RESOLUTION OF ANOVULATION INFERTILITY USING NEURO EMOTIONAL TECHNIQUE: A REPORT OF 3 CASES

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ABSTRACT

Background: The female menstrual cycle is a complicated interaction of hormonal messages that are under the control of the Hypothalamic-Pituitary-Ovarian axis. Dysfunction in this axis can lead to anovulation and infertility. Stress has the potential to produce such dysfunction.

Objectives: To review the normal menstrual cycle, and present a number of case studies on how the stress-reducing technique of Neuro Emotional Technique (NET) successfully aided the fertility of a number of female patients by resolving anovulation/menstrual irregularity.

Methods: Three chronic anovulating, infertile patients underwent NET. A visual analog scale was used to evaluate the effectiveness of the intervention.

Outcomes: Anovulating patients started to ovulate following a series of treatments. Initial visual analog scale (VAS) scale on menstrual irregularity was rated 10 out of a possible 10 (anovulation) for all patients. After treatment, these 3 patients rated 0 out of 10 on the VAS scale and had fallen pregnant with subsequent birthing. A discussion of the potential link between stress and anovulation through altered gonadotropin releasing hormone pulsitile activity and how the use of NET may have resolved the anovulation seen in these 3 patients is presented.

Conclusion: The success attributed to the NET intervention and the resumption of ovulation warrant the need for further research involving long term prospective randomized controlled trial experiments to determine a direct causal relationship. (J Chiropr Med 2006;5:13–21)

Key Indexing Terms: Anovulation; Infertility; Stress

INTRODUCTION

In order for a species to flourish, there must be a continual propagation of the genome that is passed on from the parents to the offspring. Thus the ability to reproduce is essential for the survival of the population. In many cultures, the ability to reproduce (fertility) is both a sacred and revered 'gift'. This is why news of the decreased ability to reproduce (infertility) is often met with distressing emotions. The purpose of this research is to discuss the causes of female infertility with particular focus on anovulation as a cause of infertility. This paper overviews the normal menstrual cycle and will present a case series on the use of the stress-reducing technique of NET for female patients experiencing anovulation/menstrual irregularity.

Menstrual Cycle Overview

The phases of the female menstrual cycle follows the development of follicles, which could potentially develop into an oocyte, the release of the ovum into the oviduct and the subsequent degeneration of the connective tissue. Thus, the menstrual cycle is divided into phases that follow this progression: the follicular phase, ovulation and the luteal phase. Each phase is distinct with characteristic hormone levels and uterine endometrial changes.[1,2]

The interaction of hormones produced in 3 areas (hypothalamus, anterior pituitary gland, ovary) pro-

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duce the characteristic pattern of hormone levels seen throughout the cycle (Fig 1 and 2). As such, the Hypothalamic-Pituitary-Ovarian Axis is in control of ovulation and any dysfunction of the axis results in irregular menses and potentially anovulation.

The hypothalamus produces gonadotropin releasing hormone (GnRH) in a changing pulsitile manner throughout the cycle, which stimulates the anterior pituitary gland.[2,3] The anterior pituitary gland secretes both follicle stimulating hormone (FSH) and luteinizing hormone (LH). Under stimulation from FSH and LH, the ovary releases estrogen and progestin. The pituitary gland hormones, FSH and LH, produce a negative feedback on the secretion of GnRH. At low circulating levels, estrogen also displays a negative feedback on the release of FSH and LH from the anterior pituitary gland. However, at high levels of circulating estrogen, there is a positive feedback on FSH and LH secretion.

Follicular Phase

The follicular phase spans from the first day of menstruation until ovulation.[2] Menstruation occurs at the beginning of the follicular phase where the uterine endometrial functionalis is shed. The development of a follicle capable of undergoing ovulation is the primary goal of the follicular phase. Early in the phase, FSH and LH levels are increased relative to baseline with estrogen and progesterone at low levels. FSH levels stimulate 15–20 primordial follicles to develop into primary unilaminar follicles and stimulates follicular secretion of estradiol by upregulating secretion of androgens. At approximately day 8 of the follicular phase, the increasing estrodiol levels result in a reduction in FSH levels due to negative feedback. Also at this time, primary unilaminar follicles continue to develop into primary multilaminar follicles. There is also an increase in GnRH pulse secretion which favors LH production. Also around this time, 1 follicle evolves into the dominant follicle, destined for ovulation, while the remaining follicles undergo atresia.[2] Although it is unknown how this dominant follicle is selected, this follicle always expresses an abundance of FSH receptors.[3] This results in the follicle being able to continue acquiring FSH even in decreasing levels of FSH. This follicle continues to secrete estrogen. The late follicular phase is characterized by proliferation of the functionalis and proliferation and elongation

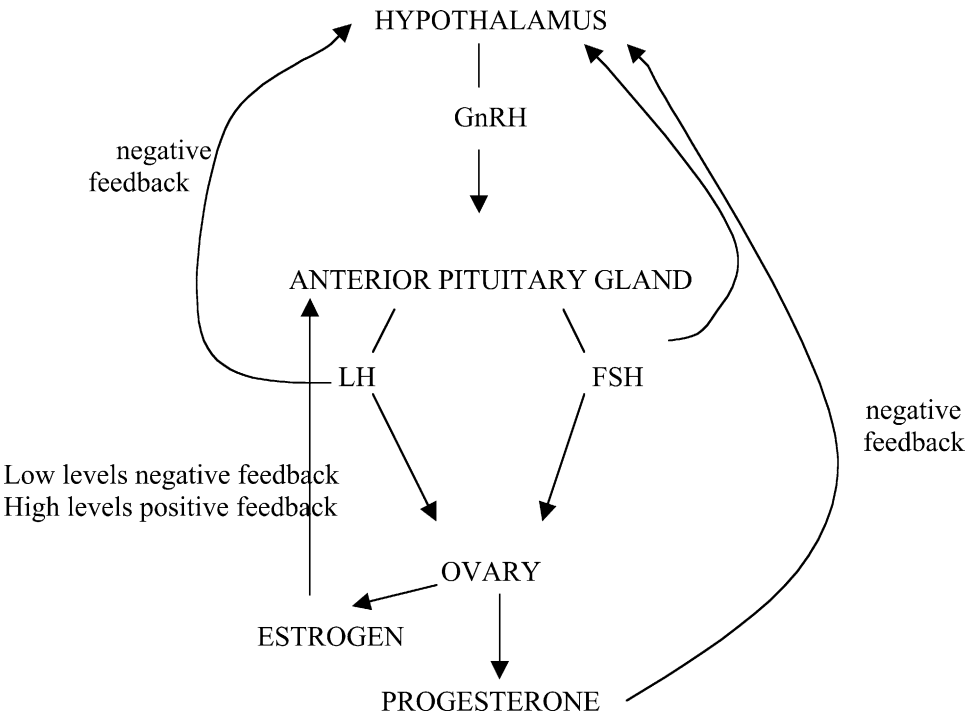

Figure 1. Overview of hormonal interaction in menstrual cycle. GnRH = gonadotropin releasing hormone; LH = luteinizing hormone; FSH = follicle stimulating hormone.

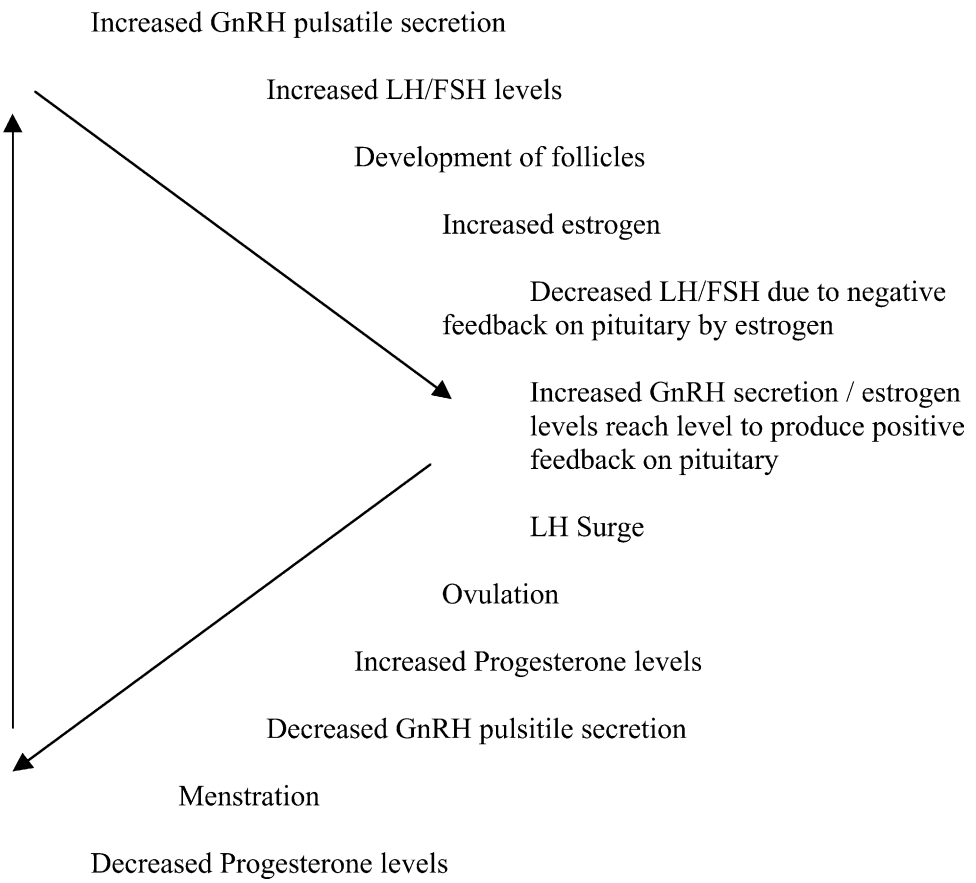

Figure 2. Overview of hormone interaction during the menstrual cycle. GnRH = gonadotropin releasing hormone; LH = luteinizing hormone; FSH = follicle stimulating hormone.

of non-secreting endometrial glands in the uterine endometrium.

On the day before ovulation, estrogen levels peak and hit a critical level where there is now a positive feedback on the anterior pituitary resulting in a surge in LH and FSH. The LH surge is critical for the luteinization of the follicle and ovulation.[3] Estrogen can only exert positive feedback on LH at this precise stage in the menstrual cycle. If estrogen is artificially provided earlier in the cycle, ovulation will not be induced. LH and FSH begin to decrease back to baseline levels almost immediately and by the time ovulation occurs, LH and FSH are on the decline.

Ovulation

The goal of ovulation is the release of the ovum into the peritoneal cavity and oviduct for transfer down the fallopian tubes to the uterus. At ovulation, the functionalis and endometrial glands have reached their maximum sizes. The endometrial glands, however, are still non-secretory. The dominant follicle (now called the Graafian follicle) develops an antrum (cavity) and completes its first meiotic division whilst the remaining primary follicles undergo atresia. Proteolytic enzymes (whose role is to degrade the cells at the surface of the follicle, to stimulate angiogenesis in the follicular wall and promote prostaglandin secretion) are released as a result of the surge in LH. The follicle swells and ruptures, resulting in the release of the oocyte and corona radiata, which is taken up by the oviduct.

Luteal Phase

The luteal phase is characterized by the luteinization of the components of the follicle that were not ovulated and is initiated by the LH surge. During the early luteal phase, progesterone stimulates the endometrial glands to secrete glycogen, mucus, and other substances. At this stage, the endometrial glands have a tortuous appearance. During the lu-

teal phase, the corpus luteum develops which is a product of the granulosa cells, theca cells, and some surrounding connective tissue. The corpus luteum produces progesterone and estrogen, with LH and FSH being once again under negative feedback control by these hormones.

Progesterone levels peak at 5 and 7 days post-ovulation. Progesterone exerts a negative feedback on GnRH by increasing opioid activity and subsequently GnRH pulse frequency decreases.[2] If fertilization fails, degeneration of the corpus luteum occurs, with subsequent falls in progesterone and estrogen levels. As progesterone and estrogen levels decrease with the degeneration of the corpus luteum, the uterine endometrium begins to undergo involution. At days 25–26, the spiral arteries begin to vasoconstrict. By day 28, marked ischemia causes apoptosis of the functionalis. Estrogen and progesterone are at their lowest levels at day 28, resulting in increased GnRH pulse secretion and increasing FSH secretion to initiate the beginning of the next cycle. If conception occurs, the production of progesterone from the corpus luteum continues for 7 weeks because of the tonic release of LH from the pituitary gland. Studies show that after 7 weeks, the placenta takes over this function. If conception does not occur, menses begins with the demise of the corpus luteum.

Ultimately, the release of GnRH from the hypothalamus in a controlled fashion is the 'conductor of the orchestra' in the complicated interaction of hormones that is the menstrual cycle. At low frequency pulses, FSH release from the pituitary is predominant, leading to the initiation follicular development. At high pulse frequency, LH release predominates leading to the release of the oocyte into the fallopian tube (along with positive feedback on LH by estrogen).[3,4,5]

In the mid lutenizing phase, progesterone negatively feeds back onto the hypothalamus decreasing GnRH pulse frequency. If conception occurs, the increased progesterone levels stop the GnRH-mediated rise in FSH leading to a ceasing of the cycle. If, however, the progesterone levels fall due to conception failure, the resultant progesterone mediated inhibition reduces. This results in an increase in GnRH pulse frequency resulting in FSH levels rising and the initiation of another cycle.

Potential Causes of Infertility

There are 3 main components of the female reproductive system, including the ovaries, the fallopian tubes, and the uterus. At each of these areas, dysfunction can lead to infertility due to ovulation disorders, fallopian tube damage or the inability for the uterine endometrium to produce an environment ready to accept the fertilized ovum.[6] Ovulation disorders and fallopian tube damage are the two main causes of infertility as seen in Table 1.[7]

The primary cause of infertility is ovulation dysfunction, either total failure (amenorrhoea) or irregular pattern to ovulation (oligomenorrhoea). There can be a number of reasons for this dysfunction, which usually relates to the regulation of GnRH secretion from the hypothalamus.[8] It appears that precisely controlled GnRH pulse frequency and amplitude are essential prerequisites for the appropriate LH surge seen just prior to ovulation. As such, any disruption to GnRH secretion will disrupt LH levels and subsequently affect ovulation. There can be a number of reasons for this altered GnRH pulse, including stress-induced adrenal stimulation, hyperprolactinemia (elevated serum prolactin), hyperandrogenism and alteration in the levels of leptin, a protein hormone that is synthesized and secreted by adipose tissue.[8] Other potential causes of ovulation dysfunction include polycystic ovary syndrome, and dysfunction of FSH and LH at the site of the ovary.[8]

Normal human fertility requires not only patent fallopian tubes but also their normal function. The role of the fallopian tube is to pick up the oocyte from the ovary and also facilitate the transport of the oocyte, sperm and potentially the embryo.[9] A highly specialized endosalpinx and delicate fimbriae, which maybe damaged by infection or surgery, are the components of the fallopian tube.[9] Tubal obstruction occurs in 12% to 33% of infertile couples.[7]

TABLE 1
FEMALE CAUSES OF INFERTILITY AND THEIR APPROXIMATE FREQUENCY. UNEXPLAINED INFERTILITY, WHERE THEIR IS AN UNKNOWN CAUSE OCCURS IN APPROXIMATELY 25% OF CASES.

CAUSE	FREQUENCY (%)
OVULATION FAILURE (AMENORRHOEA OR OLIGOMENORRHOEA)	25
TUBAL INFECTIVE DAMAGE	20
ENDOMETRIOSIS (CAUSING DAMAGE)	5
CERVICAL MUCUS DEFECTS OR DYSFUNCTION	3
UTERINE ABNORMALITIES (SUCH AS FIBROIDS OR ABNORMALITIES OF SHAPE)	(<1)

Tubal subfertility is mainly the result of pelvic infection and damage can be caused by sexually transmitted diseases, can occur after miscarriage, termination of pregnancy or insertion of an intrauterine contraceptive device. A lack of a history of pelvic inflammation, however, does not exclude fallopian tube damage. Adhesions that result in reduced fimbrial mobility, as opposed to rare complete tubal obstruction, is the primary cause of endometriosis subfertility.[9]

Despite normal progesterone levels, changes in vascularization of the endometrium may be the result of uterine abnormalities.[10] Changes in secretory endometrial patterns can be the result of myomas, uterine septa or endometriosis. Fibroids may affect fertility in up to 10% of cases. Apart from the mass effect, the precise mechanism by which fibroids may cause subfertility is unknown.[10]

CASE SERIES

Three cases are presented here. Five cases of anovulation-related infertility that have been managed by the authors with neuroemotional technique (NET) therapy were analyzed to observe potential improvements in undiagnosed anovulatory infertility. Three cases were determined to have unexplained causes of anovulation. One identified case had a subjective diagnosis of polycystic ovarian syndrome and one case had a diagnosis of endometriosis. As both of these cases had an established diagnosis, they were excluded from this report. For a discussion of polycystic ovary syndrome managed by NET, the reader is referred to another report.[11]

Case 1

A 39-year old small business operator presented with irregular painful periods, abnormal vaginal discharge, and constipation. She had been trying to conceive for 2 years and had not had a period for 14 months at the time of consultation. Seven months prior to consultation a laparoscopy was performed and was reported to be normal. She was diagnosed as having an unknown cause of anovulation. Further medical history was unremarkable. Initial visual analog scale (VAS) scale on menstrual irregularity was rated 10 out of a possible 10 (anovulation). After 2 months of NET treatments (11 treatments), she reported to be having normal pain free periods and a VAS of 0 out of 10 was recorded. Two months later, after 4 more treatments, the patient reported that she was pregnant. She had a healthy son 8 months later.

Case 2

A 38-year old recruitment consultant presented with irregular periods and painful intercourse (VAS 9 out of a possible 10). She had been trying to have a second baby for 3 years, after the birth of her first child 4 years prior to the initial consultation. She reported no period for 3 months prior to her first consultation. Her medical history was remarkable for a caesarian section for her first child in 1999 and a diagnosis of irritable bowel syndrome in 2001. She had been taking the ovary stimulant, Clomid (clomiphene citrate), for four months prior to the initial consultation with no success and had stopped taking it 1 month prior to consultation. Initial VAS scale on menstrual irregularity was rated 10 out of a possible 10 (anovulation). After 5 treatments of NET, her periods had returned and her VAS for painful intercourse was 2 out of a possible 10, and a 0 out of 10 for ovulation. She also reported becoming pregnant. Eight months later, she had a healthy son.

Case 3

A 28 year-old accountant presented with irregular periods. She had not had a period for 8 months and had been trying to conceive for 18 months at the time of her initial consultation. Her medical history was remarkable for sinus problems, varicose veins and headaches and further medical history was unremarkable. Her initial VAS scale on menstrual irregularity was rated 10 out of a possible 10 (anovulation). Within 3 months of treatment (10 consultations), her periods had resumed. At this point on a subjective comparative report, she reported an 80% improvement in her menstrual cycle and her ability to become pregnant, as she had regular periods. Five months later (5 treatments), she reported being 9 weeks pregnant.

DISCUSSION

NET was developed by Walker,[12] and may be described as a complementary and alternative medicine (CAM) modality designed to alleviate the effects of distressing stimuli.[13] NET is a 15-step, multimodal intervention that incorporates principles of several health disciplines, including cognitive-behavioral psychology, traditional Chinese medicine pulse assessment, and a feedback technique called the muscle test. NET has aspects in common with

standard cognitive-behavioral treatments for traumatic stress, such as exposure therapy.[14] A major goal of both techniques is to achieve a reversal (or extinction) of classically conditioned distressing emotional responses to trauma-related stimuli, in particular stress.

The conception of the technique is based on the Chinese medical model.[15] NET engages the energy system, making it different to similar treatments following cognitive behavioral principles, by having the patient touch the pulse point on the wrist that is determined to be involved in the body's stress reaction to the given stimuli. The practitioner helps the patient identify the particular pulse point using principles of traditional Chinese 5-element theory.[16] This theory suggests that the major energy channels or "meridians" contain specific emotional qualities. A principle of NET it that the cognitive-emotional processing of an event facilitates an expedited resolution of the event, which is enhanced by the engagement of the body's energy system. The manual muscle test is used throughout the NET protocol as a rudimentary indicator of physiological reactivity to the stimuli under consideration.[17] An objective of NET is to help patients become less physiologically reactive to distressing stimuli and to become more capable of choosing alternative responses. NET is intended to be a brief, time-limited intervention. Several recent publications have highlighted the use of NET for conditions such as hypothyroidism[18] and polycystic ovarian related infertility.[19] In the only clinical trial on the technique, investigators demonstrated a significant decrease in phobic symptoms following a brief course (2–3 visits) of a variation of NET.[20]

Stress and Effects on Ovulation

A key to the menstrual cycle and its function lies in the interaction of the hormones and their effects on the cycle. Normally, there is a controlled pulsatile release of GnRH from the hypothalamus during the cycle, which alters according to the cycle phase.[1,3] There is an increase in pulse frequency during the late follicular phase that favors increased LH levels.[3,4,21] The rise in LH levels is critical for the release of the protolytic enzymes, producing angiogenesis in the follicular wall and subsequent rupture of the follicle.[2] If this does not occur, ovulation does not result. As such, if the pulsatile nature of GnRH is disrupted for any reason, the ovulation cascade does not occur and anovulation results.[22] However, if any stage of this ovulation cascade is disrupted, ovulation does not occur. Most agree that the secretion of gonadotrophin releasing hormone (GnRH) from the hypothalamus and its effect on the release of LH and FSH from the anterior pituitary gland is the primary source of dysfunction in infertility (hypothalamic amenorrhea).[22]

There is universal recognition that there exists a link between increased stress levels and alterations in function of the reproductive system.[23–25] Stress may be defined as an event (physical or psychological) that stimulates a series of responses to restore the homeostasis of the system. When the body's response to stress is inadequate, prolonged or excessive, it can produce alterations in the function of physiological systems, including the immune, the thyroid and reproductive systems. Stress activates the hypothalamo-pituitary adrenal axis, which results in activation of parvocellular neurones of the paraventricular nuclei of the hypothalamus and the release of the neuropeptides corticotrophin releasing factor and arginine vasopressin into the hypophyseal portal system. This leads to the secretion of adrenocorticotrophin (ACTH) along with the endogenous opioid peptide, b-endorphin and a-melanocyte-stimulating hormone. ACTH acts on the cortex of the adrenal glands to stimulate the synthesis of glucocorticoids, in particular cortisol. The glucocorticoids have negative feedback actions on the hypothalamo-pituitary unit to regulate the secretion of corticotrophin releasing factor, arginine vasopressin and ACTH. Stress also activates the release of interleukin-6 as a result of the release of catocholamine. Catocholamine is released due to activation of the noradrenergic neurons of the locus ceruleus/norepinephrine nuclei of the brain stem.[26–28]

The reproduction axis can be affected by stress at any level, from the hypothalamus, the pituitary gland or the ovary. Stress appears to inhibit GnRH secretion from the hypothalamus.[29,30] It interferes with GnRH-induced release of LH at the pituitary level, whilst also altering sex steroid secretion (as a result of gonadatropin inhibition) in the ovary. This has been termed functional hypothalamic amenorrhea, a term that has been use in Medline publications since 1966,[31] and in the English literature since at least 1970.[32]

Whilst chronic stress is known to affect reproduction, the effect of acute stress on the reproductive system is unclear.[33] Studies into the effect of acute

stress on various animals have shown stimulatory, nil and inhibitory effects. Unfortunately, studies on human subjects have not been conducted and only untested hypotheses can be provided.[33]

How stress affects reproduction in terms of chemical messenger interactions has been a topic of interest for many years.[34–36] The association of elevated glucocorticoid levels with stress was thought to be primarily responsible for the effect of stress on reproduction. Whilst this may be true in some species, in humans and other primates, this is not the case.[37] It appears that endogenous opioid peptides (EOPs) are the mediators of the suppression of GnRH release during stress-related decreases in ovulation. EOPs are produced from the processing of proopiomelanacortin, a peptide in the control of adrenal steroidogenesis by corticotrophin-derived ACTH.[38]

As noted previously, alteration in GnRH secretions alters the ability of the pituitary to release LH, a critical catalyst for ovulation. This mainly occurs at the level of the hypothalamus, though its effect on the pituitary gland cannot be discounted. β-endorphin (β -EP) is the EOP that is thought to mediate the stress-related decrease in GnRH secretion. In humans, administration of β-endorphin suppresses plasma LH levels. The ability of the opioid receptor antagonist naloxone to increase LH levels and increase both frequency and amplitude of LH pulsatile release supports this assertion.[39,40] Also, there are direct synaptic connections between GnRH-releasing neurons in the medial preoptic area of the hypothalamus and β-endorphin-containing fibers from the arcuate nucleus, which further strengthens the conclusions.[39,41]

Whilst EOPs are the mediators of the stress-related inhibition of GnRH release, other neurochemicals are also involved. Corticotropin releasing hormone (CRH) is increased in times of stress, and has been shown to increase the tone of EOP both *in vivo* and *in vitro*.[42–44] Also, it is known that CRH is a regulator in the synthesis and processing of β-endorphin (and of other proopiomelanocortin-derived peptides) at the pituitary and in the hypothalamus. It is postulated that CRH acts on the arcuate nucleus to increase the production of hypothalamic EOP, thus promoting a stress-related inhibition of GnRH (and ovulation). Both prolactin and norepinephrine are released in times of stress, and have been shown to mediate the release of EOPs via their effects on CRH. Serotonin is also thought to be involved.[33] As such, it appears that EOPs, in particular β-endorphin, are the triggers in the inhibition of the GnRH pulse. Whilst β-endorphin is released in times of stress, the increase in CRH levels also mediates the release of β-endorphin in times of stress (aided by prolactin and norepinephrine release). This leads to a stress-related inhibition of the GnRH pulse and subsequent anovulation (Fig 3).

The preceding cases reported the resolution of non-physical infertility while NET treatment was provided and the patients subsequently ovulated and became pregnant. A large percentage of infertility is due to anovulation that cannot be explained by modern medicine. The NET treatment used on the patients reported in this paper focuses on past emotional responses and how they are associated with physical symptoms. This therapy is used as a stress-reduction technique. The results of the preceding 3 cases demonstrate that NET may have been associated with a successful therapeutic outcome without the need for additional medication. NET therapy is a form of therapy that aims to reduce stress, thereby allowing the restoration of the natural function of

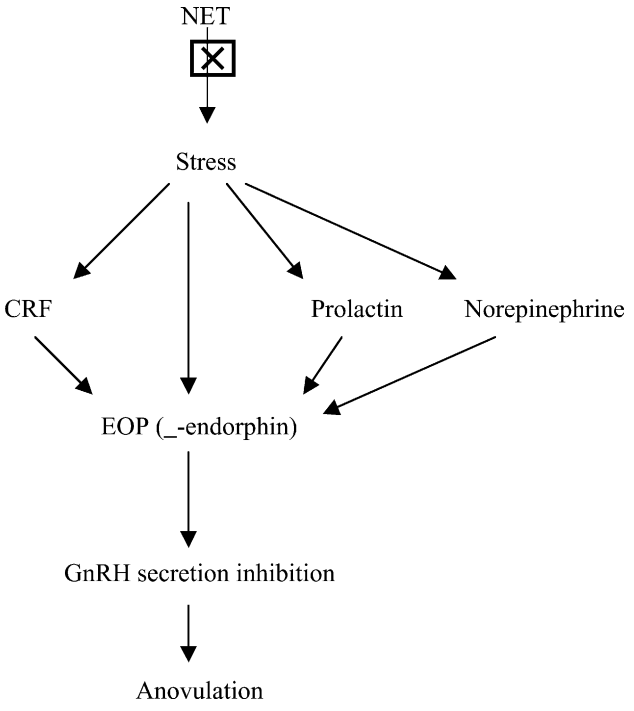

Figure 3. Overview of how stress can possibly affect ovulation and how neuroemotional technique (NET) may aid in ovulation. CRF = corticotrophin releasing factor; EOP = endogenous opioid peptide; GnRH = gonadotropin releasing hormone.

the neuroendocrine system that is affected by chronic levels of increased stress (both apparent and subconscious).

The exact pathway involved in the stress related inhibition of the reproductive axis is yet to be determined, however, it is known that chronic stress may inhibit ovulation. To restore the dysfunction induced by stress in the HPA axis, it is theorized that stress modulation to be achieved. The role of the NET practitioner is to identify experiences that produce strong emotional and stressful reactions and address how these reactions can be resolved though education and understanding. This approach is hypothesized to lower the stress level in the patient thereby allowing the possible resumption of normal function of the reproductive axis and allowing the apparent resumption of ovulation.

A case-series reports on individual patients' outcomes, there are inherent limitations such as a lack of control and an inability to generalize findings to the whole population.[45] Such a study makes it difficult to be certain of a causal link to the therapy and the improvement, despite the face value improvement of the patient. Case studies, however, are vehicles to put forward a hypothesis that can be the basis for further research. As with all case studies, the patient may have spontaneously recovered menstrual function, and the improvement coincided with the NET therapy. However, given the chronicity of the patients' condition, the long-term unsuccessful medical management and the restoration of menstrual function shortly following the NET therapy, we propose that the intervention of NET therapy may have aided in the resolution of the patients' conditions.

CONCLUSIONS

Menstrual irregularities can be due to a number of conditions. Stress-related menstrual dysfunction is a common mechanism, with alteration in the ovulation cascade being the cause. By understanding how stress may reduces ovulation, the practitioner is able to determine techniques aimed at reducing these alterations. This paper reports on sufferers of menstrual dysfunction who underwent the therapy of NET and subsequently became ovulatory. Long term prospective randomized controlled trial experiments should be implemented to determine a direct causal relationship between the resumption of ovulation and the NET treatment.

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