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Original Research Article

Influence of acupuncture on pregnancy rates in women undergoing in vitro fertilization

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ABSTRACT

Introduction: In recent years acupuncture has been used more and more often as an adjuvant infertility treatment. The first reports on the use of acupuncture in the infertility treatment were published in 1960. Many articles have been published about the effect of acupuncture on assisted reproductive techniques but the clinical significance of this technique is still controversial.

Aim: To evaluate the influence of acupuncture on the clinical pregnancy rate in infertility treatment by comparing a group of patients, who underwent acupuncture treatment during stimulation and/or before and after embryo transfer (ET) with a control group without acupuncture.

Material and methods: Patients who were undergoing in vitro fertilization or intracytoplasmic sperm injection treatment were divided into three groups through no random selection: (1) acupuncture during stimulation and on the day of ET; (2) acupuncture only on the day of ET; (3) control group treated only standard protocol, without acupuncture. Acupuncture was performed on 148 patients during stimulation and before and after ET. In the second group 142 patients received acupuncture only on the day of ET. In the control group (142 patients), embryos were transferred without acupuncture. Clinical pregnancy was defined as the presence of a fetal sac during an ultrasound examination 6–8 weeks after ET.

Results and discussion: Clinical pregnancies were documented in 66 patients (44.6%) in the first group, 55 patients (38.7%) in the second group and 50 (35.2%) in the control group.

Conclusions: There was no significant difference in the clinical pregnancy rate between groups; however, a small influence of acupuncture treatment effect cannot be excluded.

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1. Introduction

According to the European Society of Human Reproduction and Embryology 537,463 treatment cycles were reported from 33 European countries in 2009. The in vitro fertilization (IVF) is a costly method and can affect the physical and mental health of treated patients. About 70% of all assisted reproductive techniques (ART) cycles result in the transfer of at least one embryo. Pregnancy rate per embryo transfer (ET) was 32.9% after IVF and 32.0% after ICSI.[9] Failure of implantation is the main factor limiting the success of IVF treatment. Specialists are constantly trying to increase the ratio of live births. In recent years acupuncture has been used more and more often as an adjuvant infertility treatment. The first reports on the use of acupuncture in the infertility treatment were published in 1960.[7] Many articles have been published about the effect of acupuncture on ART but the clinical significance of this technique is still controversial.

Acupuncture is a traditional ancient Chinese treatment technique, which in theory is based on the qi energy flow. It is defined as a state of balance and harmony within individuals between Sky, Earth and Human. Important aspect of this balance is the relationship between yin and yang. Disorders are believed to cause diseases, which can be treated by stimulating specific points. Stimulating these points can correct imbalances in the flow of qi through channels known as meridians. Acupuncture has been recently proposed as a supplementary technique in the treatment of infertility. However scientific study has not found any histological or physiological correlation between qi, meridians and acupuncture points. Study focuses mainly on its potential role in enhancement of uterine receptivity through increased blood circulation,[13,16] perceived reduction of anxiety and stress after acupuncture.[1,14,15,22] Many meta-analyses were published regarding the impact assessment on the effectiveness of acupuncture therapy but they have provided ambiguous results.[8,10,17,19,20,21,23,24] The mechanism of the potential positive influence remains unclear and still controversial.[3,11,24]

2. Aim

The main objective was to evaluate whether acupuncture accompanying stimulation and ET increases clinical pregnancy rate in women undergoing ART. The secondary points were clinical pregnancy rates, miscarriage rates and ectopic pregnancy rates.

3. Material and methods

3.1. Patients

This prospective non-randomized one center study was carried out in the period from January 2010 to April 2012 at a fertility clinic. The main criteria of women included in this study were age more than 45 years and undergoing a IVF/ICSI and ET in the stimulated cycles. Each patient who has been included in the test groups performed stimulation and ET during the standard procedures for in vitro. Acupuncture points were chosen for their sedative effect as well as to increase uterine blood flow. Women voluntarily underwent the acupuncture. Oocytes were retrieved by ultrasound-guided aspiration, a maximum of three embryos were transferred into the uterine cavity on 5th day after oocyte retrieval. All oocyte retrievals and ET were performed in the standard method.

Patients with positive pregnancy test had an ultrasound scan after 6 weeks of gestation in order to confirm a clinical pregnancy. A complete follow-up of all pregnancies is available. Patients who were lost to follow are not included in this study.

Sterile disposable stainless steel needles of $0.20 \times 30\ mm^2$ (Lucos Med-Ultra Smoth 36GX 0.50") were inserted within a tissue level and manipulated until needle sensation was obtained *de qi* – a feeling of, for example, soreness or numbness, distension or pain. Needles will be inserted to a depth no greater than some millimeters and retained for 25 min. All the acupuncture procedures were performed by the same physician.

In our study we have compared three groups of patients.

3.1.1. *Group 1*

Medical acupuncture based on traditional Chinese medicine. Acupuncture performed on women participating in the study included core points such as (once or twice from 1 to 8 day cycle): ST6 (Jiache), HE7 (Shenmen), PC6 (Neiguan), KI6 (Zhaohai) or KI3 (Taixi), AA22 (Neifenmi), AA55 (Shenmen), AA58 (Zhigong), GV20 (Baihui), EX18 (Dongming 6), Ren3 (Zhongji), Ren4 (Guanyuan), Ren5 (Shimen), Ren6 (Qihai). Two subsequent treatments were administered on the day of ET pre and post transfer. Before ET (30 min), we used the following locations: HE7 (Shenmen), PC6 (Neiguan), EX1 (Taiyang), GV20 (Baihui), AA22 (Neifenmi), 58 (Zhigong), ST29 (Guilai) or ST30 (Qichong), KI6 (Zhaohai), Ren3 (Zhongji), Ren4 (Guanyuan), Ren5 (Shimen), Ren6 (Qihai) and after ET (30 min), the needles were inserted at the following points: LI4 (Zhongfeng), EX1 (Taiyang), GV20 (Baihui), AA22 (Neifenmi), ST36 (Zusanli), KI3 (Taixi) or KI6 (Zhaohai), LR2 (Zhongfeng), LR3 (Sanjian), Ren15 (Jiuwei).

3.1.2. *Group 2*

Therapeutic acupuncture based on traditional Chinese medicine. Acupuncture treatment was performed only on the day of the ET. Before ET (30 min), we used the following locations: HE7 (Shenmen), PC6 (Neiguan), EX1 (Taiyang), GV20 (Baihui), AA22 (Neifenmi), AA58 (Zhigong), ST29 (Guilai) or ST30 (Qichong), KI6 (Zhaohai), Ren3 (Zhongji), Ren4 (Guanyuan), Ren5 (Shimen), Ren6 (Qihai); and after ET (30 min): LI4 (Zhongfeng), EX1 (Taiyang), GV20 (Baihui), AA22 (Neifenmi), ST36 (Zusanli), KI3 (Taixi) or KI6 (Zhaohai), LR2 (Zhongfeng), LR3 (Sanjian), Ren15 (Jiuwei).

3.1.3. *Group 3 (control panel)*

Women undergoing our standard IVF protocol, who were not planning to have acupuncture.

3.2. Study endpoints

The ongoing clinical pregnancy rate was considered as the primary endpoint. Clinical pregnancies were confirmed by transvaginal ultrasound 6–8 weeks after ET demonstrating at least one gestational sac with a fetal heartbeat.

The secondary points were pregnancy (HCG positive in 2 weeks after ET), miscarriage rates and ectopic pregnancy rates.

3.3. Statistics

The primary point of the study was to determine whether acupuncture improves the clinical pregnancy rate after IVF or ICSI treatment. The statistical package Statistica (StatSoft) version 10 was used for data analysis. Continuous variables were given as mean ± standard deviation (SD). ANOVA test was used as a corrective against imbalance between the three groups regarding the following variables: age of patient, AMH level, body mass index (BMI). Categorical data were analyzed by the χ^2 test. It was performed for comparison parameters between the study and control groups. A level of significance of 5% was chosen for both tests.

4. Results

4.1. General characteristics

A total of 432 patients were recruited in the study. A group of 148 patients received acupuncture during the simulation and on the day of ET (group 1) and 142 patients received acupuncture only on day of ET (group 2). All the patients completed our study and none were lost to follow up. Table 1 presents demographic data. Groups were comparable with regard to age, BMI, duration of infertility, percentage of primary infertility, percentage of male infertility and number of previous IVF/ICSI attempts. There were no statistically significant differences between the analyzed groups and subgroups. Results were stratified by age and AMH subgroup.

4.1.1. Pregnancy rates

The values for biochemical, clinical, ectopic pregnancy and miscarriage are described in Table 2. Of the 432 women, 225 (52.1%) had a biochemical pregnancy, 171 (39.6%) had a clinical pregnancy. Generally women with acupuncture tended to achieve clinical pregnancy per transfer more often compared to women without acupuncture (44.6% in group 1, 38.7% in group 2 vs. 35.2% in group 3, $p=.255$). The absolute difference in clinical pregnancy rate per transfer between the control and acupuncture groups was 9.4% (group 1 vs. group 3) and 3.5% (group 2 vs. group 3). When we analyzed outcomes in different age and AMH subgroups we discovered that acupuncture intervention was particularly effective in women 30–35 years and AMH level 1.5–4.0 ng/mL in group 1. There was a trend towards higher rates of clinical pregnancy in subgroups, although the differences did not reach statistical significance.

There were no statistically significant differences between the miscarriage rate, biochemical and ectopic pregnancy rates between these three groups. The data demonstrate that only biochemical pregnancy rate was significantly higher in women in acupuncture subgroup 30–35 years.

5. Discussion

IVF is an expensive treatment option for women and their partners, especially when it is necessary to repeat IVF cycles. Therefore new therapies that improve reproductive and healthy outcomes are highly desirable. Acupuncture has been used in the adjunct to treatment of female infertility.

Paulus et al.[18] published the results of the first randomized controlled trial investigating the effects of acupuncture on clinical pregnancy of IVF patients. The study demonstrated an increase in the clinical pregnancy rate in the acupuncture group compared with control (42.5% vs. 26.3%; $P<.03$). Since that time, several study and case reports have been published suggesting a possible positive role of acupuncture in ART. The meta-analyses by the Cochrane Collaboration[4] and Zheng et al.[24] both reported increased pregnancy in women undergoing acupuncture, while El-Toukhy et al.[8] did not find any difference.

Although the mechanism of acupuncture in the treatment of female infertility is still unknown, many studies suggested that acupuncture has a positive influence on the treatment of infertility according to potential impact on the hypothalamic-pituitary-ovarian axis and on the uterus and may improve ovulation via modulation of the central and peripheral nervous system,[3,5] the neuroendocrine and endocrine system, the ovarian blood flow and metabolism.[22] Acupuncture can improve the result of IVF, and the mechanisms may be related to an increased uterine blood flow,[12] and reduction of depression, anxiety and stress.[1,14] Paulus et al.[18] demonstrated that acupuncture treatment does not inhibit uterine motility and suggested that other mechanisms play a positive role in the increase of pregnancy rate after acupuncture in ART.

We have observed a growing interest in the use of acupuncture by our patients. As such, we planned our study to investigate the effects of acupuncture on pregnancy outcomes in our patient population. Our data shows that both acupuncture groups (acupuncture administered on the stimulation and on day of ET; acupuncture administered only on day of ET) had not improved clinical pregnancy outcome per transfer (44.6% vs. 38.7%, vs. 35.2%, $p=.255$; see Table 2); however women who underwent acupuncture tended to achieve pregnancy (particularly if acupuncture were performed on ovarian stimulation and immediately before and immediately after ET) more often compared to women who did not receive acupuncture. There was no significant difference in the pregnancy rate per transfer between groups but, a smaller treatment effect cannot be excluded. We did not find statistical differences in miscarriage rates, biochemical pregnancy rates and ectopic pregnancy rates, but a very interesting fact is that in group 2 (acupuncture performed only immediately before and immediately after ET) there was a relatively large proportion of ectopic pregnancies compared to other groups. This may be due to the increased mobility of the tubes and uterus. However, larger studies are needed.

Table 1 – Demographic characteristics (results stratified by age and AMH level).

Characteristic	Group 1	Group 2	Group 3	P-value[a]
Total				
N cycle	148	142	142	
Age, years	32.9±3.2	33.2±3.3	32.7±3.4	.396
AMH, ng/mL	4.6±2.3	4.1±2.1	4.7±2.3	.054
BMI, kg/m^2	21.9±2.4	22.0±2.5	22.5±2.8	.107
Infertility duration, years	4.8±2.5	5.1±2.2	5.1±2.5	.47
Male factor, % (n)	17.6 (26)	13.4 (19)	17.6 (25)	.537
Primary infertility, % (n)	64.2 (95)	73.2 (104)	63.4 (90)	.145
Previous IVF/ICSI attempts, % (n)	56.1 (83)	46.5 (66)	60.6 (86)	
	25.0 (37)	23.9 (34)	21.1 (30)	.091
1	10.8 (16)	14.8 (21)	9.2 (13)	
2	6.1 (9)	5.6 (8)	5.6 (8)	
3	2.0 (3)	9.2 (13)	3.5 (5)	
>4				
AMH < 1.4 ng/mL				
Subgroup size	18	22	19	
Age, years	35.2±2.9	33.6±2.7	36.1±4.3	.061
AMH, ng/mL	1.0±0.3	0.8±0.3	0.7±0.4	.118
BMI, kg/m^2	22.2±3.0	23.0±3.1	22.2±1.5	.539
Infertility duration, years	5.1±3.4	5.2±1.9	6.1±3.3	.504
Male factor, % (n)	11.1 (2)	13.6 (3)	5.3 (1)	.668
Primary infertility, % (n)	66.7 (12)	81.8 (18)	57.9 (11)	.241
AMH 1.5–4.0 ng/mL				
Subgroup size	51	66	45	
Age, years	33.4±3.3	33.8±3.3	33.1±3.0	.521
AMH, ng/mL	2.6±0.6	2.8±0.6	2.8±0.6	.147
BMI, kg/m^2	21.9±2.3	21.4±2.2	22.0±2.7	.351
Infertility duration, years	4.7±2.7	5.0±2.3	4.7±2.2	.738
Male factor, % (n)	11.8 (6)	15.2 (10)	15.6 (7)	.833
Primary infertility, % (n)	58.8 (30)	65.2 (43)	66.7 (30)	.686
AMH > 4.1 ng/mL				
Subgroup size	79	54	78	
Age, years	32.0±2.8	32.2±3.3	32.3±3.2	.826
AMH, ng/mL	6.6±1.8	6.6±1.9	6.8±1.8	.745
BMI, kg/m^2	21.8±2.4	22.3±2.8	22.8±2.7	.087
Infertility duration, years	4.8±2.2	5.2±2.3	5.1±2.5	.576
Male factor, % (n)	22.8 (18)	11.1 (6)	21.8 (17)	.198
Primary infertility, % (n)	67.1 (53)	79.6 (43)	62.8 (49)	.114
Age ≤ 29 years				
Subgroup size	32	3	33	
Age, years	27.4±1.1	27.7±1.4	27.4±1.2	.548
AMH, ng/mL	5.1±2.0	4.6±2.5	5.6±2.8	.277
BMI, kg/m^2	21.3±2.3	22.0±2.7	22.2±3.8	.292
Infertility duration, years	3.2±1.5	3.4±1.0	3.4±1.3	.775
Male factor, % (n)	28.1 (9)	16.7 (5)	15.2 (5)	.365
Primary infertility, % (n)	75.0 (24)	80.0 (24)	66.7 (22)	.476
Age 30–35 years				
Subgroup size	79	68	72	
Age, years	32.7±1.4	32.7±1.6	32.3±1.4	.168
AMH, ng/mL	5.1±2.4	4.3±2.1	4.6±2.1	.087
BMI, kg/m^2	21.6±2.3	21.6±2.3	21.7±2.2	.954
Infertility duration, years	5.0±2.2	5.0±1.8	5.3±2.2	.647
Male factor, % (n)	13.9 (11)	10.3 (7)	16.7 (12)	.547
Primary infertility, % (n)	67.1 (53)	73.5 (50)	70.8 (51)	.691
Age ≥ 36 years				
Subgroup size	37	44	37	
Age, years	37.9±1.4	37.7±1.5	38.3±1.9	.081
AMH, ng/mL	3.0±1.6	3.1±1.6	4.1±2.4	**.022**
BMI, kg/m^2	22.9±2.7	22.4±2.6	23.4±2.8	.104

Table 1 (*continued*)

Characteristic	Group 1	Group 2	Group 3	P-value[a]
Infertility duration, years	5.8±3.8	6.3±3.1	6.2±3.4	.646
Male factor, % (n)	16.6 (6)	15.9 (7)	21.6 (8)	.763
Primary infertility, % (n)	48.6 (18)	68.2 (30)	45.9 (17)	.085

Age, AMH (Anti-Müllerian hormone), BMI (Body mass index), infertility duration – Data are given in mean ± SD, Male factor, primary infertility, previous IVF/ICSI attempts – Data are given in % (n).
[a] ANOVA test/χ^2 test.

Table 2 – Pregnancy rates.

Characteristic	Group 1	Group 2	Group 3	P-value[a]
Total				
Biochemical pregnancy	56.1 (83/148)	54.9 (78/142)	45.1 (64/142)	.122
Clinical pregnancy	44.6 (66/148)	38.7 (55/142)	35.2 (50/142)	.255
Ectopic pregnancy	2.4 (2/83)	5.1 (4/78)	1.6 (1/64)	.428
Miscarriage	18.1 (15/83)	24.4 (19/78)	20.3 (13/64)	.613
Subgroup AMH **(ng/ml)**				
Biochemical pregnancy				
<1.40	38.9 (7/18)	50.0 (11/22)	47.4 (9/19)	.770
1.50–4.00	56.9 (29/51)	57.6 (38/66)	42.2 (19/45)	.228
>4.10	59.5 (47/79)	53.7 (29/54)	46.1 (36/78)	.245
Clinical pregnancy				
<1.40	27.8 (5/18)	31.8 (7/22)	26.3 (5/19)	.921
1.50–4.00	45.1 (23/51)	40.9 (27/66)	31.1 (14/45)	.359
>4.10	48.1 (38/79)	38.9 (21/54)	39.7 (31/78)	.968
Ectopic pregnancy				
<1.40	14.3 (1/7)	27.3 (3/11)	0.0 (0/9)	.232
1.50–4.00	0.0 (0/29)	2.6 (1/38)	0.0 (0/19)	.528
>4.10	2.1 (1/47)	0.0 (0/29)	2.8 (1/36)	.684
Miscarriage				
<1.40	14.3 (1/7)	9.1 (1/11)	44.4 (4/9)	.141
1.50–4.00	20.7 (6/29)	26.1 (10/38)	26.3 (5/19)	.848
>4.10	17.0 (8/47)	27.6 (8/29)	11.1 (4/36)	.222
Subgroup age **(years)**				
Biochemical pregnancy				
≤ 29	65.7 (21/32)	50.0 (15/30)	60.6 (20/33)	.445
30–35	56.9 (45/79)	61.8 (42/68)	40.3 (29/72)	**.026**
≥ 36	45.9 (17/37)	47.7 (21/44)	40.5 (15/37)	.801
Clinical pregnancy				
≤ 29	56.3 (18/32)	30.0 (9/30)	45.5 (15/33)	.113
30–35	46.8 (37/79)	45.2 (31/68)	31.9 (23/72)	.129
≥ 36	29.7 (11/37)	34.1 (15/44)	32.4 (12/37)	.916
Ectopic pregnancy				
≤ 29	0.0 (0/21)	13.3 (2/15)	0.0 (0/20)	.059
30–35	4.4 (2/45)	0.0 (0/42)	0.0 (0/29)	.201
≥ 36	0.0 (0/17)	9.5 (2/21)	6.6 (1/15)	.442
Miscarriage				
≤ 29	14.3 (3/21)	26.7 (4/15)	25.0 (5/20)	.597
30–35	13.3 (6/45)	26.2 (11/42)	20.7 (6/29)	.320
≥ 36	35.3 (6/17)	19.0 (4/21)	13.3 (2/15)	.294

Data are given in % (number of pregnancies/patients in subgroups).
[a] χ^2 test.

The divergence between the present study and previous positive outcome reports might be related to many reasons. We sum up three key points in our trial.

The first point is the time of intervention. So far there is no research to indicate an optimal time-point for the acupuncture intervention during the in vitro fertilization – embryo transfer (IVF–ET) program, in addition, different stimulation modes could produce different results. Part of the studies have showed that acupuncture done immediately before and after ET might increase the assisted reproduction rates. In another study in which acupuncture sessions were performed on the day of controlled ovarian stimulation and

immediately before and after ET, no increase in the pregnancy rate was found in the acupuncture group.[6] In our study we examined the influence of acupuncture performed twice, on the day of controlled ovarian stimulation (1–8 days) and immediately before and after ET and performed only immediately before and after ET. We did not find any increase in the biochemical, clinical, ectopic pregnancy rate and miscarriage rate between both acupuncture groups and control group.

The second point is the placebo effect of intervention. A well-conducted trial should include a prospective randomized design in which both parties are blind to subject assignment. However, it is impossible to blind the acupuncturist. Additionally in our study the patients knew whether they were receiving acupuncture treatment; hence the placebo effect could again bias the study.

The third point is the choice of acupoints. Our needling protocols had different acupoint than those in other published studies and thus it is complicated to interpret the potential mechanisms of action. Dieterle et al.[6] and Birkeflet et al.[2] stressed on the importance of choosing the right points for achieving a favorable reproductive outcome. In our study acupoints were selected based on the clinical experience in practice, literature and traditional Chinese medicine. However, the study by Dieterle et al.[6] proved that acupuncture at inappropriate acupoints has adverse effect on the pregnancy. Most of the acupoint protocols have overlapped considerably, though there was some variation from our study. Additionally our acupuncture treatments were not standardized. Even though similar points were chosen for all women, points based on the individual traditional Chinese medicine diagnosis were also used. The acupuncture treatment protocol was designed to increase blood flow to the uterus and reduce depression, anxiety and stress. We chose acupoints related to increasing blood flow before ET, and the nourishing points after ET. In addition, the treatment group received an acupoint placed in the ear which stimulates ear point (AA22, AA55, AA58).

6. Conclusions

1. There was no significant difference in the clinical pregnancy rate between groups; however, a small influence of acupuncture treatment effect cannot be excluded.
2. Further study in this area is needed to determine whether acupuncture can and should be used as a successful adjunct to traditional medical treatment with women undergoing IVF. Research should be conducted with the use of standardized acupuncture methods to enhance comparability between studies.

Conflict of interest

None declared.

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