

## Clinical Report

# Acupuncture for the treatment of diminished ovary reserve

## 针灸治疗卵巢储备功能低下

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### ARTICLE INFO

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### ABSTRACT

**Objective** To share 20 cases of women with diminished ovary reserve (DOR) and low Anti-Müllerian Hormone (AMH), who had unsuccessful in-vitro fertilization (IVF) trials and to whom the author has successfully treated.

**Methods** Twenty women with DOR had gone through the failed IVF from 1 to 5 times. The acupuncture protocol consists of electroacupuncture, manual acupuncture, acupressure and sliding-cupping, which are the multiple interventions. The acupoints were used based on 5 phases of the menstrual cycle. The electroacupuncture was used twice a week in the follicle phase and the acupuncture without the electricity was used once a week in the luteal phase. Most of them had been treated for three menstrual cycles.

**Results** All of 20 women got pregnant by IVF (17 cases) or naturally (3 cases).

**Conclusion** Acupuncture might improve IVF outcomes for women with DOR by acupuncture treatment for three months or help them to receive naturally.

**KEY WORDS:** acupuncture; DOR; AMH; IVF; electroacupuncture

Ovarian reserve plays a crucial role in achieving pregnancy following any treatment in sub fertile women<sup>[1]</sup>. Anti-müllerian hormone (AMH) is now recognized as a principal regulator of early follicular recruitment from the primordial pool. AMH value is a good predictor for the number of oocytes, which can be retrieved during in vitro fertilization (IVF)<sup>[2,3]</sup>. Recently fertility clinics worldwide have been using AMH together with antral follicle counts as the indicator for diminished ovarian reserve (DOR)<sup>[4]</sup>. Fertility specialist doctor Bentin-Lay from the Danish fertility clinic states: an AMH below 10 pmol/L and less than 8 oocytes aspirated with maximal stimulation in women up to 40 years old indicates a DOR. DOR occupied a significant percentage of couples treated in IVF units (10–24%)<sup>[4]</sup>. Women with DOR have more difficulty in achieving pregnancy generally<sup>[1]</sup>.

Acupuncturists worldwide have been utilizing acupuncture to assist patients who were undergoing IVF or trying to get pregnant naturally. Acupuncture has become an emerging therapy used adjunct to IVF<sup>[5]</sup>. Women find acupuncture treatments an empowering adjuvant and this self-actualizing step is a part of the process of taking back control<sup>[6]</sup>.

DOR is not identified in traditional Chinese medicine<sup>[7]</sup>. There have been a couple of trials about acupuncture improving the IVF/ICSI pregnancy success rate for women with DOR or Primary Ovary Failure (POF) in China and Korea<sup>[7-9]</sup>. For instance, Zhou<sup>[7]</sup> gave 15 sessions of acupuncture for 30 DOR patients with 33 DOR patients in the control group. The acupuncture group had much better effect ( $P < 0.01$ ).

The author would like to present and analyze 20 cases of women with DOR, who had unsuccessful IVF trials behind themselves and were successfully treated in the author's clinic in Copenhagen, between January 2014 and September 2016, and to share and discuss them with acupuncturists around the world.

### CLINICAL DATA

#### General data

Twenty patients with AMH <10 pmol/L and less than 6 follicles from the previous egg retrieval in IVF/ICSI, age from 28 to 40 years old with an average of 38, diagnosed as DOR, were treated in the author's clinic in Copenhagen, Denmark from

January 2014 to September 2016. The BMI were 18 to 31 with an average of 22.2, the infertile time were 1.5 to 2.5 years and the failed IVF/ICSI times were 1 to 5. Two of them came to the author immediately after they decided to have their second child, because the author helped them to get their first child. 34% of their previous IVF/ICSI cycles had been canceled due to the lack of the follicles after one week's follicle stimulating hormone (FSH) stimulation. All, apart from two of them, had regular menstruation. They were healthy, apart from being stressed and worried, because they were told that they had low egg reserves and might have difficulty in getting pregnant.

## METHODS

The acupuncture protocol included electrical acupuncture, manual acupuncture, acupressure, sliding-cupping, which were the multiple interventions. The author treated them with a set of basic points according to their menstrual cycles, and some extra points were added based on TCM syndrome differentiation.

**Needles:** Sterile, silver-handle, single-use needles from Huacheng, with the size of 0.25 mm×25 mm were used. Ear needles were from ASP (France). All acupoints were selected bilaterally. Acupoints and locations were based on *WHO Standardized Acupuncture Point location*.

**Acupoints' selection:** in phase 1 (cycle 1-3 th day): no acupuncture was given if women have no imbalance. In phase 2 (cycle 4-7th day): Bǎihuì (百会 GV 20), Zú sān lǐ (足三里 ST 36), Sānyīnjiāo (三阴交 SP 6) were chosen, electroacupuncture were given on Guī lái (归来 ST 29) and Zǐ gōng (子宫 EX-CA 1). If blood stagnation exists, Cì liáo (次髎 BL 32), Qū quán (曲泉 LR 8), Yáng líng quán (阳陵泉 GB 34) can be added, one acupuncture session was given. In phase 3 (cycle 8-13 th day): Bǎihuì (百会 GV 20), Zú sān lǐ (足三里 ST 36), Sānyīnjiāo (三阴交 SP 6), Hé gǔ (合谷 LI 4), Tàichōng (太冲 LR 3) were chosen and electroacupuncture were given on Guī lái (归来 ST 29) and Zǐ gōng (子宫 EX-CA 1), two or more acupuncture sessions of the treatment were given (The phases are based on the 28 days' cycle. When a woman's cycle is longer than 28 days, more sessions should be given in the phase 3). During the egg transfer, the same acupoints were chosen as the Phase 3, Zhōngjí (中极 CV 3), Shénmén (神门 HT 7) and Tàixī (太溪 KI 3) were added, and no electroacupuncture was applied. In phase 4 (cycle 14-17 day): the same acupoints were chosen as Phase 3, Shénmén (神门 HT 7) and Tàixī

(太溪 KI 3) were added, one acupuncture session of the treatment was given. The quick needling was given at Shènsù (肾俞 BL 23) and BL 32 from phase 2 to phase 4. In phase 5 (cycle 18 to 28 th day), Gānshù (肝俞 BL 18), Píshù (脾俞 BL 20), Shènsù (肾俞 BL 23), BL 32, SP 6, Liè quē (列缺 LU 7) and Jiāoxìn (交信 KI 8) were chosen, and the quick needling on ST 36 was given before the patient lied down on her stomach. Two sessions of the treatment were given.

**Acupoints prescription according to syndrome differentiation:** for spleen deficiency, Xuèhǎi (血海 SP 10) were added, kidney deficiency, Zhàohǎi (照海 KI 6) were added, for liver stagnation, LR8, and GB34 were added. When patients could not come weekly, auricular acupoints were embaded on Shénmén (神门 TF 4), Nèifēnmì (内分泌 CO 18), Nèishēngzhìqì (内生殖器 TF 2), Pízhìxià (皮质下 AT 4), Gān (肝 CO 12) and Shèn (肾 CO 10) (one or more points based on patients' situations), which were just examples, one or more auricular points were chosen based on patients' situations.

**Electroacupuncture:** electroacupuncture was used in the follicle phase 4 sessions and no electroacupuncture in the luteal phase. D-D model (dilatational wave) and low frequency between 2-5 Hz. The intensity was based on individual sensitivity. The best stimulation was just below the pain threshold. The treatment time was around 30 min. The electroacupuncture was not applied during the first acupuncture session.

**Manipulation:** even reinforcing and reducing methods was used. After *deqi*, needles were retained for 30 min. with/without electricity. Needling stimulation depends on the patient's sensitivity: the more sensitive the patient is, the less stimulation is used. Each time ended, acupressure was applied on the head for 5-10 min.

**Treatments' intervals and sessions:** twice a week in the follicle phase and once a week in the luteal phase, 6 times per cycle for the women with menstrual cycle around 28 days. It is important to get one session around the ovulation. When the women's cycle is longer than 28 days, they need more than 6 times per cycle. It was recommended that It was recommended that at least 18-20 sessions of acupuncture treatments in three menstrual cycle before they attempted a new IVF trial should be given. Some of them might need more sessions.

**Sliding-cupping:** sliding-cupping was applied on

all back *shu* points one to two times per cycle depend on the individual needs.

Life style: common suggestions were to eat a healthy diet, avoid tobacco and alcohol, drink less coffee, do moderate exercise, sleep well, practice 4/6 breathing exercise (4 seconds breathing in and 6 seconds breathing out with eyes closed), 10 minutes a day.

Adverse events: there were no any adverse events occurred during all acupuncture sessions except occasionally harmless bleedings around points, temporarily tiredness and mild headache.

## RESULTS

All of these 20 women got pregnant, 17 of them became pregnant after 8 to 24 times, one of them got pregnant after 4 sessions and 2 of them got pregnant after 30 to 40 sessions. 68% of them had around 20 sessions in the period of three to five months. 17 of them got pregnant with IVF/ICSI (between 1 to 2 IVF), 3 of them got pregnant naturally (before they attempted a new IVF trial).

### Typical case

A female, 39 years old, visited the author's clinic in May 2016, immediately after she had stopped breastfeeding for her first baby whom the author had helped to come to the world after one cancelled IVF treatment. Her AMH was 7 pmol/L in 2014. She had a regular menstruation cycle. She had very few symptoms apart from poor sleep, slightly red tongue tip, thready and wiry pulse. The BMI was 19. The TCM pattern was disharmony of heart and kidney. After the author had treated her for three months with the acupuncture protocol plus *anmian* point. She felt generally well and slept well. In August 2016, after she started IVF short protocol with FSH (Menopur 300 IE), she then had headache and poor sleep again, but the author managed to get her to sleep well most of the times and the headache was tolerable. She got pregnant after the first IVF attempt and is still being pregnant at the time of the writing. She was one of them who followed her treatment plan without missing her single acupuncture session.

## DISCUSSION

Acupuncture is an ancient therapeutic art, which has been given renewed attention in light of recent scientific research and current integration with modern medical practice. The mechanisms through which acupuncture influence female fertility are believed to involve central stimulation of endorphin secretion<sup>[10]</sup>,

resulting in uterine conditions favoring implantation<sup>[11,12]</sup>. Jo's Meta analysis showed that acupuncture could decrease FSH and E<sub>2</sub> level significantly but not LH level<sup>[9]</sup>. However, the cause and mechanism of acupuncture treating DOR remain unknown.

In the holistic views of traditional Chinese medicine, all internal organs are related to the reproductive system directly or indirectly<sup>[13]</sup>. DOR is not mentioned in TCM classical books. DOR patients are healthy in general and DOR diagnose is based on age, blood test and the number of aspirated oocytes. The acupuncture protocol was based on the author's understanding of TCM's reproductive system, and direct/indirect experiences on the fertility treatment. Most of the points have been widely used in many studies about acupuncture intervention on IVF-ET<sup>[9]</sup>. Zhou<sup>[7]</sup> has used SP6, KI3, BL23, EX-CA1, ST36, and LR3 as part of her protocol to treat 30 cases of DOR. Chen<sup>[8]</sup> applied acupuncture on CV3, ST29, GV20, ST36, SP6, KI3, LR3, BL23, BL32, 3 times a week in three month for primary ovary failure (POF), which could decrease FSH, LH and E<sub>2</sub> in the serum significantly. Zhou<sup>[14]</sup> used electroacupuncture and achieved the similar results. In the author's opinion, to strengthen and active the ovary, doctor should mainly focus on the spleen and stomach to enrich the acquired *qi*, resulting in the replenishment of the kidney *qi*, so SP6 and BL23 are the main points in the protocol. SP6 is the crossing point of the spleen, kidney, and liver meridians, and is considered the key point in treating infertility<sup>[15,16]</sup>. BL23 is the back *shu* point of kidney. Needling at SP6, ST36, and ST29 were aimed to provide improved blood circulation in the uterus and ovary and regulates hormone balance. HT7 and KI3 were applied around the ovulation, because the ovulation is the place where the *yin* transforms into *yang*, and any emotional stress would disturb the ovulation. LI4 and LR3 are the so-called "four gates points," which are commonly used to open relevant meridians and calm the mind. Combining them with HT7 and GV20 would relax the patient. Back *shu* points are the *yang* points of *zang-fu* organs and they are good at strengthening and invigorating *yang qi* of the internal organs, so Back *shu* points are applied in the luteal phase to support the progesterone production.

### Choosing acupoints based on the phases of the menstrual cycle

*Qi*, blood, *yin* and *yang* are constantly changing in the menstrual cycle, and it is therefore useful to distinguish their phases within the menstrual cycle and to adapt the treatment strategy to the times of the

cycle<sup>[13]</sup>. Choosing acupoints based on the phases of the menstrual cycle to treat infertility/subfertility in connection with IVF is the general guideline, but there are many different ways to practise it<sup>[17]</sup>. In the author's acupuncture protocol, the different combinations of points were applied for the different phases, but SP6, ST36, BL23 and BL32 are used through the whole cycle so those 4 points have the lasting effect. At the same time by adding other points through the cycle to form the different points' combinations so that the patients do not gain tolerance on those four points. Moreover, there is no acupuncture treatment in the first three days of menstrual cycle unless there are some imbalances such as headache, migraine or painful menstruation, because the *qi* and blood are in the lowest level, and the estrogen and progesterone are also in the lowest level in the first three days of the menstrual cycle<sup>[13]</sup>. Therefore, it is the best to let the woman do her own cleansing job without the external disturbs<sup>[18]</sup>.

### Electroacupuncture

Electroacupuncture (EA) consists of the application of small electrical currents to needles inserted at the acupoints<sup>[19]</sup>. EA reversed most of the abnormalities in ovarian adrenergic and nerve growth factor (NGF) receptor and decreased the expression of the sympathetic marker tyrosine hydroxylase<sup>[20]</sup>. It has been shown that low-frequency EA can increase ovarian blood flow in rats and this has been shown in humans too<sup>[11]</sup>. A prospective, randomized study comparing electroacupuncture and alfentanil as anesthesia during oocyte aspiration in IVF, showed, unexpectedly, a significantly higher implantation rate and "take-home baby" rate per ET in the electroacupuncture group<sup>[21]</sup>. Ovarian response relies on nurture in the form of oxygenated blood and nutrients. Nurture is provided directly by the ovarian arteries. Ho<sup>[22]</sup> had used electroacupuncture four times over two weekends and found out that it had increased blood flow in the uterine arteries. It is a common practice that electroacupuncture uses fewer points than acupuncture without electricity does, because the stimulation from electricity is so strong that it overrules the effects from the points without electricity.

### SP6, LI4 and BL32

SP6 is the crossing points of kidney, liver and spleen meridians and LI4 is the primary point of large intestine. "Great compendium of acupuncture and moxibustion" states: To strengthen SP6 and reduce LI4 can strengthen the blood and pacify the fetus in the early pregnancy, to reduce SP6 and strengthen

LI 4 can help the woman to give birth without going past her due time<sup>[23]</sup>. Points' functions depend on the individual's condition, for example, acupuncture on LI 4 was found to suppress the uterine contraction induced by oxytocin in the pregnant rats and acupuncture on SP 6 didn't<sup>[24]</sup>. It is not so dangerous to use SP 6 and LI 4 for the pregnancy as most of textbooks indicate, if they are used for the right condition with the suitable stimulation. BL32 is the one of the most utilized points in the treatment of gynecological problems. BL32 is situated in the second sacral foramen. The main branch of the pudendal nerve that arises from the second, third and fourth sacral nerves and parasympathetic fibers from the second, third and fourth sacral nerves join the uterovaginal plexus<sup>[25]</sup>. Here BL32 is selected according to the segmental innervation. SP6 and BL 32 are main points that have been applied through whole menstrual cycle.

### Stress relieve-acupressure and breathing exercise

Women in the IVF treatment often feel powerless. It is stated in *Ling Shū (The Spiritual Pivot 《灵枢》)* "The essence of acupuncture is to treat the spirit first"<sup>[26]</sup>. The importance of establishing a positive practitioner-patient relationship is the basis for proceeding with treatment including both verbal and non-verbal communication<sup>[27]</sup>. The individualizing of treatment is usually seen as a core approach within TCM. The acupuncture protocol for DOR includes one set basic points and adds different extra points based on their individual TCM patterns. At the same time, each time ends with acupressure on the heads and the guide for breathing excises at home was given. The head is the place where all *yang* meet. The patients felt that they were in the good hands and they loved the acupressure on the head. The breathing excise, meditation or yoga would decrease daily life's stress and easy the mind and let *qi* flow.

### Acupuncture dosage

Acupuncture dosage mainly consists of the needling's stimulation, treatment frequency and treatment period. All the points are commonly used and every acupuncturist knows them all. Why do some acupuncturists have better results than the others? One of the key points is the dosage of acupuncture. As for the needling's stimulation, the author preferred the even method and adjusted the stimulation according to the patient's tolerance. Acupuncture is ideally administered once or twice a week over a period of weeks or months, especially for conditions such as infertility/sub-fertility<sup>[28]</sup>. High

dosage of acupuncture could have higher efficacy of acupuncture than the low dosage of acupuncture<sup>[28]</sup>. The definitive efficient dosages are still unknown<sup>[29]</sup>. In the author's opinion, twice a week in the follicle phase and once a week in the luteal phase in three months are the suitable acupuncture dosage for DOR, and in some cases there may be more than three months, as follicular recruitment from the sleep phase to the bioactive phase where the small antral follicles respond to FSH stimulation takes 85 days<sup>[30]</sup>. The author's own experience has shown that it is important to inform patients with DOR that they should receive three months' acupuncture for preparing the ovary before next IVF trial. In the author's practice, it has been difficult to persuade patients to wait three months to start their IVF trials. They felt that their biological clocks were ticking and they might run out of time. However, with time, more patients are willing to give a try for three months' acupuncture treatment.

The characteristics of the acupuncture protocol are: (1) Choose the points according to 5 phase of the menstruation cycle with one set of basic points, to which can be added a few points during the cycle. (2) Add extra points based on individual TCM patterns. (3) Treatment frequency: two times a week in the follicle phase and once a week in the luteal phase, (6 times per cycle for women with 28 days 4 cycle), which is different from the standard acupuncture approach in China (most of textbooks in acupuncture recommended once every day or every other day, 10 times a treatment course, which is impossible in the west: too much time and too expensive). (4) Use only electroacupuncture in the follicle phase. (5) Spirit (mind) should be taken into account by giving them acupressure on the head and advising them to do breathing exercise daily to reduce stress. (6) *Deqi* can be strong or weak based on individual reaction and the therapist's experience: sensitive patients got less *deqi* and less sensitive patients got strong *deqi*.

## CONCLUSION

TCM is unique in its improvement of ovarian reserve and increasing the ovarian responsiveness to gonadotropins and ovarian sex hormone level due to the multi system and multi-step regulatory functions<sup>[31]</sup>. To be pregnant is an objective factor. The author's personal experience showed that women with DOR are difficult to get pregnant and acupuncture might improve pregnancy related outcomes for women with DOR both by assisting IVF and in the natural way. More well-designed trials on acupuncture for DOR are needed. To look for the evidence of acupuncture's

effects on DOR, Ursula Bentin-Lay, Susanne Suenson and the author have got the research project from the Ministry of Health in Denmark to research the effect of 12 weeks acupuncture treatments on Diminished Ovary Reserve. The research is still in the process.

## DISCLOSURE STATEMENT

No competing financial interests exist.

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## ABSTRACT IN CHINESE

**[摘要]** 目的: 分享作者针灸治疗20名卵巢储备功能低下, 低AMH且人工试管受精失败患者的临床经验。方法: 20名卵巢功能低下患者均经历1~5次的人工试管受精失败。针灸综合疗法包括电针、手针、指针和走罐。基于月经周期的5个阶段来进行针灸选穴。在卵泡期行电针每周两次, 黄体期每周针灸一次。大部分患者均行3个月经周期的治疗。结果: 20个病人均人工试管受精成功(17例)或自然怀孕(3例)。结论: 针灸治疗3个月经周期可能帮助卵巢储备功能低下患者体外受精成功或自然怀孕。

**[关键词]** 针灸 卵巢储备功能低下 试管受精 电针