

Effect of Endometrium on Fertility Success Rate

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Introduction

- Ovarian stimulation commonly results in the generation of more embryos than are necessary for the fresh embryo transfer. Therefore, cryopreservation and subsequent replacement of frozen–thawed embryos is an integral part of assisted reproductive technology (ART) programs.
- It is vital that a frozen–thawed embryo is replaced during the window of **endometrial receptivity** and that there is synchronization between embryo and endometrial development.

- A number of **different protocols** have been developed to achieve this:
 - ✓ replacement during a natural ovulatory cycle;
 - ✓ hormone (estrogen and progesterone) replacement cycles (with or without prior or synchronous pituitary downregulation);
 - ✓ ovulation induction cycles.
- Endometrial receptivity may be **negatively affected** by ovarian stimulation.
- Number of studies, including a meta-analysis of 3 RCTs , have suggested that there may be an advantage to **freezing all** suitable embryos and replacing them in a natural or medicated cycle .

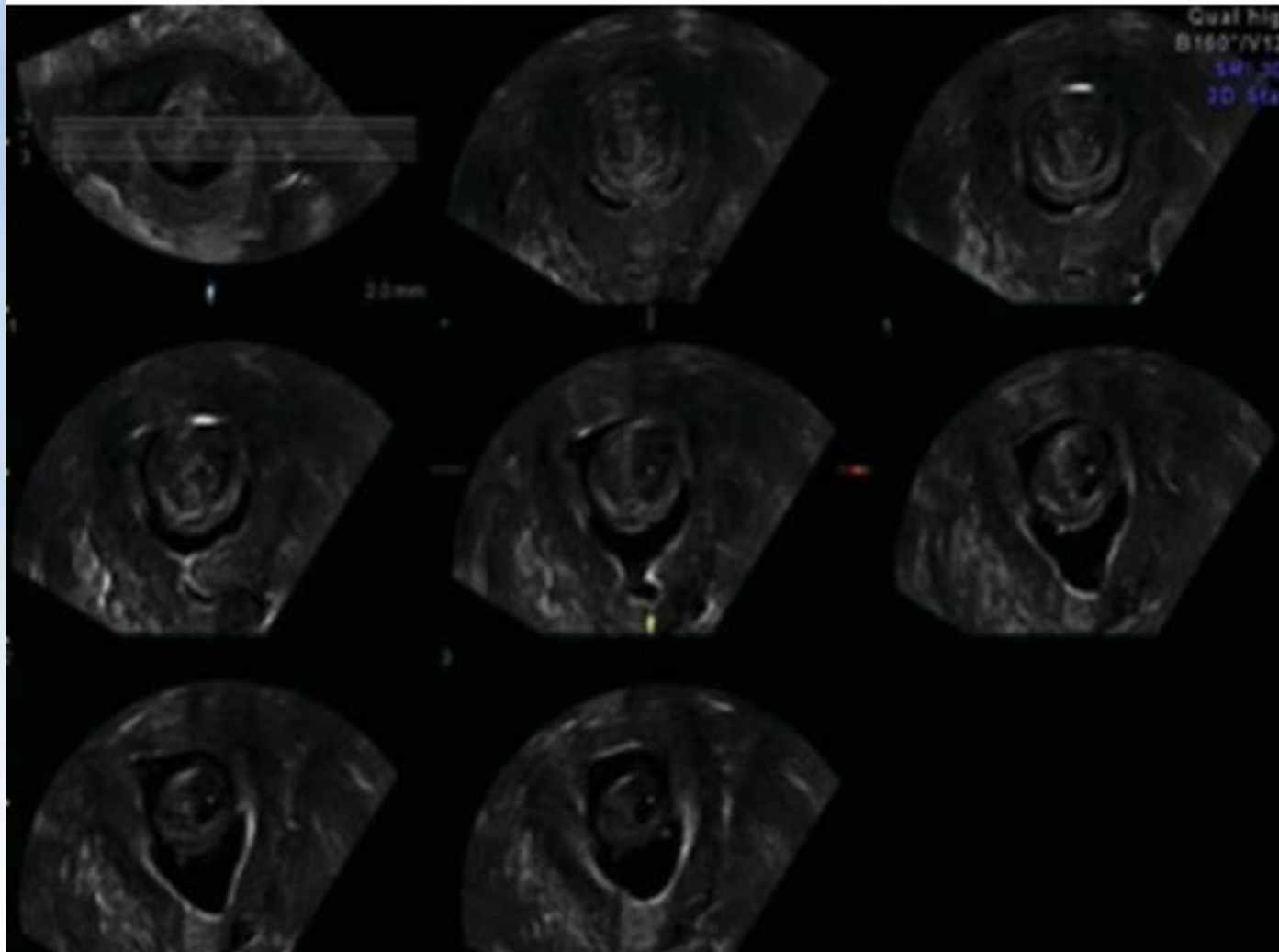
Evaluation of the uterine cavity

- To ensure proper embryo replacement, it is important to **evaluate the uterine cavity besides the endometrium before starting the IVF cycle** . (size and position of the uterus ,fibroids or polyps, adhesions, and Mullerian anomalies or adenomyosis)
- The **US** is a precise method for measuring the **length** of the uterine cavity and the cervical canal.
- It is very important in evaluating the **cervico-uterine angle** .
- US is also essential in diagnosing the presence of **fibroids** and their encroachment on the uterine cavity or cervical canal.

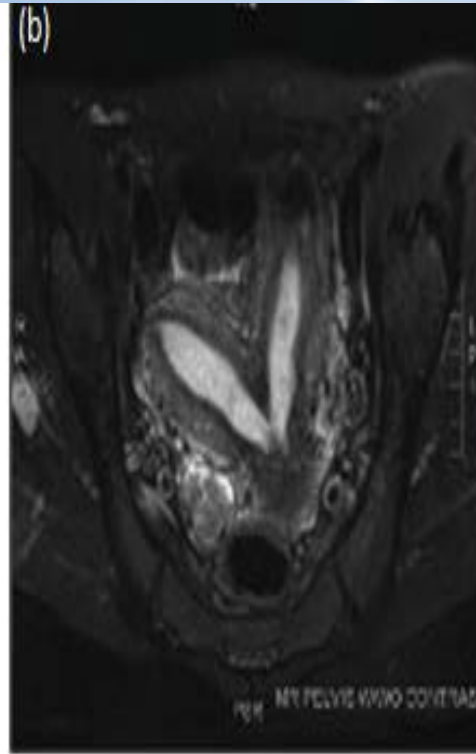
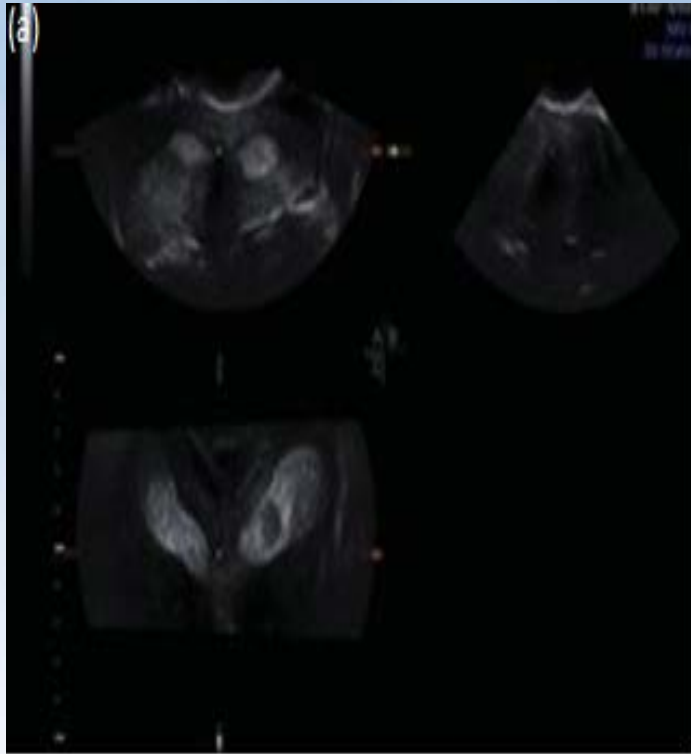
Saline sonogram of uterine polyp



Saline sonogram of submucosal fibroid



Bicornuate uterus



- **Hysteroscopy** is considered as the definitive diagnostic tool for evaluating any uterine cavity abnormalities suspected on HSG or US .
- **Chronic endometritis** should be excluded in patients with **RIF** without apparent cause.
- Several researchers have implicated endometrial inflammation as a potential etiology of RIF .
- **Adenomyosis** occurs when endometrial glandular cells invade the uterine myometrium. This condition should be considered to be a potential cause of **RIF** .

- Though adenomyosis has been implicated as having a significant negative affect on female fertility, the condition is one of **the least treatable** of all uterine pathologies .
- Limited reports in patients with RIF have suggested successful treatments with **ultra-long GnRH agonists** prior to IVF, although the data are limited and further corroboration is needed .

- Given the extent to which uterine pathology can be implicated in RIF, **diagnostic investigation of the myometrium and endometrial cavity is warranted in all patients with RIF.**
- HSG , SIS , 3D US , MRI, and hysteroscopy are all available for evaluation of uterine architecture and the endometrial cavity .

US OF UTERUS ENDOMETRIAL THICKNESS AND ART MONITORING

- Ultrasound assessment of the endometrium and the myometrium of the uterus is important in order to maximize implantation, both in natural pregnancies and in IVF.
- Endometrial thicknesses and patterns vary throughout the menstrual cycle .
- The endometrium is :
 - ✓ Thin immediately after menstruation (2–5 mm),
 - ✓ Thickens during the proliferative phase,
 - ✓ Trilaminar before ovulation,
 - ✓ Thick and echogenic in the secretory phase of the cycle .



- TVUS parameters of the endometrium have long been considered implantation markers in IVF .
- Abnormalities in the uterus explain many causes for recurrent implantation failure .
- Ultrasound examination of the endometrium in a natural or mock cycle supplemented with E + P provides a noninvasive way to evaluate endometrial development and receptivity before ET treatment.
- **Synchronization** between the endometrial and embryo development is essential for successful implantation.

ENDOMETRIAL THICKNESS AND QUALITY IN FER CYCLES

- The endometrial thickness and pattern are noted during ovarian stimulation in IVF and ovulation induction cycles, and have been noted to affect pregnancy rates.
- Several studies have failed to identify differences in endometrial thickness and morphology between conception and non-conception cycles in both natural and medicated cycles .

- Endometrial pattern can be classified as :
 - ✓ Type A, a multilayered triple-line endometrium consisting of a hyperechogenic outer and central lines;
 - ✓ Type B, an intermediate isoechogenic pattern with a non-prominent central line;
 - ✓ Type C, an entirely homogeneous endometrium.
- Most commonly, the endometrium is described as “triple-line” or “homogeneous.”

- The best pattern is the trilaminar with a central echogenic line, inner hypoechoic regions, and hyperechoic outer walls compared with the homogeneous pattern .
- Although in fresh IVF cycles a triple line is associated with an increased CPR, in FER cycles, no such association has been identified.
- However, a non-homogenous hyperechoic endometrial 3 days after FER was shown to be associated with a reduced pregnancy rate.

- **No consensus** has been reached with regard to the minimum endometrial thickness required for successful pregnancy.
- Endometrial thickness is measured from **outside to outside** in an antero-posterior view at the widest point.
- Patients with a **thin endometrium** following ovarian stimulation have a **significantly lower pregnancy rate** but have yielded a high percentage of false-positive results .

- In one study, pregnancies **did not occur** when the endometrial thickness was < 7 mm .
- Other studies found that a minimum endometrial thickness of 6 mm is **acceptable** for implantation .
- In a recent study, the thinnest endometrial lining for successful ongoing pregnancy was **5.8 mm**, and the maximum number of conceptions occurred when the thickness was **8–10 mm** .
- With increasing endometrial thickness (**>14 mm**), a high miscarriage rate was reported.

- However, a large retrospective study of medicated FER cycles found that implantation and pregnancy rates were significantly **lower** when :
 - ✓ The endometrial thickness was ≤ 7 mm
 - ✓ or ≥ 14 mm

- An excessively thick endometrium may start in a previous cycle, so ovarian stimulation should **not** be **started** following menstruation if the endometrial thickness is **> 6 mm**.
- Increased preclinical or biochemical **miscarriages** are also seen when the endometrial thickness is **6–8 mm** versus ≥ 9 mm.
- There is a high consensus to recommend embryo **cryopreservation** in cases of thin and non-trilaminar endometrium because the likelihood of implantation is low.

- Assessment of **endometrial blood flow** in IVF treatment with Doppler and 3D imaging has been studied to see if it is predictive of implantation.
- Importantly, Doppler studies of uterine arteries **do not reflect** the actual blood flow to the endometrium.
- Doppler can measure the **pulsatility index** of the uterine arteries, and elevated levels are associated with low implantation and pregnancy rates in one study, but not in others .

- The **absence** of color Doppler mapping at endometrial and sub-endometrial levels can be associated with a **significant decrease** in pregnancy and implantation rates, while flow- through vessels at the endometrial and sub-endometrial levels are associated with increased rates.
- An observational study of 165 medicated FER cycles found that the **presence** of subendometrial–endometrial blood flow on 2D power Doppler was associated with a significant **improvement** in implantation, CPR, and LBR .

- Low-dose aspirin, vaginal sildenafil (Viagra), and pentoxifylline have been used to treat patients with **thin endometrium** .
- The underlying assumption is that patients with thin endometrium have **suboptimal endometrial blood** flow and may have scar tissue, and aspirin or Viagra increase the endometrial blood flow and endometrial development .
- However, studies **do not consistently** show increased uterine receptivity and IVF success with these agents and are based on small numbers.

- The use of 3D US for calculation of the **endometrial volume** has also been studied.
- Some studies show that endometrial volume can **better** predict implantation rates over endometrial thickness .
- Endometrial volume of **<2.5 mL** is predictive of a low pregnancy rate or pregnancy loss, but it is not found to be predictive of pregnancy if the endometrium attains at least 2.5 mL or 1 mL .

- With the addition of Doppler, it was found that the endometrial and sub-endometrial **vascularity** were significantly lower for patients with **low-volume** endometrium when compared with those with normal-volume endometrium, but these **did not correlate with the endometrial thickness**.
- 3D ultrasound and power Doppler angiography are useful exams to assess endometrial receptivity in IVF/ICSI cycles .
- Doppler in 2D, however, has not been shown to benefit fertility at this time in studies with large numbers .

- A small amount of **endometrial fluid** may be seen at the end of stimulation in the middle of the cavity.
- This is thought to be mucus, and can be seen to frequently disappear.
- However, significant endometrial **fluid at the time of ET**, usually visible with hydrosalpinges, is associated with poor prognosis, and freezing all the embryos should be considered.

- Although characteristics of the human endometrium including :

- ✓ thickness (volume),
- ✓ morphology,
- ✓ endometrial blood flow,
- ✓ vascularization

can be readily and noninvasively monitored by ultrasound, there **still is not a clear correlation** between the patterns and successful implantation.

- However, the 3D studies show better correlations than 2D ones.

Endometrial “scratch”

- Significant controversy exists over the benefit (or lack thereof) of “endometrial scratch” as a method for fostering implantation.
- The method is purported to induce a “healing process” that allows for release of cytokines and other growth factors that facilitate implantation.

- Barash et al. in 2003 first suggested an association between endometrial biopsy and implantation in a study of 134 good responders who failed to conceive in one or more prior IVF cycles with at least three embryos transferred .
- The data suggesting a significant improvement in subsequent implantation rates (27.7% vs. 14.3%) following biopsies.
- Subsequent randomized controlled trials have employed a variety of inclusion criteria and frequencies/timings of biopsies, but overall have suggested an implantation benefit following the intervention.

- Whereas initial studies seemed promising, subsequent data have been mixed, with some studies revealing a decrease in pregnancy rates in women undergoing biopsies prior to IVF .
- In a RCT of women with RIF ,clinical pregnancy and live birth rates were lower in the experimental group .
- Two additional studies suggested no benefit of endometrial scratch in unselected populations undergoing IVF .

Thanks all

