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Parity is associated with better prognosis in ovarian germ cell tumors, but not in other ovarian cancer subtypes

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Abstract

Ovarian cancer is influenced by reproductive factors, with a reduced risk of epithelial ovarian cancer in parous women. Nonepithelial ovarian cancer frequently affects young women and often precedes or occurs during the childbearing years. However, the impact of reproductive factors on ovarian cancer survival remains unclear: in epithelial ovarian cancer, data are conflicting, and subtype-specific associations have not been examined, and in nonepithelial ovarian cancer, it has not been studied. Using Swedish registers, we evaluated associations between women's reproductive history and cancer-specific mortality by subtype of epithelial and nonepithelial ovarian cancer in 3791 women born 1953 and later, diagnosed from 1990 to 2018. Hazard ratios (HRs) with 95% confidence intervals (95% CIs) were calculated using Cox-proportional hazard models. Parity was associated with a 78% decreased risk of cause-specific mortality in 243 women with germ cell tumors (GCTs) (parous vs nulliparous, adjusted for age at diagnosis: HR: 0.22 [95% CI 0.07-0.62]), with a decreased risk with increasing number of births (per birth: HR: 0.60 [95% CI 0.38-0.95]). We found no evidence of associations between parity and cause-specific mortality among the 334 patients with sex-cord stromal tumors, nor among the 3214 patients with epithelial ovarian cancer; neither overall, nor by subtype. In conclusion, in our large, population-based study, parity was associated with a clearly better prognosis in GCTs but not in the other ovarian cancer subtypes. Future research on how hormone exposure impacts GCT development may lead to a better understanding of mechanisms affecting survival.

KEYWORDS
epithelial ovarian cancer, nonepithelial ovarian cancer, ovarian germ cell tumors, parity, prognosis

What's new?

While risk of epithelial ovarian cancer is known to be influenced by pregnancy, the mechanisms underlying this association remain unclear. In this population-based study, the impact of reproductive history on ovarian cancer prognosis was evaluated by ovarian cancer subtype.

Abbreviations: CI, confidence interval; GCT, germ cell tumor; HR, hazard ratios; SCST, sex cord-stromal tumor.

Among women with germ cell tumors, parity was associated with 78 percent reduction in risk of cause-specific mortality. No associations were detected between parity and prognosis among women with sex-cord stromal tumors or epithelial ovarian cancer. These observations raise new questions about relationships between ovarian cancer prognosis and reproductive factors, including possible impacts of hormone exposure in pregnancy.

1 | BACKGROUND

Ovarian cancer is a severe disorder affecting women of all ages, and due to its location, it is closely associated with childbearing. Most ovarian tumors (90%) are of *epithelial* origin, where the 5-year age-standardized relative survival is poor, reaching 44% in Swedish data.[1] The most well-known predictors of worse outcome are older age at diagnosis, advanced disease stage and macroscopic residual disease postsurgery.[2] *Nonepithelial ovarian cancer* (10%) consists of two main subtypes, germ cell tumors (GCTs) and sex cord-stromal tumors (SCSTs). GCTs are typically diagnosed in teenagers/young women and SCSTs peak in incidence between 50 and 55 years of age.[3,4] The 5-year relative survival exceeds 90% in GCTs[5] and is close to 90% in SCSTs[6]; advanced disease stage is the most important negative prognostic factor. Very few prognostic factors exist besides age and stage.[7]

Pregnancies, both complete and incomplete, reduce the risk of developing *epithelial ovarian cancer*,[8-10] though mechanisms not fully understood.[11] The question of whether parity influences prognosis remains unanswered. Previous studies addressing this question have been conflicting: one study found a worse prognosis in parous women,[12] and nine studies[13-21] found no impact of parity on prognosis but in seven of them,[13,15,16,18-21] the point estimates (<1) suggested a protective effect of parity on prognosis where the lack of significance could be explained by small sample size. Only one study stratified results by subtype of ovarian cancer and only by serous vs nonserous epithelial ovarian cancer.[13]

The etiology and molecular origins of each subtype of *non-epithelial* ovarian cancer are poorly understood.[7] Studies on reproductive factors and risk of nonepithelial ovarian cancer are also few and conflicting.[22-27] To our knowledge, no one has studied whether the prognosis in nonepithelial ovarian cancer is affected by parity.

The aim of our study was to evaluate the effect of the woman's reproductive history on ovarian cancer prognosis by ovarian cancer subtype, by performing a large population-based register study. Our hypothesis was that parous women would have a better prognosis than nulliparous women, based on tendences seen in previous studies as well as the risk-reducing effect provided by pregnancies, suggesting a favorable biological effect. Due to scarce data on both epidemiological and tumor biology in GCTs and SCSTs, our study has an exploratory and hypothesis generating purpose in these subtypes.

Better knowledge of the relationship between reproductive ovarian cancer risk factors and their impact on survival might reveal common underlying mechanisms and raise hypotheses for a better understanding of the tumor biology in these tumors.

2 | MATERIALS AND METHODS

2.1 | Study population

Our study was based on data linkage from Swedish nation-wide registers: the Medical Birth Register, founded in 1973, containing mandatory reported information from antenatal, obstetric and neonatal medical records[28]; the Cancer Register, with information on all incident tumors in the entire population since 1958,[29] and the Cause of Death Register.[30] Linkage was enabled by the unique personal identification number covering all Swedish citizens.

We included patients aged 18 and above diagnosed with invasive ovarian cancer in Sweden from 1990 to 2018 (Figure S1). As the Medical Birth Register started in 1973, we excluded women who were born before 1953 to guarantee that they were not older than 20 years, and hence unlikely to have completed their childbearing at the start of the nationwide Medical Birth Register. Cases of ovarian, fallopian tube and primary peritoneal cancer were included in our study and are referred to as ovarian cancer, since they are usually considered to be one entity due to common histology and origin.[31] Ovarian cancer cases were defined using ICD-7 code 175.0 or ICD-O-3 code C56.9; fallopian tube cancer by ICD-7 code 175.1 or ICD-O-3 code C57.0; primary peritoneal cancer by ICD-7 code 158 or ICD-O-3 code C48.1 or C48.2. ICD-O-2 and ICD-O-3 codes were used to define epithelial and nonepithelial subtypes (Table S1).

2.2 | Statistical analysis

Cox-proportional hazard models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for associations of reproductive factors with death in ovarian cancer. The reproductive variables examined were: parity, number of births (before ovarian cancer diagnosis), age at first and last birth (<25, 25-29 and ≥30 years) and time since first and last birth (<10, 10-19 and ≥20 years). Patients contributed with time from date of diagnosis until ovarian cancer-specific death (for cause-specific mortality), death of any cause (for all-cause mortality) or end of follow-up in February 2020. Women were censured at death from causes other than ovarian cancer in cause-specific mortality analyses. We adjusted all results for the prognostic factor age at diagnosis (years, as a continuous variable). Data on disease stage were available from 2003, and in subanalyses, all results were additionally adjusted for stage. We performed analyses stratified by subtype of ovarian cancer (*epithelial*: serous, mucinous, clear cell and endometrioid; *nonepithelial*: GCT and SCST) and by year of diagnosis

TABLE 1 Characteristics of patients born 1953 to 2000, diagnosed with germ cell tumors, sex cord-stromal tumors and epithelial ovarian cancer in Sweden from 1990 to 2018

	Germ cell tumors		Sex cord-stromal tumors		Epithelial, all	
Mean age at diagnosis (years)	32		42		48	
Mean age at diagnosis in parous/ nulliparous women (years)	38/27		46/36		49/45	
Total	**n 243**	**% 100**	**n 334**	**% 100**	**n 3214**	**% 100**
Year of birth						
1953-1959	31	13	96	29	1570	49
1960-1969	47	19	110	33	1200	37
1970-1979	81	33	81	24	319	9.9
1980-2000	84	35	47	14	125	3.9
Parity (ever)						
No	135	56	136	41	1164	36
Yes	108	44	198	59	2050	64
Age at first birth (years)						
<25	53	49	92	47	925	45
25-29	32	30	66	33	640	31
≥30	23	21	40	20	485	24
Age at last birth (years)						
<25	24	22	33	17	310	15
25-29	36	33	68	34	641	31
≥30	48	44	97	49	1099	54
Time since first birth (years)						
<10	49	45	39	20	220	11
10-19	37	34	51	26	509	25
≥20	22	20	108	55	1321	64
Time since last birth (years)						
<10	65	60	69	35	357	17
10-19	34	32	54	27	719	35
≥20	9	8.3	75	38	974	48
Age at diagnosis (years)						
18-29	115	47	58	17	172	5
30-39	76	31	81	24	416	13
40-49	33	14	96	29	1098	34
50-59	16	6.6	85	25	1264	39
60-65	3	1.2	14	4.2	264	8.2
Disease stage[a]						
1	108	77[b]	221	93[b]	768	32[b]
2	12	8.6[b]	9	3.8[b]	240	9.9[b]
3	16	11[b]	7	2.9[b]	1035	42[b]
4	4	2.9[b]	1	0.4[b]	392	16[b]
Missing	103	42	103	29	779	24

[a]Data on stage of disease (according to International Federation of Gynecology and Obstetrics [FIGO]) was available from 2003. In patients diagnosed 2003 and later, information on FIGO-stage was available for 90.2%.
[b]Missing cases excluded.

TABLE 2 Associations between reproductive factors and cancer-specific mortality among nonepithelial ovarian cancer cases in Sweden from 1990 to 2018, stratified by subtype, adjusted for age at diagnosis[a]

	Germ cell tumors			Sex cord-stromal tumors		
Cases (%)		239 (42.3)			326 (57.7)	
Number of deaths		20			17	
	n (col%)	HR	95% CI	n (col%)	HR	95% CI
Parity (ever)						
No	133 (56)	1.00	Ref	133 (41)	1.00	Ref
Yes	106 (44)	0.22	0.07-0.62	193 (59)	0.81	0.28-2.34
Per birth		0.60	0.38-0.95		0.94	0.63-1.41
Age at first birth (years)						
<25	52 (49)	1.00	Ref	90 (47)	1.00	Ref
25-29	32 (30)	0.90	0.13-6.12	64 (33)	—[b]	—
≥30	22 (21)	—[b]	—	39 (20)	0.66	0.14-3.19
Age at last birth (years)						
<25	24 (23)	1.00	Ref	32 (17)	1.00	Ref
25-29	35 (33)	—[b]	—	66 (34)	1.91	0.21-17.35
≥30	47 (44)	—[b]	—	95 (49)	1.25	0.14-11.43
Time since first birth (years)						
<10	49 (46)	1.00	Ref	38 (20)	1.00	Ref
10-19	36 (34)	—[b]	—	51 (26)	1.41	0.10-19.08
≥20	21 (20)	—[b]	—	104 (54)	2.40	0.11-51.88
Time since last birth (years)						
<10	65 (61)	1.00	Ref	68 (35)	1.00	Ref
10-19	32 (30)	—[b]	—	52 (27)	0.40	0.03-4.93
≥20	9 (8.5)	—[b]	—	73 (38)	1.47	0.11-19.28

[a]Hazard ratio (HR) and 95% confidence intervals (CIs) from Cox regression models adjusted for age at diagnosis.
[b]Age at first/last birth and time since first/last birth were not always possible to analyze due to limited data.

TABLE 3 Subtypes of invasive ovarian germ cell tumors (women diagnosed at age <30/≥30 years)

	Parous		Nulliparous			
	Total n (<30/≥30)	Cancer-specific deaths n (<30/≥30)	Total n (<30/≥30)	Cancer-specific deaths n (<30/≥30)	*P*-value[a] Parous vs nulliparous	*P*-value <30/≥30 years
Total	108 (19/89)	5 (1/4)	135 (96/39)	15 (6/9)	.10	1/.002
Dysgerminoma	18 (5/13)	0 (0/0)	46 (39/7)	1 (1/0)	—	—/—
Yolk sac tumor	11 (1/10)	0 (0/0)	18 (15/3)	2 (0/2)	.51	—/.04
Malignant teratoma	63 (12/51)	4 (1/3)	63 (37/26)	11 (5/6)	.10	1/.05
Carcinoid	16 (1/15)	1 (0/1)	4 (1/3)	1 (0/1)	.37	—/.31
Embryonal carcinoma	0 (0/0)	0 (0/0)	3 (3/0)	0 (0/0)	—	—/—
Mixed germ cell tumor	0 (0/0)	0 (0/0)	1 (1/0)	0 (0/0)	—	—/—

[a]Differences in proportions of cancer-specific deaths between parous and nulliparous women, and between women diagnosed at age < 30 vs >30 years, were tested with Fisher's exact test.

(1990-2002 [before available data on disease stage], 2003-2012, 2013-2018). We also performed analyses with overall survival as outcome. Due to limited data, number of births, age at first and last birth and time since first and last birth were not analyzed in nonepithelial ovarian cancer cases. As a sensitivity test, we excluded cases diagnosed with ovarian cancer within 6 months of their last birth to minimize the risk that survival in parous women was affected by earlier detection of cancer due to pregnancy. We also analyzed associations excluding women with a cancer diagnosis prior to the ovarian cancer diagnosis, to ensure that a previous malignancy did not impact on the prognosis. We used the Kaplan-Meier method to illustrate cancer-specific survival in GCTs, stratified by age at diagnoses (<30 years and ≥30 years), and

survival curves were compared using log-rank test. Differences in proportions of cancer-specific deaths between parous and nulliparous women were tested with Fisher's exact test. *P*-values were considered statistically significant if <.05. All analyses were performed using RStudio version 1.2.1335.[32]

3 | RESULTS

3.1 | Nonepithelial ovarian cancer

In total, 243 patients were diagnosed with GCTs and 334 patients with SCSTs in Sweden from 1990 to 2018. Mean age at diagnosis of GCTs was 32 years (among parous women: 38 years, nulliparous: 27 years) and 42 years in SCSTs (among parous women: 46 years, nulliparous: 36 years); Table 1.

3.1.1 | Prognosis in GCTs

Among women diagnosed with GCTs, we observed 20 cancer-specific deaths and 24 all-cause deaths over an average follow-up of 11.4 years (range: 0.1-27.0 years). Parity was associated with a decreased risk of cancer-specific mortality in GCTs (parous vs nulliparous women, adjusted for age at diagnosis: HR: 0.22 [95% CI 0.07-0.62], Table 2), as well as with all-cause mortality (adjusted for age at diagnosis: HR: 0.25 [95% CI 0.10-0.63], Table S2). The risk decreased with increasing number of births (per birth, adjusted for age at diagnosis: HR: 0.60 [95% CI 0.38-0.95]). The associations remained when additionally adjusted for stage (in patients diagnosed 2003 and later), i.e., GCTs, parous vs nulliparous women: (HR: 0.09 [95% CI 0.01-0.73]; Table S3). Among women who were 30 years or older, only 4.5% (4 out of 89) of parous women died of GCTs compared to 23% (9 out of 39) of nulliparous women ($P = .002$; Table 3).

To minimize the risk that the reduced mortality in parous women was driven by earlier detection of cancer due to pregnancy, we excluded cases diagnosed with GCTs within 6 months of their last birth in a sensitivity test (n = 8); the results were unaltered (cancer-specific mortality in parous vs nulliparous women, adjusted for age at diagnosis: HR: 0.23 [95% CI 0.08-0.68]). No major differences in subtypes of malignant ovarian GCTs were seen between parous and nulliparous women (Table 3). Malignant teratoma was the most common cause of death, and among women diagnosed with malignant teratomas at age 30 years and older, 6% (3 of 51) of the parous women died of their disease, compared to 23% (6 of 26) of the nulliparous women, $P = .03$ (Table 3).

3.1.2 | Prognosis in sex-cord stromal tumors

In women with SCSTs, 17 cancer-specific deaths occurred (25 all-cause deaths) during a follow-up period of 9.3 years (0.3-27 years). No significant association was seen between parity and cancer-specific survival in SCSTs (HR: 0.81 [95% CI 0.28-2.34], adjusted for age at diagnosis; Table 2); nor with any of the other reproductive factors.

TABLE 4 Associations between reproductive factors and cancer-specific mortality among epithelial ovarian cancer cases in Sweden from 1990 to 2018[a]

	Adjusted for age		Adjusted for age and FIGO stage[b]	
Cases (n)	2974		2260	
Number of deaths	1146		809	
	HR	**95% CI**	**HR**	**95% CI**
Parity (ever)				
No	1.00	Ref	1.00	Ref
Yes	0.99	0.87-1.11	0.96	0.83-1.12
Number of births				
0	1.00	Ref	1.00	Ref
1	1.00	0.84-1.20	0.98	0.79-1.22
2	0.94	0.81-1.09	0.95	0.80-1.13
3	1.06	0.88-1.28	1.02	0.82-1.27
4+	0.99	0.75-1.32	0.87	0.62-1.20
Per birth	1.00	0.96-1.05	0.99	0.93-1.04
Age at first birth (years)				
<25	1.00	Ref	1.00	Ref
25-29	0.79	0.67-0.94	0.76	0.62-0.94
≥30	0.91	0.76-1.10	0.92	0.74-1.14
Per year age	0.99	0.97-1.00	0.99	0.97-1.00
Age at last birth (years)				
<25	1.00	Ref	1.00	Ref
25-29	0.79	0.64-0.99	0.89	0.68-1.17
≥30	0.84	0.69-1.03	0.94	0.73-1.20
Per year age	0.99	0.98-1.01	1.00	0.98-1.02
Time since first birth (years)				
<10	1.00	Ref	1.00	Ref
10-19	1.24	0.93-1.66	1.18	0.78-1.79
≥20	1.35	0.97-1.88	1.20	0.77-1.86
Per year	1.01	1.00-1.03	1.01	1.00–1.03
Time since last birth (years)				
<10	1.00	Ref	1.00	Ref
10-19	1.13	0.89-1.45	1.09	0.79-1.52
≥20	1.17	0.86-1.59	1.10	0.74-1.62
Per year	1.01	0.99-1.02	1.00	0.98-1.01

[a]Hazard ratio (HR) and 95% confidence intervals (CIs) derived from Cox regression models.
[b]Data on stage of disease (according to the International Federation of Gynecology and Obstetrics, FIGO) was available from 2003. In patients diagnosed with epithelial ovarian cancer 2003 and later, information on disease stage was available for 90.4%.

3.2 | Epithelial ovarian cancer

Mean age at diagnosis was 48 years among the 3214 epithelial ovarian cases (parous women: 49 years; nulliparous women: 45 years); patient characteristics are summarized in Table 1. Over an average follow-up time of 6.5 years (range: 0.0-27.0 years), we observed 1146 cancer-specific deaths and 1386 all-cause deaths. Younger age at childbirth, both at first and last birth, was associated with decreased cancer-specific mortality (i.e., age at first birth

TABLE 5 Associations between reproductive factors and cancer-specific mortality among epithelial ovarian cancer cases in Sweden from 1990 to 2018, stratified by subtype, adjusted for age[a]

	Serous		Mucinous		Clear cell		Endometrioid	
Cases (%[b])	1741 (60.9)		429 (15.0)		246 (8.6)		442 (15.5)	
Number of deaths	804		98		84		103	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Parity (ever)								
No	1.00	Ref	1.00	Ref	1.00	Ref	1.00	Ref
Yes	1.01	0.87-1.18	0.79	0.51-1.23	0.82	0.53-1.27	0.88	0.59-1.30
Number of births								
0	1.00	Ref	1.00	Ref	1.00	Ref	1.00	Ref
1	1.03	0.83-1.27	0.61	0.31-1.17	1.14	0.61-2.11	0.66	0.32-1.34
2	0.99	0.83-1.18	0.90	0.54-1.50	0.71	0.41-1.25	0.73	0.44-1.21
3	1.04	0.84-1.29	0.85	0.43-1.68	0.63	0.27-1.47	1.40	0.75-2.63
≥4	1.04	0.73-1.48	0.68	0.26-1.77	1.75	0.24-12.72	1.50	0.67-3.33
Per birth	1.01	0.95-1.07	0.97	0.82-1.15	0.88	0.71-1.08	1.05	0.90-1.22
Age at first birth (years)								
<25	1.00	Ref	1.00	Ref	1.00	Ref	1.00	Ref
25-29	0.89	0.73-1.08	0.60	0.33-1.09	0.83	0.38-1.83	0.38	0.18-0.80
≥30	0.88	0.71-1.09	0.65	0.31-1.35	1.52	0.70-3.30	0.59	0.28-1.24
Age at last birth (years)								
<25	1.00	Ref	1.00	Ref	1.00	Ref	1.00	Ref
25-29	1.04	0.80-1.35	0.69	0.35-1.35	0.56	0.22-1.47	0.42	0.19-0.91
≥30	0.97	0.76-1.24	0.59	0.30-1.14	0.76	0.32-1.83	0.49	0.23-1.03
Time since first birth (years)								
<10	1.00	Ref	1.00	Ref	1.00	Ref	1.00	Ref
10-19	1.07	0.76-1.51	1.93	0.84-4.44	1.77	0.37-8.52	1.53	0.47-5.00
≥20	1.28	0.88-1.87	2.06	0.71-5.96	1.15	0.20-6.64	1.66	0.44-6.36
Time since last birth (years)								
<10	1.00	Ref	1.00	Ref	1.00	Ref	1.00	Ref
10-19	1.03	0.78-1.37	1.48	0.69-3.20	3.08	0.65-14.52	1.37	0.51-3.65
≥20	1.23	0.87-1.73	1.60	0.56-4.57	1.33	0.22-8.23	1.05	0.29-3.84

[a]Hazard ratio (HR) and 95% confidence intervals (CIs) from Cox regression models.
[b]Of cases with known histology.

25-29 years vs <25 years, adjusted for age at diagnosis: OR: 0.79 [95% CI 0.67-0.94]; Table 4).

No associations among parity, number of births, or time since first or last birth and cancer-specific mortality in epithelial ovarian cancer were seen (Table 4), nor was any association with all-cause mortality (data not shown). When the survival analyses were stratified by subtypes of epithelial ovarian cancer, no new association between reproductive factors and cancer-specific mortality appeared in any strata (Table 5); nor when the survival analyses were investigated stratified by year of diagnosis (data not shown).

4 | DISCUSSION

We evaluated the association between reproductive factors and cancer-specific mortality in 243 cases of GCTs, 334 of SCSTs and 3214 epithelial ovarian cancer cases, stratified by cancer subtype. Parity was associated with a 78% decreased risk of cancer-specific mortality in GCTs. Except for an association between younger age at childbirth and decreased risk of cancer-specific mortality in epithelial ovarian cancer, no evidence of associations between reproductive history and prognosis in SCSTs or epithelial ovarian cancer was found.

4.1 | Noneepithelial ovarian cancer

Although pregnancies seem to have a limited impact on the risk of these rare tumors,[26] we found that parous women diagnosed with GCTs had a clearly better prognosis than nulliparous women. To our knowledge, there are no previous studies on the prognostic impact of parity in nonepithelial ovarian cancer. The underlying mechanism behind the worse prognosis in nulliparous women is unclear. Parous women were diagnosed with GCTs at a substantially older age than nulliparous women (mean age at diagnosis was 38 years vs 27 years).

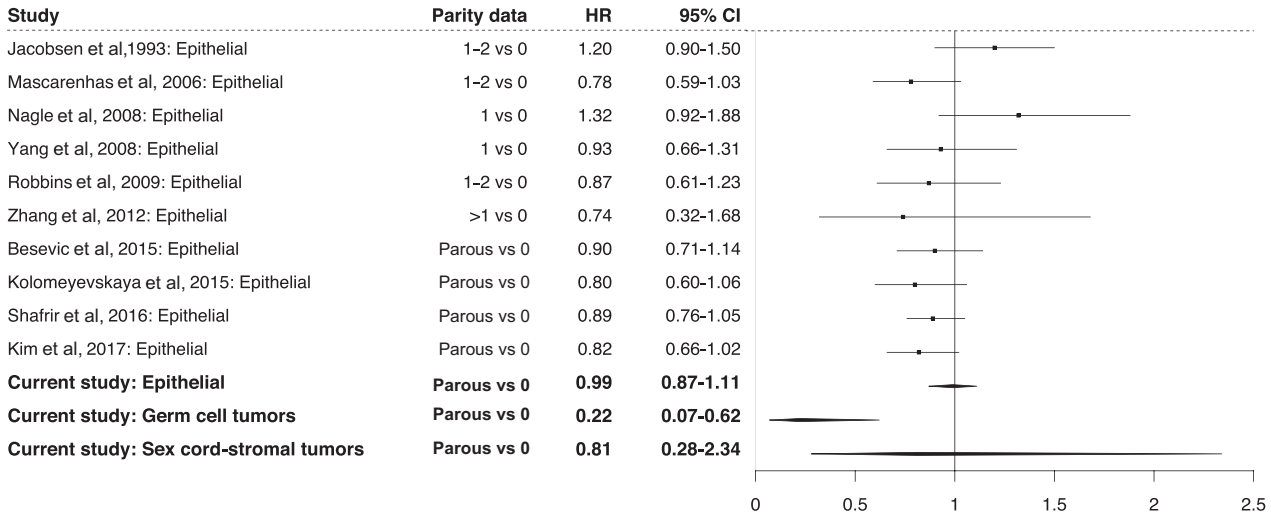

FIGURE 1 Parity and prognosis in previous studies on epithelial ovarian cancer, with results from our study on epithelial ovarian cancer, sex cord-stromal tumors and germ cell tumors added

Since it is less likely that women who are young when diagnosed with a malignancy have had children before their diagnosis, the group of nulliparous women will have a low mean age at diagnosis. The group of women who have had at least one child before diagnosis will, therefore, be of an older age at diagnosis than the nulliparous group.

GCTs occurring in girls and young women might have a different biology than GCTs occurring in women older than 30 years; that is, that parous women develop less aggressive GCTs than nulliparous women. Among women who were 30 years or older at diagnosis, only 4.5% of the parous women died during follow-up, compared to 23% of the nulliparous women. In parous women, 63 out of 108 (58%) GCTs were malignant teratomas, but only 4 of 63 (6.3%) parous women died of their malignancy. In nulliparous women, however, malignant teratomas accounted for 63 out of 135 (47%) GCTs, but were more deadly: 11 of 63 (17%) nulliparous women died of their malignancy.

A possible mechanism could be the differentiation of precarcinous cells during pregnancy, and thereby a less aggressive malignancy in women who have given birth. To our knowledge, there are, however, no preclinical studies on the subject. In breast cancer, a pregnancy causes the differentiation of glandular tissue, which reduces the breast cancer risk.[33] A similar effect might be possible in the ovarian germ cells. Although pregnancies do not seem to impact the risk of developing GCTs,[26] changes in hormone levels during puberty might be of importance, as well as oral contraceptive use and factors such as body size. Another possible explanation behind the protective effect of parity could be more frequent use of fertility-sparing surgery in nulliparous than in parous women, which could potentially result in a higher risk of relapse.

In general, a better prognosis in parous women could be due to a stronger social network among women with children. However, the women in our study were young, and hence, dependence on family is less likely to affect mortality. Moreover, it is difficult to explain why the effect would only be pronounced in GCTs and not in the other ovarian cancer subtypes. Future research on how hormone exposure impacts GCT development may lead to a better understanding of potential mechanisms affecting survival.

An American study found that unmarried women aged over 40 years at diagnosis with GCT subtypes other than dysgerminomas had a decreased cancer-specific survival compared to married women. If we assume that unmarried women are, in general, more often nulliparous than married women, this result is in line with our study.[34]

4.2 | Epithelial ovarian cancer

Our study is the largest to date with 3214 epithelial ovarian cancer cases, and we found no prognostic impact of parity status. Most previous studies have found a trend toward improved survival in parous women as visualized in Figure 1.[12,13,15,16,18-21] Contrastingly, two studies found a tendency toward worse survival in parous women compared to nulliparous.[14,17] Only Kim et al[12] found a significantly increased survival among parous women, and only in a subset of patients (59%) when adjusting for residual disease after surgery. They did not, however, find any association with increased number of births, and their cohort was based on a subgroup of ovarian cancer patients, where genetic testing had been performed with a mean time since diagnosis of 1.83 years. Information on reproductive factors was based on interviews 0.1 to 79 months after diagnosis; hence, ovarian cancer patients with short survival from diagnosis were not included in their cohort, which might explain their findings. The only association seen in our study was a decreased risk of cancer-specific death among women aged 25 to 29 years at first or last childbirth, but this finding was only seen in this age strata and clearly needs verification. We have summarized previous results and the associations found in our study in Figure 1 and Table S4 (in part adapted from Poole et al[2]).

In summary, reproductive factors seem to have little, if any, impact on prognosis in epithelial ovarian cancer.

4.3 | Strengths and limitations

This population-based study is the largest study to date reviewing the impact of reproductive factors on cancer-specific mortality in ovarian cancer. Our large cohort enabled us to study associations stratified by subtypes of both epithelial and nonepithelial ovarian cancer, which has not been previously done. However, despite the comparably large study size, statistical power was limited when calculating associations with especially GCTs and SCSTs, where CIs were wide. We had complete information on the reproductive factors studied, based on mandatory reporting in the Medical Birth Register, thus avoiding recall bias. We also had detailed information on cause of death and were, therefore, able to analyze cancer-specific mortality.

The women included in the study were young as our cohort was limited to women born 1953 and later, in order to ensure that they were not older than 20 years at the start of the Medical Birth Register in 1973 and, hence, were unlikely to have completed their childbearing. Mean age at diagnosis among women with epithelial ovarian cancer in our study was 48, compared to 63 years in all epithelial ovarian cancer patients, making our results representative mainly for women who are relatively young at diagnosis. In GCTs, the subtype where parity was associated with better prognosis, the mean age was only 32 years. Nevertheless, these rare tumors are most common in teenagers and young women, so the expected mean age is young. Since our cohort was restricted to women aged 18 years or older at diagnosis, the mean age is higher than when all GCT cases, including children, are included.

One of the limitations in our study was lack of information on the possible confounders infertility and body mass index; however, these factors have not been associated with prognosis in GCTs. We also lacked information on comorbidities, but since patients with GCTs were young, comorbidities are less likely to have affected survival in this subtype.

5 | CONCLUSION

In conclusion, we observed a noticeable reduction of cancer-specific mortality among parous women diagnosed with GCTs, suggesting that pregnancies have an effect on biology in these rare tumors. No evidence of associations between pregnancy-related factors and survival in epithelial ovarian cancer was found, suggesting that reproductive factors have a limited impact on prognosis in epithelial ovarian carcinomas.

CONFLICT OF INTEREST

Ingrid Glimelius has received Honoraria from Janssen for projects unrelated to our study. All other authors declare they have no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data in our study result from linkages of nationwide registers as described in the method section. Restrictions apply for the availability of these data according to the national data protection legislation. Data are available from the authors with the permission of the Swedish Authority for Privacy Protection. Additional information will be available from the corresponding author upon request.

ETHICS STATEMENT

Ethical approval was obtained from The Regional Ethics Committee of Uppsala University (ethical permit number 2017/003 and complementary approval 2017/003/1 and 2019-05942).

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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