

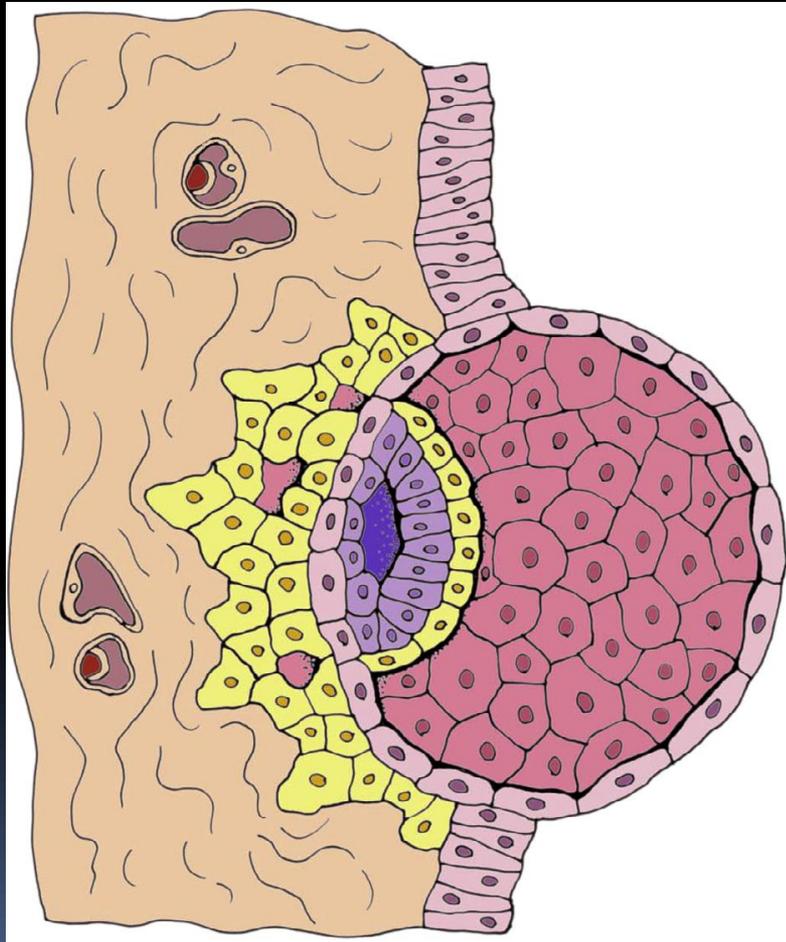
RECURRENT IMPLANTATION FAILURE IS ASSOCIATED WITH INCREASED LEVELS OF FETUIN-A/ALPHA2- HEREMANS-SCHMID-GLYCOPROTEIN

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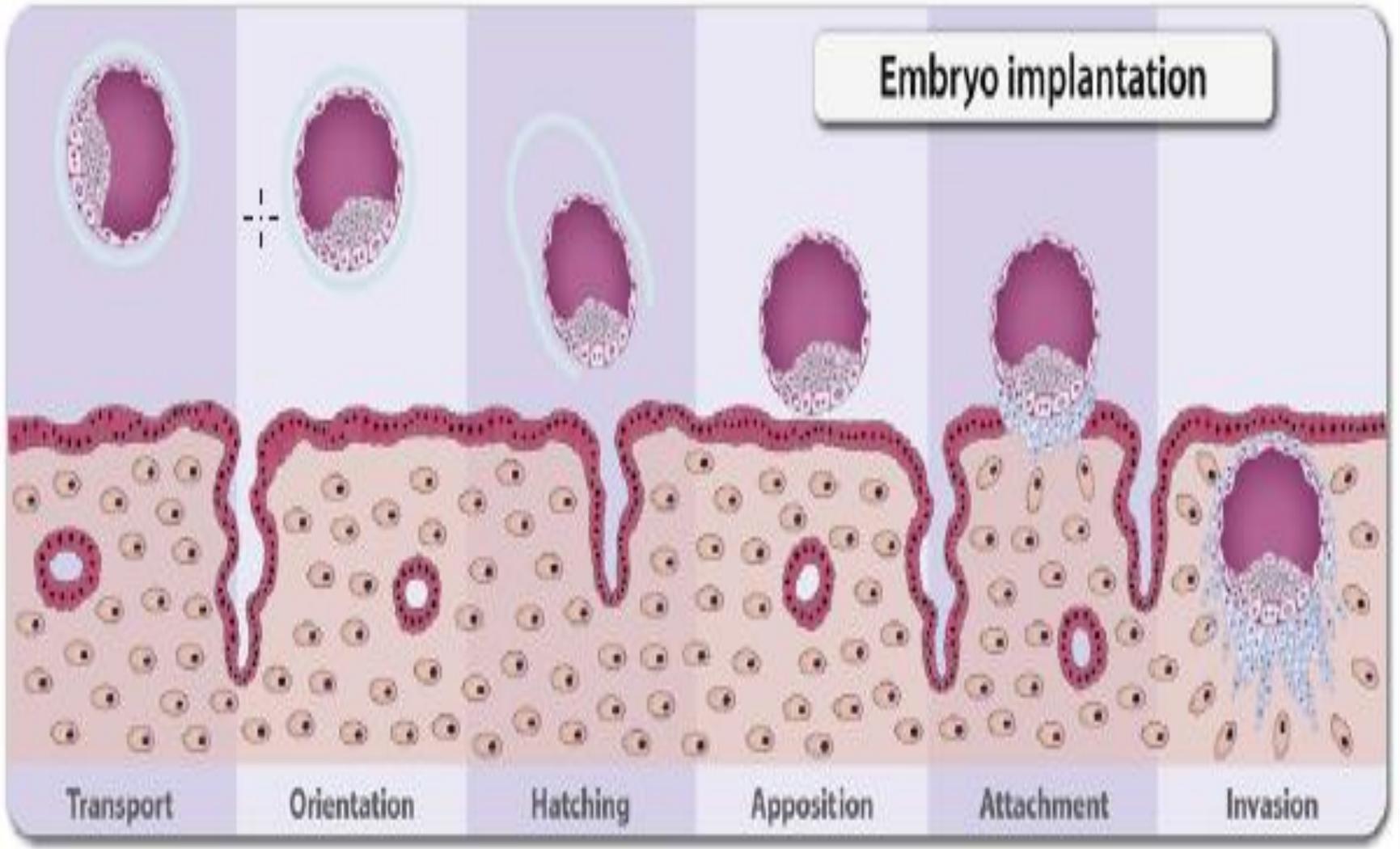
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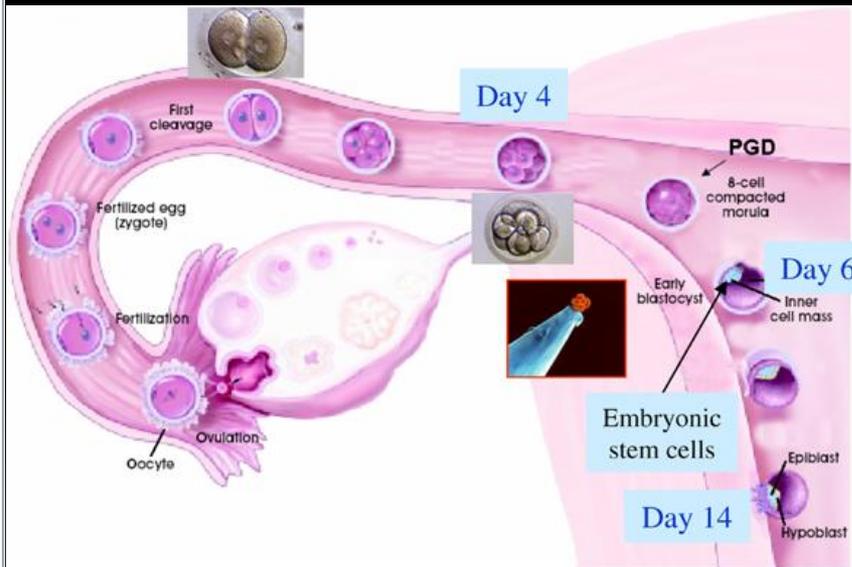
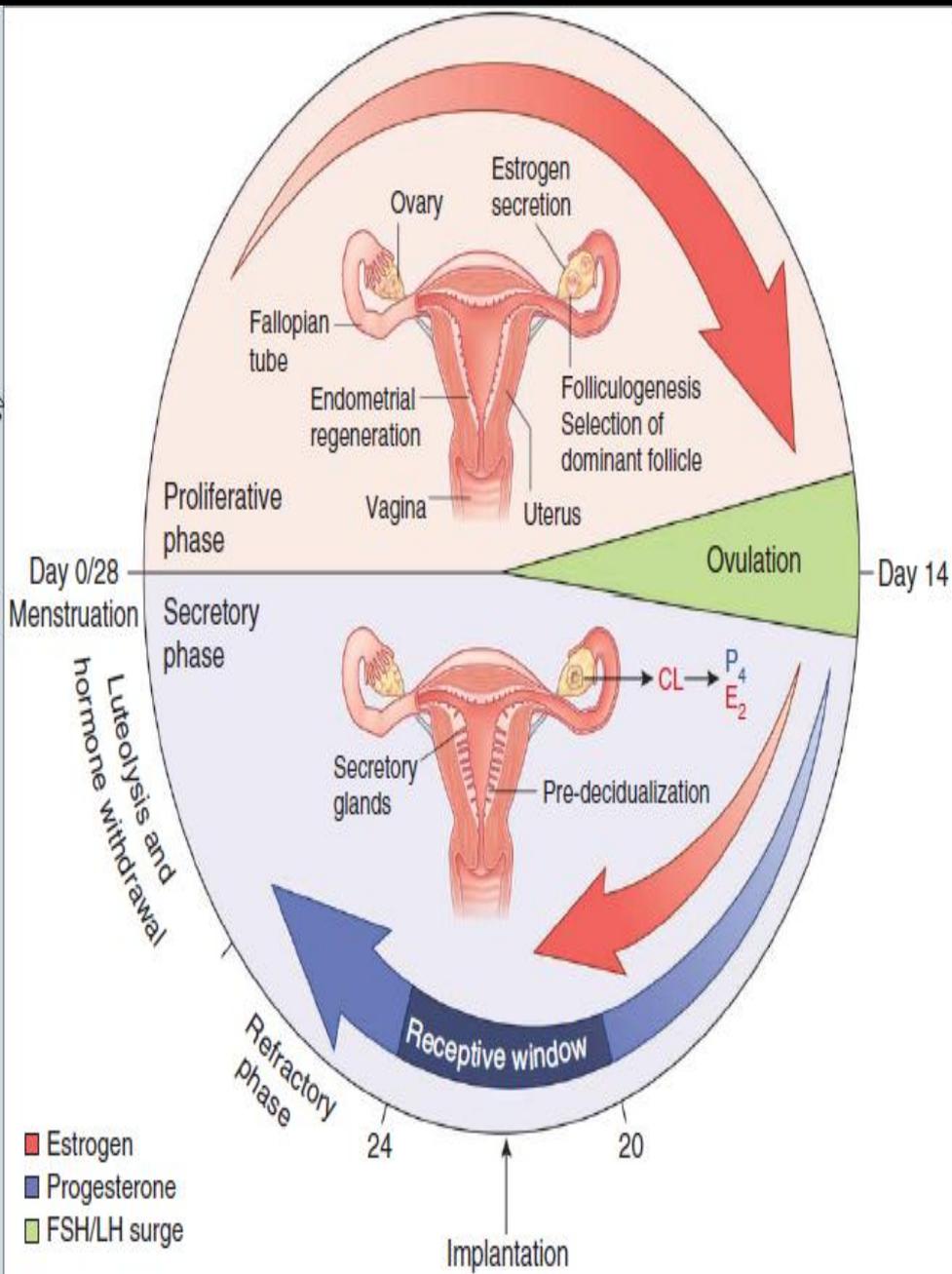
Recurrent implantation failure (RIF)



- Recurrent implantation failure (RIF) is defined as the absence of implantation, after two or three consecutive cycles of IVF, ICSI or frozen embryo replacement.

Embryo implantation





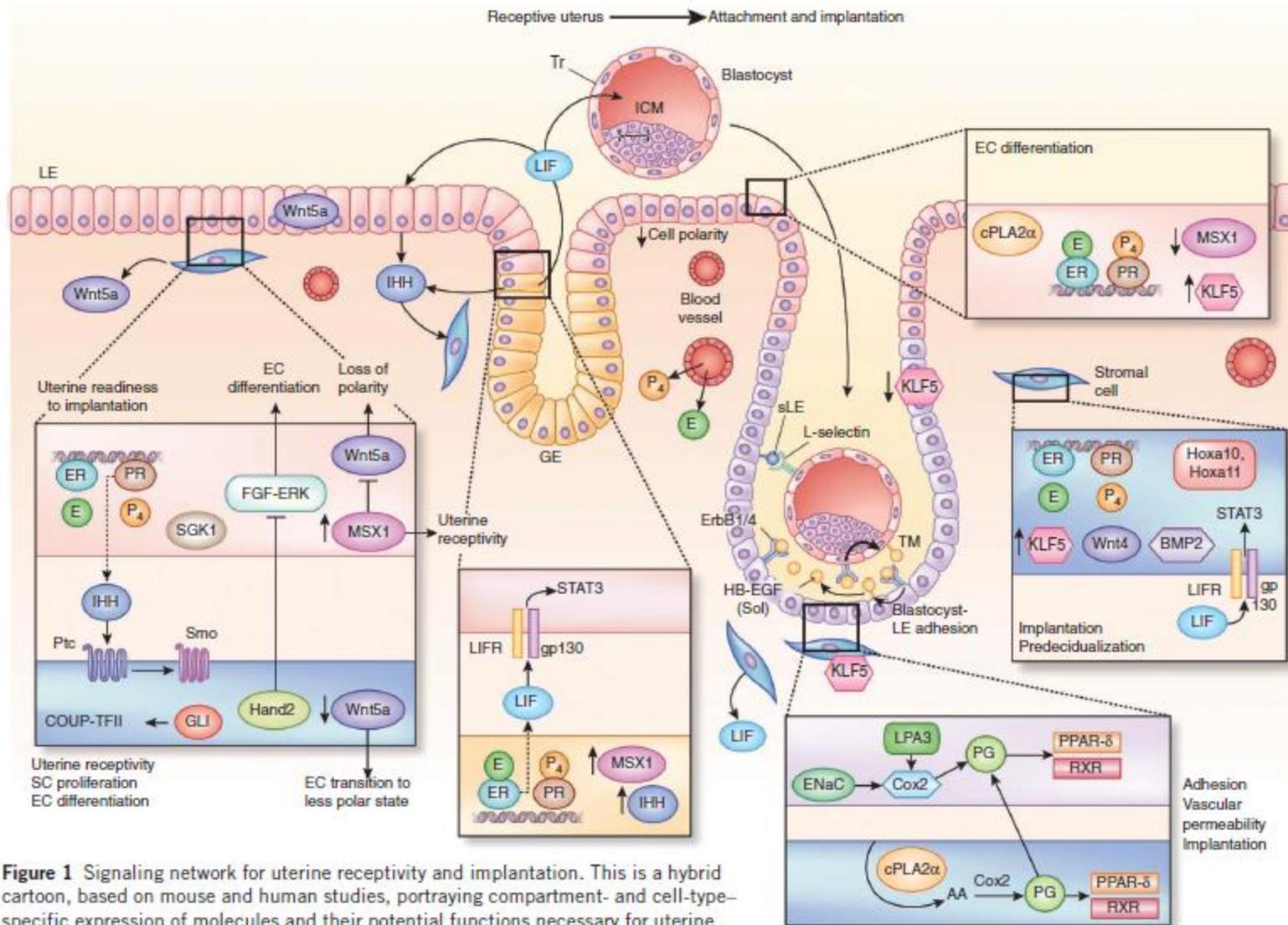


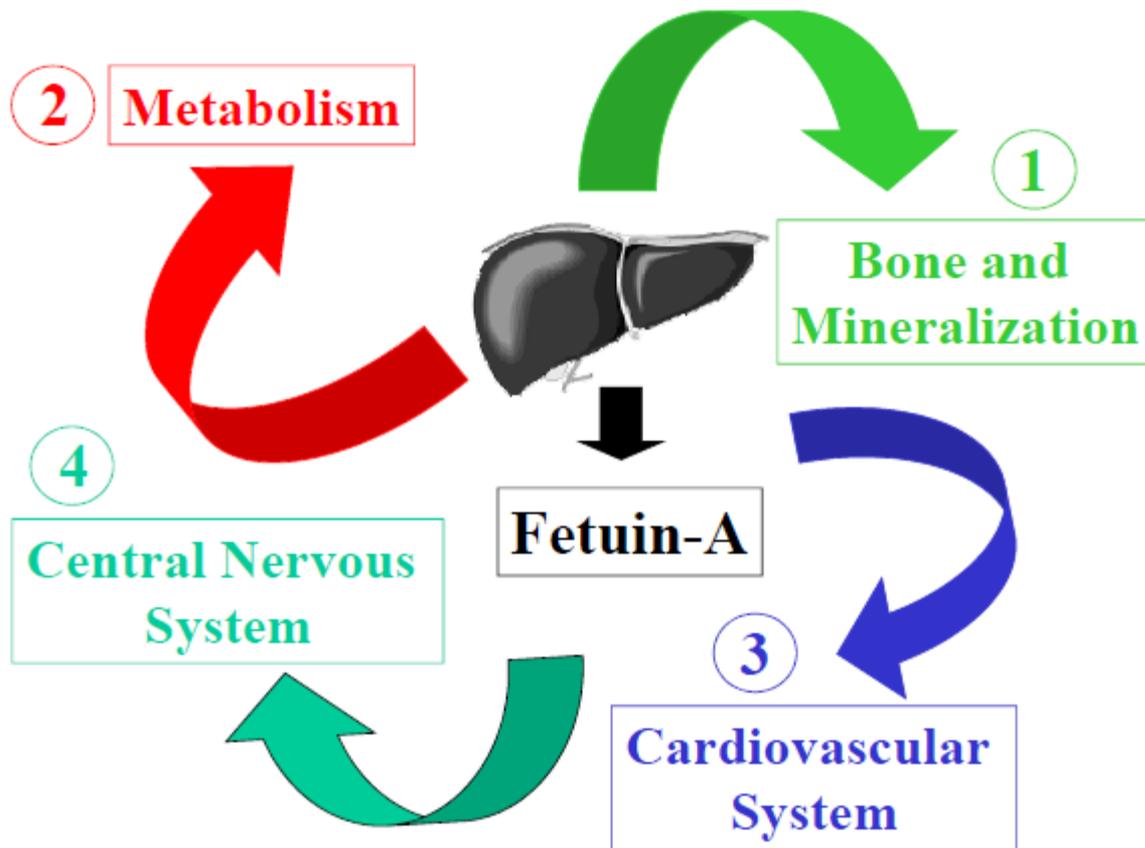
Figure 1 Signaling network for uterine receptivity and implantation. This is a hybrid cartoon, based on mouse and human studies, portraying compartment- and cell-type-specific expression of molecules and their potential functions necessary for uterine

FETUIN-A

- Pederson first isolated fetuin from bovine fetal serum in 1944
- The biological role of fetuin-A has not been fully elucidated.
- Recently, fetuin-A is considered as a negative acute phase reactant .
- Also its concentration increases in states of insulin resistance

FETUIN-A

- Fetuin-A/ α -2-Heremans-Schmid glycoprotein is the human homologue of fetuins found in all – so far investigated – mammalian species.
- It is mainly a fetal protein, since the highest concentrations are found in the serum and body fluids of fetuses.
- During fetal development, it is expressed in many organs such as the liver, kidney, gastrointestinal tract, skin and brain.
- Fetuin-A is mostly synthesised in the liver and accumulates in mineralised bone and teeth, as a major component of the non-collagenous bone matrix.



FETUIN-A

- Human fetuin-A/alpha2-Heremans-Schmid-glycoprotein (fet-A) is a plasma protein secreted by the liver that modulates insulin action in adipocytes.
- Increased fetuin-A promotes adipocyte dysfunction which results with decreased adiponectin and increased fatty acids and inflammatory cytokines.
- Elevated serum fetuin-A levels are associated with insulin resistance and metabolic syndrome.

IMPLANTATION FAILURE

- Fatty acids and inflammatory cytokines were previously reported in implantation failure.
- Several growth factors that promote trophoblast invasion (insulin-like growth factor-1 [IGF-1], epidermal growth factor [EGF], and placental growth factor [PIGF]) bind to receptors that activate tyrosine kinase.
- Analogous to its action on the insulin receptor, fetuin-A inhibits the receptor tyrosine kinase activity of trophoblast growth factors and, as a consequence affects trophoblast growth and viability, results in impaired invasion into the uterine compartment.



AIM

- This study was based on the hypothesis that circulating levels of fetuin-A might differ between patients with and without recurrent implantation failure.
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Material and Methods:

- A total of 78 women were included in this case control study between January 2013 and February 2014.
- Serum fetuin-A concentrations were measured in 42 women with recurrent IVF failure and 36 healthy women without implantation problem.
- During the study period blood samples from all participants were collected with a fasting state of 8-14 hours and were stored at -80°C until subsequent assay.
- The serum levels of fetuin-A were assessed by commercial ELISA kits (BioVendor Laboratory Medicine Inc., Brno, Czech Republic).
- Serum fetuin-A concentration values were expressed as $\mu\text{g/ml}$.

Basal characteristics of the RIF and Control patients

Mean±SD (Min-Max)	Control	RIF	P value*
Age	30,1±4,8 (21-40)	31±4,2 (24-38)	0,373
BMI	26,2±4,5 (19,1 -37,8)	25,5±3,6 (19,9-32,1)	0,548
Hb	12,7±1,4 (10,3-15,3)	13,3±1,3 (9,9-15,4)	0,083
PRL	14,4±9,0 (5,0-30,9)	13,4±6,3 (5,6-31,1)	0,773
FSH	7,1±1,7 (5,4-9,7)	6,2±1,9 (2,8-12,1)	0,194
TSH	1,6±0,9 (0,2-2,8)	2,2±0,9 (0,7-5,0)	0,095

*independent samples t test

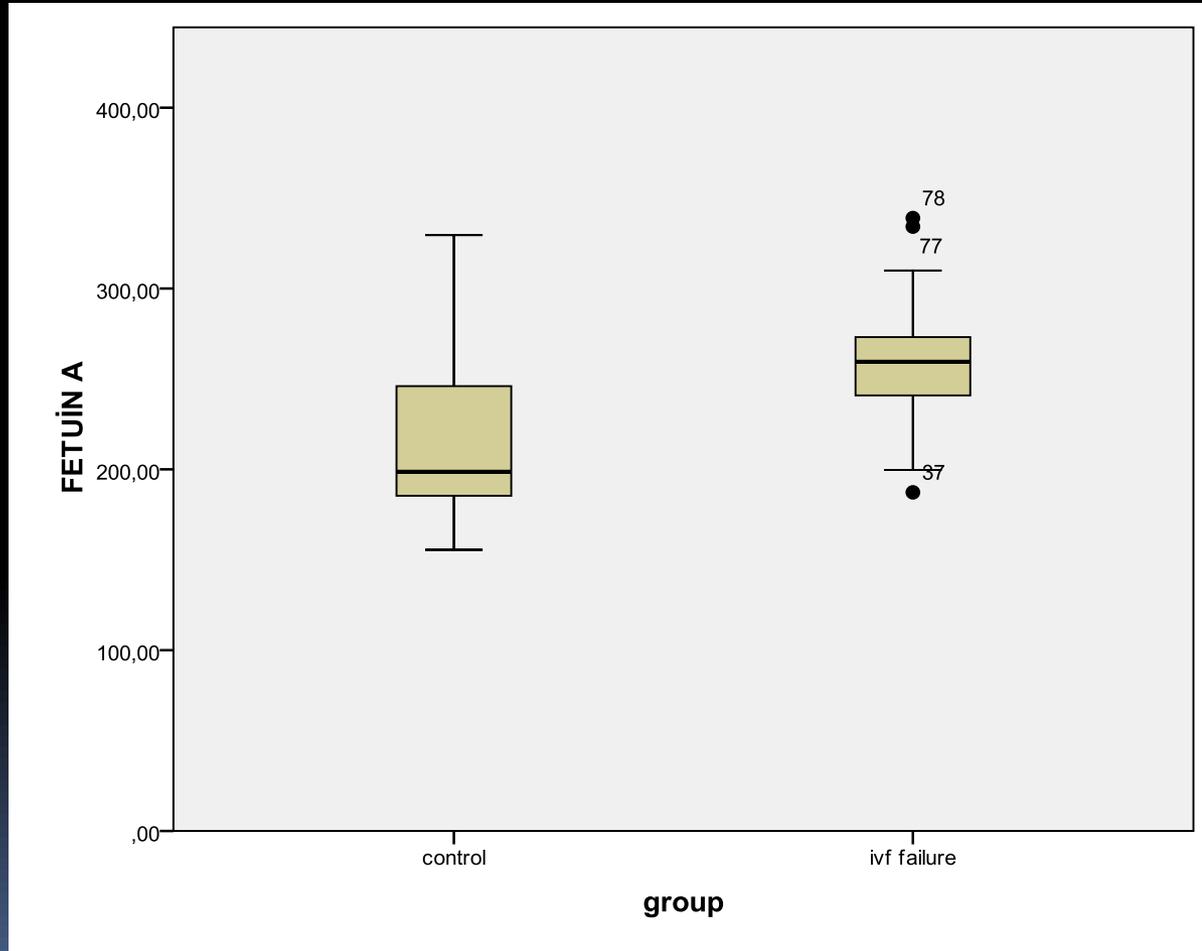
Mean±SD (Min-Max)	Control	RIF	P value*
FPG	90,5±8,2 (70,4-102,9)	88,8±8,2 (70,8-105)	0,370
WBC	7,1±1,2 (5,1-9,7)	7,3±1,4 (5,1-10,6)	0,420
Serum fetuin- A	219.59 ± 48.86 (155,5- 329,6)	257.77 ± 32.18 (187,3- 339)	<0,0001

*independent samples t test

Results:

- The mean serum fetuin-A levels of implantation failure and control women were 257.77 ± 32.18 and 219.59 ± 48.86 respectively with a p value <0.001 (independent samples t test).
- Our results showed statistically significant difference between serum fetuin-A levels of implantation failure women and controls.

FETUIN-A



OBSTETRICS

Effects of increased fetuin-A in human trophoblast cells and associated pregnancy outcomes

Luis M. Gomez, MD; Lauren Anton, PhD; Sindhu K. Srinivas, MD, MSCE; Michal A. Elovitz, MD; Samuel Parry, MD

- A previous study searched the question whether treating trophoblast cells with fetuin-A reduces cell viability and invasion and whether elevated fetuin-A levels in maternal serum are associated with adverse obstetric outcomes as the result of failed trophoblast invasion.
- They concluded that Fetuin-A may decrease trophoblast viability and invasion caused by the inhibition of receptor tyrosine kinase activity and elevated maternal fetuin-A may lead to failed placental migration and play a role in preeclampsia.
- Future research may be directed toward attempting potential therapeutic strategies that would revert the action of fetuin-A in the placenta.

Fetuin-A: A Multifunctional Protein

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- Several factors regulate fetuin-A levels, however, little is known about regulating fetuin-A levels at the clinical levels.
- Lifestyle intervention involving weight loss is known to decrease fetuin-A levels.
- Endurance training and/or lifestyle intervention can modulate fetuin-A levels.
- However, the effect of exercise depends on various factors, such as duration, intensity, length of training, and accompanying body weight change.
- Pioglitazone and niacin, both can decrease fetuin-A levels.



Conclusion:

- So far reasons of implantation failure are only partially understood.
 - Current study reveals the association between implantation failure and fetuin-A.
 - Further studies with large population size are needed to investigate whether fetuin-A can be used a marker before controlled ovarian stimulation begun or regulation of fetuin-A levels with treatment or life style interventions can improve implantation success.
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THANK YOU