Female Disorders

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Female Health in the 21st Century

Dr. Alta A. Smit

The woman of today lives in a changed environment, which plays a decisive role in the development of disease. The sociocultural environment has changed through shifting roles of women in society, who are often late parents and also support aging parents on top of their own families and work. The psychological stresses normal for our modern lives are often amplified by the dual role of career woman and housewife.

The physical environment also has a substantial influence on women’s health. Environmental toxins have been implicated as so-called endocrine disruptors and as triggers for metabolic syndrome, which in itself is closely associated with female diseases, such as polycystic ovary syndrome and infertility. Thus, the triad of chronic psychological stress, environmental toxicity, and obesity with the concomitant systemic inflammation forms the background for many female disorders. This triad often becomes a circulus vitiosus.

The eating patterns of modern women have changed, with stress eating being the order of the day. This is combined with a change in the activity of the hypothalamic-pituitary-adrenal axis. The resultant obesity increases systemic inflammation and increases the storage of fat-soluble toxins, such as the organochlorides, noted endocrine disruptors.

In this issue, Dr. Michael Greer, a gynecologist, examines the current trends in women’s health and suggests possible treatment strategies.

Dr. Olga García reports on a case of uterine fibroids, treated with bioregulatory medicine, while Dr. Gaston Orellana has two contributions, one on infertility and one on the treatment of chronic postmastectomy pain, which won him the Reckeweg Incentive Award in 2008.

As mentioned earlier, we see an increasing link between inflammation and metabolic disturbance. Dr. David Lescheid examines this phenomenon in his cutting-edge article on the link between insulin resistance and inflammation.

Dr. Robbert van Haselen continues the series on research methodologies, and Dr. Konstantin Cesnulevicius reports on a complementary research congress in Tromsø, Norway.

Last, we introduce an expert well-known to many as an excellent lecturer with a beautiful voice: Dr. Mónica Name.

References
In Focus

Current Trends in Women’s Health

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Introduction

After World War II, modern life brought special challenges for women’s health and family planning. Today, there is a growing trend for women to delay having their first baby until later in life to establish a career before embarking on parenthood; in addition, middle-aged women who remarry may want to add to their existing family with their new partner. Many epidemiological data investigating maternal age and fetal loss have confirmed that older age strongly increases a woman’s chances of stillbirth, miscarriage, and ectopic pregnancy. Older women carry risks of conceiving a trisomic oocyte and of having a less efficient uterus. Conversely, women who chose to have children early in life are returning to work and working longer into the perimenopausal and menopausal years (the so-called baby boomers turned zoomers). It is generally accepted that susceptibility to stress and stress-related illness can be affected by hormonal changes and that common menopausal symptoms (eg, tiredness and night sweats) can make women temporarily more susceptible to fatigue and stress at work. In addition to these trends in culture, the options for controlling fertility have grown during the past 50 years, affecting the age at which women bear children. Specifically, “pills” or oral contraceptives (OCs) contain hormones that suppress ovulation, thicken the cervical mucus to block sperm passage, and/or cause abortion by making the uterine lining hostile to implantation. Oral contraceptives have been used in the management of premenstrual symptoms and, although not sufficiently substantiated, endometriosis. Combined OCs have a significant protective effect on the risk of ovarian and endometrial cancer, which increases with duration of use, and can be used as chemoprevention in young women who are breast cancer gene (BRCA) mutation carriers. Indeed, none of the large prospective cohort studies with prolonged follow-up has indicated an increased overall risk of cancer incidence or mortality among women that have ever used OCs. However, OC use has been associated with an increased risk of venous thromboembolism. There is also a slightly increased breast cancer risk among current OC users that disappears 5 to 10 years after discontinuation, an increased cervical cancer risk with long-term OC use, and an increased risk of benign liver tumors and liver cancer. However, the options surrounding fertility are not always a matter of choice. Among the many chemicals and toxins released into the environment during the past decades, the endocrine disruptors can interfere with the endocrine system through their binding to intracellular receptor proteins for steroid hormones. In particular, endocrine disruptors have a strong impact on the normal functioning of the reproductive system. They ultimately interfere with the effects of endogenous steroid hormones, evoking hormonal effects in animals, humans, and cell cultures. For example, bisphenol A, used in the manufacture of plastics, has been associated with many different malformations of the female reproductive tract, including cystic ovaries, in animal models. Moreover, the detrimental effects on reproductive physiological features in animals by other medicines, such as nonsteroidal anti-inflammatory drugs, after long-term inhibition of prostaglandins in humans remain unknown. However, the most dramatic effects of endocrine disruptors may be the many reproductive organ dysfunctions observed in women exposed in utero to diethylstilbestrol. Disorders of the female reproductive system (Figure 1) have a wide range of etiologies, including infections and hormonal problems. Primary symptoms can vary from vaginal discomfort and discharge to chronic debilitating pain. Although the pathophysiological characteristics of some conditions are well-known, others are more enigmatic, with multiorgan involvement and
multiple potential targets for treatment, and require a comprehensive approach to patient management. This article reviews current thinking on some of the more challenging conditions affecting female health.

Inflammatory Disorders

Vaginitis

Vaginitis is one of the most common reasons for women to present to a family physician. In the United States each year, an estimated 10 million health care office visits to gynecologists are because of vulvovaginitis. Vulvovaginitis is a term encompassing a variety of inflammatory lower genital tract disorders. In addition to infection, other causes of vaginal itching, burning, irritation, or discharge include allergy to latex condoms, contact dermatitis, and atrophic vaginitis. Although the causes of vulvovaginitis are many and varied, women frequently assume they are the result of a yeast infection or an allergy to a new product. Consequently, the use of over-the-counter medications is very high for this condition. This can lead to considerable delay between the onset of symptoms and consultation with a clinician and establishment of a definitive diagnosis.

Infectious vaginitis can be caused by several organisms. The most common of these organisms are Gardnerella vaginalis and Mycoplasma hominis, causing bacterial vaginosis (22%-50%); Candida albicans, causing vulvovaginal candidiasis (17%-39%); and Trichomonas vaginalis causing vaginitis and/or urethritis (4%-35%). However, coinfections can exist, and the exact cause of vaginal symptoms may remain undiagnosed in many women. Approximately 75% of women will have an episode of vulvovaginal candidiasis within their lifetime; 40% to 45% will have 2 or more episodes. However, many women with symptoms of recurrent vaginitis do not have candidiasis; consequently, self-treatment with over-the-counter antifungal agents is ineffective. Trichomoniasis is estimated to be responsible for 25% of vaginitis cases in the United States and is the most common nonviral sexually transmitted infection. Patients with infectious vaginitis commonly present with vaginal or perineal vulvar irritation and abnormal vaginal discharge. Etiology cannot be confirmed without examination of the discharge specimen. The gold standard for the diagnosis of candidiasis is visualization of pseudohyphae (mycelia) and/or budding yeast on a 10% potassium hydroxide wet preparation; for bacterial vaginosis, vaginal Gram stain (Nugent or Spiegel criteria);
and for *T. vaginalis*, culture (Diamond media or InPouch TV).\textsuperscript{11} The treatment of infectious vaginitis depends on the causative organism: antifungals are used to treat candidiasis; antibiotics, such as metronidazole and clindamycin, are effective against anaerobic bacteria and are used to treat bacterial vaginosis; and either metronidazole or tinidazole are usually used to treat *T. vaginalis*, a protozoan.\textsuperscript{10} In conventional treatment for candidiasis, topical azoles are the mainstay of treatment, achieving complete relief of symptoms in 80% to 90% of patients. However, oral agents are more acceptable and convenient for many women, although they are associated with adverse effects, such as headache and gastrointestinal upset, and are more costly. A single 150-mg fluconazole dose will achieve clearance in approximately two thirds of patients, whereas a second dose, given on day 3, will yield an 80% clearance rate. In women with recurrent infections, longer courses may be needed to suppress *Candida*. Treatment failure may indicate infection with *Candida glabrata*, which does not respond well to azoles, and in which case intravaginal boric acid capsules may be effective.\textsuperscript{10} Bacterial vaginosis is usually treated with metronidazole or macrolide antibiotics, such as clindamycin.\textsuperscript{12} Although treatment of bacterial vaginosis reduces symptoms, recurrences are common: 23% of women will have a recurrence at 1 month, and 58% will experience a recurrence within 1 year.\textsuperscript{10} Trichomonas is usually treated with oral nitroimidazoles, such as metronidazole.\textsuperscript{11} In trichomonas, abstinence from alcohol is recommended for 24 hours after starting metronidazole treatment and for 72 hours after taking tinidazole because of the potential for a disulfiram-like reaction, which may include flushing, nausea, vomiting, thirst, palpitations, chest pain, vertigo, and hypotension.\textsuperscript{10} Because trichomonas is a sexually transmitted infection, and carriers may be asymptomatic, sexual partners should also be treated to prevent reinfection. Indeed, recurrences of trichomonas are commonly reinfections or may be a consequence of nonadherence to medical treatment.\textsuperscript{10} However, there are cases of resistance to metronidazole.\textsuperscript{10}

**Pelvic Inflammatory Disease**

*Pelvic inflammatory disease (PID)* is defined as an ascending infection that spreads from the vagina or cervix to the fallopian tubes, endometrium, ovaries, and peritoneum. It can lead to any combination of endometritis, salpingitis, tubo-ovarian abscess, and pelvic peritonitis.\textsuperscript{14} Pelvic inflammatory disease has the potential for fallopian tube scarring, chronic pelvic pain, ectopic pregnancies, and infertility.\textsuperscript{10,15} Indeed, approximately 25% of women who experience a single episode of PID experience tubal infertility, chronic pelvic pain, or an ectopic pregnancy; after a third episode of PID, half of the women will experience infertility.\textsuperscript{14}

In the developed world, 8% to 15% of women may be diagnosed as having PID in their lifetime, whereas much higher rates (up to 32%) are reported in the developing world.\textsuperscript{16} *Chlamydia trachomatis* and *Neisseria gonorrhoeae* are the organisms most commonly implicated in PID.\textsuperscript{14,16} Swabs of the cervix identify gonorrhea in 30% to 80% of patients and chlamydia in 20% to 40% of patients.\textsuperscript{14} There are concerns that recent increases in the incidence of chlamydia and gonorrhea may be associated with an increase in the incidence of PID.\textsuperscript{15} Pelvic inflammatory disease may develop in up to 40% of women with untreated chlamydia infection and in most women with untreated gonorrhea.\textsuperscript{10} Gonorrhea and chlamydia may initiate a polymicrobial infection, including Gram-positive and Gram-negative bacteria and anaerobes. Therapy requires multiple antibiotic regimens to ensure that all organisms are treated.\textsuperscript{10,15,16} Treatment may be oral or intravenous, depending on the status of the patient and the patient’s ability and/or willingness to take oral medication.\textsuperscript{10}
Adequate antibiotic coverage for aerobic organisms is difficult to achieve, with metronidazole appearing to have limited efficacy, possibly because poor tolerability limits compliance. Microbial resistance to other antibiotics also is a problem.

As a consequence of the prevalence of antibiotic resistance, modulation of the innate immune system to protect against infection has been discussed as an attractive alternative to antibiotic therapies in the medical literature. Study of the innate immune response has indicated that there is variation in host immunity, possibly because of genetic differences. Thus, a suboptimal innate immune response may result in a permissive environment for pathogen colonization, whereas an excessive response will result in disproportionate levels of inflammation and tissue damage. An investigation of modulation of the innate immune response in the reproductive tract could provide significant advances in the management of PID and its sequelae.

**Endometriosis**

Endometriosis can have a profound impact on a woman’s life, potentially affecting her education, career, and ability to have children. The cost of endometriosis to both the individual and society, including delayed diagnosis and ineffective treatments, is considerable and poorly quantified. The results of a health survey in the United States indicated that half of women reporting endometriosis required at least a day of bed rest within the past year, as a consequence of the condition, with the average number of days of bed rest being 17.8. More than 8% of women reported that endometriosis limited their activity, and nearly 5% reported that it limited them in their work; only cancer and prolapse provided greater levels of limitation in this survey. Confirming these findings, the first Global Study of Women's Health reporting the societal impact of endometriosis found a significant loss of work productivity among 1459 women (aged 18-45 years) who have the condition. Loss of work productivity (not caused by absence from work) was approximately 10 hours per week vs 7 hours per week for those with other disorders. Non–work-related activities, such as housework, exercise, and child care, were also significantly impaired.

Endometriosis remains an enigmatic disorder: the etiology, natural history, and mechanisms by which it causes pain are not completely understood. Endometriosis is a condition in which tissue with the characteristics of endometrial tissue is located outside the endometrial cavity. The most commonly accepted theory regarding the pathophysiological features of endometriosis is that desquamated endometrial cells are transported into the peritoneal cavity after retrograde menstruation, with viable cells subsequently implanting and growing.

For some patients, endometriosis is not significant; for others, it is aggressive and invasive, causing incapacitating pain. The pain associated with endometriosis commonly manifests as dysmenorrhea, dyspareunia, and chronic pelvic pain (noncyclic nonmenstrual pelvic pain).

The true prevalence and incidence of endometriosis are difficult to determine because diagnosis requires surgical biopsy with histological confirmation. The disorder is more common in women of reproductive age, with the prevalence estimated to be between 6% and 15%.

The annual incidence of surgically diagnosed disease is 1.6 per 1000 women aged 15 to 49 years. It is estimated that 5% to 21% of women with pelvic pain experience endometriosis, increasing to approximately 75% of women with chronic pelvic pain. Endometriosis is the third leading cause of gynecologic hospitalization in the United States. Approximately half of women with endometriosis are infertile, and endometriosis represents the leading cause of infertility.

Incomplete knowledge regarding the pathogenesis and pathophysiological features of endometriosis is a major obstacle to effective treatment. There are several factors that may be implicated in the pathogenesis of endometriosis, including hormonal dysfunction, aberrant gene expression, immunoinflammatory changes, abnormal growth (Figure 2), remodeling, and angiogenesis. It is believed that all these dysfunctions play a role in the underlying multifactorial molecular events leading to the development of endometriosis and its symptoms.

Oxidative stress has been implicated in endometriosis and infertility. An imbalance in the generation of reactive oxygen species and the scavenging capacity of antioxidants in the reproductive tract provides an environment for the development of oxidative stress. Indeed, studies have shown that oxidative stress and antioxidant biomarkers are present in both serum and peritoneal fluid of women with endometriosis. Women with endometriosis may exhibit altered expression of the enzymes involved in the defense against oxidative stress in the endometrium. Antioxidants, such as vitamin E, can play an important role in protecting biological membranes by preventing...
the activation of pathways implicated in abnormal cell proliferation and inflammatory response. However, the role of antioxidants in endometriosis is not clear. Although some studies have found that they can afford some protection against the development of endometriosis, others have found no improvement.24 There is evidence that endometriosis is a pelvic inflammatory process.22,26 Indeed, there is emerging evidence that women with endometriosis are more likely to have other inflammatory diseases, such as fibromyalgia and rheumatoid arthritis, than the general population.26 Endometriosis generates significant inflammatory responses, suggesting that much of the pain associated with endometriosis is inflammatory.22 A theory is that the presence of inflammation activates silent nociceptors and significantly enhances both the sensitivity and severity of visceral pain.22 Visceral cross sensitization is thought to be a factor in the common co-occurrence of other visceral pain syndromes, such as dyspareunia, interstitial cystitis, and irritable bowel syndrome.22 It is believed to be the result of increased persistent nociceptive input from inflamed reproductive system organs that sensitizes neurons, particularly at the dorsal root ganglion; they also receive input from unaffected visceral organs (eg, bladder and colon). This phenomenon may underlie comorbid in many functional visceral pain syndromes.22 Surgery is the first-line treatment option for endometriosis. Conservative surgical removal of endometriosis provides pain relief and increases the chances of pregnancy.19 However, this approach is far from ideal. Although surgery may alleviate pelvic pain in the short-term, it usually recurs within 2 years. Furthermore, the spontaneous pregnancy rate after surgery is generally lower than 50%.19 In addition, there are risks associated with surgery and repeated use of this modality increases the risk of complications.19 Thus, medical treatment is generally used to prevent recurrences. Despite a paucity of evidence, nonsteroidal anti-inflammatory drugs are often used to treat symptoms.19 Hormonal treatments, such as OCs, are frequently used with some success, although symptoms often return and may even worsen on cessation.19 An obvious drawback of hormonal approaches is that they disrupt the menstrual cycle and do not offer an option for women who want to conceive.27 Although research into new treatment options is ongoing, surgical and medical treatment of endometriosis is far from satisfactory.19,26,27 Ideally, treatment should alleviate the pain and address the subfertility associated with the disease, while not interfering with ovulation and menstruation. In addition, treatment should be well tolerated and have no significant adverse effects or teratogenicity.27

Bioregulatory Treatment

Vaginitis and PID

The bioregulatory treatment of vaginitis and PID is directed toward the terrain and especially toward the epithelial barrier and the restoration of symbiotic microflora. As previously mentioned, it is often difficult to contain the conditions with only antimicrobial treatment and it is difficult to deal with recurrences. Treatment options include Gynäcoheel; because of the low-dose ingredients, this agent is thought to have an action on inflammatory conditions of the female genital tract.28 Furthermore, the addition of Mucosa compositum to support the epithelial barrier is useful. For bacterial infections, Echinacea compositum is used in an adjuvant fashion, and Metro-Adnex-Injeel is added in the case of PID. Last, if the situation is recurrent, the patient should undergo a basic detoxification, as described in previous issues of this journal.29 Probiotics form an essential part of the treatment of vaginitis and may even have a preventative role.30,31 It is essential to restore the flora after antimicrobial treatment and to ensure a healthy genital tract environment.
Endometriosis

Bioregulatory therapy has a significant role to play in the treatment of endometriosis because the condition presents like a typical dysregulation syndrome. The immune and neuroendocrine systems, and local tissue cycles, are involved, making linear intervention difficult; therefore, endometriosis lends itself to the multi-targeted approach that is used in homotoxicology.

The basic treatment for endometriosis is the inflammation-regulating drug Traumeel. Ovarium compositum is added, along with Coenzyme compositum for metabolic support. Ovarium compositum also contains hypophysis suis, which supports the hypothalamic-pituitary-ovarian-adrenal axis. The immunomodulator, Tonsilla compositum, is used to support the immune system. In addition, Tonsilla compositum contains hypothalamus suis and glandula suprarenalis suis that further support the hypothalamic-pituitary-adrenal axis; and a primitive tissue, funiculus umbilicalis suis, that is postulated to support the connective tissue. Traumeel is given daily, whereas the number of cycles needed depends on the response of the patient.

Metabolic Disorders: Polycystic Ovary Syndrome

Polycystic ovary syndrome (PCOS) is the most frequent endocrinopathy in women of reproductive age, occurring in approximately 5% to 10% of these women. The Rotterdam criteria for the diagnosis of PCOS require 2 of the following 3 criteria to be met: irregular or no ovulation, clinical/paraclinical hyperandrogenemia, and polycystic ovaries (Figure 3). Other causes of hyperandrogenemia also need to be excluded. Interestingly, confirmation of the presence of polycystic ovaries is not necessary for diagnosis.

Polycystic ovary syndrome can affect women in many different ways. Common manifestations of PCOS include hirsutism, infertility, insulin resistance, and menstrual irregularities. Other conditions that may be associated with PCOS include hypertension, dyslipidemia, and type 2 diabetes mellitus, which all increase the risk of cardiovascular events, with associated morbidity and mortality.

Thus, PCOS is recognized as having a major impact throughout life on the gynecological and metabolic health of women. Treatment of PCOS is frequently targeted at specific manifestations. For example, insulin-sensitizing agents, such as metformin, may be used to treat insulin resistance; eflornithine may be used to treat hirsutism; and OCs may be used to address menstrual irregularities or, alternatively, clomiphene may be used to address infertility. Treatment should aim to break the vicious cycle of abdominal obesity and inflammation that lead to increased testosterone levels and, thus, promote the abdominal obesity/inflammation cycle.

The prevalence of insulin resistance is much higher in women with PCOS compared with an age- and weight-matched population of women. Insulin resistance is often a precursor to the development of diabetes and is a component of the metabolic syndrome, conferring an increased cardiovascular risk. Approximately 50% to 70% of women with PCOS have some degree of insulin resistance. However, the precise mechanism of insulin resistance is not clear. It seems most likely that this is a result of impaired glucose metabolism, rather than a difference in the number and affinity of insulin receptors, making the mechanism of insulin resistance in PCOS unique.

In the ovaries, high insulin levels stimulate the conversion of progesterone to androstenedione, which is then converted to testosterone. The theory that hyperinsulinemia may stimulate hyperandrogenemia in PCOS is supported by the efficacy of insulin-sensitizing agents, such as metformin. However, studies using glitazones suggest that this relationship may be more complex. High testosterone levels in women with PCOS promote abdominal obesity that, in turn, promotes insulin resistance, leading to increased testosterone activity; thus, the vicious circle ensues.

Polycystic ovary syndrome is a multiorgan disease: abdominal obesity and increased activation of the inflammatory system, seen in both normal-weight and obese patients with PCOS, lead to an increased risk of dyslipidemia, diabetes, and cardiovascular disease. Hormonal imbalance caused by PCOS can lead to hyperandrogenism that can manifest as hirsutism and/or acne. Hirsutism occurs in 5% to 25% of women of reproductive age. Between 70% and 90% of women with hirsutism are diagnosed as having PCOS. Although many treatments for hirsutism are nonpharmacological, antiandrogens, such as spironolactone and finasteride, are sometimes used. However, OCs are among the most commonly used medications for hirsutism and acne.

The elevated levels of androgens in women with PCOS can also cause menstrual irregularities with associated infertility. Although OCs are often used to address menstrual irregularities, they obviously cannot
help with infertility. Clomiphene, an ovulation-induction agent, may be used, with the risks of multiple pregnancies, ovarian hyperstimulation, thromboembolism, and visual disturbances. Alternatively, insulin-sensitizing agents, such as metformin, have shown benefit in the treatment of infertility associated with PCOS. Obesity is prevalent in women with PCOS. Approximately 60% to 70% of patients with PCOS are obese. Furthermore, the fat is distributed around the central body; such visceral obesity is associated with insulin resistance (Figure 4). However, although the obesity found in PCOS contributes to the level of insulin resistance observed, the levels of insulin resistance are greater than those that can be explained purely by the higher levels of fat. The obesity rate has increased considerably in women with PCOS during the past decades, whereas the prevalence of PCOS has increased only minimally. This suggests that genetic factors may play a more important role than environmental factors in the development of PCOS.

Obesity is associated with low-grade inflammation and increased inflammatory cytokine levels. Although obesity-related inflammation is often considered a disorder of innate immunity, there is significant cross talk between the innate and adaptive immune systems. Moreover, disorders of both innate and adaptive immunity have been implicated in obesity-related inflammation. In addition, the inflammatory process associated with obesity could underlie comorbidities, such as atherosclerosis, diabetes, and fatty liver disease. Indeed, up to 50% of women with PCOS fulfill the criteria of the metabolic syndrome. Furthermore, the incidence of diabetes is increased, with an estimated 5- to 8-fold increase in risk compared with age- and weight-matched controls. Weight loss is an important component of PCOS management. Lifestyle modification and weight loss improve ovulation rate and fertility and decrease testosterone levels. Greater than 5% to 10% weight loss can improve fertility and menstrual cycles in women with PCOS, although no specific diet has been identified as particularly effective.

Bioregulatory Treatment: PCOS

In patients with obesity and PCOS, the most important intervention is weight loss because central obesity significantly contributes to the whole syndrome. Bioregulatory treatment includes Gynäcoheel and Cutis compositum for symptomatic relief and Ovarium compositum, Placenta compositum, Coenzyme compositum, and Ubi- chinon compositum for organ and tissue support. Additional supportive treatment with Hepar compositum, Thyreoidea compositum, and Solidago compositum is also used to promote the restoration of autoregulatory pathways.

Conclusion

The management of many female disorders remains challenging, with a need to address many different components. As understanding of the pathophysiological characteristics of these conditions grows, hopefully more effective treatments will follow. In the meantime, recognition of the multiorgan involvement in many of these diseases emphasizes the importance of a comprehensive approach to patient management.
References


**Walking Reduces Stroke Risk in Women**

Moderate walking makes a difference in women’s health. A recent study indicates that walking is associated with lower risks of different types of stroke, including total, ischemic, and hemorrhagic strokes. Physical activity has been shown to modify risk factors for stroke, such as obesity and hypertension, by decreasing blood pressure and atherosclerosis and improving lipid profile and insulin sensitivity. The study included 39,315 healthy US women, aged 45 years or older, from the Women’s Health Study. These women reported overall physical activity at baseline (1992-1995) and then 36, 72, 96, 125, and 149 months later. During this lengthy period, 579 women developed incident stroke: 473 ischemic strokes, 102 hemorrhagic strokes, and 4 strokes of unknown type. Although intense physical activity was not associated with stroke risk (P = .50 for trend), walking time and pace were inversely related to total, ischemic, and hemorrhagic stroke risks (P = .002 through P = .07). Thus, all women should be encouraged to try walking as a way to prevent stroke (and other illnesses).


**Melatonin Helps Prevent Cancer in Women**

In a recent study, the effect of melatonin on breast and endometrial cancers in women was examined. Based on decades of scientific evidence, melatonin (N-acetyl-5-methoxytryptamine) is a hormone that might protect against cancer development. Melatonin has antioxidant, antiinflammatory, and antiangiogenic properties. In addition, melatonin alters fat metabolism and may regulate tumor growth. In terms of breast cancer, melatonin may block an estrogen receptor (ie, ERα) and affect aromatase (ie, an enzyme that produces estradiol). Epidemiologic studies have examined the interaction between night shift work and varied sleep duration and melatonin concentration at night. The evidence indicates lower melatonin concentration in those who work the night shift. Case-control and prospective cohort studies have indicated that the risk of breast and endometrial cancers is affected by night shift work. Overall, night shift work may become a public health concern if additional data indicate its negative effect on cancer. More studies should determine the exact advantageous effects of melatonin for the prevention of cancer.


**Antihomotoxic Therapy for Autoimmune Thyroiditis**

Thyroidea compositum, an antihomotoxic agent, may treat chronic lymphocytic thyroiditis (autoimmune thyroiditis) in women who experience habitual miscarriage. In this study, the therapeutic effectiveness of Thyreoidea compositum was estimated in 28 women of reproductive age who had autoimmune thyroiditis and experienced habitual loss of a fetus. The mean±SD age of the women was 27.14±0.69 years, and the mean±SD duration of the disease was 1.57±0.16 years. Patients were divided into 3 groups: (1) 9 women for whom L-thyroxin was prescribed (control group); (2) 9 women who took Thyreoidea compositum, 2.2 mL, intramuscularly once in 3 days (monotherapy); and (3) 10 women for whom L-thyroxin, 50 to 100 μg/d, plus Thyreoidea compositum (combination therapy) was prescribed. The researchers determined that Thyreoidea compositum, used as both a monotherapy and as part of a complex treatment, leads to decreased levels of antibodies to thyroglobulin and thyrotropin, an increased level of free thyroxine, and goiter reduction. Therefore, this antihomotoxic agent has immune-correcting, anti-inflammatory, and regenerative effects.

Infant Sensitivity to Peanut Associated with Maternal Ingestion

Peanut allergies can be lifelong and severe. In a recent study of 503 infants (age range, 3–15 months; mean age, 9.4 months), maternal ingestion of peanuts during pregnancy and lactation affected the sensitivity of infants to peanuts. The risk to the infant increased with increased peanut intake by the mother. The infants studied had already experienced allergic reactions to other products: 308 had an immediate reaction to cow’s milk and/or egg, and 204 had atopic dermatitis and a positive allergy test result to milk and/or egg. Other significant factors that affected infant peanut allergy included male sex (P = .02) and nonwhite race (P = .02).


Endometriosis and Leiomyomata Linked to Phthalate Exposure

Phthalates, chemicals in commercial products, include mono(2-ethylhexyl) phthalate (MEHP), monobutyl phthalate (MBP), monoethyl phthalate (MEP), and monobenzyl phthalate (MBzP). In this cross-sectional study, mono(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP) and mono(2-ethyl-5-oxohexyl) phthalate were also examined. When a population of women (aged 20–54 years) was studied to determine urinary phthalate levels, 7% and 12% reported endometriosis and leiomyomata, respectively. The odds ratios for MBP were as follows: 1.36 for endometriosis, 1.56 for leiomyomata, and 1.71 for both conditions combined.

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Air Pollution Affects Breast Cancer Risk

An association was found between the risk of breast cancer in postmenopausal women and exposure to urban air pollution by measuring concentrations of nitrogen dioxide (NO₂). The results of this case-control study conducted in Montreal, Quebec, Canada, indicated that an increase of 5-parts-per-billion NO₂ produced an approximately 25% increased risk of breast cancer. The NO₂ is most likely part of a complex mixture derived from combustion and is not necessarily the causal factor but a marker of level of air pollution. Additional research is needed to determine the possible critical periods of exposure to air pollution in relation to breast cancer development.

Fibroids or leiomyomas are the most common form of benign uterine tumor in women. Although fibroids are found relatively rarely in women younger than 20 years, statistically, 1 in 5 women of childbearing age will have this disorder. From the standpoint of conventional medicine, the formation of fibroids is considered a hormonal disturbance or the result of a genetic predisposition. Studies have also shown that fibroids have different distributions among the various races. Fibroids are the result of increased growth of smooth muscle tissue within the uterus and its outer mucosa. The frequency distribution of fibroid sites is as follows: subserous, 55%; intramural, 40%; and submucous, 5%. The symptoms of fibroids include unusually heavy bleeding during and between periods and nonspecific pressure in the lower abdomen, associated with a frequent urge to urinate and general bowel movement difficulties. In contrast, routine examinations sometimes reveal fibroids that cause no symptoms. The possibility that a fibroid will follow a degenerative course is relatively rare. If fibroids become so large that their blood supply is no longer adequate, they may become necrotic. In subserous fibroids, necrosis may also occur when fibroids become twisted in on themselves because of their abnormal size.

Conventional medicine suggests various treatment possibilities and methods for use in fibroid therapy that, as a rule, carry the risk of adverse effects. Surgical or drug treatment methods are used. The most commonly used surgical procedures are myomectomy, hysterectomy, and drug-induced embolization via the uterine artery. Pharmaceutical hormone treatments are also used (e.g., administration of a gonadotropin-releasing hormone analogue) to trigger early menopause in the patient. The placement of intrauterine devices that release hormones is another treatment method. From the standpoint of homotoxicology, fibroids are a chronic disease that is classified in the deposition phase and belongs to the germinodermal layer. It is assumed that the disease is caused by multiple factors and that psychological factors play a particular role in this gynecological disease. As an expert with long-term experience in biological medicine, I try, in my daily practice, to treat fibroid diseases primarily from a correspondingly different viewpoint. Of course, every physician knows that health is to be understood as an unstable equilibrium state that is constantly striving to balance itself and that the neuroendocrine system is involved in both human emotions and the hormone cascade. Physicians can come closer to treating fibroid disease by carefully observing the patient and getting to know about her life history. This begins with birth and includes dietary habits, emotional life, and physical activities. All of these individual characteristics are to be compiled in a thorough history so that physicians can successfully identify the factor that caused the disturbance and led to the disease.

I attempt to convey to the patient that a fibroid constitutes an organic enlargement in which nutrition plays a role; therefore, I recommend a diet according to the principles of Traditional Chinese Medicine. I combat the physical imbalance by using homeopathically prepared hormones and therapy with organ extracts, which normalize the functions of the pituitary and thyroid.

Clinical Case
In 2009, a 43-year-old patient presented to my practice with massive menstrual bleeding caused by an intramural fibroid measuring 8.1 x 6.6 cm (Figure 1). Her medical history showed the following: menarche at the age of 12 years, nullipara, 1 miscarriage, and no major diseases. Her first fibroid symptoms had appeared in 1994 at the age of 28 years. A myomectomy was performed. In January 2003, the fibroid symptoms recurred. To counteract the renewed heavy bleeding, which was having a serious effect on her daily life, the patient was treated with a hormonal
intrauterine system. However, her heavy bleeding continued, and the fibroid continued to grow. According to the ultrasonographic examination results from 2007, the fibroid had reached a size of 5.5 x 4.6 cm. The severe bleeding persisted, and the ultrasonographic examination from 2008 showed that the fibroid had grown to 7.0 x 5.4 cm. I immediately began homotoxicological treatment and recommended the dietary adjustment, as discussed before.

**Therapy**

The patient received Cinnamomum-Homaccord in drop form (maximum dosage, 70 drops daily) to counteract the heavy bleeding. For tissue support, I administered Mucosa compositum ampoules (1 twice a week). To reduce inflammation, she was given Traumeel drops (10 drops 3-5 times a day). To slow the fibroid growth and counteract obsessive thoughts, I prescribed Thuja granules (5 granules daily); and for hormonal balance, I prescribed Agnus castus granules (5 granules daily). The latter medication is used to restore the balance between estrogens and progesterone.

In the follow-up examination conducted by a colleague in February 2010, 6 months after the beginning of treatment, the fibroid had decreased to 6.6 x 4.5 cm (Figure 2). To date, the patient has remained symptom free, and her menstrual bleeding has become completely normal. She continues to be treated with the same medication. We await the results of future regular ultrasonographic examinations of the shrunken fibroid.

**References**


**Further reading**

Which Came First: Insulin Resistance or Inflammation?

By David W. Lescheid, PhD, ND

It is well established that persistently elevated levels of inflammatory cytokines play a significant role in the development of chronic disease. For example, persistently high levels of 1 or more of the proinflammatory cytokines (ie, interleukins 1 and 6 and tumor necrosis factor α) are common to the pathogenesis of diseases such as cardiovascular disease, cancers, inflammatory bowel disease, chronic fatigue syndrome, and neurological disorders (eg, depression, Parkinson disease, and Alzheimer disease).1

The elevation of these cytokines has become such a common thread for the development of these diseases that the term sickness behavior2,3 has recently been proposed to describe the associated signs and symptoms of fever, anorexia, fatigue, sleepiness, and social withdrawal. Additional support for the paramount importance of inflammation in disease development has recently come from the Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER). The results of this trial suggest that the proposed benefit of statin drugs in the prevention of cardiovascular disease was more likely because of their ability to reduce levels of high-sensitivity C-reactive protein (a nonspecific inflammatory marker) than their effects on lowering cholesterol.4

Although there are some similarities, the inflammatory component of chronic diseases is different from the inflammatory response associated with tissue repair and recovery that follows acute injury or infection. This subclass of inflammation may be termed metainflammation (metabolic inflammation), because of its initiation by nutrients and metabolic surplus5; or parainflammation, because it shares intermediate characteristics between the basal and acute inflammatory state.6

Chronic inflammation does play an important role in disease processes. An important question to ask is as follows: Why has the inflammation occurred in the first place (ie, what is the nature of the inflammatory inducer or trigger)? There are several different theories and proposed mechanisms; however, one of the most promising current models suggests that dysregulated cell metabolism, particularly from nutrient excess and the associated altered insulin signaling,7 is one of the most important initiating events. This article will discuss the roles of hyperinsulinemia and of a few potential triggers of excess insulin in the development of disease, with some examples of the effect on women’s health issues.

Men and women have substantial differences in body composition, such as distribution of visceral and hepatic adipose tissue and lean body mass, and in sex hormone and adipokine levels. These differences tend to improve insulin sensitivity in women compared with men8 and suggest that sex differences must be considered when preventing and treating diseases associated with insulin resistance.

There is no question that obesity has reached epidemic proportions in many parts of the world. In many countries, particularly those of industrialized and developed nations, there is a regular excess intake of calories from increasingly calorie-dense but nutrient-poor foods and drinks. The excess of calories, combined with an increasingly less physically active society, creates a daily energy surplus that eventually leads to a dysregulation of the body’s key storage hormone, insulin (Figure).9 With cells no longer sensitive to insulin and a surplus of blood glucose triggering the continued release of insulin from the pancreas, hyperinsulinemia develops. Adipose tissue is an endocrine organ releasing many different signaling molecules, some of which have direct localized and systemic inflammatory effects.10 The development of adipose tissue is preceded by an impairment of energy balance that is primarily associated with the inability of the cells to respond to insulin, either through inadequacy of insulin receptor signaling or some other defect in the biochemical pathway.
Hyperinsulinemia and Female Health

High insulin levels can modulate the activity of gonadotropin-releasing hormone in the hypothalamus (at least in lean healthy controls) and, therefore, interfere with the pattern of release of luteinizing hormone (LH). These data suggest that reproductive cycles, ovulation, and fertility could be affected. Indeed, recent evidence suggests that fasting insulin levels, fasting serum levels of sex hormone–binding globulin (SHBG), and the free androgen index had strong negative influences on the regularity of menstrual cycles in young women. Women with insulin resistance and hyperinsulinemia (and upper body obesity, which is also termed android or truncal obesity) had a greater risk of anovulatory cycles that could be reversed through the use of insulin-sensitizing drugs.

Glucose intolerance, including insulin resistance and impaired fasting glucose level, is an important part of the pathophysiological characteristics of polycystic ovary syndrome (PCOS). However, insulin infusions to women with PCOS had no effect on the secretion of LH, suggesting that the inappropriate secretion of LH observed in this disease might not be directly due to insulin resistance and hyperinsulinemia. Furthermore, there was no change in the altered pattern of LH secretion in women with PCOS after insulin infusion despite an improvement in insulin sensitivity after treatment with pioglitazone, a thiazolidinedione type of drug known to modulate transcription of insulin-sensitive genes in the muscle, liver, and adipose tissue. This suggests that the dysregulated gonadotropin release in PCOS is caused by a mechanism that is not directly related to insulin levels.

High insulin levels in the ovaries help stimulate the production of steroid hormones, such as androstenedione and testosterone, that are associated with some of the signs and symptoms of disease in women if they are in excess for a long time. Higher levels of testosterone, but not androstenedione, are correlated with higher levels of insulin resistance in women (but not in men). In particular, women with PCOS that are also insulin resistant have the highest circulating levels of insulin-stimulating effects of insulin.

Insulin is a key regulator of the synthesis of SHBG in the liver. Elevated levels of insulin down regulate the production of SHBG and, therefore, increase the amount of bioavailable estrogen; this increases the risk of diseases associated with estrogen excess. Furthermore, a decreased serum level of SHBG would result in an excess of free testosterone and, therefore, the associated signs and symptoms, such as hirsutism and acne. High testosterone and low SHBG levels are also associated with a higher risk of cardiovascular disease in postmenopausal women. Elevated levels of insulin increase the bioavailability of insulin-like growth factor 1, by directly increasing its synthesis and decreasing several of its binding proteins (eg, insulin-like growth factor-binding proteins 1 and 2). Insulin-like growth factor 1 is a hormone that is involved in several different conditions, including certain types of carcinogenesis, cognitive decline, dysregulation of the immune system, and autoimmune diseases, and in the development of female disorders, including breast cancer in premenopausal women.

High insulin, but not insulin-like growth factor 1, levels are independent risk factors for the development of breast cancer in postmenopausal women and for endometrial adenocarcinoma.

Possible Triggers of Dysregulated Insulin Levels

The interconnectivity between female pathophysiological features and insulin has been further substantiated with recent reports demonstrating that estrogen is important in glucose homeostasis. For exam-
ple, both isoforms of estrogen receptor (α and β) are present in pancreatic beta cells. The insulin content of pancreatic beta cells was increased after long-term exposure to physiological levels of 17β-estradiol, most likely by binding with estrogen receptor α.32 It is becoming increasingly evident that environmental chemicals from plastics and common household products, such as bisphenol A (BPA) and phthalates, have the potential to trigger dysregulated metabolic events that could lead to insulin resistance and contribute to the obesity epidemic.33 For example, there is evidence that the environmental estrogen mimetic BPA significantly binds and activates estrogen receptor α in pancreatic beta cells at serum levels that are plausible, suggesting that this could be one of the early triggers of dysregulated insulin levels. The putative role of BPA in disrupting the normal physiological regulation of glucose has been reported and reviewed elsewhere.34,35 It is interesting to note that in mouse models, when pregnant mice are exposed to environmentally relevant levels of BPA, glucose homeostasis is affected and insulin resistance develops not only in the mothers themselves, but also in the male offspring. These negative effects initiated in utero persisted until adulthood, suggesting that exposure to BPA early in development could influence the development of chronic disease later in life.36 Phthalates, widely found in plastic products, are additional environmental pollutants that disrupt cellular metabolism and, therefore, contribute to the development of insulin resistance and obesity (at least in men).37 This dysregulation of cell metabolism was the result of the ability of phthalates to interfere with the function of peroxisome proliferative receptors,38 transcription factors known to function at a critical intercellular junction between lipid and glucose metabolism and, therefore, storage or usage of nutrients.

A cellular event that might even precede insulin resistance and inflammation is endoplasmic reticulum (ER) stress. This organelle can be negatively affected by hypoxia, viral infections, toxins, energy, and nutrient fluctuations (both deprivation and excess of nutrients will stress the ER), imbalances of calcium levels within the organelle, excess demands on host cell synthetic biochemical machinery, inflammatory mediators, and accumulation of improperly processed proteins.11 The ER responds to these stressors by a complex response, known as the unfolded protein response, that ultimately initiates pathways that negatively affect insulin signaling and promote the inflammatory response.39 The presence of chronic oxidative stress, possibly from mitochondrial dysfunction, inadequate cell antioxidant networks, or ER stress, can promote insulin resistance and inflammation and can impair insulin secretion from pancreatic beta cells.5 Furthermore, persistent nutrient excess (and, ultimately, obesity) increases the levels of excess free fatty acids (that can activate inflammatory responses through binding with toll-like receptors33), reduces glucose availability (as the result of cellular insulin resistance), and augments the demands for protein synthesis. These variables all induce ER stress and the unfolded protein response.39 The ER might be the important sensory link between nutrient-associated signals and the development of insulin resistance and inflammation.11

It has recently been proposed that a combination of nutrient excess and physical inactivity, occurring against a background of genetic predisposition, could lead to the persistent hyperglycemia associated with the development of oxidative stress. Ultimately, this may trigger inflammatory pathways that contribute to the development of chronic disease. There are many different points along this “oxidative inflammatory” cascade that can be modulated to prevent any pathological consequences; however, reducing the persistent hyperglycemia (by improving insulin sensitivity) appears to be a critical first step.40 In conditions of nutrient excess, which are common in industrialized nations, it is more likely that a dysregulation of metabolic signals, such as insulin resistance, precedes the promotion of the inflammatory response. These metabolic signals could have been disrupted by stress on intercellular organelles, such as the ER, or, alternatively, by external stressors, such as the environmental toxins BPA and phthalates. An increased understanding of some of the key initiators of the process of chronic disease can assist with the development of prevention and treatment plans that address the root cause and, therefore, have a more profound and persistent therapeutic effect.
References


4. Mora S, Ridker PM. Justification for the Use of Statins in Primary Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER). can C-reactive protein be used to target statin therapy in primary prevention? Am J Cardiol. 2006;97(2A):33A-41A.


The burden of human papilloma virus (HPV) infections and their consequences is a major health concern worldwide in terms of the cost to society and suffering. It is estimated that 360 million persons worldwide are infected with HPV.1

Of the 100 strains that exist, only 40 have an affinity for genital sites, being primarily sexually transmitted. These can be classified into 2 general categories: high- and low-risk HPV. The low-risk strains, especially types 6 and 11, are responsible for genital warts and respiratory papillomatosis. Of the 15 high-risk types, 2 strains (16 and 18) are responsible for approximately 70% of the cervical cancers worldwide.2 Cervical cancer is the second most frequent cancer of women and is the first cancer caused solely by virological agents.3 Human papilloma virus infection is common, and most women will be infected with 1 of the HPV subtypes in their sexual lifetime. In most individuals, the infection is transient and asymptomatic and will resolve within 2 years.4 Only a subset of women infected with high-risk carcinogenic HPV will develop invasive cervical cancer, and several cofactors have been associated with HPV persistence and HPV-related disease progression. These factors include the following: (1) viral factors, such as genotype (eg, HPV 16); (2) lifestyle factors, such as tobacco smoke5 and long-term oral contraceptive use6; and (3) genetic and immunological host factors, such as innate immunity.8

Prophylactic HPV vaccines have proved to be highly effective in preventing HPV infection, despite concerns regarding their long-term safety.9-11 However, even the rigorous vaccination program in industrialized countries will not obliterate the need for cervical screening because the vaccine does not contain all the carcinogenic viral types and women already infected have no benefit from the primary intervention.

Secondary prevention with cervical screening has been extremely effective in reducing the serious sequelae from HPV infection. In the future, HPV screening (with or without cytological testing) may be used as the primary screening test in women older than 30 years.12

From a bioregulatory perspective, the emphasis in treating HPV infection should be on the factors implicated in persistence and disease progression; the immunomodulatory aspect and the tissue terrain should be addressed in a primary fashion. This type of treatment lends itself to a classic 3-pillar approach (Table). Lifestyle adjustment is of major importance, and smoking cessation should especially be encouraged. Protective sexual intercourse with condoms is advised, especially in women younger than 21 years because this is the age at which there is a peak incidence and because the presence of other sexually transmitted diseases concurrently has been implicated in the persistence of high-risk HPV types.
Table: Three-Pillar Approach for the Treatment of HPV Infection

<table>
<thead>
<tr>
<th>DET-Phase</th>
<th>Basic and/or Symptomatic</th>
<th>Regulation Therapy*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mucodermal Urogenital Impregnation</td>
<td>Gynäcoheel (inflammation)</td>
<td>- Advanced supportive detoxification and drainage^b (for 6 weeks) followed by - Basic detoxification and drainage: Detox-Kit^c (for 6 weeks)</td>
</tr>
<tr>
<td>D&amp;D</td>
<td>- Engystol</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Tonsilla compositum (if persistence is not cleared by a regimen with Engystol only)</td>
<td></td>
</tr>
<tr>
<td>IM</td>
<td>- Mucosa compositum (vaginal and cervical)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Cutis compositum (external genital warts)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Coenzyme compositum</td>
<td></td>
</tr>
<tr>
<td>COS</td>
<td>- Ubichinon compositum (if not cleared by the initial regimen)</td>
<td></td>
</tr>
</tbody>
</table>

Note: Persistent HPV is classified as being in the impregnation phase and, therefore, should be addressed aggressively. Engystol has been shown to have antiviral properties in several viruses, including the DNA viruses,\^a and can increase interferon production.\^b Thus, it is used as a supportive measure. However, if the virus is still persistent at the first follow-up after initiating treatment, a course of Tonsilla compositum (supportive of the immune system) and Ubichinon compositum (for deep cellular detoxification) should be added (3 times a week for 6 weeks) and Engystol should be continued after this period with follow-up.

In patients who are seen with persistence of the same strain for longer than 2 years, these 2 organ regulators should be the first intervention for the first cycle, followed by Engystol.

Dosages: Gynäcoheel, 10 drops 3 times daily. Regulation therapy: tablets, 1 tablet 3 times daily, ampoules, 1 ampoule of each medication, 1 to 3 times per week; Detox-Kit, 30 drops of each medication in 1.5 L of water (drink throughout the day).

Abbreviations: COS, cell and organ support; D&D, detoxification and drainage; DET, Disease Evolution Table; HPV, human papilloma virus; IM, immunomodulation.

\^aAntihomotoxic regulation therapy consists of a 3-pillar approach: D&D, IM, and COS.
\^bAdvanced supportive detoxification and drainage consists of Hepar compositum (liver), Solidago compositum (kidney), and Thyreoidea compositum (connective tissue).
\^cThe Detox-Kit consists of Lymphomyosot, Nux vomica-Homaccord, and Berberis-Homaccord.

Contributions of Biological Medicine in Infertility

By Gaston Orellana Alvarellos, MD
Obstetrician/Gynecologist

Infertility, defined as the inability to complete a pregnancy within a reasonable period (usually 12 months) in cases in which no contraceptives are used, is a problem that affects 1 in every 6 couples.1

Although it is debatable whether this figure has increased, it appears reasonably certain that women have been increasingly postponing their first pregnancy because of their studies, work, or, simply, personal fulfillment. As we will see in the following text, this produces a complex situation that is of great significance for biological medicine.2 Broadly speaking, the causes of infertility can be summarized as shown in the Figure.

Study centers specializing in infertility have developed well-designed diagnostic methods, treatment protocols, and follow-up criteria that are generally free of controversy. Nevertheless, from the standpoint of homotoxicology, which presupposes a more holistic consideration of each pathological event,4 I believe a different light can be cast on this particular subject. First, attention must be focused on the 10% of cases in which infertility is of unexplained etiology, while remaining cognizant of the fact that these considerations are valid for all cases. In addition, there is another area that has unexpectedly come to the forefront in my personal experience; therefore, it will be necessary to discuss this area from a personal standpoint.

In Chile, a forum has been set up for women being treated for infertility to share their experiences on the Internet.5 In this forum, members have mentioned the recurrent appearance of studies promoting treatment referred to as “alternative” concurrently with conventional treatment. Because my name has appeared in connection with successful cases, I have had to assume responsibility and consider, from both theoretical and practical standpoints (in combination with acupuncture), the concepts I would like to share.

Most, if not all, of my patients have been aged between 30 and 40 years. This is what I mean when I say that women have postponed pregnancy until they have reached the age of

Figure. Causes of Infertility

- Uterotubal factors
- Male factors
- Ovulatory factors
- Sperm mobility factors
- Unexplained factors
approximately 35 years, a critical point statistically with respect to fertility. These are urban women, with sedentary jobs, working under artificial light, eating the diet imposed by the cafeteria at their company, in an environment that is overpopulated and exposed to all of the toxins in a modern building. The stress of modern life must be added, resulting from a job in which one’s survival depends on performance; this is only one of the factors that contribute toward maintaining the body’s alarm system on continual alert.

**Relevant Biomedical Factors**

1. Natural light. Circadian rhythms and the role of melatonin must be addressed. Melatonin is a hormone that was formerly paid little attention but whose study is attracting ever-increasing interest, particularly with respect to a scenario that is essentially cyclic.

2. Physical exercise. Surprisingly, I have been faced with the need to recommend exercise and to occasionally restrict it. High-performance physical exercise causes severe disruption of the hypothalamic-pituitary axis.

3. Use of medicines. In particular, medicines acting on the central nervous system, which commonly cause hyperprolactinemia, should be examined.

4. Use of recreational drugs.

   - The consumption of complex carbohydrates, which are rich in fiber and have a low glycemic index, should be recommended.
   - The consumption of proteins of vegetable origin and white meat is important. There is no need to expand herein, but it is clear that excessive amounts of arachidonic acid must be avoided. This ingredient is found in red meat and contributes to the synthesis of “bad eicosanoids.”
   - For the same reasons, with a view to recommend the “good eicosanoids,” the use of extra-virgin and cold-pressed vegetable oils should be emphasized.
   - Incidentally, when I speak of good and bad eicosanoids, I am drawing attention, in an extremely general manner, to factors that play a role in persistent inflammatory syndrome and impaired endothelial function.

**Bioregulatory Treatment**

From the beginning of therapy, patients require the first pillar of treatment, detoxification and drainage, using Nux vomica-Homaccord, Berberis-Homaccord, and Lymphomyosot. However, in practice, I have had to administer the 2 other pillars earlier than planned because of the urgent nature of the patient’s situation. Homotoxicology involves acceptance of the concept that there is a minimum persistent inflammatory syndrome behind every pathological situation. In practice, this implies the use of Traumeel from the outset.
Clinicians are faced with a problem in which there is no clarity about the specific organ that requires support. From a simplistic point of view, the ovary must be considered as the main organ responsible; however, infertility is a problem of unknown origin. From this perspective, what I propose and use, in addition to Ovarium compositum, is Hepar compositum because the metabolism of steroids requires a healthy liver. If the dysfunctional tissue is unknown, I propose Coenzyme compositum and Ubichinon compositum as a second step. There are 2 resources that also must be mentioned. The first is Sepia in potency chords, as is seen in China-Homaccord, which meets the needs of a depressed and hopeless patient who requires support. The second is Placenta compositum. I have the highest opinion of its capacity to increase microcirculation at any level, including the ovaries; if applicable, this capacity should be considered. The bioregulatory treatment of infertility is summarized in the Table.

### References

Born in Sincelejo, Colombia, Mónica grew up with her parents, Judith and Assad, and at the side of her three brothers. Music, poetry, and medicine were the constant components of her surroundings and predicted her successful life. From a very early age, and thanks to her father, a psychiatrist, and her uncle, a plastic surgeon, Mónica was in close contact with medicine, the profession to which she was to devote all her energy. After graduating with a medical degree from the Universidad del Norte in Barranquilla, and with the firm intention of specializing in plastic surgery, she found her life taking an unexpected turn. She witnessed the return to health of her father, who had been treated with alternative therapy by a friend from his university days, Armando Rojas, who had dedicated himself to antihomotoxic medicine. The biological physician invited her to spend her vacation at the Center for Biological Medicine in Cali (founded by Dr. Arturo O’Byrne), and Mónica gladly accepted. During this period, her contact with the world of integrative biological medicine gave her the opportunity to witness not only the results achieved in patients, but also the possibility of practicing medicine in a holistic and integrative manner. What was planned as a brief vacation turned into a 5-year stay, beginning in 1991, during which she was trained in biological medicine and homotoxicology. Mónica came to realize the diagnostic and therapeutic benefits of electroacupuncture under the supervision of Dr. O’Byrne. Her interest and research led her to write a book in 2000, entitled Electroacupuntura de Voll (Electroacupuncture After Voll), promoting the appropriate use and interpretation of this diagnostic and therapeutic method. Thanks to the support of her husband, William Rincón, with whom she has shared her life since 1999, she began a successful medical career, resulting in the founding of her clinic in Bogota, which serves as a center of integrative biological medicine.

The young couple fulfilled their lives with the birth of their son, William David, who became Mónica’s central inspiration, driving her to be more creative, dynamic, and enterprising. She enrolled at the National University of Colombia in 2000, where she completed a variety of additional courses in cellular and molecular biology, osteopathy, neural therapy, and acupuncture. She completed her studies and obtained a master’s degree in homeopathy in 2009.

Mónica’s interest in academia has led her to develop accredited programs in molecular biology, with a specialty in homotoxicology, at several nationally and internationally recognized universities in various cities in Colombia.

Mónica’s versatility and dedication are also reflected in her choice of pastime activities. She is an accomplished singer and has mastered both the piano and the guitar. In addition, she enjoys painting and practicing her most daring hobby: riding the unicycle.

Meet the Expert

Dr. Mónica Lucia Name Guerra

By Edda Medina, MD
Purpose-Orientated Clinical Research

By Robbert van Haselen, MSc

In the previous article in this series, I provided an overview of the different medical study formats. Reference was made to an “evidence mosaic” as a multifaceted evidence base. In this article, I will delve a bit deeper into the role of clinical research as part of the evidence base.

In terms of research design, clinical studies can be interventional (clinical trials) or noninterventional (various types of observational studies). Clinical trials are experiments in which patients are usually allocated to groups at random (ie, randomized) and exposed to different treatments, with the goal of obtaining an unbiased comparison. Clinical trials can be either single blind (the nature of treatment is “masked” only for the patient) or double blind (the treatment is masked for both physicians and patients). Sometimes, reference is made to triple blind (usually this means that all the principal statistical analyses are completed on a blinded basis before the treatment allocation code is broken). In cases in which blinding of treatment is not possible, the term open label is often used.

There are many types of observational studies. The key design characteristic is that these studies are noninterventional. The most basic type of observational study is a case report. Further types of observational studies are case series, case-control studies, and cohort studies. Cohorts can be defined in different ways (eg, on the basis of exposure to toxic substances, such as tobacco smoke, or treatment[s] received). The latter studies are sometimes referred to as postmarketing surveillance studies. Such cohort studies are useful for collecting information on the safety and effectiveness of particular medicines or therapeutic approaches in routine clinical practice. In summary, the key feature that distinguishes observational studies from clinical trials is the absence of an experimental intervention.

A postauthorization safety study (PASS) is defined as a pharmacoepidemiological study performed in accordance with the terms of the marketing authorization, conducted with the aim of identifying or quantifying a safety hazard related to an authorized medicinal product. Therefore, a PASS is primarily characterized by its objective and not by its design. For instance, there is a PASS using an interventional design that confirms the safety of Traumeel tablets. On the other hand, there are numerous noninterventional (PASS) cohort studies, including approximately 9000 patients, that confirm the excellent tolerability of Traumeel in its various galenic forms. Therefore, PASSs are important for further substantiating the excellent safety profile of biotherapeutic medicines. It is often forgotten that the utility of a treatment is not only determined by its effectiveness but also by its safety, often referred to as the risk-benefit ratio. Therefore, the relative safety of bioregulatory compared with conventional medicine is an important factor in conveying the overall utility of the therapeutic approach.

The characteristics of the previously mentioned study designs are summarized in the Table.

### Dimensions of Research Design

The purposes of clinical research on products can be categorized in various dimensions. The main types of clinical studies are positioned somewhere in a space with the dimensions reality (real world vs ideal world), comparativeness (absolute effects vs relative effects), and level of confirmation (hypothesis generation vs hypothesis confirmation).

#### Real World vs Ideal World

This dimension is illustrated by contrasting the determination of relative efficacy of a treatment vs place-
bo in the “ideal world” of highly preselected patients who are willing to participate in a clinical trial vs determining the effectiveness of a treatment in patients in the “naturalistic” setting of routine clinical practice in observational studies. This dimension is weighted differently depending on the perspective. For health economists, real-world cost-effectiveness data are more valuable than placebo-controlled clinical trial data. On the other hand, for a competent authority (ie, government regulatory body) that needs to decide on allowing a new drug on the market for a particular indication, placebo-controlled data will often be preferred. Most clinicians will usually want to know the effectiveness of a proposed new treatment compared with existing treatments.

**Absolute vs Relative Effects**

As an example, a clinical case report ranks the highest on the scale of “relative efficacy.”

_Hypothesis Generation vs Hypothesis Confirmation_

Most observational studies are excellent hypothesis-generating tools. In such cases, a “proof-of-concept” clinical pilot trial could be a next step in identifying the most promising hypotheses, which can then be confirmed in larger-scale “confirmatory trials.”

The Figure illustrates how different study designs fit into these dimensions. As can be seen from the positioning on the top-to-bottom axis, clinical case reports represent maximally the “real world” of clinical practice. When looking at the horizontal axes, it can be seen from the positioning on the left-to-right axis that case reports primarily represent “absolute” rather than “relative” effects. The reason for this is obvious: in a single case, clinicians are only interested in the effect in that particular patient and not in comparing it with effects in other patients. From the positioning on the front-to-back axis, it is clear that clinical case reports are primarily hypothesis generating. The reason for this is that a single case report can rarely be a definite proof. A case series, pointing in the direction of a particular outcome, is still primarily hypothesis generating, but compared with a single case report, similar observations in repeated cases can be a first step toward confirmation of a particular hypothesis. The latter is represented by a shift in the direction of hypothesis confirmation on the front-to-back axis.

All the clinical trial designs are on the horizontal axes, firmly placed toward hypothesis confirmation and relative effects. The reason is related to the primary objective of clinical trials: to make comparisons between different treatments to confirm or refute a particular predefined hypothesis. The main variation occurs on the vertical axis. A trial with a “surrogate” marker (eg, a particular laboratory value deemed to be predictive of a particular outcome) is less representative of the real world.
than a placebo-controlled trial with a clinical outcome measure (e.g., pain). Also, placebo-controlled trials are less representative of the real world compared with trials in which the treatment of interest is compared with a well-established active treatment.

In between case reports and clinical trials, which are positioned toward the extremes of the 3-dimensional space in the Figure, there are several further study types, such as case-control studies, cohort studies, and PASSs.

Irrespective of whether a clinical study is a clinical trial or a case report, from a scientific perspective, the value of a study is determined by the appropriateness of the chosen design and the quality of its reporting.

References
The International Congress on Complementary Medicine Research in Tromsø, Norway, was an intensive 4-day event involving 6 keynote, 160 oral, and 110 poster presentations, as well as 5 symposia. The International Congress on Complementary Medicine Research 2010 was the fifth congress of the International Society for Complementary Medicine Research; these congresses take place on a yearly rotating basis in Europe, Australasia, and the Americas. The fact that so many complementary and alternative medicine (CAM) researchers from throughout the world were willing to travel such long distances further underlined the rapid increase of CAM research activity on a global scale. Dominant CAM treatment modalities were Chinese medicine, acupuncture, body-mind techniques, and homeopathy.

Several basic research studies on homeopathy were presented, including data from Kerstin Röska, PhD, suggesting that Engystol stimulates antiviral interferon type I production in cells of the innate immune system in vitro and that it might have a potent antiviral effect. Stephan Baumgartner, PhD, presented studies that suggested there were biological effects of potentized substances, including rosy apple aphid and Arsenicum album.

Jim Rogers gave an interesting presentation on the methods of homeopathic pathogenetic trials (provings). He recommended developing methods for screening participants for sensitivity to the medicine used and establishing standards of planning, conducting, reporting, and communicating provings.

Rainer Lüdtke presented the results of a systematic review that compared placebo effects in clinical trials on homeopathy with placebo effects in trials using conventional therapies. Results showed that, contrary to what is often assumed, placebo effects in randomized controlled trials using classical homeopathy were no larger than placebo effects using conventional medicine. This means that all schools of homeopathy can, in principle, be investigated in placebo-controlled studies. This study has been published in *Homeopathy*.1

Many presentations focused on “comparative effectiveness research” and the methodological challenges in CAM research. Issues that were discussed intensively during the congress included the “atypical” patient populations used in CAM research (compared with patients seen in routine CAM practice), blinding issues (eg, in acupuncture), the need for sensitive and appropriate outcome measures, and highly “context-specific” results of clinical studies.

Josephine Briggs, MD, director of the US National Center for Complementary and Alternative Medicine, gave a keynote lecture on CAM research. She highlighted that there is a need for “pharmacological signatures” of natural products to evaluate them properly in clinical trials. These pharmacological signatures are important for demonstrating and explaining changes in actual pathophysiological mechanisms. The quality and professionalism of CAM research are rapidly evolving further; the fifth congress of the International Society for Complementary Medicine Research has illustrated and confirmed this trend. Abstracts of the conference can be downloaded from the International Congress on Complementary Medicine Research 2010 web site.2

The congress also confirmed that more basic and clinical research is needed in homeopathy. The sixth congress of the International Society for Complementary Medicine Research will take place in Chengdu, China, from May 7 to 9, 2011.

References
Traumeel for the Treatment of Pain Associated With Breast Cancer

Summary

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Introduction
Breast cancer is a worldwide problem because of its high incidence. The pain associated with breast cancer treatment, including surgery, radiotherapy, and chemotherapy, often remains a long-term problem for many patients. The pain can be a result of scars after surgery or the adverse effects of radiotherapy and chemotherapy. This pain can definitely affect the quality of life of patients. Therefore, effective pain treatments are important.

The World Health Organization lists the following conventional treatments for pain associated with breast cancer: acetylsalicylic acid, paracetamol, naproxen, metamizol, and diclofenac (step 1 nonsteroidal anti-inflammatory drugs); and tramadol, codeine, and dihydrocodeine (step 2 opioid analgesic agents). However, these conventional treatments may not be effective for all patients who experience pain associated with breast cancer. Therefore, the following complementary and alternative therapies may also be used (especially for short-term pain relief): acupuncture, hypnosis, relaxation/imagery, music, massage, and herbal supplements. Finally, homotoxicological treatments, such as Traumeel (Heel GmbH, Baden-Baden, Germany), can be used to treat resistant pain associated with breast cancer.

In the study by Orellana Alvarellos et al, a Traumeel injection was used to alleviate the pain associated with breast cancer for patients who continued to experience pain after treatment with conventional medications. This study showed the advantages of Traumeel injection therapy for the relief of pain in those with breast cancer.

Methods
The study by Orellana Alvarellos et al included case observations of 9 women with unilateral breast cancer. The study was performed to assess pain relief and health-related quality of life after use of Traumeel injection therapy.
The 9 women in this study were aged 52 to 81 years (mean, 69.7 years). The cancer treatment these women received included surgery (conservative in 6 women and radical in 3 women), radiotherapy (all 9 women), and chemotherapy (only 3 women). Some of the women experienced pain immediately after treatment, whereas others only experienced pain between 2 and 12 months after surgery plus radiotherapy.
The 9 women received from 3 to 10 injections, until the pain was reduced. Injections were administered weekly. After the last injection, the patients were observed for 3- and 6-month periods. Of the 9 patients, 7 completed 6 months of observation and 2 completed 3 months of observation.
Pain was assessed by the 9 women as follows: before injection, immediately after injection, and at the 3- and 6-month observations. The sites, type, and occurrence of pain were assessed by questionnaire.

Procaine was added to the Traumeel injection to relieve the pain associated with the injection. There were a maximum of 20 sites for injection (based on Oriental acupuncture), including the breast, ipsilateral shoulder, and ipsilateral scapula.
The 9 women received from 3 to 10 injections, until the pain was reduced. Injections were administered weekly. After the last injection, the patients were observed for 3- and 6-month periods. Of the 9 patients, 7 completed 6 months of observation and 2 completed 3 months of observation.

Pain level was determined on a scale from 1 to 10, as on a visual analog scale. Patients also rated their health-related quality of life, including physical disability, insomnia,
and psychological distress. Finally, use of conventional analgesic agents before and after the Traumeel injection was noted.

Results
Three months after the final Traumeel injection, the mean±SD pain score was 3.3±2.2 points (range, 1–7 points). This indicated a slight overall increase in pain when compared with the level immediately after the Traumeel injection. However, at 3 months after the final treatment, the effects of Traumeel injection therapy tended to vary from patient to patient. For example, 1 patient experienced further pain relief, from 4 to 2 points; 3 patients maintained their pain relief (between 1 and 3 points); and 5 patients experienced increased levels of pain (between 2 and 7 points). Overall, all 9 women still had lower levels of pain than they had before the Traumeel injection was first administered.

Six months after the final Traumeel injection, the mean±SD pain score was 4.1±2.5 points (range, 1–7 points). For 5 of the women, the pain score remained the same; only 2 women experienced increased pain (this increase did not require treatment). Overall, the pain score was lower than before treatment, even after a lengthy period without any further therapy. Finally, even 12 months after the last Traumeel injection, some of the women noted that their pain had not been exacerbated.

In terms of physical disability, insomnia, and psychological symptoms, all 9 women experienced improved sleep. At the 3-month observation, 7 women continued to sustain a good quality of life, as determined by the physical and psychological symptoms.

The patients were asked about the effectiveness of Traumeel injection therapy. Of the 9 women, 8 indicated high effectiveness and 1 indicated good effectiveness. No patients reported low effectiveness. Overall, Traumeel injection therapy in these 9 women with breast cancer produced a sustained reduction in pain. Therapy also helped these women improve their management of daily work and reduce their psychological distress. Finally, the women experienced improved sleep as well.

Discussion
Traumeel has been used in Germany since 1937 to treat injuries and trauma. Research has indicated that Traumeel has analgesic and anti-inflammatory properties “by inhibiting the release of proinflammatory cytokines” (ie, interleukin 1β and tumor necrosis factor α) and a chemokine (ie, interleukin 8) in vitro.2 Other indications for which Traumeel has been used include chemotherapy-induced stomatitis, pain, and inflammation.

The pilot study performed by Orellana Alvarellos et al1 determined the effect of Traumeel injection therapy on 9 women with breast cancer. It was an open-label study and was not blinded. Each of the 9 women had taken various analgesic agents before the injection therapy, and the dosages of these agents were variable.

This study is the first to show the effectiveness of Traumeel injection therapy for pain associated with breast cancer. For example, 1 of the 9 women reduced her pain level from 10 points before the Traumeel injection to 5 points at 6 months after the last injection. Traumeel is effective because it contains neuralgia-attenuating substances used in homeopathy and homotoxicology. In conclusion, Traumeel injection therapy should be considered as an alternative therapy for pain in patients with breast cancer. Because breast cancer remains a worldwide health issue, and patients continue to experience resistant pain, effective pain medications are important. Traumeel provided tremendous pain relief immediately after final administration. This pain relief was long lasting (without using additional therapeutic agents). Therefore, because the results with Traumeel were good in this study, further clinical trials of this effective and tolerable homotoxicological agent should be planned and conducted.

References
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