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FSH DIRECTLY DOWN-REGULATED HUMAN ENDOMETRIAL AQP8, AND RESULTED IN DECREASED ENDOMETRIAL RECEPTIVITY VIA DISREGULATION OF ENDOMETRIAL RECEPTIVE FACTORS, INCLUDING LIF AND OLFM1. D. Zhang, G. Xu, J. Li, Y. Zhu, F. Qu, J. Sheng. Department of Reproductive Endocrinology, Women's Hospital, School of Medicine, Zhejiang University, Hangzhou, Zhejiang Province, China; Key Laboratory of Reproductive Genetics, Ministry of Education of China, Hangzhou, Zhejiang Province, China.

OBJECTIVE: To investigate the direct effects and mechanism of FSH on human endometrial receptivity.

DESIGN: A prospective clinical and experimental study.

MATERIALS AND METHODS: We collected 15 endometrial samples in implantation window after ovarian stimulation (OS) with exogenous FSH, and 40 samples of natural cycle as control. We detected FSHR, AQP 8, Integrinβ3, and LIF expression in human endometrial tissue and Ishikawa cell by RT-PCR and following sequencing, Western blotting, immunohistochemistry and immunofluorescence. We constructed the mouse blastocyst-adhesion model and JAr adhesion model, assessed the effect of PCMB (AQP inhibitor) pre-treatment on blastocyst adhesion, measured AQP8, receptive factors of Ishikawa cell after FSH/E2 treatment by RT-Real time PCR, assessed endometrial integrinβ3, LIF, OLFM1 expression and JAr adhesion rate after AQP8 siRNA interfering.

RESULTS: We confirmed FSHR expression in human endometrial tissue and Ishikawa cells, mainly located on cellular membrane and cytoplasma. Western blotting showed significantly up-regulated FSHR and down-regulated AQP8, Integrinβ3, and LIF expression in OS group. PCMB pre-treatment on endometrium cells lead to decreased blastocyst adhesion rate. E2 display a concentration-dependent up-regulation on expression of AQP8 mRNA of Ishikawa cell, while FSH(0,1,3,10,30 IU/L)display a concentration-dependent and time-dependent down-regulation on AQP8 and LIF mRNA. After AQP8 siRNA interfering, the expression of LIF was down-regulated and OLFM1 was up-regulated. The JAr adhesion rate significantly decreased after AQP8 siRNA.

CONCLUSION: FSH directly down-regulated human endometrial AQP8, and resulted in impaired endometrial receptivity via disregulation of endometrial receptive factors, including LIF and OLFM1.

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ARE THE CAUSES OF RECURRENT IMPLANTATION FAILURE A MYTH OR EVIDENCE BASED REALITY? P. Neelam, S. Vitthala. Reproductive Sciences Section, University of Leicester, Leicester, Leicestershire, United Kingdom; Leicester Fertility Centre, University Hospitals of Leicester, Leicester, Leicestershire, United Kingdom.

OBJECTIVE: Various investigations are performed to identify and potentially treat recurrent implantation failure (RIF). We performed a systematic review and meta-analysis of the available evidence for the causes of RIF with the aim to identify significantly associated causes that could be targeted.

DESIGN: Systematic review and meta-analysis of studies investigating causes of recurrent implantation failure from 1980-April 2011.

MATERIALS AND METHODS: Literature search was performed using Medline, Pubmed and Embase. Search strategy aimed at identifying case control and RCT studies investigting causes of RIF. Eligible studies were those that defined RIF as minimum of three failed implantations. Selection of studies and methodological quality assessment was performed by the two authors.

RESULTS: Twenty studies were identified, 11 studies were suitable for inclusion involving 655 subjects. Individual studies and results of the fixed proportion effects are shown in the table. Forest plots for fixed and random effects showed no significant association of the causes with RIF. Bias assessment indicators and plots showed no bias (Harbord: bias = P=0.19 (92.5% CI = -1.12 to 6.57).

Fixed effect results.

Study	Cause	Proportion (95%CI)
Stern 1998	Lupus/B2 GYP	.23
Wilton 2003	Aneuploidy	.19
El-Toukey 2005	Aneuploidy	.35
Coulam 2006	P53 poly(PRO/PRO)	.07
Coulam 2006	P53 poly(ARG/PRO)	.45
Coulam 2006	P53 poly(ARG/ARG)	.47
D'hooghe 2006	ANA ab	.32
D'hooghe 2006	ATA ab	.15
Pharm 2006	Aneuploidy	.37
Coulam 2008	Pro Rc Poly	.5
Goodman 2008	P53 poly	.09
Goodman 2008	PAI poly	.33
Goodman 2008	VGEF poly	.19
Farhi 2008	Male factor	.78
Firouzabadi 2009	P53 poly(PRO/PRO)	.42
Firouzabad 2009	P53 poly(ARG/ARG)	.42
Johnston Macnanny 2009	EB/endometritis	.30
Tuckerman 2010	CD56 expression	.15
Combined		.30(.28-0.32)

CONCLUSION: This meta-analysis showed no significant association of the various causes with RIF. Large multi centre randomised controlled trials are required with well defined inclusion criteria to identify causes and provide evidence based treatment for women with RIF.

LUTEAL PHASE SUPPORT

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EFFICACY OF A PROGESTERONE VAGINAL RING VERSUS PROGESTERONE GEL FOR LUTEAL PHASE SUPPLEMENTATION BY BODY MASS INDEX (BMI). K. M. Silverberg, K. Z. Reape, B. K. Howard. Texas Fertility Center, Austin, TX; Teva Branded Pharmaceutical Products R&D, Horsham, PA.

OBJECTIVE: To determine the efficacy of a novel, weekly progesterone (PGN) vaginal ring (VR) vs daily 8% progesterone vaginal gel (90 mg/day) for luteal phase supplementation after in vitro fertilization (IVF) by BMI.

DESIGN: Prospective, randomized study evaluating patients undergoing IVF. Patients were stimulated with a standard down-regulation protocol. hCG was administered when two follicles >17 mm. Transvaginal oocyte retrieval 35-37 hours after hCG administration. 1:1 randomization to initiate the VR or gel one day following retrieval. Pregnant subjects continued PGN through 12 weeks gestation.

MATERIALS AND METHODS: Serum pregnancy test 14 days following retrieval. Clinical pregnancy rates determined after stratification by BMI (defined as percentage of subjects with visualization of a gestational sac with fetal heart motion present on ultrasound at 8 & 12 weeks of pregnancy).

RESULTS: 1297 eligible women age 18-42 were randomized following retrieval. Two subjects from the PGN VR cohort not included due to missing weight data. Subjects were similarly distributed among BMI categories for both treatment groups. Clinical pregnancy rates were similar for both treatment groups regardless of BMI category. Mean BMI for users of the PGN VR (n = 646) was 25.3 with a range of 16.0-38.0. Mean BMI (kg/m^2) for users of the PGN gel (n = 651) was 25.7 with a range of 15.1-38.2.When stratified by BMI, clinical pregnancy rates at 12 weeks in subjects using the PGN VR compared to the gel were: 45.5% vs. 50.0% (BMI<18.5); 48.1% vs. 46.8% (BMI $\geq$18.5 to <25); 47.8% vs. 45.2% (BMI $\geq$25 to <30); 41.5% vs. 42.5% (BMI $\geq$30 to <34); 33.3% to 37.0% ($\geq$34 to <38+).

CONCLUSION: Subjects with highest BMI ($\geq$34 to <38+) had slightly lower pregnancy rates than those in the four lower BMI strata, but rates were similar between the treatment groups. Overall, clinical pregnancy rates were within reported ranges for both treatment groups regardless of BMI.

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