Stewart, Louise M.; Holman, C. D'Arcy J.; Finn, Judith C.; Preen, David B.; Hart, Roger. (2013) Association between in-vitro fertilization, birth and melanoma. Melanoma Research, 23(6), 489-495.

Title: Association between in vitro fertilization, birth and melanoma

Running head: IVF, birth and melanoma

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Source of funding and conflict of interest statement

This work was supported in part by a capacity building grant from the National Health and Medical Research Council, Australia; project no. 573122. Louise Stewart is the recipient of an Australian Postgraduate Award from the Australian Government Department of Innovation, Industry, Science and Research.

All authors have no conflict of interest in relation to this work. Roger Hart 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. He is a Medical Director of Fertility Specialists of Western Australia and holds shares in Western IVF.

Abstract

A connection between reproductive hormones and melanoma has long been suspected, and has been examined for numerous hormonal exposures, but the association between in vitro fertilization (IVF) and melanoma has not been studied in depth. We used whole-population linked hospital and registry data to conduct a cohort study of women aged 20-44 years seeking hospital investigation and treatment for infertility in Western Australia from 1982-2002 with follow-up to 2010. The cohort comprised a total of 21,604 women followed for an average of 17.2 years. Of these, 7,524 had IVF treatment, 14,870 gave birth and 149 women were diagnosed with an incident invasive melanoma. Using Cox regression analysis, we estimated hazard ratios (HRs) for melanoma associated with IVF and parity. Women who had IVF and gave birth had an increased rate of invasive melanoma compared with women who had IVF and remained nulliparous (HR 3.61; 95% confidence interval [CI] 1.79-7.26). There was little or no increase in the rate of invasive melanoma associated with giving birth in women who had non-IVF infertility treatment (HR 1.39; 95% CI 0.88-2.20). These results suggest an association between reproductive factors and melanoma in the subgroup of women undergoing IVF treatment.

Key words:

In vitro fertilization; birth; parity; melanoma; cohort studies; epidemiology.

Introduction

Circumstantial evidence suggests a link between reproductive hormones and melanoma. Age-specific melanoma incidence rates rise in women until the time of menopause, and then they slow; in men rates continue to rise [1]. Melanocytes are hormonally responsive: pregnant women and women taking the oral contraceptive pill often develop hyperpigmentation of the skin, while oestrogen has been shown to stimulate melanocytes in animal experiments [2]. Furthermore, oestrogen receptors have been identified in the skin [3, 4], in melanocytic nevi and in melanoma cells [5, 6].

Yet supportive evidence from epidemiological studies has remained elusive. Results from studies examining the association between pregnancy and melanoma are inconclusive. There does not appear to be an overall association between giving birth and risk of melanoma [7, 8], although there may be a protective effect of either increasing parity or earlier age at first birth [7-10]. Whether this is due to hormonal, lifestyle or socio-economic factors remains open to question [10, 11].

Oral contraceptive use has been associated with an increased melanoma risk in some studies, but not in others. Feskanich et al [12], using data from the Nurses' Health Study, and Koomen et al [13], using linked data from Holland, found an increased melanoma risk with oral contraceptive use. In contrast, early results from our own research group [14], two meta-analyses [10, 15] and a pooled analysis of case-control studies [16] found no evidence for an association between the two. With regard to hormone replacement therapy, findings have been mixed, but overall evidence suggests a weak association or none at all [10].

A number of studies [17-26] have examined the association between fertility drug use and melanoma. Most had only small numbers of melanoma cases and most found no association between the two. Of the two larger studies, one, with a total of 42 cases, found an increased risk with clomiphene use in nulliparous women [26], and the other, with 112 cases, found an increased

risk with specific fertility drugs in parous women [21]. The only study that directly addressed in vitro fertilization (IVF) took place in Australia [25], but this was limited in having only 16 cases of melanoma in the cohort.

The aim of the present study was to examine the association between IVF treatment, parity and melanoma in a large cohort of women within a high incidence population, considering also age at first birth, country of birth, cause of infertility, socioeconomic status, age and calendar year.

Methods

The study cohort and data sources

This was a whole-population cohort study, using routinely collected, de-identified administrative health data serving an entire, geographically circumscribed Australian State.

Methods for identifying the study cohort have been described previously [27-29]. In summary, using the resources of the Western Australian Data Linkage System [30, 31], we identified a cohort of women living in Western Australia (WA) undergoing hospital investigation or treatment for infertility. Women were eligible for inclusion in the cohort if they had a hospital admission with a diagnosis of either 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 diagnosis occurring within the period 1982-2002, when they were aged between 20 and 44 years (inclusive). Loss to follow-up was limited by excluding women known to be living outside WA or known to have moved interstate. Women who had a diagnosis of melanoma either prior to or within 6 months of their first hospital infertility admission were deemed not at risk of incident melanoma after the start of infertility treatment and were excluded.

We identified relevant exposures and outcomes occurring between 1980 and 2010, linking de-identified data sourced from the WA Hospital Morbidity Data System, the Midwives Notification System, the WA Cancer Registry, the WA Deaths Register, the Reproductive Technology Register and the WA Electoral Roll. The principal exposure was IVF treatment (including both IVF and ICSI [intracytoplasmic sperm injection]). IVF cycles undertaken between 1982 and 2002 were identified from either the Reproductive Technology Register, which provided information on IVF cycles from 1993 to 2002, or from the Hospital Morbidity Data System. Births occurring before and after recruitment into the cohort were identified from the Midwives Notification System, a statutory data collection that captures all births in WA. Socio-economic status was obtained from the address recorded on the woman's hospital record at the start of follow-up. Two measures of socio-economic status were estimated: the Index of Economic Resources and the Index of Education and Occupation [32]. Country of birth may influence melanoma risk through its association with skin type, cultural attitudes towards sun exposure and childhood sun exposure. Information on country of birth was extracted from each woman's hospital records, aggregated into broad geographical regions and included as a potential confounder in regression analyses.

We considered two sets of outcomes. The first was an incident diagnosis of invasive cutaneous melanoma only (ICD-10: C43.0 – C43.9), and the second was any incident diagnosis of melanoma: invasive or in situ cutaneous melanoma (ICD-10: C43.0 – C43.9 or ICD-10: D03.0 – D03.9). Both were identified through data linkage to records of the WA Cancer Registry. Results for both outcomes are presented in this paper; we present detailed results for the analysis of invasive melanoma alone and summary results for the analysis of invasive or in situ melanoma.

Data analysis

Data were analysed and hazard ratios (HRs) estimated using Cox regression analysis. We used methods described by Hosmer, Lemeshow and May [33] to develop the regression model. Women were followed from their first infertility-related hospital admission to the date of melanoma

diagnosis, date of death or censor date (15 August 2010), whichever came first. Events that could occur after the start of follow-up (births, start of IVF treatment) were entered into the model as time-dependent covariates; events that were measured at the start of follow-up (age, calendar year, country of birth, infertility diagnosis and socio-economic status) were entered as fixed covariates. Age was grouped into quartiles and included in the model as a categorical variable. Birth (yes/no), age group at first birth (less than 25 years; 25-30 years; 30-35 years and 35 years and older) and parity (0, 1, 2 or 3 or more births) were examined as categorical variables in separate models. Socio-economic status was included as a binary categorical variable, with women in the upper quartile of each index compared to women in the lower three quartiles combined. Country of birth and infertility diagnosis were included as categorical variables.

We investigated the interaction between birth and IVF and considered the association between birth and melanoma separately in women who did and did not have IVF and the association between IVF and melanoma separately in women who did and did not give birth.

We also considered the effect of birth before IVF as distinct from the effect of birth after IVF. Some women in our cohort only gave birth before IVF (they had secondary infertility and the treatment was unsuccessful); some only gave birth after IVF (women with primary infertility and successful treatment) and others gave birth both before and after IVF. So that we could examine the separate effects of giving birth before IVF and giving birth after IVF, we restricted the cohort in this additional analysis to women with a maximum of one birth. We compared the rate of invasive melanoma in women who did not give birth with women who only gave birth before IVF and women who only gave birth after IVF.

Ethics approval

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

Results

The study cohort

The study cohort was drawn from an eligible population of 22,040 women. We excluded 379 women known to be living outside WA, leaving 21,661 women. We considered two separate outcomes in this study: an incident diagnosis of invasive cutaneous melanoma and any incident diagnosis of melanoma: either invasive cutaneous melanoma or cutaneous melanoma in situ. Because these were two separate outcomes, with different endpoints and different follow-up times, we developed two separate datasets. For the study of invasive melanoma only, we excluded 57 women who had an invasive melanoma either prior to or within 6 months of the start of follow-up, leaving a total of 21,604 women under study. For the second data set we excluded 59 women with invasive or in situ melanoma, leaving a total of 21,602 women under study.

The results for the invasive melanoma analysis, which was the focus of this paper, are reported in Tables 1, 2 and 3 and in the accompanying description. The results for the invasive or in situ analysis appear at the end of the results section in summary form under the heading “Type of melanoma: invasive melanoma or melanoma in situ”.

Total duration of follow-up was 370,695 person-years. Women were followed for an average of 17.2 years, from entry into the cohort at a mean age of 31.2 years, to the end of follow-up when they were, on average, 48.3 years old. During this time, 149 out of a total of 21,604 women were diagnosed with an incident invasive melanoma. Of these, 4,861 women had IVF and gave birth (45 diagnosed with invasive melanoma); 2,663 had IVF and remained nulliparous (10 melanoma diagnoses). Of those that did not have IVF, 10,009 were parous (67 melanoma cases) and 4,071 remained nulliparous (27 melanoma cases). The average age at melanoma diagnosis was 42.0 years (Table 1). Women were diagnosed with an invasive melanoma on average 10.5 ± 6.3 years (median

10.1 years) after entry to the cohort. Women undergoing IVF were diagnosed 9.7 ± 5.7 years (median 8.9 years) after their first cycle and 8.9 ± 5.8 years (median 8.6 years) after their last cycle.

Women gave birth to their first child, either before or after entry into the cohort, at an average age of 29.6 years (Table 1).

Women undergoing IVF were older at birth of their first child (average age 32.2 years). They were mostly of lower parity, with a median of one child (Table 1). They were generally of higher socio-economic status at cohort entry and more likely to be in the upper quartile of both the Index of Education and Occupation and the Index of Economic Resources (Table 1).

Most (n= 14,109; 65.3%) of the women in the cohort were born in Australia; of these, 682 identified as being of Aboriginal or Torres Strait Islander descent. Among those born overseas, 3,410 were from the UK, with smaller numbers migrating from North Africa (n=1,094), the Pacific Islands (n=760), Europe (n=676) and Asia (n=667).

Association between IVF, potential confounders and invasive melanoma: Cox regression analysis

We examined the association between invasive melanoma and a number of factors, first in univariate analysis and then in separate age-adjusted analyses (Table 2).

We did not find an association between IVF treatment and invasive melanoma, with an age-adjusted HR of 1.16 (95% confidence interval [CI] 0.83 – 1.62) (Table 2).

We did, however, find an increased rate of invasive melanoma in women who gave birth, compared with women who remained nulliparous (HR = 1.97, 95% CI 1.34 – 2.88). There was not a clear trend with increasing age at first birth, although the relative risk appeared greatest in women who delivered their first child when they were aged 35 or older (HR = 2.32) (Table 2). Women who delivered one or two children had an increased rate of invasive melanoma compared with

nulliparous women; the HR for women who delivered two children was 2.24. The rate in women delivering three or more children was lower (HR 1.37; 95% CI 0.81 – 2.31) (Table 2).

We considered the possible association between cause of infertility and invasive melanoma. In our cohort, 2,971 women had a diagnosis of endometriosis at cohort entry and 3,882 women had a diagnosis of pelvic inflammatory disease (PID) (Table 1). Neither diagnosis was associated with an increased rate of invasive melanoma. The HR associated with a diagnosis of endometriosis was 0.95 (95% CI 0.56 – 1.60) and the HR associated with a diagnosis of PID was 1.08 (95% CI 0.71 – 1.65) (Table 2).

There was no evidence for an association between melanoma and socio-economic status in this group of women. Those in the upper quartiles of the Index of Economic Resources and the Index of Education and Occupation appeared to have the same rate of melanoma as women in the lower three quartiles combined.

We found no evidence for an increase in invasive melanoma rate with calendar time in this cohort (Table 2).

We examined the interaction between IVF treatment and birth, and found evidence for effect modification. We therefore present results separately for women who had IVF and women who did not (Table 3, and described below) and women who gave birth and women who did not (described below).

Among women who had IVF, there was a clear increase in the rate of invasive melanoma in women who gave birth, compared with those who remained nulliparous (HR 3.61, 95% CI 1.79 – 7.26) (Table 3); particularly among women who gave birth to two children (HR 4.29, 95% CI 1.97 – 9.34). In contrast, among women who had infertility treatment but not IVF, there was only a small increase in the rate of invasive melanoma in women who gave birth, and CIs included 1 (HR 1.39, 95% CI 0.88 –

2.20) (Table 3). There did not appear to be any association with either increasing parity or age at first birth in this group of women.

We found no evidence for an association between IVF treatment and invasive melanoma among women who remained nulliparous (HR = 0.63; 95% CI 0.30 – 1.31), but some evidence for an association with IVF treatment among parous women (HR = 1.45; 95% CI 0.99 – 2.13).

We included country of birth as a potential confounder in the relationship between IVF, birth and invasive melanoma. HRs derived from models which included country of birth varied little from those which did not include this variable, suggesting that country of birth was not a confounder in the relationship between IVF, birth and invasive melanoma. For example, the age adjusted HR for IVF in the whole cohort was 1.16; including country of birth in the model resulted in an HR estimate of 1.11. The age adjusted estimate for birth among women undergoing IVF treatment was 3.61; after adjustment for country of birth it was 3.47 (see also Footnotes to Tables 2 and 3).

Dose-response effect

Women in our cohort generally underwent only a small number of IVF cycles (median = 2). It was therefore not possible to examine the effect of IVF "dose" in detail. However, we compared the association between IVF treatment and invasive melanoma in women who had one cycle with women who had two or more cycles. We found no evidence for an increased rate of invasive melanoma in women who had two or more cycles compared with women who had only one cycle, with a HR of 1.04 (95% CI 0.60 – 1.81) after adjustment for age and birth.

Birth before IVF vs. birth after IVF

For this analysis, in order to examine the association between timing of birth (before IVF treatment vs. after IVF treatment) and invasive melanoma, we restricted the cohort to women with a maximum of one birth. In this subset of 4,539 women, we were thus able to compare three separate categories: women who did not give birth, with women who only gave birth before IVF and women

who only gave birth after IVF. In age-adjusted analysis, the HR for invasive melanoma associated with giving birth prior to IVF was 4.17 (95% CI 1.13 – 15.49) and the HR associated with giving birth after IVF was 3.60 (1.51 – 8.59).

Incidence Rates

We also calculated crude incidence rates (number of invasive melanoma cases/total person-years of follow-up). For women having IVF and remaining nulliparous the crude incidence rate was 20.6 cases per 100,000 person-years; for women having IVF and giving birth it was 57.1. For women having infertility treatment, but not IVF, and remaining nulliparous it was 37.0 cases per 100,000 person-years; for women having infertility treatment but not IVF and giving birth it was 39.3. Note that these are crude estimates: they are not adjusted for age and, for women who gave birth, they do not take into account the portion of follow-up time prior to the first birth when women were correctly classified, in the regression analysis, as nulliparous.

Type of melanoma: invasive melanoma or melanoma in situ

A total of 235 women in the cohort had an incident diagnosis of either invasive or in situ melanoma. The results from the analysis that considered either diagnosis as an endpoint: invasive or in situ melanoma, were similar to those from the analysis that only included invasive melanoma, except that generally, the HRs observed were smaller. As in the invasive melanoma analysis, we found no evidence for an association between IVF treatment and melanoma (HR = 1.04; 95% CI0.79 – 1.36). There was little evidence for an association with birth among women who did not have IVF, with an overall HR for the outcome of invasive or in situ melanoma of 1.29 (95% CI 0.90 – 1.84). The association between birth and melanoma among women who had IVF followed a similar pattern to the results presented in Table 3 for the invasive melanoma analysis, except that in all cases, the magnitude of the relative risk was smaller. Among women who had IVF, there was an increased rate

of invasive melanoma or melanoma in situ in women who gave birth compared with women who remained nulliparous (HR 1.83, 95% CI 1.13 – 2.97).

Discussion

The results of this study show that among women in our cohort who had IVF treatment, giving birth was associated with a 3.6-fold increase in the rate of invasive melanoma. In contrast, in women having non-IVF infertility treatment, giving birth made little or no contribution to the risk of melanoma.

This finding could be interpreted in a number of ways. The first possibility is that a causal relationship exists: exposure to both IVF treatment and birth are necessary in order for the risk of melanoma to be increased. However, arguing against this is, firstly the absence of a dose response relationship: women who had two or more cycles of IVF were not at increased risk of melanoma compared with women who had only one; and secondly, our observation that that the order in which birth or IVF occurred did not seem to matter: the rate of melanoma was elevated in women who gave birth before IVF treatment as well as in women who gave birth after IVF treatment. A second possible explanation for this finding is that women undergoing IVF share a common predisposition to melanoma that is promoted by the hormonal environment surrounding pregnancy, birth and lactation. A third alternative is that this finding is due to confounding by unmeasured confounders, in particular known melanoma risk factors including sun exposure, sunburn history, and skin complexion [34-40]. In an attempt to address this problem, we included country of birth in the regression models. Country of birth has been shown to be associated with melanoma risk [41-43] as it represents an aggregate measure of an individual's skin type, cultural attitudes to sun exposure and potential sun exposure during early life. We found no evidence for confounding by this variable. In addition, in order for these results to be explained by confounding by known

melanoma risk factors related to sun exposure, we would need to assume that women who had IVF and gave birth were more likely to have fair skin or were more likely to have a history of sunburn than women who had IVF and remained childless. This explanation seems less plausible than an explanation based on hormonal factors [44]. It is also possible that this is simply a chance finding, although one other group [21] found that exposure to fertility drugs commonly used in IVF (follicle-stimulating hormone, human menopausal gonadotropin and gonadotropin-releasing hormone) was associated with a 2 to 3-fold increase in the risk of melanoma, in parous but not nulliparous women.

It is unlikely that this observed increase in melanoma rate was due to detection bias. Increased surveillance is likely to lead to earlier detection and hence more in situ cancers. If detection bias was the explanation, we would expect to find greater relative risks in the analysis that included both invasive and in situ melanomas, whereas we actually found lower relative risks in this analysis.

We also considered a number of other potential melanoma risk factors. We did not find an association between socio-economic status and melanoma. This finding was consistent with an Australian national survey [1], but not with a US National survey where high socio-economic status was found to be associated with an increased rate of melanoma [45]. There was no evidence for an association with the most common infertility diagnoses in our cohort: endometriosis and PID. There did not appear to be an association between increasing parity or age at first birth and melanoma in women in our cohort having infertility treatment but not IVF, and no clear pattern among women who had IVF. Previous studies have identified a decreased risk with parity greater than 5, and first birth prior to age 20 [7] but both of these groups made up only a very small proportion of our infertility cohort.

The main limitation of our study was a lack of information on known melanoma risk factors, including skin type and sun exposure. We attempted to address this by including country of birth in our regression models, although we recognise that this variable may not accurately represent a woman's underlying melanoma risk related to sun exposure. In addition, we had no information on

the use of fertility drugs other than those associated with an IVF cycle: women in both the IVF and non-IVF group may have been treated with such fertility drugs. However, the levels of circulating hormones developed after fertility drug treatment are much lower than after IVF as the objective of fertility drug treatment is generally to induce ovulation, whereas the objective of IVF treatment is to induce superovulation, hence the hormone levels achieved would be much greater.

Whilst it is important that the findings of this study are replicated in future research, they are nevertheless noteworthy because they demonstrate an association between reproductive factors and melanoma in women undergoing IVF treatment. In practical terms, it may be advisable for women who have IVF treatment and give birth to be made aware of the importance of checking for changes in their skin and seeking early treatment.

Acknowledgments

This work was supported in part by a capacity building grant from the National Health and Medical Research Council, Australia; project no. 573122. Louise Stewart is the recipient of an Australian Postgraduate Award from the Australian Government Department of Innovation, Industry, Science and Research.

We wish to thank the staff at the Western Australian Data Linkage Branch and the Hospital Morbidity Data Collection; the Reproductive Technology Register; the Western Australian Cancer Registry; the WA Deaths Registry; the Midwives Notifications System and the WA Electoral Roll.

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Table 1 Characteristics of the study population [a]

Characteristic	**All women in the cohort**	**Women not undergoing IVF**	**Women undergoing IVF**
Number of women (number with a melanoma diagnosis)	21,604 (149)	14,080 (94)	7,524 (55)
Number of women who gave birth (number with a melanoma diagnosis)	14,870 (112)	10,009 (67)	4,861 (45)
Number of women with a diagnosis of endometriosis (number with a melanoma diagnosis) [b]	2,971 (16)	1,910 (10)	1,061 (6)
Number of women with a diagnosis of PID (number with a melanoma diagnosis) [b]	3,882 (27)	2,575 (18)	1,307 (9)
Total length of follow-up (person-years)	370,695	243,359	127,336
Mean length of follow-up (person-years) [c] [median]	17.2 ± 5.9 [16.9]	17.3 ± 5.9 [17.0]	16.9 ± 5.8 [16.4]
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

Mean parity (n) [median]	1.5 ± 1.4 [1]	1.7 ± 1.4 [2]	1.2 ± 1.2 [1]
Mean age at melanoma diagnosis (years)	42.0 ± 7.8	41.9 ± 8.3	42.3 ± 6.8
Mean age at end of follow-up (years)	48.3 ± 7.1	47.9 ± 7.2	48.9 ± 6.9
% of women in the upper quartile of the Index of Economic Resources	25	22	30
% of women in the upper quartile of the Index of Education and Occupation	24	21	31

[a] The study population included all women in Western Australia commencing hospital investigation or treatment for infertility between 1982 and 2002. We excluded women with a diagnosis of invasive melanoma either before or within 6 months of their first infertility admission.

Information on exposures and outcomes was collected in de-identified format over a period of 30 years, from 1980 to 2010.

[b] Infertility diagnoses of endometriosis or PID (pelvic inflammatory disease) were included in the women's hospital records at or before entry into the cohort.

[c] All means are expressed ± SD.

Table 2 Age-adjusted Cox regression analysis: estimated hazard ratios for melanoma associated with IVF, birth and potential confounding factors

Exposure	**Age adjusted HR (95% CI)** [a]
IVF	
No	1.00
Yes	1.16 (0.83 – 1.62) [b]
Birth	
No birth recorded	1.00
Birth of one or more children	1.97 (1.34 – 2.88)
Age at first birth	
No birth recorded	1.00
Age <25 at first birth	1.45 (0.80 – 2.63)
Age 25-30 at first birth	2.09 (1.27 – 3.43)
Age 30-35 at first birth	1.91 (1.18 – 3.07)
Age 35+ at first birth	2.32 (1.38 – 3.91)
Parity	
No birth recorded	1.00
1 birth	1.88 (1.19 – 3.00)
2 births	2.24 (1.46 – 3.43)
3 or more births	1.37 (0.81 – 2.31)
Infertility diagnosis: endometriosis	
No diagnosis of endometriosis	1.00
Diagnosis of endometriosis	0.95 (0.56 – 1.60)

Infertility diagnosis: PID	
No diagnosis of PID	1.00
Diagnosis of PID	1.08 (0.71 – 1.65)
SES: Index of Economic Resources	
Women in the lower 3 quartiles	1.00
Women in the upper quartile	0.99 (0.68 – 1.45)
SES: Index of Education and Occupation	
Women in the lower 3 quartiles	1.00
Women in the upper quartile	0.98 (0.67 – 1.42)
Calendar year (for each successive year)	1.00 (0.97 – 1.04)

[a] HRs are estimated from separate models that include only age at start of follow-up and the listed variable.

[b] Further adjustment by country of birth yielded estimates that were only slightly different from the above. The HR for IVF after adjustment for age and country of birth was 1.11 (95% CI 0.79 – 1.55), suggesting that country of birth did not confound the relationship between IVF and melanoma rate in this analysis.

Table 3 Age adjusted Cox regression analysis: estimated hazard ratios for birth, age at first birth and parity in women exposed and not exposed to IVF [a]

Exposure	**Age adjusted HR (95% CI) for women not undergoing IVF**	**Age adjusted HR (95% CI) for women undergoing IVF**
Birth		
No birth recorded	1.00	1.00
Birth of one or more children	1.39 (0.88 – 2.20) [b]	3.61 (1.79 – 7.26) [b]
Age at first birth		
No birth recorded	1.00	1.00
Age <25 at first birth	1.14 (0.58 – 2.23)	2.87 (0.77 – 10.65)
Age 25-30 at first birth	1.62 (0.91 – 2.89)	3.71 (1.43 – 9.66)
Age 30-35 at first birth	1.38 (0.76 – 2.52)	3.29 (1.44 – 7.53)
Age 35+ at first birth	1.37 (0.63 – 2.99)	3.98 (1.78 – 8.90)
Parity		
No birth recorded	1.00	1.00
1 birth	1.21 (0.65 – 2.22)	3.61 (1.67 – 7.79)
2 births	1.60 (0.96 – 2.69)	4.29 (1.97 – 9.34)
3 or more births	1.08 (0.59 – 1.97)	2.34 (0.79 – 7.00)

[a] Results were analysed separately for women having infertility treatment but not IVF and for women having IVF. HRs are estimated from separate models that include only age at start of follow-up and the listed variable.

[b] Further adjustment by country of birth yielded estimates that were only slightly different from the above. The HR for birth in non-IVF women was 1.32 (95% CI 0.83 – 2.10) and for birth in IVF women it was 3.47 (95% CI 1.72 – 6.99), suggesting that country of birth did not confound the relationship between birth and melanoma rate in this analysis.