REVIEW ARTICLE

Evaluation and management of cases of primary amenorrhoea with MRKH syndrome

N Akhter[1], B Begum[2]

Abstract

The Mayer-Rokitansky-Kuster-Hauser (MRKH) syndrome, the second most common cause of primary amenorrhoea usually remains undetected until puberty and is characterized by congenital aplasia or hypoplasia of the uterus and most of the vagina in women showing normal secondary sexual characteristics. MRKH syndrome may be isolated (type I) but is more frequently associated with renal, vertebral, and, to a lesser extent, auditory and cardiac defects (MRKH type II or MURCS association). Complete evaluation of MRKH patient includes genital, urinary tract, cardiac, spinal and auditory assessment which need multidisciplinary approach. This review is an attempt to discuss the subtypes, associated anomalies, diagnostic consideration and treatment recommendations of patients with MRKH syndrome and aimed to make the specialists of other discipline, general physicians and the gynaecologists well aware about the entity.

Bang Med J (Khulna) 2012; 45 : 24-29

Introduction:

Mullerian or paramesonephric ducts are the primordial anlage of female reproductive organs which are differentiated to form falllopian tubes, uterus, cervix and upper part of vagina. A wide variety of malformations can occur when this system is disrupted. The most widely accepted classification of mullerian anomalies is the AFS (American Fertility Society-1988) classification in which anomalies are categorized into seven classes.1 Among these, class-1 anomalies include hypoplasia or agenesis of vagina, cervix and in most cases uterus and fallopian tubes or any combination.2 MRKH syndrome is the most common example of this category. This syndrome was first described by Mayer in 1829 and Rokitansky in 1838. Uterine and vaginal agenesis were reported by Rokitansky and Mayer described some vaginal duplication.3 In 1910, Kuster recognized urologic association and in 1961 Hauser differentiated MRKH from androgen insensitivity syndrome (AIS).5 MRKH syndrome represents 15% of cases of primary amenorrhoea and is usually undetected until adolescence owing to the age appropriate developmental milestones and normal external genitalia.

MRKH syndrome is subdivided into two types: type I (isolated) and type II (Atypical) or MURCS association (Mullerian duct aplasia, Renal dysplasia and Cervical Somite anomalies). Type I (isolated) MRKH is less frequent than MURCS association.4 With the advent of improved techniques of reconstructive vaginal surgery,

increased number of centers including medical college hospitals are providing the service by experts with high success rate. More and more patients are demanding the treatment now a days to improve their quality of life. Moreover, as the patient have functional ovaries, most of them are becoming keenly interested to avail assisted reproductive techniques including IVF-ET to have their own genetic offspring.

This review article is aimed to make the gynecologists, specialists of other discipline and general physicians aware about the possible existence of associated anomalies with MRKH syndrome with primary amenorrhoea. These patients need evaluation which needs multidisciplinary approach with involvement of gynecologist, urologist, orthopedic specialist, radiologist, cardiologist, psychiatrist and some times audiologist and pediatric gynaecologist.3,4 This article will also provide the overview of types, aetiopathogenesis, updates of diagnostic aids and treatment options including fertility and psychological management of patients with MRKH syndrome.

Clinical presentation:

Primary amenorrhoea with or without cyclic lower abdominal pain usually is the first clinical signal. Patients of MRKH syndrome (Type-I) have normal female phenotype with normal secondary sexual characteristics without onset of menstruation. Pubic hair and breast development are of Tanner stage.5 Patients may seek treatment for infertility

with or without evaluating amenorrhea. Usually patients are of normal height with no sign of androgen excess.3,5 Speculum examination not possible owing to shallow blind vagina or a dimple. Per rectal examination may reveal cord like structure representing uterine anlage.

Associated malformations in MRKH type II or MURCS association are renal malformations (1540%) which includes unilateral agenesis (23-28%), ectopic kidney (17%) or horseshoe kidney (4%) may be discovered incidentally.3,6 Some patients may complain voiding difficulties, incontinence and

1. Nasreen Akhter FCPS, Asst. Professor of Obs & Gynae, Khulna Medical College, Khulna.
2. Badrunnesa Begum FCPS, Asst. Professor of Obs & Gynae, Khulna Medical College, Khulna.

recurrent UTI. Skeletal anomalies mainly involve the spine (30 to 40%) mostly scoliosis (20%) and less frequently anomalies of the face and limb extremities.4,13 Hearing defects, cardiac and digital anomalies (syndactyly, polydactyly) are reported.1,5 Reported cardiac malformations are aorto-pulmonary window, atrial septal defect and conotruncal defects such as pulmonary valvular stenosis or Tetralogy of Fallot.4,7,8

Aetiopathogenesis:

MRKH syndrome is one of the type-1 mullerian anomalies (AFS Classification-1988) present in one in 4500 female at births. Previously MRKH syndrome was thought to be a sporadic anomaly but increased number of familial cases support the hypothesis of genetic aetiology with more attention. In familial cases the syndrome appears to be transmitted as an autosomal dominant trait with incomplete penetrance and variable expressibility.4,8 The genetics of mullerian aplasia are complex. Wnt genes are responsible for differentiation and regulatory steps in development of female reproductive tract. Other genes involved are Hoxa genes located in chromosome 2,7,12 & 17.8 The fused caudal end of mullerian (paramesonephric) ducts form uterus, cervix, and most of the vagina in normal individual in embryonic life. When an interruption or dysregulation occurs in any of the dynamic process of differentiation, migration, fusion and canalization, a wide spectrum of mullerian anomalies can result. Well known factors are genetics and teratogens (e.g. DES, thalidomide).1,9 Complete uterine aplasia in the presence of two rudimentary horns linked by a Peritoneal fold and normal fallopian tubes correspond to isolated or MRKH type I syndrome.10 Type II MRKH is characterized by uterine symmetric or asymmetric hypoplasia or cord like rudimentary structures with associated anomalies. Other defects frequently accompany are developing kidneys and urinary system which are closely related to the reproductive system. Disruption of developing local mesoderm and its contiguous somites may cause some axial skeletal abnormalities.11, 12

At the end of the fourth week of fetal life, the blastemas of the lower cervical-upper thoracic somite arm buds and pronephric buds are in close proximity to one another.12 The MURCS association could be produced at that time by a teratogenic event and is considered as the consequence of developmental field defect.9,12 Ovarian function is preserved because the ovaries originate within the primitive ectoderm, independent of the ducts system.13

In 1979, Duncan et al reported nonrandom association of MURCS (MRKH type-II) and various other anomalies in 30 cases. So far 65 case reports of MURCS patients have been published.7,14 In these patients there was a high incidence of mullerian aplasia/hypoplasia (96%) renal agenesis or ectopy (80%) and vertebral anomalies (C5 - T1) (80%). In 1992, P. Mahajan et al in India described & analysed 7 cases of MURCS association of which all cases had absent uterus, 85% had cervical spine abnormalities, and 28% had renal agenesis or ectopy.11,14 Males with combinations of wolffian duct agenesis or severe hypoplasia with or without renal and/or skeletal anomalies and/or hearing impairment are reported. Interestingly, such male cases were found in families with female patients with MRKH syndrome demanding further research.4,15

Diagnostic methods:

a) Imaging Studies:

1. Abdomino-pelvic ultrasound is a simple and noninvasive method, and must be the first investigation in evaluating patients with suspected mullerian aplasia. It reveals an absence of uterus between the bladder and the rectum and is useful in detection of hematometra, hematocolpos, ovarian cysts, pelvic kidney if patient presents with pelvic mass.6,16 Ultransonography easily detect the upper level of the vagina and the length of its obstruction and also be used to identify uterine duplications and tubal obstruction. Simultaneously it allows assessment of renal system and spine abnormalities.

2. Magnetic resonance imaging (MRI) is a non-invasive technique that provides a more sensitive and specific means of diagnosis than ultrasonography and provides excellent images of superficial and deep tissue planes (Fig-1). It should be performed when ultrasonographic findings are inconclusive or incomplete. MRI includes assessment of subperitoneal structures including, cervix and uterine cavity and for searching associated renal and skeletal malformations.2,5,16 MR urography (MRU) can be used to visualise both the reproductive and the urinary system, as well as to evaluate functional status.

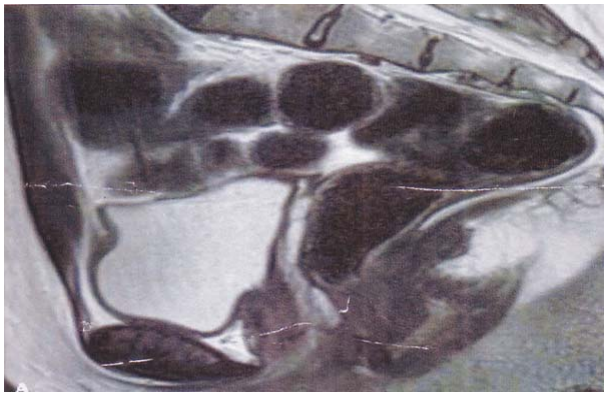

Fig 1 : MRI T2 weighted sagittal sequence-lack of structure compatible with uterus.

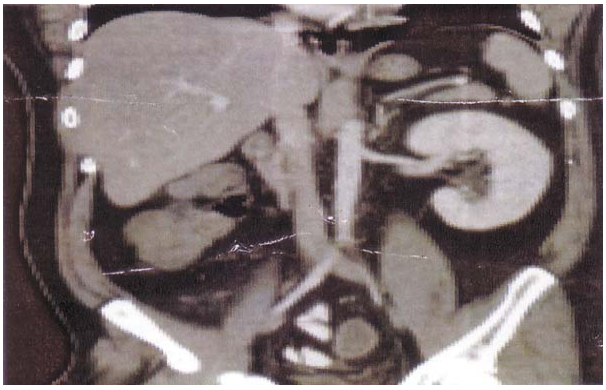

Fig 2 : CT Scan-unilateral agenesis of kidney in MRKH syndrome type-II

3. CT Scan is another alternative to detect associated agenesis and malformations of renal and skeletal system (Fig-2).

4. Pyelography: Intravenous pyelography can be performed to assess renal structure. Retrograde pyelography can be used to assess the renal collecting system, but requires cystoscopy.2,16

5. Spine radiography: May show short spine, congenital fusion of vertebrae at different levels, degenerative and osteoarthritic changes and variable degree of sacral agenesis.16 (Fig-3).

b) Laboratory Studies:

Chromosomal analysis is essential to determine the biological status. The karyotype of MRKH is always 46XX and that of androgen insensitivity syndrome (AIS) is 46XY and the gonads with Y chromosomes need to be resected due to malignant potential.3,17 Normal circulating levels of LH, FSH and 17 b estradiol indicate appropriate ovarian function.6,17 Testosterone levels are in the normal female range for MRKH syndrome and in normal male range for AIS.

c) Laparoscopy or Celioscopy is performed in cases of doubtful diagnosis after ultrasonography and/or MRI. Laparoscopy is nowadays mainly reserved for women in whom interventional therapy is likely to be undertaken (construction of a neo-vagina).18 Laparoscopy provides only indirect assessment of uterine cavitation. Hysteroscopy (examining inside the endometrial cavity) confirms cavitation but not always possible.

Once MRKH syndrome is diagnosed, a full check-up must be undertaken to search for associated malformations. Since renal and skeletal abnormalities may not be symptomatic, it is necessary to perform at least transabdominal ultrasonography, radiography of chest and spine (Fig-3 & 4). In case of suspicion of hearing impairment and/or a cardiac anomaly, complementary audiogram and/or heart echography must also be carried out.

Moreover, when diagnosing an MRKH syndrome in a patient, it is important to consider the family history. Investigation of the patient's relatives may also be recommended, mainly for renal but also for skeletal malformations.

Differential Diagnosis

The differential diagnosis of MRKH syndrome includes androgen insensitivity syndrome (AIS), congenital adrenal hyperplasia, Turner's syndrome, Hermaphroditism, MIS deficiency, 5a reductase deficiency and isolated vaginal atresia.3

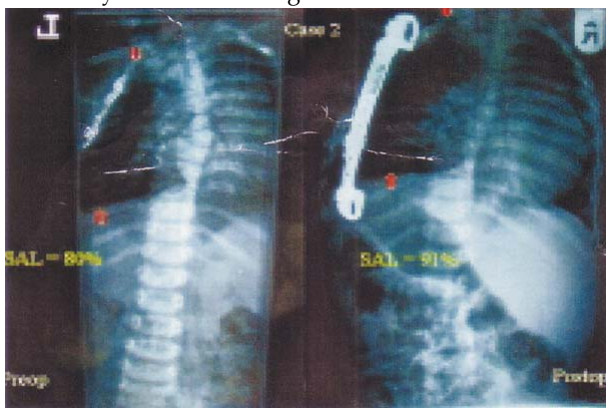

Fig 3 : Spine radiography- fusion, scoliotic and degenerative changes in spine in MRKH syndrome type-II

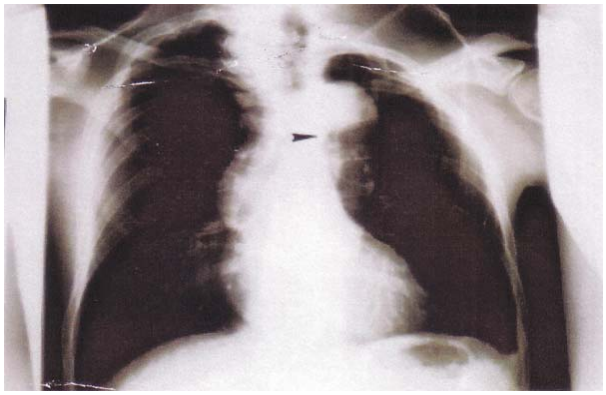

Fig 4 : Chest X-ray-Coarctation of aorta in MRKH type-II

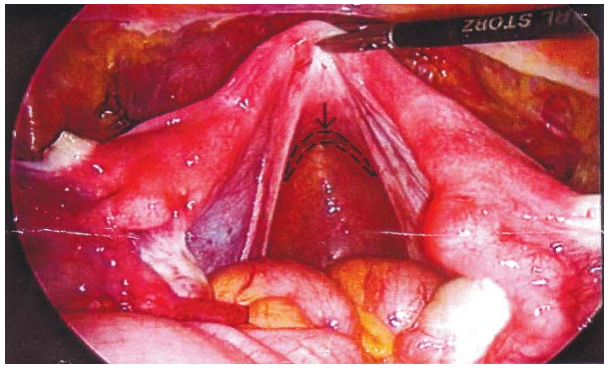

Fig 5 : Laparoscopic neovagina: Pelvic peritoneum as lining of new vaginal canal. The arrow dotted lines depict the top of vagina.

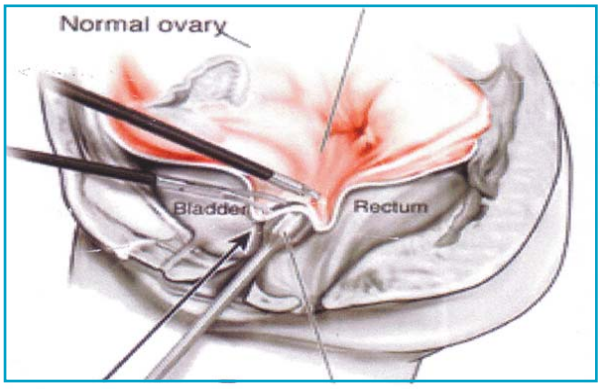

Fig 6 : Laparoscopic neovagina: Probe through newly developed vaginal canal

Transverse vaginal septum and imperforate hymen, which can be initially misleading but patients with these conditions have normal cervix and uterus, both of which are palpable on rectal examination.16,18 Differential diagnosis of MURCS association includes MRKH type-1, Klippel feil anomaly, goldenhar syndrome, VATER association with Vertebral defect, Anal atresia, Tracheo, Esophageal fistula, Renal defect.14,18

Management

MRKH syndrome generates anxiety and psychological distress with consequences on the patient's quality of life because of absence of menstruation and inability for conception. Surgical and nonsurgical creation of neovagina should be tried which may allow these patients normal sexual life. If the surgical approach is chosen, uterine remnants can be removed to avoid further endometriosis.13,19 Therapeutic laparos-copic surgery is the preferred procedure when uterine remnants or endometriosis cause cyclic pelvic pain requiring excision. Moreover, cases of MRKH type-II may need multidisciplinary approach with consultation of a reproductive endocrinologist, a pediatric and adolescent gynecologist, geneticist, orthopedic specialist, urologist, psychiatrist and audiologist.3,20

Nonsurgical creation of neovagina

Frank Technique or perenial dilation is the most commonly used nonsurgical procedure. It involves the application, first by the clinician and then by
the patient herself, of vaginal dilators (Hegar candles), progressively increasing its length and diameter. Ingram described a variation of this procedure, using a bicycle stool.14,20 The whole process takes six weeks to several months, with a success rate varying from 78% to 92%.3,20 Complications are rare. However, it can be applied only when the vaginal dimple is deep enough (2-4 cm).19,20 As this approach is noninvasive and often successful, it is recommended as a first-line therapy.19,20

Surgical techniques

A number of techniques are employed, the approach being most often based on the surgeon's experience.19,20 Treatment must be offered when the patients are ready to start sexual activity. Currently used methods are:

a. The Abbe-McIndoe operation: Most commonly practiced method and involves the dissection of a space between the rectum and the bladder, placement of a mold covered with a skin graft or amnion graft into the space for spontaneous epithelialization, and diligent postoperative vaginal dilatation. Peritoneum, labia minora grafting, and synthetic materials are also used.

b. The Vecchietti operation: is a combined of surgical and nonsurgical methods.19,20 This procedure involves the creation of a neovagina via dilatation with a traction device attached to the abdomen, sutures placed subperitoneally by laparotomy, and a plastic olive placed in the vaginal dimple.

c. Sigmoidal colpoplasty: involves creation of a neovagina by grafting a 12-18 cm long segment of sigmoid colon.

d. Rotational flap procedures use the pudendal thigh, gracilis myocutaneous, labia minora, and other fasciocutaneous flaps. Disadvantages of these techniques include extensive skin scarring.

e. Williams vaginoplasty uses a vulval flap to make a vaginal tube. This is a simple procedure but the neovagina has a physiologically abnomal angle.

f. Laparoscopic neovagina: The Davydov Procedure is used to create vagina with patients own peritoneum (Fig 5 & 6). Some international experts are able to complete the procedure laparoscopically with more precision, less blood loss, less infections, and lowest risk of scarring.19,20 Post operative complications are minimized by proper post operative care, proper dilation and pelvic floor therapy.

Success rate of different techniques of vaginoplasty ranges from 61-100% depending on techniques and quality of surgery.5,21 Complications of vaginoplasty include post operative rectovaginal or urethrovaginal fistula, hemorrhage, infection, graft failure, excessive skin scarring and vaginal stenosis, discharge, dyspareunia, poor and non compliance of post surgical dilatation regimen.

Fertility

Jeopardized fertility is an important issue affecting patients wellbeing. A woman with MRKH will never be able to get pregnant and carry a baby herself. So her options are gestational surrogacy or adoption. Uterine transplantation is another options but still experimental. Surrogacy means hiring one woman to carry a baby for the adoptive parents. Women with MRKH can have their own oocytes harvested, fertilized and implanted in a surrogate mothers womb

and pregnancy is carried till term. Surrogacy can be straight (using the surrogates own egg to conceive the baby) or host (using the adoptive mother's egg).22 It is done in a licensed clinic via artificial insemination or IVF. Currently gestational surrogacy remains standard for woman without uteri to create a family of genetic offspring.23 Alternately the patient can think for adoption personally or through agencies. But legal, cultural and religious issues are being considered.

Counseling and Support groups

Physicians should be well equipped to counsel a patient with MRKH syndrome regarding her option for future fertility, diagnosis and available therapies. Counseling of patient and her family about the procedures of vaginoplasty, necessity of regular coitus thereafter to prevent stenosis, Artificial Reproductive Technique (ART) & surrogacy for pregnancy are important issues. Marriage to a person who does not want baby or already have, emphasis for education and self_ reliance can be discussed in the perspective of low socio economic situation. There are MRKH support groups in abroad consisting of forums, private groups and websites.24,25 There are national centers for these patients worldwide which provide information and service about fertility, surrogacy, gamete donation, IVF and adoption. Psychological distress, affecting the patients' quality of life may be relieved by surgical or nonsurgical treatments, in course of time, by counseling, by family's support and by support groups.

Conclusions

The prevalence of MRKH syndrome is often underestimated due to lack of indepth evaluation, late diagnosis and undefined aetiology. The number of service providers with advanced techniques of vaginoplasty are increasing with more patient satisfaction. Having genetic offspring of MRKH patients is encouraging but management with gestational surrogacy is critical. Apart from management with creation of neovagina, these patients need multidisciplinary approach.

References

1. Lawrence S Amesse, MD, PhD, MMM; Chief Editor: Richard Scott Lucidi. Mullerian Duct Anomalies, Emedicine. medscape.com /article/273534, 2012
2. Ibrahim Syed, MD; Chief Editor: Eugene C Lin, MD. Imaging in mulleran duct abnormality emedicine.medscape.com/article/405335 Jun, 7, 2011
3. Andrew J, Kirsch. Mayer Rokitansky syndrome. ttp/medicine.medscape.com/article/953492
4. K Morcel - Mayer-Rokitansky-Kuster-Hauser (MRKH) syndrome Orphanet Journal of Rare Diseases 2007, 2:13 doi:10.1186/1750-1172-2-13
5. Griffin JE, Edwards C, Madden JD, Harrod MJ, Wilson JD. Congenital absence of the vagina. The MayerRokitansky-Kuster-Hauser syndrome. Ann Intern Med. 1976; 85:224-236
6. Orphanet: MURCS association, Orpha no-ORPHA2578
7. Duncan PA, Shapiro LR, Stange! JJ, Klein RM, Addonizio JC. The MURCS association: Mullerian duct aplasia, renal , aplasia, and cervicothoracic somite dysplasia. J Pediatr. 1979;95:399-402. doi: 10.1016/S0022-3476
8. Pavanello Rde C, Eigier A, Otto PA. Relationship between Mayer-Rokitansky-Kuster (MRK) anomaly and hereditary renal adysplasia (HRA) Am J Med Genet. 1988;29:845-849. doi: 10.1002/ajmg. 1320290414
9. Kobayashi A, Behringer RR. Developmental genetics of the female reproductive tract in mammals. Nat Rev Genet. 2003;4:969-980. doi: 10.1038/nrg1225
10. Guerrier D, Mouchel T, Pasquier L, Pellerin I. The Mayer-Rokitansky-Kuster-Hauser syndrome (congenital absence of uterus and vagina)- J Negat Results Biomed. 2006;5:1. doi: 10.1186/1477-5751-5-1
11. P Mahajan, A Kher, A Khungar, M Bhat, M Sanklecha, BA Bharucha, MURCS association-a review of 7 cases 1992; 38:3 Page: 109-11
12. C Braun-Quentin, C Billes, B Bowing, D Kotzot J Med Genet, MURCS Association, 1996; 33:618-620 doi:10.1136/jmg.33.7.618
13. Lindenman E, Shepard MK, Pescovitz OH. Mullerian agenesis: an update. Obstet Gynecol. 1997; 90:307-312. doi:10.1016/S0029-7844
14. Strubbe EH, Cremers CW, Willemsen WN, Rolland R, Thijn CJ. The Mayer-Rokitansky-Kuster-Hauser (MRKH) syndrome without and with associated features: two separate entities Clin Dysmorphol. 1994; 3:192-199
15. Peter Oppelt, Stefan P.Renner, Anja Kellermann, Sara Brucker, Georges A. Hauser, Reproduction 2006;21: 3: 792-797
16. MJ Govindarajan, Revathi S Rajan, Arjun Kalyanpur, Ravikumar, Diagnosis of Mayer-Rokitansky-KusterHauser syndrome. J Hum Reprod Sci. 2008, 1: 83-85
17. Quint EH, Smith YR. Primary amenorrhea in a teenager. Obstet Gynecol. 2006;107:414-417
18. Valeria Fiaschetti, Amedeo Taglieri, Vito Gisone, Irene Coco, Giovanni Mayer-Rokitansky-Kuster-Hauser Syndrome diagnosed by Magnetic Resonance Imaging. Radiology Case. 2012; 6:17-24 : DOI: 10.3941/jrcr.v6i4.992

19. ACOG Committee Opinion. Number 274. Nonsurgical diagnosis and management of vaginal agenesis. Obstet Gynecol. 2002;100:213-216. doi: 10.1016/S0029-7844
20. Keith Edmonds, L. Rose, Michelle G. Lipton, D.clin, Psy Julic Quek, RN. Fertility & sterility, 2012; 97: 3
21. Zhou JH, Sun J, Yang CB, Xie ZW, Shao WQ, Jin HM. Long-term outcomes of transvestibular vaginoplasty with pelvic peritoneum in 182 patients with Rokitansky's syndrome. 2010; 94(6) : 2281-5
22. Joanna Karpasea-Jones, Mayer Rokitansky Kuster Hauser Syndrome and Infertility/2011-suit I0I.com
23. David E. Reichman, M.D., Marc R. Laufer, M.D. Mayer-Rokitansky-K uster-Hauser syndrome: fertility counseling and treatment. Fertility and Sterility, 2010;94:5:1941-43
24. MRKH support group - Patients - Imperial College Healthcare NHS.www.imperial.nhs.uk > Patients > Help and support > Support groups
25. Helplines MRKH, fertility and adoption helplines - ITV This Morning. www.itv.com/thismomin /mrkhfertilityandadoptionhelplines/18 Oct 2011

.