## Endocrine Disorders in Adolescent and Young Female Athletes: Impact on Growth, Menstrual Cycles, and Bone Mass Acquisition **R e v i e w**

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**Context:** Puberty is a crucial period of dramatic hormonal changes, accelerated growth, attainment of reproductive capacity, and acquisition of peak bone mass. Participation in recreational physical activity is widely acknowledged to provide significant health benefits in this period. Conversely, intense training imposes several constraints, such as training stress and maintenance of very low body fat to maximize performance. Adolescent female athletes are therefor eat risk of overtraining and/or poor dietary intake, which may have several consequences for endocrine function. The “adaptive” changes in the hypothalamic-pituitary-gonadal, -adrenal,and somatotropic axes and the secretory role of the adipose tissue are reviewed, as are their effects on growth, menstrual cycles, and bone mass acquisition.
**Design:**Asystematic searchonMedline between 1990 and 2013 was conducted using the following terms: “intense training,” “physical activity,” or “exercise” combined with “hormone,” “endocrine,” and “girls,” “women,” or “elite female athletes.” All articles reporting on the endocrine changes related to intense training and their potential implications for growth, menstrual cycles, and bone mass acquisition were considered.
**Results and Conclusion:** Young female athletes present a high prevalence of menstrual disorders, including delayed menarche, oligomenorrhea, and amenorrhea, characterized by a high degree of variability according to the type of sport. Exercise-related reproductive dysfunction may have consequences for growth velocity and peak bone mass acquisition. Recent findings highlight the endocrine role of adipose tissue and energy balance in the regulation of homeostasis and reproductive function. A better understanding of the mechanisms whereby intense training affects the endocrine system may orient research to develop innovative strategies (ie, based on nutritional or pharmacological approaches and individualized modalities of training and competition) to improve the medical care of these adolescentsandprotect their reproductive function. **(*J Clin Endocrino lMetab* 99: 4037–4050, 2014)**

## Serum Androgen Levels in Elite Female Athletes

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**Objective:** Prior to the implementation of the blood steroidal module of the Athlete Biological Passport, we measured the serum androgen levels among a large population of high-level female athletes as well as the prevalence of biochemical hyperandrogenism and some disorders of sex development (DSD).
**Methods and Results:** In 849 elite female athletes, serum T, dehydroepiandrosterone sulphate, androstenedione, SHBG, and gonadotrophins were measured by liquid chromatography-mass spectrometry high resolution or immunoassay. Free T was calculated. The sampling hour, age, and type of athletic event only had a small influence on T concentration, whereas ethnicity had not. Among the 85.5% that did not use oral contraceptives, 168 of 717 athletes were oligo- or amenorrhoic. The oral contraceptive users showed the lowest serum androgen and gonadotrophin and the highest SHBG concentrations. After having removed five doped athletes and five DSD women from our population, median T and free T values were close to those reported in sedentary young women. The 99th percentile for T concentration was calculated at 3.08 nmol/L, which is below the 10 nmol/L threshold used for competition eligibility of hyperandrogenic women with normal androgen sensitivity. Prevalence of hyperandrogenic 46 XY DSD in our athletic population is approximately 7 per 1000, which is 140 times higher than expected in the general population.
**Conclusion:** This is the first study to establish normative serum androgens values in elite female athletes, while taking into account the possible influence of menstrual status, oral contraceptive use, type of athletic event, and ethnicity. These findings should help to develop the blood steroidal module of the Athlete Biological Passport and to refine more evidence-

based fair policies and recommendations concerning hyperandrogenism in female athletes. **(*J Clin Endocrinol Metab* 99:4328–4335, 2014)**

## Luteal phase dynamics of follicle-stimulating and luteinizing hormones in obese and normal weight women

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**Summary** Objectives Female obesity is a state of relative hypogonadotrophic hypogonadism. The aim of this study is to examine gonadotrophin secretion and response to gonadotrophin-releasing hormone (GnRH) in the luteal phase of the menstrual cycle and to investigate the pharmacodynamics and pharmacokinetics of endogenous and exogenous luteinizing hormone (LH) in obese women.
**Design** Participants underwent a luteal phase frequent blood sampling study. Endogenous LH pulsatility was observed, gonadotrophin- releasing hormone (GnRH) was given in two weight based doses, and GnRH antagonist was administered followed by recombinant LH. Patients Regularly menstruating obese (n = 10) and normal weight (n = 10) women.
**Measurements** Endogenous hypothalamic-pituitary function (as measured by LH pulsatility), pituitary sensitivity (GnRH induced LH secretion), pharmacodynamics of endogenous LH and pharmacokinetics of exogenous LH were compared between the obese and normal weight groups.
**Results** There were no statistically significant differences in endogenous LH pulsatility or pituitary responses to two weight based doses of GnRH between the obese and normal weight women. There were no differences in the pharmacodynamics of endogenous LH or the pharmacokinetics of exogenous LH between the groups. FSH dynamics did not differ between the groups throughout the study.
**Conclusions** The relative hypogonadotrophic hypogonadism of obesity cannot be explained by differences in LH and FSH luteal phase dynamics or differences in endogenous LH pharmacodynamics or exogenous LH pharmacokinetics. **Clinical Endocrinology (2014) 81, 418–425**

## Increasing LH Pulsatility in Women With Hypothalamic Amenorrhoea Using Intravenous Infusion of Kisspeptin-54

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**Background:** Hypothalamic amenorrhea (HA) is the one of the most common causes of period loss in women of reproductive age and is associated with deficient LH pulsatility. High-dose kisspeptin- 54 acutely stimulates LH secretion in women with HA, but chronic administration causes desensitization. GnRH has paradoxical effects on reproductive activity; we therefore hypothesized that a dose-dependent therapeutic window exists within which kisspeptin treatment restores the GnRH/LH pulsatility in women with HA.
**Aim:** The aim of the study was to determine whether constant iv infusion of kisspeptin-54 temporarily increases pulsatile LH secretion in women with HA.
**Methods:** Five patients with HA each underwent six assessments of LH pulsatility. Single-blinded continuous iv infusion of vehicle or kisspeptin-54 (0.01, 0.03, 0.10, 0.30, or 1.00 nmol/kg/h) was administered. The LH pulses were detected using blinded deconvolution.
**Results:** Kisspeptin increased LH pulsatility in all patients with HA, with peak responses observed at different doses in each patient.Themean peak number of pulses during infusion of kisspeptin-54 was3-fold higher when compared with vehicle (number of LH pulses per 8h: 1.6 ± 0.4, vehicle; 5.0 ± 0.5, kisspeptin-54, $P$ <.01 vs vehicle). The mean peak LH pulse secretory mass during kisspeptin-54 was 6-fold higher when compared with vehicle (LH pulse secretory mass in international units per liter: 3.92 ± 2.31, vehicle; 23.44 ± 12.59, kisspeptin-54; $P$ <.05 vs vehicle).
**Conclusions:** Kisspeptin-54 infusion temporarily increases LH pulsatility in women with HA. Furthermore, we have determined the dose range within which kisspeptin-54 treatment increases basal and pulsatile LH secretion in women with HA. This work provides a basis for studying the potential of kisspeptin-based therapies to treat women with HA. **(*J Clin Endocrinol Metab* 99:E953–E961, 2014)**

## Follicle number, not assessments of the ovarian stroma, represents the best ultrasonographic marker of polycystic ovary syndrome

Jacob P. Christ, Amy D. Willis, Eric D. Brooks, Heidi Vanden Brink, Brittany Y. Jarrett, Roger A. Pierson, Donna R. Chizen, Marla E. Lujan.

**Objective:** To compare the diagnostic potential of ultrasonographic markers of ovarian morphology, used alone or in combination, to predict polycystic ovary syndrome (PCOS).
**Design:** A diagnostic test study using cross-sectional data collected from 2006–2011.
Setting: Academic hospital and clinical research unit.
**Patient(s):** Eighty-two women with PCOS and 60 healthy female volunteers.
**Main Outcome Measure(s):** Follicle number per ovary (FNPO), ovarian volume (OV), follicle number per single cross-section (FNPS), follicle distribution pattern, stromal area, ovarian area, stromal-to-ovarian area ratio (S:A), and stromal index (SI).
**Result(s):** Follicle number per ovary best predicted PCOS ($R^2$ = 67%) with 85% sensitivity and 98% specificity, followed by OV ($R^2$ =44%), and FNPS ($R^2$ =36%). Neither S:A nor SI had predictive power for PCOS. In combination, FNPO+S:A and FNPO+SI most significantly predicted PCOS ($R^2$ =74% vs. 73%, respectively). The diagnostic potentials of OV and FNPS were substantially improved when used in combination (OV+FNPO, $R^2$ = 55%).
**Conclusion(s):** As a single metric, FNPO best predicted PCOS. Although the addition of S:A or SI improved the predictive power of FNPO, gains were marginal, suggesting limited use in clinical practice. When image quality precludes a reliable estimation of FNPO, measurements of OV+FNPS provide the next closest level of diagnostic potential. **Fertil Steril 14;101:280–7. 2014**

## Endocrine disruptors and human reproductive failure: the in vitro effect of phthalates on human luteal cells

Federica Romani, Anna Tropea, Elisa Scarinci, Alex Federico, Cinzia Dello Russo, Lucia Lisi, Stefania Catino, Antonio Lanzone, and Rosanna Apa.

**Objective:** To evaluate the influence of phthalates on human luteal cell function.
**Design:** Laboratory study.
**Setting:** University hospital.
**Patient(s):** Twenty-three normally menstruating patients in the midluteal phase.
**Intervention(s):** Human luteal cells isolated from corpora lutea for primary cultures.
**Main Outcome Measure(s):** Progesterone (P4) and prostaglandin release assayed by enzyme immunoassay, vascular endothelial growth factor (VEGF) secretion by enzyme-linked immunosorbent assay (ELISA), and VEGF mRNA expression by real-time polymerase chain reaction.
**Result(s):** We investigated the effect of di(2-ethylhexyl)phthalate (DEHP), di-n-butyl phthalate (DBP), and butyl benzyl phthalate (BBP) on basal and hCG-induced progesterone (P4) release, as well as DEHP effect on the balance between prostaglandin (PG) E2, vascular endothelial growth factor (VEGF)-luteotrophic factors, and the luteolitic PGF2a in isolated human steroidogenc cells. Phthalates influence on VEGF expression has been also evaluated. DEHP, DBP, and BBP were able to reduce both basal and hCG-stimulated P4 as well as PGE2 release. PGF2a release was reduced after DEHP incubation. VEGF protein release was decreased by the incubation with the tested phthalates. VEGF mRNA expression was not affected by DEHP, DBP, and BBP. As expected, both hCG and cobalt chloride were able to induce P4 release and VEGF release and mRNA expression in human luteal cells respectively.
**Conclusion(s):** The results show the ability of phthalates to affect luteal steroidogenesis as well as the balance between luteotrophic and luteolytic factors suggesting an interference of phthalates in human luteal function. These data may contribute to clarify the classically known impaired reproductive health observed after phthalates exposure**. Fertil Steril, 2014 ;102:831–7.**

## Obesity-Induced Infertility and Hyperandrogenism Are Corrected by Deletion of the Insulin Receptor in the Ovarian Theca Cell

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Women with polycystic ovary syndrome (PCOS) exhibit elevated androgen levels, oligoanovulation, infertility, and insulin resistance in metabolic tissues.
The aims of these studies were to determine the role of insulin signaling in the development and function of ovarian theca cells and the pathophysiologic effects of hyperinsulinism on ovarian function in obesity. We disrupted the insulin receptor (IR) gene specifically in the theca-interstitial (TI) cells of the ovaries (Cyp17IRKO). No changes in reproductive development or function were observed in lean Cyp17IRKO female mice, suggesting that insulin signaling in TI cell is not essential for reproduction.
**However**, when females were fed a high-fat diet,diet-induced obesity (DIO) wild-type (DIO-WT) mice were infertile and experienced increased circulating testosterone levels, whereas DIO-Cyp17IRKO mice exhibited improved fertility and testosterone levels
comparable to those found in lean mice. The levels of phosphorylated IRS1 and CYP17 protein were higher in the ovary of DIO-WT compared with DIO-Cyp17IRKO or lean mice. Ex vivo studies using a whole ovary culture model demonstrated that insulin acts independently or additively with human chorionic gonadotropin to enhance androstenedione secretion. These studies reveal the causal pathway linking hyperinsulinism with ovarian hyperandrogenism and the infertility of obesity. **Diabetes 2014;63:1270–1282**

## Prolactin is associated with metabolic risk and cortisol in 1007 women with polycystic ovary syndrome

Dorte Glintborg, Magda Altinok, Hanne Mumm, Kristian Buch, Pernille Ravn, and Marianne Andersen
**study question:** Is there an association between prolactin and markers of metabolic risk in polycystic ovary syndrome (PCOS)?
**summary answer:** Low serum prolactin was a metabolic risk marker in PCOS.
**what is known already:** Prolactin is routinely measured to exclude endocrine diseases in PCOS. Recent studies have suggested that prolactin can be used as a marker for metabolic and cardiovascular risk.
**study design, size, duration:** Retrospective cross-sectional study in an academic tertiary-care medical center. Data were collected during 1997–2012. Premenopausal women (n Ό 1007) with hirsutism and/or PCOS and 116 healthy, age-matched controls were included. Prolactin levels were measured in blood samples taken in the morning after a minimum of 2 h awakening time. Macroprolactinemia was excluded by the precipitation of serum with polyethylene glycol in patients with increased prolactin levels.
**participants/materials, setting, methods:** Serum prolactin levels were measured along with a clinical evaluation (Ferriman– Gallwey score, BMI, waist circumference, blood pressure) plus hormone analyses (sex hormones, fasting lipids, insulin, glucose), transvaginal ultrasound, and oral glucose tolerance (n = 234) and adrenocorticotrophic hormone tests (n =201). All patients had prolactin levels below the upper reference limit (23 μg/l).
**main results and the role of chance:** Prolactin levels were significantly lower in patients versus controls; median (quartiles) prolactin levels 7 (5–10) versus 9 (7–13) μg/l ($P < 0.001$). In the patient population prolactin levels were inversely associated with age, smoking status, waist circumference, total cholesterol, triglyceride and low-density lipoprotein (LDL) and positively associated with high-density lipoprotein, estradiol, total testosterone, dehydroepiandrosterone sulfate, 17- hydroxyprogesterone and cortisol levels. In multiple regression analyses, prolactin was inversely associated with LDL and positively associated with estradiol, 17-hydroxyprogesterone and cortisol after correcting for age, BMI and smoking status in patients with PCOS.
**limitations, reasons for caution:** The study design was cross-sectional and prospective studies are needed to further determine the impact of prolactin levels on cardiovascular outcomes. Patients included in the study were relatively lean and only 20 had diabetes, which could have affected our findings. In addition, the collection of blood samples when estrogen levels were low (follicular phase) could be related to the lower levels of prolactin. Furthermore, as prolactin is secreted in a pulsatile manner, several measures of prolactin may be needed to further investigate associations between prolactin and metabolic risk.
**wider implications of the findings:** Our findings of inverse associations between prolactin levels and metabolic risk markers are supported by studies in populations of women without

PCOS. The association between prolactin and adrenal activity should be evaluated in future studies. **Human Reproduction, Vol.29, No.8 pp. 1773–1779, 2014**

## Androgen Therapy in Women: A Reappraisal: An Endocrine Society Clinical Practice Guideline

Margaret E. Wierman, Wiebke Arlt, Rosemary Basson, Susan R. Davis, Karen K. Miller, Mohammad H. Murad, William Rosner, and Nanette Santoro

**Objective:** To update practice guidelines for the therapeutic use of androgens in women.
**Participants:** A Task Force appointed by the Endocrine Society, American Congress of Obestricians and Gynecologists (ACOG), American Society for Reproductive Medicine (ASRM), European Society of Endocrinology (ESE), and International Menopause Society (IMS) consisting of six experts, a methodologist, and a medical writer.
**Evidence:** The Task Force commissioned two systematic reviews of published data and considered several other existing meta-analyses and trials. The GRADE methodology was used; the strength of a recommendation is indicated by a number "1" (strong recommendation, we recommend) or "2" (weak recommendation, we suggest).
**Consensus Process:** Multiple e-mail communications and conference calls determined consensus. Committees of the Endocrine Society, ASRM, ACOG, ESE, and IMS reviewed and commented on the drafts of the guidelines.
**Conclusions: We continue to recommend against** making a diagnosis of androgen deficiency syndrome in healthy women because there is a lack of a well-defined syndrome, and data correlating androgen levels with specific signs or symptoms are unavailable.
**We recommend against** the general use of T for the following indications: infertility; sexual dysfunction other than hypoactive sexual desire disorder; cognitive, cardiovascular, metabolic, or bone health; or general well-being.
**We recommend against** the routine use of dehydroepiandrosterone due to limited data concerning its effectiveness and safety in normal women or those with adrenal insufficiency.
**We recommend against** the routine prescription of Tor dehydroepiandrosterone for the treatment of women with low androgen levels due to hypopituitarism, adrenal insufficiency, surgical menopause, pharmacological glucocorticoid administration, or other conditions associated with low androgen levels because there are limited data supporting improvement in signs and symptoms with therapy and no long-term studies of risk.
**Evidence supports** the short-term efficacy and safety of high physiological doses of T treatment of postmenopausal women with sexual dysfunction due to hypoactive sexual desire disorder.
**Importantly,** endogenous T levels did not predict response to therapy.
**At present**, physiological T preparations for use in women are not available in many countries including the United States, and long-term safety data are lacking.
**We recommend** that any woman receiving T therapy be monitored for signs and symptoms of androgen excess. We outline areas for future research. Ongoing improvement in androgen assays will allow a redefinition of normal ranges across the lifespan; this may help to clarify the impact of varying concentrations of plasma androgens on the biology, physiology, and psychology in women and lead to indications for therapeutic interventions. **(*J Clin Endocrinol Metab* 99: 3489–3510, 2014)**

## Hyperandrogenic Oligomenorrhea and Metabolic Risks Across Menopausal Transition

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**Context:** Although there is evidence of metabolic risks in young women with irregular menses and androgen excess, persistence of risks after menopause is unclear.
**Objective:** The objective of the study was to determine the impact of menopause on the cardiometabolic profile in women with high androgens and a history of menstrual irregularity.
**Methods:** Study of Women's Health Across the Nation is a longitudinal cohort study. Data from 1929 women without metabolic syndrome (MetS) at baseline were analyzed for incidence of MetS, self-reported stroke, and myocardial infarction. Cox hazard ratios (HRs)

were estimated, adjusting for age, ethnicity, body mass, smoking, menopausal status, and study site.
**Results:** Among MetS-free women at baseline, 497 new cases were identified during 20 249 woman-years of follow-up over 12 years. Women with hyperandrogenemia (HA) and oligomenorrhea (Oligo) developed incident cases of MetS at a comparable rate compared with their counterparts: umenorrheic, normoandrogenic women [HR 1.4 (0.9 –2.2)], oligomenorrheic, normoandrogenic women [HR 1.3 (0.8 –2.2)], and eumenorrheic hyperandrogenic women [HR 1.2 (0.7–1.8)]. Smoking and obesity were the strongest predictors of incident MetS. There was no significant difference in incidence of self-reported stroke or MI by HA/Oligo status.
**Conclusions:** Longitudinal evidence suggests that a history of androgen excess and menstrual irregularity is not associated with worsening of metabolic health after menopause. Our findings challenge the notion that a history of concurrent HA and Oligo reflects ongoing cardiometabolic risk in postmenopausal women. **(*J Clin Endocrinol Metab* 99: 2120–2127, 2014)**

## Leptin-dependent neuronal NO signaling in the preoptic hypothalamus facilitates reproduction

Nicole Bellefontaine, Konstantina Chachlaki,Jyoti Parkash, Charlotte Vanacker, William Colledge, Xavier d'Anglemont de Tassigny,John Garthwaite, Sebastien G. Bouret,Vincent Prevot

The transition to puberty and adult fertility both require a minimum level of energy availability. The adipocyte-derived hormone leptin signals the long-term status of peripheral energy stores and serves as a key metabolic messenger to the neuroendocrine reproductive axis. Humans and mice lacking leptin or its receptor fail to complete puberty and are infertile. Restoration of leptin levels in these individuals promotes sexual maturation, which requires the pulsatile, coordinated delivery of gonadotropin-releasing hormone to the pituitary and the resulting surge of luteinizing hormone (LH); however, the neural circuits that control the leptin-mediated induction of the reproductive axis are not fully understood. Here, we found that leptin coordinated fertility by acting on neurons in the preoptic region of the hypothalamus and inducing the synthesis of the freely diffusible volume-based transmitter NO, through the activation of neuronal NO synthase (nNOS) in these neurons. The deletion of the gene encoding nNOS or its pharmacological inhibition in the preoptic region blunted the stimulatory action of exogenous leptin on LH secretion and prevented the restoration of fertility in leptin-deficient female mice by leptin treatment. Together, these data indicate that leptin plays a central role in regulating the hypothalamo-pituitary-gonadal axis in vivo through the activation of nNOS in neurons of the preoptic region. **The Journal of Clinical Investigation , 124 ,6 June 2014**

## Influence of oral contraceptives on anthropomorphometric, endocrine, and metabolic profiles of anovulatory polycystic ovary syndrome patients

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**Objective:** To evaluate the influence of oral contraceptive pills (OCPs) on anthromorphometric, endocrine, and metabolic parameters in women with polycystic ovary syndrome (PCOS).
**Design:** Retrospective cross-sectional cohort study for the period 1993–2011.
Setting: Tertiary university hospital.
**Patient(s):** PCOS patients, who never, ever, or at time of screening were using OCPs were included. A total of 1,297 patients, of whom 827 were white, were included. All PCOS patients diagnosed according to the Rotterdam 2003 consensus criteria were divided into three groups: current users, (n = 76; 6% of total), ever users (n = 1,018; 78%), and never users (n = 203; 16%). Ever users were subdivided based on the OCP-free interval.
Main Outcome Measure(s): Anthromorphometric (blood pressure, cycle duration) and ultrasound (follicle count, mean ovarian volume) parameters, endocrine (SHBG, testosterone, free androgen index, antimullerian hormone [AMH]) and lipid profiles.

**Result(s):** Current users and ever users were compared with never users. In current users, SHBG was increased and androgen levels decreased. Patients with an OCP-free interval of <1 year had a higher mean follicle count, higher AMH level, and increased serum androgen level compared with never users. SHBG levels remained increased until 5–10 years after cessation of OCP use.
**Conclusion(s):** OCP use causes a milder phenotypic presentation of PCOS regarding hyperandrogenism. However, it does not alter parameters associated with increased health risks. **Fertil Steril_ 2014;101:1757–65.**

## High-dose vitamin D supplementation and measures of insulin sensitivity in polycystic ovary syndrome: a randomized, controlled pilot trial

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**Objective**: To determine the effects of high-dose vitamin D on insulin sensitivity in polycystic ovary syndrome (PCOS).
**Design:** Randomized, placebo-controlled trial.
**Setting:** Academic medical center.
**Patient(s):** Twenty-eight women with PCOS.
**Intervention(s):** Vitamin D3, 12,000 IU, or placebo daily for 12 weeks.
**Main Outcome Measure(s):** The primary outcome was quantitative insulin sensitivity check index. Secondary outcomes included glucose and insulin levels during a 75-g oral glucose tolerance test and blood pressure.
**Result(s):** Twenty-two women completed the study. Compared with placebo, vitamin D significantly increased 25-hydroxyvitamin D (mean [95% confidence interval] in vitamin D group 20.1 [15.7 to 24.5] ng/mL at baseline and 65.7 [52.3 to 79.2] ng/mL at 12 weeks; placebo 22.5 [18.1 to 26.8] ng/mL at baseline and 23.8 [10.4 to 37.2] ng/mL at 12 weeks). There were no significant differences in quantitative insulin sensitivity check index and other measures of insulin sensitivity; however, we observed trends toward lower 2-hour insulin and lower 2-hour glucose. We also observed a protective effect of vitamin D on blood pressure.
**Conclusion(s):** In women with PCOS, insulin sensitivity was unchanged with high-dose vitamin D, but there was a trend toward decreased 2-hour insulin and a protective effect on blood pressure. **Fertil Steril, 2014;101:1740–6.**