Various clinical presentations of impaired endometrial receptivity – a series of 3 cases

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Abstract

Endometrial receptivity disorders are common for subfertility, but patients selection for this procedure is not easy. The publications on the item of endometrial receptivity usually focus on implantation failures in IVF setting, or multiple pregnancy losses in both in vitro and in vivo pregnancies without mentioning clinical signs and symptoms (1,2) . There are few data about correlation of clinical presentations and impaired endometrial receptivity in women with reproductive disorders looking for restorative reproductive treatment.
We present the case series of 3 subfertile women in whom endometrial biopsy with immunohistichemical evaluation was performed. In these patients, similar non-CD138-associated immunohistochemical findings coexisted with various clinical presentations.. In all these patients, similar immunologic treatment chosen on the basis of endometrial evaluation led to live birth.
Thus, endometrial receptivity evaluation can be a useful tool in subfertile women looking for in vivo conception.
Understanding clinical presentations in which endometrial biopsy can be the most useful can improve diagnostic and shorten time to effective treatment and successful pregnancy.

Key words: endometrium, receptivity, natural conception, immunohistochemistry.

Case 1

Woman 23 years & Man 28 years, normal semen analysis, healthy, no alcohol, no smoking
History: 4 years trying for baby, no pregnancy, one ineffective IUI procedure
Clinical presentation:, long cycles (up to 5 months), weight gain 20 kg during the last 3 years (176 см/83 kg, BMI 27). Patent uterine tubes (HSG).
Laboratory findings and USG consistent with PCOS**,**
Diagnosis: PCOS
Treatment:Metformin 2000/d, , Letrozol 2,5 mg x 15 tab, HCG 10 000 , vaginal micronised progesteron 200 mg nocte from P+3 10 nights, folic acid 1 mg/day, vit D3 2000 IU, mucus enhancers (vit B complex, acetylcystein 600 mg bid days 5-16.
Pregnancy in the 8th cycle of treatment, ended with miscarriage 4-5 wks.
Endometrial biopsy – elevated CD4 cells (Table 1, Figure 1-2)
Adjusted treatment: for 3 months before trying to conceive Hydroxychloroqiune 200 mg bid , which led to significant improvement of the cycle and spontaneous ovulation without letrozol.
Pregnancy in the 4th cycle of treatment, 1st cycle of trying (figure 1-1). Hydroxychloroquine 200 mg bid continued to delivery, prednisolon 5 mg bid to 15 week, aspirin 150 mg from 9 weeks to 34 weeks, micronised progesteron 600 mg/d up to 34 wk
C**omplications**: shortened uterine cervix (26 mm at 20 weeks), gestational hypertension from 28 weeks,
Outcome
C-section at 39 weeks, healthy boy 3400g/53cm,

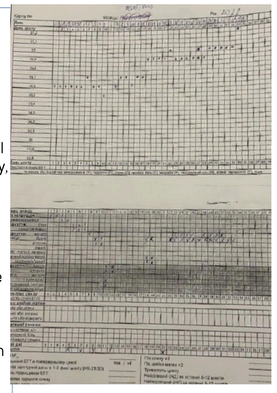


Figure 1-2. Chart of the Patient 1 (symptothermal), beginning of the pregnancy.
High-quality cervical mucus observed on Days 11-12 (Peak of mucus on Day 12), and temperature shift on Day 13 with long phase of higher basal temperatures

Table 1. The results of immunohistochemical evaluation of endometrium in Patient 1

Cells	N cells in field x40	References
CD3	27	30
CD4	24	15
CD56	19	30
CD138	0	1 in fieldx10

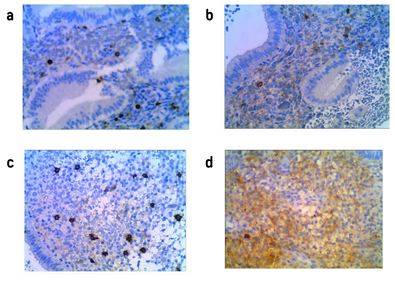


Figure 1-1. The results of immunohistochemical evaluation of endometrium in Patient 1: a) CD3x40, b) CD4x40, c) CD56x40, d) CD138x40

Methods and Materials

The patients applied for restorative reproductive treatment in 2018-2021. Endometrial biopsy was recommended as a secondary evaluation following uneffective initial treatment, in 2021-2022.
Endometrial boipsy was performed in the mid-lutheal phase to evaluate the endometrium during implantation window (5-9 days post-Peak). Sections of the paraffin-embedded blocks with immunohistochemical reactions were obtained using manual method with Master Polymer Plus Detection System (Peroxidase) (Incl. DAB Chromogen) and antibodies against – CD3 (Polyclonal, Dako), CD4 (Clone 4B12, Thermo Scientific), CD56 /NCAM-1 Ab-4 (Clone 56C04, Thermo Scientific), CD138 Ab-2 (Clone MI15,Thermo Scientific). The results were interpreted according to IPLE test (immunohistological profile of endometrial leucocytes) (3).

Case 2

Woman 33 years & Man 34 years, normal semen analysis, healthy, no alcohol, no smoking
History: miscarriage at 6 weeks , the woman got pregnant from the first attempt.
C**linical presentation**: regular cycles, mild hiperprolactinemia, BMI 21 (weight 54 kg, height 159 cm)
L**aboratory finding**s day 3: AMH 0,96 ng/ml , FSH 10 mIU/ml ,LH 8 mIU/ml, estradiol 69 pg/ml, , prolactin fluctuating from 18 to 47 ng/ml
D**iagnosis**: low ovarian reserve, mild hiperprolactinemia
Treatment: Cabergolin 0.25 мг twice a week, DHEA 10 mg/day, Vitamin D3 2000 IU daily, Omega 3 2000 mg daily, Folic acid 1 mg daily, Clomifene 25 mg on Days 3,4,5 + micronized progesterone 200 mg from P+3 for 10 nights
Pregnancy in the first cycle of trying – miscarriage 3 weeks.
Endometrial biopsy – borderline high CD3, CD56 (Table 2, Figure 2-1)
Adjusted treatment: for 3 months before trying to conceive Hydroxychloroquine 200 mg od+Prednisolone 5 mg od added to initial treatment
Pregnancy in the 1st cycle of trying (figure 2-2).
Hydroxychloroquine 200 mg od, prednizolone 5 mg od continued until delivery, vaginal micronised progesteron to 36 weeks
Complications: cervical opening at 32 weeks – pessary, USG 32 weeks – fetal weight in lower percentiles
Outcome: delivery *per vias naturalis* at 39-40 weeks, healthy boy 2950g, 51 cm

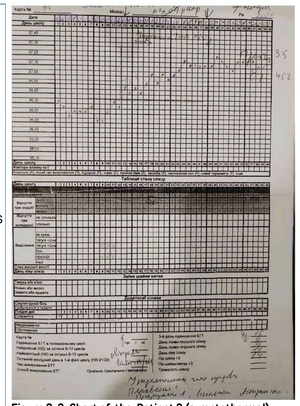


Figure 2-2. Chart of the Patient 2 (symptothermal), beginning of the pregnancy.
High-quality cervical mucus observed on Days 9-11 (Peak of mucus on Day 11), and temperature shift on Day 13 with long phase of higher basal temperatures

Table 2. The results of immunohistochemical evaluation of endometrium in Patient 2

Cells	N cells in field x40	References
CD3	19	30
CD4	9	15
CD56	30	30
CD138	0-1	1 in fieldx10

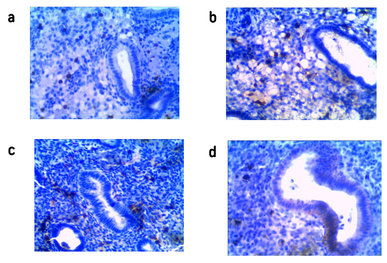
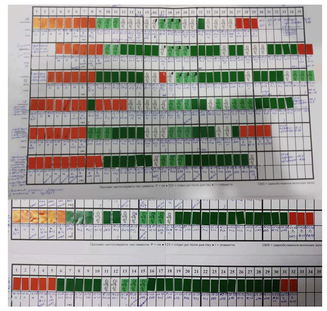


Figure 2-1. The results of immunohistochemical evaluation of endometrium in Patient 2: a) CD3x40, b) CD4x40, c) CD56x40, d) CD138x40

Case 3

Woman 27 years & Man 29 years, normal semen analysis, healthy, no alcohol, no smoking
History: trying for baby 6 years, no pregnancy, urogenital infections -antibiotic treatment
Clinical presentation: mild underweight (56 kg, 165 cm, BMI 20) occasional stomach ache, easy weight loss, mild galactorrhea.
CrMS chart – TEBB, intermenstrual bleeding, short post-Peak phase (figure 3-1, a)
Laboratory findings: prolactin 33 ng/ml , 1 hour after metoclopramide 10 mg – 241 ng/ml, homocystein 14 mcmol/l.
Diagnosis; mild hyperprolactinemia, infections, homocysteinemia
T**reatment**: Antibiotics – doxycycline 100 mg bid + metronidazole 500 mg bid for 2 weeks, amoxicilline-clavulonic acid 650 mg bid + metronidazole 500 mg bid for 2 weeks – disappeared inermenstrual bleeding and TEBB.
Cabergolin 0,25 mg 2 times a week, methylfolate 800 mcg, Vit B complex, Vit D3 2000 IU daily, Clomifene 50 mg days 2,3,4, HCG periovulatory, Micronized progesterone 200 mg nocte from P+3 for 10 days,
Perfect cycles but no pregnancy,, and long post-Peak phase up to 20 days – implantation failures? (fig3-1, a)
Endometrial biopsy – significantly elevated numbers of CD56, CD3, CD4 (Table 3, figure 3-2).
Adjusted treatment: for 3 months before trying to conceive – Hydroxychloroquine 200 mg bid, prednizolone 5 mg bid in addition to previous treatment.
Pregnancy in the 4th cycle of trying (7th cycle of adjusted treatment) (figure 3-1, b)
Hydroxychloroquine 200 mg bid, prednizolone 5 mg bid continued until delivery., vaginal micronised progesteron for 21 weeks, aspirin 150 mg 12 – 36 wks.
Complications: ultrasound 30 weeks – fetal weight in lower percentiles
Outcome: delivery *per vias naturalis* at 40 weeks, healthy girl 2500 g, 51 cm

a



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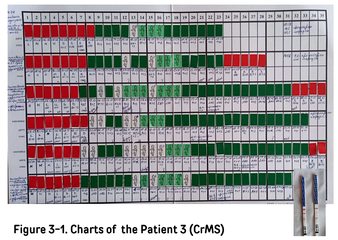

Figure 3-1. Charts of the Patient 3 (CrMS)

a) cycles on initial treatment – TEBB, intermenstrual and premenstrual bleeding, post-Peak phase 20 days – probable implantation failure,
b) cycles on adjusted treatment. Pregnancy in the last cycle.

Table 3. The results of immunohistochemical evaluation of endometrium in Patient 3

Cells	N cells in field x40	References
CD3	120	30
CD4	25	15
CD56	190	30
CD138	12*	1 in fieldx10

*This result exceeds the reference value, but the patient showed clinical improvement after 4 weeks of antibiotics, so further antibacterial therapy did not seem necessary.

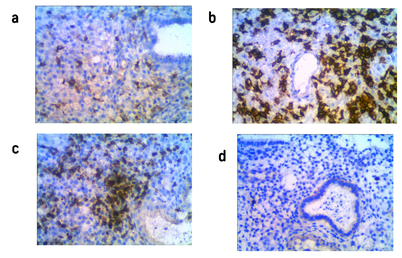

Figure 3-2. The results of immunohistochemical evaluation of endometrium in Patient 1: a) CD3x40, b) CD4x40, c) CD56x40, d) CD138x40

Discussion

Our patients with endometrial receptivity disorders had heterogenous presentations of reproductive problems: PCOS, low ovarian reserve with recurrent miscarriage, unexplained infertility with long lutheal phase. In all these patients, endometrial receptivity disorders were successfully treated by Hydroxychloroquine with/without Prednisolone, which are considered a safe and promising treatment for patients with reproductive disorders. The mechanism of action of these drugs may include inhibition of the expression of Th-1 cytokines, elevation the count of Tregs and triggering maternofetal tolerance (4).
Interestingly, we observed significant clinical effects of these medications, including a notable improvement in the cycle quality with spontaneous ovulation without the use of letrozole (in case 1), as well as an improvement in overall well-being, increased appetite, and moderate weight gain in the patient with a low BMI (in case 3).
For our patients, we proposed an endometrial receptivity evaluation as a second-line procedure, following ineffective previous treatment. This took a lot of time, led to unsuccessful pregnancies, and caused additional distress. Understanding clinical presentations in which endometrial biopsy can be most useful can improve diagnostic and shorten time to effective treatment and successful pregnancy in subfertile women seeking *in vivo* conception.

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Disclosure

The authors declare no competing financial interest.