, Australia. We included all women who gave birth between 1994 and 2013, with a follow-up period extending to September 30, 2018. Three groups were analyzed: a gestational PAGC group (women diagnosed during pregnancy), a postpartum PAGC group (women diagnosed within 1 year of giving birth), and a control group (women with control diagnosis during pregnancy or within 1 year of giving birth). We used generalized estimation equations to compare perinatal outcomes between study groups.

Results: There were 1 786 137 deliveries during the study period; 70 women were diagnosed with gestational PAGC and 191 with postpartum PAGC. The incidence of PAGC was 14.6/100 000 deliveries and did not change during the study period. Women with gestational PAGC (adjusted odds ratio [aAOR] 6.81, 95% confidence interval [CI] 2.97–15.62) and with postpartum PAGC (aOR 2.65, 95% CI 1.25–5.61) had significantly increased odds of a severe maternal morbidity outcome compared with the control group. Babies born to women with gestational PAGC were more likely to be born preterm (aOR 3.11, 95% CI 1.47–6.59) and were at increased odds of severe neonatal complications (aOR 3.47, 95% CI 1.45–8.31) compared with babies born to women without PAC.

Abbreviations: aOR, adjusted odds ratios; CI, confidence intervals; HPV, human papillomavirus; NICU, neonatal intensive care unit; NSW, New South Wales; OR, odds ratios; PAGC, pregnancy-associated gynecological cancer.

Conclusions: The incidence of PAGC has not increased over time perhaps reflecting, in part, the effectiveness of cervical screening and early impacts of human papillomavirus vaccination programs in Australia. The higher rate of preterm birth among the gestational PAGC group is associated with adverse outcomes in babies born to these women.

KEYWORDS
cancer in pregnancy, gynecological cancer, iatrogenic prematurity, maternal outcome, neonatal outcome, perinatal outcome

1 | INTRODUCTION

Pregnancy-associated gynecological cancer (PAGC) refers to cancers of the ovary, uterus, fallopian tube, cervix, vagina, and vulva diagnosed during pregnancy or in the 12 months postpartum. Of these, cervical and ovarian cancer are the most frequently diagnosed PAGCs.[1] Cervical cancer is preventable through measures such as vaccination and screening.[2] A diagnosis of PAGC, and the type, location, and stage of cancer, may impact the continuation of the pregnancy and clinical decisions regarding oncological and obstetric management. In addition, recent population-based studies have reported that PAGC is associated with increased risks of adverse maternal and perinatal outcomes.[3,4] For example, PAGC has been associated with an increased risk of iatrogenic preterm delivery, low birthweight, respiratory distress syndrome, and admission to neonatal intensive care units (NICU).[3,4]

Current recommendations for the management of PAGC[1,5,6] are based upon a combination of limited published evidence and expert clinical opinion. Such guidelines may vary geographically as the result of differences in local clinical opinion.[5,7] Nonetheless, management is generally directed by the type and stage of gynecological cancer and the timing of diagnosis during the pregnancy.

Detailed population-level data regarding a broader range of maternal and perinatal outcomes associated with PAGC and their relationship to timing of cancer diagnosis are required to better inform practice and guideline development, particularly for PAGC types other than cervical and ovarian cancer. The aim of this study is to describe the incidence of, and perinatal and survival outcomes associated with, PAGC in New South Wales (NSW), Australia.

Key message

The incidence of pregnancy-associated gynecological cancer is not increasing in New South Wales, Australia, which may reflect the effectiveness of cervical screening and early impacts of human papillomavirus vaccination programs. Nonetheless, clinicians face challenges balancing maternal and fetal outcomes in women with gestational gynecological cancer.

2 | MATERIAL AND METHODS

2.1 | Study design and population

A population-based historical cohort study was performed using linked data from NSW, Australia. The study population comprised all women who gave birth between January 1, 1994 and December 31, 2013 and their babies. Birth was defined as all live births, and stillbirths of at least 20 weeks' gestation or at least 400 grams birthweight.[8] For women with more than one birth during the study, each pregnancy that met the inclusion criteria was included as a separate data point.

For each eligible pregnancy, the woman and her baby were stratified into one of three groups. The first group comprised women who were diagnosed with any gynecological cancer during pregnancy and their babies (the "gestational PAGC group"). The second group comprised women who were diagnosed with any gynecological cancer within 1 year of giving birth and their babies (the "postpartum PAGC group"). The comparison group comprised all women who were not diagnosed with cancer during pregnancy or within 1 year of giving birth and their babies (the "control group"). Women diagnosed with cancers other than gynecological cancer during pregnancy or within 1 year of giving birth were excluded as their management and outcomes may differ from those of women with PAGC.

2.2 | Data sources

Data from seven population data sets were linked and analyzed: the NSW Perinatal Data Collection, the NSW Central Cancer Registry, the NSW Admitted Patient Data Collection, the Register of Congenital Conditions, the Registrar of Births, Deaths and Marriages, the Cause of Death Unit Record File, and the Perinatal Death Review. Probabilistic data linkage was performed by the NSW Centre for Health Record Linkage[9] (Table S1).

2.3 | Main outcome measures

Maternal outcomes comprised: maternal morbidities (including gestational diabetes and gestational hypertension), outcomes relating to pregnancy and birth management (including induction of labor

and birth by cesarean section), maternal death, discharge status, and a composite severe maternal morbidity outcome index.[10] Any woman admitted to hospital during pregnancy, or within 42 days postpartum, with any of the diagnoses or procedures included in this validated list was deemed to have had a severe maternal morbidity outcome (Appendix S1).

Neonatal outcomes comprised: perinatal death (stillbirth ≥20 weeks, neonatal death <28 days after delivery), preterm birth (<37 weeks), iatrogenic preterm birth (induced labor or cesarean section without labor where the main indication for cesarean section was not failure to progress or fetal distress), low birthweight (<2500 g), small for gestational age,[10,11] large for gestational age,[10,11] low 5-minute Apgar score (<7), admission to special care nursery or NICU, prolonged hospital stay (≥5 days), congenital malformation, and a composite neonatal adverse outcome indicator[12] (Appendix S1).

2.4 | Statistical analyses

Descriptive statistics for nominal data are presented as counts and percentages. Continuous measures are presented as means and standard deviations. When comparing study groups, differences in continuous variables were assessed using the *t* test or one-way analysis of variance, whereas for categorical variables, the chi-squared test or Fisher–Freeman–Halton exact test was used. We used a Poisson regression model, both unadjusted and adjusted for women's ages, to estimate the yearly change in the incidence of PAGC (gestational, postpartum, and all PAGC). Kaplan–Meier curves and the log-rank test were used to compare all-cause mortality between the gestational and postpartum PAGC groups. Incidence was calculated using the denominator of number of births per year. A year was defined as January 1 to December 31, according to the year of birth for the child.

A generalized estimating equation models were used to compare the likelihood of adverse maternal and neonatal outcomes between study groups. The generalized estimating equation model was used to address the lack of independence associated with the repeated appearance of maternal factors for women who had multiple pregnancies over the study period (previous and subsequent birth episodes to the birth episode associated with a diagnosis of PAGC) and siblings during the study period.

Covariates included in the multivariate analysis are described in the footnotes to Tables 3 and 4. Variables with a *p* value less than 0.25 in univariate analyses were entered into multivariate models in addition to other biologically plausible variables irrespective of whether they returned *p* values less than 0.25 in univariate analyses.

Final models were determined by considering collinearity, statistical significance, and goodness-of-fit. Results from these models are presented as odds ratios (OR), adjusted odds ratios (aOR), and 95% confidence intervals (CI). Findings with a *p* value less than 0.05, or a CI not including 1, were considered statistically significant. Data were analyzed using R Core Team software (2013)[13] and IBM SPSS Version 27 (IBM Corporation).

2.5 | Ethics statement

This project received ethics approval from the NSW Population & Health Services Research Ethics Committee (reference HREC/17/CIPHS/11). Ethical approval was originally granted on November 23, 2017 for 5 years. This has been extended for 2 further years and is valid until November 23, 2024.

3 | RESULTS

A total of 1 786 339 pregnancies were identified in NSW during the 20-year study period (Table 1). Seventy women who gave birth to 72 babies (68 singletons and two pairs of twins) were diagnosed with gestational PAGC and 191 women who gave birth to 195 babies (187 singletons and four pairs of twins) were diagnosed with postpartum PAGC.

3.1 | Maternal characteristics

Maternal demographic characteristics are presented in Table 1. Maternal age increased over the study period with the proportion of mothers aged 35 years or older almost doubling between 1994 (13.1%) and 2013 (23.4%).

The mean ages of women with gestational PAGC (32.5 ± 5.1 years) and of women with postpartum PAGC (32.5 ± 5.0 years) were significantly higher than the mean age of women in the control group (29.6 ± 5.6 years; mean difference 2.9 years [95% CI 1.4–4.5] and 2.9 years [95% CI 1.9–3.8], respectively).

Table 2 presents the cancer characteristics of women diagnosed with PAGC. Among women with gestational PAGC, cervical cancer was the most diagnosed ($n = 30$, 42.9%), followed by ovarian cancer ($n = 27$, 38.6%). Similarly, among women with postpartum PAGC, the most common diagnosis was cervical cancer ($n = 128$, 67%), followed by ovarian cancer ($n = 32$, 16.8%). Most cancers were diagnosed at a localized stage in both the gestational ($n = 36$, 51.4%) and postpartum ($n = 107$, 56%) groups. There was no significant difference in cancer stage between the two groups ($p = 0.401$).

3.2 | Incidence

The overall estimated incidence of PAGC during the study period was 14.6/100 000 women giving birth. The estimated incidence of gestational PAGC was 3.9/100 000 women giving birth while for postpartum PAGC it was 10.7/100 000 women giving birth.

During the study period, there was no significant change in the incidence of PAGC (calculated unadjusted annual change = 0.6% per year [95% CI −1.5% to 2.7%], $p = 0.601$; calculated age-adjusted change = −0.5% per year [95% CI −2.6% to 1.6%], $p = 0.645$). Similarly, there was no significant change in the incidence of gestational PAGC (calculated unadjusted annual change = 1.1% per year [95% CI −2.9%

TABLE 1 Demographic characteristics.

Factors	Gestational *N* (%)	Postpartum *N* (%)	Control *N* (%)	Total *N* (%)
Total	70 (100.0)	191 (100.0)	1 786 078 (100.0)	1 786 339 (100.0)
Age group (years)				
<30	17 (24.3)	47 (24.6)	863 125 (48.3)	863 189 (48.3)
30–34	30 (42.9)	77 (40.3)	570 119 (31.9)	570 226 (31.9)
35–39	18 (25.7)	53 (27.7)	292 292 (16.4)	292 363 (16.4)
≥40	5 (7.1)	14 (7.3)	59 829 (3.3)	59 848 (3.4)
Unknown	0 (0)	0 (0)	713 (0.0)	713 (0)
Country of birth				
Australia	50 (71.4)	145 (75.9)	1 263 082 (70.7)	1 263 277 (70.7)
Overseas	20 (28.6)	46 (24.1)	522 996 (29.3)	523 062 (29.3)
Remoteness				
Major cities	59 (84.3)	144 (75.4)	1 356 994 (76.0)	1 357 197 (76.0)
Inner regional	8 (11.4)	36 (18.8)	305 696 (17.1)	305 740 (17.1)
Outer regional	3 (4.3)	6 (3.1)	91 655 (5.1)	91 664 (5.1)
Remote or very remote	0 (0.0)	5 (2.6)	13 262 (0.7)	13 267 (0.7)
Unknown	0 (0.0)	0 (0.0)	18 471 (1.0)	18 471 (1.0)
Parity				
0	29 (41.4)	67 (35.1)	732 969 (41)	733 065 (41)
≥1	41 (58.6)	124 (64.9)	1 052 856 (58.9)	1 053 021 (58.9)
Unknown	0 (0.0)	0 (0.0)	253 (0.0)	253 (0.0)
History of cesarean section[a]				
Yes	7 (10.0)	25 (13.1)	194 555 (10.9)	194 587 (10.9)
No	55 (78.6)	142 (74.3)	1 363 503 (76.3)	1 363 700 (76.3)
Unknown	8 (11.4)	24 (12.6)	228 020 (12.8)	228 052 (12.8)
Plurality				
Singleton	68 (97.1)	187 (97.9)	1 759 408 (98.5)	1 759 663 (98.5)
Multiple birth	2 (2.9)	4 (2.1)	26 670 (1.5)	26 676 (1.5)
Antenatal care				
<14 weeks	49 (70.0)	132 (69.1)	1 203 102 (67.4)	1 203 283 (67.4)
14–20 weeks	12 (17.1)	35 (18.3)	384 915 (21.6)	384 962 (21.6)
>20 weeks	8 (11.4)	21 (11.0)	170 828 (9.6)	170 857 (9.6)
Unknown	1 (1.4)	3 (1.6)	27 233 (1.5)	27 237 (1.5)
Smoking during pregnancy				
Yes	9 (12.9)	26 (13.6)	276 270 (15.5)	276 305 (15.5)
No	61 (87.1)	165 (86.4)	1 504 790 (84.3)	1 505 016 (84.3)
Unknown	0 (0.0)	0 (0.0)	5018 (0.3)	5018 (0.3)
Place of birth				
Tertiary hospital	32 (45.7)	49 (25.7)	490 763 (27.5)	490 844 (27.5)
Private hospital	16 (22.9)	44 (23)	388 892 (21.8)	388 952 (21.8)
Public hospital	22 (31.4)	98 (51.3)	906 420 (50.7)	906 540 (50.7)
Unknown	0 (0.0)	0 (0.0)	3 (0.0)	3 (0.0)
Pre-existing hypertension				
Yes	1 (1.4)	2 (1.0)	15 723 (0.9)	15 726 (0.9)
No	69 (98.6)	189 (99.0)	1 770 355 (99.1)	1 770 613 (99.1)

TABLE 1 (Continued)

Factors	Gestational N (%)	Postpartum N (%)	Control N (%)	Total N (%)
Pre-existing diabetes				
Yes	1 (1.4)	1 (0.5)	10037 (0.6)	10039 (0.6)
No	69 (98.6)	190 (99.5)	1776041 (99.4)	1776300 (99.4)
CKD[b,c]				
Yes	1 (2.3)	0 (0.0)	6402 (0.6)	6403 (0.6)
No	43 (97.7)	117 (100.0)	1077957 (99.4)	1078117 (99.4)
CVD[b,d]				
Yes	3 (6.8)	1 (0.9)	28534 (2.6)	28538 (2.6)
No	41 (93.2)	116 (99.1)	1055825 (97.4)	1055982 (97.4)

[a]Data were available from 1998 onwards for cesarean section.

[b]Data were available from July 2001 onwards.

[c]Hospital admission due to chronic kidney disease (CKD) before pregnancy.

[d]Hospital admission due to cardiovascular disease (CVD) before pregnancy.

TABLE 2 Cancer characteristics.

Factors	Gestational N (%)	Postpartum N (%)	Total
Total	70 (100.0)	191 (100.0)	261 (100.0)
Age at diagnosis (years)			
<25	4 (5.7)	7 (3.7)	11 (4.2)
25–39	12 (17.1)	34 (17.8)	46 (17.6)
30–34	30 (42.9)	75 (39.3)	105 (40.2)
35–39	19 (27.1)	53 (27.7)	72 (27.6)
≥40	5 (7.1)	22 (11.5)	27 (10.3)
Cancer group			
Cervix	30 (42.9)	128 (67)	158 (60.5)
Uterus, body & NOS[a]	3 (4.3)	9 (4.7)	12 (4.6)
Ovary	27 (38.6)	32 (16.8)	59 (22.6)
Placenta	1 (1.4)	10 (5.2)	11 (4.2)
Other female genital organs	9 (12.9)	12 (6.3)	21 (8)
Stage of cancer			
Localized	36 (51.4)	107 (56)	143 (54.8)
Regional	10 (14.3)	20 (10.5)	30 (11.5)
Distant	7 (10)	30 (15.7)	37 (14.2)
Unknown	17 (24.3)	34 (17.8)	51 (19.5)

[a]Refers to International Classification of Diseases 10th revision code C58: Choriocarcinoma not otherwise specified (NOS) or Chorionepithelioma NOS.

to 5.3%], $p = 0.580$; calculated age-adjusted change = 0.1% per year [95% CI −3.9% to 4.3%], $p = 0.967$), or postpartum PAGC (calculated unadjusted annual change = 0.3% per year [95% CI −2.1% to 2.8%], $p = 0.783$; calculated age-adjusted change = −0.7% per year [95% CI −3.1% to 1.8%], $p = 0.573$) (Figure 1).

3.3 | Survival outcome

Overall survival for the gestational and postpartum PAGC groups is presented in Figure 2. Thirty-two (16.8%) women in the postpartum PAGC group died by the end of the follow-up period (mortality rate = 14.0 [95% CI 9.8–19.6] deaths per 1000 person-years follow-up time). Seven (10%) women in the gestational PAGC group died by the end of the follow-up period (mortality rate = 7.6 [95% CI 3.3–15.1] deaths per 1000 person-years follow-up time). The cause of death was cancer-related in 93% (28/30; cause of death unknown in two) of the postpartum PAGC group and 86% (6/7) of the gestational PAGC group. There was no statistically significant difference in the mortality rate between these two groups (mortality rate ratio = 1.8 [95% CI 0.8–4.9], $p = 0.136$). Similarly, there was no significant difference in the survival probability for women in the gestational cancer group when compared with the postpartum group ($p = 0.178$).

3.4 | Pregnancy outcomes

Table 3 presents the obstetric morbidities, and labor and birth outcomes for the cohort. Women with gestational PAGC (aOR 6.81, 95% CI 2.97–15.62) and those with postpartum PAGC (aOR 2.65, 95% CI 1.25–5.61) had significantly increased odds of experiencing a severe maternal morbidity outcome when compared with women in the control group.

There were differences in the mode of delivery for women with gestational PAGC compared with women in the control group. Women with gestational PAGC were at significantly increased odds of induction of labor or no labor compared with women in the control group (aOR 3.4, 95% CI 2.04–5.65). Furthermore, women with gestational PAGC were at increased odds of experiencing birth by cesarean section compared with women in the control group (aOR 5.38, 95% CI 3.14–9.21).

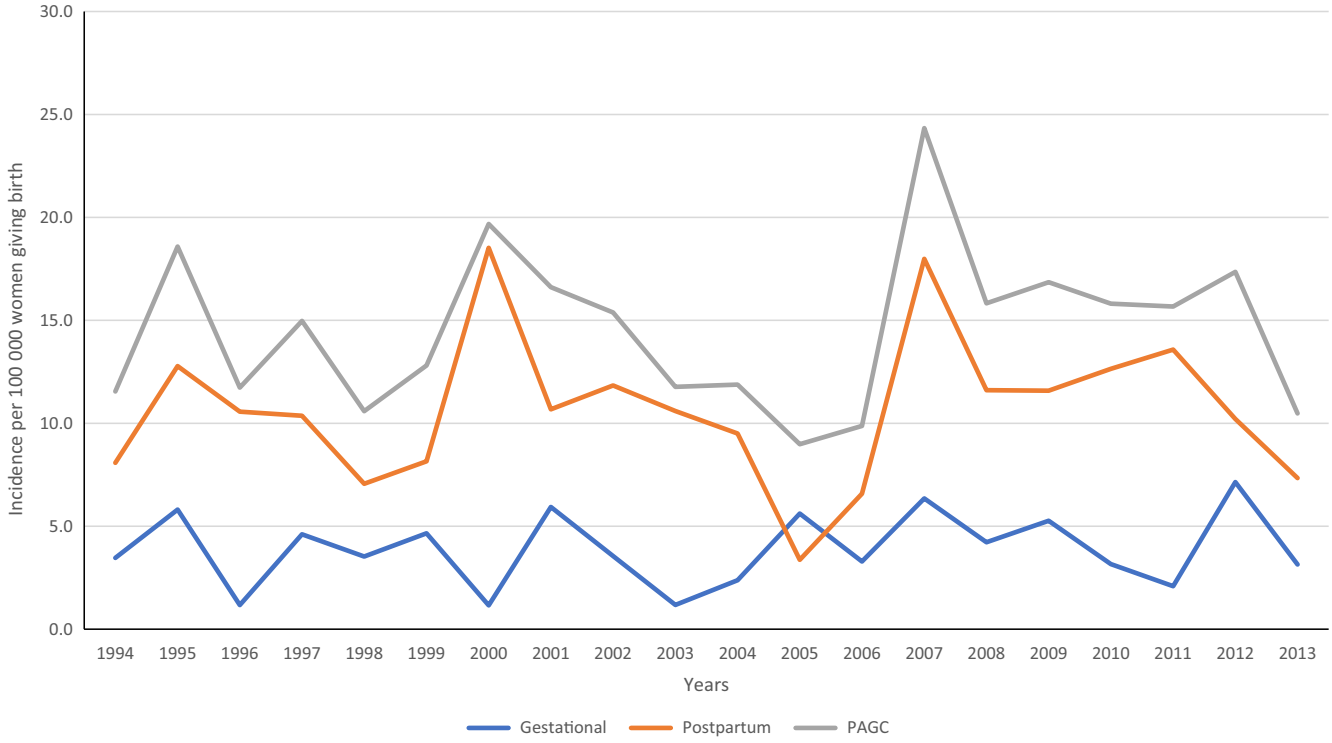

FIGURE 1 Crude incidence of pregnancy-associated gynecological cancer.

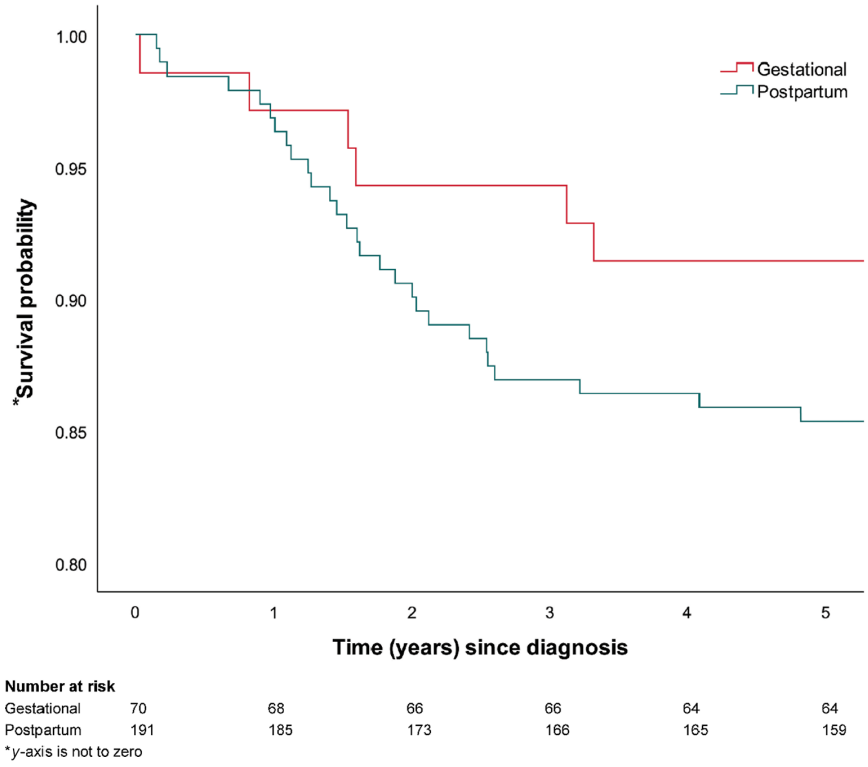

FIGURE 2 Overall survival for gestational and postpartum groups.

3.5 | Neonatal outcomes

Table 4 presents perinatal outcomes for babies born to women in the study. Women in the gestational PAGC group (aOR 3.11, 95% CI 1.47–6.59) and postpartum PAGC group (aOR 1.69, 95% CI 1.03–2.76) were at increased odds of having a preterm delivery compared with women in the control group. The odds of iatrogenic preterm delivery were also higher in both the gestational PAGC group (aOR 4.61, 95% CI 1.60–13.33) and the postpartum PAGC group (aOR 2.36, 95% CI 1.22–4.58) compared with the control group.

Babies born to women with gestational PAGC were at increased odds of experiencing severe neonatal complications compared with

TABLE 3 Obstetric morbidities, labor, and birth.

Factors	Gestational *N* (%)	Postpartum *N* (%)	Control *N* (%)	Gestational[c] aOR (95% CI)	Postpartum[c] aOR (95% CI)
Total	70 (100.0)	191 (100.0)	1 786 078 (100.0)		
MMOI[a,b]					
Yes	7 (15.9)	7 (6)	26 444 (2.4)	6.94 (2.96–16.28)	2.63 (1.24–5.59)
No	37 (84.1)	110 (94)	1 057 915 (97.6)		
Gestational diabetes					
Yes	2 (2.9)	14 (7.3)	81 623 (4.6)	0.54 (0.15–1.99)	1.34 (0.75–2.39)
No	68 (97.1)	177 (92.7)	1 704 455 (95.4)		
Gestational hypertension					
Yes	4 (5.7)	9 (4.7)	109 051 (6.1)	0.76 (0.27–2.14)	0.76 (0.40–1.44)
No	66 (94.3)	182 (95.3)	1 677 027 (93.9)		
Onset of labor					
Spontaneous	21 (30)	99 (51.8)	1 088 985 (61)		
Induced	15 (21.4)	54 (28.3)	438 995 (24.6)	3.14 (1.91–5.17)[d]	1.26 (0.95–1.67)[d]
No labor	34 (48.6)	38 (19.9)	257 643 (14.4)		
Unknown	0 (0)	0 (0)	455 (0)		
Type of delivery					
Vaginal	21 (30)	111 (58.1)	1 140 733 (63.9)		
Instrumental vaginal	5 (7.1)	16 (8.4)	191 746 (10.7)		
Cesarean section	44 (62.9)	64 (33.5)	452 709 (25.3)	4.1 (2.49–6.73)[e]	1.16 (0.90–1.49)[e]
Unknown	0 (0)	0 (0)	890 (0)		
Discharge status (transferred)					
Yes	3 (4.3)	6 (3.1)	59 176 (3.3)	1.7 (0.58–4.98)[f]	0.89 (0.36–2.18)[f]
No	67 (95.7)	185 (96.9)	1 726 902 (96.7)		

[a]Maternal Morbidity Outcome Indicator (MMOI) occurred during pregnancy or within 42 days postpartum (Appendix S1).

[b]Data were available from July 2001 onwards.

[c]All outcomes are dichotomous in Generalized Estimating Equation models; "unknown" category is combined with "no" unless otherwise specified.

[d](induced + no labor) versus (spontaneous + unknown).

[e]Cesarean section versus (vaginal + instrumental vaginal + unknown).

[f]Transferred versus (discharged home + died + unknown).

those born to women without PAC (aOR 3.47, 95% CI 1.45–8.31) and were more likely to be of low birthweight (aOR 3.82, 95% CI 2.02–7.23). In contrast, babies born to women with postpartum PAGC were at increased odds of low Apgar scores (aOR 3.42, 95% CI 1.73–6.77). Babies of both PAGC groups were at increased odds of admission to NICU (aOR 2.4 [95% CI 1.39–4.15] for the gestational PAGC group, and aOR 1.56 [95% CI 1.10–2.21] for the postpartum PAGC group). Only babies born to women with gestational PAGCs had higher odds of experiencing an increased length of stay in NICU (aOR 4.39, 95% CI 2.54–7.57).

4 | DISCUSSION

We report an overall incidence of PAGC in NSW between 1994 and 2013 of 14.6/100 000 women giving birth, with more women diagnosed postpartum than during pregnancy. The incidence of PAGC did not increase during the study period. Women diagnosed with gynecological cancer during pregnancy had increased odds of induced labor or elective cesarean section compared with women without cancer. Women with PAGC also had increased odds of a severe maternal morbidity outcome compared with women without cancer. Babies born to women with PAGC were more likely to be born preterm in a planned preterm delivery and require admission to the NICU.

Women with PAGC in this study were significantly older than those without cancer. Previously reported population studies of pregnancy-associated cancer have described the association between maternal age and a diagnosis of pregnancy-associated cancer.[14] The incidence of cancer is known to increase with age and the average maternal age in Australia has increased over recent decades (mean maternal age in 1994 was 28.3 years compared with 30.1 years in 2013).[12,15] In our NSW cohort, the proportion of mothers older than 35 years of age almost doubled between 1994 (13.1%) and 2013 (23.4%). Based on

TABLE 4 Neonatal outcomes (perinatal period).

Factors	Gestational *N* (%)	Postpartum *N* (%)	No-PAC (reference) *N* (%)	Gestational[a] aOR (95% CI)	Postpartum[a] aOR (95% CI)
N	72 (100.0)	195 (100.0)	1 813 292 (100.0)		
Perinatal death					
Live >28 days	71 (98.6)	191 (97.9)	1 795 978 (99.0)		
Perinatal death	1 (1.4)	4 (2.1)	17 059 (0.9)	1.23 (0.17–8.71)	2.19 (0.64–7.56)
Unknown	0 (0.0)	0 (0.0)	255 (0.0)		
Preterm					
<37 weeks	16 (22.2)	24 (12.3)	129 637 (7.1)	3.13 (1.41–6.99)	1.71 (1.05–2.79)
≥37 weeks	56 (77.8)	171 (87.7)	1 683 411 (92.8)		
Unknown	0 (0.0)	0 (0.0)	244 (0.0)		
Iatrogenic preterm[b]					
Yes	9 (12.5)	10 (5.1)	43 853 (2.4)	4.43 (1.49–13.18)[c]	2.26 (1.16–4.38)[c]
No	7 (9.7)	14 (7.2)	85 784 (4.7)		
Not applicable	56 (77.8)	171 (87.7)	1 683 655 (92.9)		
NAOI[d,e]					
Yes	10 (20.8)	11 (8.9)	60 062 (5.2)	3.24 (1.19–8.83)	1.87 (0.97–3.62)
No	38 (79.2)	113 (91.1)	1 093 389 (94.8)		
Low birthweight[e]					
<2500 g	16 (22.2)	15 (7.7)	103 896 (5.8)	3.21 (1.34–7.66)	1.39 (0.79–2.46)
≥2500 g	56 (77.8)	180 (92.3)	1 697 220 (94.2)		
Unknown	0 (0.0)	0 (0.0)	713 (0.0)		
Small for gestational age[e]					
Yes	6 (8.3)	17 (8.7)	184 110 (10.2)	0.79 (0.35–1.81)	0.92 (0.56–1.51)
No	66 (91.7)	178 (91.3)	1 614 179 (89.6)		
Unknown	0 (0.0)	0 (0.0)	3540 (0.2)		
Large for gestational age[e]					
Yes	10 (13.9)	22 (11.3)	177 888 (9.9)	1.49 (0.83–2.70)	1.04 (0.65–1.66)
No	62 (86.1)	173 (88.7)	1 620 401 (89.9)		
Unknown	0 (0.0)	0 (0.0)	3540 (0.2)		
Apgar at 5 min[e]					
0 to 3	2 (2.8)	3 (1.5)	5770 (0.3)	2.28 (0.67–7.81)[f]	3.75 (1.99–7.08)[f]
4 to 6	1 (1.4)	8 (4.1)	23 050 (1.3)		
7 to 10	69 (95.8)	183 (93.8)	1 767 191 (98.1)		
Unknown	0 (0.0)	1 (0.5)	5818 (0.3)		
Admit to SC/NICU[e,g]					
Yes	25 (34.7)	47 (24.1)	296 258 (16.4)	2.46 (1.43–4.23)	1.57 (1.11–2.21)
No	47 (65.3)	148 (75.9)	1 504 455 (83.5)		
Unknown	0 (0.0)	0 (0.0)	1116 (0.1)		
Length of stay[e,h]					
<5 days	22 (33.8)	109 (59.9)	1 185 803 (69.3)	3.8 (2.34–6.17)	1.21 (0.89–1.66)
5 or more	43 (66.2)	71 (39.0)	523 106 (30.6)		
Unknown	0 (0.0)	2 (1.1)	1698 (0.1)		

TABLE 4 (Continued)

Factors	Gestational N (%)	Postpartum N (%)	No-PAC (reference) N (%)	Gestational[a] aOR (95% CI)	Postpartum[a] aOR (95% CI)
Congenital condition[i]					
Yes	0 (0.0)	1 (3.3)	4765 (1.6)	NA	1.89 (0.25–14.30)
No	13 (100.0)	29 (96.7)	288073 (98.4)		

[a]All outcomes are dichotomous in Generalized Estimation Equation models; "unknown" category is combined with "no"' unless otherwise specified.

[b]Including labor induction and cesarean delivery without labor where main indications for cesarean section are not "Failure to progress" or "Fetal distress" preterm birth.

[c]Yes versus (no + not applicable).

[d]Neonatal Adverse Outcome Indicator (NAOI) identified from a birth record or in any hospital transfer admission before the first discharge home (Appendix S1).

[e]Live births only.

[f](0–3 + 4–6) versus (7–10 + Unknown).

[g]Admission to Special Care (SC) or Neonatal Intensive Care unit (NICU) for 4 h or more.

[h]Only babies who were discharged home.

[i]Register of Congenital Conditions is available for babies born in 2011–2013 only.

this increase in maternal age, it may be expected that the incidence of PAGC would also increase.[16] However, we found that the incidence of PAGC in NSW did not significantly change over the 20-year study period, from our data comprising all women giving birth as defined in the methodology. This may, in part, be associated with the introduction of the Australian National Cervical Screening program in 1991 and the National Human Papillomavirus (HPV) Vaccination Program in 2007, which initially offered HPV vaccination to 12- to 13-year-old girls and a catch-up vaccination schedule for women aged up to 26 years of age from 2007 to 2009. Long-term follow-up studies of these programs have demonstrated their effectiveness in preventing cervical cancer.[17–19] Given the time frame of the data in this study, it is likely that the Australian National Cervical Screening program had an impact on reducing the incidence of cervical cancer in all cohorts reported. The impact of HPV vaccination would only be reported in data for women aged 35 years or less, encompassing the impact of the initial vaccination program for 13-year-old girls and the 1.7 million women aged 18–26 years who received the vaccination according to the Australian Government follow-up data.[20]

We report that the incidence and survival probability of the gestational and postpartum PAGC groups were not significantly different. It has been previously reported that the normal physiological changes during pregnancy may mask clinical signs and symptoms of cancer; this may result in women who develop cancer during pregnancy remaining undiagnosed until the postpartum period,[21–24] explaining the difference we report between the two groups. Our data are similar to previously published 5-year relative survival data for women of reproductive age with gynecological cancer outside pregnancy.[25] Nonetheless, this finding should be interpreted with caution because the perinatal data collection does not capture pregnancies that do not continue beyond 20 weeks of gestation. This means that women diagnosed with gestational PAGC whose pregnancies were terminated before 20 weeks of gestation were not included in our gestational PAGC group. Approximately 15% of women diagnosed with cervical cancer during pregnancy will undergo termination of pregnancy,[4] in part as a result of clinical guidelines that recommend first-trimester termination where the cancer is advanced, particularly in cases of cervical cancer.[5] Hence, it is likely that many of the women diagnosed with advanced-stage gestational cervical cancer during the study period were not included in our cohort. Such women are more likely to have poorer long-term survival than women diagnosed with less advanced stages of gynecological cancer during pregnancy. It follows that our estimate of the survival probability of women diagnosed with gestational PAGC overestimates the actual survival (Figure 2).

Women in the gestational PAGC group were at increased odds of cesarean section and induction of labor for delivery, suggesting that for this group, treating oncologists and obstetricians were more likely to recommend planned deliveries to limit any delay in cancer treatment. Vaginal delivery is usually avoided in situations where cervical cancer has been diagnosed during pregnancy because of the risks of hemorrhage, tumor disruption, and secondary cancer in an episiotomy scar.[5,16,26,27] Equally, delivery by cesarean section may be chosen in cases of a diagnosis of ovarian cancer during pregnancy to allow for concurrent surgical staging or interval debulking.[16,27] Previous studies of gestational PAGC have reported high rates of cesarean section for this indication.[28] This interpretation may also account for the increased odds of a severe maternal morbidity outcome observed in women with gestational PAGC in this study, as the complications listed are relevant to the surgical treatment of cervical and ovarian cancers[29] and would capture women who undergo gynecological oncology surgery at the time of delivery. Nonetheless, our ability to infer reasons for the higher maternal morbidity observed in women with gestational PAGC was limited by the fact that we were not able to access data regarding cancer treatments for these women.

We report that women with gestational PAGC had increased odds of preterm delivery compared with women without cancer. Previous research has reported an association between pregnancy-associated

cancer, preterm delivery, and poorer neonatal outcomes associated with prematurity.[3] Our findings do support the suggestion that the management of gestational PAGC may influence delivery timing; that is, that clinicians may recommend preterm delivery to avoid delaying surgical or medical treatments for cancer that have the potential to negatively impact on the developing fetus. Nonetheless, there is a trade-off for the fetus as planned preterm birth comes at the cost of increased risks of adverse neonatal outcomes associated with prematurity. Indeed, we found that the odds of severe neonatal morbidity and low birthweight were significantly increased for babies born to women in the gestational PAGC group. These findings reflect the challenge that obstetricians and oncologists face in trying to balance maternal care and fetal development in cases of gestational cancer. For this reason, management guidelines for gestational PAGC recommend delaying delivery (if possible) to at least 37 weeks of gestation to minimize neonatal risks such as those demonstrated in our findings.[5]

The population-based design of this study that allowed us to report all births in NSW over a 20-year period and identify all cases of PAGC that resulted in a birth during this time frame, is a major strength of this study. However, owing to the limitations of the perinatal data collection, the data set excluded women who did not continue with their pregnancy beyond 20 weeks of gestation. This potentially led to an underestimation of the incidence of, and severity of maternal and perinatal outcomes associated with, gestational PAGC. Our inability to link treatment data to reported outcomes limited our capacity to interpret the findings in relation to these parameters.

5 | CONCLUSION

Despite an increase in maternal age in NSW over recent decades, we report that the incidence of PAGC has remained stable over this time. This finding may be associated with the introduction of two public health strategies for the prevention of cervical cancer, namely HPV vaccination and cervical screening. We found that obstetric outcomes of induction of labor, cesarean section, and preterm delivery were significantly higher in women with gestational PAGC compared with women without PAGC, suggesting that medical intervention for maternal cancer treatment influences obstetric management. We also report an increased risk of a severe neonatal morbidity and NICU admissions, and longer length of stay in NICU, in babies born to women with gestational PAGC. These findings demonstrate the increased intervention that may occur when a diagnosis of gestational PAGC is made, and the challenges surrounding balancing maternal treatment needs against potential adverse fetal impacts.

AUTHOR CONTRIBUTION

All authors contributed to the conception and design of the study. NS and ZL verified the underlying data and performed the data analysis. All authors have access to the aggregate data and are responsible for data interpretation. PF, MR, and NS drafted the manuscript. All authors reviewed, edited, and approved the manuscript.

FUNDING INFORMATION

This study received funding from the Cancer Council NSW grant (reference RG 18–02).

CONFLICT OF INTEREST STATEMENT

All authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Primary data cannot be shared publicly because they are confidential health data held by the New South Wales Ministry of Health and subject to Australian privacy regulations. Ethics approval for this project only authorizes specific researchers named in the original ethics application access to the de-identified linked data derived from the primary health data sets held by New South Wales Health.

ORCID

Penelope Fotheringham https://orcid.org/0000-0003-1853-8194
Nadom Safi https://orcid.org/0000-0001-8473-0980
Marc Remond https://orcid.org/0000-0001-7796-4447

REFERENCES

1. Botha MH, Rajaram S, Karunaratne K. Cancer in pregnancy. *Int J Gynaecol Obstet*. 2018;143:137-142.
2. World Health Organisation. Cervical Cancer. 2022. Available from: https://www.who.int/health-topics/cervical-cancer#tab=tab_1
3. Greiber IK, Viuff JH, Mellemkjær L, et al. Cancer in pregnancy and the risk of adverse pregnancy and neonatal outcomes: a nationwide cohort study. *BJOG*. 2022;129:1492-1502.
4. de Haan J, Verheecke M, Van Calsteren K, et al. Oncological management and obstetric and neonatal outcomes for women diagnosed with cancer during pregnancy: a 20-year international cohort study of 1170 patients. *Lancet Oncol*. 2018;19:337-346.
5. Amant F, Berveiller P, Boere IA, et al. Gynecologic cancers in pregnancy: guidelines based on a third international consensus meeting. *Ann Oncol*. 2019;30:1601-1612.
6. Wolters V, Heimovaara J, Maggen C, et al. Management of pregnancy in women with cancer. *Int J Gynecol Cancer*. 2021;31:314-322.
7. Cibula D, Pötter R, Planchamp F, et al. The European Society of Gynaecological Oncology/European Society for Radiotherapy and Oncology/European Society of Pathology guidelines for the management of patients with cervical cancer. *Virchows Arch*. 2018;472:919-936.
8. Centre for Epidemiology and Evidence. *New South Wales Mothers and Babies 2019*. NSW Ministry of Health; 2021.
9. CHeReL. How record linkage works. Sydney, Australia: Centre of Health Record Linkage (CHeReL). 2021. Available from: https://www.cherel.org.au/how-record-linkage-works
10. Li Z, Umstad MP, Hilder L, Xu F, Sullivan EA. Australian national birthweight percentiles by sex and gestational age for twins, 2001–2010. *BMC Pediatri*. 2015;15:1-7.
11. Dobbins TA, Sullivan EA, Roberts CL, Simpson JM. Australian national birthweight percentiles by sex and gestational age, 1998–2007. *Med J Aust*. 2012;197:291-294.
12. Australian Institute of Health and Welfare. *Australia's mothers and their babies 1994*. Australian Institute of Health and Welfare; 1994.
13. R Core Team. *R: A Language and Environment for Statistical Computing*. R Foundation for Statistical Computing; 2021.

14. Dalmartello M, Negri E, La Vecchia C, et al. Frequency of pregnancy-associated cancer: a systematic review of population-based studies. *Cancers (Basel)*. 2020;12:1356.
15. Australian Institute of Health and Welfare. *Australia's mothers and babies 2013—in brief*. Australian Institute of Health and Welfare; 2013.
16. Korenaga T-RK, Tewari KS. Gynecologic cancer in pregnancy. *Gynecol Oncol*. 2020;157:799-809.
17. Lei J, Ploner A, Elfström KM, et al. HPV vaccination and the risk of invasive cervical cancer. *N Engl J Med*. 2020;383:1340-1348.
18. Patel C, Brotherton JM, Pillsbury A, et al. The impact of 10 years of human papillomavirus (HPV) vaccination in Australia: what additional disease burden will a nonavalent vaccine prevent? *Euro Surveill*. 2018;23:1700737.
19. Smith M, Canfell K. Impact of the Australian National Cervical Screening Program in women of different ages. *Med J Aust*. 2016;205:359-364.
20. Brotherton J, Gertig D, Chappell G, Rowlands L, Saville M. Catching up with the catch-up: HPV vaccination coverage data for Australian women aged 18-26 years from the national HPV vaccination program register. *Commun Dis Intell Q Rep*. 2011;35:197-201.
21. Salani R, Billingsley CC, Crafton SM. Cancer and pregnancy: an overview for obstetricians and gynecologists. *Am J Obstet Gynecol*. 2014;211:7-14.
22. Smith LH, Danielsen B, Allen ME, Cress R. Cancer associated with obstetric delivery: results of linkage with the California cancer registry. *Am J Obstet Gynecol*. 2003;189:1128-1135.
23. Stensheim H, Moller B, van Dijk T, Fossa SD. Cause-specific survival for women diagnosed with cancer during pregnancy or lactation: a registry-based cohort study. *J Clin Oncol*. 2009;27:45-51.
24. Amant F, Loibl S, Neven P, Van Calsteren K. Breast cancer in pregnancy. *Lancet*. 2012;379:570-579.
25. Australian Institute of Health and Welfare & Cancer Australia. *Gynaecological Cancers in Australia: An Overview*. Cancer series no. 70. Cat. no. CAN 66. AIHW; 2012.
26. Cliby WA, Dodson MK, Podratz KC. Cervical cancer complicated by pregnancy: episiotomy site recurrences following vaginal delivery. *Obstet Gynecol*. 1994;84:179-182.
27. China S, Sinha Y, Sinha D, Hillaby K. Management of gynaecological cancer in pregnancy. *Obstet Gynaecol*. 2017;19:139-146.
28. Masturzo B, Parpinel G, Macchi C, et al. Impact of cancer in the management of delivery: 10 years of variations. *J Matern Fetal Neonatal Med*. 2020;33:2006-2011.
29. Roberts CL, Cameron CA, Bell JC, Algert CS, Morris JM. Measuring maternal morbidity in routinely collected health data: development and validation of a maternal morbidity outcome indicator. *Med Care*. 2008;786-94:786-794.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Fotheringham P, Safi N, Li Z, et al. Pregnancy-associated gynecological cancer in New South Wales, Australia 1994–2013: A population-based historical cohort study. *Acta Obstet Gynecol Scand*. 2023;00:1-11. doi:10.1111/aogs.14530