Antimüllerian hormone, the assessment of the ovarian reserve, and the reproductive outcome of the young patient with cancer

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The accurate assessment of the ovarian reserve has long been a key goal in reproductive medicine. The recognition that serum antimüllerian hormone provides an indirect measure of the ovarian reserve has led to its rapid adoption in assisted conception, and wide exploration of its potential across the reproductive lifespan from the neonate to the menopause. In this short review we discuss its relationship with the ovarian reserve in its varied meanings, and in various contexts. These include in childhood and adolescence, and in the assessment of the impact of cancer therapy on the female reproductive tract. These therapies can adversely impact all aspects of female reproduction, including hypothalamic, pituitary, and ovarian hormonal activity, and the ability of the uterus to support a successful pregnancy. (Fertil Steril® 2013;99:1469–75. ©2013 by American Society for Reproductive Medicine.)

Key Words: AMH, cancer, fertility, chemotherapy, radiotherapy, ovarian reserve

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It is still widely believed that the human ovary establishes several million nongrowing follicles (NGF) at around 5 months of gestational age, which is followed by a decline to the menopause when approximately 1,000 remain at an average age of 50–51 years (1, 2). With approximately 450 ovulatory monthly cycles in the normal human reproductive lifespan, the majority of follicles are destined to become atretic during the growth phase. The term ovarian reserve is used to mean either the population of NGFs within the ovary (perhaps more properly termed the true ovarian reserve) or the population of small growing follicles that can be recruited by exogenous FSH, most often used in the context of assisted reproduction. Recently this long-held view of mammalian reproductive biology has been challenged by reports of the presence of mitotically active germ stem cells in juvenile and adult mouse ovaries (3, 4). Certainly the presence of germ stem cells within the mammalian ovary that are capable of neo-oogenesis remains controversial (5), and a better understanding of the establishment and decline of the NGF population will be important in determining whether neo-oogenesis occurs as part of normal human physiological aging. Toward this goal, we recently developed the first model of human ovarian reserve from conception to menopause that best fits the combined histologic evidence (6). This model allows us to estimate the number of NGF present in the ovary at any given age (Fig. 1) and suggests that 81% of the variance in NGF populations is due to age alone. We have also demonstrated than the rate of NGF recruitment increases from birth to age 14 years then declines with age until the menopause. Further analysis demonstrated that 95% of the NGF population variation is due to age alone for ages up to 25 years.

The importance of the nongrowing pool of follicles (the true ovarian reserve) as the basis for the length of the reproductive lifespan is based on the concept of complete and nonrenewable formation of primordial follicles in the human during fetal life. However,

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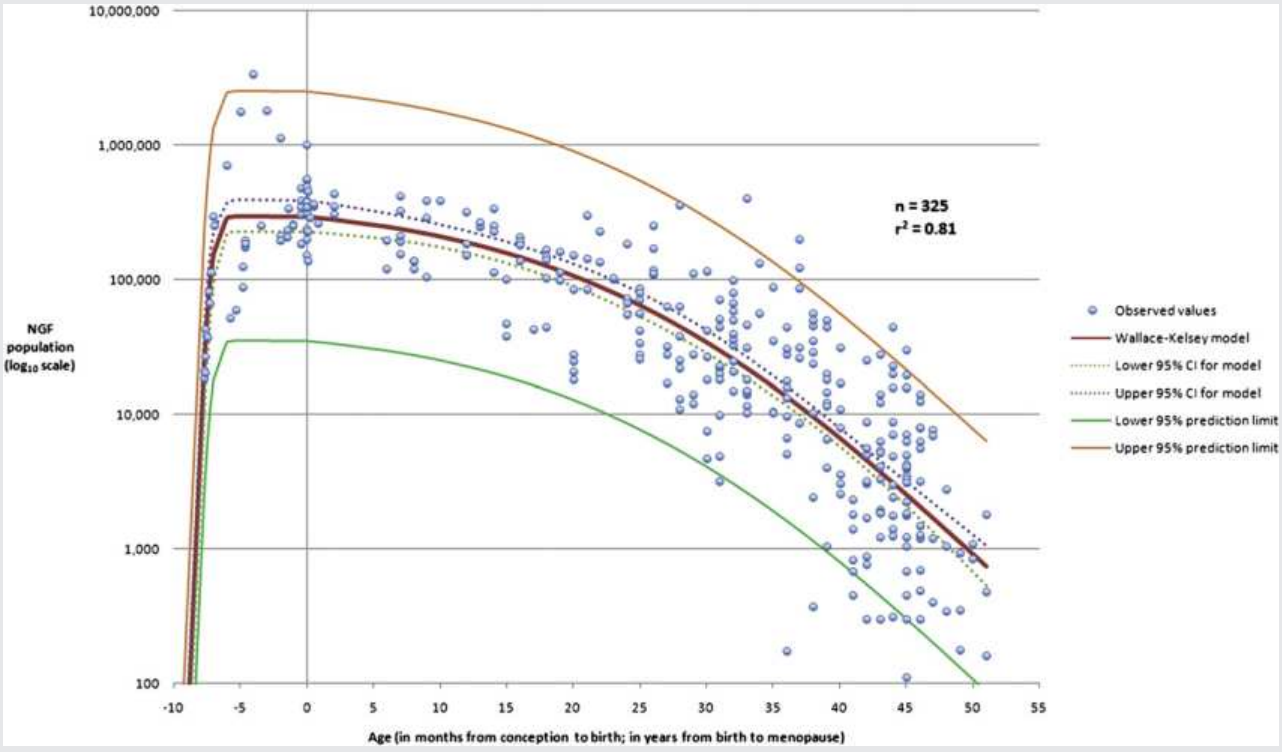
FIGURE 1



Model of nongrowing follicle (NGF) populations from conception to menopause. The figure shows the dataset (n = 325), the model, the 95% prediction limits of the model, and the 95% confidence interval (CI) for the model. The horizontal axis denotes age in months up to birth at age zero, and age in years from birth to 51 years. Reproduced, with permission, from Wallace WH, et al. Human ovarian reserve from conception to the menopause. PLoS One 2010;5:e8772. http://dx.doi.org/10.1371/journal.pone.0008772.

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the possibility of neo-oogenesis does not detract from the importance of the nongrowing pool as the key determinant of ovarian function and lifespan. A germ stem cell has to become an oocyte within a primordial follicle (i.e., enter the NGF pool before it can contribute to ovarian function and fertility). Thus the size of the pool remains of central importance. A detectable product of the primordial follicle pool would therefore be of huge value but remains elusive, and imaging in vivo at sufficient resolution is also impossible. Antimüllerian hormone (AMH) offers considerable potential both clinically and scientifically as its concentration in blood in adult women correlates directly with the number of primordial follicles, although it is not a direct product of them (7). Instead it is secreted by the granulosa cells (GC) of growing follicles (8). Expression of AMH increases as soon as follicles start to grow but preantral follicles contain relatively few GCs and the largest contribution to serum AMH is probably from the small antral follicles. Critically for its clinical and scientific value, the expression of AMH decreases abruptly at follicle diameter of approximately 8 mm, which is the stage at which follicles are selected for dominance. This, therefore, reflects a switch to estrogen (E) dominance of the later stages of follicle growth associated with the final development of the follicle in the lead up to ovulation. The major contribution of the smaller antral follicle population to serum AMH underlies the close correlation between AMH and ultrasound-derived antral follicle count (9) and both show a similar level of correlation with the primordial follicle pool determined histologically (7).

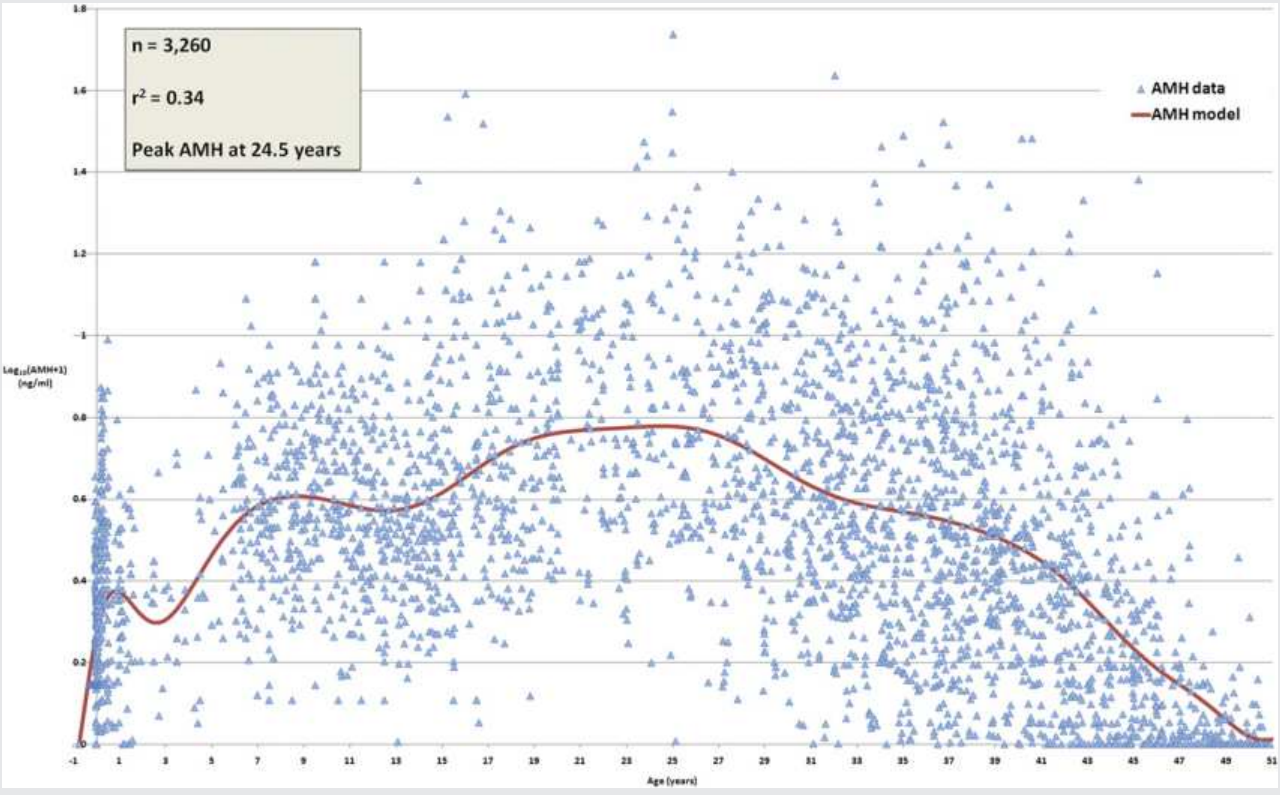
A key early finding was that serum AMH declines with age and that it may therefore be of value in the prediction of the menopause (10). Several studies have now addressed this directly (11–14) and, in essence, have confirmed that this is the case. It remains to be clarified, however, how accurately AMH can be used in this context, particularly in younger women, as in the largest study to date AMH and age were independent predictors of time to menopause (14). Thus in women with a low AMH (<0.2 ng/mL), the median time to menopause was 6.0 years in the age group 40–45 years, but just under 10 years in women aged 35–39 years. Conversely, in women with a high AMH (>1.5 ng/mL), the median times to menopause were 6.2 and 13.0 years in the two age groups.

Consistent with these two now established aspects of the use of AMH, has been a rapid growth in the measurement of AMH in women before IVF to provide a measure of the recruitable ovarian reserve and thus their potential response to stimulation. The AMH level predicts oocyte yield more accurately than FSH and can be used to identify women who will either over-respond to a stimulation regimen and will thus be at risk of ovarian hyperstimulation syndrome (OHSS), and those who are likely to be poor responders whose expectations can thus be managed (15, 16). In this context AMH nomograms

have been published based on very substantial populations of women revealing a quadratic model of decline across the main reproductive years. An initial analysis based on 9,600 infertile women (17) has subsequently been validated in 15,800 US women (18), giving confidence that this accurately reflects the rate of decline and range of values between individuals in those populations, although ethnicity-based nomograms are also required. Unfortunately due to the absence of an internationally recognized standard, the different assays that have been and are available do not all give the same results. Descriptions of the background to this and the relative values obtained with different assays have been published (19, 20). It is likely that the near future will see AMH assays becoming more standardized and platform-based with anticipated benefits in the robustness and comparability of the results obtained.

The preponderance of data in the literature being from infertile patients and particularly those undergoing assisted reproduction has meant that the normal range in younger adults, and in adolescents and children, has been less clear (21), and secondary to that, an accurate indication of the pattern of change of AMH across life has been missing. A data mining approach led to the identification of more than 3,000 data points from 20 publications and revealed a complex pattern of change in serum AMH across the lifespan (Fig. 2) (22). There is a clear temporary increase in AMH level in neonatal girls, which has been confirmed in a study specifically addressing this issue (23). Some neonatal females will have serum AMH concentrations similar to those of young adult women at their reproductive peak. This is strikingly analogous to the adult serum T concentrations achieved in neonatal males. Following this, there is a steady increase in AMH level through childhood, the important point of which is that AMH is readily detectible in normal prepubertal girls. It therefore offers substantial opportunity for assessment of ovarian function in childhood, previously impossible with other reproductive hormones, in concert with improved imaging modalities. Intriguingly an inflection at the age of puberty was also identified, with a slight decrease during adolescence followed by a second increase to a peak at age 24 years. This modest but reproducible decrease in AMH at puberty has now been confirmed in a longitudinal study from Denmark, which also demonstrated a relative stability of serum AMH across puberty with girls retaining their relative AMH levels compared to each other (24). These observations raise intriguing questions as to the nature of the ovarian maturation that occurs at puberty, and the basis for the progressive increase thereafter through early adulthood that takes approximately a decade to reach its peak, and occurs in the face of declining

FIGURE 2



A validated model of serum antimüllerian hormone (AMH) from conception to menopause. The *red line* is the model that best fits the 3,260 data points shown as triangles. The coefficient of determination $r^2 = 0.34$, indicating that 34% of variation in serum AMH concentrations is due to age alone. Peak serum AMH is at 24.5 years. Reproduced, with permission from Kelsey TW, Wright P, Nelson SM, Anderson RA, Wallace WH. A validated model of serum anti-M€ullerian hormone from conception to menopause. PLoS One 2011;6:e22024. http://dx.doi.org/10.1371/journal.pone.0022024.

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NGF pool size. A comparison of the number of NGFs leaving that pool against serum AMH reveals a positive correlation between the two in childhood when both are increasing. This, if followed by a negative correlation during adolescence and early adulthood when AMH is increasing and the rate of NGF recruitment is decreasing, and then by a very close positive relationship beyond that when both decrease (25). These data were calculated based on the change in the number of NGFs observed with increasing age, which may occur either through growth activation or direct atresia. The question as to which of these two outcomes predominates has long been debated, but one interpretation of the close and positive relationship between increasing AMH level and increasing rate of NGF loss is that the latter is mostly through recruitment to growth and not directly to atresia, although, of course, the majority of follicles are eventually destined to become atretic.

This demonstrates the many areas in which AMH is becoming of clinical value, particularly in assisted conception. But its relationship with the ovarian reserve indicates much wider potential value in assessing the ovarian reserve in health and disease. This will include damage caused by diseases affecting the ovary and their treatments, such as endometriosis, or other iatrogenic damage prominent among which is that due to anticancer therapies.

RADIATION AND THE OVARY

The ovaries may be damaged by radiation to a field that includes the pelvis (e.g., total body, abdominal, or pelvic irradiation) and the magnitude of the effect is related to the radiation dose, fractionation schedule, and age at time of treatment. The human oocyte is exquisitely sensitive to radiation, with an estimated LD_{50} (the lethal dose required to destroy 50% of NGFs) of less than 2 Gy (26). Premature primary ovarian insufficiency (POI) has been reported in 90% of patients followed up long term after total body irradiation (10–15.75 Gy) and in 97% of females treated with total abdominal irradiation (20–30 Gy) during childhood (27, 28). Using our understanding of the effect of radiotherapy on the human oocyte we can estimate the age at POI and the estimated sterilizing dose after any given dose of radiotherapy at any given age (29). This not only provides a useful basis for clinicians to provide accurate information when counseling women about fertility after treatment for childhood cancer, but also provides a scientific rationale for clinicians to select the patients at highest risk of POI and urge ovarian cryopreservation.

CHEMOTHERAPY AND THE OVARY

Chemotherapy treatment in premenopausal women is associated with an increased risk of POI, but the exact mechanisms through which this occurs are uncertain (30). Ovarian damage is drug and dose dependent and is related to age at time of treatment, with progressively smaller doses required to produce POI with increasing age. The age-related difference is most likely to be due to older women having a smaller primordial follicle reserve at the start of treatment compared with young women, therefore that loss from a smaller follicle pool is more likely to induce POI.

Chemotherapy treatment that is gonadotoxic (e.g., alkylating agents) appears to have two distinct effects on ovarian function. The first is immediate, occurring during treatment, and is characterized by amenorrhea and results from loss of the growing follicle population. However, provided that sufficient primordial follicles remain in the resting pool upon the cessation of treatment, the population of growing follicles will then be replenished, and menses resume. Depending on the extent of the loss of the primordial follicle pool, POI and amenorrhea may result at a later date. Where there is only partial loss of primordial follicles, this longer term effect may not manifest itself until years or even decades after treatment, when the patient then undergoes POI. Where the reduction in the primordial follicle pool is near complete, the patient undergoes POI manifest by permanent amenorrhea shortly after treatment. Important, many women may experience infertility after cancer treatment yet not having POI (31).

RADIATION AND THE UTERUS

It is important to remember the uterus when discussing the effects of cancer treatment in young women. The uterus is at substantial risk of damage after radiation to a field that includes the pelvis, in a dose- and age-dependent manner (32). A large cohort study has confirmed that survivors who received pelvic radiation are at increased risk of preterm delivery (33). Chemotherapy per se (both alkylating and nonalkylating) without radiotherapy was not associated with an increased risk of prematurity or low birth weight. Pregnancy in survivors of childhood cancer who have received radiotherapy to a field that includes their pelvis should therefore be considered as high risk, essentially related to uterine dysfunction (34).

ASSESSMENT OF THE RISK OF TREATMENT ON FERTILITY PROGNOSIS

It is often difficult to give an accurate prediction/fertility prognosis before treatment starts for the young patient with cancer (Table 1). It is important to be aware that it is the treatment planned and not the disease itself that determines the fertility risk/prognosis. The patient who is prepubertal at diagnosis is unprotected from the effects of the treatment on gonadal function. A young female with Hodgkin lymphoma is a good example of the difficulties faced in making an accurate assessment of fertility prognosis. Depending on the nature of the planned treatment her risk of POI varies from low to high. If she is likely to receive radiation treatment to an area that includes her pelvis, then she is at high risk of POI (as well as possible uterine damage) (35). If she has a low stage disease and is not planned to receive alkylating agent therapy, she can be considered to be at low risk. Of course patients classified initially as low risk for POI may become high risk later if they relapse or their treatment plan changes.

AMH AND OVARIAN FUNCTION AFTER CANCER TREATMENT

We have shown that AMH is detectible in girls of all ages, unlike other reproductive hormones (Fig. 2), and increases

TABLE 1

Risk of infertility.

Low risk (< 20%)	Medium risk	High risk (> 80%)
Acute lymphoblastic leukemia	Acute myeloid leukemia	Total body irradiation
Wilms' tumor	Osteosarcoma	Pelvic/testes RT
Brain tumor (Surgery, RT <24 Gy)	Ewing sarcoma	Chemotherapy before BMT
Soft tissue sarcoma (stage 1)	Soft tissue sarcoma (stage II/III)	Metastatic Ewing sarcoma
Hodgkin lymphoma (low stage)	Neuroblastoma	Hodgkin lymphoma (pelvic RT)
	NHL	
	Brain tumor (RT >24 Gy)	
	Hodgkin lymphoma (high stage)	

Note: Adapted from Wallace et al. 2005 (35). BMT = bone marrow transplant; NHL = non-Hodgkin lymphoma; RT = radiation therapy.

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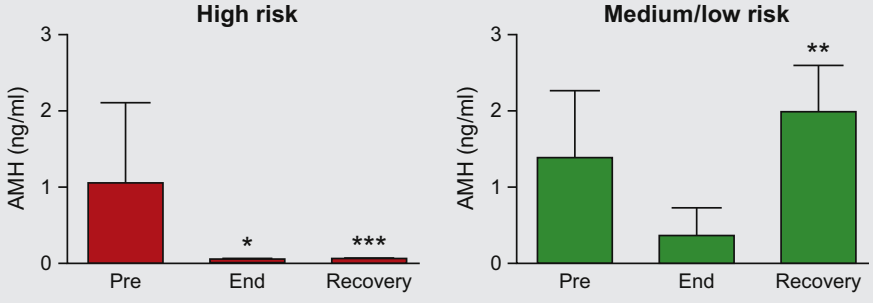
steadily through childhood, suggesting that measurement may be of value in the assessment of ovarian function in prepubertal girls (22). In a prospective analysis (36) of young females with different cancers at different ages, the AMH level was shown to decline steadily during the course of repeated chemotherapy treatments, with variable recovery. Noticeably, in girls judged to be at medium or low risk of POI, AMH recovered to concentrations similar to pretreatment, whereas in girls judged to be at high risk of POI, serum AMH level at the end of treatment was undetectable and showed no evidence of recovery (Fig. 3). Post-treatment AMH therefore appeared to identify prepubertal young girls who may require pubertal induction, in contrast to those whose AMH recovered to pretreatment levels and who may be able to be reassured that they are likely to have a window of opportunity for normal fertility. Some girls showed partial recovery only, and long-term follow-up of these young patients is required to determine whether they are at risk of POI and may not have a real opportunity for normal fertility and a reasonable reproductive lifespan. Perhaps this is a group of young women who after cure of their original cancer could be considered for oocyte cryopreservation. This is an area that requires further clinical research.

The number of girls included in that study across a wide range of ages and diagnoses precluded analysis of the potential value of assessment of AMH before cancer therapy. More focused prospective studies will be required to assess this, which will be challenging in the field of pediatric oncology. Comparable studies are, however, starting to appear in relation to ovarian function in adults. Higher pretreatment AMH level was associated with postchemotherapy ovarian activity in two studies in women with breast cancer (37, 38). Similarly, pretreatment AMH has recently been demonstrated to correlate with postchemotherapy AMH level (39), and there are several reports of retrospective analyses showing reduced AMH level in cancer survivors, both in childhood and adulthood, with relationships to the treatment received and on-going ovarian activity (40–44). We have proposed that in the context of assessment for fertility preservation that "intrinsic" patient factors are considered as well as the treatment to be received (45). This includes assessment of the ovarian reserve. It will be important, however, to assess robustly the value of either pretreatment or post-treatment AMH for prediction of pregnancy (or other key end points, such as time to or age at menopause). Currently available evidence shows that a low AMH level was not predictive of reduced fecundability in a prospective time to pregnancy study in healthy young women (46), and may be of limited value in childhood cancer survivors (47). In the latter study, 44% of 45 female childhood cancer

FIGURE 3



Antimüllerian hormone (AMH) concentrations before treatment (Pre), at the end of treatment (End), and at more than 6 months recovery after treatment (Recovery). Patients were stratified according to predicted risk of gonadotoxicity. Median ± interquartile range n = 9, high risk; n = 13, medium/low risk. *P<.01 versus before treatment; **P<.01 versus end of treatment; ***P<.001 vs. before treatment. Reprinted, with permission, from Brougham et al. J Clin Endocrinol Metab 2012;97:2059–67.

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survivors had low AMH concentrations, but nearly all (93%) had had successful pregnancies, including some women with very low AMH concentrations. In keeping with this, AMH may remain undetectable after replacement of cryopreserved ovarian tissue, even with sufficient ovarian function to allow pregnancy (48).

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