

## Mayer-Rokitansky-Küster-Hauser syndrome: fertility counseling and treatment

To date, no literature has focused on the counseling of patients with Mayer-Rokitansky-Küster-Hauser syndrome as relates to their unique fertility challenges. This article is presented as a guide to practitioners in the counseling of patients with varying Mayer-Rokitansky-Küster-Hauser phenotypes regarding individual reproductive potential. (Fertil Steril® 2010; ■: ■–■. ©2010 by American Society for Reproductive Medicine.)

Mayer-Rokitansky-Küster-Hauser syndrome (MRKH) is a devastating diagnosis for a young woman to receive, carrying with it considerable medical, psychological, social, and reproductive implications. The syndrome is characterized by vaginal agenesis and typically is accompanied by cervical and uterine agenesis. Several variants exist, with 7% to 10% of patients exhibiting either an obstructed uterus or obstructed rudimentary uterine horns with functional endometrium (1). Much literature has focused on the absence of the vagina and various approaches to restoring functional anatomy.

Relatively little, in comparison, has been written on the fertility options for such patients; early on, the patient is informed regarding the ability to have a genetic child via gestational surrogacy, and further counseling typically surrounds solutions to create a functional vagina. It is our experience, however, that lack of innate reproductive potential has been one of the most emotionally detrimental aspects of this syndrome for our patients, and thorough fertility counseling a cornerstone of care between the patient with MRKH and her physician. We present the following as a guide for counseling patients with MRKH on the implications of their diagnosis as relates to their reproductive potential.

Various studies have reported on the emotional hardship associated with the realization of an inability to bear children. Survey of women receiving the diagnosis has revealed that, to some patients, infertility is the hardest psychological aspect of the condition to

accept (2–6). We do not shy away from these issues when conveying the diagnosis and its implications, but rather acknowledge their existence and offer services designed to explore the personal experience of the patient on an individual basis. We have found that an integrative approach incorporating medical care, psychological counseling, and, for those patients who are interested, group-based intervention allows for the best transition to post-diagnosis acceptance and understanding.

At the time of initial diagnosis, we discuss müllerian agenesis, whether complete or partial, and discuss its implications on child-bearing in simple-to-understand, non-medical language; we explain that lack of child-bearing does not preclude child-having and that patients today have the option of pursuing gestational surrogacy as a means to provide them with genetically related offspring. It is important to emphasize that, although most patients may never carry a pregnancy themselves, they can still, if they so choose, become mothers. Once patients reach initial acceptance of the diagnosis, we have found that they may have many detailed questions regarding their fertility options; we find that a separate physician session dedicated exclusively to fertility counseling is beneficial.

Age at diagnosis often differs dramatically between patients, ranging from infancy to early adulthood. For young children, counseling regarding reduced fertility potential and available options is targeted to the child's parents; similarly, when diagnosis occurs in late adolescence or adulthood, involvement of parents in counseling is determined by the preferences of the patient. The intervening ages, however, pose a challenge for the practitioner in terms of counseling. On the basis purely of our clinical experience, we make such decisions on a case-by-case basis according to the maturity of the patient, input from the patient's parents, and assessment by our entire multidisciplinary team.

Before the advent of assisted reproductive technologies, fertility options for women with uterine agenesis or bilateral rudimentary horns were limited to adoption. Today, however, "gestational" or "IVF" surrogacy allows for women unable to carry a pregnancy to have a genetically related child. Typically, the initial step in moving toward a gestational surrogate pregnancy is a referral to an infertility specialist, as these are the physicians who coordinate and perform ovulation induction in the genetic mother, as well as hormonal regulation and ET in the intended host. Often, however, it is the gynecologist or primary care physician who, for several visits, sees the patient before this referral, and it is helpful to

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have a thorough understanding of how the process works. Gestational surrogates are often sisters, cousins, or other related family who agree to carry a pregnancy for the patient; such arrangements typically do not involve the exchange of money between the two parties, and infertility expenses for the patient are limited to the costs of ovulation induction and transfer. Surrogacy agencies exist that provide unrelated gestational carriers to patients who do not have or do not wish to pursue a related surrogate, at a considerable financial cost.

Unfortunately, IVF cycles are quite expensive (7). Although expense varies across state and national borders, the cost of assisted reproduction remains for many patients prohibitive. Several nations do provide coverage as part of national health care, and several states now mandate coverage in the United States, albeit with limitations placed on number and type of treatments covered. Surrogacy, on the other hand, remains universally uncovered, with nonrelated surrogacy IVF costing anywhere between \$20,000 and \$120,000 in the United States, including surrogate agency broker fees, a fee paid to the surrogate, legal expenses, coverage of the gestational carrier's medical costs, and the price of ovulation induction and oocyte retrieval in the genetic mother (8). Once the initial grief of the diagnosis is overcome, we believe it is helpful to disclose the various financial and legal complexities of surrogacy arrangements with our patients, as much planning—logistic, financial, and psychological—is involved in such arrangements.

Our patients have found it helpful to know that other patients with the same condition have become mothers successfully. Because we are a referral center that sees a proportionally large number of patients with MRKH, we often connect patients via phone or E-mail, if mutual consent is provided, at various time points since diagnosis; in this way, patients feel less alone, and older patients who have successfully traversed vaginal dilation, surgical neovagina creation, adoption, or gestational surrogacy arrangements can act as mentors to younger patients facing daunting decisions. Our patients often have found the existing literature, while limited, helpful as well, and we share with them the fact that successful gestational pregnancies have been carried out for patients with MRKH, that IVF success rates are not diminished in this setting, and that evidence suggests that parenting and child development is not jeopardized as compared with naturally conceived families (9–13).

Rarely, absence of the vagina is associated with a normal midline uterus and isolated cervical agenesis. Clinical experience indicates that surgical connection between the obstructed uterus and a created neovagina is inadvisable, as ascending infection, recurrent obstruction, sepsis, and even death have been reported in this setting (14). Patients with MRKH with this specific phenotype are unique, however, in that they have the potential to carry a pregnancy in the obstructed uterus via zygote intrafallopian transfer (ZIFT) or GIFT. In fact, successful pregnancies have been reported (15). Such women thus can be offered continuous combination estrogen-progestin, progestin alone, or GnRH agonist with add-back treatment for menstrual suppression until conception is desired; at that time ZIFT or GIFT may be performed, with a planned abdominal delivery at term (1). Thus, hysterectomy should not be performed in this setting until thorough counseling regarding potential fertility has been performed. We recommend in cases of vaginal and cervical agenesis with a midline uterus that the uterus remain in place at least until the young woman is >18 years of age,

at which time she can make an informed decision for her own reproductive future.

Patients with MRKH with rudimentary uterine horns, in addition to receiving the above-mentioned counseling regarding gestational surrogacy and adoption, should be counseled on surgical removal of their uterine anlagen. In addition to amenorrhea, such patients often present with severe cyclic pelvic pain, as their obstructed horns, which contain functional endometrium, give rise to extensive endometriosis. Magnetic resonance imaging is helpful in determining whether a functional endometrium is present, in which case the hemiuteri should be removed. It also has been reported that women with MRKH without an obstructed uterus or hemiuterus can have endometriosis, and thus the diagnosis should be considered in these patients as well (16). As relates to the reproductive potential of such patients, endometriosis has been implicated in reduced responsiveness to gonadotropins, reduction in the number of oocytes retrieved, and worse overall IVF–intracytoplasmic sperm injection outcomes, although this has not been studied specifically in gestational carrier recipients who are not affected by endometriosis (17–19). Uterine horn removal for patients with MRKH thus should be viewed as an essential element of fertility preservation, as removal has been associated with resolution of endometriotic lesions (20).

Ovulation induction is typically straightforward in individuals with MRKH, with hormonal responses similar to those of women with normal pelvic anatomy (21, 22). Oocyte retrieval in patients with MRKH, however, poses several challenges and requires an experienced IVF physician well trained in less-conventional oocyte recovery. Vaginal elasticity is typically absent in a surgically reconstructed vagina, and to a lesser extent in dilated vaginas, making transvaginal oocyte recovery challenging. Moreover, the often high and lateral position of the ovaries along the pelvic sidewalls can make transvaginal retrieval technically difficult or impossible (21). Thus, laparoscopic or transabdominal recovery may be necessitated. It should be remembered that müllerian anomalies are associated with a high incidence of ectopically located gonads and that, in rare instances, an ovary may be congenitally absent, as the müllerian structures and gonads both arise from the genital ridge embryologically (23). Magnetic resonance imaging or other imaging modality should be used to locate ectopically located gonads before ovulation induction, as ovarian tissue may be found in the upper abdomen, at the level of the pelvic brim, or within the inguinal canal.

“Will my child have a uterus?” is a question we have often encountered. Typically, müllerian anomalies display multifactorial rather than genetic inheritance (24). We recently reported a case of monozygotic twins in which only one twin exhibited MRKH, lending evidence in support of this claim (25). A recent study performing mutational analysis of WNT, a gene family involved in regulation of müllerian duct development, failed to reveal a pattern of genetic inheritance involving this gene in subjects with MRKH (26). Women in whom MRKH presents as one aspect of a broader syndrome affecting numerous organ systems, however, may be more likely to pass such syndromes on to their offspring (27, 28). In a study of 58 women with MRKH undergoing infertility treatment with gestational surrogates, none of the 17 female infants born exhibited MRKH (29). In general, patients with MRKH should be counseled that their genetic offspring are likely to exhibit normal müllerian anatomy at birth; as yet, there is no genetic test that would

allow for preimplantation genetic diagnosis of the condition. Women in whom MRKH coincides with musculoskeletal, vertebral, or neurologic illness may be more likely to pass their disorders to their children, although more work must be done before such inheritance can be completely understood.

At this time, adoption and gestational surrogacy are the only fertility options available to patients with uterine agenesis. Although present options are limited, provocative research has been undertaken to explore the boundaries of therapy for such patients. Successful human uterus retrieval from multiorgan donors recently has been reported (30). Moreover, in 2000, a Saudi-Arabian woman who 6 years earlier had lost her uterus because of postpartum hemorrhage underwent human uterine transplantation from an unrelated 46-year-old donor undergoing hysterectomy; the patient had 2 months of endometrial proliferation and associated cyclic menses; however after 99 days acute vascular thrombosis developed necessitating transplant removal (31). To date, this is the only human uterine transplantation to have been attempted. Uterine transplantation has been investigated in various animals with

varying degrees of success, although pregnancy has not yet been achieved (32). Although we are far from being able to offer uterine transplantation as a therapy for patients with MRKH wishing to conceive, such research may pave the way to novel therapies allowing for pregnancy, in addition to motherhood, for women with congenital uterine agenesis. Although such therapies remain strictly experimental, we do disclose to our patients the existence of such research and its future prospects in the treatment of this disorder, as well as current research aimed at better understanding genetic inheritance patterns for syndromic MRKH.

As conveyed above, the implications of MRKH go far beyond vaginal agenesis; jeopardized fertility is an important element affecting patient well-being. The physician should thus be well equipped to counsel a patient with MRKH regarding her options for future fertility and to do so be well versed in the nuances of the diagnosis, as well as available therapies. Further research may provide novel therapies in the future, but currently gestational surrogacy remains the standard for women without uteri to create a family of genetic offspring.

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