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ORIGINAL ARTICLE

A NEW FRONTIER IN LIVING DONOR TRANSPLANTATION: UTERUS TRANSPLANTATION

Massimiliano Veroux[1], Martina Giambra[1], Giuseppe Roscitano[1], Paolo Scollo[2], Alessia Giaquinta[1], Francesco Setacci[1], Roberta Granata[1], Marianna Scribano[1], Giordana Riccioli[1], Chiara Di Grazia[1], Pierfrancesco Veroux[1]

[1] Vascular Surgery and Organ Transplant Unit, University Hospital of Catania, Catania, Italy; [2] Maternal and Child Department, Obstetrics and Gynecology, Cannizzaro Hospital, Catania, Italy

Summary

Uterus transplantation (UTx) is currently the only available treatment for absolute uterine factor infertility. Living donor (LD) UTx is a challenging surgical procedure since it poses ethical issues, and it is a high-risk and invasive surgery with higher hysterectomy-related risks compared to conventional hysterectomy. In this systematic review, 52 articles concerning the safety and efficacy of living donor uterus transplantation were analyzed. A total of 59 living donor hysterectomies have been reported in literature, including 35 performed with laparotomic approach, 20 with robotic approach and 4 with laparoscopic approach. Robotic living donor hysterectomy had the longest operative time,but resulted in a lower blood loss and postoperative stay compared to laparotomic and laparoscopic approaches. Twenty-nine births from LD-UTx have been reported, 4 after robotic living donor hysterectomy and 25 after laparotomic procedure. Living donor uterus transplantation offers the extraordinary opportunity for women with infertility to deliver a live birth. However, many concerns about the ethics and the risks related to living donation should be addressed, including the potential risk for life-threatening complications in living donors.

Key words: Mayer-Rokitansky-Küster-Hauser syndrome, hysterectomy, robotic, laparoscopic, live births, deceased donor

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Correspondence

Massimiliano Veroux
E-mail: veroux@unict.it

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INTRODUCTION

Uterus transplantation (UTx) represents an emerging approach for women with uterine factor infertility (UFI), related either to iatrogenic cause (eg, hysterectomy for benign disease, post-partum bleeding, or Ashermann syndrome) or congenital cause (uterine agenesis in Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome) [1-5].

After the first successful uterus transplantation performed in Turkey from a deceased donor [6,7], Brännström et al. [8] in Sweden reported the first successful live birth after uterus transplantation from a living donor, and uterus transplantation has become more attractive for women with UFI, particularly those with MRKH syndrome [9]. A recent web-based survey [10], conducted among 148 MRKH patients, found that the 88% of participants reported a desire for parenthood, and 61% opted for UTx as their first choice to reach this

aim. An interesting study from Japan [11] found that 32% of female respondents may well seek to become a donor if one's daughter suffered from UFI, while in Sweden, 80% of a population of women 30-39 years of age supported the UTx as a potential treatment for UFI [12].

Living donor UTx is a challenging surgical procedure since it poses ethical issues, and it is a high-risk and invasive surgery with higher hysterectomy-related risks compared to conventional hysterectomy [1,10,13]. This systematic review would explore the current data reported in literature about the UTx from a living donor, evaluating the potential harm and risks related to this procedure and the recent advancements in surgical technique.

MATERIALS AND METHODS

A thorough search of the PubMed database was conducted, using the terms "uterus transplantation" and/or "living donor" and/or "living donor uterus transplantation" up to 10 November 2023 (last access) without time, location, and language limitations.

All types of articles, including prospective studies, original studies, reviews, case reports, and commentaries were included and the more relevant articles from the reference lists were manually searched and included. Two reviewers (MV and PV) independently assessed each article and evaluated all data about living donor UTx for inclusion in this review. Nonhuman UTx studies, video articles, letters to the editor and editorials were excluded from this review. A total of 176 English articles were retrieved from the PubMed database. After excluding unrelated articles and those without available full-text versions, the full texts of 52 articles were reviewed (Fig. 1).

The results of the studies, including the risks and the advantages for the donor, the recipient and the child, the procurement of uterus from the living donor, the transplantation procedure and the outcomes of the transplantations were discussed in the present review.

RESULTS

Data of 59 living donor hysterectomies have been completely reported in literature (Tab. I), including 35 performed with laparotomic approach, 20 with robotic approach and 4 with laparoscopic approach [14-32]. Mean donor age was 45.6 ± 9.1 years and 34 were emotionally-related with the recipient (27 Mothers, 5 Sisters, 2 Mother's sister), 22 were unrelated, while in three cases the relationship was not reported. Mean recipient age was 28.8 ± 4.5 years and the MRKH syndrome was the most common indication for uterus transplant (52 patients), while 2 patients required UTx after hysterectomy

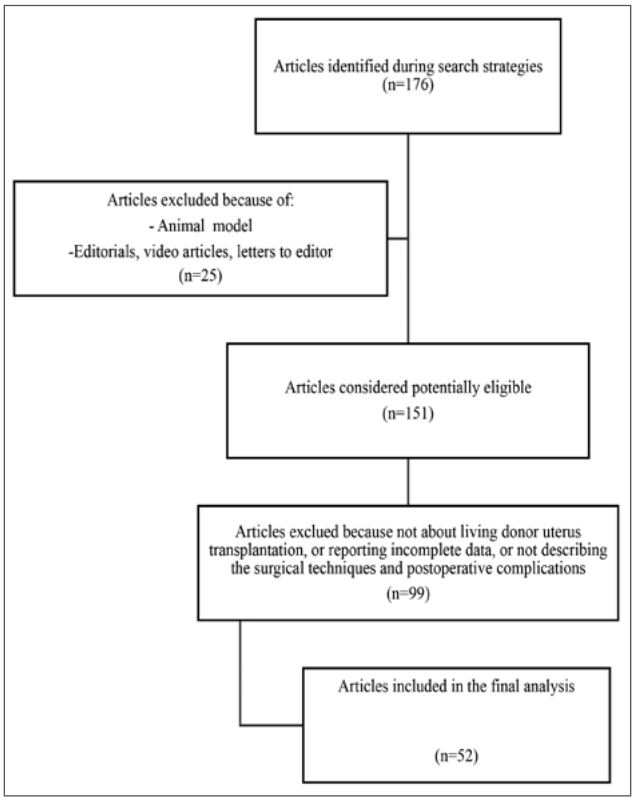

Figure 1. Flow-chart of article selection.

for myomectomy and 1 patient following hysterectomy for cervical cancer.

Robotic living donor hysterectomy had the longest operative time (11h 45 min ± 2 h 21 min) compared to laparoscopic approach (3 h 30 min ± 0 h 33 min) and laparotomic surgical technique (8 h 10 min ± 30 min). Blood loss was significantly lower in robotic hysterectomy (202.22 ± 469 ml) compared with laparotomic procedure (720.31 ± 566.89 mL), and postoperative stay was lower for robotic hysterectomy compared with laparotomic procedure (5.13 ± 2.7 *vs* 7.1 ± 2.6, days, respectively) [14-32]. Two retrieved grafts were not transplanted because of poor venous outflow and the failure to provide adequate flow through uterine arteries during back-table preparation [26,30].

A total of 32 donors (54.2%) experienced at least one complication after the hysterectomy: in most cases, the complications were of low grade of the Clavien-Dindo (C-D) classification (Tab. II): there were 11 C-D grade I, 5 C-D grade II, 1 C-D grade IIIa, 7 C-D grade IIIb, 1 C-D grade IVa, while in 7 patients the C-D grade was not reported. Laparotomic procedure had the highest incidence of postoperative complications (26/35 patients,74%), although most of them were of low clinical impact (C-D grade I-II), while a complication was reported in 35% of patients (7/20) after robotic living donor hysterectomy.

Seven patients (11.8%) required a re-intervention for a postoperative complication, mostly related to the urinary system: there were two ureteric lacerations, treated surgically during donor surgery [14,30], and one left side distal ureteral injury necessitating an ureteral stenting and, six months later, an ureteral reimplantation because of ureteral stenosis [27]. One living donor developed left-sided hydronephrosis after half a year, resulting in re-operation 16 months after uterine procurement with direct ureterocystoneostomy into the left side of the bladder roof [26]. One donor with ureteral blood clot and one donor with bilateral injury were treated with ureteral stent placement [22], one donor with uretero-vaginal fistula was treated a pyelostomy catheter and a subsequent ureter re-implantation [15]. Finally, one donor developed a left-sided pyelonephritis 25 days after surgery, that was treated with a double-J stent placement [18].

A total of 11 grafts were lost (18.6%), leading to an overall surgical success of UTx, defined as normal blood flow post-transplantation with regular menstruations at 4-month follow-up [26], of 71.4%: surgical success was achieved in 75% of laparotomic LD-UTx, which was lower than laparoscopic LD- UTx (100%) and robotic LD-UTx (90%). Main causes for graft loss include vascular thrombosis (8 grafts), recurrent infections (1 graft), venous outflow obstruction (2 grafts) and poor reperfusion after vascular declamping (1 graft) [14-18,22,23,26,33-35]. Mean time from transplant to graft failure was 50.3 ± 72 days [33].

Twenty-nine live births from LD-UTx have been reported so far (Tab. I), 4 after robotic living donor hysterectomy and 25 after laparotomic procedure [15-19,22-27,30,35]. Almost all deliveries were by Caesarean section and have all occurred with a median gestational age at birth between 35 completed weeks (range: 31-38,weeks) [2] and 36 weeks 6 days (range: 30.1 to 38.0, weeks) [34].

DISCUSSION

Uterus transplantation is unique in the field of solid organ transplantation, since it is not intended to cure a chronic illness leading to death of progressive worsening of quality of life, but it aims at restoring anatomical normalcy in women with UFI, giving them the possibility of carrying their own pregnancy and delivering their children. In this view, UTx represents an alternative treatment for UFI to adoption or gestational surrogacy [35]. Moreover, UTx is a temporary transplant, because it can be removed once the mother has delivered her child or children, and the ability to give a live birth represents the measure of the success of this transplantation, rather than its longevity [35].

The first report of the Registry of the International Society of Uterus Transplantation [2] reported 45 UTx procedures with 19 newborns, most of which (78%) were performed from a living donor (LD), but with additional personal communications from all centers discussed at the Third International Congress of the International Society of Uterus Transplantation and press release a total of 91 UTx (71 LDs and 25 DDs) have been performed worldwide, resulting in 49 live births, 40 after LD UTx and 9 after DD UTx [31-33,36]. In this systematic review, we explored the surgical outcomes for donor and recipients of 59 LD-UTx, whose details have been fully described in literature.

Uterus transplantation from living donor has many advantages compared to UTx from deceased donor: living donors have a complete clinical and radiological assessment, including uterine vasculature, that is not feasible in deceased donors. In uterus living donors, the magnetic resonance angiogram (MRA)could be useful to acquire valuable details of uterine arteries. However, in 43% of cases the uterine arteries may be not fully visualized by MRA and this mandates the need for a computed tomography angiography [37]: however, magnetic resonance, MRA and computed tomography angiography are equally efficient in estimating the diameter of uterine arteries [36,37].

Living donor UTx is a preventable procedure and the recipient assessment could be more accurate; deceased donor procurement technique, although faster and potentially simpler, is not standardized and may conflict with the procurement of vital organs and only 1-8.5% of all potential deceased donors are finally considered potentially suitable for uterus transplantation [36,38,39]. However, like in every organ transplantation from a living donor, we should keep in mind that there are potential life-threatening complications for the donor and that UTx is not a life-saving transplant, so that only slight harm to donor is acceptable [26]. Indeed, living donor hysterectomy is a challenging and long surgical procedure with a higher risk compared to conventional hysterectomy. The long surgical duration for donor surgery in LD-UTx may increase the risk of thrombo-embolic events, particularly pulmonary embolism: this life-threatening complication may be prevented, but not eliminated, with pre-operative and post-operative anticoagulation and early mobilization after surgery [40]. If the living donor hysterectomy is performed in a premenopausal LD, there is an increased risk of early menopause [41] due to the injury of ovarian blood flow and excision of the ovaries, which could lead in turn to long-term health risk, because of the sudden cessation of ovarian-derived estradiol which will increase the long-term risk for cardiovascular disease [41].

Living donor hysterectomy is a time-consuming surgical procedure, mostly due to the dissection of the ureteric tunnel: Robotic living donor hysterectomy had the longest mean operative time (11h 45 min ± 2 h 21 min), compared to laparoscopic approach (3 h 30 min ± 0 h 33 min) and laparotomic surgical technique (8 h 10 min ± 30 min), but resulted in lower blood loss and post-operative stay.

Table I. Analysis of living donor uterus transplantation reported in literature.

Reference	Year	Number of cases	Donor age	Recipient age	Relationship	Indication for transplant	
Fageeh et al. [43]	2000	1	46	26	Unrelated	Hysterectomy for post-partum bleeding	
Brännström et al. [12]	2014	9	52, 54, 58, 61, 50, 53, 50, 37, 52 (total 53.0 ± 7.0)	33, 38, 28, 27, 35, 27, 28, 33, 35 (total 31.5 ± 3.9)	Mother (5), Mother-in-law (1), Mother's sister (1), Sister (1), Unrelated (1)	MRKH (8), Hysterectomy for cervical cancer (1)	
Brännström et al. [12, 49,50,79]	2020	8	49, 62, 55, 48, 45, 57, 37, 46 (total 49.8 ± 7.8)	22, 32, 33, 29, 24, 30, 31, 23 (total 28 ± 4.3)	Mother (6), Sister (1), Unrelated (1)	MRKH (8)	
Wei et al. [46]	2017	1	42	22	Mother	MRKH	
Puntambekar et al. [47,48]	2018	4	45, 42, 48, 47 (total 45.5 ± 2.6)	26, 21, 24, 30 Total (25.2 ± 3.7)	Mother (4)	MRKH(4)	
Testa et al. [51-53]	2020	13	42, 56, 45, 34, 36, 39, 35, 48, 32, 33, 39, 32, 43 (total 39.5 ± 7.1)	31, 33, 34, 29, 27, 24, 22, 29, 20, 23, 30, 21, 31 (total 27.3 ± 4.7)	Unrelated (12), Related (1)	MRKH (11), Myomectomy (2)	
Testa et al. [51-54]	2021	8	30, 30, 37, 32, 38 (total 33.4 ± 3.8)	30, 34, 33, 34, 29 (total 32 ± 2.3)	Unrelated (5)	MRKH (5)	
Akouri et al. [55]	2020	1	50	24	Mother	MRKH	
Fronek et al. [74]	2021	6 (1 not transplanted)	53, 58, 47, 49, 48 (total 51 ± 5)	30, 26, 23, 25, 26 (Total 28 ± 3)	Mother (4), Mother's sister (1)	MRKH (5)	
Brucker et al. [56]	2020	5 (1 not transplanted)	46, 46, 56, 32 (total 45 ± 9)	23, 23, 32, 35 (total 28 ± 6)	Mother (3), Sister (1)	MRKH (4)	
Viera et al. [45]	2021	1	50	33	Unrelated	MRKH	
Carmona et al. [44]	2021	1	NA	31	Sister	MRKH	
Ayoubi et al. [57]	2022	1	57	34	Mother	MRKH	
Deans et al. [17]	2023	1	47	25	Unrelated	MRKH	
Jones et al. [18]	2023	1	40	34	Sister	MRKH	

MRKH: Mayer-Rokitanski Küster-Hauser syndrome; NA: not available; NR: not reported; C-D: Clavien-Dindo Classification.

	Surgical technique	Donor's operative time (hr)	Blood loss (mL)	Complications (C-D grade)	Post-operative discharge (days)	Graft failure	Success rate	Live birth
	Laparotomy	NA	NA	Intraoperative ureteric injury (NA)	NA	Yes (graft failure for vascular thrombosis)	0%	0
	Laparotomy	12.1 (mean)	922 ± 772	Nocturia (1) Wound Infection (2)Ureterovagina fistula (3b) Unilateral sensibility (2) Impairment of the tigh (1)	6	2/9 (1 graft failure for graft thrombosis, e 1 for recurrent infections)	75%	9
	Robotic	11,5 ± 0.9	500 ± 221 (mean)	Gluteal pain (NA) Pressure Alopecia (2) Pyelonephritis (3b)	5 (7 NR)	2/8 (2 hysterectomy for graft necrosis)	75%	1
	Robotic	6	100	None	5	No	100%	1
	Laparoscopic	3,5 ± 1.1	100	None	7 (2) + 6(2)	No	100%	NR
	Laparotomy	6.5 ± 0.7	873 ± 441 (mean)	Leg Buttock Pain (1) UTI (6 patients, 1) Vaginal cuff dehiscence (3b) Depression (2) Faecal impaction (1) Anemia (2) Symptomatic anemia (4a) Prolonged inthubation Hemorrhage	5.2 (mean)	5/13 (2 outflow obstruction, 1 arterial thrombosis, 1 poor reperfusion, 1 graft ischemia)	62%	11
	Robotic	10.5 ± 1.2	114 ± 66.9	Ureteral Bool clot (3b) Temporary alopecia (1) Bilateral ureteral injury (3b)	4 (mean)	No	100%	1
	Laparotomy	10	900	NA	7	No	100%	1
	Laparotomy	6 ± 0.5	500 ± 440 (mean)	Bladder Hypotonia (2) Ureter laceration (3a) Climateric symptoms (NR)	8 (mean)	1/5 (1 venous thrombosis)	80%	2
	Laparotomy	10 ± 1	100 (mean)	Climateric symtpoms (1), Hydroureteronephrosis (3b)	12.7 ± 1.5	No	100%	2
	Robotic	8	NA	None	2	No	100%	NR
	Robotic	10	NA	None	4	no	100%	NR
	Robotic	13	150	Ureteral injury (3b)	11	no	100%	1
	Laparotomy	10	750	No bladder sensation initially	8	No	100%	NR
	Laparotomy	8	900	None	5	No	100%	NR

Table II. Clavien-Dindo classification of surgical complications.

Grade	
I	Any deviation from the normal post-operative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions
	Acceptable therapeutic regimens are: drugs as antiemetics, antipyretics, analgesics, diuretics and electrolytes and physiotherapy
	This grade also includes wound infections opened at the bedside
II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions, antibiotics and total parenteral nutrition are also included
III	Requiring surgical, endoscopic or radiological intervention
IIIa	Intervention under regional/local anesthesia
IIIb	Intervention under general anesthesia
IV	Life-threatening complication requiring intensive care/intensive care unit management
IVa	Single-organ dysfunction
IVb	Multi-organ dysfunction
V	Patient death

The complication rate was 54.2%, although most of the reported complications were C-D classification Grade I-II, but seven donors required a surgical re-intervention for a postoperative complication. Most of surgical complications were related to the urinary system, mostly related to the difficult dissection of deep uterine veins close to the ureteric tunnel, with laceration and thermal injuries to the ureter [26,41]. Alternative strategies to reduce the incidence of such complications include using the ovarian branches of the utero-ovarian veins with anastomosis to the external iliac veins, without the need for oophorectomy [35], the use of ureteric stents and the use of indocyanine green to identify ureters and vessels [26,41].

The most common complication after uterus transplantation is graft failure: a recent review [33] reported an overall graft failure of 19.8% (19/96), 16.9% (12/71) from living donors and 28% (7/25) from deceased donors. Among the 59 LD- UTx reported in literature, a total of 11 grafts were lost (18.6%), leading to an overall surgical success of UTx of 71.4%: surgical success was lower in laparotomic LD-UTx (75%) compared to robotic (90%) and laparoscopic LD-UTx (100%). The main causes of graft failure were vascular thrombosis (8 grafts), and venous outflow obstruction (2 grafts) [14-17,22,23,26,33,35]. Uterus transplantation from living donor resulted in 29 live births, almost all by Caesarean section. Among the 18 live births reported by Johannesson et al. [42], planned term deliveries occurred in 44% (8/18) of live births, while unplanned deliveries occurred more frequently in women with spontaneous preterm labor, severe rejection, subchorionic hematoma, and placenta previa. Almost half of UTx neonates may require at least 1 day in neonatal intensive care [42], mainly due to respiratory distress syndrome [16]. Although children born after UTx are *in utero* exposed to immunosuppression, most of the infants had a neonatal course that reflected the gestational age at delivery, and no baby was born with an identified malformation or organ dysfunction [43]. At 2-year follow-up, all children's growth and physical, neurological and cognitive developments were age appropriate within the first 2 years of life [44]. Histocompatibility, like in other solid organ transplantation, may have a role in reduced graft function: however, most of LD-UTx are performed using intrafamilial LDs and this significantly reduces the risk of acute rejection [5]. At our center, UTx recipients from deceased donors usually receive an induction therapy with thymoglobulin+steroids and a maintenance therapy with tacrolimus, mycofenolate and steroids. Mycofenolate is usually replaced with azathioprine 6-8 months after transplantation, when the first embryo transfer could be planned [45]. However, Jones et al. [46], suggested that, although azathioprine is safe to take during pregnancy with no increased risk of congenital abnormality, there is an association with pre-term delivery and low birth weight.

Uterus transplantation is a temporary transplant, and graft hysterectomy (GH) is planned either at the time of delivery or at a later date [22,47]. While GH is usually performed with a traditional open approach, Finotti et al. [48] recently presented the first 2 cases of robotic GH in UTx. The advantages of robotic technique are a better control of hemostasis, better operative field vision particularly useful in presence of adhesions, and superior intra-operative maneuverability, together with less postoperative pain and a shorter length of stay [48]. Brucker et al. [49] reported the first successful laparoscopic GH three months after delivery in a young LD-UTx recipients who developed a bilateral hydronephrosis during pregnancy with impaired renal function.

With increasing experience, it is likely that UTx could be offered to a growing number of women with UFI, not only because of MRKH syndrome but also for hysterectomy for benign disease [50]. Although there is a general agreement that UTx could be beneficial for women with UFI [10-12], in USA only 45% of surveyed reproductive endocrinologists and gynecologists felt UTx could be a safe alternative for UFI patients, due to the potential high risk of medical and surgical complications [51]. Another important issue is the costs of UTx. In many countries, UTx is not covered by public healthcare system: a recent study from Denmark [10], evaluated the estimated total costs for LD UTx at € 93,850, including pre-operative investigations, transplantation

surgeries, 2-year follow-up with IS, and hysterectomy and the authors concluded that the potential benefits of UTx do not justify the associated risks and costs of the procedure [10]. In this view, UTx may represent an inappropriate use of limited healthcare resources towards of life-threatening conditions that should prioritized over non-life-saving conditions such as UTx [52].

One of the major limitations for the widespread adoption of UTx as treatment for UFI is the donor availability. A potential recipient rarely has a suitable LD and very few females have uteri suitable for donation [41]. One possible solution is the non-direct LD uterus donation which has been extensively practiced with success [24,27], especially with the use of robotic hysterectomy. However, a special care should be devoted to donors < 40 years, where an extensive psychological assessment is mandatory to be certain that would not later regret their permanent loss of childbearing capacity [41]. Another option to increase the donor pool would be to reuse a transplanted uterus after planned hysterectomy in a first recipients after a live birth [41], since the uterus could be easily procured with long vascular pedicles, but the chronic rejection and the progressive aging of the uterus could significantly affect the outcome of a re-transplanted uterus. Another potential way to increase the donor pool is to accept older donors, as already done in other solid organ living transplantations: with a careful pre-donation imaging evaluation of uterine arteries calibers [37], LD Utx is potentially feasible even from donors > 60 years [16]. Another futuristic opportunity is the bioengineered uterus, which could overcome the shortage of suitable uterus donor by using a scaffold, which is colonized by the patient's own cells to generate patient-specific uterine material [41], as has been already reported for liver 3D bioprinting [53].

CONCLUSIONS

Uterus transplantation represents the last frontiers in the management of women with uterine factor infertility and it is the results of a fully multidisciplinary process involving many professionals in the field of transplantation and gynecology. However, living donor UTx is still considered an emerging procedure and, as this, it carries many un-explored potential challenges including the potential risks for donors, and the efficacy of UTx in the recipients, giving the potential harm of immunosuppression in a recipient of a non-life-saving organ. Moreover, there are many debates about the ethical feasibility and acceptability and, above all, sustainability of UTx transplantation, that should be evaluated on a basis of cost-to-benefit ratio. However, as experience increases, safety and efficacy for the LD, recipient and child will improve, and costs will probably decrease, and this could be a step forward to pave the way for UTx to become the preferred infertility treatment for women with UFI.

Conflict of interest statement

The authors declare no conflict of interest.

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Author contributions

MV, PS, PV: substantial contributions to the conception or design of the work; MG, GR, RG, GR, CDG, MS: the acquisition, analysis, or interpretation of data for the work; MV: drafting the article; PV: revising it critically for important intellectual content; MV, PV: final approval of the version to be published.

Ethical consideration

Not applicable.

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