# Fertility preservation in pre-pubertal girls with cancer: the role of ovarian tissue cryopreservation

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With the increasing numbers of survivors of cancer in young people, future fertility and ovarian function are important considerations that should be discussed before treatment commences. Some young people, by nature of the treatment they will receive, are at high risk of premature ovarian insufficiency and infertility. For them, ovarian tissue cryopreservation (OTC) is one approach to fertility preservation that remains both invasive and for young patients experimental. There are important ethical and consent issues that need to be explored and accepted before OTC can be considered established in children with cancer. In this review we have discussed a framework for patient selection which has been shown to be effective in identifying those patients at high risk of premature ovarian insufficiency and who can be offered OTC safely. (Fertil Steril® 2016;105:6–12. ©2016 by American Society for Reproductive Medicine.)

**Key Words:** Ovarian tissue cryopreservation, pediatric cancer, fertility preservation

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The number of survivors of childhood cancers has increased over the last four decades. In the U.S., the five-year actuarial survival rate of the age group 0–14 years for the period 1950–1954 was only 20% (1) whereas for the period 2008–2012, the crude survival rate (incidence less mortality per 100,000 children) was 87% (2). Across the E.U., the crude death rate from cancer for the 0–14 age group has fallen from 3.9 per 100,000 in 1997 to 2.1 per 100,000 in 2012 (3). The corollary to these improvements is that the general population contains a progressively larger proportion of survivors of childhood cancer (4), many of whom are at risk of multi-faceted chronic morbidity as a result of their successful treatment (5). Although many survivors of childhood cancer go on to have children, the potential loss of fertility is a frequent concern of both patients, their parents, and medical caregivers (6). Some children, by nature of the treatment they will receive, are at high risk of infertility. For example, a large-scale study by the Childhood Cancer Survivor Study found that, compared to their siblings, the relative risk for survivors of ever being pregnant is 0.56 after 5–10 Gy to a field including the ovaries, with the relative falling to 0.18 after more than 10 Gy to a field including the ovaries (7). Recent data from the Childhood Cancer Survivor Study also suggest that the prevalence of subfertility, even where ovarian function is retained, is increased (8). The focus of this review is to discuss the indications for ovarian tissue cryopreservation in young patients with cancer, and future potential uses for this tissue.

At diagnosis, all patients deserve an informed consultation about their fertility prognosis (9, 10). For some, their prognosis is uncertain, but for the majority of patients it is clear whether, for the individual, the risk of compromising fertility with first line treatment is low, medium, or high (11).

At the time of diagnosis, the young patient is often unwell, and the family is facing an extraordinarily difficult time. The patient is undergoing many complex investigations and procedures, and the treating pediatric team may be able to offer entry into complex research studies that require informed consent from the patient and the family. These investigations, procedures and discussions take time, and are challenging for the patient and their family. However, we believe that informed discussion about the fertility prognosis,

Received October 17, 2015; revised November 19, 2015; accepted November 20, 2015; published online December 8, 2015.
W.H.B.W. has nothing to disclose. T.W.K. has nothing to disclose. R.A.A. has nothing to disclose.
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Fertility and Sterility® Vol. 105, No. 1, January 2016 0015-0282/$36.00

http://dx.doi.org/10.1016/j.fertnstert.2015.11.041

while potentially an additional burden, can be a positive experience, even if a fertility preservation procedure is not indicated (because the assessed risk to future fertility is low) or indeed is not possible.

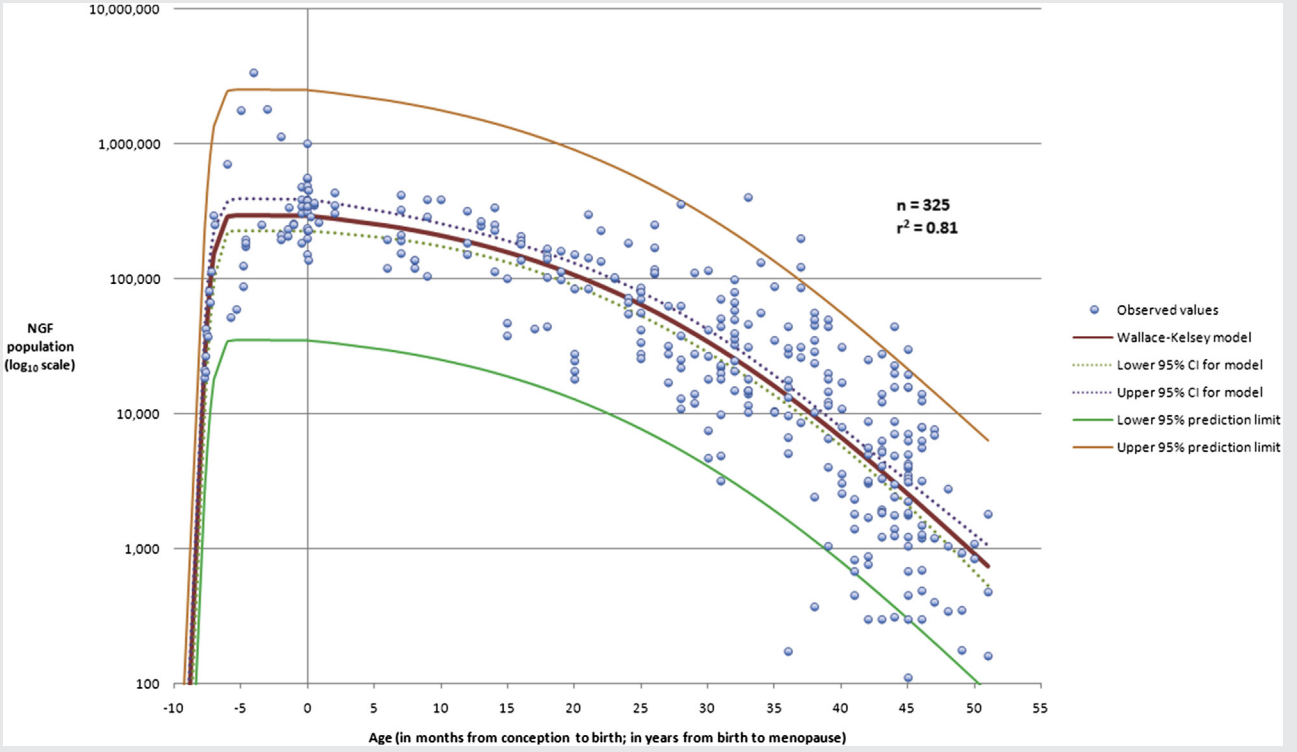
It is regrettably clear these discussions do not always take place (12, 13). Assessment of U.K. practice relating to information provision about the effects of cancer treatment on fertility and options for fertility preservation showed discussions were less common with girls than with boys, with young age of the girl being the most common reason cited for not having such a discussion (10). The American Society of Clinical Oncology has produced two evidence-based recommendations for fertility preservation for patients with childhood cancer (14, 15). A recent study of compliance with these recommendations reported that none of 136 patients older than 13 years at their last visit were counselled on fertility preservation (16).

## BACKGROUND

The human ovary is active during childhood (17). Follicles are recruited towards maturation at all ages, differentiate to pre-antral and antral follicles, but, for pre-pubertal ages, in the absence of sufficient gonadotropic support undergo atresia before they reach pre-ovulatory sizes (18). We have devised an age-related model of the non-growing follicle (NGF) population in healthy females (Fig. 1), and additionally calculated the age-related rates of recruitment of NGFs towards maturation (Fig. 2) (19). Interestingly, the rate of recruitment peaks at around 14–15 years of age, irrespective of whether there is a high, medium, or low ovarian reserve. In theory, the pre-pubertal ovary is an ideal candidate for ovarian tissue cryopreservation (OTC), with plentiful follicles available for cryopreservation and future re-implantation although there is evidence that the childhood ovary contains a significant proportion of morphologically abnormal follicles, that are lost in adolescence (20). No perfect index of ovarian reserve exists, but the best available indirect biomarker is antimüllerian hormone (AMH) (Fig. 3) (21) which is of established value in adult women (22). However, its utility as an indirect marker of ovarian reserve in the pre-pubertal child remains uncertain. There is some evidence that AMH in children newly diagnosed with cancer is lower than healthy age-matched children (23), with comparable data in adult women (24). The role for AMH in the assessment of ovarian reserve in young patients with cancer remains a subject of on-going research.

Treatment with cytotoxic drugs inhibits follicular growth (18, 25, 26), but other mechanisms for the reduction of ovarian reserve have been suggested. Cyclophosphamide is known to increase the rate at which follicles are recruited towards maturation, leading to what has been termed 'burnout' of the NGF population (27). A recent in vitro study in a mouse model indicates that different chemotherapy drugs are likely

## FIGURE 1




Normative model for non-growing follicle (NGF) population. The best model for the establishment of the non-growing follicle population after conception, and the subsequent decline until age at menopause. CI = confidence interval. Reprinted with permission (19).

*Wallace. Fertility preservation for girls with cancer. Fertil Steril 2016.*