Oil injection into uteri horns after E2P4 or E2CDB treatment. Uteri were removed,weighed,stained with H+E 24 hrs later.

RESULTS: A dose-response for uteri weight and PI in the LE/GE was seen in an inverse fashion.Analysis revealed a difference in the PI for E2 controls(78.4%)vs.E2CDB(16.6% at 2.0 mg/mouse), $P=<0.001$. Stromal cell PI differed amongst E2P4(47.5%) vs.E2CDB(1.0%) groups,yet similar to E2 controls(0.4%), $P=0.005$. The uteri injected with PBS vs. oil in E2P4 group had a change in uteri weight (0.04gvs.0.06g,$P=0.03$) and evidence of stromal cell decidualization.The uteri in E2CDB group had no change in weight after oil injection(0.04 g vs.0.04 g, $P=0.44$) or stromal decidualization.HAND-2 expression was increased in the E2P4 stromal cells but absent in E2CDB stromal cells,consistent with the impairment of decidualization. MCM2 and CYA expression were increased in E2 group and decreased in E2P4 and E2CDB groups in the LE/GE(MCM2 PI=92.9%vs.0.3%vs.18.6%, $P=0.046$, CYA PI=76.0%vs.0.0%vs.16.7%,$P=0.024$).MCM-2 and CYA expression were increased in the stroma for E2P4 group,but decreased in the E2 and E2CDB groups.

CONCLUSION: CDB is a partial P4 agonist in the LE/GE and prevents stromal cell proliferation, decidualization and HAND-2 expression, providing a mechanism for contraceptive function and treatment of P4 dependent disorders.

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ENDOMETRIAL QUALITY AT THE END OF CONTROLLED OVARIAN STIMULATION PREDICTS ONGOING PREGNANCY RATE AFTER TRANSFER OF A SINGLE EXPANDED OR HATCHING/HATCHED BLASTOCYST ON DAY 5 IN A FRESH CYCLE.

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OBJECTIVE: To investigate the association between endometrial quality assessed by quantitative and qualitative image analysis and ongoing pregnancy rate in single blastocyst transfer cycles.

DESIGN: Prospective analysis of a subgroup of patients participating in an assessor-blind RCT (MEGASET) [ClinicalTrials.gov NCT00884221].

MATERIALS AND METHODS: 117 of the 749 trial patients who underwent stimulation with highly purified menotropin or rFSH in a GnRH antagonist protocol participated in this subgroup investigation. Single still 2-D transvaginal ultrasound (Voluson i, GE Healthcare) images of the uterus in the transverse plane were made at the end of stimulation. A blinded assessor categorized endometrial quality as very poor, poor, fair to good, very good or excellent using a computer-enhanced 3-D model. The evaluation included echotextual pattern, numeric pixel values of endometrial tissues and detailed colorometric assessment. Single blastocyst transfer was done on day 5. Ongoing pregnancy rate (10-11 weeks after transfer) was analyzed for all transfers (n=93) and transfers of only an expanded or hatching/hatched blastocyst (stage 4-6; Gardner and Schoolcraft, 1999) (n=51).

RESULTS: Ongoing pregnancies were not observed in the very poor or poor endometrium categories. The ongoing pregnancy rate per transfer was 31% with fair to good endometrium, 37% with very good endometrium and 60% with excellent endometrium ($P=0.302$). The pattern was further strengthened when analyzing only transfers of an expanded or hatching/hatched blastocyst, yielding ongoing pregnancy rates of 48%, 64% and 100% for fair to good, very good and excellent endometrium ($P=0.038$), respectively.

CONCLUSION: This pilot investigation suggests that scoring endometrial 2-D images by computer-enhanced 3-D modeling can provide additional information about the chance of ongoing pregnancy when transferring a blastocyst of the highest implantation potential. Validation of this model in a large sample of IVF/ICSI patients is to be considered.

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PERSONALIZING EMBRYO TRANSFER (PET) USING AN ENDOMETRIAL CUSTOMIZED ARRAY AS DIAGNOSTIC AND THERAPEUTIC STRATEGY IN PATIENTS WITH IMPLANTATION FAILURE.

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OBJECTIVE: Personalized medicine is a well-accepted concept in reproductive medicine except for the endometrial factor which is still neglected. Our group has developed the endometrial receptivity array (ERA) [Fertil Steril, 2011], a customized array of 238 genes with a computational predictor capable of diagnosing a receptive endometrium. The aim of this study was to demonstrate the diagnostic and therapeutic efficiency of the ERA in patients with implantation failure (IF), through personalization of the day of embryo transfer (pET).

DESIGN: Multicenter prospective clinical study analyzing the results of ERA in 116 IF patients (5.7 previous failed cycles), either with their own oocytes (IVF) (n=69) or ovum donation (OD) (n=47). In non-receptive, ERA was repeated on the day indicated by the predictor, and pET was guided according to ERA results.

MATERIALS AND METHODS: Endometrial biopsies were collected at LH+7, or in HRT after 5 days of P impregnation. RNA was extracted and hybridized according to ERA technology. Data were analysed by the predictor using the SVM+KNN algorithm for the 238 genes and results were given as receptive (R) or non-receptive (NR).

RESULTS: In 91 IF patients (78.45%) ERA test was R. In 53 of them, ART was performed in the following 6 months, resulting in a 60% PR, 32.98% IR (IRs per month were 17.4% 1st, 41.4% 2nd, 35% 3rd, 38.5% 4th, 33.3% 5th, 33.3% 6th) demonstrating that pregnancy was not related to the local injury rather to the improvement of embryo assessment using PGD and time-lapse after R ERA results. In 25 patients (21.5%), results were NR affecting to 15 OD patients (31.9%) and 10 IVF (14.5%). The majority of NR were classified by the predictor as pre-receptive, and in 10 of them ERA was repeated at LH+9 or P+7 resulting in R. Up to this point, pET has been performed in 4 NR cases resulting in 100%PR with 62,5% IR.

CONCLUSION: We propose for the first time the concept of pET in patients with IF guided by ERA as they have a displacement of the endometrial window of receptivity.

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ENDOMETRIAL THYROID AND VITAMIN D SIGNALING PATHWAYS DURING OVARIAN STIMULATION FOR ASSISTED REPRODUCTIVE TECHNOLOGY (ART).

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OBJECTIVE: The endometrium is a site of extrathyroidal production of T3 and T4. Regulation of synthesis and activation processes is by pituitary TSH and seems to be regulated, in part, by progesterone. TSH receptors (TSHR), as well as T3 and T4 receptors (TRα1, TRα2, and TRß1), and iodothyronine deiodinases (DIO2, the most abundant) have been shown in the endometrium. The active form of vitamin D (1,25-OH2-D3) is a regulator of mineral homeostasis and modulates reproduction and the immune system. Its receptor, VDR, has been isolated in endometrium and decidua. We studied the biochemical implications of ovarian stimulation for ART in the expression of these receptors.

DESIGN: Prospective controlled study.

MATERIALS AND METHODS: We followed 11 women during a natural cycle (controls) and 11 oocyte donors during an ART cycle (treated). At the time of the hypothetical day 3 embryo transfer (LH+5 or hCG+5), we performed an endometrial biopsy in all women. Real-time RT-PCR was used to measure mRNA levels for the receptors in the endometrial tissue.

RESULTS: TSHR mRNA decreased 57%, from 6.0+0.2 fg/μg RNA in controls to 2.6+0.1 fg/μg RNA in treated patients ($P=0.01$). TRα1 and TRα2 expression did not change, but TRß1 increased 63%, from 0.97+0.08 fg/μg RNA in controls to 1.7+0.09 fg/μg RNA in treated patients ($P=0.04$). DIO2 decreased 63%, from 3.2+0.2 pg/μg RNA in controls to