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In vitro fertilization is associated with an increased risk of borderline ovarian tumors

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Abstract

Objectives

To compare the risk of borderline ovarian tumors in women having in vitro fertilization (IVF) with women diagnosed with infertility but not having IVF.

Methods

This was a whole-population cohort study of women aged 20-44 years seeking hospital infertility treatment or investigation in Western Australia in 1982-2002. Using Cox regression, we examined the effects of IVF treatment and potential confounders on the rate of borderline ovarian tumors. Potential confounders included parity, age, calendar year, socio-economic status, infertility diagnoses including pelvic inflammatory disorders and endometriosis and surgical procedures including hysterectomy and tubal ligation.

Results

Women undergoing IVF had an increased rate of borderline ovarian tumors with a hazard ratio (HR) of 2.46 (95% confidence interval [CI] 1.20–5.04). Unlike invasive epithelial ovarian cancer, neither birth (HR 0.89; 95% CI 0.43–1.88) nor hysterectomy (1.02; 0.24–4.37) nor sterilization (1.48; 0.63–3.48) appeared protective and the rate was not increased in women with a diagnosis of endometriosis (HR 0.31; 95% CI 0.04–2.29).

Conclusions

Women undergoing IVF treatment are at increased risk of being diagnosed with borderline ovarian tumors. Risk factors for borderline ovarian tumors appear different from those for invasive ovarian cancer.

77 Key Words

78 In vitro fertilization; borderline ovarian tumors; cohort study; hazard ratios; risk factors;
79 epidemiology

Introduction

Borderline epithelial ovarian tumors are a heterogeneous group of neoplasms, first described in 1929 [1]. For some time they were believed to be precursors of invasive epithelial ovarian cancer, but they have been gradually recognised as a separate entity and were classified as such by the International Federation of Gynecology and Obstetrics (FIGO) in 1970 [2]. Unlike invasive epithelial ovarian cancer, borderline epithelial ovarian tumors, also known as tumors of low malignant potential, have an indolent disposition, do not destructively invade the underlying ovarian stroma [3], are more likely to be diagnosed in women of reproductive age [4], and have a favourable prognosis, with more than 95% of women surviving five years beyond diagnosis [5]. They represent around 15% of all ovarian neoplasms [6].

Some authors maintain that risk factors for borderline ovarian tumors are the same as those for invasive epithelial ovarian cancer, but the evidence is scant and contradictory. For example, giving birth has been found to be protective in some studies [7, 8], possibly protective in another [9] and not protective in others [10-12]. Oral contraceptive use appears in some studies [9, 12] to confer protection, but not in others [7, 11]. Harris et al [8] found a protective effect of sterilization; Mosgaard et al [10] found no effect.

With regard to treatment with fertility drugs, most studies have found an increased risk of borderline ovarian tumors after fertility drug treatment [8, 12-15], although some have not [10, 11]. The only study that focussed specifically on in vitro fertilization (IVF) found that IVF treatment was associated with a four-fold increase in the risk of borderline ovarian tumors [16].

Given the important role that IVF plays in the current management of infertility, we believe the relationship between IVF and borderline ovarian tumors deserves further investigation. The aim of the present study was to examine the association between IVF treatment and risk of borderline ovarian tumors in a cohort of women seeking treatment for infertility, considering also the

confounding effects of known or potential ovarian cancer risk factors including parity, infertility diagnosis, sterilization, hysterectomy and socio-economic status.

Methods

The study cohort

This was a population-based cohort study using routinely collected linked administrative data from an entire Australian State. Methods for identifying the study cohort have been described in previous reports of breast [17] and ovarian cancer [18]. To recapitulate, we identified a cohort of women seeking hospital investigation and treatment for infertility at all hospitals in Western Australia (WA). The cohort was restricted to women who were known to be resident in WA according to the address attached to their hospital records, and who did not move out of the State according to the WA Electoral Roll, which had data available to us from 1988 onward.

Women were included in the cohort if their hospital records contained a diagnosis of infertility or procreative management (ICD-9 628.0 - 628.9; ICD-10 N97.0 - N97.9 or ICD-9 V26.1 - V26.9; ICD-10 Z31.1 - Z31.9), with their first such diagnosis occurring when they were aged between 20 and 44 years. The recruitment period for this study ranged from 1982 to 2002. Data on exposures and outcomes (listed below) were collected in de-identified form from 1980 to 2010 using the resources of the WA Data Linkage System [19] which connects administrative datasets covering the whole population of WA. The required information was obtained by accessing and combining de-identified data from six separate data collections: the Hospital Morbidity Data System, the WA Cancer Registry, the Midwives Notification System, the WA Deaths Register, the Reproductive Technology Register and the WA Electoral Roll. These are statutory based data collections ensuring routine and complete data collection.

Exposure variables

The main exposure was IVF treatment. Women undergoing IVF were identified from either the diagnostic and procedure codes contained in their hospital records, or by linkage to the Reproductive Technology Register. Since 1993, all clinics in WA have been required by law to report all IVF cycles to this register.

We also considered a number of potential confounders: those believed to influence the risk of invasive epithelial ovarian cancer, which may also impact on the risk of borderline ovarian tumors. These included diagnoses of endometriosis and pelvic inflammatory disorders (PID – ICD-9 614.0 - 614.9; ICD-10 N70.1, N70.9, N73.0 - N73.9: predominantly 614.6 and N73.6 [pelvic peritoneal adhesions]), and procedures including tubal ligation, hysterectomy, unilateral oophorectomy or salpingo-oophorectomy (USO); parity (we compared parous women with nulliparous women), age at first birth, socio-economic status using the Index of Education and Occupation [20], and age and calendar year at the start of follow-up.

We captured all births in WA during 1980 to 2010 and correctly recorded prior births in women who gave birth within the State during this time period. However, some women may have delivered outside WA or prior to 1980 and not subsequently given birth in WA – this small proportion of women would have been incorrectly classified as nulliparous. Similarly, all women who had a tubal ligation in WA between 1980 and 2010 were correctly classified, as were women who had a reversal with no mention of a prior sterilization. However, there would remain a small proportion that had a tubal ligation outside the State or prior to 1980 without having a subsequent reversal, presumably going straight to IVF: sterilization status in this small proportion of women would have been incorrect. We categorised women as having a diagnosis of endometriosis or PID if either of these was recorded at or on any record prior to the first infertility admission. It is possible that some women would have been diagnosed later during follow-up or remained undiagnosed: these would

have been classified as not having endometriosis or PID, when in fact they did suffer from these conditions.

Outcome variable

The outcome was an incident diagnosis of borderline ovarian tumor, identified from data collected by the WA Cancer Registry.

Data analysis

Data were analysed using Cox regression analysis. Women were followed from their first hospital infertility admission to the date of diagnosis of borderline ovarian tumor, date of bilateral oophorectomy/salpingo-oophorectomy, date of death or the censor date (15 August 2010), whichever came first. Hazard ratios (HRs) were estimated in univariate and multivariate adjusted analysis for each of the exposure variables. Covariates were entered into the model as either fixed or time dependent variables, depending on when they occurred or were measured. Socio-economic status, age and calendar year were measured at baseline; endometriosis and pelvic inflammatory disorders were diagnosed at baseline. These were entered into the regression model as fixed categorical variables. Women gave birth either before or after the start of follow-up. Birth (parous vs. nulliparous) and age group at first birth (less than 30 years and 30 years or older) were entered into separate models as categorical time dependent variables. Tubal ligation could occur either before or after the start of follow-up; IVF could occur at the start of follow-up or sometime later; hysterectomy occurred after the start of follow-up. These were all entered into Cox regression models as categorical time dependent variables to allow for the correct allocation of follow-up time into time before and time after exposure.

175 Ethics approval

176 This study received ethics approval from The University of Western Australia Human Research Ethics
177 Committee and the Department of Health WA Human Research Ethics Committee.

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Results

Characteristics of the study participants

The eligible population included 22,045 women. We excluded women who were not resident of WA or who were known to have moved out of WA (n=379) as well as women who were deemed to be no longer at risk of a borderline ovarian tumor diagnosis. These included women who had a bilateral oophorectomy/salpingo-oophorectomy before their first infertility admission (n=13), women who had a diagnosis of invasive ovarian cancer either before or within six months of their first infertility admission (n=7) and women who were diagnosed with a borderline ovarian tumor before their first infertility admission (n=7). None of the women in the cohort were diagnosed with borderline ovarian tumors within six months of their first infertility admission. The final cohort comprised a total of 21,639 women.

Women were, on average, 31.2 years of age at their first infertility admission and were followed for a mean of 16.9 years. Total observation of the cohort amounted to 365,775 woman-years. Out of a total of 21,639 women, 31 were diagnosed with borderline ovarian tumors, including 17 women who had IVF and 14 women who did not. The average age at diagnosis was 43.2 years (Table 1). Women having IVF were older at the birth of their first child and more likely to be in the upper quartile of the Index of Education and Occupation (Table 1).

Borderline ovarian tumor risk factors

We examined the association between IVF and potential confounding factors in univariate and then multivariate adjusted analyses (Table 2).

IVF treatment was associated with an increased rate of borderline ovarian tumors in univariate and adjusted analysis. The HR was 2.48 (95% confidence interval [CI] 1.22 – 5.04) in unadjusted analysis, and changed only slightly after adjustment for confounding by age, calendar year and socio-economic status to 2.46 (95% CI 1.20 – 5.04) (Table 2).

In unadjusted analysis, there appeared to be a slight protective effect of giving birth, in particular giving birth at a young age, however, most of this apparent protection disappeared after adjustment for IVF, socio-economic status, age and calendar year (Table 2). A part of this effect was due to confounding by IVF: women who gave birth, and women who gave birth at a young age were less likely to have had IVF (Table 1) and consequently appeared to have a reduced rate of borderline ovarian tumor diagnosis in the analysis that did not adjust for IVF.

We also examined the effect of IVF in parous and nulliparous women separately. In parous women the adjusted HR ratio associated with IVF treatment was 2.96 (95% CI 1.15 – 7.61); in nulliparous women it was 1.88 (95% CI 0.63 – 5.63).

Women in the highest quartile of socio-economic status, as measured by the Index of Education and Occupation, had a reduced rate of borderline ovarian tumors. This was particularly apparent in the adjusted analysis where the HR was 0.36 (95% CI 0.12 – 1.03) (Table 2). Women undergoing IVF were more likely to be in the upper quartile of socio-economic status (Table 1) and adjusting for IVF allowed for a more accurate estimate of the effect of socio-economic status.

We observed no association between a diagnosis of PID and the rate of borderline ovarian tumors, with an adjusted HR of 0.96 (95% CI 0.37 – 2.51) (Table 2). We did not observe an increased rate with a diagnosis of endometriosis (adjusted HR 0.31, 95% CI 0.04 – 2.29) (Table 2). We found no evidence for a protective effect of either sterilization or hysterectomy with HRs of 1.48 and 1.02 (Table 2).

Discussion

The results of this study support the proposition that women undergoing IVF treatment are at increased risk of borderline ovarian tumors. Within our cohort, the rate of diagnosis of borderline ovarian tumors was 2.5 times greater in women who sought infertility treatment and had IVF than in women who had infertility treatment but not IVF. These findings are consistent with the only other study of IVF and borderline ovarian tumors [16], and also consistent with most studies of fertility drug treatment and borderline ovarian tumors [8, 12-15].

A number of authors [14, 21-23] have suggested that this apparent increase in risk may not be causal, but rather due to surveillance bias. Surveillance bias is a case of "the more you look, the more you find"; the premise being that women who have IVF will be examined more often than women who do not, providing more opportunities for detection. Women undergoing IVF may be exposed to more routine examinations; or, because they are concerned about their IVF exposure, they may be more aware of symptoms of disease and be more pro-active in seeking diagnosis and treatment; alternatively they may be more health conscious and therefore actively seek screening. Any of these could lead to earlier detection and an apparent (though false) increase in risk of disease.

This is a logical explanation, but is it true? In order to answer this question, we considered the following: time from last infertility admission to diagnosis of borderline ovarian tumors, age at diagnosis, and risk of borderline tumors in women of high socio-economic status. Women were diagnosed with borderline ovarian tumors, on average 8.6 years after their last hospital infertility admission. Although there was some variability in the time to diagnosis, this considerable lapse of time suggests that borderline tumors were generally not being detected during routine infertility investigation. This counters the first concern. Secondly, if IVF women were more pro-active in seeking diagnosis and treatment, we would expect them to be diagnosed sooner, and at a younger age. This was not the case. The average time from last infertility admission to diagnosis in IVF

women was 9.4 years, and in women not undergoing IVF it was 7.3 years. Furthermore, IVF women were diagnosed with borderline tumors at a mean age of 44.7 years, compared with 41.1 years in non-IVF women. IVF women were not diagnosed sooner, or at a younger age. Our third point is that if detection bias was the main reason for the apparent increase in risk of borderline tumors, we would expect women of higher socio-economic status to be more likely to be diagnosed, as they are generally found to be more active in seeking health screening [24]. This was also not the case. We found that women of high socio-economic status had only one third the risk of borderline tumors compared with women of lower socio-economic status.

We conclude, therefore, that the results of this study, although not offering definitive evidence in favour of a causal relationship, do not support the hypothesis that the observed increase in risk of borderline tumors after IVF treatment is due to detection bias.

We considered a number of known ovarian cancer risk factors [25, 26], to determine whether they were also associated with the development of borderline ovarian tumors. In contrast to previous studies of invasive epithelial ovarian cancer (for example, [18, 27]), we found no evidence for a protective effect of parity. Neither sterilization nor hysterectomy appeared to confer any protection. These observations support the proposition that borderline ovarian tumors are a separate entity with a different (and perhaps heteregenous) etiology. Unfortunately, we had no information about other potential risk factors, including use of oral contraceptives and hormone replacement therapy.

Like Pearce et al [28], we found no evidence for an increased risk of borderline tumors in women diagnosed with endometriosis, with an adjusted HR of 0.31 (95% CI 0.04 – 2.29). This is in direct contrast to most research, including our own [18], on invasive epithelial ovarian cancer. The reason for this could be because borderline tumors are generally found to be of serous and mucinous sub-types [3] while endometriosis is more commonly associated with clear cell and endometrioid invasive ovarian cancer [28].

In summary, this study shows an increased rate of borderline ovarian tumors in women who undergo IVF treatment. These are uncommon neoplasms, but with more and more couples relying on IVF to conceive, they may increase in number. Continued data monitoring is warranted.

Conflict of interest statement

LMS, CDJH, JCF and DBP have nothing to declare. RH is a member of the Medical Advisory Board of Schering-Plough, Australia and the Medical Advisory Board of Merck-Serono, Australia and has received travel and accommodation support from the above to attend conferences. RH is a Medical Director of Fertility Specialists of Western Australia and holds shares in Western IVF.

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296 References

297 1. Taylor HC. Malignant and semimalignant tumors of the ovary. Surg Gynecol Obstet
298 1929;48:204-30.
299 2. International Federation of Gynecology and Obstetrics. Classification and Staging of
300 Malignant Tumours in the Female Pelvis. Acta Obstet Gynecol Scand 1971;50:1-7.
301 3. Acs G. Serous and mucinous borderline (low malignant potential) tumors of the ovary. Am J
302 Clin Path 2005;123:S13-57.
303 4. Auranen A, Grenman S, Makinen J, Pukkala E, Sankila R, Salmi T. Borderline ovarian tumors
304 in Finland: epidemiology and familial occurrence. Am J Epidemiol 1996;144:548-53.
305 5. Cusido M, Balaguero L, Hernandez G, Falcon O, Rodriguez-Escudero FJ, Vargas JA, et al.
306 Results of the national survey of borderline ovarian tumors in Spain. Gynecol Oncol 2007;104:617-
307 22.
308 6. Skirnisdottir I, Garmo H, Wilander E, Holmberg L. Borderline ovarian tumors in Sweden 1960-
309 2005: trends in incidence and age at diagnosis compared to ovarian cancer. Int J Cancer
310 2008;123:1897-901.
311 7. Riman T, Dickman PW, Nilsson S, Correia N, Nordlinder H, Magnusson CM, et al. Risk factors
312 for epithelial borderline ovarian tumors: results of a Swedish case-control study. Gynecol Oncol
313 2001;83:575-85.
314 8. Harris R, Whittemore AS, Itnyre J. Characteristics relating to ovarian cancer risk:
315 collaborative analysis of 12 US case-control studies. III. Epithelial tumors of low malignant potential
316 in white women. Collaborative Ovarian Cancer Group. Am J Epidemiol 1992;136:1204-11.
317 9. Harlow BL, Weiss NS, Roth GJ, Chu J, Daling JR. Case-control study of borderline ovarian
318 tumors: reproductive history and exposure to exogenous female hormones. Cancer Res
319 1988;48:5849-52.
320 10. Mosgaard BJ, Lidegaard O, Kjaer SK, Schou G, Andersen AN. Ovarian stimulation and
321 borderline ovarian tumors: a case-control study. Fertil Steril 1998;70:1049-55.

11. Cusidó M, Fábregas R, Pere BS, Escayola C, Barri PN. Ovulation induction treatment and risk of borderline ovarian tumors. Gynecol Endocrinol 2007;23:373-6.

12. Parazzini F, Negri E, La Vecchia C, Moroni S, Polatti A, Chiaffarino F, et al. Treatment for Fertility and Risk of Ovarian Tumors of Borderline Malignancy. Gynecol Oncol 1998;68:226-8.

13. Sanner K, Conner P, Bergfeldt K, Dickman P, Sundfeldt K, Bergh T, et al. Ovarian epithelial neoplasia after hormonal infertility treatment: long-term follow-up of a historical cohort in Sweden. Fertil Steril 2009;91:1152-8.

14. Shushan A, Paltiel O, Iscovich J, Elchalal U, Peretz T, Schenker JG. Human menopausal gonadotropin and the risk of epithelial ovarian cancer. Fertil Steril 1996;65:13-8.

15. Rossing MA, Daling JR, Weiss NS, Moore DE, Self SG. Ovarian tumors in a cohort of infertile women. N Engl J Med 1994;331:771-6.

16. van Leeuwen FE, Klip H, Mooij TM, van de Swaluw AM, Lambalk CB, Kortman M, et al. Risk of borderline and invasive ovarian tumours after ovarian stimulation for in vitro fertilization in a large Dutch cohort. Hum Reprod 2011;26:3456-65.

17. Stewart LM, Holman CD, Hart R, Bulsara MK, Preen DB, Finn JC. In vitro fertilization and breast cancer: is there cause for concern? Fertil Steril 2012;98:334-40.

18. Stewart LM, Holman CDJ, Aboagye-Sarfo P, Finn JC, Preen DB, Hart R. In vitro fertilization, endometriosis, nulliparity and ovarian cancer risk. Gynecol Oncol 2012;submitted for publication.

19. Holman CD, Bass AJ, Rouse IL, Hobbs MS. Population-based linkage of health records in Western Australia: development of a health services research linked database. Aust N Z J Public Health 1999;23:453-9.

20. Information Paper: An Introduction to Socio-Economic Indexes for Areas (SEIFA), 2006. ABS catalogue no 2039.0. Australian Bureau of Statistics, 2008. Available at http://www.abs.gov.au/ausstats/abs@.nsf/mf/2039.0/ Accessed July 25, 2012. 2008.

21. Lerner-Geva L, Rabinovici J, Lunenfeld B. Ovarian stimulation: is there a long-term risk for ovarian, breast and endometrial cancer? Womens Health 2010;6:831-9.

22. Ness RB, Cramer DW, Goodman MT, Kjaer SK, Mallin K, Mosgaard BJ, et al. Infertility, fertility drugs, and ovarian cancer: a pooled analysis of case-control studies. Am J Epidemiol 2002;155:217-24.

23. Brinton LA, Moghissi KS, Scoccia B, Westhoff CL, Lamb EJ. Ovulation induction and cancer risk. Fertil Steril 2005;83:261-74.

24. Link BG, Northridge ME, Phelan JC, Ganz ML. Social Epidemiology and the Fundamental Cause Concept: On the Structuring of Effective Cancer Screens by Socioeconomic Status. Milbank Quarterly 1998;76:375-402.

25. Sueblinvong T, Carney ME. Current understanding of risk factors for ovarian cancer. Curr Treat Options Oncol 2009;10:67-81.

26. Permuth-Wey J, Sellers TA. Epidemiology of ovarian cancer. Methods Mol Biol 2009;472:413-37.

27. Wu ML, Whittemore AS, Paffenbarger RS, Jr., Sarles DL, Kampert JB, Grosser S, et al. Personal and environmental characteristics related to epithelial ovarian cancer. I. Reproductive and menstrual events and oral contraceptive use. Am J Epidemiol 1988;128:1216-27.

28. Pearce CL, Templeman C, Rossing MA, Lee A, Near AM, Webb PM, et al. Association between endometriosis and risk of histological subtypes of ovarian cancer: a pooled analysis of case-control studies. Lancet Oncol 13:385-94.

367

368 Table 1. Characteristics of the study cohort [1]

369

Characteristic	All women in the cohort	Women not undergoing IVF	Women undergoing IVF
Number of women	21,639	14,095	7,544
Number of women who gave birth (%)	14,902	10,029 (71.1%)	4,873 (64.6%)
Mean[2] duration of follow-up (years)	16.9 ± 5.9	17.0 ± 5.9	16.7 ± 5.9
Median duration of follow-up (years)	16.5	16.7	16.1
Total duration of follow-up (person-years)	365,775	240,069	125,706
Mean age at first infertility admission (years)	31.2 ± 5.2	30.8 ± 5.3	32.1 ± 4.8
Mean age at first birth (years)	29.6 ± 6.0	28.4 ± 5.8	32.2 ± 5.4
Number of women with a diagnosis of borderline ovarian tumor	31	14	17
Mean age at borderline ovarian tumor diagnosis (years)	43.2 ± 7.5	41.1 ± 8.1	44.7 ± 6.9
Median age at borderline ovarian tumor diagnosis (years)	43.0	40.5	43.5
Mean time from last infertility admission to borderline ovarian tumor diagnosis (years)	8.6 ± 6.4	7.3 ± 5.6	9.4 ± 7.0

Median time from last infertility admission to borderline tumor diagnosis (years)	8.2	7.5	10.8
% of women in the upper quartile of the Index of Education and Occupation	24	21	31

370

371 [1] The study cohort included all women in Western Australia seeking hospital investigation and
372 treatment for infertility in the period 1982-2002 when they were aged between 20 and 44.

373 [2] All means are reported ± SD

374 Table 2. Potential borderline ovarian tumor risk and protective factors

375

Exposure	Number in exposed group	Crude (unadjusted) HR (95% CI) [1]	Adjusted HR (95% CI) [2]
IVF	7,544	2.48 (1.22 – 5.04)	2.46 (1.20 – 5.04)
Birth [3]	14,902	0.70 (0.34 – 1.43)	0.89 (0.43 – 1.88)
Age at first birth			
No birth recorded	6,737	1.00	1.00
Age < 30 at first birth	7,047	0.41 (0.15 – 1.13)	0.62 (0.20 – 1.87)
Age ≥ 30 at first birth	7,855	1.01 (0.46 – 2.21)	1.05 (0.48 – 2.34)
High socio-economic status [4]	5,268	0.46 (0.16 – 1.30)	0.36 (0.12 – 1.03)
Diagnoses at baseline			
PID	3,885	0.94 (0.36 – 2.45)	0.96 (0.37 – 2.51)
Endometriosis	2,978	0.26 (0.04 – 1.92)	0.31 (0.04 – 2.29)
Procedures			
Sterilization	3,740	1.55 (0.66 – 3.63)	1.48 (0.63 – 3.48)
Hysterectomy without USO [5]	2,186	1.01 (0.24 – 4.34)	1.02 (0.24 – 4.37)

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377 [1] The crude HR is estimated from a model that includes only the variable listed. In each case, it
378 compares the rate of borderline ovarian tumors in women in the exposed group with all other
379 women in the cohort.

380 [2] Each adjusted HR is estimated from a separate model that includes the variable listed, plus IVF,
381 socio-economic status, age and calendar year at the first infertility admission.

382 [3] Women known to have given birth were compared with women who had no recorded births.

[4] Socio-economic status was measured using the Index of Education and Occupation. Women in the upper quartile were compared with women in the lower three quartiles combined.

[5] A further 690 women had a hysterectomy and a USO, either in the same or separate admissions. None of these were diagnosed with borderline ovarian tumors. A total of 497 women had a USO without hysterectomy in the same or any other admission. None of these were diagnosed with borderline ovarian tumors more than 12 months after USO.