PROBE-BASED CONFOCAL LASER ENDOMICROSCOPY FOR PREDICTION OF UTERINE REJECTION IN A PATIENT SUBMITTED TO LIVE-DONOR UTERUS TRANSPLANTATION

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PROBE-BASED CONFOCAL LASER ENDOMICROSCOPY FOR PREDICTION OF UTERINE REJECTION IN A PATIENT SUBMITTED TO LIVE-DONOR UTERUS TRANSPLANTATION

Endomicroscopia confocal a laser baseada em sonda para predição de rejeição uterina em paciente submetida a transplante de útero com doadora viva.

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ABSTRACT

Uterus transplantation is a relatively new procedure, with successful births having been performed using living donors in Sweden since 2014 and a deceased donor, in the first time in Brazil, in 2016. Probe-based confocal endomicroscopy it is considered an optical biopsy method (1000 times magnification) allowing detailed visualization of tissue cytoarchitecture and microvascular patterns at a penetration depth of approximately 50 to 60 μm. The application of confocal endomicroscopy to the uterine cervix emerges as a promising alternative to weekly cervical examinations in the follow-up of patients who have undergone uterus transplantation. The authors report the case of a 34-year-old woman with Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome, diagnosed at 15 years of age, that in August 2026 was underwent to the first successful live-donor uterus transplantation performed in Latin America. The surgical procedure was uneventful. The confocal endomicroscopy to the uterine cervix was employed to evaluate its potential utility in identifying inflammatory changes that might precede graft rejection. No irregular or distorted epithelium neither severe inflammation was observed and this finding were confirmed by biopsies and histological analysis. They concluded that the probe-based confocal endomicroscopy may support more effective and individualized post-transplant management, representing a meaningful advancement in the fields of regenerative medicine and transplantation.

HEADINGS: Infertility. Transplantation. Uterus. Endoscopy. Microscopy. Fluorescence.

RESUMO

O transplante de útero é um procedimento relativamente novo, com nascimentos bem sucedidos realizados com doadoras vivas na Suécia, desde 2014, e com uma doadora falecida, pela primeira vez no Brasil, em 2016. A endomicroscopia confocal baseada em sonda é considerada um método de biópsia óptica (ampliação de 1000 vezes) que permite a visualização detalhada da citoarquitetura tecidual e dos padrões microvasculares a uma profundidade de penetração de aproximadamente 50 a 60 µm. A aplicação da endomicroscopia confocal ao colo do útero surge como uma alternativa promissora aos exames cervicais semanais no acompanhamento de pacientes submetidas a transplante de útero. Os autores relatam o caso de uma mulher de 34 anos com síndrome de Mayer-Rokitansky-Küster-Hauser (MRKH), diagnosticada aos 15 anos de idade, que em agosto de 2026 foi submetida ao primeiro transplante de útero com doadora viva bem sucedido, realizado na América Latina. O procedimento cirúrgico transcorreu sem intercorrências. A endomicroscopia confocal do colo do útero foi empregada para avaliar a potencial utilidade na identificação de alterações inflamatórias que podem preceder a rejeição do enxerto. Não foram observadas irregularidades ou distorções no epitélio, nem inflamação grave, e esse achado foi confirmado por biópsias e análises histológicas. Os autores concluíram que a endomicroscopia confocal baseada em sonda pode auxiliar em um manejo pós-transplante mais eficaz e individualizado, representando um avanço significativo nos campos da medicina regenerativa e do transplante.

DESCRITORES: Infertilidade. Transplante. Útero. Endoscopia. Microscopia. Fluorescência.

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Conflicts of Interest: None

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Image

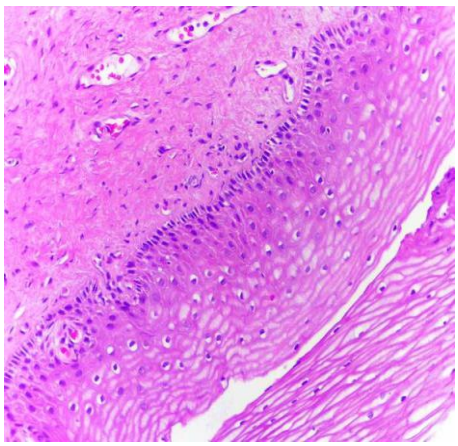


Figure 2D. Ectocervix showing minimal spongiosis.

No evidence of rejection (H&E 200X)

Central Message

Uterus transplantation is a relatively new procedure, with successful births having been performed using living donors in Sweden since 2014 and a deceased donor, in the first time in Brazil, in 2016. Probe-based confocal endomicroscopy (pCLE) it is considered an optical biopsy method (1000 times magnification) allowing detailed visualization of tissue cytoarchitecture and microvascular patterns at a penetration depth of approximately 50 to 60 μm. The application of

confocal endomicroscopy to the uterine cervix emerges as a promising alternative to weekly cervical examinations in the follow-up of patients who have undergone uterus transplantation.

Perspectives

The use of pCLE in the follow-up of patients undergoing uterus transplantation appears to be a feasible and promising strategy for cervical monitoring, enabling early detection of graft rejection without the risks associated with biopsy. Furthermore, pCLE may support more effective and individualized post-transplant management, representing a meaningful advancement in the fields of regenerative medicine and transplantation.

Authors' contributions

Conceptualization: Wellington Andraus, Adriana Vaz Safatle-Ribeiro

Investigation: Adriana Vaz Safatle-Ribeiro, Fernanda Carvalho Franco, Pedro Augusto Monteleone,

Methodology: Wellington Andraus Adriana Vaz Safatle-Ribeiro, Dani Ejzenberg, Fernanda Carvalho Franco ;

Data analysis: Adriana Vaz Safatle-Ribeiro, Dani Ejzenberg, Jose Maria Soares Jr

Writing original article: Adriana Vaz Safatle-Ribeiro, Wellington Andraus, Edmundo Chada Baracat, Pedro Augusto Monteleone

Literature review: Adriana Vaz Safatle-Ribeiro, Fernanda Carvalho Franco, Pedro Augusto Monteleone,

HIGHLIGHTS

1. Uterus transplantation is a relatively new procedure, with successful births having been performed using living donors;
2. more than 100 transplants already performed, in recent years, in various countries around the world, achieving excellent results;
3. Probe-based confocal endomicroscopy (pCLE) is considered an optical biopsy method (1000 times magnification) allowing detailed visualization of tissue cytoarchitecture and microvascular patterns at a penetration depth of approximately 50 to 60 µm.
4. The application of confocal endomicroscopy to the uterine cervix has previously been reported as an adjunctive tool for guiding targeted biopsies during colposcopy evaluation ;
5. The use of pCLE in the follow-up of patients undergoing uterus transplantation enabling early detection of graft rejection without the risks associated with biopsy

INTRODUCTION

Uterus transplantation is a relatively new procedure, with successful births having been performed using living donors in Sweden since 2014[2] and a deceased donor in Brazil in 2016[4]. It has grown in recent years, with more than 100 transplants already performed in various countries around the world, achieving excellent results[1].

Unlike other solid organs such as the liver, where serum enzymes can be markers of organ rejection, the uterus does not have a serum marker that can signal rejection. This control is usually performed with serial biopsies of the transplanted cervix, which is an invasive examination.

Probe-based confocal endomicroscopy (pCLE) is a real time, *in vivo*, high-resolution imaging technique that has been improving the diagnosis of early neoplastic and pre-neoplastic lesions, particularly within the gastrointestinal tract[6]. It is considered an optical biopsy method (1000 times magnification) allowing detailed visualization of tissue cytoarchitecture and microvascular patterns at a penetration depth of approximately 50 to 60 μm.

The application of confocal endomicroscopy to the uterine cervix has previously been reported as an adjunctive tool for guiding targeted biopsies during colposcopy evaluation.[3,6,7] Given that the cervical epithelium typically measures between 50 and 100 μm in thickness, pCLE emerges as a promising alternative to weekly cervical examinations in the follow-up of patients who have undergone uterus transplantation.

Case Report

We report the case of a 34-year-old woman with Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome, diagnosed at 15 years of age. MRKH syndrome is a congenital anomaly resulting from failure of Müllerian duct development, leading to uterine agenesis and partial or complete vaginal absence. Affected individuals typically present with normal female external genitalia and normal secondary sexual characteristics, including breast development and pubic hair.

In August 2024, after approval from an Ethics Committee of thE Institution (number 81297224.8.0000.0068) and written informed consent, the patient underwent the first successful live-donor uterus transplantation performed in Latin America. The surgical procedure was uneventful. Postoperatively, the

patient was maintained on an immunosuppressive therapy with tacrolimus, azathioprine and prednisone. Weekly cervical biopsies were performed to detect early signs of graft rejection.

pCLE of the uterine cervix was performed to evaluate its potential utility in identifying inflammatory changes that might precede graft rejection. Two sessions of pCLE were conducted on postoperatively days 10 and 52. Both procedures were carried out without sedation, with the patient in lithotomy position, following intravenous administration of fluorescein.

The first pCLE cervix examination demonstrated preserved squamous epithelium with regular squamous cells, normal intra-papillary capillary loops, and scattered inflammatory cells. (Figure 1. A and B). The second pCLE examination revealed regular squamous cells, slightly fluorescein extravasation between them and no features of rejection. No irregular or distorted epithelium neither severe inflammation was observed. (Figure 2.A and B).

To assess the diagnostic assertiveness of pCLE and to confirm the histological findings, target cervical biopsies were obtained immediately following each procedure. Histological analysis confirmed no signs of rejection in both instances. At the first evaluation, histology demonstrated minimal spongiosis and sparce intraepithelial lymphocytes. (Figure 1. C and D). At the second evaluation, histological findings were limited to spongiosis. (Figure 2. C and D)

Few months later, she underwent *in vitro* fertilization and became pregnant. The pregnancy was uneventful.

DISCUSSION

Uterus transplantation has been growing worldwide, and the number of transplant recipients and births through this method has increased over the years, with prospects for continued growth in the future [5]. Because it is a relatively new transplant method, the assessment of organ rejection is not yet fully established by global experience. Furthermore, it suffers from the lack of a good serum marker.

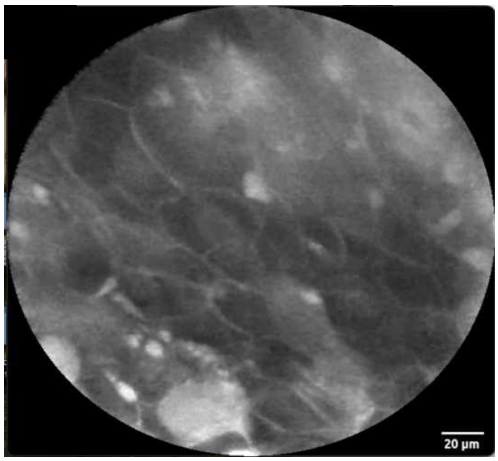
pCLE enables detailed analysis of the cervical tissue cytoarchitecture and local vascularization. Similarly to histology, it may allow early detection of inflammatory cells and features suggestive of graft rejection, while mitigating the risks associated with repeated biopsies in an immunosuppressed patient.

Through *in vivo* examination of the cervix, this minimally invasive approach has the potential to decrease the need for frequent invasive procedures, thereby minimizing procedure-related complications, including bleeding and post-procedural infections, and providing a safer surveillance strategy. Moreover, pCLE may reduce the costs by limiting unnecessary biopsies and subsequent histopathological analyses.

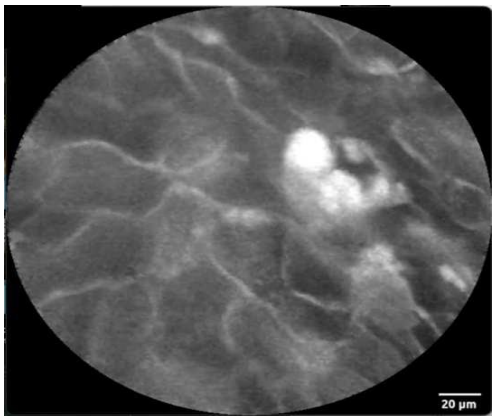
CONCLUSIONS

The use of pCLE in the follow-up of patients undergoing uterus transplantation appears to be a feasible and promising strategy for cervical monitoring, enabling early detection of graft rejection without the risks associated with biopsy. Furthermore, pCLE may support more effective and individualized

post-transplant management, representing a meaningful advancement in the fields of regenerative medicine and transplantation.

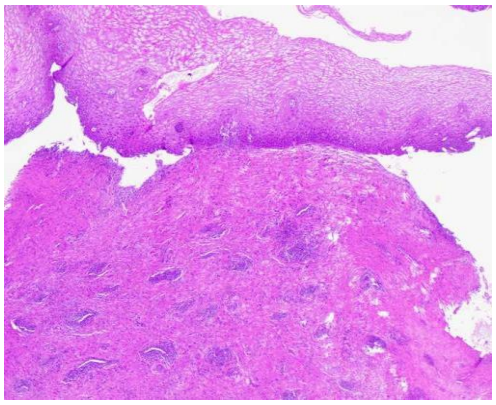


A

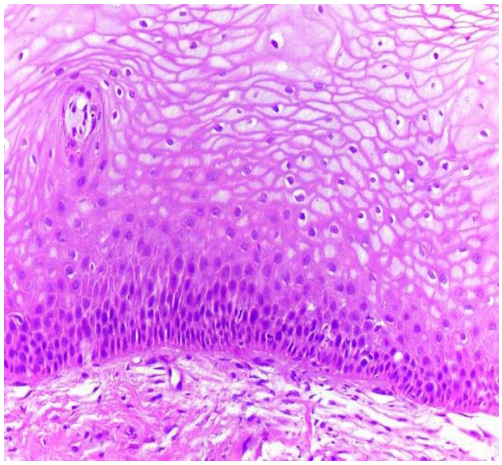


B

Figure 1. A and B. pCLE shows regular squamous cells, normal intra-papillary capillary loop, and scattered inflammatory cells.



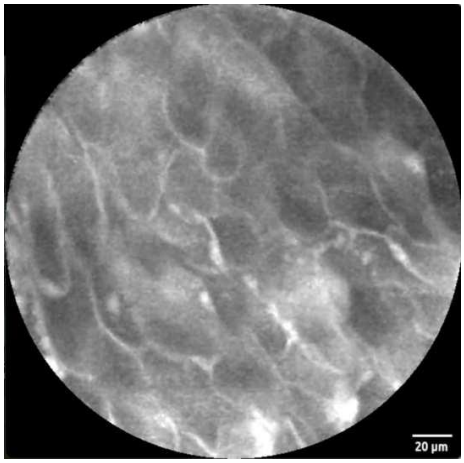
C



D

Figure 1. C and D. Minimal spongiosis and scant intraepithelial lymphocytes are present. No evidence of rejection (H&E, 40X and 200X)

A



B

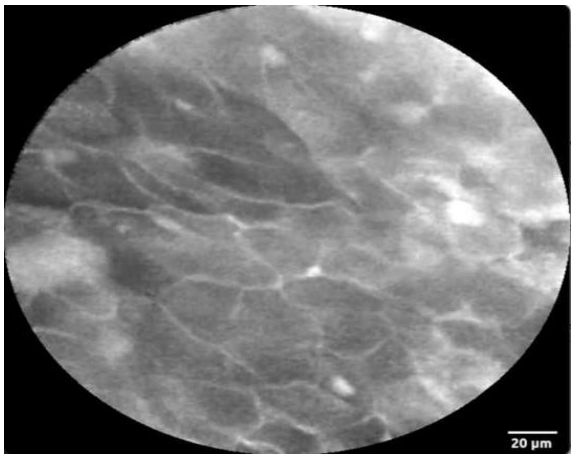
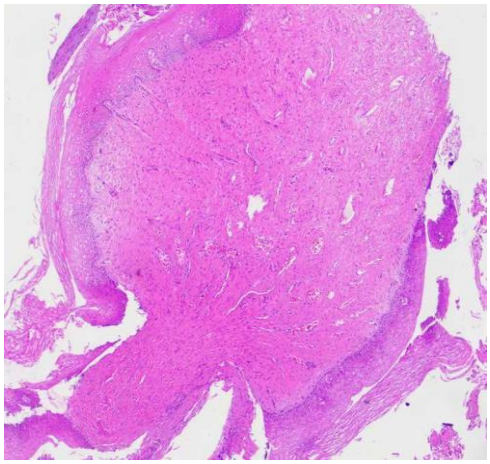


Figure 2. A and B. pCLE shows regular squamous cells, slightly fluorescein extravasation between them and no features of rejection.

C



D

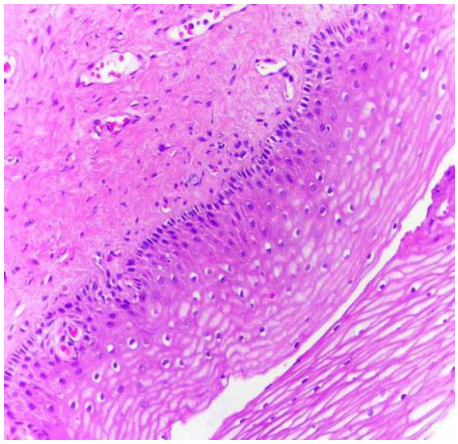


Figure 2. C and D. Ectocervix showing minimal spongiosis. No evidence of rejection (H&E, 40X and 200X)

DATA AVAILABILITY STATEMENT

The research data is contained in the manuscript

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