Protocol Title: Clinical efficacy and safety evaluation of thumbtack needle in nausea and vomiting in pregnancy: a randomized controlled clinical trial

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Informed consent
Information page

Dear patient:

Your doctor has confirmed that you have nausea and vomiting of pregnancy (NVP). We cordially invite you to participate in this study to observe the outcomes of thumbtack needler (TN) on NVP. This program has been approved by the medical ethics committee of Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology (TJ-IRB202409086). Please read the following carefully so that you can understand the purpose, procedures and duration of the study, the benefits, risks, and discomfort it may bring to you. Assistance to help you understand the following information is available from our team, and of course you can consult any of your interest related persons or professionals, such as families, workmates, friends, and health professionals.

1. The background and purpose of the study

1.1 The burden of the disease causes, and status of available treatment choices

NVP is the most common and intractable problem in the first trimester and is the second most common presentation during pregnancy. All types of NVP affect the quality of life of pregnant women, and the intensity of influence increases with the frequency of symptoms. Due to the lack of awareness of NVP and the concern about the teratogenicity of drugs to embryos, the treatment of NVP is always insufficient, and the choice of drug regimen is conservative.

Acupuncture using traditional millineedle is effective on NVP, however, it is generally painful when the millineedle is inserted into the body, and the needling sensation of soreness, numbness, swelling and pain during acupuncture is sometimes beyond patient's acceptability, or even produce adverse effects on pregnancy. Moreover, patients may have to visit acupuncturist daily using millineedle, which may causes high financial costs and reduce the medial adherence. Therefore, although acupuncture with millineedle is effective on NVP, its application in clinical practice is still very limited.

1.2 Research objectives

The aim of the study is to observe the outcomes of thumbtack needle (TN) on NVP.

1.3 Research centers and number of expected subjects

320 moderate or severe VNP patients will be accepted from Oct 2024 to Oct 2028 in the following centers in China: Department of Integrated Traditional Chinese and Western Medicine, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology; Fujian Provincial Maternal and Child Health Care Hospital; Jingzhou Traditional Chinese Medicine Hospital, Jingzhou, Hubei, China; Qianjiang Maternal and Child Health Care Hospital, Qianjiang, Hubei, China; Xiaogan Maternal and Child Health Care Hospital, Xiaogan, Hubei, China; Qianjiang Central Hospital, Qianjiang, Hubei, China; Shiyan People's Hospital, Shiyan, Hubei, China; Wuhan Jinxin Gynecology and Obstetrics Hospital of Integrative Medicine, Wuhan, Hubei, China; Xiangyang Traditional Chinese Medicine Hospital, Xiangyang, Hubei, China; Suizhou Maternal and Child Health Care Hospital, Suizhou, Hubei, China; Nanzhang County Traditional Chinese Medicine Hospital, Nanzhang, Hubei, China; Dongchangfu District Maternal and Child Health Care Hospital of Liaocheng City, Liaocheng, Shandong, China; Xiangyang Central Hospital, Xiangyang, Hubei, China; Aksu Prefecture Maternal and Child Health Hospital, Aksu, Xinjiang, China.

According to the network version of the central randomization system, patients are allocated randomly as 1:1 to TN group and sham TN group with 160 patients in each group.

You will be included in this study if you fulfill the following conditions:

1) The pregnant women's age is 20 ~ 45 years old, the gestational age is 6 ~ 12 weeks, and the ultrasound confirms that it is an intrauterine single or multiple pregnancy, and less than 10% weight loss during pregnancy as compared to before pregnancy.
2) Women diagnosed with moderate to severe NVP in the first trimester: the severity of NVP was determined by the PUQE score, and the PUQE score ranged from 3 ~ 15, < 6 was mild NVP, 6 ~ 12 was moderate NVP, and ≥13 was severe NVP. PUQE score ≥ 6 may be included in this study.
3) Women voluntarily sign the informed consent form.

2. Who should not participate in the study

You will not be included in this study if you are in the following conditions:

1) Age < 20 years, or > 45 years.

2) Gestational age < 6 weeks, or > 12 weeks.

3) PUQE score < 6.

4) frequent nausea and vomiting, weight loss of >10% compared with before pregnancy; or symptoms such as listlessness, paleness, dry skin, sunken eye sockets, and a marked decrease in urine output (less than 400ml of urine in 24 hours or less than 5 times and a small amount of urine in 24 hours).

5) At rest, body temperature > 38 ℃, systolic blood pressure < 90 mmHg or > 140 mmHg, diastolic blood pressure < 60 mmHg or > 90 mmHg, heart rate ⩾ 100 beats per minute, or oxygen saturation < 95%.

6) Urinalysis: urine ketones: +++ and above; or (and) urine protein: ++ and above.

7) Blood biochemistry: serum potassium ⩽ 3.0mmol/L, serum sodium ⩽ 130mmol/L; or abnormal liver function: elevated liver enzymes ≥ 2 times the upper limit of normal; or renal dysfunction: elevated serum creatinine and urea nitrogen.

8) Other digestive diseases that cause nausea and vomiting, such as gastrointestinal infections (with diarrhea), gastric ulcers (with epigastric pain or hematemesis), cholecystitis, biliary roundworms, pancreatitis (with abdominal pain, plasma amylase levels rise to 5 ~ 10 times normal), viral hepatitis (positive hepatitis virology, liver enzyme levels ≥ 1 000 U/L) or acute fatty liver during pregnancy, tumors of the digestive tract.

9) Suffering from immune diseases such as systemic lupus erythematosus, scleroderma, dermatomyositis, IgG4-related diseases, immune nephropathy, etc.

10) Have uncorrected diseases of the endocrine system, such as diabetes, Addison's disease, hyperthyroidism, hypothyroidism, thyroid tumors, adrenal tumors, etc.

11) Suffering from neurological diseases such as migraine, neuromyelitis optica, epilepsy, neurologic tumors, etc.

12) In the past 1 week, have taken antiemetic drugs such as ondansetron, metoclopramide (metoclopramide), promethazine, anti-vomiting Chinese medicine, etc.

13) Monoamine oxidase inhibitors are used.

14) Have received TN treatment in recent 3 months.

15) Unwilling to sign the informed consent of this study.

In addition: ①Patients participating in other clinical study; ②Patients with other reasons that considered by investigators as inappropriate.

3. What should I do if I participate in the study?

3.1 Prior to the start of the study, your doctor will take your medical history, conduct a questionnaire survey of PUQE, and record all pregnancy-related conditions and the scores.

If you are an eligible subject, you can volunteer to participate in the study and sign the informed consent.

If you won't participate in the study, we will treat you as you wish.

3.2 If you volunteer to participate in the study, the procedures will be conducted as below:

You will be allocated to TN group (protocol 1) or sham TN group (protocol 2) randomly.

If you fulfil the including criteria and would like to participate in, a preliminary measurement will be taken: weight, height, etc., and you will fill out questionnaires about PUQE score, nausea and vomiting of pregnancy Quality of Life Specific Scale (NVPQOL) score, anxiety and depression, and sleep. You will be treated in one of our research centers: once every 3 days, for a total of 5 treatments in 15 days. The interventions for each group were as follows:

3.2.1 Protocol 1 for TN group

The main acupoints of treatment are Zhongwan (CV12), bilateral Neiguan (SP6), and bilateral Zusanli (ST36), with a total of 5 acupoints. Patients with Qi stagnation should be given Danzhong (CV17) or Ashi acupoint. Patients with liver and stomach disharmony should be given bilateral Geshu (BL17), patients with phlegm-dampness obstruction should be added bilateral Fenglong (ST40), and patients with weak spleen and stomach should be added bilateral Weishu (BL21). The above acupoints are treated with TN. The TN will be kept in the acupoints for 3 days. After 3 days of retention of TN, the patient is instructed to go to the hospital, where the doctor removes the TN, disinfects the local skin of acupoints and conducts the next TN treatment. A total of 5 treatment sessions were applied for a duration of 15 days.

3.2.2 Protocol 2 for sham TN group

The acupoints of sham TN group are the same as those of TN group. The sham TN is used for sham TN group. The use method of sham TN is the same as that of the TN group. After 3 days retention of sham TN, the patient will be instructed to go to the hospital, where the doctor

removed the sham TN, and conducted the next treatment after local skin disinfection. A total of 5 treatments will be done in 15 days.

3.3 Other items that need your cooperation

After the treatment, we will reassess your PUQE score, NVPQOL score, anxiety and depression, and sleep status, and follow up on your pregnancy status, pregnancy outcome, and neonatal outcome.

You must come to the hospital at appointment time. During the follow-up phase, your doctor may care about your condition by phone, WeChat, QQ or visit your home. Your follow-up is very important because your doctor will determine whether your treatment really works and guide you in time.

During the study, you cannot use acupuncture or other drugs that treat NVP. When you need additional treatment, please contact your doctor in advance.

4. Probable benefits of participating in the study

You may benefit from this study. Such benefits include but not limited to:

Although no guarantee, your NVP symptoms may be relieved. If it does not work for you, possible alternate treatments may be available with free consultation. You may get detailed health status information from the Questionnaires.

You will be treated warmly by our professionals in the whole process.

5. Possible adverse reactions, risks and discomfort, inconveniences of participating in the study

We will exclude subjects who meet the excluding criteria. We will assess and record whether there are abnormal side effects. We will systematically collect the data of adverse reactions and severe adverse reactions. All the data will be quarterly reviewed by the data security oversight board, and the serious adverse reactions will be immediately ruled out. Personal information leakage may occur during the study. We will discuss privacy protection in detail below.

The main risk is the side-effects of acupuncture. TN therapy is designed to have much less uncomfortable sensation as compared to traditional acupuncture using millineedles. Painful sensation, bruised skin, minor bleeding, fainting, needle stitching/bending/broken hardly occurs in thumbtack needling due to the extremely thin and short needle body of TN.

Disposable sterile needles will be used to avoid cross-infection.

During the study period, if you have any discomfort, any new changes in your condition, or any unexpected circumstances, whether related to the study or not, you should inform your doctor in time, and he/she will make a judgment and give appropriate medical treatment.

You need to go to the hospital for treatment on time during the study, and you need to do some examinations before and after the treatment, which will take up some of your time and may cause trouble or inconvenience to you.

6. The costs

In addition, you will receive the routine examination and treatment procedures for infertility, and the payment is on your own. The routine examination and treatment procedures are consistent in all our study centers. Before you agree to participate in this study, we will present and explain all the routine examination and treatment procedures.

Throughout the study, the treatments of TN are free. The urinalysis, liver and kidney function tests, and electrolyte (sodium, potassium, chloride) tests before and after your treatment are free of charge. Your pre- and post-treatment PUQE, NVPQOL, anxiety and depression, and sleep status assessments are also free of charge. The treatments and examinations required for other comorbid medical conditions will not be covered free of charge.

Doctors will do their best to prevent and treat possible injuries caused by the study. If adverse events occur in clinical trials, the committee of medical experts will determine if is related to TN. The sponsor will provide the cost of treatment and the corresponding economic compensation for test-related damages in accordance with the provisions of China's code for the quality management of clinical trials for drugs.

7. Confidentiality for personal information

Your medical records (research medical records /CRF, laboratory tests, etc.) will be kept intact in your hospital. The doctor will record the results of the tests and other examinations on your medical record. Researchers, ethics committees and drug regulatory authorities will be allowed to access your medical records. Your personal identity will not be disclosed in any public report on the results of this study. We will make every effort to protect the privacy of your personal medical data as far as the law allows.

According to medical research ethics, in addition to personal privacy information, test data will be available for public inquiry and sharing, and inquiry and sharing will be limited to web-based electronic databases to ensure that no personal privacy information will be disclosed.

8. How to get more information?

You can ask any questions about this study at any time and get answers accordingly.

Your doctor will keep you informed of any important new information that may affect your willingness to continue the study.

9. It's free participating in or dropping out of the study

Whether you participate in the study entirely up to you. You may refuse to participate in this study or withdraw from this study at any time during the study, which will not affect your relationship with your doctor, nor will it affect the loss of your medical care or other benefits.

For the best interest of you, a doctor or researcher may discontinue your participation at any time during the study.

If you withdraw from the study for any reason, you may be asked about your use of TN. You may also be required to have a laboratory and physical examination if the doctor deems it necessary.

10. What should I do now?

It up to you (and your family) to participate in this study.

Please ask your doctor as many questions as possible before you make your decision to participate in the study.

Thank you for reading the above materials. If you decide to participate in this study, please tell your doctor that he or she will arrange for you all matters related to the study.

Please keep this information.

If you have any questions during participating in this study, please call: Office of the Medical Ethics Committee of Tongji Hospital, affiliated to Tongji Medical College, Huazhong University of Science and Technology, Tel: 86-27-83663625.

Clinical efficacy and safety evaluation of thumbtack needle in nausea and vomiting in pregnancy: a randomized controlled clinical trial

Informed consent · Signature page

The name of the clinical study project: Clinical efficacy and safety evaluation of thumbtack needle in nausea and vomiting in pregnancy: a randomized controlled clinical trial.

Project undertaking department: Tongji Hospital affiliated to Tongji Medical College Huazhong University of Science and Technology.

Project cooperating department:

Fujian Provincial Maternal and Child Health Care Hospital;

Jingzhou Traditional Chinese Medicine Hospital;

Qianjiang Maternal and Child Health Care Hospital;

Xiaogan Maternal and Child Health Care Hospital;

Qianjiang Central Hospital;

Shiyan People's Hospital;

Wuhan Jinxin Gynecology and Obstetrics Hospital of Integrative Medicine;

Xiangyang Traditional Chinese Medicine Hospital;

Suizhou Maternal and Child Health Care Hospital;

Nanzhang County Traditional Chinese Medicine Hospital;

Dongchangfu District Maternal and Child Health Care Hospital of Liaocheng City, Liaocheng;

Xiangyang Central Hospital;

Aksu Prefecture Maternal and Child Health Hospital.

Project assignment number: TTN-NVP (Version number: 3.0)

Declaration of Consent

I have read the above introduction of the study and have the opportunity to discuss this study with my doctor and ask questions. All my questions have been answered satisfactorily.

I know the risks and benefits of participating in this study. I know that participating in the study is voluntary, and I am sure that there is sufficient time to consider it, and I understand that:

I can ask my doctor for more information at any time.

I can withdraw from this study at any time without being discriminated or reprimanded, and my medical treatment and rights and interests will not be affected.

I am also aware that if I withdraw from the study at the middle of the study, especially when I withdraw from the study due to the treatment, it will be very beneficial for the whole study if I tell the doctor about my changes of illness and complete the corresponding physical examination and physical and chemical examination.

If I need to take any other medication because of the change in my condition, I will consult my doctor in advance or tell the doctor truthfully afterwards.

I agree that the ethics committee of the drug regulatory authority or the representative of the applicant should consult my research materials.

I will receive a signed and dated copy of the informed consent.

In the end, I decide to agree to participate in this study, and I promised to follow the doctor's instructions.

Patient’s signature:_____ Date:

Phone:

I confirm that I have explained the details of the trial to the patient, including its rights and potential benefits and risks, and have given a signed copy of the informed consent.

Doctor’s signature:_____ Date:

Doctor’s work phone: