Aging and the environment affect gamete and embryo potential: can we intervene?

David R. Meldrum, M.D.,[a] Robert F. Casper, M.D.,[b,c,d] Antonio Diez-Juan, Ph.D.,[e] Carlos Simon, M.D., Ph.D.,[f,g] Alice D. Domar, Ph.D.,[h] and Rene Frydman, M.D., Ph.D.[i]

[a] Reproductive Partners San Diego and Division of Reproductive Endocrinology and Infertility, University of California, San Diego, California; [b] Division of Reproductive Sciences, University of Toronto, Toronto, Ontario, Canada; [c] Lunenfeld-Tanenbaum Research Institute, Mount Sinai Hospital, Toronto, Ontario, Canada; [d] TCART Fertility Partners, Toronto, Ontario, Canada; [e] Igenomix, Parc Cientific Valencia University, Valencia, Spain; [f] Fundación Instituto Valenciano de Infertilidad, Department of Obstetrics and Gynecology, School of Medicine, Valencia University, Valencia, Spain; [g] Instituto Universitario IVI/INCLIVA, Valencia, Spain; [h] Domar Center for Mind/Body Health, Boston IVF, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts; and [i] Department of Obstetrics and Gynecology, Hopital Foch de Suresnes, Suresnes, France

Optimal maturation of the oocyte depends on its environment and determines embryo competence, because the embryonic genome is not active until the cleavage stage and new mitochondria are not produced until blastulation. Adverse environmental factors include aging, andropause, oxidative stress, obesity, smoking, alcohol, and psychologic stress, whereas androgen supplementation, a prudent diet, exercise, nutritional supplements, and psychologic interventions have beneficial effects. Mitochondrial function and energy production deteriorate with age, adversely affecting ovarian reserve, chromosome segregation, and embryo competence. In aging mice, the mitochondrial cofactor coenzyme Q10 reverses most of these changes. Early human experience has been encouraging, although only a small study using a shorter duration of intervention compared with the murine model has been carried out. Mitochondrial metabolic stress can result in an abnormal compensatory increase in mitochondrial DNA, which can be assessed in biopsied blastomeres of trophectoderm as a predictive biomarker of implantation failure. Psychologic stress may reduce oocyte competence by shifting blood flow away from the ovary as part of the classic "fight or flight" physiologic response, and methods to reduce stress or the body's reaction to stress improve pregnancy success. Enhancing oocyte competence is a key intervention that promises to reduce the number of euploid embryos failing to produce viable deliveries. (Fertil Steril® 2016;105:548–59. ©2016 by American Society for Reproductive Medicine.)

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The oocyte is supported and nourished by intimate cross-talk with its surrounding granulosa cells (GCs) and by endocrine and paracrine interactions with its environment (1, 2). During controlled ovarian hyperstimulation (COH), gonadotropin stimulation results in growth of multiple follicles yielding oocytes. However, only 7% result in a term delivery (3), and of oocytes that fertilize and are found by means of comprehensive chromosome screening (CCS) to be euploid, still only approximately two-thirds result in a viable birth. During maturation, the oocyte undergoes a tremendous increase in the quantity and quality of the cytoplasm referred to as cytoplasmic maturation, which determines the capability of the resulting embryo to achieve a viable pregnancy. Oocyte mitochondria are a critical example of cytoplasmic maturation, described below in detail. Gathering evidence indicates that the maternal environment, including changes brought about by aging, have a major impact on the quality of cytoplasmic maturation and ultimate success of in vitro fertilization (IVF).

The sperm loses most of its antioxidant defenses during maturation by shedding its cytoplasm to facilitate motility, making it extremely sensitive

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Reprint requests: David R. Meldrum, M.D., Reproductive Partners San Diego, 9850 Genesee Ave, Ste 800, La Jolla, CA 90237 (E-mail: drmeldrum@gmail.com).

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to oxidative stress (OS). OS primarily affects the sperm during passage through the collecting system; exposure to OS is therefore worsened by infrequent ejaculation and minimized by retrieval of sperm directly from the testicle. Sperm membranes have a high concentration of omega-3 fatty acids (FAs), which are highly sensitive to oxidation.

AGING

Aging affects the number of oocytes that can be retrieved with the use of COH. However, the modest decline of term delivery per euploid embryo with increasing age (4) indicates that either aging of cytoplasmic quality is of minor importance or, more likely, cytoplasmic quality influences oocyte competence both by affecting chromosome redistribution as well as by other mechanisms (also, available CCS data, particularly in older women, is skewed toward a select group of more normal responders who may have inherently better cytoplasmic quality). An example illustrating these parallel effects is that treatment of the aging mouse with coenzyme Q10 (CoQ10, an essential component of the electron transport chain involved in energy generation), described in detail below, affects the quality of the oocyte spindle as well as energy available for cell divisions and other functions (5). Factors impairing cytoplasmic maturation may also reduce follicle growth. In the aging mouse, the decline in ovarian follicles and litter size with age were also prevented by CoQ10 administration, and interference with CoQ10 production caused decreased ovarian reserve (5). Follicle depletion therefore may also be influenced by decreasing cytoplasmic quality through communication with the GCs or by the general decline of CoQ10 and mitochondrial energy production with aging (5).

Another example of parallel defects of ovarian reserve and cytoplasmic quality is the impact of decreased androgen levels exposed to the follicles with advancing age (6). With increasing age, serum levels of the adrenal androgen DHEA and circulating T and free T (7) decrease. Basal T levels correlate with reduced ovarian response when controlled for age (8) (unfortunately, usual T assays are not accurate in that low range, so measuring serum T for this purpose is generally not practical). One-half of the intrafollicular T results from conversion from DHEA. T increases antral follicles, increases GC proliferation, and decreases GC apoptosis, which in turn would be expected to favorably affect oocyte competence (9). Randomized studies have shown improved stimulation with administration of oral DHEA (10), T gel (11), and T patch (12), resulting in higher circulating T levels that are modest with the use of DHEA, moderate with the use of T gel, and rising toward the low male range with the use of T patch (systemic administration of T would cause relatively small local increases of ovarian T). Consequently, it appears to require at least 2–3 months of oral DHEA, a minimum of 3 weeks with the use of T gel, and at least 5 days with the use of T patch to increase the ovarian response to stimulation. Therefore, preparation for stimulation in such patients must be planned well in advance of the start of gonadotropins. Poor responders have been the predominant group where androgen treatment has been applied (9–11), although improved oocyte competence may also occur.

Oxidative stress increases with age (13), owing in part to lowered endogenous antioxidant defenses generating tissue glutathione levels (14). OS is associated with increased GC apoptosis, which is in turn associated with reduced embryo quality and successful birth (2, 15). OS is also implicated in shortening of telomeres, most likely as a long-term process while oocytes remain in limbo during this era of delayed childbirth, and shortened telomeres contribute to aneuploidy (16).

Aging has prominent effects on sperm DNA fragmentation (17), which is correlated with OS (18), and may account for the adverse effects of male age on IVF success. The cytoplasm of younger oocytes may correct DNA fragmentation, explaining the lesser impact with the use of egg donation or a younger female partner (19). Different assays (20) or assay conditions (21) may vary in their detection of sperm DNA fragmentation; therefore, increased intake of antioxidants should be recommended for all men over the age of 40 years, regardless of testing.

OBESITY

Obesity is a state of high OS (22), including as documented in follicular fluid (23), and is associated with decreased clinical pregnancy, with the odds ratio for failure increasing from 1.26 for body mass index (BMI) 35–39.9 kg/m^2 to 1.53 for BMI $>$50 kg/m^2. The odds ratio of failing to achieve a viable birth was reduced even more significantly, varying from 1.14 with BMI 25–29.9 kg/m^2 to 2.3 with BMI $>$50 kg/m^2 (24). The effect of obesity in recipients of egg donation in some studies suggests effects on the endometrium as well as the oocyte (25). The incidence of IVF live birth is reduced even more when obese women have twins (26) or are black, Hispanic, or Asian. Strikingly, the significant adjusted odds ratios for failure to achieve live birth comparing nonwhite and white women were 1.24 for normal weight, 1.52 for overweight, and 1.86 for obese, the latter two being significant at $P<.0001$ (27). Obesity also increases miscarriage (28). Most importantly, a BMI $>$35 kg/m^2 more than doubles deliveries at $<$32 weeks, and with twins the risk of deliveries at $<$28 weeks triples (26). Authors cite multiple possible mechanisms, including systemic inflammation, as possible effectors of these adverse outcomes. These data emphasize the need to focus maximal attention on obesity in ethnic minorities to improve IVF outcomes, with particular emphasis on elective single-embryo transfer.

All obese women, particularly with a BMI $>$35 kg/m^2, should be advised of the above risks and encouraged to lose weight before starting IVF, especially women aged $\leq$38 years. Increased antioxidant intake is logical, given their systemic and ovarian OS and inflammation. The antiinflammatory effects of omega-3 FA supplements may also be beneficial (29). An exercise program may be the most promising modality. In a case-control study, exercise (including at a vigorous level) was associated with a more than threefold increase of the clinical pregnancy rate in obese women having IVF (30).

SMOKING

Smoking by the female partner reduces the IVF pregnancy rate by about one-half (31) and increases miscarriage by almost one-fourth (32). Adverse effects are also observed