David B. Seifer, MD is a Professor of Obstetrics & Gynecology at The Geisel School of Medicine at Dartmouth and serves as the Director of the Division of Reproductive Endocrinology & Infertility at Dartmouth-Hitchcock Medical Center in Lebanon, New Hampshire. Dr. Seifer received his medical degree from the University of Illinois (Chicago) Medical School and completed his residency in Obstetrics and Gynecology at Stanford University Medical Center. He subsequently completed a fellowship in Reproductive Endocrinology and Infertility at the Yale University School of Medicine. Dr. Seifer is a consultant for the Food and Drug Administration and has published over 140 medical studies in peer-reviewed journals. He has served as a member of the National Institutes of Health (NIH) study sections and presently Co-Editor-in-Chief of *Reproductive Biology and Endocrinology*. His sustained translational research has focused upon the biology of ovarian function, particularly the aging ovary. This research has resulted in a better understanding of normal and abnormal follicular development during ART and in identifying novel human ovarian growth factors (ie. neurotrophins, inhibin B and AMH) which inform the clinical practice of reproductive medicine**.** His clinical research has focused upon health care disparities among women with infertility and the role of vitamin D in female reproductive health.

Physiology and clinical utility of AMH in follicle recruitment and growth

AMH plays a fundamental role in folliculogenesis by regulating both primordial follicular recruitment and cyclic selection of the antral follicles. It is produced by both cumulus and mural granulosa cells of small and large preantral and small antral follicles. Thus, folliculogenesis could be viewed in two stages, early and late. Early folliculogenesis is when in the preantral stage the follicle is functionally an AMH secreting and paracrine signaling unit. Late folliculogenesis begins after gonadotropin receptor expression and responsiveness converts the follicle into an estradiol secreting endocrine organ using androgens as substrate. AMH is absent in larger antral stage follicles measuring greater than 6–8 mm in diameter and thus, is not

detected in granulosa cells of preovulatory follicles. This decrease and eventual absence of AMH production in follicles destined to become larger antral follicles may represent a critical mechanism by which a few individual follicles compete to become the single dominant preovulatory follicle in late folliculogenesis. Therefore, AMH acts as a leading negative paracrine regulator by inhibiting recruitment of primary follicles from the primordial pool, preventing selection of follicles by FSH as well as inhibiting aromatase. It is due to the timing of its expression during normal early folliculogenesis that AMH is relatively stable throughout the menstrual cycle in normo-ovulatory women and is relatively and clinically independent of gonadotropins circulating at physiologic levels. Furthermore, serum AMH levels are essentially unaffected by short term use of GnRH agonists or use of oral contraceptives for less than 2 months. As normal values for AMH have been demonstrated to be age-specific they are most informative in the context of chronological age. AMH levels rise in young women beginning in adolescence and peak at around 25 years of age, then gradually declining till reaching undetectable levels a few years prior to menopause. The rate of decline of AMH is most likely impacted by both genetic and environmental influences (ie. obesity, vitamin D deficiency, smoking, chemotherapy).

Through its role in regulation of normal folliculogenesis AMH has emerged as a useful biomarker of reproductive aging of the ovary. It is well established that AMH is an indirect marker of the primordial follicular pool. AMH has evolved to become the most clinically informative biochemical marker of the ovary and its validity as an ovarian reserve biomarker is supported by four lines of compelling evidence. 1. AMH correlates strongly with the primordial follicle pool 2. AMH has a strong inverse relationship with chronologic age 3. AMH reliably

predicts ovarian response in ART and 4. AMH is predictive of the onset of menopause. The ability of AMH in conjunction with age to predict the timing of menopause may be increasingly useful for individualized counselling of women regarding their reproductive lifespan and family planning. The accuracy of AMH in predicting ovarian response to hyperstimulation in ART has lead to AMH-based counselling and individualization of ART stimulation protocols. AMH testing in young cancer patients both pre- and post-treatment has become a useful tool in the assessment of iatrogenic damage to the ovarian follicular reserve inflicted by chemotherapeutic agents or pelvic irradiation and may assist in counselling for strategies regarding fertility preservation. In addition, AMH has been shown to be useful in the diagnosis and detection of recurrence of ovarian granulosa cell tumors. Recent availability of automated platforms have offered increased speed, sensitivity and precision and have led to wide spread use of AMH throughout Europe and Asia thus expanding its clinical utility in determining ovarian reserve, avoiding OHSS in ovulation induction, predicting the onset of menopause and detecting polycystic ovarian disease.