

DIAGNOSIS-SPECIFIC ACRS (AUTOLOGOUS CYTOKINE-RICH SERUM)-ENDOMETRIUM INTERACTIONS: EFFECT ON IVF OUTCOME

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ACRS

AUTOLOGOUS CYTOKINE-RICH SERUM

During the blood serum processing cytokines are being activated and released:

- **Elevated concentration of – IL1 Ra (IL1 receptor antagonist)**
- Elevated concentration of growth factors (many times higher than in PRP)
- Does not include blood cells, foreign substances (e.g. citrate)
- It is autologous (no immunogenic and allergic reactions)

THEORETICAL BACKGROUND

SUMMARY

ACRS used in our study has an enhanced concentration of **IL1-R α** (**interleukin-1 receptor antagonist**) which is well known to inhibit and **decrease the pro-inflammatory activity** and the stimulation of cytokine IL-1 production.

Malik et al. Function and regulation of IL-1 α in inflammatory disease and cancer. *Immunol Rev.* 2018 January; 281(1): 124 – 137. doi: 10.1111/imr.12615.

Garlanda C, Dinarello CA, Mantovani A. The interleukin-1 family: back to the future. *Immunity.* 2013; 39:1003–1018. [PubMed: 24332029]

THEORETICAL BACKGROUND

SUMMARY

There is evidence about **increased IL-1 cytokine cascade activity** in **ectopic endometrium and peritoneal fluid of women with diagnosed endometriosis**. **IL-1 α** (member of IL-1 cytokine family) is an **apical driver of inflammation** and **can be upregulated by a diverse array of inflammatory stimuli**.

We wanted to investigate the diagnosis-specific effect of ACRS in women with infertility and failed embryotransfer undergoing IVF treatment.

Wu MY, Ho HN. The role of cytokines in endometriosis. *Am J Reprod Immunol* 2003;49:285–96.

Hill JA, Faris HM, Schiff I, Anderson DJ. Characterization of leukocyte subpopulations in the peritoneal fluid of women with endometriosis. *Fertil Steril* 1988;50:216–22.

Kharfi A, Akoum A. Soluble interleukin-1 receptor type II blocks monocyte chemotactic protein-1 secretion by U937 cells in response to peripheral blood serum of women with endometriosis. *Fertil Steril* 2002;78:836–42.

OUR QUESTION:

What is the effect of **ACRS application prior to embryotransfer** on **pregnancy rates** (PR,CPR,OPR) in infertile patients according to diagnosis subgroups.

SUMMARY ANSWER:

We observed significant **enhancement** of endometrium thickness-pregnancy associations in **endometriosis** and **idiopathic sterility** patients (up to 8% absolute CPR improvement in odds increase per mm of endometrial thickness).

STUDY DESIGN, SIZE, DURATION:

WE INCLUDED **423 IVF PATIENTS** IN THIS RETROSPECTIVE ANALYSIS ; PATIENTS WERE FROM **2 CENTERS** FOLLOWING **PILOT STUDY AND POWER ANALYSIS.**

Pilot study:

We compared PR/effectiveness before and after the application in the same patients (no control group) – observed tendencies.

Power analysis:

Assesed the number of patients to obtain relevant results.

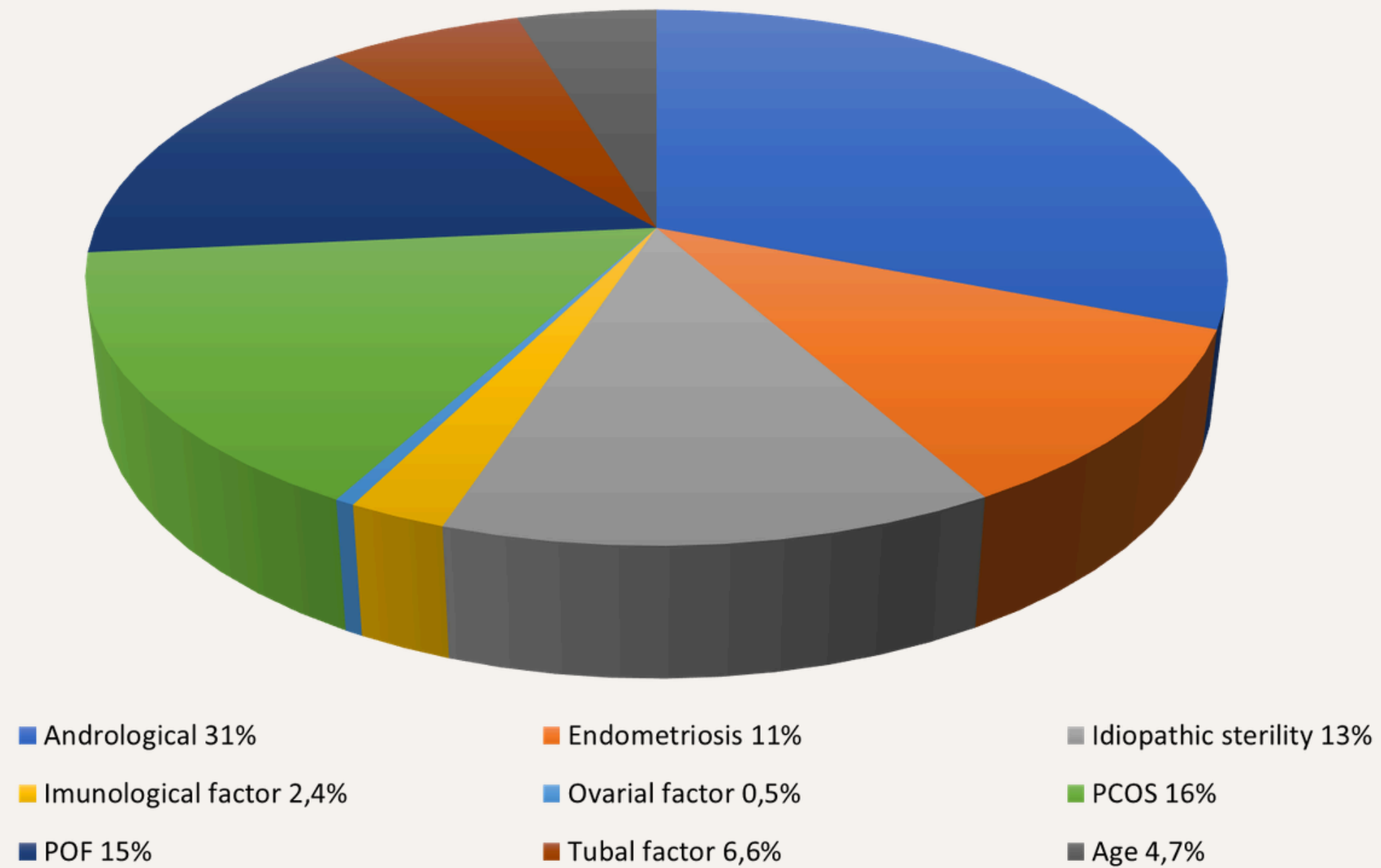
Six diagnostic groups analyzed

Endometriosis, idiopathic sterility, andrological factor of sterility, PCOS, POF, and tubal factor. Patients from 2023 – 2025 were evaluated.

Patients

From 2023 – 2025 were evaluated.

REPRESENTATION OF DIAGNOSES:



DESCRIPTION OF THE COHORTS

	ACRS group (yes) MEAN	CONTROL group (no) MEAN	WMW test p-value
AGE	35.6	35.2	0.495
BMI	24.4	23.7	0.247
AMH ng/ml	3.6	3.8	0.22
No. of transfers prior to ACRS	3.2	2.7	0.078
ENDOMETRIUM mm	10.3	10.1	0.205

Fig No.2 : Cohort descriptors comparison. There was no significant difference between above mentioned parameters between the studied and control group (Man-Whitney U-test).

The jamovi project (2025). *jamovi*. (Version 2.7) [Computer Software]. Retrieved from <https://www.jamovi.org>.

R Core Team (2025). *R: A Language and environment for statistical computing*. (Version 4.5) [Computer software]. Retrieved from <https://cran.r-project.org>. (R packages retrieved from CRAN snapshot 2025-05-25).

GYN-FIV

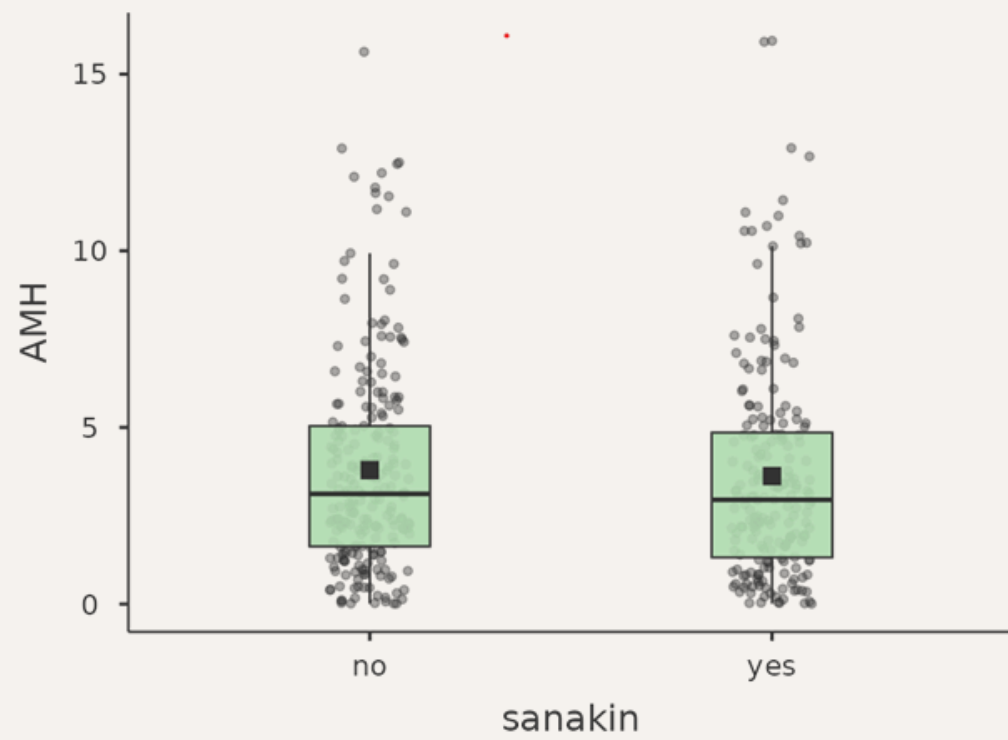
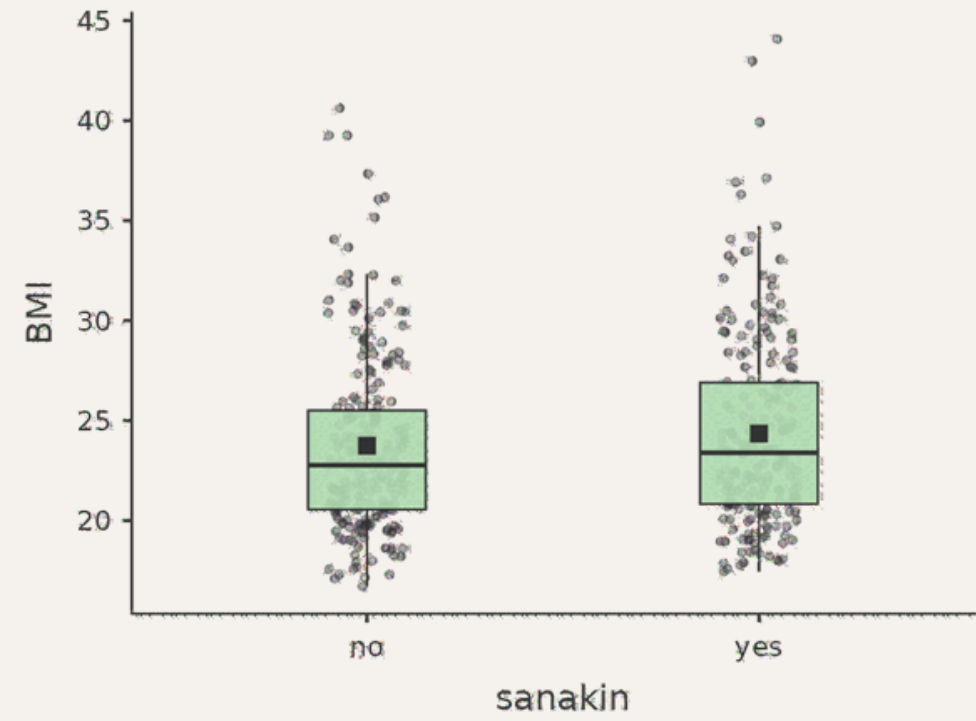
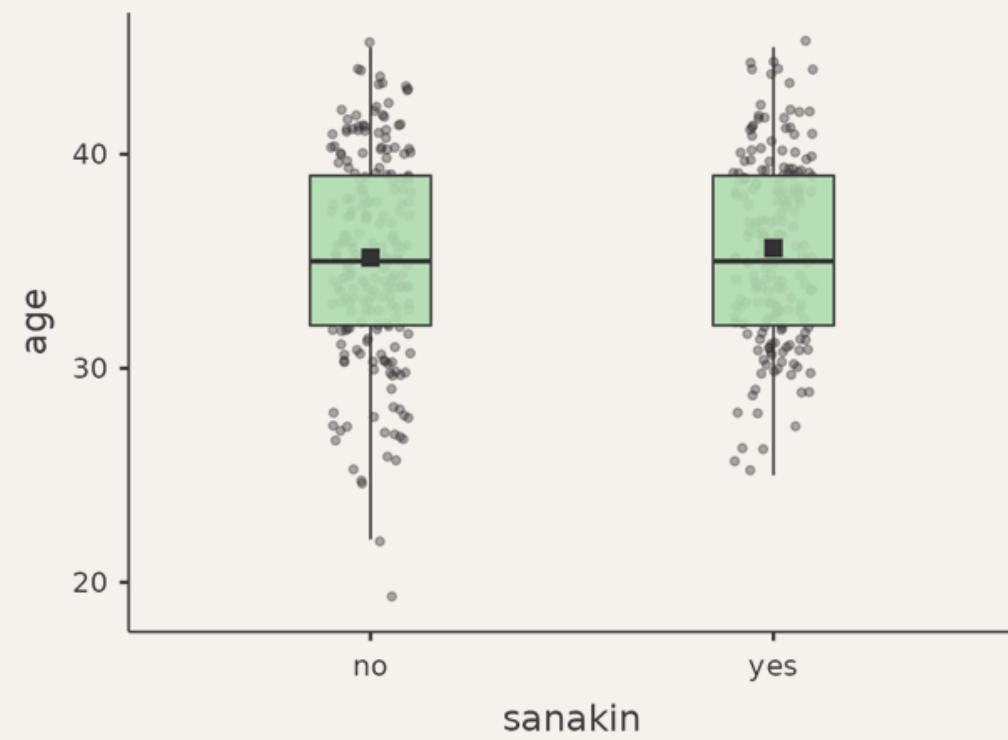
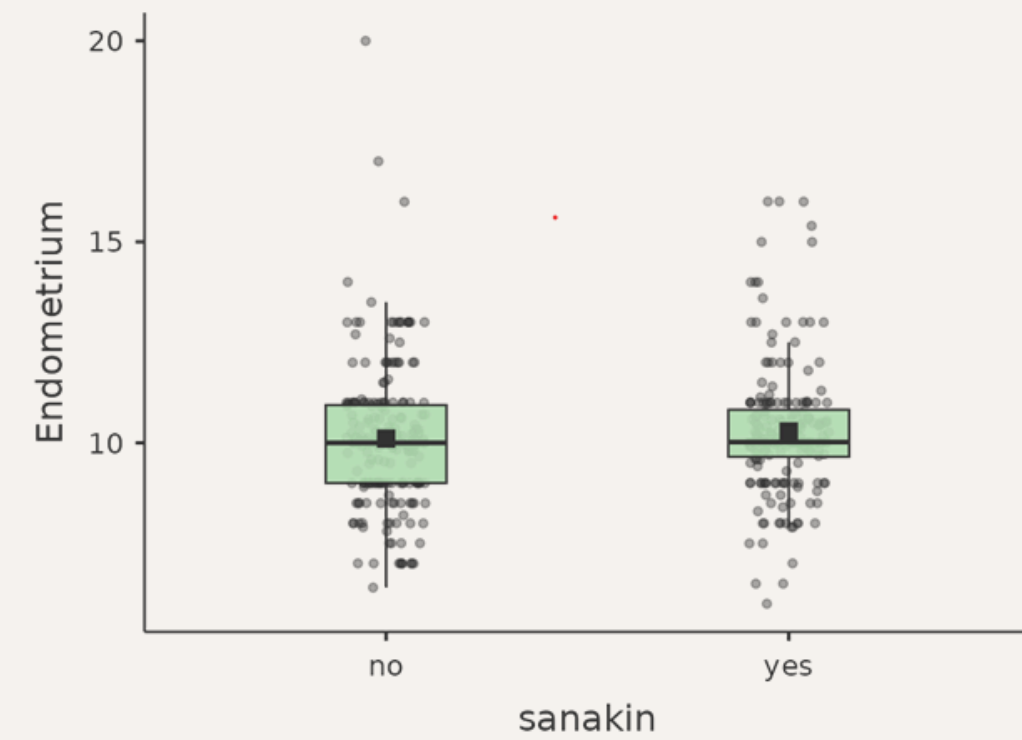


Fig No.3 : BOX PLOTS for descriptive parameters of cohorts.
Age, BMI, AMH, No. of transfers before ACRS, Endometrial thickness.



PARTICIPANTS, SETTING, METHODS:

- We evaluated the PR, CPR and OPR **after the first application in the patients in ACRS group (n=200)**. The **endometrium preparation was consistent** - hormone replacement treatment (HRT) without GnRH. (No fresh transfers, no natural cycles).
- Strict inclusion and exclusion criteria were followed both in ACRS and **control group (n=223)**.
- Multivariate logistic regression examined three-way interactions (Endometrium × ACRS × Diagnosis) for PR, CPR and OPR.
- (Primary analysis focused on CPR with consistency evaluation across outcomes.)

MAIN RESULTS- CPR

- **Enhancement pattern:** In **endometriosis** patients, each 1mm endometrium increase associated with 14% higher CPR odds without ACRS vs. 22% with ACRS (OR: 1.14→1.22, $p=0.110$ → **$p=0.018$**). That proves **8% absolute CPR improvement in odds increase per mm of endometrial thickness.**
- Similar significant enhancement in **idiopathic infertility** (12%→20% odds increase, OR: 1.12→1.20, $p=0.168$ → **$p=0.035$**).

MAIN RESULTS- CPR

- **Reduction pattern:** PCOS patients showed concerning **opposite effect** - strong natural endometrium-CPR association (23% odds increase, OR=1.23, p=0.014) **diminished with ACRS to non-significant levels** (14% odds increase, OR=1.14, p=0.127).
- Results **consistent across PR, CPR, and OPR** outcomes with strongest effects in CPR.

ACRS-ENDOMETRIUM INTERACTION

EFFECTS BY DIAGNOSIS GROUP - CPR

DIAGNOSIS	CONTROL GROUP OR (95% CI)	P-value	ACRS GROUP OR (95% CI)	P-value	ACRS effect Relative multiplier (OR)
ENDOMETRIOSIS	1.14 (0.97-1.35)	0.11	1.22 (1.03-1.44)	0.018	Enhancement 1.07 (+0.08)
IDIOPATHIC STERILITY	1.12 (0.95-1.30)	0.168	1.20 (1.01-1.43)	0.035	Enhancement 1.07 (+0.08)
PCOS	1.23 (1.04-1.46)	0.014	1.14 (0.96-1.35)	0.127	Reduction 0.93 (-0.09)

Fig No.4 : Fig No.4.: OR = Odds Ratio per unit increase in endometrium thickness. P-values < 0,05 are coloured red.

RESULTS - CONSISTENCY ACROSS ALL PREGNANCY OUTCOMES (OR; P-VALUES)

OUTCOME	ENDOMETRIOSIS	IDIOPATHIC STERILITY	PCOS	CLINICAL CONSISTENCY
PR	1.14→1.16 (p=0.090→0.061)	1.14→1.12 (p=0.070→0.168)	1.16→1.10 (p=0.067→0.263) (enhancement→neutral)	✓ Consistent
CPR	1.14→1.22 (p=0.110→0.018)	1.12→1.20 (p=0.168→0.035)	1.23→1.14 (p=0.014→0.127) (positive→neutral)	✓ Strongest
OPR	1.14→1.18 (p=0.140→0.068)	1.10→1.17 (p=0.248→0.096)	1.11→1.07 (p=0.256→0.504) (stable→stable)	✓ Consistent

Fig No.5 : Results consistent across PR, CPR, and OPR outcomes with strongest effects in CPR.

LIMITATIONS, REASONS FOR CAUTION:

- The effect of ACRS is visible in the statistical regression model via enhancement of the effect of endometrial thickness – **so it is indirect, but significant** (in several studied subgroups).
- A many times **larger cohort** of patients is necessary to assess the direct effect of ACRS in a retrospective type of study.

LIMITATIONS, REASONS FOR CAUTION:

- Definitely a **prospective study (RCT) with a larger cohort** of patients is necessary to support our findings.
- It is also necessary to **evaluate multiple application of ACRS** because the effect could be **dose-dependent**.
- **Results warrant validation studies** and mechanistic investigation to optimize personalized IVF treatment approaches.

WIDER IMPLICATIONS OF THE FINDINGS:

- Evidence supports **diagnostic-guided ACRS protocols with favorable indications for endometriosis/idiopathic infertility and caution in PCOS patients.**
- Findings suggest **pathway-specific mechanisms requiring diagnostic stratification** rather than universal ACRS application.

CONCLUSIONS:

- This properly powered study provides evidence for diagnosis-specific ACRS protocols for embryotransfer.
- Enhancement of endometrium-pregnancy associations in endometriosis and idiopathic infertility patients group (up to 8% absolute improvement in odds increase per mm) contrasts with potential contraindication signals in PCOS patients.