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Influence of adjuvant chemotherapy on anti-Müllerian hormone in women below 35 years treated for early breast cancer

Anne Perdrix [a,b,*], *Mathilde Saint-Ghislain* [c], *Marie Degremont* [a], *Marion David* [a], *Zena Khaznadar* [a], *Agnès Loeb* [d], *Marianne Leheurteur* [c], *Frédéric Di Fiore* [b,c,e,1], *Florian Clatot* [b,c,1]

[a] *Clinical Laboratory, Department of Biopathology, Henri Becquerel Centre, Rouen, France*
[b] *Equipe de Recherche en Oncologie (IRON), Inserm U1245, Rouen University Hospital, Rouen, France*
[c] *Department of Oncology, Henri Becquerel Centre, Rouen, France*
[d] *Department of Biomedical Informatics, Henri Becquerel Centre, Rouen, France*
[e] *Department of Gastroenterology, Rouen University Hospital, Rouen, France*

Anne Perdrix, MD-PhD, is working as a medical biologist in a French Comprehensive Cancer Center, specialized in tumor markers. She has been working from 2006 to 2013 in the Reproductive Laboratory of Rouen University Hospital, with an activity in Assisted Reproductive Technology and fertility preservation.

KEY MESSAGE

Anti-Müllerian hormone in women younger than 35 years decreased markedly after treatment with adjuvant chemotherapy for early breast cancer and remained under the age-expected values at 3 and 5 years post-diagnosis.

A B S T R A C T

The impact of chemotherapy on fertility appears to be of essential importance for the youngest cancer survivors. The aim of this study was to assess plasma anti-Mullërian hormone (AMH) evolution, using an automated sensitive AMH immunoassay in women younger than 35 years old before and after treatment with adjuvant chemotherapy for early breast cancer. We selected 54 women aged less than 35 years old, at the time of breast cancer diagnosis, who received chemotherapy between 2008 and 2014, and with plasma samples collected from the diagnosis, to 1 year, 3 years and 5 years post-diagnosis. The median AMH decreased markedly in the year after the diagnosis compared with the pretreatment values ($P < 0.0001$), and slightly increased 2 years later ($P = 0.007$, comparing 1-year and 3-years post-diagnosis concentrations), without any additional AMH recovery 5 years after diagnosis. This recovery did not reach age-dependent AMH expected values ($P < 0.0001$, comparing AMH measured values to AMH expected values). Addition of taxanes to an anthracyclines + alkylating-based regimen was associated with a worse AMH decrease ($P = 0.007$). Ovarian tissue cryopreservation before treatment did not influence the AMH recovery. These results highlight the necessity of fertility counselling before treatment, especially in women wanting children.

* Corresponding author.
E-mail address: anne.perdrix@chb.unicancer.fr (A Perdrix).
[1] Authors contributed equally to this work.

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Introduction

Women younger than 35 years of age represent 2.4% of all cases of breast cancer and approximately one-third of all cancers diagnosed in women below 35 years are breast cancer (Anders et al., 2009). In young women, the use of adjuvant chemotherapy to improve overall survival (Early Breast Cancer Trialists' Collaborative Group [EBCTCG] et al, 2012; Senkus et al, 2015) pointed new questions, in particular about fertility impact. Indeed, due to the childbearing delay observed in most of the Western countries (Habbema et al., 2015), the number of young patients treated with adjuvant chemotherapy for early breast cancer who have a desire for pregnancy after treatment is increasing. For these patients, the question of age becomes essential and is influenced by the necessary delay to start a pregnancy after a breast cancer diagnosis (Anders et al., 2008; Anderson et al., 2006, 2013; Chai et al., 2014; Hadji et al., 2014; Hamy et al., 2014; Henry et al., 2014; Lutchman Singh et al., 2007; Partridge et al., 2010; Su et al., 2010; Yu et al., 2010), the age-negative impact on spontaneous fertility (Dunson et al., 2004) or assisted reproductive technology results (Tigges et al., 2016). In this setting, an assessment of the post-chemotherapy gonadotoxicity in the youngest patients appears to be crucial.

Since the 2000s, anti-Müllerian hormone (AMH) has become the major biochemical marker of ovarian reserve. Initially dedicated to the assisted reproductive technology context, AMH use has been progressively extended to explore ovarian reserve after chemotherapy (Dewailly et al., 2014), in several malignant diseases: breast cancer (Anders et al., 2008; Anderson et al., 2006, 2013; Ben-Aharon et al., 2015; Chai et al., 2014; D'Avila et al., 2015; Hadji et al., 2014; Hamy et al., 2014; Henry et al., 2014; Lutchman Singh et al., 2007; Partridge et al., 2010; Su et al., 2010; Yu et al., 2010), lymphoma (Decanter et al., 2010; Lawrenz et al, 2012), haematological malignancies (Gupta et al., 2016; Lie Fong et al., 2008; Rosendahl et al., 2010; van Beek et al., 2007) or for cancers during childhood (Thomas-Teinturier et al., 2015; van der Kooi et al., 2017). Indeed, AMH measurements appeared more sensitive than traditional biomarkers (inhibin B and FSH) and transvaginal ultrasound examination (the determination of ovarian volume and count of antral follicles) (Anderson et al., 2006; Chai et al., 2014; Dewailly et al., 2014; Fréour et al., 2017).

The aim of the present study was to evaluate the AMH evolution in women aged less than 35 years, who were treated with adjuvant chemotherapy for early breast cancer, from the diagnosis to 1 year, 3 years and 5 years after the diagnosis, to better understand the middle- to long-term effects of chemotherapy on the ovarian reserve in this specific population.

Materials and methods

Subjects

All women aged less than 35 years old who were treated in the Henri Becquerel Centre for early breast cancer from 2008 to 2014 were retrospectively included. The patients' characteristics (e.g. tumour characteristics, treatment and evolution) and fertility history (before cancer and after treatment) were collected. Because of the retrospective design of this study, no information about the menstrual status was analysed. Blood samples were collected for routine analyses related to the biological follow-up before and after treatment: around 1 year (between 6 months to 18 months) from diagnosis, around 3 years (between 2 years and 4 years) from diagnosis, and around 5 years. Remaining heparinized plasma samples were stored frozen (–20°C).

Due to the evolution of adjuvant chemotherapy recommendations during the study period, patients were treated with either six cycles of FEC (5 fluorouracil 500 mg/m^2, epirubicin 100 mg/m^2, cyclophosphamide 500 mg/m^2) or three cycles of FEC followed by three cycles of taxanes (docetaxel [D] [100 mg/m^2]).

Ethical approval

All patients signed a consent form allowing their biological samples to be conserved. The study was approved by the Institutional Review Board of our Centre on 14 March 2016 (registration number: 1602B).

AMH measurements

AMH measurements were performed from heparinized plasma samples using the fully automated Elecsys® AMH assay on the Cobas® e 601 instrument (Roche Diagnostics, Mannheim, Germany). According to the manufacturer's data sheet, the detection limit was 0.01 ng/ml, the quantification limit was 0.03 ng/ml, and the intra-assay imprecision coefficient of variation was 1.2% at 1.19 ng/ml, and 0.9% at 5.89 ng/ml. All measurements were performed in one run, excluding inter-assay variation.

Statistical methods

The primary objective was to evaluate the evolution of AMH values between pre- and post-treatment settings. For the secondary objectives, the AMH variations were analysed from baseline to 1, 3 and 5-year post-diagnosis in the available samples according to: the age group (above or below the median age); the type of chemotherapy regimen received; the exposure to adjuvant hormonotherapy; and the ovarian tissue preservation before the treatment. The impact of adjuvant hormonal therapy has been analysed at 3 years after the diagnosis considering the need of a minimal drug exposure. Comparisons of AMH evolution over time were restricted to the same patients, using paired tests (Wilcoxon). The tests were performed using the MedCalc® statistical software (MedCalc Software, Belgium). Calculation of the theoretical AMH decrease expected in the study population without treatment was performed according to the physiological published AMH decrease of 5.6% per year (Bentzen et al., 2013). The 95% confidence intervals (CI) were calculated based on a bootstrap method using 10,000 permutations and were performed by the R free software (https://cran.rstudio.com/). The data are presented as the median [min-max]. A P-value of <0.05 was considered statistically significant. In case of no significant differences between the study sub-groups of population, the conclusions must be moderate, considering a possible risk of underpowered comparisons.

Results

Patient and sample characteristics

Among the 5775 patients treated for breast cancer during the study period, 119 were aged less than 35 years old. Of these, 65 were excluded due to a lack of remaining plasma before the treatment (n = 31) or after the diagnosis (n = 16), metastatic disease (n = 10),

Table 1 – Patient characteristics.

Patient characteristics (*n* = 54)	
Age at diagnosis (years), median [range]	31.5 [11–35]
Body mass index (kg/m^2), median [range]	22.18 [17.85–36.06]
Smoker, *n* (%)	16 (30)
Genetic mutations, *n* (%)	
BRCA	14 (26)
Other	1 (1.9)
Tumor characteristics, *n* (%)	
Hormonal receptor positivity, *n* (%)	29 (54)
Oestrogen receptor	28 (52)
Progesterone receptor	21 (39)
Her2 positive	10 (19)
Triple negative	23 (43)
Treatments, *n* (%)	
Surgery	54 (100)
Tumorectomy	23 (43)
Mastectomy	31 (57)
Radiotherapy	49 (91)
Chemotherapy	54 (100)
3FEC-3D[a]	45 (83)
6FEC[b]	9 (17)
Hormonotherapy[c]	27 (50)
Fertility history, *n* (%)	
Pregnancy before treatment	45 (83)
Child birth before treatment	43 (80)
Ovarian tissue cryopreservation	11 (20)
Disease history, *n* (%)	
Cancer recurrence	7 (13)

[a] 3FEC-3D = Fluorouracil 500 mg/m^2 + epirubicin 100 mg/m^2 + cyclophosphamide 500 mg/m^2, every 21 days for three cycles, followed by sequential docetaxel 100 mg/m^2 every 21 days for three cycles.
[b] 6FEC = Fluorouracil 500 mg/m^2 + epirubicin 100 mg/m^2 + cyclophosphamide 500 mg/m^2, every 21 days for six cycles.
[c] Two patients refused hormonotherapy.

or no chemotherapy after surgery (*n* = 8). Thus, 54 patients were finally included with at least one AMH measurement before and one measurement after diagnosis. AMH post-treatment measurements were evaluated at 1 year, 3 years and 5 years in 49, 32 and 11 patients, respectively. Due to missing samples, for each included patient, the median number of samples analysed was 3[2–4], with a median number of samples analysed after chemotherapy of 2[1–3]. The patients' characteristics are presented in **Table 1**.

For the 54 patients included, a total of 144 samples were analysed. The concentrations of AMH were non-detectable (<0.01 ng/ml) in 14 samples (none in the pretreatment analysis, 10 from 49 patients at the 1-year analysis, 2 from 32 patients at the 3-years analysis and 2 from 11 patients at the 5-years analysis) obtained from 11 patients. No ovarian suppression function was used in the cohort from this study.

Pre-treatment AMH concentrations

The median AMH at diagnosis was 2.12 ng/ml [0.33–17.49] with AMH values decreasing not significantly with age as follows: median AMH = 3.37 ng/ml [3.09–3.65] for women aged 20–24 years old (*n* = 2), median AMH = 2.29 ng/ml [1.18–17.49] for women aged 25–29 years old (*n* = 10) and median AMH = 1.95 ng/ml [0.34–7.2] for women aged 30–35 years old (*n* = 42).

AMH did not vary significantly according to smoking status (median AMH = 2.54 ng/ml [0.83–6.5] and 1.95 ng/ml [0.37–17.49] in smokers (*n* = 16) and non-smokers (*n* = 38), respectively), or BRCA mutations (median AMH = 2.13 ng/ml [0.33–6.50] and 2.12 ng/ml [0.57–17.49] in mutated [*n* = 14] or non-mutated [*n* = 40], respectively). A body mass index (BMI) > 25 kg/m^2 was associated with a higher AMH concentration (median AMH = 3.29 ng/ml [0.78–17.49] for *n* = 14 patients with a BMI >25 kg/m^2, versus 1.82 ng/ml [0.33–7.2] for *n* = 40 patients with a BMI <25 kg/m^2, *P* = 0.046).

The median AMH was not different in women with a history of pregnancy before the treatment compared with women without any previous pregnancies (median AMH = 2.00 ng/ml [0.33–17.49] versus 2.25 ng/ml [0.56–5.13]). Of note, these two groups had comparable ages (median age = 32 years [23–35] and 30 years [22–34], respectively).

Post-treatment AMH concentrations

After a median delay of 379 [172–571] days from the diagnosis, the median AMH decreased to 0.13 ng/ml [0.01–6.11]; this decrease was significant compared with the pretreatment values (*n* = 49, *P* < 0.0001). There was a slight increase in the median AMH to 0.31 ng/ml [0.01–3.28] after two more years of survey (when comparing 1-year and 3-years post-diagnosis concentrations, *n* = 32, *P* = 0.007) (median delay from the diagnosis = 1128 [730–1490] days). No additional AMH recovery was observed 5 years after the diagnosis (median delay from the diagnosis = 1913 [1770–1913] days) compared with the 3-years post-diagnosis values (*n* = 9) (**Figure 1**).

The median AMH was not different in women younger or older than the median age (31.5 years old) at 1, 3 or 5 years after the diagnosis. To estimate the specific effect of breast cancer treatment on the AMH decrease, the study compared AMH values observed 1, 3 and 5 years after the diagnosis to theoretical AMH values that were calculated according to the physiological decline rate of 5.6% per year (Bentzen et al., 2013). The observed median AMH values were significantly lower than the theoretical expected medians at 1, 3 and 5 years after the diagnosis (*P* < 0.0001 for each point) (**Figure 2**).

At 1 year after the diagnosis, the median AMH was significantly lower after 3FEC-3D (median AMH = 0.09 ng/ml [0.01–6.11], *n* = 41) than after 6FEC (median AMH = 0.39 ng/ml [0.21–2.33], *n* = 8) (*P* = 0.007). The median age at diagnosis of these two groups was not significantly different. A comparison between 3FEC-3D versus 6FEC was not performed at 3- and 5-years post-diagnosis because the subgroups were too small. Considering the hormonal therapy, every patient (except one, who was treated with letrozole) received tamoxifen. The hormonal therapy did not influence the 3-years post-diagnosis AMH concentrations (median AMH = 0.34 ng/ml [0.01–2.76] among the 15 patients with hormonal therapy versus 0.25 ng/ml [0.01–3.28] among the 17 patients without hormonal therapy). At 5-years post-diagnosis, the impact of hormonal therapy on AMH concentrations could not be analysed because of the lack of data.

The median AMH concentration at 1-year post-diagnosis was not decreased in patients who had benefitted from an ovarian tissue cryopreservation (median AMH = 0.138 ng/ml [0.01–0.52] for 11 patients) compared with those who had not (median AMH = 0.13 ng/ml [0.01–6.11] for 43 patients). Of note, the median ages were similar between these two groups (31 years [22–34] and 32 years [23–35], respectively).

Discussion

In this study, focused on the AMH evolution in patients younger than 35 years of age during and after adjuvant treatment for early breast

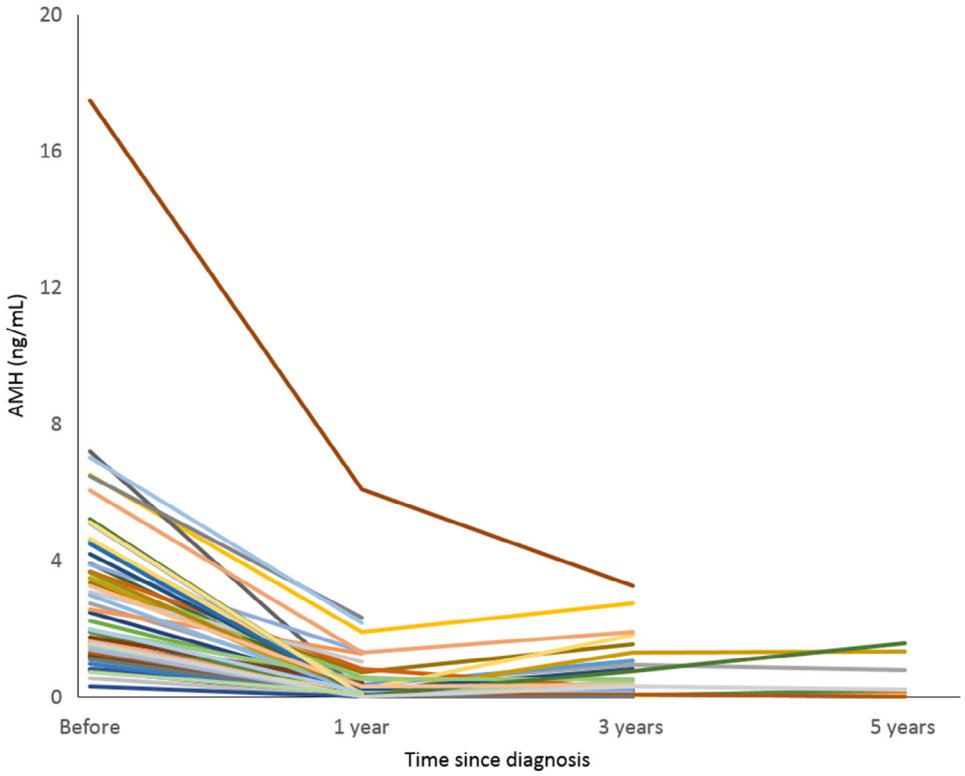

Figure 1 – Evolution of anti-Müllerian hormone (AMH) concentrations from the time of diagnosis to 1, 3 and 5 years after diagnosis. Each coloured line represents a patient. The median AMH decreases drastically 1 year after diagnosis (n = 49, P < 0.0001, comparing pre-diagnosis and 1-year post-diagnosis concentrations) and increases slightly 3 years after (n = 32, P = 0.007, comparing 1-year and 3-years post-diagnosis concentrations), but it does not recover to pretreatment concentrations. No further improvement is observed 2 years later (n = 9, P = 1, comparing 3-year and 5-years post-diagnosis concentrations). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

cancer, a marked decrease in AMH concentrations after chemotherapy was observed, which remained below the age-expected values despite 3 to 5 years of follow-up, and was influenced by the chemotherapy regimen. AMH analysis was performed using the automated Elecsys AMH assay (Roche Diagnostics), which has been reported as sensitive (Anckaert et al., 2016), reproducible (Anckaert et al., 2016; Anderson et al., 2015; Nelson et al., 2015), and correlated with age (Anderson et al., 2015) and antral follicle count (Anderson et al., 2015; Nelson et al., 2015; Tadros et al., 2016). The improvement of the sensitivity enables us to minimize the proportion of undetectable specimens. In this study, only 20% of the specimens were undetectable 1 year after chemotherapy, which represents an improvement compared with the previously published ratios: using the MIS ELISA assay (Diagnostic Systems Laboratories), Yu et al. (2010), observed 96% of undetectable samples; this proportion was of 86% (Henry et al., 2014) and about 100% (Anderson et al., 2013) using the Gen II Enzyme-linked immunosorbent assay (ELISA) kit (Beckman Coulter).

Before the treatment, no impact was observed on AMH concentrations according to smoking status and a slight increase observed of AMH concentrations in the heaviest patients. These confounding factors have been previously discussed without any consensus (Dewailly et al., 2014). For tobacco, one of the key factors may be the intensity of tobacco intoxication (White et al., 2016). For BMI, one hypothesis could be the classical relationship between overweight and polycystic ovary syndrome (Orio et al., 2016), that is associated with high AMH concentrations. Regarding the breast cancer context, the impact of BRCA mutations has also been reported. Two recent studies concluded that there was a negative impact of BRCA1 mutations on AMH concentrations (Giordano et al., 2016; Phillips et al, 2016). In the present study, this phenomenon was not observed; one explanation could be the increase in the impact of BRCA mutation on AMH concentrations after 35 years (Giordano et al., 2016), which spares the current study population.

The AMH decrease after breast cancer treatment has been previously reported. Its early characteristic, in the first 2 months post-chemotherapy (Anders et al., 2008; Hamy et al., 2014; Henry et al., 2014; Lutchman Singh et al., 2007; Yu et al., 2010) seems well established. In contrast, AMH evolution 1 year after breast cancer treatment has differed across the studies. Several works (Anders et al., 2008; Anderson et al., 2006; Yu et al., 2010) observed persistent low values, whereas others (Hamy et al., 2014; Henry et al., 2014) demonstrated an improvement of AMH values, quantified as a recovery of AMH concentrations above the detection level for 13% of the patients, in the first case, or an increase of about +1.2% per month, in the second case. Data from this study, with a marked fall of AMH values at one year post-diagnosis and a slight increase 3 years after diagnosis, without any supplementary improvement 5 years after diagnosis, confirmed a trend for a partial recovery that was not enough to reach the age-dependent AMH expected values (Bentzen et al., 2013). The data obtained after a longer follow-up confirmed the negative and persistent impact on the ovarian reserve of women treated for breast cancer, compared with age-matched controls (Partridge et al., 2010; Su et al., 2010).

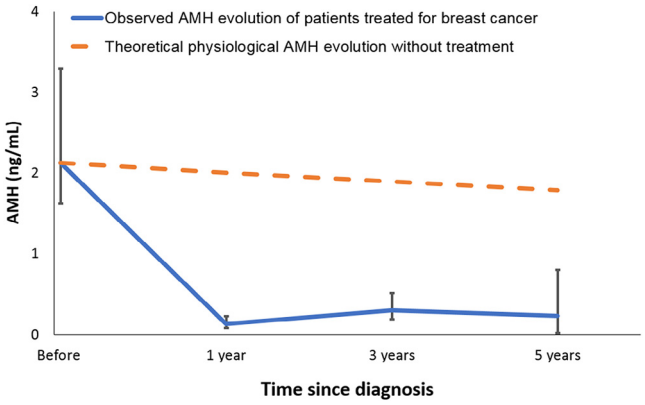

Figure 2 – Evolution of median anti-Müllerian hormone (AMH) concentrations from the pretreatment to 1, 3 and 5 years after the diagnosis, compared with the theoretical physiological AMH decrease. The solid line represents the AMH decrease observed in this study population, women <35 years treated for a breast cancer at 1, 3 and 5 years after the diagnosis. The dashed line represents the theoretical AMH decrease that would have been expected in this population without treatment. This decrease was calculated from the median AMH concentration observed in the population before the diagnosis, and assuming the physiological rate of decline of 5.6% per year (Bentzen et al., 2013). The AMH concentrations of the patients were reported using the median value. The 95% confidence intervals were calculated based on a bootstrap method using 10,000 permutations and were performed by the R free software. (*) indicates a significant difference ($P <$ 0.0001) between the AMH measurements in patients, represented with the full line, and the expected AMH values according to the theoretical physiological AMH decrease, represented with the dashed line.

The data obtained on post-treatment amenorrhoea have regularly suggested a better recovery of ovarian function in younger patients (Silva et al., 2016). Age <32 years (D'Avila et al., 2015), or <35 years (Ben-Aharon et al., 2015; Yu et al., 2010) have been demonstrated to be good prognostic factors for menses recovery. In terms of AMH, the studied populations were frequently older, with median ages ranging from 37 years to more than 43 years (Anders et al., 2008; Anderson et al., 2006; Chai et al., 2014; Henry et al., 2014; Su et al., 2010; Yu et al., 2010). With the exception of Hamy et al. (2014) (Hamy et al., 2014), which presented a cohort with a median age = 35.5 years and with 57 patients younger than 35 years, all previous studies included less than eight breast cancer patients younger than 35 years in their cohort (Anders et al., 2008; Anderson et al., 2006; Henry et al., 2014; Yu et al., 2010). When considering the data from other malignancies, two main observations have been reported: (i) a marked and early fall of AMH after treatment (Decanter et al., 2010; Dillon et al., 2013; Gupta et al., 2016; Rosendahl et al., 2010); and (ii) a possible post-treatment recovery depending on the chemotherapy protocols (Decanter et al., 2010; Dillon et al., 2013; Rosendahl et al., 2010). Indeed, use of alkylating agents appeared to be associated with a worse recovery of AMH values (Peigné and Decanter, 2014). The essential role of the alkylating agents in breast cancer treatments makes indispensable specific studies on the ovarian reserve in young breast cancer patients.

This study confirmed a persistent negative impact of anthracyclines and alkylating agents on the ovarian reserve in women <35 years and demonstrated the supplementary toxicity of taxanes, added to the anthracyclines + alkylating combination. The effect of the association anthracyclines + alkylating + taxanes on ovarian function continues to be debated (Mailliez et al., 2011). The effect of taxanes on menses recovery seems inconsistent being absent for Reh et al. (2008) and present for Silva et al. (2016). In terms of their impact on AMH values, Anderson et al. (2006) reported a significant decrease of AMH 6 months after an anthracyclines + alkylating + taxanes-based chemotherapy; however this has not been confirmed with a longer period of follow-up (Anderson and Cameron, 2011; Hamy et al., 2014). Nevertheless, Hamy et al. (2016) showed a lower probability of pregnancy after breast cancer chemotherapy containing anthracyclines + alkylating + taxanes, compared with an anthracyclines + alkylating only regimen. To our knowledge, only two studies analysed AMH following the use of hormonal therapy (tamoxifen) after chemotherapy for breast cancer, with contradictory results: whereas Partridge et al. (2010) reported a lower AMH concentration in cases of endocrine therapy (n = 10), Su et al. (2010) did not observe any significant difference (n = 87). Independent of the impact of chemotherapy, the hormonal therapy has been associated with an AMH decrease (Anderson and Cameron, 2011; Anderson et al., 2006). This question is crucial to correctly interpret the AMH values in breast cancer patients who have received chemotherapy as an adjuvant treatment and are under hormonal therapy to adapt fertility counselling.

Any supplementary negative impact of ovarian tissue cryopreservation on AMH values after treatment was not observed. These results are consistent with those obtained by Rosendahl et al. (2010), who observed slightly lower concentrations of AMH immediately after chemotherapy, no matter the initial malignancy, in patients who had an ovary removed, but no difference after a median delay of 8 months after the last chemotherapy treatment.

In conclusion, this study shows that: (i) the use of an automated sensitive AMH immunoassay improves the biological assessment of the ovarian reserve after breast cancer treatment, reducing the number of non-detectable concentrations compared with the published data; (ii) a marked AMH decrease exists after adjuvant chemotherapy for breast cancer, despite the young age of the patients; (iii) a slight increase of AMH 3 years after diagnosis does not reach the normal age-expected values; (iv) an anthracyclines + alkylating + taxanes regimen has a worse effect on AMH concentrations compared with anthracyclines + alkylating alone; and (v) ovarian tissue cryopreservation does not affect post-treatment AMH values. Although the role of AMH values in predicting the chances of pregnancy after chemotherapy remains to be established (Hamy et al., 2016), results from this study, which indicate a negative impact of breast cancer chemotherapy on the ovarian reserve in young patients, highlight the necessity of fertility counselling before treatment, even in women younger than 35 years, especially when they have not yet borne children.

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REFERENCES

Anckaert, E., Öktem, M., Thies, A., Cohen-Bacrie, M., Daan, N.M.P., Schiettecatte, J., Müller, C., Topcu, D., Gröning, A., Ternaux, F., Engel, C., Engelmann, S., Milczynski, C., 2016. Multicenter analytical performance evaluation of a fully automated anti-Müllerian hormone assay and reference interval determination. Clin. Biochem. 49, 260–267. doi:10.1016/j.clinbiochem.2015.10.008.

Anders, C., Marcom, P.K., Peterson, B., Gu, L., Unruhe, S., Welch, R., Lyons, P., Behera, M., Copland, S., Kimmick, G., Shaw, H., Snyder, S., Antenos, M., Woodruff, T., Blackwell, K., 2008. A pilot study of predictive markers of chemotherapy-related amenorrhea among premenopausal women with early stage breast cancer. Cancer Invest. 26, 286–295. doi:10.1080/07357900701829777.

Anders, C.K., Johnson, R., Litton, J., Phillips, M., Bleyer, A., 2009. Breast cancer before age 40 years. Semin. Oncol. 36, 237–249. doi:10.1053/j.seminoncol.2009.03.001.

Anderson, R.A., Cameron, D.A., 2011. Pretreatment serum anti-müllerian hormone predicts long-term ovarian function and bone mass after chemotherapy for early breast cancer. J. Clin. Endocrinol. Metab. 96, 1336–1343. doi:10.1210/jc.2010-2582.

Anderson, R.A., Themmen, A.P.N., Al-Qahtani, A., Groome, N.P., Cameron, D.A., 2006. The effects of chemotherapy and long-term gonadotrophin suppression on the ovarian reserve in premenopausal women with breast cancer. Hum. Reprod. 21, 2583–2592. doi:10.1093/humrep/del201.

Anderson, R.A., Rosendahl, M., Kelsey, T.W., Cameron, D.A., 2013. Pretreatment anti-Müllerian hormone predicts for loss of ovarian function after chemotherapy for early breast cancer. Eur. J. Cancer 49, 3404–3411. doi:10.1016/j.ejca.2013.07.014.

Anderson, R.A., Anckaert, E., Bosch, E., Dewailly, D., Dunlop, C.E., Fehr, D., Nardo, L., Smitz, J., Tremellen, K., Denk, B., Geistanger, A., Hund, M., 2015. Prospective study into the value of the automated Elecsys antimüllerian hormone assay for the assessment of the ovarian growing follicle pool. Fertil. Steril. 103, 1074–1080, e4. doi:10.1016/j.fertnstert.2015.01.004.

Ben-Aharon, I., Granot, T., Meizner, I., Hasky, N., Tobar, A., Rizel, S., Yerushalmi, R., Ben-Haroush, A., Fisch, B., Stemmer, S.M., 2015. Long-term follow-up of chemotherapy-induced ovarian failure in young breast cancer patients: the role of vascular toxicity. Oncologist 20, 985–991. doi:10.1634/theoncologist.2015-0044.

Bentzen, J.G., Forman, J.L., Johannsen, T.H., Pinborg, A., Larsen, E.C., Andersen, A.N., 2013. Ovarian antral follicle subclasses and anti-mullerian hormone during normal reproductive aging. J. Clin. Endocrinol. Metab. 98, 1602–1611. doi:10.1210/jc.2012-1829.

Chai, J., Howie, A.F., Cameron, D.A., Anderson, R.A., 2014. A highly-sensitive anti-Müllerian hormone assay improves analysis of ovarian function following chemotherapy for early breast cancer. Eur. J. Cancer 50, 2367–2374. doi:10.1016/j.ejca.2014.06.011.

D'Avila, Â.M., Biolchi, V., Capp, E., von Eye Corleta, H., 2015. Age, anti-müllerian hormone, antral follicles count to predict amenorrhea or oligomenorrhea after chemotherapy with cyclophosphamide. J. Ovarian Res. 8, 82. doi:10.1186/s13048-015-0209-4.

Decanter, C., Morschhauser, F., Pigny, P., Lefebvre, C., Gallo, C., Dewailly, D., 2010. Anti-Müllerian hormone follow-up in young women treated by chemotherapy for lymphoma: preliminary results. Reprod. Biomed. Online 20, 280–285. doi:10.1016/j.rbmo.2009.11.010.

Dewailly, D., Andersen, C.Y., Balen, A., Broekmans, F., Dilaver, N., Fanchin, R., Griesinger, G., Kelsey, T.W., La Marca, A., Lambalk, C., Mason, H., Nelson, S.M., Visser, J.A., Wallace, W.H., Anderson, R.A., 2014. The physiology and clinical utility of anti-Mullerian hormone in women. Hum. Reprod. Update 20, 370–385. doi:10.1093/humupd/dmt062.

Dillon, K.E., Sammel, M.D., Prewitt, M., Ginsberg, J.P., Walker, D., Mersereau, J.E., Gosiengfiao, Y., Gracia, C.R., 2013. Pretreatment antimüllerian hormone levels determine rate of posttherapy ovarian reserve recovery: acute changes in ovarian reserve during and after chemotherapy. Fertil. Steril. 99, 477–483. doi:10.1016/j.fertnstert.2012.09.039.

Dunson, D.B., Baird, D.D., Colombo, B., 2004. Increased infertility with age in men and women. Obstet. Gynecol. 103, 51–56. doi:10.1097/01.AOG.0000100153.24061.45.

Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Peto, R., Davies, C., Godwin, J., Gray, R., Pan, H.C., Clarke, M., Cutter, D., Darby, S., McGale, P., Taylor, C., Wang, Y.C., Bergh, J., Di Leo, A., Albain, K., Swain, S., Piccart, M., Pritchard, K., 2012. Comparisons between different polychemotherapy regimens for early breast cancer: meta-analyses of long-term outcome among 100,000 women in 123 randomised trials. Lancet 379, 432–444. doi:10.1016/S0140-6736(11)61625-5.

Fréour, T., Barrière, P., Masson, D., 2017. Anti-müllerian hormone levels and evolution in women of reproductive age with breast cancer treated with chemotherapy. Eur. J. Cancer 74, 1–8. doi:10.1016/j.ejca.2016.12.008.

Giordano, S., Garrett-Mayer, E., Mittal, N., Smith, K., Shulman, L., Passaglia, C., Gradishar, W., Pavone, M.E., 2016. Association of BRCA1 mutations with impaired ovarian reserve: connection between infertility and breast/ovarian cancer risk. J. Adolesc. Young Adult Oncol. 5, 337–343. doi:10.1089/jayao.2016.0009.

Gupta, A.A., Lee Chong, A., Deveault, C., Traubici, J., Maloney, A.M., Knight, S., Lorenzo, A., Allen, L., 2016. Anti-müllerian hormone in female adolescent cancer patients before, during, and after completion of therapy: a pilot feasibility study. J. Pediatr. Adolesc. Gynecol. 29, 599–603. doi:10.1016/j.jpag.2016.04.009.

Habbema, J.D.F., Eijkemans, M.J.C., Leridon, H., te Velde, E.R., 2015. Realizing a desired family size: when should couples start? Hum. Reprod. 30, 2215–2221. doi:10.1093/humrep/dev148.

Hadji, P., Kauka, A., Ziller, M., Birkholz, K., Baier, M., Muth, M., Kann, P., 2014. Effect of adjuvant endocrine therapy on hormonal levels in premenopausal women with breast cancer: the ProBONE II study. Breast Cancer Res. Treat. 144, 343–351. doi:10.1007/s10549-014-2860-7.

Hamy, A.-S., Porcher, R., Cuvier, C., Giacchetti, S., Schlageter, M.-H., Coussieu, C., Gronier, H., Feugeas, J.-P., Adoui, N., Lacorte, J.-M., Poirot, C., Habdous, M., Espié, M., 2014. Ovarian reserve in breast cancer: assessment with anti-Müllerian hormone. Reprod. Biomed. Online 29, 573–580. doi:10.1016/j.rbmo.2014.07.008.

Hamy, A.-S., Porcher, R., Eskenazi, S., Cuvier, C., Giacchetti, S., Coussy, F., Hocini, H., Tournant, B., Perret, F., Bonfils, S., Charvériat, P., Lacorte, J.-M., Espie, M., 2016. Anti-Müllerian hormone in breast cancer patients treated with chemotherapy: a retrospective evaluation of subsequent pregnancies. Reprod. Biomed. Online 32, 299–307. doi:10.1016/j.rbmo.2015.12.008.

Henry, N.L., Xia, R., Schott, A.F., McConnell, D., Banerjee, M., Hayes, D.F., 2014. Prediction of postchemotherapy ovarian function using markers of ovarian reserve. Oncologist 19, 68–74. doi:10.1634/theoncologist.2013-0145.

Lawrenz, B., Fehm, T., von Wolff, M., Soekler, M., Huebner, S., Henes, J., Henes, M., Centers of FertiPROTEKT Network, 2012. Reduced pretreatment ovarian reserve in premenopausal female patients with Hodgkin lymphoma or non-Hodgkin-lymphoma–evaluation by using antimüllerian hormone and retrieved oocytes. Fertil. Steril. 98, 141–144. doi:10.1016/j.fertnstert.2012.04.021.

Lie Fong, S., Lugtenburg, P.J., Schipper, I., Themmen, A.P.N., de Jong, F.H., Sonneveld, P., Laven, J.S.E., 2008. Anti-müllerian hormone as

a marker of ovarian function in women after chemotherapy and radiotherapy for haematological malignancies. Hum. Reprod. 23, 674–678. doi:10.1093/humrep/dem392.

Lutchman Singh, K., Muttukrishna, S., Stein, R.C., McGarrigle, H.H., Patel, A., Parikh, B., Groome, N.P., Davies, M.C., Chatterjee, R., 2007. Predictors of ovarian reserve in young women with breast cancer. Br. J. Cancer 96, 1808–1816. doi:10.1038/sj.bjc.6603814.

Mailliez, A., Decanter, C., Bonneterre, J., 2011. [Adjuvant chemotherapy for breast cancer and fertility: estimation of the impact, options of preservation and role of the oncologist]. Bull. Cancer 98, 741–751. doi:10.1684/bdc.2011.1391.

Nelson, S.M., Pastuszek, E., Kloss, G., Malinowska, I., Liss, J., Lukaszuk, A., Plociennik, L., Lukaszuk, K., 2015. Two new automated, compared with two enzyme-linked immunosorbent, antimüllerian hormone assays. Fertil. Steril. 104, 1016–1021, e6. doi:10.1016/j.fertnstert.2015.06.024.

Orio, F., Muscogiuri, G., Nese, C., Palomba, S., Savastano, S., Tafuri, D., Colarieti, G., La Sala, G., Colao, A., Yildiz, B.O., 2016. Obesity, type 2 diabetes mellitus and cardiovascular disease risk: an uptodate in the management of polycystic ovary syndrome. Eur. J. Obstet. Gynecol. Reprod. Biol. 207, 214–219. doi:10.1016/j.ejogrb.2016.08.026.

Partridge, A.H., Ruddy, K.J., Gelber, S., Schapira, L., Abusief, M., Meyer, M., Ginsburg, E., 2010. Ovarian reserve in women who remain premenopausal after chemotherapy for early stage breast cancer. Fertil. Steril. 94, 638–644. doi:10.1016/j.fertnstert.2009.03.045.

Peigné, M., Decanter, C., 2014. Serum AMH level as a marker of acute and long-term effects of chemotherapy on the ovarian follicular content: a systematic review. Reprod. Biol. Endocrinol. 26, 12–26. doi:10.1186/1477-7827-12-2.

Phillips, K.-A., Collins, I.M., Milne, R.L., McLachlan, S.A., Friedlander, M., Hickey, M., Stern, C., Hopper, J.L., Fisher, R., Kannemeyer, G., Picken, S., Smith, C.D., Kelsey, T.W., Anderson, R.A., Kathleen Cuningham Consortium for Research into Familial Breast Cancer (kConFab), 2016. Anti-Müllerian hormone serum concentrations of women with germline BRCA1 or BRCA2 mutations. Hum. Reprod. 31, 1126–1132. doi:10.1093/humrep/dew044.

Reh, A., Oktem, O., Oktay, K., 2008. Impact of breast cancer chemotherapy on ovarian reserve: a prospective observational analysis by menstrual history and ovarian reserve markers. Fertil. Steril. 90, 1635–1639. doi:10.1016/j.fertnstert.2007.09.048.

Rosendahl, M., Andersen, C.Y., la Cour Freiesleben, N., Juul, A., Løssl, K., Andersen, A.N., 2010. Dynamics and mechanisms of chemotherapy-induced ovarian follicular depletion in women of fertile age. Fertil. Steril. 94, 156–166. doi:10.1016/j.fertnstert.2009.02.043.

Senkus, E., Kyriakides, S., Ohno, S., Penault-Llorca, F., Poortmans, P., Rutgers, E., Zackrisson, S., Cardoso, F., ESMO Guidelines Committee, 2015. Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann. Oncol. 26 (Suppl. 5), v8–v30. doi:10.1093/annonc/mdv298.

Silva, C., Caramelo, O., Almeida-Santos, T., Ribeiro Rama, A.C., 2016. Factors associated with ovarian function recovery after chemotherapy for breast cancer: a systematic review and meta-analysis. Hum. Reprod. 31, 2737–2749. doi:10.1093/humrep/dew224.

Su, H.I., Sammel, M.D., Green, J., Velders, L., Stankiewicz, C., Matro, J., Freeman, E.W., Gracia, C.R., DeMichele, A., 2010. Antimullerian hormone and inhibin B are hormone measures of ovarian function in late reproductive-aged breast cancer survivors. Cancer 116, 592–599. doi:10.1002/cncr.24746.

Tadros, T., Tarasconi, B., Nassar, J., Benhaim, J.-L., Taieb, J., Fanchin, R., 2016. New automated antimüllerian hormone assays are more reliable than the manual assay in patients with reduced antral follicle count. Fertil. Steril. 106, 1800–1806. doi:10.1016/j.fertnstert.2016.08.045.

Thomas-Teinturier, C., Allodji, R.S., Svetlova, E., Frey, M.-A., Oberlin, O., Millischer, A.-E., Epelboin, S., Decanter, C., Pacquement, H., Tabone, M.-D., Sudour-Bonnange, H., Baruchel, A., Lahlou, N., De Vathaire, F., 2015. Ovarian reserve after treatment with alkylating agents during childhood. Hum. Reprod. 30, 1437–1446. doi:10.1093/humrep/dev060.

Tigges, J., Godehardt, E., Soepenberg, T., Maxrath, B., Friol, K., Gnoth, C., 2016. Determinants of cumulative ART live-birth rates in a single-center study: age, fertilization modality, and first-cycle outcome. Arch. Gynecol. Obstet. 294, 1081–1089. doi:10.1007/s00404-016-4162-2.

van Beek, R.D., van den Heuvel-Eibrink, M.M., Laven, J.S.E., de Jong, F.H., Themmen, A.P.N., Hakvoort-Cammel, F.G., van den Bos, C., van den Berg, H., Pieters, R., de Muinck Keizer-Schrama, S.M.P.F., 2007. Anti-Mullerian hormone is a sensitive serum marker for gonadal function in women treated for Hodgkin's lymphoma during childhood. J. Clin. Endocrinol. Metab. 92, 3869–3874. doi:10.1210/jc.2006-2374.

van der Kooi, A.L.F., van den Heuvel-Eibrink, M.M., van Noortwijk, A., Neggers, S.J.C.M.M., Pluijm, S.M.F., van Dulmen-den Broeder, E., van Dorp, W., Laven, J.S.E., 2017. Longitudinal follow-up in female Childhood Cancer Survivors: no signs of accelerated ovarian function loss. Hum. Reprod. 32, 193–200. doi:10.1093/humrep/dew278.

White, A.J., Sandler, D.P., D'Aloisio, A.A., Stanczyk, F., Whitworth, K.W., Baird, D.D., Nichols, H.B., 2016. Antimüllerian hormone in relation to tobacco and marijuana use and sources of indoor heating/cooking. Fertil. Steril. 106, 723–730. doi:10.1016/j.fertnstert.2016.05.015.

Yu, B., Douglas, N., Ferin, M.J., Nakhuda, G.S., Crew, K., Lobo, R.A., Hershman, D.L., 2010. Changes in markers of ovarian reserve and endocrine function in young women with breast cancer undergoing adjuvant chemotherapy. Cancer 116, 2099–2105. doi:10.1002/cncr.25037.