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CASE REPORT

Does metroplasty on dysmorphic uterus improve displaced and disrupted implantation window? A Case Report

Short title: uterine metroplasty and its influence on implantation window

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Abstract

Background:

Different studies have shown that dysmorphic uterus may be associated with reproductive failure and adverse reproductive outcomes. Euploid embryos may fail to implant if the uterine environment is not appropriate. Nevertheless, a causal relationship between dysmorphic uterus and impaired endometrial receptivity remains unproven.

Case presentation:

Therapeutic management of T-shaped uterus is challenging while some authors advice expectant management others find encouraging results after enlargement of uterine cavity by hysteroscopic metroplasty. Here we present a case of primary infertility in a 35 years-old woman, who presented a dysmorphic uterus on her fertility workup. She followed IVF cycle and had two failed embryo transfers besides personalized embryo transfer according to ERA test result and correction of mild dysbiosis according to EMMA test recommendations. She was offered hysteroscopic metroplasty and a sequential oestrogen-progestagen therapy for two months. The anatomical outcome was evaluated through second look hysteroscopy and 3D transvaginal ultrasound, and a new evaluation of endometrial receptivity was performed: her ERA test result before hysteroscopy was post-receptive and after the procedure showed receptive endometrium with 5 full days of progesterone administration, an optimal window of implantation, Alice test found no pathogens and no dysbiotic endometrial microenvironment. She had a spontaneous pregnancy afterwards.

Conclusion:

This is first report to describe the impact of hysteroscopic metroplasty for U1a dysmorphic uterus on endometrial receptivity. This could shed some light for further research in order to explain improvement on reproductive outcome found by different authors after hysteroscopic metroplasty for correction of T-shaped uterus.

Keywords: dysmorphic uterus; uterine metroplasty; implantation window; T shaped uterus

Introduction

Assisted reproductive techniques have lately experienced great advance, they have improved the means of tissue culture, updated the criteria of embryonic selection, extended culture to blastocyst, which has allowed in selected patients, to reach pregnancy rates up to 66% [1]. Many factors involved in the implantation are still unknown, and it is possible that the uterus plays a much more relevant role than the one considered until now.

Different studies have shown that genetically normal embryos may fail to implant if the uterine environment is not adequate for implantation. Structural abnormalities of the uterus have a negative impact on fertility. Changes in normal myometrial architecture, can potentially alter the junctional zone (JZ), modify contractility pattern, and affect sperm transport, embryo transport as well as subsequent embryo implantation. These structural anomalies may also have an impact on the expression of different genes and cytokines involved in adequate decidualization and endometrial receptivity [2,3].

Since 2002 many gene expression signatures associated with endometrial receptivity have been described. The endometrium is receptive to embryo implantation during the window of implantation, a temporarily restricted phase, during which changes occur at the molecular, cellular and tissue levels. In 2011 a transcriptomic signature of 238 genes with an artificial intelligence platform and algorithm lead to the creation of the endometrial receptivity analysis (ERA), a new tool for endometrial receptivity evaluation [4].

Since anatomical integrity of the uterine cavity is crucial for endometrial receptivity [5-8]Müllerian uterine anomalies have been linked to infertility, recurrent pregnancy loss and severe obstetric complications 9,10]

Dysmorphic uterus is a Müllerian anomaly that has been long underestimated, most commonly observed in patients with in-utero exposure to diethylstilbestrol (DES). Because DES is no longer available, today no cases of DES-associated T shaped uterus are found in patients undergoing reproductive treatment. The European Society of Human Reproduction and Embriology (ESHRE) and the European Society for Gynaecological Endoscopy (ESGE) have described a new classification system for the uterine anomalies [][11] defining the so called dysmorphic uterus which has been categorized as a class 1 anomaly. This class incorporates three different subgroups of anomalies: U1a (T-shaped uterus), U1b (infantilis uterus), and U1c (t-shaped uterus with partial septum). Prevalence varies from 0,2-10% [12,13,14,15]. The pathogenesis remains unclear and its cause is still unknown, it may also be primary or secondary to intrauterine adhesions by uterine infections or previous surgery [12,16,17], adenomyosis [15], tuberculosis [18] as well as long-term oral contraception [19].

There is no consensus on clinical management of this entity: while some authors consider expectant management as the most appropriate choice for daily practice [20,21], other authors find encouraging results in terms of fertility after hysteroscopic metroplasty [22,23,24,25]. These authors consider that improvement on reproductive outcomes maybe explained by the restoration of the uterine cavity to its normal size and volume, enhancement of uterine compliance, reduction of abnormal myometrial contractions, improvement of uterine vascularization, as well as microscopic changes with a positive impact on endometrial receptivity [26,29].

Case presentation

We describe a case of 35 years old lady suffering from primary infertility after two years and a half of unprotected intercourse. She had no history of surgery or any other disease. Additionally, patient had no family disease history.

Her gynecological examination revealed no abnormal findings.

During her fertility work up, ovarian reserve was evaluated we found that antral follicle count was 7, and her AMH: 1,28ng/ml. Hysterosalpingography showed normal tubal patency, 3D transvaginal sonography was carried out during luteal phase of the cycle (day 21-25, when the endometrium appears thick and echogenic, so the uterine cavity can be clearly differentiated from the myometrium), uterine architecture was evaluated a coronal view of the uterus was obtained and the distance between tubal ostia (R0) was 23mm, and the width 10 mm bellow the fundus of the cavity (R10) was 8mm, this is compatible with T-shaped uterus following the recently proposed "Rule of ten" [30].

Physical examination of her partner did not show any abnormal findings.Semen analysis showed normal parameters as well as normal FISH test and DNA fragmentation in sperm.

Different options were discussed with the patient and decision on an in vitro fertilization cycle (IVF) was made. She followed pretreatment with daily testosterone in gel 25mg per day (Testogel 50mg, laboratoires Besins International, Paris, France) on the previous cycle as well as oestradiol plasters 100mcg (Evopad) (Janssen,Toledo, Spain) every other day during luteal phase in order to improve the synchronization of the pool of follicles available for stimulation. On day 2, she was given 150 IU of Coripholitropin alpha (Elonva 150; Merck Sharp&Dohme, Spain) followed by 150 IU of recombinant FSH (Puregon) (Merck Sharp&Dohme, Spain) and 75 IU of HMG-HP Menotropin (Menopur) (Ferring SAU, Madrid, Spain); on day 7 of gonadotropin stimulation she started co-treatment with a GnRH antagonist (Ganirelix 0,25mg, Merck Sharp&Dohme B.V., Nethearlands) until the day of ovulation triggering. Transvaginal ultrasound guided oocyte retrieval was performed 36 hours after dual triggering with recombinant human chorionic gonadotrophin (rHCG) (Ovitrelle 250 mcg, Merck Serono S.p.A, Bari, Italy) plus 0,2 mg GnRH analogue Triptorelin (Decapeptyl 0,1, Ipsen Pharma, S.A. Barcelona, Spain) Oocyte pick up was performed with 17-gauge needle (cook Medical) under sedation. The oocytes-corona complexes were denuded, after retrieval; there were seven oocytes retrieved, six metaphase II, and ICSI was performed after 2 hours of incubation. Fertilization was assessed 17-19h after insemination and was defined by the presence of two pronuclears (2PN) and two PBs. Extended embryo culture was performed in close system, morphological grading was evaluated through time lapse system, and two blastocysts were obtained; quality of blastocyst was assessed according to the criteria by ASEBIR [31]: one blastocyst AA and a second one AB were vitrified due to thin endometrium (6 mm at oocyte retrieval).

She then followed endometrial preparation, using transdermal oestradiol plasters 100mcg (Evopad) every other day (Janssen, Toledo, Spain) as well as daily vaginal oestradiol 6 mg a day (Progynova, Schering Berlin, Germany), when the endometrial thickness reached 7,4mm, luteal support with micronized intravaginal progesterone 800mg per day (Progeffik 200, Effik,S.A.Madrid Spain) was added and single embryo transfer was performed after five days, with a soft catheter (K-soft 5100; Cook, Queensland, Australia) under ultrasound guidance. Pregnancy test was negative. In order to improve her chances of positive result, patient was offered personalized

embryo transfer through endometrial receptivity array (ERA test) [32], as well endometrial microbioma analysis using NGS to evaluate percent composition of lactobacillus (EMMA test) [][33] as well as presence of pathogens (Alice test) [34] and uterine immune profile [35]. She followed endometrial preparation via a hormone replacement cycle like the one used for frozen embryo transfer cycle. When endometrial thickness was 7 mm, she was given 800 mg vaginal micronized progesterone for 5 full days, endometrial tissue was biopsied using Cornier Pipet, the biopsied endometrial tissue was placed in a cryotube, shaken a few times, and store at 4º C for 4 hours or more according to manufacturer´s protocol.

The ERA test showed post-receptive endometria with 102 ± 3 hours as the recommended timing for embryo transfer. Percentage of lactobacilli was 84,02% (mild dysbiosis), no pathogens were present. Immune profile revealed a proinflammatory profile (ratio Th1/Th2 11,3, VR 2.0-8,8). She received oral and vaginal probiotics before new personalized embryo transfer according to ERA test result, but hCG levels were not detected at 10 days post embryo transfer. After two failed embryo transfers besides good quality embryos and personalized embryo transfer, an hysteroscopic enlargement metroplasty was performed in the first part of the cycle, immediately following menses, under conscious sedation using a 18,5Fr mini hystero-resectoscope 5 mm operating hysteroscope (Gubbini mini Hystero-resectoscope 18,5 Fr,Tontarra Medizintechnik GmbH, Germany). The myometrium was incised with a needle at the lateral uterine sidewall on each side, perpendicular to the uterus wall to restore a satisfactory cavity size, without exceeding an incision depth of 7 mm for safety reasons. Incisions were made from the isthmus to the uterine fundus under visual control, till tubal ostia were visible and aligned as seen from the isthmus. Patient was prescribed a sequential oestro-progestogen treatment for two months and the anatomical outcome was assessed with hysteroscopy, the tubal ostia were visible with the hysteroscope in the isthmic position. A 3D transvaginal ultrasound showed increased uterine measurements (interostium R0 24mm and R10 11,5 mm). Considering the improved intrauterine volume, a second biopsy was conducted for ERA test following previous ERA test recommendation (biopsy was performed after 4 full days of progesterone administration) as well as microbioma study and immune test to evaluate endometrial function after metroplasty and before new embryo transfer. EMMA test revealed microbioma with very low biomass, no pathogens were found on Alice test, and this time Era test was pre-receptive meaning that embryo transfer should be performed after full five days of progesterone administration. The result of ERA was different after metroplasty, she had an optimal window of implantation (WOI) after restoration of the uterine cavity. Immune profile showed no abnormal findings.

After metroplasty and while waiting for new attempt on ART she conceived spontaneously, and she has an ongoing pregnancy 22 weeks. Patient gave written consent to allow presentation of her clinical case.

Discussion

We presume that dysmorphic uterus will be diagnosed more frequently than reported, as the practice of 3D ultrasound becomes more widespread nowadays [30,36]. Management of patients with dysmorphic uterus is controversial, the beneficial effect of hysteroscopic metroplasty is under question. There is no RCT evaluating life birth rate after metroplasty or expectant management. Hysteroscopic metroplasty is performed during the follicular phase of the cycle, it can be performed in an ambulatory setting

under conscious sedation, without cervical dilatation, as in our case report either with the use of bipolar electrosurgical system or monopolar hook [37,38]. The remodeling of uterine morphology can improve uterine compliance as well as vascularization and induce changes on endometrial receptivity. Several studies show increased volume of the uterus and improved morphology of the uterine cavity that persist in time after hysteroscopic metroplasty [][39]. Low endometrial volume is associated with lower ongoing pregnancy rate: in the study by Labarta et al. patients with endometrial volume 1,4 ml were associated with a clinically lower overall pregnancy rate (22,2%versus 48,3%) (P>0,05) [][40].

There is no clear evidence how dysmorphic uterus can affect fertility. As uterine shape might not be the only factor, endometrial, myometrial, structural, or functional differences can be present in these patients. Expression levels of HOXA 10, EMX2, TENM1 mRNA and proteins differ significantly in mid-secretory endometrium in infertile women with Müllerian duct anomaly compared with controls. On the one hand, abnormal expression of these factors might contribute to the pathogenesis of uterine anomalies and might be a common cause of infertility [][41]. Altered expression of genes and cytokines involved in optimal decidual transformation of the endometrium, may also have a negative impact on the window of implantation leading to acquired implantation failure. On the other hand, some authors find lower endometrial thickness in women with dysmorphic uterus compared to unexplained infertile patients without Müllerian anomalies][42]. It has been proposed that thin endometrium maybe associated with altered oxygen tension. After ovulation, spiral arteries in the endometrium constrict and lead to a diminished blood flow and reduced oxygen tension in the functional epithelium around the time of implantation. Implantation in a thin functional endometrium would result in an increased proximity of the embryo to the spiral arteries, to higher vascularity, and therefore higher oxygen concentrations, which might be detrimental compared with the usual low oxygen tension of the endometrial surface. Patients with a thin endometrium have less endothelial growth factor (VEGF) expression, causing poor vascular development and ultimately defective placentation [[43].

Conclusion

To the best of our knowledge, this is the first report describing the impact of hysteroscopic metroplasty for T shaped uterus on ERA test results. The ERA is a test to identify the timing for an individual´s WOI, based on the assumption that the individual WOI is constant. Human endometrium transiently acquires a specific phenotype for receiving a competent embryo for implantation. T shaped uterus may have a negative impact on endometrial receptivity through different pathways, changes on microbioma, immunological factors, cytokines, different gene expression, that could alter the WOI. In this particular case, the WOI was brought forward and a proinflammatory profile was encountered, besides dysbiotic endometrial microbiota; embryo implantation is associated with a transient inflammatory reaction [] [44] and this could explain an earlier WOI rather than an optimal WOI in this patient. After metroplasty new ERA test revealed an optimal WOI allowing embryo-endometrial synchrony. Therefore, a window of implantation that is impaired by dysmorphic uterus maybe reversible, with appropriate therapy. Adequate evaluation of the uterine cavity and treatment should be done before performing ERA test, or new fertility therapies, as they are very expensive. Despite this is just a case report, differences on endometrial receptivity in a dysmorphic uterus before and after metroplasty should be taken into

consideration allowing further research that could explain improved pregnancy outcomes reported by different authors after surgery.

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Compliance with Ethical Standards

Authors contribution: E.P. designed the case report and wrote the paper; E.P.,A.V. and A.L. screened the literature and included relevant data. L.A. edited the manuscript for intellectual content. All the authors fulfill the International Committee of Medical Journal Editors (ICMJE) criteria, the Committee on Publications Ethics (COPE) and the specific guidelines the Enhancing the Quality and Transparency of Health research (EQUATOR), and gave approval for the submission of the current version of the manuscript.

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