

Role of Ultrasonography and Uterine Doppler Parameters to predict Endometrial Receptivity in Infertile Patients

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Abstract

Infertility is on increase with rising trend observed in carrier-oriented couples. The influence of infertility can be immense and devastating. The impact affects the social wellbeing with loss of self-esteem, disappointment and depression. The investigations of many such couples do not exhibit any perceptible cause and are labeled as 'unexplained infertile' - which accounts for around 15-30 percent of the cause of infertility. Such couples have normal ovulatory function, normal semen analysis, normal tubal patency and normal endometrial cavity. It is often hard to explain to such couples their inability to reproduce. The vital step in conception is the efficacious implantation which necessitates a normal and functioning embryo at developmental stage of blastocyst, a receptive endometrium and a synchrony between embryonic and maternal tissue. The article discusses the role of ultrasound and color Doppler compiled with Uterine Biophysical scores (UBP), Uterine Scoring System for Reproduction (USSR) as noninvasive tools to assess endometrial receptivity and pregnancy outcome.

Keywords: Infertility; Endometrial Receptivity; Uterine Biophysical Profile (Ubp); Uterine Scoring System for Reproduction (Ussr)

Introduction

Infertility is on increase with rising trend observed in carrier-oriented couples [1]. However, the influence of infertility can be immense and devastating. The impact affects the social wellbeing with loss of self-esteem, disappointment and depression. The investigations of many such couples do not exhibit any perceptible cause and are labeled as 'unexplained infertile' [2] - which accounts for around 15-30 percent of the cause of infertility [3]. Such couples have normal ovulatory function, normal semen analysis, normal tubal patency, and normal endometrial cavity [4]. It is often hard to explain to such couples their inability to reproduce. The vital step in conception is the efficacious implantation which necessitates a normal and functioning embryo at developmental stage of blastocyst, a receptive endometrium, and a synchrony between embryonic and maternal tissue [5]. Implantation is an important step in establishing pregnancy and scientific basis of failure of implantation is still to be deciphered. Implantation is difficult to study because our knowledge of what happens during

the first week of human life in vivo is limited. It requires decoding the interaction between a blastocyst and a receptive endometrium [6-8]. Numerous diagnostic parameters have been projected to estimate endometrial receptivity. These tools include histologic dating of an endometrial biopsy, endometrial cytokines in uterine flushing, or molecular expression of vasoactive compounds, the genomic study of a timed endometrial biopsy or more commonly a noninvasive ultrasound examination of endometrium with Colour Doppler -all relying on angiogenic factors helping in implantation. The recent approach is to visualize endometrial perfusion non-invasively or vascularity of endometrium during peri implantation period at endometrial -sub endometrial junction and assessing the Uterine Biophysical Profile [9].

Physiology Of Implantation

The physiological process of implantation is a well-organized and orchestrated process. The endometrium undergoes series

of changes which synchronize with formation of blastocyst. The changes include –

1. Attachment of blastocyst to endometrium
2. Penetration of blastocyst into the stroma

The stroma helps in anchoring, sustaining the embryo, control the invasiveness of trophoblast, produce growth factors and substrates and functions in response to proteins and hormones of ovary and embryo.

Endometrial Changes During Implantation

The change in endometrium occurs in response to the blastocyst development and are in a way picked up on Ultrasound

1. In follicular phase the endometrial growth is tortuous
2. Till ovulation there is increase in glands
3. At ovulation, the glands become tortuous and formation of spiral arteries
4. During implantation time (20, 21, 22 days) the endometrium becomes thick, edematous with predecidual cells. Epithelial lining is filled with mucus film, microvilli and pin pods. These changes are not present at day 16 and vanish by day24 in both spontaneous and induced cycles. These changes and pin pods are said to help in the process of anchoring and sustaining the embryo.

Ultrasound Assessment of Endometrium

During the reproductive years of normal female, the uterus undergoes ultrasonographically detectable changes which are characterized by cyclical changes in the echo pattern of the endometrium. From the first day of the menstrual cycle till the midcycle, the normal endometrium progressively thickens and develops sonographically detectable strata. The appearance is described as layered, trilaminar or five lines. After the mid cycle, the normal endometrium brightens and progressively thins. These

sonographically patterns are related to the changes in the glandular and vascular elements of endometrium during the menstrual cycle. The endometrium either sloughs off if no pregnancy or will undergo changes in the event of pregnancy. In preparation for implantation, the endometrium undergoes transformations influenced by the ovarian hormones produced in the early secretory phase. These modifications include increase in the blood flow, number of cells populating the stroma and epithelium, uterine oxygen consumption oxygen diffusion into the uterine lumen and a generalized edema. The endothelium of spiral arteries undergoes proliferation, thickening of the wall and coiling. The chances for a normal implantation may be reduced if the spiral arteries are inadequately developed. Changes in the endometrial vascularity may be picked up on color Doppler. By Ultrasound and color Doppler the endometrial changes picked up on histologic examination by pathologist may be complemented or substantiated. The endometrial and peri endometrial areas can be divided into four zones:

- Zone 1- A 2mm thick area surrounding the hyperechoic outer layer of endometrium
- Zone 2- The hyperechoic outer layer of the endometrium
- Zone 3 – The hypoechoic inner layer of endometrium
- Zone 4- The endometrial cavity

The variations in the depth of vascular penetration before, during and mid cycle of menstrual cycle can be seen on ultrasound. Most patients demonstrate flow into zone 3 by mid –cycle and are presumed normal (Tables 1 & 2). Also sub endometrial arteries doppler indices (RI and PI) are studied at 1-2 mm lateral to the outer edge of the endometrium. Uterine artery PI and RI were recorded from the uterine artery main branch on the lateral edge of the cervix. Applebaum [10] in his scoring system proposed USSR perfect score of 20 has been associated with 100 percent chances of conception Scores of 17-19 have been associated with 80 percent chances of conception. Scores of 14 to 16 have 60 percent while score of 13 or less resulted in no pregnancy.

Table 1: Uterine Biophysical Profile [10] Certain sonographic qualities of the uterus may be noted during the normal mid cycle. These include 7 parameters.

S. No	Parameters
1	Endometrial thickness in greatest AP dimension of 7 mm or greater (full thickness measurement)
2	A layered (five –line) appearance of endometrium
3	Blood flow in zone 3 during colour Doppler technique
4	Myometrial contraction causing a wave like motion of the endometrium
5	Uterine artery blood flow, as measured by PI, less than 3.0
6	Homogenous myometrial echogenicity
7	Myometrial blood flow seen on gray –scale examination (internal to the arcuate vessels)

Table 2: The Uterine scoring system for reproduction (USSR) comprises evaluation of the following parameters with a score.

1	Endometrial thickness (full thickness measured from the myometrial –endometrial junction to the endometrial –myometrial junction)
a	Mm=0
b	7-9 mm =2

c	10-1mm =3
d	>14 mm =1
2	Endometrial layering (i.e five –line appearance)
a	No layering =0
b	Hazy five-line appearance = 1
c	Distinct five-line appearance =3
3	Myometrial contraction seen as endometrial motion. (Seen as wave like endometrial motion high speed playback from videotape)
a	0 contractions in 2 minutes (real time) =0
b	3 contractions in 2 minutes (real time) =3
4	Myometrial echogenicity
a	Coarse /inhomogeneous echogenicity =1
b	Relatively homogenous echogenicity =2
5	Uterine artery Doppler flow evaluation
a	PI -3=0
b	PI-2.99=0
c	PI -2.49= 1
d	PI <2= 2
6	Endometrial blood flow within zone 3
a	Absent =0
b	present but sparse =2
c	present multifocally =5
7	Gray scale myometrial blood flow (internal to the arcuate vessels seen on gray scale examination)
a	Absent =0
b	Present =2

Discussion

Implantation appears to be the weakest link for the success of any ART procedure. Several parameters and techniques have been studied to assess the implantation potential of endometrium. Several studies have found better implantation rates when the endometrium was multilayered with echogenicity's in the hypoechoic areas in between the lines [11,12]. Conventionally, endometrial thickness (ET) of greater than 7 mm and a triple-layered endometrial pattern were considered as markers of endometrial receptivity. No doubt other factors apart from sonographic signs of 'uterine receptivity' are at work in determining conception. However, Doppler Ultrasound could be used as a parameter to predict negative outcome especially in IVF cycle pretransfer. If failure could be predicted, the embryos could be frozen until a more favorable cycle appears based on scoring criteria like USP and USSR [10,13]. This could prevent embryo wastage and subsequent patient disappointment. Human placentation is a complex interplay of factors involving the endometrium and the blastocyst and abnormalities of placentation are associated with diseases such as miscarriage and pre-eclampsia [14]. Both these complications stem from a defect in early trophoblast invasion and a failure to convert the spiral arteries into low resistance channels. Therefore, defective placentation's is mainly characterized by a thinner and fragmented trophoblastic shell and reduced cytotrophoblast invasion of the lumen at the tips of the spiral arteries [15]. It is now

possible to predict early, and late pregnancy complications related to abnormal placentation on account of the ability of the colour Doppler imaging to detect small vessels such as the terminal part of the uteroplacental circulation.

A temporary but exclusive sequence of factors that make the endometrium amenable to embryonic implantation has been referred to as endometrial receptivity [16]. It is only the period of implantation window that there is an optimal time for blastocyst implantation. The endometrium otherwise gives a non-receptive environment for blastocyst implantation. During a regulated implantation window on day 6-10 post ovulation can a human embryo develop while rest of the time is surrounded by refractory endometrial status [16]? Tissue remodeling and angiogenesis are hallmark events during implantation and decidualization. The dynamic changes in the endocrine state of female during the menstrual cycles and pregnancy result in extensive remodeling of the uterine tissue. The secretory phase of 21 to 22 days of cycle is characterized by endometrial stromal edema with an increase in vascular surface area. These changes may be the result of estrogen and progesterone mediated increase in prostaglandins and VEGF production in the endometrium causing vascular permeability. One of the strongest predictors of implantation is ET, which is dependent on several factors including reproductive age, phase of menstrual cycle, ovarian hormone concentration and endometrial hormone receptor density [17]. Substantiating information has

been reported in various other cases where the assessment of ET was used to predict pregnancy outcome following IVF-E [18]. Studies suggest that the highest pregnancy rate (50%) was seen when ET was around 8-10 mm, least (2.5%) when the ET was either more than 14 mm or less than 8 mm [19] Oliveria JB [20] by their study concluded that pregnancies did not occur when the endometrial thickness was less than 7 mm. others reported a minimal endometrial thickness of 6 mm to be acceptable for implantation [21].

However, the implantation rates may be more correlated to the vascularity of the endometrium rather than only the thickness and morphology of the endometrium. Varying distribution of vascular zones suggesting poor vascularity has also been recognized as endometrial receptivity marker. Reports from studies show higher pregnancy rates in highly vascular endometrium in contrast to increased miscarriages in pre-pregnancy poor vascular endometrium even after successful IVF-ET [22-24]. A substantially higher concentration of growth factors and interleukins are produced by good healthy vascular endometrium aiding in better implantation and better pregnancy outcome. The zones of vascularity as defined by Appelbaum [10] as zone 1 when the vascularity on power doppler is seen only at endometrial myometrial junction, zone 2 when vessel penetrate through the hypoechogenic endometrial edge, zone 3 when it reaches the intervening hyperechogenic zone and zone 4 when they reach the endometrial cavity Singh et al [25] in their study found a higher pregnancy rate when the blood flow to the endometrium was in the zone III (51.8%) as compared to Zone I (14.8%). Another study [26] emphasized that sub endometrial flow is vital to determine pregnancy outcome.

Conclusion

Infertile couples undergo immense stress and depression. If the basic treatment does not make them conceive then various methods of assisted reproduction techniques demand great amount of time, energy, mental, physical exhaustion and substantial finances drainage. UBP and USSR may be utilized as simple, rapid, noninvasive parameters to predict uterine environment and assess the pregnancy outcome. The article highlights the role of UBP and USSR, endometrial thickness and peri ovulatory endometrial blood flow in predicting favorable outcome in the form of pregnancy in couples of unexplained fertility while undergoing IVF. However, its role in spontaneous conceptions is limited and yet to be assessed.

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Conflict of Interest

Nil.

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