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Uterine artery blood flow in the periimplantation period in embryo transfer cycles

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ABSTRACT

Objective: To assess the role of the uterine artery blood flow in the prediction of implantation in women undergoing embryo transfer during the periimplantation period. **Methods:** A total of 233 couples were included in this prospective study. All patients had embryo transfer, 125 were performed in *in-vitro* fertilization/intracytoplasmic sperm injection (IVF/ICSI) and 108 in cryo cycles. Ultrasound measurements were performed immediately before transfer. The pulsatility index (PI), Resistance index (RI) and the peak systolic velocity (PSV) were measured in both uterine arteries using endovaginal ultrasound. **Results:** In IVF/ICSI cycles the doppler parameters PI (2.48 vs. 2.15), RI (0.78 vs. 1.30) and PSV (60 vs. 63) did not differ significantly between the pregnant and non-pregnant group. The pregnancy rate per transfer was similar in women showing an unilateral (24%), bilateral (33%) or no (27%) notch in the uterine blood flow. In cryo cycles the uterine artery blood flow parameters PI (3.2 vs. 3.0), RI (0.9 vs. 0.9) and PSV (53.2 vs. 51.2) did not differ either between pregnant and not pregnant patients. **Conclusions:** Previous studies were aiming at the measurement of arterial doppler parameters during the follicular phase which may not be adequate for the prediction of implantation. However, our results show that doppler studies during the early luteal phase of assisted reproductive technology cycles are not indicative for the likelihood of pregnancy, too.

1. Introduction

In obstetrics, Doppler sonography of both uterine arteries plays a major role. It is known that pathological uterine Doppler spectrums are accompanied by an elevated rate of preeclampsias and intrauterine growth restrictions (IUGR)[1]. A pathological Doppler sonography of the Aa. uterinae at 23–24 weeks of pregnancy defines 40% of the later preeclampsias, 80% of the later preeclampsias < 34th pregnancy week, 20% of the later IUGR's and 70% of the later IUGR's < 34th pregnancy week[2]. People assume that these diseases are caused by an implantation disorder or are a concomittant factor. Here both embryonal

factors (fetal malformations, chromosomal anomalies, immunological factors) as well as the mother's nidation conditions (hypertension, vasculopathies, thrombophiles, kidney diseases, Diabetes mellitus) play a role. Recently, the study of the uterine arteries has been propagated more and more in the first trimester. If the Pulsatility Index (PI) or the Resistance Index (RI) are above the 90%–95% percentile, as a result 23%–44% of the later preeclampsias, 43% of premature placenta solutions and 14%–37% of the later IUGR pregnancies can be predicted[3–5].

With the physiological implantation, haemodynamic changes occur from which the transformation of maternal spiral arteries into uteroplacental vessels results. This results in a vascular dilation which in turn results in a considerable flow deceleration and a reduction in resistance.

A state following sterility therapy constitutes an independent risk factor for a disrupted invasion of the

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trophoblasts. It is assumed that a non-implantation with artificial insemination constitutes a disrupted invasion of the trophoblasts on the highest level. This can be caused by both insufficient embryo quality as well as unfavourable nidation conditions, caused by the mother.

It was therefore the goal of this study to measure the nidation conditions in *in-vitro* fertilization (IVF) treatment at the time of implantation by Doppler sonography of both uterine arteries and to evaluate whether the Doppler parameters differ in the periimplantation perspective in women who conceive through treatment and those who do not conceive. In a next step, we could be able to study whether a low-dose of aspirin administered to women with a pathological uterine Doppler could result in an improved implantation.

In most previous studies on this topic, the Doppler sonography occurred at the time of the ovulation induction or follicle puncture. In this study, due to the measurement of the uterine blood flow in the early luteal phase, the conditions at the time of implantation were reflected. We also addressed the significance of the notch in the uterine arteries. A notch constitutes a post-systolic incision in the Doppler flow curve which seems to be physiological outside of the pregnancy. Also the distinction between the transfer of fresh and cryo-conserved embryos, where it was more of a matter of the embryos than the uterine situation, was clinically significant. For a fresh embryo transfer (ET) cycle, generally a high-dosed gonadotropin stimulation occurred, a cryo-ET occurs in a spontaneous or estrogen-supported cycle.

2. Material and Methods

2.1. Patients

A total of 233 couples were included in this prospective study (one cycle per couple). 125 patients underwent the IVF or intracytoplasmic sperm injection (ICSI) program. In 60 patients conventional IVF was performed and in 65 cases the ICSI procedure was applied. 108 infertile couples in whom a transfer of cryopreserved embryos was performed were also included in this trial. Women with myomata of the uterus or with uterine abnormalities were excluded. Patients were unselected for age, sperm parameters or infertility criteria. Couples were included only if at least one fertilized oocyte could be transferred.

The indications for assisted reproduction were one or several of the following: tubal factor (28%), endometriosis (8%), male factor (50%), abnormalities of the cycle/polycystic ovary syndrome (15%) or idiopathic infertility (10%). The indication for ICSI was male subfertility in all cases. The mean age of the women was 33 years and that of their partners 35, and did not differ significantly between the IVF/ICSI or cryo cycles. The mean length of infertility was 4.3

years. Informed consent was obtained from all patients.

2.2. IVF/ICSI procedure

Ovarian stimulation, oocyte recovery, IVF and ICSI procedures were carried out using standard protocols as described previously^[6,7]. Ovarian hyperstimulation was performed with recombinant follicle stimulating hormone (FSH) or human menopausal gonadotropin (HMG) using gonadotropin-releasing hormone agonists or antagonists for pituitary suppression. Oocyte recovery was performed by the vaginal route 34–36 hours after human chorionic gonadotropin (HCG) administration.

Embryo transfer was performed three to five days after oocyte retrieval. After incubation for 16–18 hours, the oocytes were checked for the presence of pronuclei as evidence of fertilization. Regular fertilization was defined as extrusion of the second polar body and presence of two pronuclei. A zygote score including the size, number and alignment of pronuclei and nucleoli, cytoplasmic halo effect, the presence of vacuoles and granularity of ooplasm was evaluated as described in detail previously^[8].

According to the patients' age, individual history or desire, two or three zygotes with the lowest zygote score were selected for further culture and transfer. On day 3 the embryo score (ES) based on Steer *et al*^[9] was evaluated. The morphological grade of the embryo was multiplied by the number of blastomeres. The cumulative scores of all embryos selected at the PN stage per patient were calculated to obtain the cumulative embryo score (CES). The mean CES is calculated as CES divided by number of transferred embryos. Embryos were then placed into G2.2TM medium (Scandinavian IVF). After two days of culture in G2.2TM medium, blastocyst formation was evaluated as described previously^[8]. A maximum of three embryos were transferred into the uterus three to five days after oocyte recovery. The luteal phase was routinely supported by vaginal progesterone.

2.3. Cryo cycles

If surplus zygotes were available, they were frozen and used in frozen-thaw cycle if no pregnancy occurred with fresh embryos. For patients who menstruate regularly, the transfer of frozen-thawed embryos was performed in a spontaneous cycle. Embryos were thawed after the luteinizing hormone peak signalling ovulation. According to the patients' age, individual history or desire, two or three zygotes were thawed and cultured until days three to five. After three to five days of embryo culture the transfer was performed. In patients suffering oligomenorrhoea or amenorrhoea an artificial cycle was performed. Oestradiol was given daily either orally or transdermally. Once the endometrium reached a thickness of at least 8 mm, the zygotes were thawed, cultured for three to five days and transferred. In both patient groups, the luteal

phase was supported by vaginal progesterone.

2.4. Doppler studies

Each patient underwent sonography immediately before embryo transfer. Ultrasound was performed transvaginally with a 7.5 MHz endovaginal probe with the patient in a lithotomy position. When a transversal view of the uterus was obtained, the uterine artery blood flow was measured using color Doppler sonography at the level of the internal cervical os. The insonation angle was between 0° and 30°. The pulsatility index (PI), resistance index (RI) and the peak systolic velocity (PSV) were measured in both uterine arteries (Figure 1). The indices were calculated according to Figure 2. As there were no significant differences between the right and the left side, the mean indices were calculated and used for statistics.

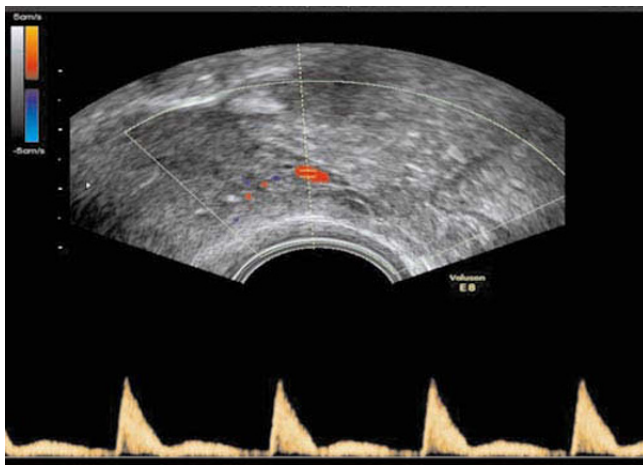


Figure 1. Measurement of uterine artery blood flow.

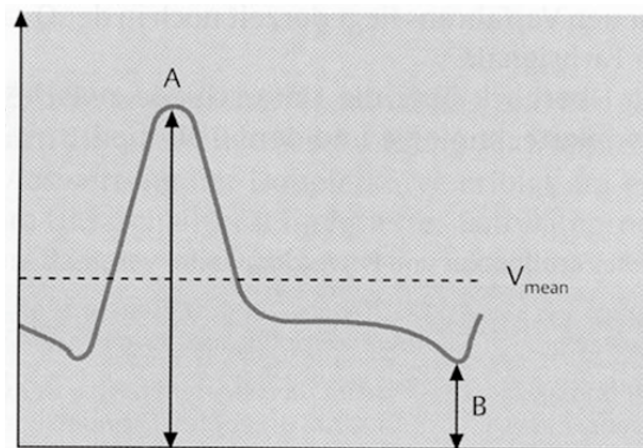


Figure 2. Calculation of Doppler indices [PI = (A-B)/V_{mean}].
RI = (A-B)/A, PSV = A.

2.5. Pregnancy assessment

A single serum β-HCG measurement was performed 14

days after embryo transfer. Clinical pregnancy was defined as presence of a gestational sac on an ultrasound scan.

2.6. Statistical analysis

Statistical analysis was performed using SPSS 16.0. Results were expressed as mean±standard deviation. The student's *t*-test or the Mann and Whitney test was used to compare differences between groups. A *P* value < 0.05 was considered as significant.

3. Results

All 233 patients underwent an assessment of uterine artery blood flow immediately before embryo transfer. As the Doppler parameters were significantly different between IVF/ICSI and cryo cycles (Table 1), the statistical evaluations are given separately for each group.

Table 1

Doppler parameters in IVF/ICSI and cryo cycles.

Parameter	IVF/ICSI cycles (n = 125)	Cryo cycles (n = 108)	<i>P</i>
A. Uterina PI	2.25±0.87	3.04±1.37	< 0.05
A. Uterina RI	1.14±0.37	0.90±0.44	< 0.05
A. Uterina PSV (cm/s)	62.1±41.2	51.6±24.33	ns

In IVF/ICSI cycles the overall mean fertilization rate (FR) was 73% and did not differ significantly between pregnant and non-pregnant women. A mean of 2.6 embryos (median 3, range 1–3) were replaced into the uterus in 125 cycles, 63% of which were triple embryo transfers. In all, 34 clinical pregnancies were recorded (27.2% per cycle and per transfer). As 6 pregnancies were terminated as miscarriages or ectopics, the baby take-home rate was 22.4%.

No differences in terms of body mass index, duration of infertility, cause of infertility, sperm parameters, duration and total dose of gonadotropins administered, serum oestradiol concentrations, and number of oocytes collected and fertilized were noticed between pregnant and non-pregnant patients (Table 2). The uterine artery blood flow parameters PI (2.48 vs. 2.15), RI (0.78 vs. 1.30) and PSV (60 vs. 63) did not differ significantly between the pregnant and non-pregnant group.

Patients' age and the embryo score on day 3 showed significant differences between conceiving and non-conceiving patients (Table 2). Therefore only the good prognosis patient group with an embryo score > 18 was evaluated. In this group of patients no differences in uterine artery blood flow parameters PI (2.48 vs. 2.16), RI (0.78 vs. 0.77) and PSV (63 vs. 54) could be observed between pregnant and non-pregnant patients either (Table 3).

Table 2

Clinical data and Doppler parameters in IVF/ICSI cycles.

IVF/ICSI cycles	Pregnant (n = 34)	Not pregnant (n = 91)	P
Age	31.30±4.00	33.30±3.90	< 0.05
Duration of infertility	3.90±2.00	4.40±2.80	ns
Body mass index (kg/m ²)	23.40±4.00	23.30±3.50	ns
Collected oocytes	12.30±6.70	10.60±6.70	ns
Fertilisation rate (%)	69.40±24.30	74.70±30.00	ns
Mean embryo–score	28.00±9.30	20.20±9.10	< 0.01
Nr of transferred embryos	2.65±0.59	2.55±0.61	ns
A. Uterina PI	2.48±1.40	2.15±0.52	ns
A. Uterina RI	0.78±0.10	1.30±0.80	ns
A. Uterina PSV (cm/s)	60.00±26.20	63.00±46.30	ns

Table 3

Doppler parameters in IVF/ICSI cycles with good embryo morphology.

IVF/ICSI cycles embryo–score > 18	Pregnant (n = 28)	Not pregnant (n = 37)
A. Uterina PI	2.48±1.40	2.16±0.54
A. Uterina RI	0.78±0.09	0.77±0.10
A. Uterina PSV (cm/s)	62.6±26.2	54.70±46.30

The pregnancy rate per transfer (all IVF/ICSI cycles) was similar in women showing a unilateral (23.8%), bilateral (33.3%) or no (27.3%) notch in the uterine blood flow. There were no differences in pregnancy rates in uterine artery PI <3 (29.6%) and > 3 (50.0%).

In the 108 cryo cycles a mean of 2.5 embryos (median 3, range 1–3) were replaced into the uterus, 59% of which were triple embryo transfers. In all, 20 clinical pregnancies were achieved (pregnancy rate 18.5% per cycle and transfer). As 4 pregnancies were terminated as miscarriages or ectopics, the baby take–home rate was 14.8%.

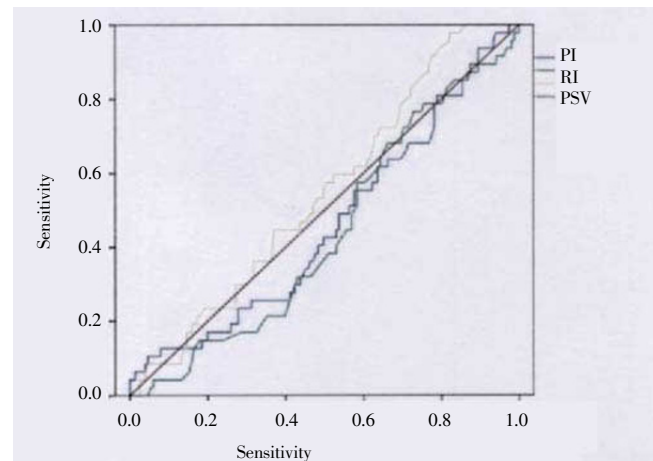
No differences in terms of age, duration of infertility, body mass index, cause of infertility, quality and number of transferred embryos were noticed between pregnant and non–pregnant patients (Table 4). The uterine artery blood flow parameters PI (3.2 vs. 3.0), RI (0.9 vs. 0.9) and PSV (53.2 vs. 51.2) did not differ significantly between the pregnant and non–pregnant group (Table 4). The pregnancy rate per transfer was similar in women showing a unilateral (20%), bilateral (25%) or no (14%) notch in the uterine blood flow. There were no differences in pregnancy rates in uterine artery PI <3 (17.5%) and > 3 (15.4%).

The ROC curve shows that the Doppler parameters uterine artery PI, PI and PSV are not suitable to predict the pregnancy rates in ART cycles (Figure 3).

Table 4

Clinical data and Doppler parameters in cryo cycles .

Cryo cycles	pregnant (n = 20)	not pregnant (n = 88)	P
Age	32.5±2.9	32.9±4.0	< 0.05
Duration of infertility	4.8±3.4	5.0±2.9	ns
Body mass index (kg/m ²)	23.5±4.5	22.7±3.7	ns
Nr of transferred embryos	2.7±0.6	2.5±0.6	ns
A. Uterina PI	3.2±1.7	3.0±1.3	ns
A. Uterina RI	0.9±0.8	0.9±0.5	ns
A. Uterina PSV (cm/s)	53.2±21.8	51.2±24.9	ns

**Figure 3.** ROC curve.

4. Discussion

In this prospective study, no correlation can be found between uterine vascularization and the implantation in ET cycles. In previous studies it was shown that the Doppler parameters of the Aa. uterinae do not correlate with the result of pregnancy following IVF or ICSI. However, the measurements were performed at these studies at the time of egg cell collection^[10] or the time of HCG administration^[11,12]. In smaller studies with only 46 or 53 patients, a significantly lower PI in the uterine arteries in pregnant women compared to non–pregnant women could be found at the time of the HCG injection.

Only a few studies have performed the measurements at the time of the embryo transfer. Here, in the early years the transfer most often occurred on day 2 so that the periimplantation conditions were possibly not recorded^[13–15]. Chien *et al* on the other hand, were able to measure in a larger group of 317 women a significantly lower resistance index at the time of the embryo transfer^[16].

In a more recent study of 83 IVF / ICSI patients upon whom an embryo transfer was performed, there were serial Doppler ultrasound tests on different cycle days, including on the date of the embryo transfer (day 2–3 following puncture) and in the mid–luteal phase (cycle day 24). It could be shown that, during the cycle, there was a continuous decline of the PI up to the mid–luteal phase but no differences between pregnant and non–pregnant patients[17]. In this study, as in ours, the embryo score was the only parameter which distinguished between pregnant and non–pregnant women. That is why we performed an analysis of only those cases with good embryonic quality to be able to not consider the factor embryo score. But also in this group of “good prognosis patients”, differences in the Doppler parameters between conceiving and non–conceiving women could not be determined.

Regarding the different PI values on different cycle days, these discoveries were proven by another study which showed that there are no significant differences in the PI and RI values between different cycle phases or different measurement locations[18].

If it could have been proven true that increased resistance indices (PI, RI) could result in the uterine arteries in the periimplantation phase with a low pregnancy rate, in a next step a treatment with low–dose aspirin could be effective. Haapsamo *et al* shown in 2009 in a prospective–randomised study that, in IVF patients who had been administered aspirin, there were less cases with a suboptimum PI (≥ 3) in the uterine arteries than without aspirin but without differences in the average PI and RI values[19]. The pregnancy rate was also not different in both groups (113 cases). If a pregnancy occurs after IVF/ICSI, it can be shown that, in patients taking aspirin, the uterine PI at 18 weeks of pregnancy was significantly lower than without aspirin.

Uterine vascularization has so far hardly been studied in cryo–transfer studies. In our study, we could demonstrate a significantly higher PI in the cryo–cycles than in “fresh” IVF/ICSI cycles. However, we could also prove no difference in the Doppler parameters between pregnant and non–pregnant women. Differences in the resistance index of the uterine arteries between IVF and natural cycles have already been proven[20]. Zaccova *et al* found no differences in endometrial vascularisation between conceiving and non–conceiving women[21].

In contrast to the first trimester screening in early pregnancy uterine artery doppler studies immediately before implantation seem not to be associated with implantation conditions. Therefore doppler studies during the early luteal phase of ART cycles are not indicative for the likelihood of pregnancy.

Conflict of interest statement

We declare that we have no conflict of interest.

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