Mayer-Rokitansky-Küster-Hauser syndrome patients' interest, expectations and demands concerning uterus transplantation

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Original Article

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ABSTRACT

Objective: To better understand patients' conditions and expectations before starting a uterus transplantation (UTx) program for women suffering from Mayer-Rokitansky-Küster-Hauser syndrome (MRKH syndrome).

Method: A web-based survey was conducted among MRKH patients via the French national association network from March to August 2020. The questionnaire comprised twenty-eight questions about their desire for parenthood, their condition's characteristics and previous reconstructive procedures, opinions and knowledge about UTx.

Results: Among the 148 participants, 88% reported a desire for parenthood, and 61% opted for UTx as their first choice to reach this aim. The possibility of bearing a child and having the same genetic heritage were the main motivations. Once informed about the usual course of an UTx protocol, only 13% of the participants changed their mind and 3 out of 4 of them opted for UT.

Conclusion: Uterus transplantation seems to be the first option to reach motherhood in patients suffering from MRKH syndrome. The development of UTx programs could meet the demands of this already well-informed population.

Keywords : uterus transplantation, infertility, Mayer–Rokitansky–Küster–Hauser syndrome, nation-wide survey.

INTRODUCTION

Uterus transplantation is a new opportunity for women suffering from absolute uterine factor infertility (AUFI) to access motherhood. AUFI patients are deprived of a uterus either from birth, the Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome being the main congenital cause with a prevalence estimated at 1 in 4500 women(1) ; or linked to iatrogenic causes of AUFI (mainly due to hemostasis hysterectomy or cervical cancer surgery). The prevalence of these surgery-related causes varies from one country to another due to differences in post-partum hemorrhage care and cancer management(2) ; precise data is still needed to this day.
Uterus transplantation is the only opportunity for these women to be the bearing mother, the genetic mother and the legal mother of the child to be. Since the first live birth after UTx achieved by the Swedish team led by Pr Brannstrom in 2014 (3), more than 80 UTx procedures have been performed around the globe and at least 40 children were born (4),(5). Some teams work with living donors (LD) (Saudi Arabia(6), Sweden (7), Germany (8), China (9) and India (10)), others with brain-dead donors (DBD) (Cleveland (11), Brazil (12)), and others with both strategies (Dallas (13), (14), Czech Republic(15)). Live births were achieved with both types of donors (16),(5). The MRKH syndrome is the most frequent indication for UTx, accounting for more than 90% of all the UTx reported to date(5).

To this day, in most countries, UTx is mainly available after inclusion in clinical trials. These clinical trials all over the world included highly selected women with strong assessments of clinical and psychological aspects, but the volume of demand of UTx and AUFI woman wishes were unknown.

We conducted a survey in order to define patients' demands concerning UTx. This survey delved not only into how many women would be interested in participating in the program, but also what their background, expectations, and knowledge on this new field of reproductive care were. The aims of this study are to identify MRKH syndrome patients' demands concerning parenthood, to better characterize their condition (type 1 or 2, reconstructive surgery eventually performed previously) and their knowledge of UTx.

MATERIALS AND METHODS:

This study is an opinion survey carried out prospectively from the 1rst March 2020 to the 1rst August 2020. The web-based questionnaire was created on the Drag'n Survey website according to the data protection legislation, and submitted as a link (https://www.dragnsurvey.com/survey/r/977f83d) on the French "Rokitansky syndrome" Association (https://asso-markh.org).

Patients

All the women suffering from the MRKH syndrome were invited to take part in the survey through the association's website and social media.

At the time of our study, the association had 70 members, and 266 subscribers on their Facebook page (patients, but also relatives). The questionnaire was anonymously completed by volunteers. Participants could withdraw their contribution to the study any time.

Questionnaire

This 28-questions survey was divided in 4 sections:

- Demographics: patients' age, professional situation, personal situation (in a relationship, or single), presence of a child or more in the household or not, and if so the circumstances, desire for parenthood or absence thereof.
- Characteristics of the MRKH syndrome: diagnosis circumstances, type, reconstruction procedure or not and if so, type of reconstruction (surgical or non-surgical), and if so, surgical technique (Vecchietti, Davydov, McIndoe, other).
- Knowledge about UTx: self-assessment of their awareness about available options to access parenthood, first choice concerning parenthood, UTx development around the globe, number of live children born through UTx, type of donors, opinion concerning the spread of the procedure and comments.

Summarized information about UTx was then delivered: state of the art, requirements (IVF…), surgical procedure and complications.

- Opinion after receiving the previously mentioned information: change in opinion on their first choice concerning parenthood, will to contact a team involved in UTx in France, opinion on geographic distance of the center as an obstacle for patients, opinion on funding (Social security, donation).

The questionnaire can be found in supplementary data.

Data analysis

Data were registered in an Excel© sheet (2018, version 16.16.20). For each question, the percentage of missing answers was calculated ; for qualitative data percentages were calculated, and for quantitative data median and measures of statistical dispersion were calculated. A two-tailed Fisher's exact test was conducted for categorical variables, using the TGV biostat software from Sorbonne-Paris University based on the R statistic software for its calculations **(**http://biostatgv.sentiweb.fr**).** Missing data were not included in the statistical analysis.

Ethics:

This study was approved by the local ethics committee.

RESULTS

One hundred and forty eight women took part in this study ; all the demographics are summarized in Table 1. Ninety six percent (142/148) of the women were of bearing age. Most participants (88.4%, 129/136) expressed a desire for parenthood, and only 9% (13/136) had at least a child in the household (56% through gestational surrogacy, and 44% through adoption). Two out of three women presented with type 1 MRKH syndrome. Seventy-six percent of the participants (101/132) had undergone a reconstructive procedure, either Frank's method (55%) or a surgical procedure (45%). Seventy percent of the surgical procedures did not include digestive tract tissue (Vecchietti, Davydov or McIndoe techniques). Participants' disease characteristics are presented in Table 2.

Only 31% (36/115) participants felt they were well informed about the options available to access parenthood. Nevertheless, their knowledge about UTx was good (UTx already happening in the world, type of donors, live births). Sixty-one percent of the participants stated UTx as their 1rst choice to access motherhood (70/115) ; 87% (84/97) were for or rather for UTx spread in their country. The two main motivations were the possibility to bear the child and having the same genetic heritage. Only 7% of the interrogated women opposed the spread of the technique, stating the risks and complications of the surgery for living donors (62%) and the need for immunosuppressive therapy (46%). Data about participants' knowledge about UTx are shown in Table 3.

Patients against or rather against UTx spread were significantly older than women for or rather for UTx spread ; thus, 29% (2/7) of the women against or rather against UTx spread

were 42 or older, against only 1% (1/84) of the women supporting UTx spread (P=0.019). No statistical difference was found concerning their personal situation, their desire for parenthood, or the presence or absence of a child within the household. Once informed about the usual course of a UTx protocol (brief state of the art, oocyte stimulation, surgery and its complications, the need for immunosuppressive therapy), only 13% (11/97) changed their mind about their first choice to access parenthood, and 73% (8/11) of these women opted for UTx. Thus, once informed, more MRKH syndrome women were in favor of UTx. Geographic distance between the patients and the center was an obstacle to their participation in a UTx protocol for 28% (26/92) of them. A strategic distribution of UTx centers must therefore be established on a national scale. All the information reported after information about UTx are shown in Table 4.

DISCUSSION

Our study shows the motivation and interest for UTx among patients suffering from MRKH syndrome. The association is composed of only 70 members (MRKH patients) and 266 people (MRKH patients but also relatives, friends) are followers of their Facebook page. In one week, a hundred women had taken part in this study, which shows a great interest for UTx in this population.

In 2015, the French team of the Limoges University Hospital had conducted a similar survey among women suffering from AUFI (MRKH syndrome patients but also women who had undergone a hemostasis hysterectomy)(17). The questionnaire had been distributed before the publication of Pr Brännstrom's team technical success(7) and before the first livebirth(3). Sixty women had participated in the survey, 85% of them suffering from MRKH syndrome ; adoption and surrogacy were not acceptable options for 32% et 35% of them respectively. Uterus transplantation was an acceptable option for 77% of them, and 58% were motivated to get involved in a UTx clinical trial. This interest in UTx was therefore already important despite the lack of results in terms of feasibility and success back in 2015. In our study, this interest was shown to be stable as 70% of the participants were considering UTx as a first option. Only a third of the surveyed women felt well informed about the three options available to them, but once thorough information was given about the course of a UTx protocol, 13% of them changed their mind about their first choice, mainly in favor of UTx (73%).

In other countries, similar surveys were conducted prior to clinical trials. Chmel et al(18) sent a questionnaire to 90 patients with MRKH syndrome who had undergone a

Vecchietti procedure between 2003 and 2013 ; 50 (58%) responded. Sixty-two percent of them were interested in UTx, and the questionnaire helped select the nine first recipients of UTx in the first Czech clinical trial. A British study was conducted among women diagnosed with AUFI — 50% of them suffering from MRKH syndrome — with questions repeated before and after a short educational intervention via video and a questions and answers session(19). Forty women were interrogated: all of them supported UTx, and 87.5% of them would undergo UTx ahead of surrogacy or adoption, knowing full well that these two other options were safer. However, a selection bias may exist in both studies: Czech participants received a questionnaire at home stating clearly that it also aimed to select patients for a clinical trial to come, therefore it cannot be excluded that women opposing UTx did not respond to the questionnaire ; the latter study recruited women who had contacted them, seeking information and already interested in UTx.

To date, the largest study was published by the Cleveland team: a sixty-items questionnaire submitted to the members of the Beautiful You MRKH Foundation via their social media gathered the opinion of 281 women(20). Participants from 31 different countries, mostly from the U.S (71.7%), answered questions about their knowledge about UTx, then received a short information about the procedure, with its risks and benefits, and answered again the same questions, as well as demographics, financial and ethical perspective on UTx. Results showed that 73% would consider receiving a uterine transplant, and most of them (67%) considered the benefits outweigh the risks, and that it was an ethical procedure (82%). However, authors acknowledged that most of the respondents were white, educated, employed and insured, which only represents a subset of the patients with MRKH ; furthermore, even though the number of participants is higher than the previous studies, it only represented 7.6% of the total number followers on the Facebook group of the Foundation. An Australian study using the same diffusion strategy with a fifty-items online questionnaire found that among the 57 AUFI respondents (82% of MRKH patients), all of them knew of UTx to varying degrees, and eighty percent of them thought there was a need for UTx in their country(21). After receiving a short information about the procedure, 60.9% would still consider it despite the risks, 39% of them indicating they would immediately apply for UTx clinical trials. Among the women desiring parenthood, more than two thirds of them indicated a strong desire to carry their own child. Interestingly, contrary to our own results, there was a significantly negative association with age (with a 35 years threshold) and the need for UTx (OR: 0.88 ; p=0.043).

In a 2014 Japanese study, among 3098 women of bearing age (25-39 ans), 35% of them were in favor of UTx(22). This small percentage could be explained by the fact that, the respondents being from the general population, most of them were fertile (86%) and therefore not concerned by the topic ; furthermore, there was still no proof of the feasibility of UTx then (only 18% of the respondents were aware of its existence) and cultural differences may interfere in a comparison with European countries. In 2013, a Swedish opinion survey concerning the development of assisted-reproductive technologies was similarly conducted in the general population and found that among the 1661 participants 80% were in favor of the spread of uterus transplantation(23). A web-based survey conducted in 2016 in the US found that among 1444 participants, 78% supported UTx and 66% thought it was an acceptable alternative to gestational surrogacy (24).

In our study, the main motivations for UTx were the possibility of bearing a child (89% of the respondents) and having the same genetic heritage (60%). Such demands are strong arguments in favor of the development of UTx, this procedure being the only option for these patients to bear their own child, meaning being the bearing, genetic, and legal mother of the child-to-be. Interestingly, UTx remains the first choice among AUFI women, even in countries where surrogacy and adoption are both available (18), (21), as opposed to the French situation where gestational surrogacy is not allowed. Therefore, even if surrogacy meets AUFI patients' demands for genetic motherhood, only UTx will enable them to bear their child, with all the symbolism associated. Furthermore, for French patients, the only option available is a long and uncertain process. In 2021, 5426 requests for adoption were being reviewed by the French agency for adoption. Only 55 adoptions were granted by the agency, 6.8% less than the previous year(25), and 252 international adoptions were identified by the authorities(26). Therefore, adoption is not enough to meet the demands of French couples and often does not meet their expectations. Most couples wish for the adoption of a caucasian child of three months or less, when only 6% of the adopted children in France are less than one year old and only 11% are Europeans(26). The administrative burden is also an important obstacle, the average waiting time being of 3 to 4 years, up to 9 years(25).

Our study was inherently limited by its design. The population is only a small sample of women with MRKH syndrome: it is estimated that 1 in 4500 women is born without a uterus in France(1). There is an obvious selection bias, as we can imagine that the women participating in this survey were amongst the most informed about the condition, and the most

motivated for UTx, as the questionnaire was distributed by the association's website. Nevertheless, we found that a well-structured information about UTx increased the proportion of women opting for UTx as their first option to reach motherhood by 13% in this already well-informed population, suggesting that in non-informed MRKH syndrome patients, this proportion could rise even more.

CONCLUSION

Our study showed the importance of the desire for parenthood in women with MRKH syndrome. These women were largely interested in UTx, the main motivation being the possibility of bearing their own child, a possibility offered neither by surrogacy nor adoption. Furthermore, the proportion of women suffering from MRKH syndrome does not seem to be impacted by gestational surrogacy being a legal option or not. Geographic distance seems to be an obstacle to the participation in a clinical trial ; therefore, UTx centers should be strategically located across the country.

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TABLES

Table 1: Demographics of the 148 participants.

	Number (%)	Participation (%)
Age (years)		148 (100)
< 25	50 (33.8)	
25-42	92 (62.2)	
> 42	6 (4)	
Profession		148 (100)
Independant	5 (3,4)	
Employee	101 (68.2)	
Student	27 (18.2)	
Unemployed	12 (8.2)	
Other	3 (2)	
Personal situation		147 (99.4)
Couple	116 (78.9)	

Single	31 (21.1)	
Desire for parenthood		146 (98.6%)
Yes	129 (88.4)	
No	17 (11.6)	
Child within the household		146 (98.6%)
Yes	13 (8.9)	
No	133 (91.1)	
Circumstances for children (N =13)		9 (69.2%)
Surrogacy	5 (55.6)	
Adoption	4 (44.4)	
Uterus transplantation	0 (0)	

Table 2: Patients' syndrome characteristics.

	Number (%)	Participation (%)
Diagnosis		132 (89.2)
Childhood	16 (12.1)	
Adolescence	96 (72.7)	
Intercourse	19 (14.4)	
Others	1 (0.8)	
Mayer-Rokitansky-Küster-Hauser type		132 (892)
1	85 (64.4)	
2	41 (31.1)	
Unknown	6 (4.5)	
Reconstruction		132 (89.2)
Yes	101 (76.5)	
No	31 (23.5)	
Age at reconstruction (years) (N=101)		64 (63.4)
Median	17	
Minimum	14	
Maximum	25	
Reconstructive procedure (N=101)		101 (100)
Frank's method	56 (55.5)	
Surgery	45 (44.5)	
Type of surgical reconstruction (N=45)		45 (100)
With digestive tract tissue	14 (31.1)	
Without digestive tract tissue	31 (68.9)	
Reconstruction without digestive tract		23 (74.2)

(N=31)		
Davydov	9 (39.1)	
Vecchietti	9 (39.1)	
Others (McIndoe..)	5 (27)	

Table 3: Knowledge about the technique among participants. IS: immunosuppressive.

	Number (%)	Participation (%)
Feeling well informed		115 (77.7)
Yes	36 (31.3)	
No	68 (59.1)	
Does not know	11 (9.6)	
First choice		115 (77.7)
Surrogacy	23 (20)	
Adoption	22 (19.1)	
Uterus transplantation	70 (60.9)	
Uterus transplantation already performed in women		115 (77.7)
Yes	113 (98.2)	
No	1 (0.9)	
Does not know	1 (0.9)	
Live birth from a uterus transplantation		115 (77.7)
Yes	102 (89.5)	
No	5 (4.4)	
Does not know	7 (6.1)	
Number of live births from uterus transplantations		115 (77.7)
Median	7	
Minimum	1	
Maximum	15 000	
Uterus transplantation possible with living donors		97 (65.5)
Yes	88 (90.7)	
No	3 (3.1)	
Does not know	6 (6.2)	
Uterus transplantation possible with deceased donors		97 (65.5)
Yes	83 (85.6)	
No	8 (8.2)	
Does not know	6 (6.2)	
Spread of uterus transplantation		97 (65.5)
For	74 (76.3)	

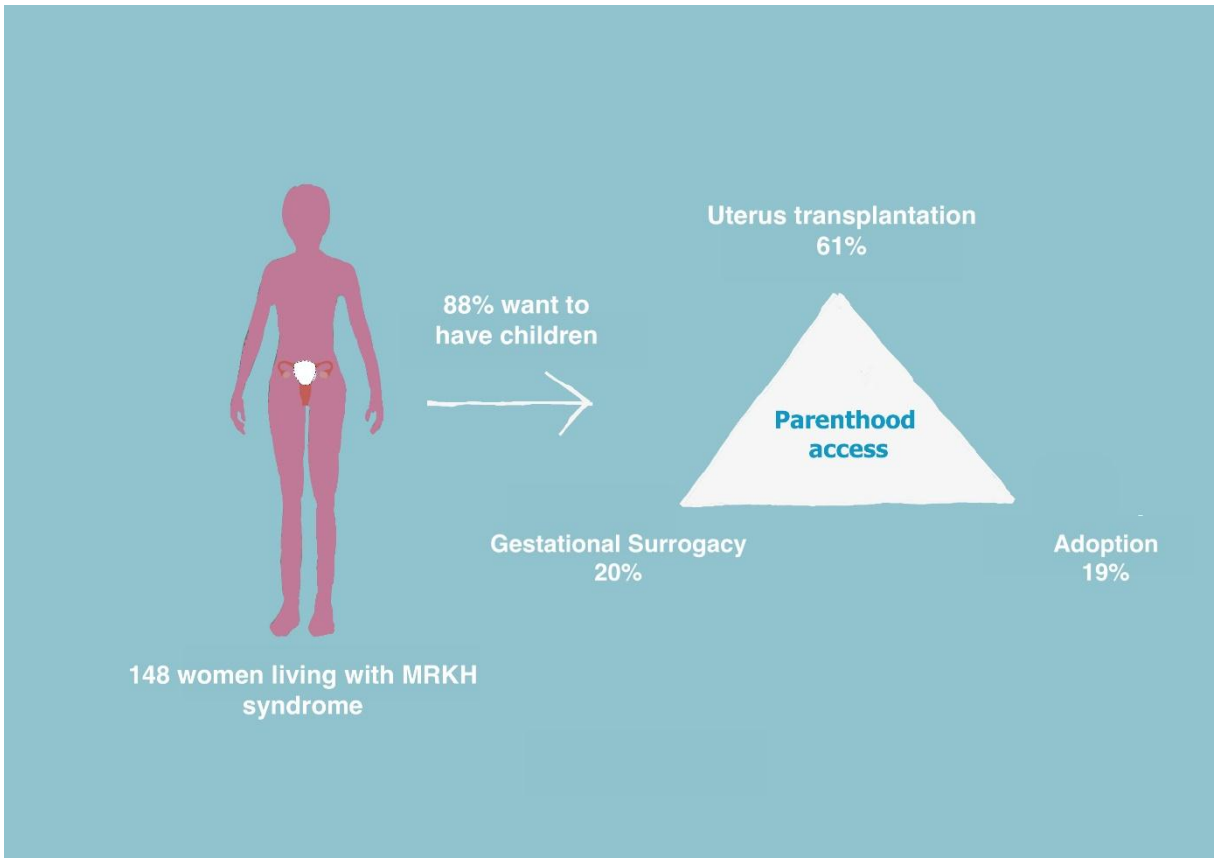
Rather for	10 (10.3)	
Rather against	3 (3.1)	
Against	4 (4.1)	
No opinion	6 (6.2)	
Justification for the spread of uterus transplantation (N=90)		89 (98.9)
Bearing their own child	80 (88.9)	
Same genetic heritage	54 (60)	
Temporary immunosuppressive therapy	11 (12.2)	
Hysterectomy at the end of pregnancy	9 (10)	
Other	2 (2.2)	
Justification against the spread of uterus transplantation (N=13)		9 (69.2)
Complications for donors	8 (61.5)	
IS therapy for the recipient	6 (46.2)	
IS therapy for the fetus	3 (23.1)	
Fear of the surgery	2 (15.4)	
Transplantation only for vital organs	0 (0)	
Other	0 (0)	

Table 4: Answers after information about Uterus Transplantation. UTx: uterus transplantation. OBGYN: obstetrician-gynecologist.

	Number (%)	Participation (%)
Change of mind		88 (68.8)
Yes	11 (12.6)	
No	76 (87.4)	
If so, in favor of which option (N=11)		11 (100)
Surrogacy	2 (18.2)	
Adoption	1 (9.1)	
Uterus Transplantation	8 (72.7)	
Did you discuss UTx with your OBGYN ?		93 (62.8)
Yes	23 (24.7)	
No	70 (75.3)	
Did you contact the Limoges team ?		94 (63.5)
Yes	11 (11.7)	
No	83 (88.3)	
Is geographic distance an obstacle ?		92 (62.2)
Yes	26 (28.3)	

No	54 (58.7)	
No opinion	12 (13)	
Funding		92 (62.2)
100% by Social Security	73 (79.3)	
In part by Social Security	18 (19.6)	
In part by the recipient	1 (1.1)	
Totally by the recipient	0 (0)	
Funding by a donation		92 (62.2)
Yes	48 (52.2)	
No	20 (21.7)	
No opinion	24 (26.1)	

Graphical abstract



Declaration of interests

☒The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: