A Guide to Regulating Hormone Function Utilizing Traditional Chinese Medicine: A Comprehensive Literature Review

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Abstract

The purpose of the current retrospective literature synthesis was to investigate whether Traditional Chinese Medicine provides an effective alternative to Western Medicine in attenuating the physiological disturbances and disease progression and the accompanying hormonal variation of estrogen, testosterone, progesterone, oxytocin, cortisol, follicle stimulating hormone (FSH), and luteinizing hormone (LH) commonly associated with aging and the decline of reproductive capacity. For the purpose of the present research, electroacupuncture (EA) was identified as the specific component of TCM to be investigated. The seven hormones listed above were chosen based upon their relevance to fertility, reproduction, and the endocrine system in general. Upon comprehensive review of the relevant literature and scientific data, the investigator concludes that EA asserts a significant modulatory effect of varied strength on the hormones examined under the present investigation, as well as on underlying processes of disease and dysregulation. Accordingly, the hypothesis of the present investigation was deemed to be correct. Further, this investigation serves to inform future research on the meaningful impact of EA on neuroendocrine pathways and associated substances and hormones.

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Chapter 1: Introduction

Intent

The purpose of the current retrospective literature synthesis is to demonstrate that Traditional Chinese Medicine provides an effective alternative to Western Medicine in attenuating the physiological disturbances and disease progression and the accompanying hormonal variation of estrogen, testosterone, progesterone, oxytocin, cortisol, follicle stimulating hormone (FSH), and luteinizing hormone (LH) commonly associated with aging and the decline of reproductive capacity.

Definition of Terms

acupoints – designated locations along nerves or organ meridians for inserting acupuncture needles (Medical Dictionary, n.d.).

amenorrhea - the absence of menstruation. Women who have missed at least three menstrual periods in a row have amenorrhea, as do girls who haven't begun menstruation by age 15 (Mayo Clinic, n.d.).

Assisted reproductive technology (ART) - any fertility treatment in which the egg and sperm are handled. An ART health team includes physicians, psychologists, embryologists, lab technicians, nurses and allied health professionals who work together to help infertile couples achieve pregnancy. Procedures include fertility medication, artificial insemination, in vitro fertilization and surrogacy (Mayo Clinic, n.d.).

auricular concha – the hollow next to the ear canal (Medical Dictionary, n.d.).

autism spectrum disorder - a serious neurodevelopmental disorder that impairs a child's ability to communicate and interact with others. It also includes restricted repetitive behaviors, interests and activities. These issues cause significant impairment in social, occupational and other areas of functioning (Mayo Clinic, n.d.).

bioidentical hormones - hormones that come from plant or animal sources that are chemically identical to those the body produces. Hormones that are not synthesized in a lab (Mayo Clinic, n.d.).

Biomedicine – medicine based on the application of the principles of the natural sciences, especially biology and biochemistry (Merriam-Webster, n.d.).

control group – the group that serves as a standard for comparison in experimental studies. They are similar in relevant characteristics to the experimental group but do not receive the experimental intervention (Medical Dictionary, n.d.).

corticosterone – an adrenocortical steroid that has modest but significant activities as a mineralocorticoid and a glucocorticoid (Medical Dictionary, n.d.).

cortisol – a hormone produced in the adrenal glands that plays a variety of roles in the body. For example, cortisol helps regulate blood pressure and the cardiovascular system. It also helps the body respond to stress and regulates conversion of proteins, carbohydrates and fats in the diet into usable energy (Mayo Clinic, n.d.).

electroacupuncture (EA) – a form of acupuncture with electrical impulses passing through the needles to stimulate nerve tissue (Medical Dictionary, n.d.).

endometriosis - an often painful disorder in which tissue that normally lines the inside of your uterus — the endometrium — grows outside your uterus. Endometriosis most commonly involves the ovaries, fallopian tubes and the tissue lining the pelvis. Rarely, endometrial tissue may spread beyond pelvic organs (Mayo Clinic, n.d.).

estradiol (E2) – The most potent form of mammalian estrogenic steroids. In humans, produced by the cyclic ovaries and placenta (Medical Dictionary, n.d.).

estrogen – a major sex hormone that stimulates the female reproductive organs, and the development of secondary female sex characteristics (Medical Dictionary, n.d.).

experimental group – in an experiment or clinical trial, the group of subjects who are exposed to the variable under study (Medical Dictionary, n.d.).

follicle stimulating hormone (FSH) - a major gonadotropin secreted by the anterior pituitary gland. It stimulates gametogenesis and the supporting cells such as the ovarian granulosa cells, the testicular sertoli cells, and leydig cells (Medical Dictionary, n.d.).

glucocorticoids- a group of corticosteroids that affect carbohydrate metabolism, inhibit adrenocorticotropic hormone secretion, and possess pronounced anti-inflammatory activity (Medical Dictionary, n.d.).

gonadotropins – hormones that stimulate gonadal functions and sex steroid hormone production in the ovary and testes (Medical Dictionary, n.d.).

gonadotropin releasing hormone (GnRH) – a decapeptide that stimulates the synthesis and secretion of follicle stimulating hormone and luteinizing hormone, both pituitary gonadotropins (Medical Dictionary, n.d.).

homeostasis – a relatively stable state of equilibrium (Merriam-Webster, n.d.).

hormone – a natural substance that is produced in the body and influences the way the body grows and develops (Merriam-Webster, n.d.).

hyperandrogenism – a condition caused by excessive secretion of androgens from the adrenal cortex, the ovaries, or testes. The clinical significance in males is negligible. In women, the common manifestations are hirsutism and virilism as seen in patients with polycystic ovary syndrome and adrenocortical hyperfunction (Medical Dictionary, n.d.).

hypothalamic-pituitary-adrenal axis (HPAA) – a complex set of direct influences and feedback interactions among three endocrine glands: the hypothalamus, pituitary, and adrenals (Medical Dictionary, n.d.).

hypothalamic-pituitary-gonadal axis (HPGA) - refers to the hypothalamus, pituitary gland, and ovaries as if these individual endocrine glands were a single entity. Fluctuations in this axis cause changes in the hormones produced by each gland and have various local and systemic effects on the body (Medical Dictionary, n.d.).

hypothalamic-pituitary-ovarian axis (HPOA) – refers to the hypothalamus, pituitary gland, and ovaries as if these individual endocrine glands were a single entity. Fluctuations in this axis cause changes in the hormones produced by each gland and have various local and systemic effects on the body (Medical Dictionary, n.d.).

Kidney Essence – in TCM, one of the vital fluids of the body that is stored in the Kidneys and contains the map of our genetic makeup (Lewis, 2004, p. 286).

Kidney meridian – one of the 12 primary meridians of the body in TCM, controls the reproductive system and hormones, and stores the Essence (Lewis, 2004, p. 289).

Kidney yang - the aspect of the Kidney meridian that is one of the two opposites that create the universe and are present in everything; hot, light, and masculine energy (Lewis, 2004, p. 291).

Kidney yin – the aspect of the Kidney meridian that is one of the two opposites that create the universe and are present in everything; cold, dark, and feminine energy (Lewis, 2004, p. 291).

luitenizing hormone (LH) - a major gonadotropin secreted by the anterior pituitary gland. It regulates steroid production by the interstitial cells of the testis and the ovary. The preovulatory luteinizing hormone surge in females induces ovulation, and subsequent luteinization of the follicle (Medical Dictionary, n.d.).

menopause – permanent cessation of menses. Usually defined after 6 to 12 months of amenorrhea in women over age 45 (Medical Dictionary, n.d.).

oral contraceptives - compounds, usually hormonal, taken orally in order to block ovulation and prevent the occurrence of pregnancy. The hormones are generally estrogen or progesterone or both (Medical Dictionary, n.d.).

ovarian hyperstimulation syndrome (OHSS) – a complication of ovulation induction in infertility treatment. It is graded by severity of symptoms which include ovarian enlargement, multiple ovarian follicles, ovarian cysts, ascites, and generalized edema (Medical Dictionary, n.d.).

oxytocin – a nonapeptide hormone released from the posterior pituitary gland. It acts on smooth muscle cells, such as causing uterine contractions and milk ejection (Medical Dictionary, n.d.).

ovariectomy – surgical removal of one or both ovaries (Medical Dictionary, n.d.).

polycystic ovary syndrome - complex disorder characterized by infertility, hirsutism; obesity; and various menstrual disturbances such as oligomenorrhea; amenorrhea; anovulation. It is usually associated with bilateral enlarged ovaries studded with atretic follicles (Medical Dictionary, n.d.).

perimenopause – the transitional period before and after menopause. Perimenopausal symptoms are associated with irregular menstrual cycle and widely fluctuated hormone levels. They may appear 6 years before and 2 -5 years after menopause (Medical Dictionary, n.d.).

primary ovarian insufficiency (POI) – a syndrome characterized by amenorrhea, sex steroid deficiency, and elevated gonadotrophins occurring in women under the age of 40. Also known as premature ovarian failure (POF), premature ovarian dysfunction, premature menopause (Zhou, Jiang, Wu, & Liu, 2013).

practical significance - refers to how those practicing in a profession will benefit form research work. A study may produce statistically significant results but lack practical significance (Cottrell & McKenzie, 2011, p. 41).

progesterone - the major progestational steroid that is secreted primarily by the corpus luteum and the placenta. It acts on the uterus, the mammary glands and the brain. It is required in embryo implantation; pregnancy maintenance, and the development of mammary tissue for milk production (Medical Dictionary, n.d.).

sex steroid hormones – steroid hormones produced by the gonads that stimulate reproductive organs, germ cell maturation, and the secondary sex characteristics in males and females. The major sex steroid hormones include estradiol, progesterone, and testosterone (Medical Dictionary, n.d.).

testosterone - potent androgenic steroid and major product secreted by the leydig cells of the testis. Its production is stimulated by luteinizing hormone from the pituitary gland. In turn, testosterone exerts feedback control of the pituitary LH and FSH secretion. Depending on the tissues, testosterone can be further converted to dihydrotestosterone or estradiol (Medical Dictionary, n.d.).

Traditional Chinese Medicine (TCM) – a system of medicine originating in China thousands of years ago that incorporates acupuncture and Traditional Chinese herbal prescriptions (Lewis, 2004, p. 291).

Problem Statement

While the most obvious consideration for conception and pregnancy, reproductive and endocrine health bear consequence that extends far beyond reproduction to encompass all aspects of total health and well being. Reproductive health proves to be one of the unique areas in the body in which disharmony and disease commonly become symptomatic with greater significance much earlier in the lifespan in comparison to those of most other pathological processes. Early issues pertaining to dysregulation of endocrine function commonly presented clinically are seemingly minor complaints such as energy and weight concerns, menstrual irregularity, poor sleep quality, mood disturbances, and low libido. Although apparently minimal, these concerns are an indication of endocrine disturbance that may lead to subfertility during reproductive years, as well as more severe health concerns as aging and degeneration occur (Cochrane, Smith, Possamai-Inesedy, & Bensoussan, 2014). There is substantial research and evidence largely implicating endocrine and hormone dysregulation in the inflammatory and degenerative disease processes commonly associated with ordinary and premature aging. Specifically, infertility, metabolic disorder, osteoporosis, and impaired cardiovascular and cognitive function have all been demonstrated to be related to the hormonal variation commonly associated with aging, whether natural or premature (Cochrane et al., 2014).

This is not to imply that the natural process of aging is indicative of an undesirable or pathological state, but instead to create an awareness that the understanding and optimization of hormonal variation commonly associated with aging gains importance and allows for adaptation to modern culture and trends for longevity, lifelong well-being, and late reproduction. Further, this expansive body of information provides a theoretical explanation for the manifestation and progression of disease with age, and therefore, illuminates the necessity for broader research and understanding of reproductive and endocrine function optimization as they relate to general health, prevention, and longevity.

Similarly, the importance of reproductive and sexual health as essential components to total health and well-being across the lifespan is well-known and documented (Appt & Ethun, 2010). Rojas et al. (2015) illustrate the broader implications of poor reproductive health for women in regards to generalized physical and mental health, as well as the impact on the health of offspring and future generations. Rojas et al. (2015) maintain that there are a multitude of potential endocrine-metabolic disturbances that may result from impaired reproductive health for women, and as many adverse consequences for offspring both prenatally and postpartum. For both mother and child, the affects of endocrine-metabolic disturbances have true potential to be detrimental and far-reaching. As a result, it is demonstrated that rigorous regulation of the processes governing endocrine function at each stage of the lifespan is critical, and not merely beneficial as is commonly implied by the current standard of care for common endocrine disturbances.

Rojas et al. (2015) explain:

> Indeed, female reproductive physiology entails intricate interactions among hormonal, metabolic-energetic, genetic-epigenetic, and intra- and extraovarian factors, which in coordination modulate the successive development of the female gamete [5]. Disruptions in any of these components may lead to infertility, an alarming problem in women's global health, currently affecting 48.5 million females aged 20–44 years [6]. Moreover, alterations of female reproductive physiology often bear implications in other organ systems, as in the classical example of polycystic ovary syndrome [7]. Beyond the physical and mental implications in women [8], these alterations may also reflect on the ulterior health of their potential offspring [9]. There are an abundance of mediators from many interconnected and overlapping neuroendocrine regulation systems, where both reproductive and metabolic signals are integrated [10]. The genetic, endocrine, and metabolic mechanisms underlying female reproduction are numerous and sophisticated, displaying complex functional evolution throughout a woman's lifetime.

Appropriately, understanding and addressing optimal reproductive and endocrine health provides practitioners great opportunity to significantly impact patients' quality of life and health in a positive direction, in addition to optimizing reproductive capacity. Through their expertise, practitioners trained to identify and treat reproductive health dysfunction are afforded the opportunity to provide alternative treatment options that may be more effective or pose less risk of unwanted side effects. Progressive diagnosis and treatment of reproductive and endocrine dysfunction will additionally allow for early intervention of associated disease development and premature aging related to hormonal insufficiency before advancement to a state of ill-health and diminished quality of life that has the potential to impact gene expression and, as a consequence, multiple generations.

Traditional Chinese Medicine (TCM) provides a feasible and accessible alternative for early and safe identification and intervention of endocrine and reproductive disturbances regardless of etiology. Traditional Chinese Medical theory, diagnosis, and treatment are based on the balance of basic principles that govern meridians, organs, and the body at large. The underlying tenant of TCM is to return the body, mind, and lifestyle to an existence of homeostasis. As such, TCM seeks to impact the root cause of disease while simultaneously alleviating clinical manifestations and taking into consideration the whole person, and it appears to do so with very little risk. Additionally, the appeal of TCM is increased by virtue of the fact that it offers care in a form that is both holistic and adapted to the individual. This is particularly meaningful as it relates to the function of hormones and the endocrine system, as there are many particularized factors involved in the treatment of reproductive and sexual health (Lewis, 2004, p. 55).

There is wide-spanning research documenting the relevance of Traditional Chinese Medicine in regards to the treatment of specific and individualized aspects of endocrine and reproductive function. For example, the current literature illustrates the usefulness of Traditional Chinese Medical herbal prescriptions in the treatment of age-related estrogen decline in perimenopause, as well as surgically induced waning of estrogen (Xie et al., 2012). Likewise, there is substantial research on the use of electroacupuncture to induce ovulation and normalize testosterone levels in PCOS patients with mild to moderate androgenic complications (Feng et al., 2012).

While helpful and integral in setting a strong basis for the current understanding of many of the numerous manifestations and considerations related to reproductive and endocrine dysfunction, the contemporary literature does not offer broader clinical application as it relates to generalized manifestations of reproductive and endocrine dysregulation and the associated hormonal variation (Cochrane et al., 2014).

The current literature remains fragmented and falls short in creating a comprehensive picture of the ways in which practitioners of Traditional Chinese Medicine can successfully treat generalized and less specific hormone and endocrine dysregulation in a clinical setting. The intention of the present investigation is to create a literature synthesis that serves to provide a framework and standard of care by which practitioners of Traditional Chinese Medicine can successfully treat hormone function early in the lifespan in order to positively impact quality of life and attenuate the disease progression at the source of less than optimal hormonal variation.

This systematic review seeks to expand on the existing literature by connecting essential components of current diagnostic and treatment principles. For the purpose of this particular review, the principal investigator has identified seven major hormones of the hypothalamic-pituitary-gonadal axis to be considered: estrogen, testosterone, progesterone, oxytocin, cortisol, follicle stimulating hormone (FSH), and luteinizing hormone (LH). Each of these hormones is related through positive and negative physiological feedback loops and is largely relevant to quality of life and reproduction.

In addition to providing a compilation of the existing research, this literature synthesis serves to provide an opportunity for both patients and practitioners alike, as it will inform future research, provide alternative treatment options, and provide early intervention of associated hormonal variation resulting from disease progression and natural aging.

Background Discussion

In order to provide patients with treatment that is comprehensive and integrative in nature, it is essential to highlight the correlation between endocrine and reproductive function from a Biomedical perspective and that of Traditional Chinese Medical theory.

The Endocrine System and its Functions According to Biomedicine

According to the professional edition of Merck Manuals Online (n.d.), the endocrine system includes a collection of glands that produce hormones that affect a multitude of diverse processes in the body, affecting nearly every organ and cell in the human body. The major physiological processes governed by the endocrine system include, and extend far beyond, metabolism regulation, growth and development, tissue health and regeneration, sexual function, reproductive capacity, mood, sleep and wake cycles, and aging.

Additionally, it is well-known that hormones undergo many changes, not only as a consequence of aging, but also, as a consequence of variation from an individual's unique spectrum of physiological homeostasis (Merck Manuals, n.d.). In general, the secretion of each hormone must be regulated within precise and individualized limits in order to adequately control and modulate healthy endocrine function (Lewis, 2004, p. 13- 56). These precise limits are largely defined by our genetic makeup or constitution, and expressed by the interplay between our genes and our environment, as well as the interconnectedness of hormones in relationship to one another (Gottfried, 2013, p. 50).

Optimal Endocrine Function

Dr. Sara Gottfried provides a picture of optimum endocrine and hormone function as a relaxed state with increased stability that is free from excess tension and stress (Gottfried, 2013, p. 65-66). She goes on to say that hormonal balance is our natural state, as it requires less energy to maintain homeostasis than it does to be in a state of disequilibrium (Gottfried, 2013, p. 54). In addition to providing a protective function against major manifestations of endocrine dysfunction such as infertility and stress response, a balanced and healthy endocrine system provides the appropriate amount and fluctuation of hormones to impact every aspect of life.

For example, adequate estrogen promotes pleasurable states such as stable mood, restful sleep, and sexual satisfaction, while healthy levels of cortisol function to appropriately alert the nervous system to perceived threats and danger. Each of these hormones have far-reaching potential to be beneficial and health-promoting when functioning at optimal capacity and in harmony with the body's natural rhythms and the environment (Gottfried, 2013, p. 50-51).

Similarly, Traditional Chinese Medical fertility specialist Dr. Randine Lewis describes fertility and the ability to conceive as the natural state for all women of childbearing age with their reproductive organs intact (2004, p. 9).

Variation from the optimal states depicted above by Doctors Gottfried and Lewis is indicative of hormonal and endocrine disruption. Further, progression of these states of suboptimal functioning has the potential to lead to a myriad of reproductive, endocrine, and systemic diseases. Disorders involving the endocrine glands and their feedback mechanisms, regardless of etiology, fall under the classification of either hypo- or hyperfunctioning. When too little of a hormone is produced, this is a state of hypofunction, while hyperfunction occurs when too much of a hormone is produced. In both instances, the body is in a state of disequilibrium and becomes more susceptible to disease.

Common Treatment of Endocrine Dysfunction

Typical Biomedical treatment of hypofunctioning hormones involves introducing exogenous hormones through oral contraceptives, hormone replacement therapy, or bioidentical hormone replacement therapy in order to replace deficient hormones. In order to manage hyperfunctioning hormones, treatments are targeted to suppress hormone production through radiation therapy, surgery, and pharmaceuticals (Merck Manuals, n.d.). Additionally, it is common for western physicians to prescribe antidepressants and/or antianxiety medications to manage cognitive and emotional symptoms associated with suboptimal hormone levels (Gottfried, 2013, p. 65).

Common Dysfunctions According to Biomedicine and their Relationship to Hormones

Common dysfunctions in the body arising from various etiologies that involve the interplay of hormones and the endocrine feedback mechanism are listed below according to associated hormones.

Estrogen

Vaginal dryness – an issue common in postmenopausal women that may be associated with vaginal atrophy in which vaginal tissues become thinner and more easily irritated. Vaginal dryness and atrophy is a consequence of the natural decline in estrogen levels during menopause. In order to remedy vaginal dryness and the associated painful intercourse, low-dose vaginal estrogen creams, tablets, or rings may be utilized to restore healthy vaginal tissue (Mayo Clinic, n.d.).

Bone loss - osteopenia (mild bone loss) and osteoporosis (progressed bone loss) dramatically increase with menopause due to declining estrogen levels. Prolonged absence of menstruation prior to menopause resulting in insufficient estrogen also increases the risk of osteoporosis. In both cases, supplemental estrogen therapy may be administered to prevent or reduce bone loss (Mayo Clinic, n.d.).

Endometriosis – a painful disorder in which tissue that normally lines the inside of the uterine cavity grows outside of the uterus, generally within the pelvic cavity. Endometriosis most commonly involves the ovaries, fallopian tubes, and the tissue lining the pelvis. With endometriosis, displaced endometrial tissue continues to thicken, break down and bleed each month due to the natural hormonal fluctuations of a normal menstrual cycle. As a result, surrounding tissue can become inflamed and develop scar tissue and adhesions potentially causing tissues and organs to stick together. Supplemental hormones may be effective in reducing or eliminating the pain and symptoms of endometriosis due to their interference of natural monthly hormonal fluctuations that cause changes to the endometrial tissue that exacerbates endometriosis. Combinations of supplemental exogenous hormones that include estrogen may slow endometrial tissue growth and accompanying symptoms by decreasing the body's production of its own endogenous hormones (Mayo Clinic, n.d.).

Endometrial cancer – malignancy that forms in the endometrial lining of the uterus. Endometrial cancer is additionally called uterine cancer. Medications to reduce the amount of estrogen and hinder the body's utilization of available estrogen may be administered in order to prevent the growth of malignant cells that rely on estrogen for growth (Mayo Clinic, n.d.).

Premature ovarian failure — also known as primary ovarian insufficiency. A loss of normal ovarian function before age 40 resulting in diminished production of hormones, including estrogen. Premature ovarian failure differs from premature menopause in that women with premature ovarian failure may have irregular or occasional periods allowing for the possibility of pregnancy, while women with premature menopause experience cessation of menses and are unable to become pregnant. Restoring estrogen levels in women with premature ovarian failure may prevent complications related to diminished estrogen (Mayo Clinic, n.d.).

Polycystic ovary syndrome - a common endocrine system disorder among women of reproductive age. Common manifestations of PCOS are infrequent or prolonged menstrual periods, abnormal hair growth and acne due to excessive androgens, obesity, and diagnostically enlarged ovaries that contain small collections of fluid-filled sacs. Two of the above manifestations must be present in order for a diagnosis of PCOS. Combination hormone therapy that includes estrogen, typically in the form of oral contraceptives and vaginal rings, are utilized to regulate menstrual cycles and to address the underlying excessive androgens (Mayo Clinic, n.d.).

Progesterone

Endometriosis – please see the disease description above under estrogen. In addition to supplemental exogenous hormone therapy involving estrogen, progesterone is also administered in order to impede natural monthly hormonal fluctuations to treat the pain and symptoms of endometriosis (Mayo Clinic, n.d.).

Endometrial cancer – please see the disease description above under estrogen. Exogenous hormone therapy to increase the amount of progesterone in the body is sometimes utilized to treat endometrial cancer for the purpose of preventing the continued growth of malignant cells (Mayo Clinic, n.d.).

Premature ovarian failure – please see the disease description above under estrogen. Exogenous progesterone therapy may be incorporated along with supplemental estrogen in order to enhance treatment and alleviate associated symptoms (Mayo Clinic, n.d.).

Polycystic ovary syndrome - please see the disease description above under estrogen. Supplemental progesterone is used in conjunction with estrogen in order to regulate menstrual cycles and alleviate symptoms of PCOS while reducing excessive androgens (Mayo Clinic, n.d.).

Testosterone

Polycystic ovary syndrome – please see the disease description above under estrogen. Since excessive androgens such as testosterone is the underlying etiology, hormone therapy targeted to reduce androgens may be incorporated in the management of the clinical manifestations of PCOS (Mayo Clinic, n.d.).

Oxytocin

Detachment – oxytocin stimulates uterine contractions in labor and delivery and is produced in abundance during breastfeeding to promote bonding between mother and baby. Insufficient oxytocin may interfere with a mother's ability to nurse and easily bond with her baby. Additionally, synthetic oxytocin is commonly administered in the form of pitocin to promote labor and delivery (Bell, Erickson, & Carter, 2014).

Cortisol

Cushing Syndrome – also called hypercortisolism, occurs when the body is exposed to excessive cortisol for a prolonged length of time. This can result from exogenous cortisol such as oral corticosteroid medications or when excessive endogenous cortisol is produced by the body. Specific manifestations such as a fatty hump between the shoulders, a rounded face, and pink or purple stretch marks on the skin of the abdomen are hallmarks of Cushing Syndrome. Medications to reduce adrenal gland production of cortisol, as well as medications to block the effect of cortisol on the tissues may be administered in the treatment of Cushing Syndrome (Mayo Clinic, n.d.).

Addison's disease – also called adrenal insufficiency, a disorder that occurs when the body produces insufficient cortisol and other adrenal hormones. Addison's disease occurs in all age groups and can be life-threatening. Treatment of Addison's disease involves oral or injectable hormone replacement therapy of corticosteroids in order to replenish insufficient cortisol (Mayo Clinic, n.d.).

Follicle stimulating hormone (FSH)

Infertility – elevated FSH is indicative of diminished reproductive capacity either due to natural sex steroid hormonal decline resulting from perimenopause, menopause, or premature ovarian insufficiency. Standard clinical management of increased FSH levels in the treatment infertility involves exogenous hormone therapy in order to supplement diminished hormone levels (Gottfried, 2013 p. 182).

Luteinizing hormone (LH)

Infertility – similarly to elevated FSH, increased levels of LH is indicative of diminished reproductive capacity, whether due to a natural or premature decline of sex hormones. In the care of infertility, elevated LH is addressed by replacing diminished hormones through the introduction of exogenous hormone therapy (Gottfried, 2013, p. 126).

The Endocrine System According to Traditional Chinese Medicine

In comparison, the Kidney meridian in Traditional Chinese Medicine is a representation of the precise relationships governed by the reproductive and endocrine systems in western medicine. Further, the Kidney meridian stores a substance referred to as Essence. This Kidney Essence represents a constituent that is synonymous with the biomedical perspective of hormones (Xiufeng et al., 2015). An individual's Essence is comprised of both the prenatal or congenital

Essence and postnatal or acquired Essence of the parents, both of which are a product of genetics and circumstantial factors such as health at time of conception, emotional well-being and stability, and lifestyle factors such as diet, exercise, and living and working conditions. The Essence is the most fundamental expression of an individual's constitution, strength, and vitality, and forms the basis of each unique individual (Maciocia, 2005, p. 44 -45).

Together, the Kidney yin and Kidney yang energies interact with the Essence to function in the same capacity as the intricate and complex feedback mechanisms required to maintain endocrine function and hormonal sufficiency that is equalized and harmonious (Xiufeng et al., 2015).

These congruent systems are involved in virtually every physiological function required to sustain life. Growth, development, reproduction, metabolic and cellular homeostasis, adaptation to external influences, capacity for resistance and healing, and aging all rely on the elaborate balance and vitality of the Essence in Traditional Chinese Medicine, just as they rely on the regulatory function of the endocrine system in Biomedicine (Xiufeng et al., 2015).

Endocrine Dysfunction According to Traditional Chinese Medicine

Similarly to Biomedical dysfunctions related to hormones that arise, disequilibrium and eventual disease are the result when the harmonious balance and vitality of the Kidney energies is altered. Accordingly, potential imbalanced states of the Kidney meridian would encompass components of deficiency of Kidney yin, Kidney yang, and Kidney Essence, as well as the resulting imbalance between all components of the Kidney meridian. In TCM, there is no recognition of excess pathology of the Kidney energies, and instead, strictly deficiency patterns are presented. This is likely due to the fact that all physiological processes draw on Kidney reserves starting from the time of conception, a process which can be conceptualized as the aging process.

Clinical Manifestations and the Treatment of Kidney Yin and Kidney Yang Deficiencies

Reproductive symptoms of Kidney yin deficiency include menorrhagia, amenorrhea, early menses, scanty menses, eclampsia, and infertility. More generalized symptoms of Kidney yin deficiency would include dizziness, tinnitus, backache, feeling of heat, and night sweats. Reproductive symptoms of Kidney yang deficiency are menorrhagia, late menses, leukorrhea, diarrhea with menses, edema in pregnancy, and infertility, whereas generalized symptoms of Kidney yang deficiency include cold temperature, backache, depression, and frequent pale urination (Maciocia, 2011, p. 52).

It is common and likely to have simultaneous deficiencies and presentation of both the Kidney yin and yang energies due to their interdependence. This is especially true after the age of 40, which aligns with the typical onset of perimenopause in Biomedicine (Maciocia, 2011, p. 52) The treatment of these deficiencies entails the strengthening and balancing of all components of the Kidney meridian through acupuncture, herbal medicine, and dietary and lifestyle modifications, as well as any act or practice that is utilized to preserve or enhance Kidney reserves, and therefore, promote longevity (Lewis, 2004, p. 56-57).

Factors Related to Reproductive Capacity and Aging According to Biomedicine and Traditional Chinese Medicine

Biomedicine and Traditional Chinese Medicine alike provide a framework for the understanding that the blueprint for an individual's reproductive health and capacity is largely determined at the time of conception, while lifestyle and individual circumstance dictate the expression of this genetic blueprint. Biomedical research demonstrates that reproductive health begins at conception with the development of ovarian follicle cells in utero. There are approximately 6,000,000 primordial follicles present at the time of ovary formation in a developing fetus. This number decreases exponentially to approximately 600,000 at birth, and again to approximately 300,000 by the time menarche is reached (Geber, Megale, R., Vale, F., Lanna, & Cabral, 2012). Congruently, the prenatal Essence, which is derived from the combination of maternal and paternal Essence, is also present from the time of conception and largely dictates an individual's reproductive capacity (Maciocia, 2005, p. 44-45).

Accordingly, the Biomedical understanding that reproductive health begins in utero is aligned with and substantiated by Traditional Chinese Medical theory. This alliance of east and west further serves to illustrate and form a comprehensive basis for the perspective that reproductive health is essential to and provides an early depiction of overall health and well-being, as well as potential for longevity (Maciocia, 2005, p. 275).

Similarly, the natural decline of Essence throughout the lifespan is synonymous with a natural reduction in reproductive capacity and the aging process alike. Appropriately, according to Traditional Chinese

Medical theory, reproductive failure, whether premature or due to natural waning, is strongly tied to deficiency of Kidney Essence. Equally, aging, also whether premature or due to natural decline, is similarly conceived of as a weakening of Kidney Essence. Therefore, the mechanisms and physiology of reproduction and aging are further demonstrated to be governed by the same origin and are shown to be elaborately interdependent and intertwined in both Biomedicine and Traditional Chinese Medicine. (Szmelskyj, I., Aquilina, & Szmelskyj, A. O. 2015, p. 46-47).

Both orientations highlight a life of balance of utmost importance when considering preservation of this potential. In Biomedicine, premature aging is considered to be a consequence of lifestyle factors, such as chronic stress, inadequate diet, lack of exercise, and exposure to environmental toxins. Congruently, in Traditional Chinese Medical theory, conservation of vital Essence equally requires an approach of balance when considering quantity and quality of nourishment from food, drink, and air, as well as balance in physical, emotional, and sexual energetic expenditures (Maciocia, 2005, p.45).

Although vastly different approaches to medicine and the treatment of disease, Biomedicine and Traditional Chinese Medicine share great commonality and are mutually supportive in regards to reproduction and longevity. Both systems of medicine have demonstrated that reproductive health is of critical importance and serves as an early indicator of overall health and well-being, as well as aging potential. Furthermore, both classifications validate that there are countless physiological functions governed by the systems responsible for reproduction and fertility, and therefore, that the impact of optimization of reproductive health extends far beyond pregnancy and conception. In fact, virtually every physiological function necessary to sustain life is impacted by the mechanisms that govern procreation. As such, both Traditional Chinese Medicine and Biomedicine provide a framework for maximizing fertility and regulating hormone function while simultaneously promoting health and longevity. Accordingly, physicians from both orientations are equipped with a unique opportunity to provide integrative and comprehensive solutions for treatment and prevention of reproductive and degenerative disease processes associated with aging at every stage of the lifespan, beginning with conception.

Research Question

The current investigation seeks to answer the question: Does Traditional Chinese Medicine provide an effective alternative to

Western Medicine in attenuating the physiological disturbances and disease progression and the accompanying hormonal variation of estrogen, testosterone, progesterone, oxytocin, cortisol, follicle stimulating hormone (FSH), and luteinizing hormone (LH) commonly associated with aging and the decline of reproductive capacity?

Hypothesis

Traditional Chinese Medicine provides an effective alternative to Western Medicine in attenuating the physiological disturbances and disease progression and the accompanying hormonal variation of estrogen, testosterone, progesterone, oxytocin, cortisol, follicle stimulating hormone (FSH), and luteinizing hormone (LH) commonly associated with aging and the decline of reproductive capacity.

Null and Alternate Hypotheses

The researcher of the present study acknowledges that null and alternate hypotheses are equally possible additional outcomes of the current investigation, and as such, remains fully inclusive of all possibilities and outcomes.

Chapter 2: Review of Literature

Estrogen: Estradiol (E2)

A literature synthesis conducted by Zhou et al. (2013) documents numerous studies in support of electroacupuncture's ability to increase E2. Further, Zhou et al. (2013) performed a study investigating the effect of EA on women with primary ovarian insufficiency (POI). POI is a syndrome occurring in women below the age of 40 with amenorrhea who also exhibit sex steroid deficiency and elevated gonadotrophins due to suboptimal ovarian function. As a result, symptoms of POI mimic menopausal symptoms, including hot flashes, vaginal dryness, painful intercourse, and sleep and mood disturbances. The differentiating factor between POI and menopause, however, is that menopause is a true and definite cessation of menses due to ovarian aging, whereas POI is characterized by amenorrhea as a result of varying and unpredictable ovarian function. Zhou et al. (2013) sought to determine the impact of EA on three vital markers of reproductive function, including serum E2. The outcome was that there was a statistically significant increase in E2 at the end of the three-month treatment period compared to baseline measurements. Furthermore, this difference was found to remain constant at follow-up three months post-treatment.

Similarly, after a decade of studying the impact of acupuncture on reproductive disorders, Zhao, Tian, Cheng, and Chen, (2004) have consistently demonstrated that repeated EA increases serum E2 in ovariectomized rats despite the fact that the ovaries are primarily responsible for the production of E2. Appropriately, findings related to ovariectomized rats can be applied clinically to issues of inadequate E2 and hormonal insufficiency resulting from absent and suboptimal ovarian function.

Estrogen plays a critical role in bone health for women. Consequently, in both natural and premature reproductive aging, bone density, restoration, and formation are a major consideration as estrogen levels diminish (Zheng, Wu, Nie, & Lin, 2015). A literature synthesis performed by Zheng et al. (2015), further substantiates that numerous clinical studies have demonstrated EA to be an effective treatment for various issues of reproductive dysfunction characterized by dysregulated estrogen, including bone loss, even in ovariectomized rats. Consistent with previous research, in an experiment performed by Zheng et al. (2015), EA was demonstrated to increase serum E2 in ovariectomized rodents, thereby providing a method of protection against bone loss and supporting a mechanism for bone formation and remineralization.

While most of the research demonstrates the ability of EA to increase serum E2, there is evidence that it also reduces serum E2. A randomized controlled trial conducted by Jedel et al. (2011) investigating the impact of repeated EA demonstrated a statistically significant reduction in serum E2 in women with PCOS when compared to a no treatment control group.

Progesterone

A study by Chen, L. et al. (2016) investigating ovarian hyperstimulation syndrome (OHSS) in rodents provides some insight into the relationship between EA and progesterone. Although ovarian stimulation is a necessary aspect of assisted reproductive therapy (ART), varying degrees of OHSS is a common complication that becomes increasingly detrimental upon progression. The results of the current study led the investigators to conclude that it may be possible that EA moderates the symptoms and progression of OHSS by down-regulating progesterone.

The opposite was found in an investigation on the effect of EA on clinically induced PCOS models in rats conducted by Feng et al. (2012). In this study, it was discovered that when animals deemed to be non-respondent to treatment were excluded from results serum progesterone was increased by EA.

Testosterone

While Zhao et al. (2004), have been successful in demonstrating that EA increases serum E2 in ovariectomized rats, they were unsuccessful at demonstrating a significant impact on testosterone levels also measured in the study.

However, in addition to the down-regulation of progesterone in OHSS demonstrated by Chen, L. et al. (2016), EA similarly appeared to down-regulate testosterone, further easing the symptoms and progression of OHSS in rodents.

Likewise, in an investigation into the effect of EA on clinically induced PCOS models in rats conducted by Feng et al. (2012), it was found that EA decreased serum testosterone excluding animals non-respondent to treatment. PCOS is primarily an issue of hyperandrogenism that has a number of accompanying symptoms and health implications. Therefore, decreased serum testosterone is a major factor in the successful treatment of this condition (Feng et al., 2009). Still, while PCOS has been identified as the most common disorder associated with endocrine disruption and infertility in reproductive age women, there is typically no standard for its long-term management outside of the context of the treatment of infertility (Jedel et al., 2011).

A randomized controlled trial conducted by Jedel et al. (2011), investigated the impact of repeated EA on serum testosterone in comparison to physical exercise or no treatment at all in PCOS subjects. The outcome of this trial demonstrated that EA and physical exercise both offered statistically significant decreases in serum testosterone as compared to the no treatment group. Further, EA was found to have an even greater impact on lowering serum testosterone, offering a statistically significant difference when compared to physical exercise alone.

Oxytocin

Oxytocin is largely implicated in social behaviors and interactions in both humans and animals. According to a literature synthesis performed by Zhang et al. (2015), administration of exogenous oxytocin in rodents resulted in enhanced social proximity and helped to overcome social defeat-induced social avoidance. On the other hand, rodents with inhibited oxytocin receptors exhibited impaired social communication and preference.

Similarly, in human clinical trials, exogenous oxytocin has been found to impact various aspects of human sociability such as empathy, in-group trust and cooperation, social recognition, and emotion encoding. Research with autistic children exhibiting marked social impairment behavior has shown that long-term EA simultaneously alleviated social impairment while impacting peripheral levels of oxytocin. Specifically, an improvement in the children's social interaction and communication, as well as emotional response, was noted (Zhang et al., 2015).

In an animal study conducted by Zhang et al. (2015) in order to expand on current literature, results were found to be consistent with previous animal research in regards to oxytocin. Zhang et al. (2015) identified low socially interacting (LSI) rodents based on social interaction time during a sociability test. The outcome of this study demonstrated that EA increased neuronal expressions of oxytocin in the hypothalamus and elevated central nervous system and peripheral oxytocin levels while also providing a statistically significant improvement in the social behaviors and measures of the LSI rodents.

Further, research conducted by Liu, et al. (2008) compared various labor and delivery indices among women receiving exogenous oxytocin to assist with progression and ease of labor. The experimental group received EA in conjunction with the exogenous oxytocin while the control group received exogenous oxytocin without EA. The results of this study demonstrated EA to impact the expansion of the uterus while intensifying the strength and frequency of uterine contractions when compared to the control group. From this, it is possible to infer that EA has the potential to enhance and/or simulate the mechanism of oxytocin during labor and delivery.

A clinical study by Chen, Liu, & Gao (2007) lends further insight into the mechanism by which EA acts upon oxytocin. In this study, uterine contractions were observed in pregnant rodents administered exogenous oxytocin or progesterone. While oxytocin is utilized clinically to speed up contractions in order to assist progression of labor and delivery, progesterone has the opposite effect, thereby relaxing the uterus and calming contractions. Accordingly, in the case of this research, the uterus was either in a state of activity or passivity, depending upon which exogenous hormone was being introduced. With this research design, Chen et al. (2007) demonstrated that EA could be used to impact the amplitude and frequency of uterine contractions in either direction, depending on whether exogenous oxytocin or progesterone was introduced and the consequent need of this initiation. As such, it appears that EA has a modulatory effect on the mechanisms governed by oxytocin, and therefore, that it demonstrates potential to directly regulate levels of oxytocin in the body. This in mind, there is great potential for EA to provide benefit in the management of threatened premature labor in addition to its more commonly recognized function of supporting the progression of labor and delivery.

Cortisol

A compilation of a decade long study of the effects of EA on ovariectomized rats illustrated the ability of EA to increase the glucocorticoid corticosterone (Zhao et al., 2004). This increase was noted, not only in comparison to ovariectomized rats not receiving EA, but also in comparison to rats that still had their ovaries in tact. Although cortisol is the primary glucocorticoid responsible for energy, immunity, and stress response in humans, corticosterone is the primary glucocorticoid responsible for these physiological functions in some animals, such as is the case in the rodents used in the Zhao et al. (2004) study. Accordingly, it is feasible that, in human studies, EA may exhibit a similar effect on serum cortisol levels.

A clinical investigation into the effect of EA on the depressive status of unpredictable and chronic mild stress rodent models (UCMS) provided further insight into the mechanism by which EA effects cortisol levels (Liu et al., 2013). In this study, scientifically established stressors were administered to the animals randomly for 21 consecutive days in order to simulate an environment of chronic and unpredictable mild stress. Serum cortisol and other stress measures were taken following the period of administration of stressors in order to verify the validity of the process. Upon establishing elevation of stress markers, 14 days of EA was administered to two experimental groups while a third control group was administered no treatment. The experimental groups consisted of EA administered to the auricular concha region of the ear or EA administered to the tip of the ear. Both were found to offer a statistically significant decrease in cortisol when compared to the control group. In a comparison of the two auricular areas, it was found that administration to the auricular concha region was superior to the ear tip. The proposed reason for this difference was that the auricular concha region provided a more direct access to the vagus nerve in comparison to the tip of the ear.

Similarly, a review of the literature summarized by Liu et al. (2013) indicated that body acupoints were additionally successful in lowering serum cortisol, as well as other stress markers.

Finally, an investigation into the effect of EA on serum cortisol in rabbits demonstrated that EA administered to acupoints on the body could also increase production of serum cortisol during physical stress (Parmen et al., 2015). Further, based on their review of current pertinent literature, Parmen, Pestean, Ober, Mircean, & Oana (2015) concluded that EA could reduce, inhibit, or trigger stress measures depending on the degree of stimulation administered. Once again, this provides important insight as the majority of research pertaining to EA in relation to hormones and endocrine regulation indicates that its primary function is one of regulation.

Follicle stimulating hormone (FSH)

While women diagnosed with POI exhibit serum follicle stimulating hormone (FSH) levels that fall within menopausal range (>40 IU/L), 5-10% of women diagnosed with POI will go on to conceive and deliver a child even after having been diagnosed as such. Appropriately, it is clinically understood that, although these women are amenorrheic, the absence of menses is due to unpredictable and diminished ovarian function rather than a lack of function prohibiting pregnancy (Zhou et al., 2013).

Perimenopause is characterized by unpredictable and unstable ovarian function similarly to POI and other disorders of reproductive dysfunction. A literature synthesis of research conducted on women in China with reproductive dysfunction indicated that EA has consistently been documented to decrease levels of FSH (Liu et al., 2014).

Additionally, in another study of POI investigating the effect of EA on FSH, LH, FSH/LH ratio, and E2, the investigators concluded that FSH levels seemed to be the measure most easily impacted by EA (Wang et al., 2016).

On the contrary, a randomized controlled trial by Jedel et al. (2011) investigating the impact of repeated EA did not demonstrate a statistically significant change in serum FSH when compared to a no treatment control group. The investigators of the study, however, acknowledged this to be a plausibly inaccurate measure as serum samples were taken independently of menstrual cycle day despite this being a critical factor in acquiring accurate numbers.

Luteinizing hormone (LH)

Literature syntheses conducted by Zhou et al. (2013) and Liu et al. (2014) highlighted consistency of success in reducing serum levels of LH utilizing EA.

Similarly, Zhao et al. (2004), through a decade of investigation into the impact of repeated EA on serum LH in ovariectomized rats, have provided substantial evidence that EA decreases this measure despite its elevation as a consequence of ovariectomy.

PCOS is another reproductive dysfunction that manifests with elevated LH, among other symptoms. Despite the consistency provided by prior reviews and clinical trials in favor of utilizing EA to impact serum LH, an investigation into clinically induced PCOS models in rodents conducted by Feng et al. (2012) was unsuccessful at uncovering any impact on serum LH when excluding animals non-respondent to treatment from overall results.

Similarly, a randomized controlled trial conducted by Jedel et al. (2011) investigating the impact of repeated EA did not demonstrate a statistically significant reduction in serum LH when compared to a no treatment control group. However, the investigators identified the timing of serum testing as a likely limitation to the accuracy of this outcome.

Non-specified Hormones

Although the mechanism by which EA works to impact hormones, in general, is not entirely understood, the current understanding is that it functions as a modulator of the hypothalamic-pituitary-ovary axis (HPOA). Appropriately, the compilation of research demonstrating EA to be beneficial for various specified reproductive dysfunctions such as infertility and PCOS further substantiates this understanding, as each is essentially characterized by suboptimal functioning of the HPOA that is being expressed through the body in a recognized form of dysregulation (Zhou et al., 2013).

This literature review conducted by Zhou et al. (2013) mainly providing support for the substantiation of the HPOA consideration, also documented contrary research indicating that, although it appears to be an effective treatment for specific dysfunctions such as PCOS, EA may not impact individual hormones. An alternative possibility to consider is that EA is not effective at modulating the HPOA, but rather that it is effective at treating the symptoms of reproductive dysfunction.

However, the work of Zhao et al. (2004) highlights the probability that EA enhances HPOA function as it was well-documented in a compilation of research conducted over a decade that EA restores the number of gonadotropin releasing hormone neurons in ovariectomized rats.

Finally, a research synthesis conducted by Chen et al. (2016) concluded that, in regards to reproductive and endocrine function, EA demonstrates a regulatory effect on the HPOA that is multi-channeled and multi-targeted. Additionally, it is important to emphasize that EA appears to have a modulatory effect so that it is useful in issues of hypo- and hyper-function.

Similarly, clinical investigation into the effect of EA on the depressive status of unpredictable and chronic mild stress rodent models (UCMS) demonstrated that EA applied to the auricular concha region of the ear regulated hyperactivity of the HPAA, in addition to adrenal stress hormones (Liu et al., 2013). Therefore, providing further substantiation that EA likely has a therapeutic modulatory effect on the HPO and HPA axes, and may be useful in the treatment and management of a variety of disorders that impact these axes and the individual hormones that interact with one another within a physiological feedback mechanism.

Chapter 3: Methodology

Specific Components for Investigation

The legacy of Traditional Chinese Medicine encompasses a broad range of treatment modalities and styles. For the purpose of the present research, electroacupuncture (EA) was identified as the specific component of TCM to be investigated. Regarding endocrine system measures and optimal hormone function, seven hormones related to the hypothalamic-pituitary-gonadal axis were chosen to be examined based upon their relevance to fertility, reproduction, and the endocrine system in general. The hormones reviewed in the present study were: estrogen (specifically in the form of E2), progesterone, testosterone, oxytocin, cortisol, follicle stimulating hormone (FSH), and luteinizing hormone (LH).

Systematic Literature Review

A literature synthesis was performed in order to determine the current understanding of the role that EA plays in impacting estrogen, progesterone, testosterone, oxytocin, cortisol, FSH, and LH. Cottrell & McKenzie (2011) highlight that, in the context of scientific research, a comprehensive literature synthesis serves to assist in formulating a hypothesis and direction of study, while also providing the historical framework of a research topic by illuminating the contemporary depth of knowledge available and offering justification for its importance (pg. 40-41).

In addition, the current retrospective systematic review uncovered gaps and conflicting outcomes in the existing literature that potentially impede accurate interpretation, practical significance (Cottrell & McKenzie, 2011, p. 41), and clinical application.

Key Search Terms

The investigator submitted a proposal to conduct the present retrospective literature synthesis to the Yo San University Institutional Review Board (IRB) in December 2015. Upon IRB approval, a listing of relevant key search terms was explored and compiled. Key search terms included electroacupuncture AND estrogen/ testosterone/ progesterone/ oxytocin/ cortisol/ follicle stimulating hormone/ FSH/ luteinizing hormone/ LH/ hormones, and endocrine system/ hormones AND TCM/ TCM Kidney/ TCM Kidney yin/ TCM Kidney yang/ TCM Kidney Essence.

Article Discernment

The researcher utilized Internet resources Pubmed and Google Scholar to execute online key term searches. Key term searches generated 224 journal articles, of which 41 were identified as being relevant for the purpose of the present study, while meeting all additional filtering criteria. The exclusion and inclusion criteria were as follows:

Exclusion Criteria:

All journal articles older than the year 2000 were excluded from the current study in order to prioritize focus to the most current research. Additionally, articles that were non-peer reviewed and those that did not conduct statistical analysis have been excluded. Due to posed limitations, articles not written or translated into English were also excluded. Finally, articles that were not public record, including articles that met all other inclusion criteria where the abstract only was of public record, were also excluded during the literature search.

Inclusion Criteria

Peer-reviewed full text journal articles of public record were included in the current retrospective literature synthesis. Of these, human-control, animal-control, in vitro trials, in vivo trials, and literature syntheses were all deemed appropriate for inclusion. Due to the limitations of allowing otherwise, only full text articles written or translated into English were included. Additionally, only articles published in the year 2000 or later were included in order to allow for review of the most contemporary understanding and research pertaining to the subject matter.

Classification and Summarization of Data

Excel spreadsheets and Internet resources Pubmed and myNCBI online were utilized to manage research activity, and for the classification and summarization of information from all relevant journal articles. Accordingly, articles were sorted by individual hormones: estrogen/ testosterone/ progesterone/ oxytocin/ cortisol/ follicle stimulating hormone (FSH)/ luteinizing hormone (LH), hormones in general, Biomedical endocrine system, and TCM Kidney.

Tables and charts were created directly from the Excel spreadsheets for further organization and demonstration of data. The following information extracted from the Excel documents was summarized and presented: statistical significance, numerical effect size, and strength of effect size.

Statistical Analysis

Statistical significance was established at $p < 0.05$ and considered for all measures. With the exception of one journal article, all of the research articles provided *p* values in order to demonstrate statistical significance. The majority of journal articles provided variation from the mean results in the form of standard error of the mean (*sem*) rather than standard deviation (*sd*). Standard deviation calculations were required in order to determine numerical effect size (*r*) values, however. A formula of $sd = sem \; X \sqrt{n}$ was used in order to calculate *sd* values.

In all cases, *r* values were calculated using the University of Colorado, Colorado Springs effect size calculator online (http://www.uccs.edu/~lbecker/). Additionally, strength of effect size was determined based upon classifications of: strong, moderate, weak, or no effect in order to highlight practical application to a clinical setting, or a lack thereof. In pre-post studies using dependent *t*-tests to determine statistical significance, the effect sizes have not been corrected for the correlation between means since raw data was not provided.

Variables

The variables investigated and measured were estradiol (E2), testosterone, progesterone, oxytocin, cortisol, follicle stimulating hormone (FSH), luteinizing hormone and (LH). The primary consideration was deemed to be whether the results of a study found EA to significantly increase, significantly reduce, or if no statistically significant change was uncovered for each variable. In the table demonstrating statistical significance directions of impact were indicated by a + for increase, - for decrease, or *NS* for no statistical significance.

Considerations

For the purpose of the present investigation, the majority of research subjects studied were female. However, there were findings pertinent to the present study in which all or a portion of the research subjects were male. This is specifically the case in studies investigating the impact of EA on cortisol. The investigator of the present study made the determination to include these studies as they provide further support for the possible regulatory effect of EA. In this circumstance, it was assumed that gender would not have had an impact on the outcome of the measures being investigated.

Implementation

All activities relating to the research and writing of the present literature synthesis were conducted on the investigator's private laptop computer or on a desktop computer in the student library at Yo San University of Traditional Chinese Medicine.

Chapter 4: Results

The current investigation sought to answer the question of whether Traditional Chinese Medicine provides an effective alternative to Western Medicine in attenuating the physiological disturbances and disease progression and accompanying hormonal variation in estrogen, testosterone, progesterone, oxytocin, cortisol, follicle stimulating hormone (FSH), and luteinizing hormone (LH) commonly associated with aging and the decline of reproductive capacity. The present systematic literature synthesis reviewed statistical data from eleven studies relevant to the impact of EA on the specific hormones discussed. Within these eleven studies, there were 24 individual measures of statistical significance (See Table 1: Statistical Significance Table). Of these 24 measures, 19 were found to be statistically significant at either a value of $p < 0.01$ or $p < 0.05$ (Chen et al., 2016; Feng et al., 2012; Jedel et al., 2011; Liu et al., 2013;

Wang et al., 2016; Yu et al., 2014; Zhang et al., 2015; Zhao et al., 2004; Zheng et al., 2015; Zhou et al., 2013), four were found to be non-statistically significant (Feng et al., 2012; Jedel et al., 2011), and for the final measure, no *p* value was provided (Parmen et al., 2015).

Further, a largely regulatory mechanism of EA was demonstrated by the current literature synthesis as results illustrate the ability of EA to modulate upwards or downwards for three of the seven hormone measures depending on the circumstantial physiological need. This directional impact is indicated by plus or minus signs wherever relevant in results reporting (See Table 1: Statistical Significance Table).

Table 1: Statistical Significance Table

Article Number	Article Name	Estradiol	Progesterone	Testosterone	Oxytocin	Cortisol	FSH	LH
1	Chen, L. et al. 2016	$p < 0.01$ +	$p < 0.01$ +	$p < 0.01$ +				
2	Feng, Y. et al. 2012	NS -	$p < 0.05$ +	$p < 0.05$ -				NS -
3	Jedel, E. et al. 2011	$p < 0.05$ -		$p < 0.01$ -			NS -	NS -
4	Liu, R.P. et al. 2013					$p < 0.01$ -		
5	Parmen, V. et al. 2015					not provided -		
6	Wang, Y. et al. 2016						$p < 0.01$ -	$p < 0.01$ -
7	Yu, J.B. et al. 2014					$p < 0.05$ +		
8	Zhang, H.F. et al. 2015				$p < 0.01$ +			
9	Zhao, H. et al. 2004	$p < 0.01$ +		$p < 0.01$ -		$p < 0.05$ +		
10	Zheng, X. et al. 2015	$p < 0.01$ +						
11	Zhou, K. et al. 2013	$p < 0.01$ +					$p < 0.01$ -	$p < 0.01$ -

Statistical Significance ($p<0.01$, $p<0.05$) = $p<0.05$ or less
Non-Statistical Significance (NS) = $p<0.05$ or greater
+ = EA resulted in increase of hormone
- = EA resulted in decrease of hormone

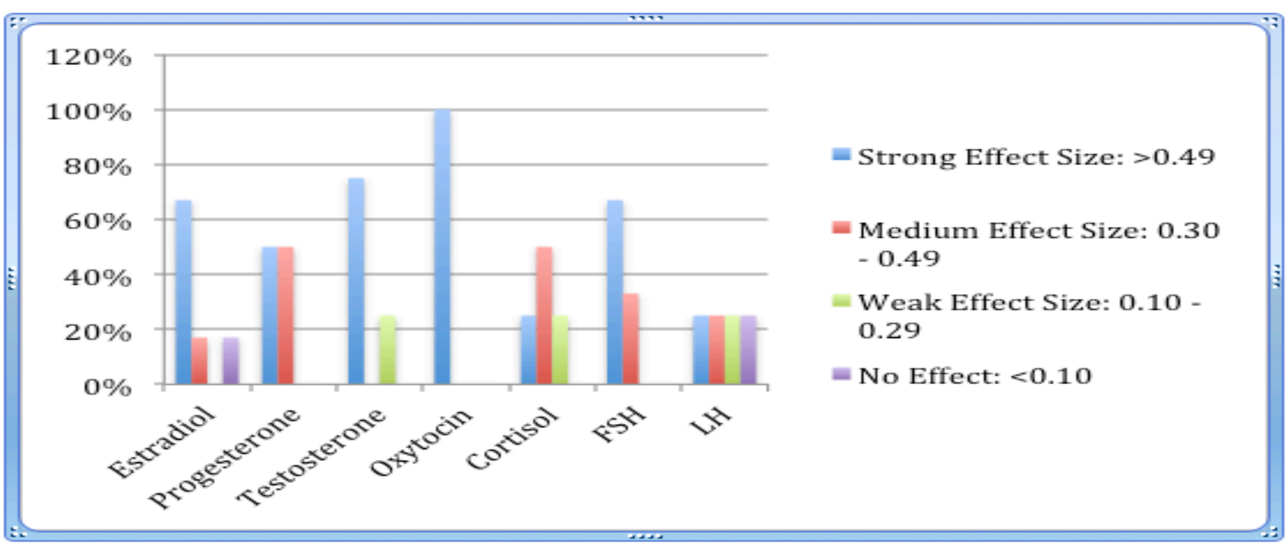
In addition to statistical significance, the effect size and strength of effect size was calculated for all 24 measures (See Table 2: Numerical Effect Size Table and Table 3: Strength of Effect Size Graph). Accordingly, for each of the individual hormone measures, 25% or more of the studies established a strong effect size and 50% or greater uncovered a medium to strong effect size. Overall, a medium to strong effect size was substantiated for nineteen measures, while only three of the measures showed a weak effect size, and two provided for no effect at all (See Table 3: Strength of Effect Size Graph).

Table 2: Numerical Effect Size Table

Article Number	Article Name	Estradiol	Progesterone	Testosterone	Oxytocin	Cortisol	FSH	LH
1	Chen, L. et al. 2016	r = 0.51	r = 0.89	r = 0.94				
2	Feng, Y. et al. 2012	r = 0.03	r = 0.43	r = 0.53				*r = 0.07*
3	Jedel, E. et al. 2011	r = 0.58		r = 0.71			r = 0.76	r = 0.25
4	Liu, R.P. et al. 2013					r = 0.47		
5	Parmen, V. et al. 2015					r = 0.98		
6	Wang, Y. et al. 2016						r = 0.44	r = 0.33
7	Yu, J.B. et al. 2014					r = 0.21		
8	Zhang, H.F. et al. 2015				r = 0.77			
9	Zhao, H. et al. 2004	r = 0.83		r = 0.22		r = 0.39		
10	Zheng, X. et al. 2015	r = 0.36						
11	Zhou, K. et al. 2013	r = 0.65					r = 0.56	r = 0.54

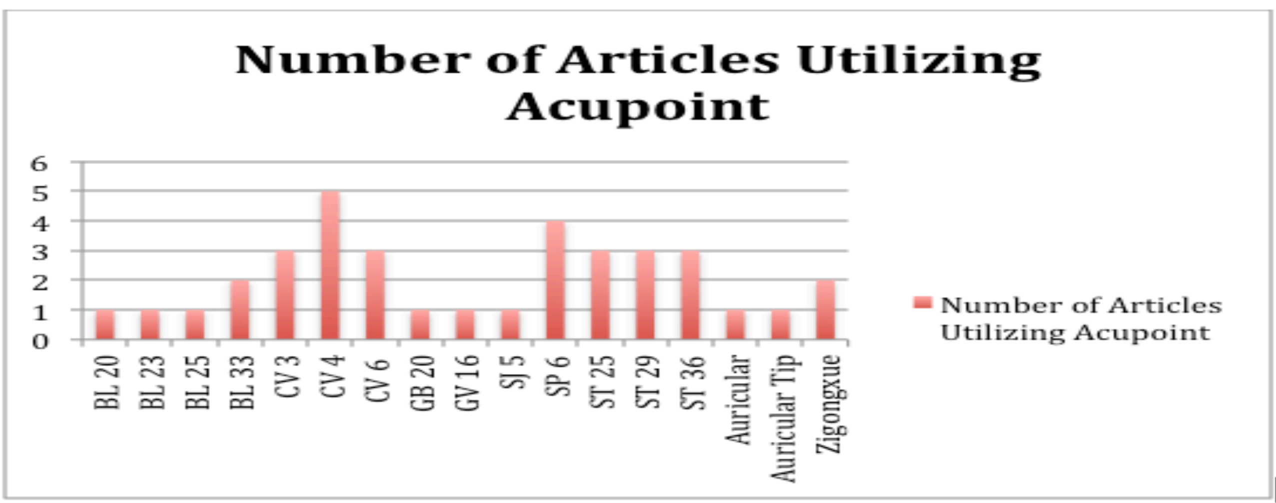
r = Numerical Effect Size

Table 3: Strength of Effect Size Graph



Selection of acupoints varied among studies (See Table 4: Acupoint Selection Graph), however the most frequently used points were: 3, 4, and 6 on the Conception Vessel (CV); 25, 29, and 36 on the Stomach (ST) meridian; Spleen (SP) 6; and extra point Zigongxue. With the exception of SP 6, each of the points above are located in the lower abdomen local to the reproductive organs. Acupoint SP 6 has broad clinical application for all reproductive and gynecological issues.

Table 4: Acupoint Selection Graph



BL = Urinary Bladder Meridian Point
CV = Conception Vessel Point
GB = Gall Bladder Meridian Point
GV = Governing Vessel Point
SJ = San Jiao Meridian Point
SP = Spleen Meridian Point
ST = Stomach Meridian Point
Auricular = Auricular Concha of Ear
Auricular Tip = Auricular Tip of Ear
Zigongxue = Extra point located local to the reproductive organs

While the type of electroacupuncture equipment utilized similarly varied among studies, the frequency administered remained consistently low and continuous across studies at a level ranging from 2 to 20 hertz. Two hertz was the most commonly chosen level with treatment time extending from 20 to 30 minutes. Finally, there was a wide variation in number of treatments administered across studies. Accordingly, treatment courses ranged from as little as five sessions administered over ten days to twenty-five sessions administered over sixteen weeks.

Estrogen/ Estradiol (E2)

The estradiol (E2) form of estrogen was the most commonly studied of the seven individual hormone measures included in the present investigation. Of the six papers examining the effect of EA on E2, five were established as statistically significant (Chen et al., 2016; Feng et al., 2012; Jedel et al., 2011; Zhao et al., 2004; Zheng et al., 2015; Zhou et al., 2013). Of these five, four demonstrated a strong effect size and one provided for a moderate effect size. Further, E2 was shown by the various studies to be impacted in a dual direction thereby providing substantiation for EA as a regulatory treatment.

Progesterone

Progesterone was impacted in a positive direction with both relevant studies demonstrating statistical significance and a moderate to strong effect size (Chen et al., 2016; Feng et al., 2012).

Testosterone

The four studies investigating testosterone proved statistically significant with 75% of them establishing a strong effect size and 25% a weak effect size (Chen et al., 2016; Feng et al., 2012; Jedel et al., 2011; Zhao et al., 2004). EA was shown to act upon testosterone in a dual direction similarly to E2.

Oxytocin

Just one of the relevant studies spoke to the direct impact of EA on oxytocin measures. The outcome of this study was a statistically significant increase in oxytocin with a strong effect size (Zhang et al., 2015).

Cortisol

Cortisol demonstrated a dually directional impact among four studies. While three of the studies established statistical significance, one study did not provide *p* values. The strength of effect size was variable among the cortisol studies with 50% indicating moderate strength and 25% each falling under the classifications of strong and weak effects (Liu et al., 2013; Parmen et al., 2015; Yu et al., 2014; Zhao et al., 2004).

Follicle Stimulating Hormone (FSH)

While only two of the three studies investigating FSH demonstrated statistical significance, all three of them were found to have a moderate to strong effect. In all studies the value of FSH was decreased by EA treatment (Jedel et al., 2011; Wang et al., 2016; Zhou et al., 2013).

Luteinizing Hormone (LH)

LH similarly decreased in all relevant studies. Here we find the weakest outcomes with only two out of four studies establishing statistical significance and a 25% effect strength falling under each classification (Feng et al., 2012; Jedel et al., 2011; Wang et al., 2016; Zhou et al., 2013).

Accordingly, compilation of the results of the present investigation validate that Traditional Chinese Medicine provides an effective alternative to Western Medicine in attenuating the physiological disturbances and disease progression and the accompanying hormonal variation of estrogen, testosterone, progesterone, oxytocin, cortisol, follicle stimulating hormone (FSH), and luteinizing hormone (LH) commonly associated with aging and the decline of reproductive capacity.

Chapter 5: Discussion

Summary of Findings

The current retrospective literature synthesis illuminated a substantial regulatory mechanism of EA by demonstrating EA to modulate upwards or downwards for many of the hormone measures depending on the circumstantial physiological need. There were 24 individual measures of statistical significance investigated in the present study. Of these 24 measures, 19 were found to be statistically significant at either a value of $p < 0.01$ or $p < 0.05$. Additionally, for each of the seven hormone classifications investigated, 50% or more of the studies uncovered a medium to strong effect size. Measure of strength of effect size provides information that is critical and beyond statistical significance as it demonstrates value in terms of practical application.

Theoretical Implications

The outcome of the present study indicates that results for each of the seven hormone measures investigated appear to be generally consistent and reliable, although to varying degrees of strength. In particular, there is substantial literature pertaining to direct measurements of the impact of EA on E2, testosterone, and cortisol, all of which demonstrate a multi-directional impact (Chen et al., 2016; Feng et al., 2012; Jedel et al., 2011; Liu et al., 2013; Parmen et al., 2015; Yu et al., 2014; Zhao et al., 2004; Zheng et al., 2015; Zhou et al., 2013). In all of the studies pertaining to FSH and LH, a reduction direction only was demonstrated, as would be expected based upon the clinical significance of this (Feng et al., 2012; Jedel et al., 2011; Wang et al., 2016; Zhou et al., 2013). It is expected that the overall results pertaining to each of the hormones above would be reasonably consistent and repeatable in similar studies, appropriately maintaining validity of results.

Oxytocin and progesterone, on the other hand, were found to be the least directly examined of the individual hormone measures (Chen et al., 2016; Feng et al., 2012; Zhang et al., 2015). Therefore, while the investigator of the present study presumes that EA would demonstrate a significant impact on these two hormones in further scientific studies based upon literature uncovered during the present investigation, there is less evidence to substantiate this generalization.

Practical Implications

It is clear that EA demonstrates strong capability to substantially impact endocrine and reproductive health (Chen et al., 2016; Feng et al., 2012; Jedel et al., 2011; Liu et al., 2013; Parmen et al., 2015; Wang et al., 2016; Yu et al., 2014; Zhang et al., 2015; Zhao et al., 2004; Zheng et al., 2015; Zhou et al., 2013). Based upon the results of the current review, there is considerable evidence to support the use of EA to impact the hormones investigated in the present study individually, and therefore, potentially to treat the underlying dysfunction or disease processes that initiated the hormone’s suboptimization.

Furthermore, it is apparent that EA demonstrates a regulatory function that is influenced by the physiological need associated with the dysregulation being treated. Even in the hormone measures where only one direction of impact was shown (Feng et al., 2012; Jedel et al., 2011; Wang et al., 2016; Zhou et al., 2013), it is believed that this is merely a consequence of clinical relevance. For example, it is more likely that a dysregulation or disease process would occur due to elevation of FSH and LH rather than a decrease in these hormones. Accordingly, it follows that EA treatment implemented in order to restore equilibrium would be found to reduce FSH and LH in a clinical setting.

Additionally worth mentioning, EA offers enhanced clinical benefit in that it allows for an additional measure of objectivity by providing a standardized mechanism for manipulation of acupoints that is impossible with manual stimulation (Stener-Victorin, Kobayashi, Watanabe, Lundeberg, & Kurosawa, 2004a).

Present Study Limitations

An enduring fundamental limitation of the present investigation is that a prominent majority of the scientific research on this topic, and in the field of TCM in general, is not published in English. An explicit amount of the clinical research on EA, and acupuncture in general, is conducted in Asia where TCM remains seamlessly integrated into the contemporary culture and health care systems based upon its origin and extensive history throughout the continent. Unfortunately, the science relating to TCM published in Asia is largely untranslated into English, and therefore not easily accessible in the circumstance where there is no means of translation. As such, there is a rich and extensive body of information that is fundamentally untapped by the current literature synthesis.

Another limitation worth considering is that the sample sizes of the studies included in the present literature synthesis tended to be small, thereby diminishing validity and clinical significance. Additionally, the bulk of the studies were conducted on rodents presenting further potential limitations to generalizability and significance to human subjects.

Recommendations for Future Research

In order to contribute to the advancement of research relevant to the topic investigated by the present literature synthesis, as well as to the continued assimilation of TCM into mainstream western culture, it is essential to encourage further investigation and collaboration of modern research conducted in English. Similarly, it remains imperative to encourage alliance in research among practitioners of Biomedicine and TCM in order to promote a culture of integration and a comprehensive standard of care comparable to the model which exists in China and other Asian countries.

Conclusion

While the mechanism by which acupuncture and EA functions remains largely misunderstood, it is increasingly accepted that EA asserts meaningful impact on neuroendocrine pathways and associated substances and hormones (Corradino, 2012, p. 30). Based upon research uncovered under the present investigation, the examiner concludes that EA has a significant impact on hormone modulation and underlying processes of disease and dysregulation. Upon comprehensive review of the relevant literature and scientific data, it is deemed that the hypothesis was correct, and accordingly, that Traditional Chinese Medicine provides an effective alternative to Western Medicine in attenuating the physiological disturbances and disease progression and the accompanying hormonal variation of estrogen, testosterone, progesterone, oxytocin, cortisol, follicle stimulating hormone (FSH), and luteinizing hormone (LH) commonly associated with aging and the decline of reproductive capacity.

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