Reproductive aging results in a reconfigured ovarian antioxidant defense profile in rats

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Objective: To test our hypothesis that reproductive aging changes the ovarian oxidative stress defense profile, in response to prostaglandin F2α (PGF2α) during corpus luteum regression, because how a cell or an organ handles reactive oxygen intermediates may be dependent on the biological age of the organism.
Design: Animal experimentation using rat model of corpus luteum regression.
Setting: University reproductive biology laboratory.
Animal(s): Control (26-day-old) and 8- to 9-month-old (reproductive aging) rats.
Intervention(s): Corpus luteum formation was induced in control and 8- to 9-month-old (reproductive aging) rats with pregnant mare serum gonadotropin followed by human chorionic gonadotropin. Regression was then initiated with PGF2α.
Main Outcome Measure(s): Vitamin E, glutathione reductase, glutathione peroxidase, catalase, and thiobarbituric acid–reacting substances were measured.
Result(s): Ovaries from reproductive aging rats, compared with the control (26-day-old) group, had elevated vitamin E levels at 0, 2, and 24 hours after PGF2α. At 2 and 24 hours after PGF2α, the aging ovaries had lower glutathione reductase levels.
Conclusion(s): These data suggest that the reproductive aging ovary has a transformed oxidative stress defense profile and that this may account for some of the physiological changes found in reproductive aging. (Fertil Steril® 2005;84(Suppl 2):1109–13. ©2005 by American Society for Reproductive Medicine.)

Key Words: Oxidative stress, aging, corpus luteum, glutathione reductase, vitamin E

It is hypothesized that the process of aging is associated with alterations in the way that the organism handles the hydrogen peroxide that is generated in response to physiological processes. How a cell or an organ handles reactive oxygen intermediates may be dependent on the biological age of the organism. The ovarian corpus luteum is an essential, transient endocrine gland that produces the progesterone required for pregnancy (1). Measurement of oxidative stress defenses, that is, vitamin E, glutathione peroxidase, glutathione reductase, and catalase, may indicate how a cell or organ might respond to reactive oxygen intermediates. High levels of vitamin E are found in the corpus luteum (2), an antioxidant that scavenges free radicals and inhibits oxidation, which results in the suppression of lipoperoxides (2, 3). Glutathione peroxidase catalyzes the reduction of various organic hydroperoxides, as well as hydrogen peroxide, to water, and glutathione reductase catalyzes the reduction of oxidized glutathione to reduced glutathione (2). Lower levels of glutathione are found in regression, indicating an increase in oxidative stress (4–6). Catalase is involved in protecting cells from the toxic effects of hydrogen peroxide by catalyzing its decomposition into oxygen and water.

In the corpus luteum, reactive oxygen species exert luteolytic effects, affect progesterone levels, and may damage the luteal cell membrane (7). Prostaglandin F2α (PGF2α) may increase levels of reactive oxygen species (8). Prostaglandin F2α produces reactive oxygen species and induces apoptosis in luteal cells, indicating that reactive oxygen species may induce apoptotic death in luteolysis (9). These studies support the vital roles of antioxidant defenses in the normal function of the ovarian life cycle.

The fecundity of mammals declines with advancing maternal age. Carbone et al. (10) found that the enzymatic activity levels of catalase and glutathione transferases are reduced in follicular fluid from older women undergoing IVF, but the activity level of superoxide dismutase is increased. At middle age in the rat (8–9 months), there is decreased frequency of pregnancy, a reduction in litter size, increased developmental anomalies, and embryonic death (11–14). The ovary may be the primary site of reproductive aging and may be responsible for the decline of reproductive processes (15). This reproductive aging results in declines in regular estrous cyclicity and fertility (16).

An altered antioxidant status in reproductive aging ultimately may be a contributor to functional disturbances in steroidogenesis and apoptosis during corpus luteum regres-

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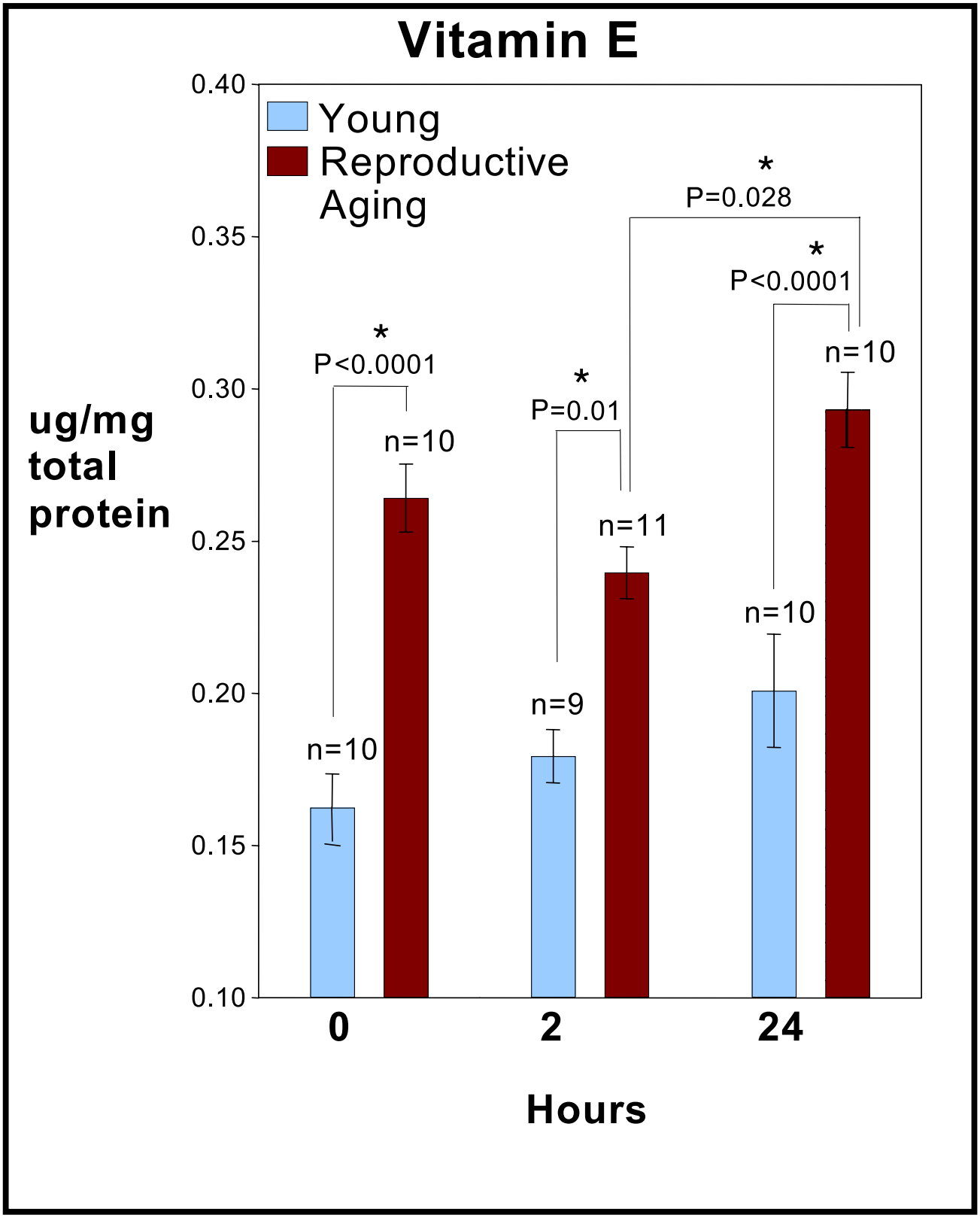
FIGURE 1

Vitamin E levels of control and reproductive aging rat ovaries. The baseline levels are indicated at 0 hours, followed by the levels of these markers at 2 and 24 hours after PGF2α injection. Groups are indicated as follows: *shaded bars*, young; *solid bars*, reproductive aging. *Statistically significant difference between paired groups.



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