The clinical value of Doppler ultrasound

The clinical value of transvaginal colour Doppler ultrasound in assisted reproductive technology procedures

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Introduction

Previous research has shown that uterine blood flow is an important factor contributing to uterine receptivity (Goswamy et al., 1988) and which can be studied by means of transvaginal pulsed and colour Doppler ultrasound (Tekay, 1995; Tekay et al., 1995a). Utilizing this technique, some authors have been able to distinguish between conception and non-conception cycles in in-vitro fertilization (IVF) patients before the embryo transfer (Strohmer et al., 1991; Steer et al., 1992). The predictive role of Doppler velocimetry has been based on the difference found in mean uterine (Sterzik et al., 1989; Strohmer et al., 1991; Steer et al., 1992, 1995) or ovarian (Baber et al., 1988) artery pulsatility (PI) or resistance index (RI) values between the conception and non-conception cycles. Patients who had become pregnant showed a lower vascular impedance than those who had not.

Consequently, during the last few years Doppler velocimetry has gained an increasing popularity among clinicians treating infertility patients. Recent data (Favre et al., 1993; Coulam et al., 1994; Bassil et al., 1995; Bustillo et al., 1995; Tekay et al., 1995a, 1996) have challenged the earlier assumptions on the predictive role of Doppler measurements in assisted reproductive technology (ART) procedures.

Discussion

Considerable heterogeneity with respect to stimulation protocols, study material, and timing of Doppler ultrasound evaluation has been seen in earlier studies. In some investigations, measurements were performed before human chorionic gonadotrophin (HCG) administration (Strohmer et al., 1991), while in others they were performed before follicular aspiration (Sterzik et al., 1989) or embryo transfer (Steer et al., 1992; Favre et al., 1993; Steer et al., 1995; Tekay et al., 1996). A valid comparison between different studies is, therefore, very difficult to make.

Nevertheless, the following conclusions can be drawn from the earlier studies. First, the sole use of impedance indices (either PI or RI) cannot distinguish between conception and non-conception cycles in IVF patients undergoing down-regulation with gonadotrophin hormone-releasing hormone (GnRH) analogues (Favre et al., 1993; Coulam et al., 1994; Bassil et al., 1995; Tekay et al., 1995a, 1996). Second, there are some distinct differences in blood flow characteristics between spontaneous and stimulated cycles, with vascular resistance being lower in the latter (Coulam et al., 1994; Tekay et al., 1996). In addition, different stimulation protocols may lead to different levels of vascular impedance (Favre et al., 1993). Finally, a high resistance (e.g. PI >4) or the absence of an end-diastolic blood flow in uterine arteries before embryo transfer is inconsistent with implantation (Steer et al., 1992; Favre et al., 1993; Tekay et al., 1995a, 1996).

IVF protocols which include GnRH-analouges seem to increase the uterine blood flow to its upper physiological limit. Accordingly, the variance in PI values between the subjects is considerably decreased (Tekay et al., 1995a). This might explain why many authors have failed to detect a significant difference between conception and non-conception cycles in patients undergoing similar stimulation protocols. Finding a statistically significant difference between these groups might require the recruitment of a very large number of patients, but the literature does not provide such data. Regardless of this, the data available at present suggest that there will be an indisputable overlap in the measured PI values between conception and non-conception cycles, which makes a clinical judgement concerning the uterine receptivity rather difficult.

Various threshold levels for uterine artery PI values have been suggested to be associated with subsequent implantation failure. In the literature, these cut-off values have varied between 3.0-4.0 (Steer et al., 1992; Favre et al., 1993; Coulam et al., 1994; Tekay et al., 1995, 1996). In our opinion, information concerning the level of vascular resistance in terms of a PI or RI value only, does not appear to be very helpful for the clinician during a stimulated cycle. As a consequence of the reasons detailed above, in our IVF patients (Tekay et al., 1995a, 1996) we found that there were very few women who had considerably high resistance in their uterine vasculature immediately before embryo transfer. Many patients, instead, had an intermediate or low resistance, indicating adequate tissue perfusion, but were still unable to conceive. Among these patients, an enhancement in uterine artery blood flow does not seem to be associated with the outcome of the IVF treatment. Implantation failure in these subjects must, therefore, be related to factors other than inadequate uterine perfusion.

In contrast, in women undergoing frozen-thawed embryo transfer during their spontaneous cycles, a broad range in PI values could be seen (Tekay et al., 1996). This is perhaps due to a considerable variability in hormonal profiles and endometrial environment among the patients. As a consequence, the development of the spiral arteries, which is
considered important for implantation, can be asynchronous. In patients with well developed endometrial vessels, downstream resistance to blood flow will be decreased, resulting in low PI or RI values in the uterine arteries. On the contrary, insufficient vascularization will lead to high PI or RI values. Implantation failure among these women with high resistance, therefore, could be attributed to inadequate vascularization or poor uterine blood perfusion.

The failure to find a stronger correlation between the outcome of IVF and impedance indices can also be explained in light of the interesting observations made by Dickey et al. (1994). These authors have performed Doppler velocimetry investigations on non-pregnant patients attending an infertility clinic. The patients were first examined in a recumbent and subsequently in an upright position during the mid-luteal phase of their menstrual cycles. After standing for 9-14 min, the uterine artery blood flow volume had decreased by an average of 34% and RI increased in 70% of their population. In addition, the number of flow velocity waveforms in which blood flow was discontinuous between the systole and diastole had increased. These findings imply that standing may impair the uterine blood perfusion and that Doppler observations made in recumbent patients might not be valid in those who are standing. In previous Doppler studies, the subjects have been examined solely in the recumbent position. It might be possible that the uterine blood flow which can be considered as being adequate (i.e. having a PI value lower than a given threshold level) during a Doppler examination made in the recumbent position may become inadequate after the patient stands up and continues her daily activities. This impairment in uterine blood perfusion might be fatal for the conceptus, in particular during the early pregnancy.

Another noteworthy observation which might influence Doppler results was recently made by Zaidi et al. (1995). This was the presence of a circadian rhythm in uterine artery blood flow during the periovulatory period. According to these authors, uterine artery PI values were most commonly lowest during the early morning hours and increased towards the afternoon and evening. This fluctuation has not been previously addressed. This study could not show any significant correlation between the uterine artery PI and serum concentrations of luteinizing hormone (LH), follicle stimulating hormone (FSH), oestradiol and progesterone.

More insight into the Doppler research on infertility patients may be gained by studying the flow velocity waveform patterns visually. According to our experiences (Tekay et al., 1996), a uterine artery flow velocity waveform with an absent end-diastolic flow component is strongly associated with inadequate uterine perfusion and implantation failure. The visual analysis of the waveform patterns was first introduced by Goswamy et al. (1988) and was later modified by Dickey et al. (1994) to cover most of the flow velocity waveform patterns one might encounter in the Doppler ultrasound assessment of uterine artery blood flow. In addition to the earlier descriptions, an early reversed diastolic flow can occasionally be observed (Tekay et al., 1996). Nevertheless, the visual waveform analysis had been overlooked by many investigators who, instead, had mainly focused their interest on the impedance indices.

Only a few studies have evaluated the intraovarian blood circulation in IVF patients. In our opinion, it is very difficult to detect minor changes in intraovarian blood circulation during the stimulated cycles (Tekay et al., 1995a,b). Firstly, intraovarian arteries offer minimal resistance to blood flow and operate as if they are maximally dilated (Wiltbank et al., 1990; Tekay, 1995). Secondly, the hormonal profile achieved with GnRH analogue treatment is different from that observed in natural cycles, the most important feature being the lack of a physiological LH surge prior to follicular aspiration. The external administration of HCG has an effect which lasts longer than that of a spontaneous LH surge. Thus, the alterations of intraovarian Doppler parameters which take place in the normal menstrual cycles (Campbell et al., 1993; Kupesic and Kurjak, 1993; Sladkevicius et al., 1993) might not occur during human menopausal gonadotrophin (HMG)/HCG stimulation (Tekay et al., 1996). Nevertheless, the implantation site (i.e. endometrium) receives its blood supply from the uterine arteries. Therefore, as far as uterine receptivity is concerned, the uterine vascular bed seems to be a more relevant site for Doppler measurements than is the ovarian vasculature.

Conclusion

All in all, cancelling a scheduled fresh embryo transfer during an IVF programme due to the detection of higher PI value than a previously suggested cut-off level does not appear to be justified at present. On the contrary, if a high resistance (i.e. absence of an end-diastolic flow or PI >4) is encountered in a patient undergoing a frozen-thawed embryo transfer after previous unsuccessful attempts, and already having limited chances (e.g. a scarce number of embryos available or older age), one would prefer to postpone thawing to prevent unnecessary embryo wastage.

References

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Doppler-sonographic pelvic blood flow measurements and their prognostic value in terms of luteal phase and implantation

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Adequate pelvic blood flow is an important precondition for physiological ovarian function. An abnormal uterine response to decreased uterine perfusion has been suspected. This observation on the basis of pulse wave Doppler measurements has been first described by Goswamy et al. (1988). These authors speculated that this has been seen to occur in ~50% of women, who failed to conceive despite repeated attempts at in-vitro fertilization therapy (IVF).

Some studies followed using pulse wave Doppler flow or colour Doppler ultrasound to support the predictive role of Doppler velocity for conception. Recently it was suggested that the measurement of uterine artery pulsatility index (PI) on the day of human chorionic gonadotrophin (HCG) administration predicts subsequent implantation rate in IVF cycles (Zaidi et al., 1996). Furthermore, a physiological relationship between follicular blood flow velocity, oocyte recovery or production of a high rate preimplantation embryo was supposed (Nagund et al., 1996; Oyesanya et al., 1996).

As pointed out by the authors of the first article in this debate series, other investigators could not distinguish between the conception and non-conception cycles in IVF patients (Tekay et al., 1996). At least in part some of these studies are difficult to compare. There are three possible reasons: (i) some of these studies deal with patients in spontaneous and some in stimulated ovarian cycles; (ii) the stimulation protocols show different regimes; and (iii) the times of measurement were different, i.e. some investigators measured on the day of the HCG, some before embryo transfer and others immediately before follicle aspiration. Intra-observer variation of ~4% and inter-observer variation of ~12% and differences due to the endovaginal or transabdominal route in colour Doppler assessment have also to be respected (Steer et al., 1995).

On the other hand there is evidence for a certain correlation between the pelvic blood flow and the concentrations of the sexual hormones (oestrogen and progesterone) in the luteal phase of a spontaneous cycle (Glock and Bromsted, 1995), in early pregnancy (Jauniaux et al., 1992) and in patients with hormonal replacement therapy (Achiron et al., 1995). Hence in stimulated cycles with high levels of sexual hormones (because of multiple follicular development) the vascular resistance could be measured significantly lower than in comparison with spontaneous cycles (Strigini et al., 1995; Tekay et al., 1996a). Thus stimulation therapy could probably improve the pelvic blood flow at peri-ovulatory time.

However, those cases under stimulation treatment demonstrating still high pulsatility indices (>4) and/or an end-diastolic zeroflow in the uterine arteries just before embryo transfer may indicate an insufficient uterine perfusion with deleterious effects on the implantation (Steer et al., 1992; Favre et al., 1993; Tekay et al., 1996a,b). Below these rough alterations in uterine perfusion there should be a wide range of variation and other factors should be more evident to determine the later success of implantation.

Flow alterations in the early luteal phase and around the time of implantation— their relationship to serum concentrations of the sexual hormones

In spontaneous ovarian cycles of volunteers, typical courses of the Doppler indices resistance index (RI) and PI were found by pulse wave Doppler measurements not only in the main pelvic arteries: the internal, external and communical artery respectively; but also in the smaller pelvic arteries: the uterine and the ovarian artery. For the blood flow in the uterine artery a circadian rhythm during the peri-ovulatory period is described (Strigini et al., 1995). In all of the mentioned pelvic vessels, the lowest impedance during the course of cycle was registered on the first post-ovulatory day, which coincides with a maximum perfusion in the cycle (Deichert et al., 1994; Deichert and Burman, 1995). Also for induced ovarian cycles the lowest midcycle PI in uterine spiral arteries was observed on the day after ovulation (Kupesic and Jurkac, 1993).