Decreasing rates of ovulation, hormonal changes, and increasing bone loss pre-date menopause by several years. Data suggest that, in addition to estradiol, progesterone may play a significant role in the interrelationship between the ovaries and the skeleton in women. Indeed, the differentiation of human osteoblasts from perimenopausal women has been shown to be dose-dependent on progesterone at physiological concentrations. Data from a pilot study in perimenopausal women also suggested that higher progesterone levels, as seen in the luteal phase of ovulatory cycles, may be associated with more bone formation and with slightly less bone resorption than anovulatory cycles in which progesterone levels are low (< 5.8 ng/ml). These data led to the initiation of a large, prospective, 2-year observational study in perimenopausal women (the PEKNO study). Interim data from the PEKNO study indicate that a decrease in ovulation correlated with an increase in the loss of bone mineral density (BMD). A meta-analysis estimated a BMD increase of 0.5% per year in women with normal ovulation, and a BMD decrease of 0.7% per year in young women with ovulatory disturbances (anovulation or short luteal phase). A meta-analysis in postmenopausal women demonstrated a 1.3% increase per year in BMD when receiving hormone replacement therapy with unopposed estrogens, and a further 0.4% increase in BMD in women receiving
estrogens plus progestogens. The role of progesterone in bone metabolism in perimenopausal women who are estrogen-replete requires further study.

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