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<u>ACUPUNCTURE ENHANCES REPRODUCTIVE FUNCTION WORLDWIDE –</u> <u>A HISTORICAL PERSPECTIVE</u>

Chinese medicine has treated infertility for thousands of years in Eastern Cultures. It wasn't until the early 1990's, however, that the World Health Organization of the United Nations issued a statement that acupuncture was effective at treating infertility. That statement was enough to encourage the world's reproductive community to evaluate the validity of this claim. Since that time, scientific studies are proving that acupuncture has measurable effects on:

- Balancing hormones
- Reducing the sympathetic nervous system response
- Increasing blood flow to the reproductive organs
- Improving implantation and pregnancy rates

Some of the first controlled studies were conducted in Eastern countries, evaluating the effect acupuncture had on reducing the sympathetic nervous system (fight or flight) response. One study, published in 1991, evaluated the hand skin temperature as the measurable variant. When acupuncture was performed at various points, the hand temperature increased. This exciting finding was beginning to show that acupuncture had some measurable effect of reducing the sympathetic nervous system's contractile function, increasing beta-endorphins, and moderating the release of GnRH from the hypothalamus, and shifting the body's emphasis toward the reproductive function.

ACUPUNCTURE & ELECTRO-THERAPEUTICS RES., Vol. 16, pp. 1-5, 1991 - Relationship Between Blood Radioimmunoreactive Beta-Endorphin and Hand Skin Temperature During The Electro-Acupuncture Induction of Ovulation, Chen Bo Ying M.D. Lecturer of Neurobiology, Institute of Acupuncture Research, and Yu Jin, MD., Prof of Gynecology Obstetricus and Gynecology Hospital Shanghai Medical University Shanghai, People's Republic of China Abstract: Thirteen cycles of anovulation menstruation in 11 cases were treated with Electro-Acupuncture (EA) ovulation induction. In 6 of these cycles which showed ovulation, the hand skin temperature (HST) of these patients was increased after EA treatment. In the other 7 cycles ovulation was not induced. There were no regular changes in HST of 5 normal subjects. The level of radioimmunoreactive beta-endorphin ($r\beta$ -E) fluctuated, and returned to the preacupunctural level in 30 min. after withdrawal of needles in normal subjects. After EA, the level of blood $r\beta$ -E in cycles with ovulation declined or maintained the range of normal subjects. But the level of blood $r\beta$ -E and increase of HST after EA (r=-0.677, P <0.01). EA is able to regulate the function of the hypothalamic pituitary-ovarian axis. Since a good response is usually accompanied with the

increase of HST, monitoring HST may provide a rough but simple method for prediciting the curative effect of EA. The role of $r\beta$ -E in the mechanism of EA ovulation induction was discussed.

In 1992, a four year study conducted by the Obstetrical & Gynecological Hospital, Zhejiang Medical University, China, reported acupuncture's measurable ability to induce ovulation in cases where women who developed ovarian hyperstimulation syndrome, and therefore could not safely be administered HCG for ovulation induction.

In 1996, a groundbreaking study from the University of Gothenburg, Sweden, Department of Obstetrics and Gynecology, revealed that eight electroacupuncture treatments significantly reduced the blood flow impedence of the uterine arteries, due to central inhibition of sympathetic activity. This resulted in vasodilation in the uterine arteries, improving the response to IVF medication.

Reduction of blood flow impedance in the uterine arteries of infertile women with electro-acupuncture, Elisabet Stener-Victorin[1.4], Urban Waldenström[2], Sven A. Andersson[3] and Matts Wikland[2]. [1]Department of Obstetrics and Gynaecology [2]Fertility Centre Scandinavia. Department of Obstetrics and Gynaecology and [3]Department of Physiology University of Gothenburg. S-413 45 Gothenburg, Sweden [4]To whom correspondence should be addressed: Department of Obstetrics and Gynecology. Kvinnokliniken Sahlgrensh sjukhuset, S- 413 45 Golhenburg, Sweden. Source: European Society for Human Reproduction and Embryology

In order to assess whether electro-acupuncture (EA) can reduce a high uterine artery blood flow impedance, 10 infertile but otherwise healthy women with a pulsatility index (PI) \geq 3.0 in the uterine arteries were treated with EA in a prospective, non-randomized study. Before inclusion in the study and throughout the entire study period, the women were down-regulated with a gonadotrophin-releasing hormone analogue (GnRHa) in order to exclude any fluctuating endogenous hormone effects on the PI. The baseline PI was measured when the serum oestradiol was \leq 0.1 nmol/l, and thereafter the women were given EA eight times, twice a week for 4 weeks. The PI was measured again closely after the eighth EA treatment, and once more 10-14 days after the EA period. Skin temperature on the forehead (STFH) and in the lumbosacral area (STLS) was measured during the first, fifth and eighth EA treatments. Compared to the mean baseline PI, the mean PI was significantly reduced both shortly after the eighth EA treatment (P < 0.0001) and 10-14 days after the EA period (P < 0.0001). STFH increased significantly during the EA treatments. It is suggested that both of these effects are due to a central inhibition of the sympathetic activity.

In July of 2000, the Society of Reproduction, Inc., reported another Swedish study in which a group of rats, injected with estradiol valerate developed polycystic ovaries, associated with increased nerve growth factor, and increased ovarian weight. In the rats that developed PCOs, electroacupuncture reduced the effects of the experimentally induced polycystic ovaries. Those in the control group remained unchanged.

Effects of Electro-Acupuncture on Nerve Growth Factor and Ovarian Morphology in Rats with Experimentally Induced Polycystic Ovaries1 Elisabet Stener-Victorin,[2,3] Thomas Lundeberg,[4] Urban Waldenström,[3] Luigi Manni,[5] Luigi Aloe,[5] Stefan Gunnarsson,[6] and Per Olof Janson[3] Department of Obstetrics and Gynecology,[3] Göteborg University, SE-413 45 Goteborg, Sweden Department of Physiology and Pharmacology,[4] Karolinska Institutet, SE-164 01 Stockholm, Sweden, Institute of Neurobiology (CNR),[5] Rome, Italy; Department of Evolutionary Biology,[6] SE-752 36 Uppsala, Sweden ABSTRACT: Despite extensive research on the pathogenesis of polycystic ovary syndrome (PCOS), there is still disagreement on the underlying mechanisms. The rat model for experimentally induced polycystic ovaries (PCO)--produced by a single injection of estradiol valerate--has similarities with human PCOS, and both are associated with hyperactivity in the sympathetic nervous system. Nerve growth factor (NGF) is known to serve as a neurotrophin for both the sympathetic and the sensory nervous systems and to enhance the activity of catecholaminergic and possibly other neuron types. Electro-acupuncture (EA) is known to reduce hyperactivity in the sympathetic nervous system. For these reasons, the model was used in the present study to investigate the effects of EA (12 treatments, approximately 25 min each, over 30 days) by analyzing NGF in the central nervous system and the endocrine organs, including the ovaries. The main findings in the present study were first, that significantly higher concentrations of NGF were found in the ovaries and the adrenal glands in the rats in the PCO model than in the control rats that were only injected with the vehicle (oil or NaCI). Second, that repeated EA treatments in PCO rats resulted in concentrations of NGF in the ovaries that were significantly lower than those in non-EA-treated PCO rats but were within a normal range that did not differ from those in the untreated oil and NaCI control groups. The results in the present study provide support for the theory that EA inhibits hyperactivity in the sympathetic nervous system.

In the summer of 2000, a small prospective study published in the Medical Acupuncture Journal reported that acupuncture may be a useful adjunct to gonadotropin therapy to produce follicles in women undergoing in vitro fertilization.

Acupuncture Treatment For Infertile Women Undergoing Intracytoplasmic Sperm injection Sandra L. Emmons, MD Phillip Patton, MD: Medical Acupuncture, A Journal For Physicians By Physicians Spring / Summer 2000- Volume 12 / Number 2 ABSTRACT Background Little information exists regarding the use of acupuncture in combination with allopathic treatment of infertility. Objective To describe the use of acupuncture to stimulate follicle development in women undergoing in vitro fertilization. Design, Setting, and Patients Prospective case series of 6 women receiving intracytoplasmic sperm injection and acupuncture along with agents for ovarian stimulation. Main Outcome Measures Number of follicles retrieved, conception, and pregnancy past the 1st trimester before and after acupuncture treatment. Results No pregnancies occurred in the non-acupuncture cycles. Three women produced more follicles with acupuncture treatment (mean, 11.3 vs 3.9 prior to acupuncture; P=.005). All 3 women conceived, but only 1 pregnancy lasted past the 1st trimester. Conclusion Acupuncture may be a useful adjunct to gonadotropin therapy to produce follicles in women undergoing in vitro fertilization.

In one of the most publicized studies on acupuncture and fertility, published by the ASRM in April 2002, acupuncture used 25 minutes before and 25 minutes after fetal embryo transfer dramatically improved pregnancy rates. Patients in this study were controlled for age, previous cycles, diagnostic criteria for infertility, endometrial thickness, pulsatility index of uterine arteries. Still, acupuncture rates were dramatically higher for the acupuncture group (42.5%) vs. the non-acupuncture group (26/3%).

FERTILITY AND STERILITY® VOL. 77, NO. 4, APRIL 2002 ©2002 American Society for Reproductive Medicine Wolfgang E. Paulus, M.D.,[a] Mingmin Zhang, M.D.,[b] Erwin Strehler, M.D.,[a] Imam El-Danasouri, Ph.D.,[a] and Karl Sterzik, M.D.[a] Objective: To evaluate the effect of acupuncture on the pregnancy rate in assisted reproduction therapy (ART) by comparing a group of patients receiving acupuncture treatment shortly before and after embryo transfer with a control group receiving no acupuncture. Design: Prospective randomized study. Setting: Fertility center. Patient(s): After giving informed consent, 160 patients who were undergoing ART and who had good quality embryos were divided into the following two groups through random selection: embryo transfer with acupuncture (n = 80) and embryo transfer without acupuncture (n = 80).

Intervention(s): Acupuncture was performed in 80 patients 25 minutes before and after embryo transfer. In the control group, embryos were transferred without any supportive therapy. Main Outcome Measure(s): Clinical pregnancy was defined as the presence of a fetal sac during an ultrasound examination 6 weeks after embryo transfer.

Result(s): Clinical pregnancies were documented in 34 of 80 patients (42.5%) in the acupuncture group, whereas pregnancy rate was only 26.3% (21 out of 80 patients) in the control group. Conclusion(s): Acupuncture seems to be a useful tool for improving pregnancy rate after ART.

In December of the same year, Cornell published a retrospective study of the literature, reporting that acupuncture seems to be able to: normalize function of the HPO axis; increase peripheral vascularization, and reduce the body's response to stress.

Role of acupuncture in the treatment of female infertility Raymond Chang, M.D.[a,b] Pak H. Chung, M.D.[b] and Zev Rosenwaks, M.D.[c] The Institute of East-West Medicine and the Center for Reproductive Medicine and Infertility, Weill Medical College of Cornell University, New York, New York. Received June 24, 2002; revised and accepted July 19, 2002. Reprint requests: Pak H. Chung, M.D., The Center for Reproductive Medicine and Infertility, Weill Medical College of Cornell University [a]The Institute of East-West Medicine. [b]The Department of Internal Medicine, Weill Medical College of Cornell University. [c]The Center for Reproductive Medicine and Infertility.

Objective: To review existing scientific rationale and clinical data in the utilization of acupuncture in the treatment of female infertility. **Design:** A MEDLINE computer search was performed to identify relevant articles. **Result(s):** Although the understanding of acupuncture is based on ancient medical theory, studies have suggested that certain effects of acupuncture are mediated through endogenous opioid peptides in the central nervous system, particularly β -endorphin. Because these neuropeptides influence gonadotropin secretion through their action on GnRH, it is logical to hypothesize that acupuncture may impact on the menstrual cycle through these neuropeptides. Although studies of adequate design, sample size, and appropriate control on the use of acupuncture on ovulation induction are lacking, there is only one prospective randomized controlled study examining the efficacy of acupuncture in patients undergoing IVF. Besides its central effect, the sympathoinhibitory effects of acupuncture may impact on uterine blood flow. Conclusion(s): Although the definitive role of acupuncture in the treatment of female infertility is yet to be established, its potential impact centrally on the hypothalamic-pituitary-ovarian axis and peripherally on the uterus needs to be systemically examined. Prospective randomized controlled studies are needed to evaluate the efficacy of acupuncture in the female fertility treatment. (Fertil Steril® 2002;78:1149-53. ©2002 by ASRM.)

September 2005 – a single blind, randomized, controlled trial using sham acupuncture conducted by the University of South Astrialia, reported these results: Two hundred twenty-eight subjects were randomized. The pregnancy rate was 31% in the acupuncture group and 23% in the control group. For those subjects receiving acupuncture, the odds of achieving a pregnancy were 1.5 higher than for the control group. The ongoing pregnancy rate at 18 weeks was higher in the treatment group (28% vs. 18%).

In 2006 the ASRM's Fertility & Sterility Journal reported a prospective, ramdomized trial performed in Denmark, entitled: Acupuncture on the day of embryo transfer significantly improves the reproductive outcome in infertile women, concluding Acupuncture on the day of ET significantly improves the reproductive outcome of IVF/ICSI, compared with no acupuncture.

Again the same year, Fertility & Sterility 2006 published a randomized, prospective, controlled clinical study jointly conducted in Germany and China, reporting that pregnancy rates were significantly higher when acupuncture was employed during the luteal phase after IVF/ICSI:

Effect of acupuncture on the outcome of in vitro fertilization and intracytoplasmic sperm injection: a randomized, prospective, controlled clinical study. Stefan Dieterle, M.D., a Gao Ying, M.D.,a,b Wolfgang Hatzmann, M.D.,a and Andreas Neuer, M.D.a Division of Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynecology, University of Witten/ Herdecke, Dortmund, Germany; and b Department of Obstetrics and Gynecology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China Objective: To determine the effect of luteal-phase acupuncture on the outcome of IVF/intracytoplasmic sperm injection (ICSI). Design: Randomized, prospective, controlled clinical study. Setting: University IVF center. Patient(s): Two hundred twenty-five infertile patients undergoing IVF/ICSI. Intervention(s): In group I, 116 patients received luteal-phase acupuncture according to the principles of traditional Chinese medicine. In group II, 109 patients received placebo acupuncture. Main Outcome Measure(s): Clinical and ongoing pregnancy rates. Result(s): In group I, the clinical pregnancy rate and ongoing pregnancy rate (33.6% and 28.4%, respectively) were significantly higher than in group II (15.6% and 13.8%). Conclusion(s): Luteal-phase acupuncture has a positive effect on the outcome of IVF/ICSI. (Fertil Steril ©2006 by American Society for Reproductive Medicine.)

In 2007, the Journal of Neuroendocrinology published a favorable study on clinical evidence in the use of acupuncture to treat PCOS:

This review describes the aetiology and pathogenesis of polycystic ovary syndrome (PCOS) and evaluates the use of acupuncture to prevent and reduce symptoms related with PCOS. PCOS is the most common female endocrine disorder and it is strongly associated with hyperandrogenism, ovulatory dysfunction and obesity. PCOS increases the risk for metabolic disturbances such as hyperinsulinaemia and insulin resistance, which can lead to type 2 diabetes, hypertension and an increased likelihood of developing cardiovascular risk factors and impaired mental health later in life. Despite extensive research, little is known about the aetiology of PCOS. The syndrome is associated with peripheral and central factors that influence sympathetic nerve activity. Thus, the sympathetic nervous system may be an important factor in the development and maintenance of PCOS. Many women with PCOS require prolonged treatment. Current pharmacological approaches are effective but have adverse effects. Therefore, nonpharmacological treatment strategies need to be evaluated. Clearly, acupuncture can affect PCOS via modulation of endogenous regulatory systems, including the sympathetic nervous system, the endocrine and the neuroendocrine system. Experimental observations in rat models of steroid-induced polycystic ovaries and clinical data from studies in women with PCOS suggest that acupuncture exert long-lasting beneficial effects on metabolic and endocrine systems and ovulation.

Fertility & Sterility, July 2008 reported on the positive role of acupuncture in the management of subfertility, ovulation induction, enhanced blood flow, increased sperm motility, and stress reduction.

Ernest Hung Yu Ng, M.D., Wing Sze So, B.Sc., Jing Gao, B.Sc., Yu Yeuk Wong, M.D. and Pak Chung Ho, M.D. Department of Obstetrics & Gynaecology, The University of Hong Kong, Hong Kong Special Administrative Region, People's Republic of China Objective: To review systematically the use of acupuncture in the management of subfertility. Design: A computer search was performed via several English and Chinese databases to identify journals relevant to the subject. Result(s): The positive effect of acupuncture in the treatment of subfertility may be related to the central sympathetic inhibition by the endorphin system, the change in uterine blood flow and motility, and stress reduction. Acupuncture may help restore ovulation in patients with polycystic ovary syndrome, although there are not enough randomized studies to validate this. There is also no sufficient evidence supporting the role of acupuncture in male subfertility, as most of the studies are uncontrolled case reports or case series in which the sample sizes were small. Despite these deficiencies, acupuncture can be considered as an effective alternative for pain relief during oocyte retrieval in patients who cannot tolerate side effects of conscious sedation. The pregnancy rate of IVF treatment is significantly increased, especially when acupuncture is administered on the day of embryo transfer. Conclusion(s): Although acupuncture has gained increasing popularity in the management of subfertility, its effectiveness has remained controversial. (Fertil Steril 2008;90:1–13 ASRM.)

To date, it appears that although almost every single study conducted over the last twenty years around the world demonstrates improved reproductive function, acupuncture remains controversial as an accepted treatment. Because Chinese medicine is not meant to be randomized or controlled, perhaps it can be concluded that although acupuncture has been demonstrated to improve overall fertility and pregnancy rates, acupuncture does not conform well to scientific measurement.