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Predicting chemotherapy-induced menopause using baseline and post-chemotherapy anti-Müllerian hormone levels: Results of a pilot study

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Abstract

Background: Chemotherapy can cause premature menopause which may result in adverse effects such as fertility loss, osteoporosis, cardiovascular disease and menopausal symptoms. It is thus very important that women are provided with accurate information regarding their risk of premature menopause as a consequence of proposed chemotherapy. Unfortunately, at present there are no reliable tools which can be applied in clinical practice to estimate the risk of premature menopause in women undergoing chemotherapy, beyond age of the patient and form of chemotherapy utilized.

Aim: This was a pilot study to determine whether AMH levels pre and during chemotherapy are able to predict for chemotherapy induced menopause, and to assess quality of life and menopausal symptoms.

Methods and results: Premenopausal women between 18 to 45 who were planned to undergo gonadotoxic chemotherapy with curative intent for either breast cancer or haematologic malignancy were recruited from a single centre. AMH, FSH, LH and oestradiol levels were recorded prior to commencement of therapy, during and following completion of chemotherapy. Menstrual status, menopausal symptoms and quality of life data were collected at baseline and during follow-up. Twenty two women were recruited. The baseline AMH was higher in women who regained menses post-chemotherapy (median 23.1 vs 9.9 pM (P = .06). Menopausal symptoms were significantly higher at 1 year post diagnosis than at baseline however quality of life was similar.

Conclusion: AMH may be useful for predicting chemotherapy induced menopause. Further research is still required to determine the place of such testing for patient counselling and management.

KEYWORDS
breast cancer, chemotherapy, chemotherapy-induced ovarian failure

1 | BACKGROUND

Chemotherapy can cause premature menopause through direct toxic effects on ovarian follicles and stroma.[1] While the suppression of ovarian function may be advantageous for the treatment of some cancers, such as breast cancer,[2] it may cause adverse effects, such as fertility loss, osteoporosis, cardiovascular disease, and menopausal symptoms.[3] It is thus very important that women are provided with accurate information regarding their risk of premature menopause as a consequence of proposed chemotherapy. Unfortunately, at present, there are no reliable tools to estimate the risk of premature menopause in women undergoing chemotherapy.

Anti-Müllerian hormone (AMH), produced by the granulosa cells of primary, preantral, and antral follicles, correlates with ovarian reserve and has been shown to be useful for predicting the age of menopause in premenopausal women in the general population with an accuracy of ±6 months.[4]

To date, there have been a number of studies exploring AMH change in patients undergoing chemotherapy.[5-10] These studies have suggested an association between AMH levels and future ovarian function in these patients. For example, in a cohort of 44 women with early stage breast cancer, pre-chemotherapy inhibin B and AMH levels were lower in women who developed amenorrhea.[5] Another study of 17 patients showed a correlation between pre-treatment and post-treatment AMH levels, but was not able to show conclusively that pre-treatment AMH levels correlated with premature ovarian failure.[6] Results in these studies thus far have not provided sufficient evidence for AMH to be utilized routinely in this patient population for prediction of ovarian failure.

We conducted a pilot study assessing the AMH levels before and after chemotherapy for patients with breast cancer or lymphoma and correlating AMH levels with menopausal status post-chemotherapy, menopausal symptoms, and quality of life.

2 | METHODS

This was a prospective single-center study. Pre-menopausal women who planned to undergo potentially gonadotoxic chemotherapy for either breast cancer or lymphoma were recruited. Patients received treatment with curative intent. Pre-menopausal status was defined as two or more menstrual periods in the 120 days preceding commencement of chemotherapy in women aged 18 to 45 years. Patients were excluded if planned for long-term gonadotropin-releasing hormone (GnRH) analogue during or following chemotherapy. Menstrual history, smoking history, medications, and demographic data were collected at enrolment. Baseline testing included AMH, estradiol, FSH, and LH levels. Subsequent blood tests were performed prior to the commencement of the final cycle of chemotherapy as well as 1 year following completion of chemotherapy. Two additional AMH levels were recorded at commencement of chemotherapy cycles 2 and 3. Menstruation was recorded during chemotherapy and at follow-up. EORTC-QOL33[11] and menopause symptoms scale[12] were administered at baseline, start of cycles 2 and 3, and at the start of the final cycle of chemotherapy.

AMH levels were tested at a single laboratory. in a batch, with all serial samples for an individual tested together. In March 2015, the AMH assay changed from the Immunotech ELISA, which had a lower limit of reporting of 3pM to the Roche assay, which reported to a lowest level of 0.1pM. Therefore, for testing performed using the Immunotech assay, AMH levels below 3 were not able to be quantified. To ensure consistent results, all Roche assay values were multiplied by a factor of 1.4 to convert to a level comparable with Immunotech assays. This conversion factor has been validated and is accepted within this field as the standard conversion factor to utilize. Given the minimum level of detection for the earlier assay was 3.0 all levels below this with either assay were considered as below 3.0 and were considered undetectable and assigned a value of 2.9 pM for statistical analysis.

Ethical approval was obtained from Southern Adelaide Clinical Human Research Ethics Committee.

Data management and statistical analyses were performed using Stata version 16.0 (StataCorp LP, College Station, TX, USA). Median and interquartile ranges (IQR) were calculated given the skewed nature of the data. Mann-Whitney *U* test, Wilcoxon matched-pairs signed-rank test, and Fisher's exact test were conducted to test the significant differences of outcome measures between groups and time.

3 | RESULTS

Twenty-two patients were recruited from July 2011 to March 2015, all but one with breast cancer. Median age was 40.5 years (IQR 37.0 to 43.0). All patients received regimens containing a taxane, an anthracycline, or a combination of anthracycline and taxane. Details of regimen received, age, and AMH levels are in Table S1.

AMH levels by patient over time are shown in Figure 1. The baseline median AMH level was 13.0 pM (IQR 5.2 to 26.5 pM). At week 3, the median AMH level dropped to <3.0 pM (IQR <3 to 7.2 pM) and continued at same median level until 1 year (IQR <3.0 to <3.0 pM). All patients with AMH levels >3.0 at 1 year follow-up were below 40 years of age.

Baseline and 1 year AMH levels were inversely correlated with age (P = .032 and P = .001, respectively). Baseline AMH was lower in patients with amenorrhea at 1 year than in patients who returned to menses at 1 year (median 9.9 pM vs 23.1 pM; P = .06). This is shown in Figure 2.

The two subjects in this cohort who had an AMH level at 1 year follow-up above 3 had continued to have menstrual cycles throughout the study, and both were on the younger end of the spectrum for this study at 26 and 35, compared with median age for the study of 40.5 (IQR 37.0 to 43.0).

The percentage of women with amenorrhea at 1 year of those who had received a chemotherapy regimen containing both

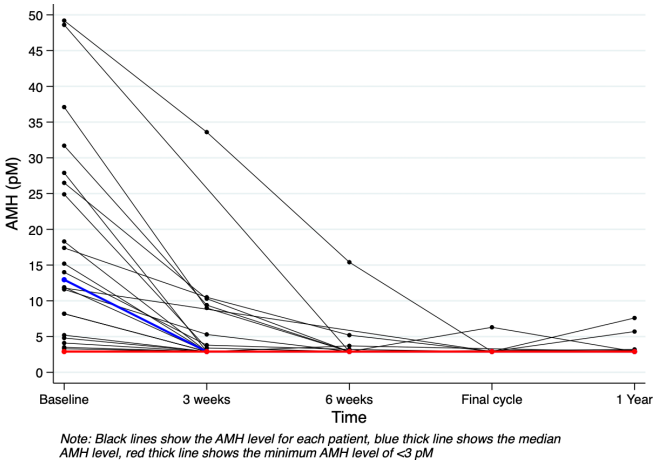

FIGURE 1 Anti-Mullerian hormone levels over time

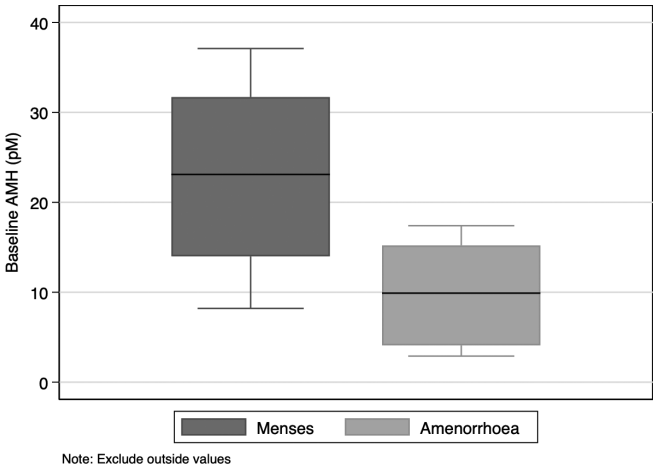

FIGURE 2 Baseline AMH for those with and those without amenorrhea at 1 year follow-up

anthracycline and taxane was 83% compared to 40% for those who received a regimen that did not use a combination of these agents (P = .024).

Menopause symptom scale scores were significantly higher at 1 year compared to baseline before treatment (median 0.33 vs 0.78; P < .001). There was no significant difference in global QOL scores between baseline and 1 year follow-up (median 58.6 vs 58.6; P = .16).

4 | DISCUSSION

This pilot study has shown that AMH levels fall rapidly following commencement of chemotherapy in premenopausal women. Baseline AMH levels were lower in women who remained menopausal than in those whose menses resumed, but the difference was not statistically significant, likely due to the small sample size.

Baseline AMH levels correlated inversely with age, consistent with findings in the general population[13] also associated with post-treatment AMH. Age also was associated with amenorrhea with no patient over 40 regaining menstrual function after chemotherapy during the follow-up.

Differences in gonadotoxicity between treatment regimens are another factor, which was associated with amenorrhea in this study population. The proportion of women who remained amenorrheic at 1 year after treatment for those who had received both anthracycline and taxane containing regimens was more than double that of those who had received regimens that did not include both these agents. This study was stopped early because of the introduction of ovarian suppression therapy as part of recommended management of breast cancer.[2] This change in practice would make further recruitment to the present study difficult but it does not negate the importance of predicting ovarian reserve. Due to the small sample size, therefore the analyses are exploratory.

The finding of an increased burden of menopausal symptoms at 1 year follow-up compared to baseline was anticipated for this population, given the majority developed chemotherapy-induced menopause that was sustained at last follow-up. The finding that despite these symptoms being worse at this time, quality of life was not significantly worse than at baseline is a finding of interest from this study. The majority of patients were breast cancer patients treated with curative intent and would not have been anticipated to have disease-related symptoms at the time of diagnosis. However, quality of life at baseline may have been influenced by anxiety regarding their diagnosis and planned treatment and potential toxicity. It is reassuring that for this cohort of young women at the 1 year follow-up point, quality of life was similar to baseline in terms of counseling patients regarding recovery after chemotherapy.

This study was limited by small numbers due to early closure. One strength of the study is that it examines a cohort of patients with sequential testing and follow-up. This study also has quality of life data available, which were not collected in most of the previously published studies. There are not yet sufficient data available for us to apply AMH findings in a meaningful manner in clinical practice. Our study contributes important additional data to this field, which could potentially be pooled in later meta-analyses of AMH levels and their role. Furthermore, due to changes in practice for management of hormone-receptor-positive breast cancer patients with the increasing use of goserelin after chemotherapy, the potential for expansion of a study with this design will be more limited. Future studies examining AMH, guided by the findings of this current study and others in this field, may be able to determine which patients who may be able to omit goserelin safely for those also who have been recommended ovarian suppression plus an aromatase inhibitor, or who may be able to safely switch to an aromatase inhibitor from tamoxifen without the need for ovarian suppression if an algorithm is developed that can accurately determine which patients will not regain ovarian function after their chemotherapy. If found to be predictive of permanent menopause in the older cohort, AMH would have the potential to result in significant cost savings from goserelin administration as well as direct patient benefit, should they not require monthly injections. Such

studies will also be able to be utilized to validate our interpretation of the results of this study.

5 | CONCLUSION

Lower levels of AMH at baseline were associated with a higher risk of amenorrhea at 1 year. Further research, or meta-analysis across available studies in this area, is required to further determine the role of AMH in predicting chemotherapy-induced menopause.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest relevant to this publication.

AUTHOR CONTRIBUTIONS

All authors had full access to the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. *Conceptualization*, H.M., G.K., C.K., D.R., B.K.; *Data curation*, H.M., S.U., M.A., A.S-H., B.K.; Formal analysis, H.M., S.U., B.K.; *Investigation*, H.M., A.S-H., G.K., S.S., D.R., A.K., B.K.; *Methodology*, H.M., G.K., C.K., B.K.; *Writing-Original Draft*, H.M., S.U., M.A., A.S-H., G.K., C.K., A.R., S.S., D.R., A.K., B.K.; *Writing-Review & Editing*, H.M., S.U., M.A., A.S-H., G.K.,C.K., A.R., S.S., D.R., A.K., B.K.; Funding Acquisition, B.K.; *Project Administration*, B.K.

ETHICS APPROVAL

Ethics approval was obtained from the Southern Adelaide Clinical Human Research Ethics Committee.

INFORMED CONSENT

Informed consent was obtained for all study participants at enrolment.

PERMISSION TO REPRODUCE MATERIAL FROM OTHER SOURCES

No such material is within this paper.

DATA AVAILABILITY STATEMENT

Authors can confirm that all relevant data are included in the article and/or its supplementary information files.

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SUPPORTING INFORMATION

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

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