ORIGINAL ARTICLE

Five-year study assessing the clinical utility of Anti-Müllerian Hormone (AMH) measurements in reproductive age women with cancer

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Abstract (MAX 255 words)

Research question:

An important discussion point prior to chemotherapy is ovarian toxicity, a side effect that profoundly affects young women with cancer. Their quality of life after successful treatment, including the ability to conceive, is a major concern. We asked whether serum Anti-Müllerian hormone (AMH) measurements before chemotherapy for two most common malignancies are predictive of long-term changes in ovarian reserve?

Design

A prospective cohort study measured serum AMH in 66 young, female, lymphoma and breast cancer patients, before and at 1 year and 5 years after chemotherapy, compared with 124 healthy volunteers of the same age range (18-43). Contemporaneously, patients reported their menses and live births during 5-year follow-up.

Results

After adjustment for age, serum AMH was 1.4 times higher (95% CI, 1.1-1.9, $p<0.02$) in healthy volunteers than in cancer patients even before chemotherapy. There was a strong correlation between baseline and 5-year AMH in the breast cancer group ($p<0.001$, regression coefficient = 0.58, 95% CI, 0.29-0.89). There was no significant association between presence of menses at 5 years and serum

AMH at baseline (likelihood ratio test (LRT) from logistics regression analysis; *p*=0.37).

Conclusions

Reproductive age women with malignancy have lower serum AMH than healthy controls even before starting chemotherapy. Pre-chemotherapy AMH was significantly associated with long term ovarian function in women with breast cancer. AMH measurements at key time points could be utilised as a reproductive health advisory tool for young women with cancer. Our results highlight the unsuitability of return of menstruation as a clinical indicator of ovarian reserve post-chemotherapy.

Key words (6):

AMH, ovarian toxicity, ovarian reserve, oncofertility

Key message (50 words)

Reproductive age women with malignancy have lower serum AMH than healthy controls before starting chemotherapy. Pre-chemotherapy AMH relates to long term ovarian function in women with breast cancer. Return of menstruation is unsuitable as a clinical indicator of ovarian reserve post-chemotherapy.

INTRODUCTION

Early detection of cancer and improving survival rates have resulted in young women diagnosed with cancer having increased life expectancy (Quaresma *et al.*, 2015). Their quality of life after successful treatment, including the ability to conceive, is a major concern (Howard-Anderson *et al.*, 2012). Unfortunately, long-term effects of chemotherapy upon ovarian function in women of reproductive age are difficult to quantify (Dunlop e Anderson, 2015). Young women who regain menses may yet have undergone premature depletion of ovarian follicles and have less time in which to become pregnant due to early menopause (Bath *et al.*, 2003; Larsen *et al.*, 2003; Reh *et al.*, 2008).

Measuring ovarian reserve before and after cancer treatment could inform patients regarding their individual risk of future subfertility and premature menopause (Barnabei *et al.*, 2015). At present, serum Anti-Müllerian hormone (AMH) is the most accurate biological marker of ovarian reserve (Broekmans *et al.*, 2006; Fleming *et al.*, 2015; Iliodromiti *et al.*, 2015). There is growing evidence for its use in women undergoing chemotherapy (Anderson *et al.*, 2013; Dillon *et al.*, 2013; Henry *et al.*, 2014; Freour *et al.*, 2017), however long-term studies with repeated AMH measurements are still missing due to the challenges of extended follow-up in this population. Most of the longitudinal studies published so far have studied into different time frames for AMH measurements, older age groups (particularly breast cancer), and used previous suboptimal assays of AMH. Most of the studies have 2- year follow-ups (Anders *et al.*, 2008; Decanter *et al.*, 2010; Hamy *et al.*, 2014; Freour *et al.*, 2017; Decanter *et al.*, 2018).

Our study assesses whether serum AMH, as a marker of ovarian function, may facilitate reproductive counselling in women treated with chemotherapy.

Therefore, we assessed the correlation between serum AMH at baseline and 1 and 5 years after starting chemotherapy. Additionally, pre-chemotherapy serum AMH was compared between healthy volunteers and cancer patients. Furthermore, we investigated the association between pre-chemotherapy AMH and the presence of menses at 5-year follow-up.

MATERIAL AND METHODS

Ethics approval

Approval was gained from Coventry and Warwickshire Research Ethics Committee and each clinical site. The trial was included in the UK Clinical Research Network (UKCRN: 8445) Portfolio. Trial registration number: ISRCTN28988709.

Study design

A prospective cohort study measured the effect of chemotherapy on ovarian function, assessed by serum AMH during 5 years. Patients aged 18-43 years with newly diagnosed breast cancer or lymphoma were recruited across multiple oncology clinics in the UK and followed up for 5 years**.** Female patients meeting the criteria were identified through the direct healthcare team and recruited consecutively where possible. Women with advanced breast cancer (stage IV), previous chemotherapy/radiotherapy, or oophorectomy were excluded.

The control group comprised healthy volunteer women of the same age range, without prior exposure to chemotherapy, radiotherapy or oophorectomy. All participants had serum AMH measured at recruitment (before chemotherapy in cancer patients) and at scheduled follow-up intervals of 1 and 5 years where possible. A detailed medical questionnaire was completed at each blood test.

Information concerning the type and stage of cancer, dose, duration and number of courses of chemotherapy was provided from the medical records by oncology teams using a proforma.

Study procedures

Participants' whole blood samples were collected locally in serum tubes that were sent immediately by first class post, to arrive at the laboratory within 24 hours. Cancer patients had their initial samples obtained before the first dose of chemotherapy.

Upon arrival at the central laboratory, samples were processed on day of receipt according to assay manufacturer's instructions, rendered acellular by centrifugation and prepared serum was stored in aliquots at -20°C.

Samples were initially analysed for AMH using modified gen II protocol (using buffer) and then verified using the new automated Access assay, Beckman Coulter Diagnostics (detection limit 0.14 pmol/L, mean inter- and intra-assay coefficients of variation 2.8 % and 1.7% respectively). Researchers and laboratory personnel were blinded to either patient clinical progress or AMH concentration. The results were not used to manage cancer patients.

Statistical analysis

Baseline characteristics of study participants were summarized by means and standard deviations (SDs) for continuous outcome variables and counts and percentages for categorical variables. Analysis of variance (ANOVA) and independent samples t-tests and Tukey's honest significance (HSD) test were used to assess differences in mean responses between cancer groups for continuous outcomes, based on assumed approximate normality, and Fisher's exact test was used for comparing categorical variables between groups.

AMH data were log-transformed prior to analysis. Differences in AMH between cancer groups (breast, lymphoma and control) were visualized using box-plots. Linear regression analysis was used to model the relationship between serum AMH concentration, cancer group and age at baseline, and to model 5-year and 1-year AMH adjusting for age group (<37 years and 37+ years), baseline (pre-chemotherapy) AMH and cancer group (control, breast or lymphoma) as explanatory variables. Logistics regression was used in an analogous manner to model binary out variables. All tests were considered to provide evidence of a statistically significant difference if $p<0.05$. All analysis was undertaken in R (Version 3.2.2).

RESULTS

Baseline characteristics

In total, 190 women completed the first medical questionnaire, comprising 54 breast cancer patients, 12 lymphoma patients and 124 healthy volunteers. Their baseline demographical and clinical characteristics are presented in **Table 1**. The sample size comprised all those consented in oncology units over a two-year period. Chemotherapy protocols are described in **Table 2**. These were administered according to local protocols by the local care team. Within the 5-year period, in the cancer group 13/66 (19.6%) patients died and 10/66 (15.1%) declined final follow-up or were lost to follow-up**.**

Baseline results

Prior to chemotherapy, there was a significant difference in serum AMH between cancer patients and healthy controls (z-test; p=0.02) **Figure 1**. Regression analysis of log-transformed (base 10) AMH, after adjusting for age and other confounding factors (smoking, use of COCP), showed that serum AMH was 1.4 (95% CI; 1.1 to 1.9) times higher in the control group than in the cancer group (breast and lymphoma combined).

Longitudinal results

Overall, 49/54 (90.7%) of breast cancer patients had detectable AMH at 1-year follow-up and 35/41 (85.3%) at 5-years. While serum AMH at 1-year was low in this group, it remained similar between 1-year and 5-year follow-ups, which is interesting because some further decline might have been expected over this time period as observed in the volunteer group (**Figure 2**). All women with breast cancer aged ≤37 at diagnosis with pre-chemotherapy AMH >11 pmol/ had detectable

AMH>2 pmol/L at 5-year follow-up. In contrast to the breast cancer group, in the lymphoma group, all patients had detectable AMH at 1-year and 5-year follow-ups. The recovery of ovarian function was more noticeable in young patients with Hodgkin lymphoma who received ABVD regimen. **Figure 3** shows summary plots of regression for AMH at 5-year follow-up in relation to chemotherapy regimen.

Is pre-chemotherapy AMH predictive of post-chemotherapy AMH at 1 and 5 years?

1-year

As shown in **Figure 3**, there was a significant association between baseline and 1-year AMH for breast cancer (p<0.001; regression coefficient = 0.56, 95%CI 0.3 to 0.7), and lymphoma patients (p<0.001; regression coefficient = 1.6, 95% CI 1.1 to 2.2). The overall percentage of variance explained by the model was 90.2%.

5-year

Figure 4 presents regression models for 5-year data showing significant associations between baseline AMH and 5-year AMH for the breast cancer (p<0.001; regression coefficient = 0.58, 95%CI 0.29 to 0.89), but not the lymphoma group (p=0.343). The overall percentage of variance explained by the model was 81.3%.

Prevalence of chemotherapy-related amenorrhea and reported live births.

There was no significant association between menses at 5 years and serum AMH measurements before chemotherapy (likelihood ratio test (LRT) from logistics regression analysis; p=0.37).

At 5-year follow-up, serum AMH was significantly lower in women who reported amenorrhea over last ≥12 months in comparison to women who still reported presence of menstrual cycles either regular or irregular (p=0.003).

However, amongst women who reported presence of menses at 5-year follow-up (regular or irregular), 7/17 (40%) had AMH less than 1.

Amongst the 41 cancer patients who completed 5-year follow-up, 3 have reported life births, all of whom were patients with Hodgkin lymphoma aged ≤31 at diagnosis treated with ABVD.

None of the breast cancer patients had had a live birth. Although many women with breast cancer would have been advised against pregnancy while they were taking hormone therapy, the decision would be multifactorial. We therefore do not know how many breast cancer patients actively tried to become pregnant during the study period.

There were no important adverse events or unintended effects in this study.

DISCUSSION

First, our study confirmed that in young women with cancer, serum AMH is already significantly lower before chemotherapy than in healthy volunteers. In the breast cancer group at diagnosis, we found significantly lower serum AMH compared to healthy volunteers, adjusting for age, parity, smoking, use of contraceptive pill and BMI. This differs from some previous reports (Lutchman Singh *et al.*, 2007; Yu *et al.*, 2010; Su *et al.*, 2013), but agrees with others (Bala *et al.*, 2016). For example, Su et al, in 2013, found that 108 patients with breast cancer had similar serum AMH to healthy controls (Su *et al.*, 2013), however, a more recent study found significantly reduced AMH compared to healthy volunteers (Bala *et al.*, 2016). This is a particularly important finding for women considering fertility preservation before chemotherapy. Importantly, our results' prediction model estimates a 6 year difference in 'fertility age' between healthy volunteers and women newly diagnosed with cancer, which may be useful in clinical practice while advising patients about fertility preservation. Interestingly this difference was stable across the whole age span.

The biological explanation of diminished ovarian reserve in cancer sufferers, even before gonadotoxic therapy, is currently unclear. At present, it is uncertain whether there is a cause and effect relationship: does the lower ovarian reserve in some way predispose to breast cancer initiation, or does it arise in response to the malignant disease or depend upon its stage? Titus et al., reported that women with BRCA1 mutation may have lower levels of serum AMH as a result of impaired DNA repair mechanisms in oocytes. Expression of BRCA1 gene in oocytes was found to

be important in the process of ovarian aging related to DNA double–strand break repair (Titus *et al.*, 2013). Others have reported that BRCA mutation may be associated with a lower age at natural menopause that would support the finding of reduced ovarian reserve in this group (Finch *et al.*, 2013; Lin *et al.*, 2013). In contrast, others have recently found similar serum AMH concentrations in healthy BRCA1/2 mutation carriers age 26-40, compared with the general population (Michaelson-Cohen *et al.*, 2014; Gunnala *et al.*, 2019).

Apart from widespread metastatic disease, the mechanisms potentially responsible for decreased fertility potential in women with other malignancies are uncertain. The consumptive character of systemic illness, increased catabolism, and elevated stress hormones cause an increase in prolactin, which may impact on ovulation, have all been proposed as possible pathways affecting ovarian reserve (Agarwal e Said, 2004). Additionally, poor health at the time of cancer diagnosis measured using serum markers e.g. increased C Reactive Protein (CRP), high body temperature and low haemoglobin have been shown to correlate with low serum AMH concentrations in girls aged 0-18 years, newly diagnosed with cancer (Van Dorp *et al.*, 2014). The nature of this relationship is unclear, but the authors hypothesised that factors other than the size of the pool of follicles in the ovary might be contributing to low serum AMH in cancer patients.

At a cellular level, AMH is one of the mediators of growth regulatory signals in breast tissue (Hoshiya *et al.*, 2003). Exposure of breast cancer cells to AMH was found to inhibit growth and induce apoptosis. These authors suggested that lowered circulating AMH concentrations may be one of the predisposing factors for

developing breast cancer (Hoshiya *et al.*, 2003). Similarly, Gupta et al (2005) suggested that AMH can suppress the growth of mammary tumours in vivo.

This is the first study to report the use of AMH in a cancer population prospectively over 5 years using the most recent AMH assay with improved reliability. Importantly, in the breast cancer group, we found a strong association between AMH at baseline, at one year and at five years. While serum AMH post-chemotherapy was significantly reduced, there was no difference between 1-year and 5-year follow-ups, which is interesting because decline might have been expected over this period due to time passed, however, this may perhaps be balanced by some ongoing recovery of follicular function in the ovary between 1 and 5 years post-chemotherapy. Dynamics of folliculogenesis and steroidogenesis disrupted by chemotherapy might take significant amount of time to be restored to its normal function. Chemotherapy leads to loss of growing follicles in human ovaries (Meirow *et al.*, 2010). In order to reliably measure remained ovarian reserve post-chemotherapy using AMH, the test may need to be undertaken more than a year from chemotherapy. As AMH can be detected most strongly in growing pre-antral and small antral follicles, some weak signals have been observed in primary follicles but none in primordial follicles (Weenen *et al.*, 2004). Depending on surviving pool of primordial follicles, if folliculogenesis is restored, on average it take >300 days for primordial follicle to reach preantral stage.

This point requires confirmation by other studies but may offer reassurance to women with breast cancer who have been advised to delay pregnancy by oncologists. Patients may worry that delay may reduce their chances of pregnancy.

However, in our 5 year study, no further significant decline in ovarian reserve was observed beyond 1 year, despite the expected age-related decline .

We conclude that AMH measurements at key time points could be utilised as a reproductive health advisory tool for young women with cancer, supporting our initial idea. Routine AMH measurements before chemotherapy may detect already diminished ovarian reserve and help women to make informed decisions about fertility preservation. Our study results highlight that all women with breast cancer had profoundly lowered ovarian reserve in comparison to volunteers at 5-year follow-up, regardless of chemotherapy protocol used. In that context, counselling for future fertility planning, however challenging at the time of cancer diagnosis, should be an integrated part of clinical care. Serial serum AMH can help to make it more individualised.

Although, at 5-year follow-up, AMH was significantly lower in the non-menstruating group, some women still reported presence of menses despite very low AMH. Additionally, there was no association between pre-chemotherapy AMH and presence of menses at 5-year follow-up, which highlights the unsuitability of return of menstruation as a clinical indicator of changes in the ovarian reserve in such patients. Return of menses post-chemotherapy does not reflect the degree of damage done to the ovaries and may be falsely reassuring.

Importantly, our samples were analysed using recent automated assays, with improved precision. Many previous studies used older AMH assays with poor reproducibility (Rustamov *et al.*, 2012). The AMH assay has historically had a number of technical concerns. Lack of international standards for AMH, differences in sample handling, different antibodies used by kits and late discovery of complement interference in updated Gen II AMH assay all resulted in

inconsistent data being published on AMH. These problems questioned the validity of AMH assay and delayed its widespread use in clinical practice. However, the new automated assays seem to have finally overcome those issues offering better precision, lower limit of quantification and short test duration and better availability (Li *et al.*, 2016; Pigny *et al.*, 2016). Additionally, using recently developed ultrasensitive AMH assays allows the detection of extremely low serum concentrations which might offer an advantage in serial AMH measurements post-chemotherapy in order to improve understanding of dynamics of follicular recovery (Decanter *et al.*, 2014).

Our lymphoma group was not large enough to be suitable for subanalysis. Considering the paucity of long-term, prospective, longitudinal studies assessing changes in ovarian reserve in this group of patients, we present our descriptive findings, which remain valuable for clinicians and as a contribution to future meta-analyses. Our findings are consistent with previous results on Hodgkin's lymphoma survivors which concluded that women aged <32 years, treated with ABVD had a significantly reduced risk of premature ovarian failure in comparison to older population using different regimen (Van Der Kaaij *et al.*, 2012).

Considering 5-year follow-up of breast cancer patients, we found that baseline pre-chemotherapy serum AMH was significantly associated with AMH after 1 and 5 years. Su et al. (2010) enrolled women ~2 years post-chemotherapy for breast cancer and found that patients had lower AMH than controls and that women menstruating following chemotherapy had higher AMH than those without menses (Su, 2010). Conversely, another study found that AMH and antral follicle count (AFC) were the most sensitive markers of reduced ovarian reserve in the cancer

population (Partridge *et al.*, 2010). Anderson *et al.* recruited women with breast cancer (mean age 42.6) with two-year follow-up, showing that women with return of menses (n=9) had higher pre-chemotherapy AMH than amenorrhoeic women (n=30) (Anderson *et al.*, 2013). Similarly, Anderson and Cameron found that pre-chemotherapy AMH was higher in menstruating women at 5-year follow-up. In contrast to our study, their multivariate logistic regression model found AMH to be a significant predictor for menses post-chemotherapy (Anderson e Cameron, 2011b). Most previous studies evaluated AMH during 12-24 months follow-up, while our study assessed AMH prospectively over 5 years (Yu *et al.*, 2010; Anderson e Cameron, 2011a; Decanter *et al.*, 2018; Passildas *et al.*, 2019). Additionally, some studies used previously stored blood samples obtained at different times postchemotherapy (Hamy *et al.*, 2016). Issues surrounding the development of AMH assays highlighted sample instability as an important factor (Han *et al.*, 2014). Other studies included patients who were older at the time of recruitment, including women up to age of 50, who would have had a reduced ovarian reserve already (Anderson *et al.*, 2013; Henry *et al.*, 2014). Furthermore, heterogeneity of data (Rosendahl *et al.*, 2010; Dillon *et al.*, 2013), and combined use of ovarian suppression protocols (Kim *et al.*, 2018) may have contributed to the suboptimal quality of evidence regarding the use of AMH in cancer populations. Our study has overcome those issues providing prospective data collection in selected younger women, using the most reliable AMH assay.

The recruitment of young women with breast cancer into fertility studies is limited by the condition's relatively rare presentation and difficulties with recruitment, both of which add to heterogeneity of the cancer groups. Oncologists initially focus on cancer treatment and patient survival rather than the long-term consequences of

gonadotoxic chemotherapy upon quality of life. The findings of our study regarding AMH in young breast cancer patients should therefore be evaluated in a large, internationally recruiting study with long term follow-up and using an automated AMH assay.

Our study does have some limitations. We aimed to recruit two age-matched controls per case, however, some cases did not have exact age-matched controls. Statistical analysis was therefore performed with adjustment for age imbalance between groups.

In order to ensure similar cohorts in cancer and non-cancer groups, women who reported having PCOS and AMH more than 40 pmol/L were not included in the analysis. Women suffering from PCOS are known to have higher AMH than normo-ovulatory women (Iliodromiti *et al.*, 2013; Bozdag *et al.*, 2016; Pigny *et al.*, 2016). The pattern of changes in serum AMH or ovarian reserve following chemotherapy might be different in women suffering from this endocrinopathy.

The dropout rate over the 5-year period was higher than anticipated. Our patient groups were recruited from a range of centres and had demographics within the expected ranges, given our study's focus on reproductive age women. Those lost to follow-up were deceased, seriously ill or had moved away from the recruiting centre. Our volunteer group comprised female hospital workers and was self-selected so may not be fully reflective of the general population but individuals were drawn from a wide range of backgrounds.

In summary, our 5-year prospective study results support the use of repeat serum AMH measurements, as an ovarian reserve marker in reproductive age women suffering breast cancer and lymphoma.

Disclosure

The authors have declared no conflicts of interest.

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