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GV 20's Role in *In-Vitro* Fertilization and Frozen Embryo Transfer

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ABSTRACT

Background: Unexplained infertility is failure to conceive after 1 year in couples with normal semen samples and no abnormalities. Acupuncture to certain points along a meridian can affect the hypothalamic–pituitary–axis (HPA) by affecting the sensory nerve fibers, blood vasculature, and autonomic nervous system. GV 20, a point at the vertex of the head, is commonly utilized in acupuncture for infertility. Engagement of the HPA axis via GV 20 stimulation should always be considered when treating a woman, with a history of ovarian dysfunction and subsequent infertility, undergoing *in-vitro* fertilization (IVF). This point, due to its systemic effects, should be considered prior to undergoing frozen embryo transfer (FET).

Case: A patient was diagnosed with unexplained infertility when she underwent IVF and FET procedures. GV 20 stimulation helped this patient by improving her mood and ameliorating her psychiatric symptoms via suspected engagement of the HPA axis.

Results: As of this writing, the patient has had a relatively uneventful, successful pregnancy and is currently at 28 weeks' gestation. The couple are happily expecting a baby boy.

Conclusions: Practitioners should use GV 20 to address psychologic concerns, especially in patients seeking assistive reproductive technologies. The general sense of well-being induced by GV 20 stimulation involves engaging the HPA axis. More research on GV 20's effect on regulation of hormonal imbalances, mood, anxiety, and depression via the HPA axis is warranted as is research on how GV 20 stimulation affects prolactin levels when treating hyperprolactinemia, and subsequently, dopamine utilization.

Keywords: acupuncture, IVF, FET, GV 20, stress, HPA axi0s

INTRODUCTION

NEXPLAINED INFERTILITY, sometimes referred to as subfertility, is defined as failure to conceive after 1 year in couples who have normal semen samples and have been found to have no abnormality during their infertility workups. Couples with unexplained infertility might want to consider another year of intercourse before moving to morecostly and invasive therapies, such as assisted reproductive technology (ART). Patients should be counseled that 50% of couples who have not conceived in the first year of trying will conceive in the second year. Unexplained infertility in

women or men may be managed with another year of unprotected intercourse, or may proceed to ARTs, such as intrauterine insemination (IUI) or *in-vitro* fertilization (IVF). Interestingly enough, IUI and ovulation-induction procedures might not result in increased pregnancy rates in women with unexplained infertility. Thus, the next step for a couple to pursue is IVF. In 1995, of women between ages 15 and 44, 15% received an infertility service—an increase of 3% over the previous decade.

Clearly, IVF is becoming an increasingly more-preferred and common treatment option for treating unexplained infertility. In IVF, the patient's ovaries are stimulated with

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gonadotropins, after which eggs are retrieved surgically from the ovaries, fertilized with sperm in a laboratory, and then transferred to the patient's uterus. IVF is widely used and accepted because it can overcome many of the factors considered to be causes of unexplained infertility, such as ovarian dysfunction, cervical problems, and difficulties with sperm–egg interaction and fertilization. Pregnancy rates with IVF can approach 30%, making IVF a favorable option, compared with expectant management.⁴

The World Health Organization (WHO) categorizes all ovulatory disorders into 3 groups, depending on whether the dysfunction is caused by hypothalamic pituitary failure (group I, 10%), by dysfunction of the hypothalamic-pituitary-ovarian axis (group II, 85%), or by ovarian failure (group III, 5%). Women in group II include those with polycystic ovary syndrome and hyperprolactinemia. Dysfunctions of the hypothalamic-pituitary-ovarian axis can have varied clinical manifestations, particularly at psychologic and emotional levels. A couple undergoing IVF can endure several extremes of emotions as well as significant financial and psychologic burdens. These stressors can participate in exacerbating underlying dysfunctions of the hypothalamicpituitary-ovarian axis. The couple and the attending health care professional should be prepared to recognize, accept, and attempt to treat every aspect of the clinical diagnosis throughout the entire process in order to provide hope for a desirable outcome.

The overall goal of acupuncture can be described as stimulating physiologic functions mediated through particular meridians. In practice, while investigating effects of acupuncture on blood-vessel tone, Tam and Yiu concluded that acupuncture "stimulates some sensory nerves and the autonomic nervous system, inducing the recovery of blood circulation." Additionally, Ma reported in 2003, that nitric oxide (NO) content and NO synthase expression became consistently higher at skin acupuncture points or meridians.⁶ It has been suggested that the mechanisms underlying the increased blood flow induced by acupuncture treatment rely on the activation of thin nerve fibers, which release vasoactive neuropeptides and NO from their peripheral terminals upon activation and, as a result, vasodilation occurs and blood flow increases.⁷ The resulting decreases in vascular tone (vasodilation) and blood pressure might directly and indirectly contribute to the regulation of brain activity as well as hemodynamic actions.

Acupuncture applied to certain points along a meridian might affect the hypothalamic–pituitary axis (HPA) via an effect on the sensory nerve fibers, the blood vasculature, and the autonomic nervous system, which are mostly directed by the hypothalamus.

Baihui (GV 20) is an acupoint of the *Du* meridian (the Governing Vessel), which literally translates to "hundred meetings." The Governing Vessel wraps around the external genitalia and the anus to emerge between the anus and coccyx, to then ascend the spine to the brain and vertex of the

head. From the vertex of the head, the meridian sends extensions of itself to the lateral region of the skull and brain, probably because the midline can exist only when supported by lateral stability. The meridian then continues to track along the midline to the nose and philtrum, to terminate at the superior frenulum inside the mouth. This channel or vessel is said to be the confluence of all Yang channels in the body, over which it is considered to influence.

GV 20 is located at the intersection of the line connecting the apexes of the two auricles and the median line of the head, 7 cun directly above the posterior hairline and 5 cun behind the anterior hairline according to the Traditional Chinese Medicine (TCM) theory of acupuncture and the WHO definition. 10 This point is situated within the galea aponeurotica of the cranium, to the left and right of which small parietal foramen are located. GV 20 has a vascular supply provided by the anastomoses of the left and right superficial temporal arteries and veins, and receives neural input from branches of the greater occipital and frontal nerves.⁸ Traditionally, this point is utilized to treat headaches, pain at the vertex of the head, dizziness, tinnitus, deafness, nasal congestion, locked jaw, prolapsed uterus and rectum, hemorrhoids, madness, hemiplegia, and stroke. Based on TCM theory, because GV 20 is located on the highest place of the head where all the Yang meridians meet, acupuncture on this point has also been used to clear the Mind, lift the Spirit, tonify Yang, strengthen the Ascending Function of the Spleen, eliminate Interior Wind, and promote Resuscitation.11

In modern times, various studies have revealed that GV 20-based scalp acupuncture has neuroprotective effects on multiple aspects of the pathophysiology in animal models of ischemic stroke and other causes of significant functional impairment. ¹² This point can be so significant at a physiologic level that Hwang et al. described electroacupuncture at GV 20 (in conjunction with ST 36) as enhancing cell proliferation and neuroblast differentiation in the dentate gyri of rats. ¹³

CASE

A 33-year-old female diagnosed with unexplained infertility presented for evaluation and treatment for her infertility. She had a diagnosis of hyperprolactinemia (for which she took bromocriptine [a 2.5-mg half of a tablet daily]) and was under the care of reproductive endocrinologists. She had been—and still was—in a stable, monogamous marriage for 6 years, and the couple had been attempting pregnancy for slightly more than 1 year. In addition to the above diagnosis, she had a past medical history significant for seasonal asthma for which she used an albuterol inhaler as needed. She had no history of any surgeries and, other than a daily fortified multivitamin, her social history was negative for any over-the-counter medications, illicit drug use, or tobacco or alcohol use. Her family history was positive for a mother with hypertension (well-controlled

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with medications) and a father for dyslipidemia (well-controlled with medications), who were both alive and well. She had a drug allergy to penicillin (which had given her a rash). This patient's spouse had no significant past medical history and was in good health. Other than a very mild dextroscoliosis in the thoracic spine, this patient's physical examination was unremarkable, and she was in good overall health with a body mass index of 20.3.

On initial presentation, the patient had a *Tai Yang* Water structural biospsychotype, with Water being identified as her constitutional factor. Exquisite tenderness was elicited at KI 1, KI 3, LV 3, SP 6, ST 36, SP 10, BL 13, SI 9, and GV 20. The sensation of soreness and tenderness experienced by the patient at GV 20 guided the practitioner to identify and use this point as a key component in her treatment and subsequent healing process.

Initial laboratory values, including her follicle-stimulating hormone(FSH)/luteinizing hormone (LH), progesterone, anti-Müllerian hormone, and her husband's male semen analysis, were all within normal limits. Imaging studies, specifically, transvaginal ultrasound of her pelvis and abdomen, hysterosalpingogram, and magnetic resonance imaging of her brain to rule out pituitary adenomas, were negative for any pathology.

At that time, the patient was counseled by her doctors to continue with attempts of to achieve pregnancy and continue with current daily use of bromocriptine. Two years later, the couple experienced a threatened abortion, after which they decided to revisit the reproductive endocrinologists for a reevaluation. Based on the specialists' recommendations, the couple decided to undergo IUI for at least 3 attempts prior to considering IVF. Clomiphene induction was performed on the first try, which resulted in a failed pregnancy attempt. Next, 2 successive attempts of an injectable solution of follitropinalpha (Gonal-f®), essentially an FSH, were performed without the desired outcome. The 3 failed attempts of IUI were disheartening for the couple.

The patient and her husband decided to continue with natural attempts of conception for a year and a half until they considered that they were emotionally prepared for IVF. Prior to the scheduling of IVF, she had to undergo further imaging testing and clearance. This included a hystoscopy (which was normal), after which she was able to start on oral contraceptive pills to prepare her reproductive system for the upcoming hormonal administrations. For the actual IVF procedure, she was started on menotropin injections (MENOPUR®) and follitropin-alpha injectable solutions daily for ~ 10 days until her FSH/LH and estradiol levels were optimized and ultrasound (US) imaging showed that her uterine lining was appropriate for an IVF attempt to work. On the eighth day of this 10-day cycle, this patient was administered ganirelix acetate, a gonadotropin-releasing hormone antagonist, to prevent premature ovulation. On the tenth day, human chorionic gonadotropin hormone was administered to encourage the release of the follicles, which would take place within 24–36 hours.

The patient's ovaries released 26 follicles from which the reproductive specialists were able to obtain 16 mature ova. Intracytoplasmic sperm injection was performed on these and eight ova were fertilized successfully within 24 hours. By the fifth day, the couple had 6 fertilized blastocytes and chose to undergo preimplantation genetic screening, which revealed 2 genetically healthy embryos. These 2 embryos were then preserved as the patient had to await normal menses in order to resume the next phase of the treatment process: the frozen embryo transfer (FET). She was started on leuprolide (Lupron®) and an oral contraceptive to downregulate her reproductive cycle and HPA until her bloodwork and US results were within acceptable limits. At this point, the patient was started on estrogen pills and patches for ~ 1 week, then, she was started on progesterone suppositories and progesterone-in-oil intramuscularly daily for 5 days before the FET. The FET was successful and, thus, the patient was advised to continue the estrogen and progesterone for 12 weeks until the placenta assumed its appropriate functions.

RESULTS

At the time of this writing, the patient has had a relatively uneventful successful pregnancy and is currently at 28 weeks' gestation. The couple were happily expecting a baby boy.

DISCUSSION

The patient in question, surely as well as other patients who undergo IVF, experienced a sense of relative uncertainty with the entire process, as patients undergoing IVF can develop symptoms related to anxiety and feelings of depression. During the IVF hormonal cycle, this patient reported that the medications affected her mood and psyche while the lack of control she was experiencing over her own body during this process was also a significant stressor. The hormonal fluctuations involved, added to her concerns involving her own abilities to go through the entire process, the financial implications of it, and the fear for her own future as a provider and mother, accumulated together. Overall, this was an extremely difficult process for the couple. The magnitude of this stress continued to increase exponentially as the number of follicles, mature ova, fertilized ova, and actually genetically healthy embryos kept diminishing.

Although this patient had a diagnosis of hyperprolactinemia, reproductive endocrinologists insisted that this diagnosis was so mild that they did not have any Western medical explanations clearly identified as a cause of her infertility. She was categorized as experiencing unspecified/unexplained infertility. She sought acupuncture treatment once she and her husband made the decision to commence

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the IVF. She received 8 acupuncture treatments approximately once per week, with each treatment lasting between 30 and 60 minutes.

According to Chinese Medicine, a complete balancing of Yin, Yang, Qi, and Blood are essential for fertility to occur. Liang mentioned that a fundamental aspect of diagnoses is to differentiate between cases of Vacuity and cases of Repletion. 14 If Liver Blood and Kidney Yin are lacking, an inappropriate nourishment of the Uterus and surrounding vessels can be present, while, if Vacuity of Qi and Yang of the Spleen and Kidneys are present, there could be inadequate energy to transform and activate the Uterus and surrounding vessels. 14 Both of these Vacuity patterns, if present, can lead to inadequate fertilization of an egg or to ineffective implantation of the fertilized ovum. Repletion cases of infertility would involve invasion of pathogenic factors such as Phlegm, Cold, Dampness, or Stasis of Blood and Stagnation of Oi and can be more associated with a history of infections of the reproductive tract or with clearly defined structural abnormalities (fibroids, ovarian cysts, etc.). Due to the "unexplained" nature of this patient's infertility, however, it was determined that she was experiencing symptoms associated with Vacuity of either Kidney Yin or Liver Blood. The Vacuity of Liver Blood was suspected to be the greater culprit.

During the majority of the acupuncture sessions, a combination of points selected included: SP 6, ST 36, LR 3, LI 4, KI 3, KI 13, M-HN-3 (Yin Tang), GV 20 and Si Shen Cong (M-HN-1). The practitioner mostly applied the TCM-style of diagnosis and treatment, and utilized disposable stainless-steel needles (0.20×30 mm, Seirin®) for all points. Per Liang, ¹⁴ KI 13 helps loosen the cervical opening to facilitate embryo transfer, as well as increasing circulation to the Uterus which thickens uterine lining. The Liver and Spleen points helped soothe her Qi and nourish her Blood. 14 Slowly, over the treatment sessions, this patient's exquisite tenderness at SP 6-considered a Warmer of the Middle and Lower Body Heaters, a fortifier of Kidney energy, and a regulator of Liver energy, ¹⁵—dissipated. Due to the practitioner's preference, osteopathic manipulative medicine was also applied to the patient's entire body, especially to the thoracolumbar junction to assist with normalizing sympathetic input into the reproductive tract, and to the sacrum and cranial base, to address parasympathetic input. The patient's mood started to show significant improvement.

To address the patient's stress response, *Bai Hui* (GV 20) was heavily emphasized and utilized in every treatment. *Bai Hui* stimulates the pituitary gland, thereby increasing FSH levels and stimulating the ovaries.¹⁴ However, the original intention was to engage the HPA via this point. Obtaining the De Qi response was never difficult, as GV 20's anatomical location puts the point in the middle of an extremely significant cranial suture—the sagittal suture. In fact, after the lambdoidal suture, research suggests that the next suture likely to remain patent throughout a lifetime is the sagittal suture, which, through myofascial continuity patterns, har-

bors a lot of the repetitive stress from muscle tension. ¹⁶ This stress along the sagittal suture can be dissipated and transmitted to the coronal and the lambdoidal sutures as well, which would assist in maintaining a minimal amount of potency of these sutures.

In addition, the sagittal suture has cogged, deep interlocking serrations or digitations. From a structural-functional viewpoint, reciprocal reception of these fingerlike projections can only be present to accommodate some form of subtle motion present. Of greater significance is that the parasagittal area is considered to be the chief location for the arachnoid granulations, through which part of the cerebrospinal fluid leaves the waterbeds of the brain. 17 This cerebrospinal fluid described in 1899 by A.T. Still, MD, DO, as the "highest known element that is contained in the human body" 18 permeates the entire body and reflects an extremely similar description in Western medical terms to Qi in TCM. Osteopathic practitioners utilizing cranial osteopathic manipulative medicine understand that it is essential that there be no dural tension along this serrated sagittal suture to allow for proper delivery of nutrients and free exchange of all fluids.

The evening prior to the FET, due to the patient's underlying concerns regarding a successful outcome, both GV 20 and Si Shen Cong were identified as being the most important set of points to be addressed. Si Shen Cong with GV 20 can be used to hold the embryo in the Uterus and to quiet the Spirit.¹⁴ In the treatment room, the lights were dimmed, relaxing ocean music was turned on, and an incense with a "beachy" scent was lit. The effect that these interventions along with the acupuncture treatment had on the patient were remarkable. After a few minutes, it seemed like months' worth of stress and uncertainties were literally dispersing into the surrounding environment. If GV 20 has been described as "lifting the spirit," this was perceived by the patient as an overwhelming sensation of relief, calmness, health, and privilege for being witness to a spontaneous and dynamic healing process. She felt lighter; her eyes were full of shen. This was expressed by the teary patient in the following words: "No matter what happens tomorrow, somehow I just know that everything will be OK" (personal communication, 10/17/18).

Five Element constitutional authors mention that GV 20 connects with the deep pathway of the Liver and can be used to treat the Spirit when the Liver is affected. ¹⁹ Referred to as a point in which influences of Heaven may enter the body, GV 20 can have a therapeutic effect of "lifting the spirits when a patient is depressed or dejected," as well as being used to release the External Dragons. ¹⁹

Although several acupuncture points and osteopathic manipulation were utilized throughout the sessions for this particular patient, the practitioner had a firm conviction that the effect of the stimulation to GV 20 had the most influence and produced the most-significant results. This conviction was based on the historical and physiologic aspects related to this point that have been described as well as the emotional and psychosomatic changes experienced by the patient.

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CONCLUSIONS

In addition to the traditional indications for GV 20–point stimulation, practitioners should always consider this point to address psychologic concerns, especially for patients seeking ART. This particular patient population is at increased risk of being exposed to significant psychologic stressors, as explained in this case report. Retrospective reviews involving acupuncture and IVF seem to include the GV 20 point consistently, especially emphasizing its importance if utilized at least 24 hours before the FET. ^{20,21} Although some research has been conducted showing a downregulation of adrenal cortisol content and normalization of the HPA axis in depressed rats, thus, relieving symptoms of depression, there has been difficulty with replicating these findings. ²² In addition, similar research involving anxiety is not as readily available. ^{22–26}

However, in clinical practice, it is very easy to comprehend that the general sense of well-being that this patient experienced with stimulation of GV 20 involved engagement of the HPA axis, as suggested by Chen.²⁷ Finally, a concern identified regarding the success of acupuncture with IVF and FET involved the importance of an appropriate TCM diagnosis to address the patient's symptoms properly.²⁸ In this current case, the patient's diagnosis was obtained with a lot of investigative effort and a relative dose of serendipity, which, on occasion, is just enough required.

Further research involving GV 20 and its effect on regulation of hormonal imbalances, mood, anxiety, and depression via involvement of the HPA axis would be an interesting area of future investigation. This case report might also identify a need to investigate a possible effect GV 20 stimulation may have on prolactin levels, in treating hyperprolactinemia and, subsequently, dopamine utilization as well.

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