

## In women, the reproductive harm of toxins such as tobacco smoke is reversible in 6 months: basis for the “olive tree” hypothesis

It is recognized that ovarian function and/or oocyte quality may be altered by exposure to environmental toxins. In the case of smoking, one would have predicted that the longer the exposure, the worse would be the impact on reproductive function. Yet, there is no organized understanding of the time course over which toxic substances affect the ovaries and even less knowledge of the duration of the recovery process once exposure to toxins such as tobacco smoke is discontinued.

Chemotherapy—an extreme model of toxic exposure—has allowed studying the recovery of ovarian function after toxin exposures are stopped (1). The less toxic regimens are followed by a return of circulating antimüllerian hormone (AMH) levels to prechemotherapy values in 6 months, indicating that chemotherapy primarily affected the growing follicles (1). The short recovery process found—6 months—lets us extrapolate a similar time frame for recuperating from the gonadotoxic effects of smoking or other environmental insults on stopping exposure. We named this postulate the “olive tree” hypothesis, rooting the metaphor in the fact that after severe cold spells, olive trees recuperate from their trunk while the leaves, more sensitive to the toxic effects of cold, succumb.

### Two Types of Ovarian Follicles

Functionally speaking, we can characterize the ovarian follicles present in the ovary into two primary types: 1) the resting (or primordial) follicles; and 2) the growing follicles (2). The former reflect a person’s endowment of oocytes. The latter develop for 3–6 months in humans until they acquire FSH receptors and a fluid-filled cavity, after which they are termed antral follicles (2). In the menstrual cycle, antral follicles respond to FSH, with one fully maturing and ovulating while the others undergo atresia.

The majority of growing ovarian follicles produce AMH, which is measured in the peripheral blood. Because AMH is not affected by hormonal changes, random measurements serve for assessing ovarian reserve.

### Chemotherapy, an Extreme Case of Environmental Toxins

Chemotherapy agents are highly toxic substances administered for treating cancer. Practically, chemotherapy represents a much stronger toxic exposure compared with the milder environmental toxins encountered in everyday life (e.g., tobacco smoke). Chemotherapy is thus a model for studying how resting and growing ovarian follicles respond to the exposure to and, most importantly, withdrawal from a toxin. AMH measurements, which reflect the population of growing follicles, allow studying the impact of chemotherapy and the recovery of ovarian function after chemotherapy is discontinued.

In a seminal trial, Decanter et al. observed that chemotherapy induces an abrupt drop in AMH levels, indicating a destruction of the growing follicles that produce AMH (1). The recovery of ovarian function

characteristically seen on stopping certain less gonadotoxic chemotherapy regimens was studied by serial AMH measurements. In these women, AMH started rising 3 months after chemotherapy was stopped, with prechemotherapy levels seen at 6 months after treatment, when menses commonly resume (1). This 6-month interval corresponds to the time taken in humans for new follicles to grow from the resting (primordial) stage to the antral follicle stage (2). Therefore, less toxic chemotherapy regimens that are associated with a recovery of ovarian function affect the growing follicles (abrupt drop in AMH) but spare the resting (primordial) follicles from which new follicles develop in 6 months.

### The “Olive Tree” Hypothesis

In Southern France, olive trees survive serious cold spells that strike every 40 years or so. Typically the leaves die, leaving bare, seemingly dead, trees. Yet these later resuscitate, regrowing branches and leaves, and soon produce new olive crops.

Thus, the trunk and leaves of the olive tree react differently to cold, a finding resembling the differing resistance to chemotherapy of the growing and resting ovarian follicles discussed above. Like the olive tree, the ovary resuscitates after chemotherapy, growing follicles (“the leaves”) from a pool of resting follicles (“the trunk”) that resisted the toxic effects.

The chemotherapy analysis leads one to postulate that environmental toxins such as active or passive exposure to tobacco smoke, which is less harmful than chemotherapy, generally spare the resting follicles. Considering the time frame of follicular growth in humans (2), a new cohort of toxin-free antral follicles is expected 6 months after the toxic exposure is stopped. The olive tree hypothesis suggests that the reproductive harm of environmental toxins such as tobacco smoke is not a fatality, but is in large part rapidly reversible on stopping.

### Smoking Is One of the Most Common Environmental Exposures to Oxidative Stress

Comparing reproductive function in current, past, and never-smokers is in agreement with the olive tree hypothesis proposed above. Troves of data indeed indicate that it is current, not past, smoking that affects fertility, being associated with poorer assisted reproduction technologies (ART) outcome, higher FSH, and, more recently, lower AMH levels (3). In contrast, findings in past smokers were not different from those of never-smokers (3).

Generally, therefore, the alterations seen in current smokers reflect an effect on the growing follicles, and the lack of harm observed in past smokers speaks to resistance of the resting follicles. The latter implies that new growing follicles not exposed to the toxic effects will be available shortly after smoking is stopped.

### Other Oxidative Stresses

The postulate that the benefit of cessation of cigarette smoking is reached in 6 months—the time taken for renewing

the cohort of growing follicles—can be expanded to other sources of oxidative stress to the ovaries. For example, reducing oxidative stress through improved lifestyle, nutrition, or intake of antioxidants (4) should be recommended for 3–6 months to conduct ART in a more ideal environment.

### Limits of the Olive Tree Hypothesis

The olive tree hypothesis, like most rules encompassing medical findings, has its limits. The recovery pattern seen after certain chemotherapy regimens—return of menses and AMH levels—would lead us to believe that only the growing ovarian follicles are affected while the resting follicles are entirely spared. This, we know, is not true. Women who recover their ovarian function after chemotherapy may undergo ovarian failure somewhat earlier than expected, which speaks for some alterations on the resting follicles as well (5). Likewise, smokers may suffer long-term effects on reproductive function, evidenced by the fact that they likely undergo menopause 1–2 years earlier. Furthermore, if the number of ovarian follicles leaving the resting pool increased on stopping chemotherapy, it might create a falsely reassuring “rebound” in circulating AMH levels. These limits of the olive tree hypothesis, however, should not distract from the fact that the primary effects of environmental toxins are on the growing follicles.

Underscoring the short recovery of the growing follicles after toxins are discontinued is not meant to trivialize the use of such toxins on the basis that it suffices to stop 6 months before conceiving. This is not the intended message put forth here.

### Practical Implications and Conclusion

The olive tree hypothesis postulates that environmental toxins—first among them tobacco smoke—primarily affect the growing, not the resting, ovarian follicles. Extrapolating from the recovery process after chemotherapy suggests that new growing follicles containing oocytes nourished by newly formed granulosa cells are expected 6 months after active or passive exposure to tobacco smoke (and other toxins) is stopped. Therefore, women wishing to conceive should discontinue all exposure to toxins, including tobacco smoke, for 6 months. Clinicians should particularly recommend postponing reproductive treatments such as ART until the patient's status would promote an ideal outcome. The short recovery process postulated in the olive tree hypothesis, based on postchemotherapy AMH data, should encourage women to optimize their health before such complex treatment. The olive tree metaphor is meant to emphasize and help promote the concept that the reproductive damage done by environmental toxins such as tobacco smoke is not definitive. Although the olive tree hypothesis aims to promote the value of discontinuing exposure to gonadotoxic substances before

conceiving, it does not intend to minimize the general harm of these toxics.

The olive tree hypothesis, for all its appeal, should be submitted to the scrutiny of the medical community for confirmation and so that its possible limitations are better defined. Because the size of the task exceeds the capabilities of a single clinical and investigative group, we felt that the hypothesis needed to be shared.

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