**ORIGINAL ARTICLE**  
**Infertility**  

**Surrogate in vitro fertilization outcome in typical and atypical forms of Mayer–Rokitansky–Küster–Hauser syndrome**

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Submitted on March 21, 2011; resubmitted on September 12, 2011; accepted on September 20, 2011

**BACKGROUND:** The genital malformations in Mayer–Rokitansky–Küster–Hauser syndrome (MRKH) are frequently accompanied by associated malformations whose forms were recently classified as typical (isolated uterovaginal aplasia/hypoplasia) and atypical (the addition of malformations in the ovary or renal system). The aim of this study was to compare the surrogate IVF performance of women with typical and atypical forms including their chances of achieving pregnancy.

**METHODS:** The follow-up data on a total of 102 cycles of surrogate IVF in 27 MRKH patients treated in our department between 2000 and 2010 were analysed. Twenty patients with the typical form who underwent 72 IVF cycles were compared with seven patients with the atypical form who underwent 30 IVF cycles. The various examined parameters of these intended mothers were age, hormonal profile during controlled ovarian hyperstimulation and laboratory outcome.

**RESULTS:** The mean number of gonadotrophin ampoules needed for stimulation and treatment duration was significantly higher in the atypical form (3600 ± 1297 IU for 13 ± 2.3 days versus 2975 ± 967 IU for 11.6 ± 1.6 days, \( P \leq 0.01 \)). Serum estradiol and progesterone levels measured on the hCG administration day were similar. A significantly higher mean number of follicles 12.6 ± 6 versus 8.9 ± 5.4, \( P \leq 0.03 \), metaphase II (MII) oocytes 8.7 ± 5.1 versus 6.7 ± 4.8, \( P \leq 0.05 \), fertilizations 6 ± 3.6 versus 4.4 ± 3.3, \( P \leq 0.03 \) and cleaving embryos 5.7 ± 3.8 versus 4.1 ± 3.3, \( P \leq 0.01 \) were available in patients with the typical form compared with those with the atypical form, respectively. There was no significant difference in fertilization rate, cleavage rate or the mean number of transferred embryos. Embryo quality of the transferred ones and pregnancy rate per cycle were also similar between the two groups.

**CONCLUSIONS:** Women with the typical form of MRKH needed fewer gonadotrophins and for a shorter duration for ovarian hyperstimulation. The mean number of follicles, oocytes, MII oocytes, fertilizations and cleaving embryos was higher among women with the typical form. Pregnancy rates were similar since the available number and quality of transferred embryos to the surrogate mother were not affected.

**Key words:** genital or Müllerian duct malformations / MRKH syndrome / vaginal agenesis / surrogacy / surrogate IVF

**Introduction**

Mayer–Rokitansky–Küster–Hauser syndrome (MRKH) is a congenital anomaly of the genital tract with an incidence of 1:4000 female births (Capraro and Gallego, 1976). Primary amenorrhea leads to its diagnosis in adolescence. The syndrome includes vaginal aplasia with an absent or rudimentary uterus consisting of two small bilateral fibromuscular remnants, normal fallopian tubes and normally functioning ovaries (Egarter et al., 1998). The karyotype is 46,XX, and the secondary sex characteristics are usually feminine.

MRKH is frequently associated with urinary (Creatsas et al., 1990), skeletal and cardiac defects (Willemsen, 1982; Griesinger et al., 2005). Urinary tract anomalies are the most prevalent ones, with a frequency of between 20 and 40%. Renal agenesis/aplasia, pelvic kidney, horseshoe kidney, renal sclerosis and double ureter have also been reported (Wottgen et al., 2008). Skeletal anomalies related to MRKH (vertebral, rib, digits and palate) have been linked to the gene on the long arm of chromosome 12 (12q24.1) that encodes a T-Box containing the transcription factor TBX5 (McDonough, 2005). The association between MRKH and hyperandrogenism as a new clinical and genetic disorder has recently been reported (Sultan et al., 2009).

In the past, the main medical interest in this syndrome was to enable normal sexual intercourse by the use of different operative techniques for the reconstruction of the vagina (Chapron et al., 1995). With the advance of various assisted reproductive techniques...
(ARTs), there has been an increase of interest in the motherhood by means of IVF surrogacy for patients with MRKH (Beski et al., 2000; Raziel et al., 2005).

Indirect evidence from the radiologic literature has shown that there are two distinct forms of MRKH: one (type A) has symmetric muscular buds and fallopian tubes and the other (type B) has asymmetric muscular buds or abnormally developed fallopian tubes (Strubbe et al., 1993). This classification, however, is descriptive, and probably has no relevant clinical value.

Oppelt et al. (2006) reported a series of 53 MRKH patients and showed the presence of associated malformations in more than one-third of them. This led to a new and clinical diagnostic classification of the syndrome: the typical form in which the fallopian tubes, ovaries and renal system are generated and well-developed, and the atypical form in which additional malformations of the ovaries and/or the renal system are present. Duncan et al. (1979) proposed the term MURCS (Malformations Urinary Cardiac and Skeletal), for cases where systemic involvement was present. This term was ‘incorporated’ as a third form in Oppelt’s clinical classification.

The aim of the present study was to provide data on the baseline pregnancy and live birth rate of patients with MRKH and to further determine which type of syndrome is associated with better chances of the surrogate conceiving.

Materials and Methods

Patients

Between January 2000 and December 2010, a total of 102 cycles of surrogate IVF were initiated in 27 MRKH patients. Cycles with thawed embryos or blastocyst transfers were not included. Twenty patients with the typical form of MRKH underwent 72 IVF cycles and seven patients with the atypical form underwent 30 IVF cycles.

The associated anomalies were renal in five of the latter seven patients: an isolated single kidney in two, and a right pelvic horseshoe kidney in one, a single kidney combined with obesity, migraine, hypothyroidism and ovaries in the subcostal position in one, and a single kidney post-ovarian cystectomy in another one. The ovaries were in an abnormal location in the remaining two cases: a left subcostal ovary in a patient with a 47,XXX anomaly (Raziel et al., 2010) and subcostal ovaries in a woman with a body weight of 40 kg.

Blood samples were taken from the patients for karyotype analysis, as part of the investigation of primary amenorrhea at adolescence. The patients had also received genetic counselling upon diagnosis and further explanations on fertility options when relevant after marriage. All karyotype results were normal 46,XX except for one patient with a mosaic 47,XXX anomaly with high penetration (Raziel et al., 2010).

The gametes of the infertile couple were used and the embryos were transferred to the surrogate uterus. The MRKH patients were stimulated with a long protocol starting at the mid-luteal phase. Treatment of these women included weekly determination of serum progesterone to identify the luteal phase for precise timing of the administered GnRH analogue preparation as recommended by Ben-Rafael et al. (1998).

In order to synchronize between the commissioning mother and the surrogate, the latter used oral contraceptives during the pituitary desensitization of the intended mothers. The surrogate was instructed to stop using oral contraceptives and to undergo withdrawal bleeding in parallel to the start of individualized gonadotrophin injection in the MRKH patient. Pituitary desensitization in the gestational carrier was not used for synchronization. The surrogate started daily oral estradiol valerate on an escalating dose schedule, from 2 mg per day up to a maximum of 6 mg per day. The desired thickness of the triphasic endometrium was at least 6 mm. I.m. progesterone in oil (Gestone, Pains & Byrne, Surrey, UK) 50 mg per day or vaginal micronized progesterone (Utrogestan; Besins International Laboratories, Paris, France) 200 mg every 8 h were added to the surrogate’s regimen, starting on the day the MRKH patient was administered hCG. If pregnancy was confirmed, this combined regimen was continued until 8 weeks of gestation.

Controlled ovarian stimulation and IVF outcome

Controlled ovarian hyperstimulation (COH) was carried out by the daily subcutaneous administration of 0.1 mg triptorelin (Decapeptyl, Ferring, Malmo, Sweden) or 600 μg intranasal Napharelin (Synarel, Delpharm, France) 2 weeks prior to individualized administration of human menopausal gonadotrophins (Menogon, Ferring, Mannheim, Germany) or recombinant preparations (Gonal F, Serono, Aubans, Switzerland and Puregon, Organon, Lausanne, Switzerland). The duration of treatment and the number of gonadotrophin ampoules needed for hyperstimulation, hormonal profile [estradiol (E2) and progesterone], the number of follicles, aspirated oocytes and total number of developing and transferred embryos were compared and evaluated for the two forms of the syndrome.

Oocyte retrieval was preferably performed by the vaginal route guided by ultrasound and with the patient under general anaesthesia. We also retrieved oocytes by abdominal puncture or combined retrieval (abdominal and vaginal) as described by our group (Raziel et al., 2006). The morphology of each of the aspirated oocytes was described after denudation with hyaluronidase. ICSI was carried out in all patients according the method of Van Steirteghem et al. (1993). It is our rule to perform ICSI when possible. As in other IVF units, ICSI is performed when the semen quality of the patient is low, or fertilization failure in previous IVF cycles and in low responders. Since the number of oocytes in the MRKH patients is relatively low compared with the average number of metaphase II (MII) oocytes per cycle in our program (9.8 ± 6.3) and the fertilization rate is higher with ICSI than with IVF, we decided to perform ICSI rather than classical IVF in these unique cases of surrogacy.

Fertilization was confirmed after 16–18 h by visualization of two distinct pronuclei. Cleavage was assessed 24 h later. Grade I embryos were defined as those in which all blastomeres were of equal size. Grade II embryos had blastomeres with unequal or equal size with a maximum of 20% fragments of the embryo volume. In grade III embryos, 20–50% of the volume contained fragmentation, and >50% fragmentation was present in grade IV embryos (Plachot et al., 1986). In 2004, The Israeli Ministry of Health published guidelines for embryo transfer in IVF. Less than 35 year old, two embryos are allowed to be transferred for at least three IVF trials before the transfer of three embryos is considered. After 35 years old, two embryos are allowed to be transferred in the first two trials before the transfer of three embryos is considered. Three embryos can be transferred from the first trial in patients of ≥41 years old. We decided that the management of embryo transfer in surrogacy should be the same as the management in our other indications for IVF.

Embryos were considered for transfer and introduced into the uterine cavity from 48 to 72 h after the ICSI procedure. Embryo transfer was performed with a Wallace catheter (Simcare, Lancing, UK).

The pregnancy rate was calculated by considering only clinical pregnancies, determined by the visualization of a gestational sac by transvaginal ultrasound 3–4 weeks after embryo transfer. Early abortion was defined as pregnancy loss that occurred before 12 weeks of gestation and late abortion was defined as pregnancy loss after 12 and before 20 weeks of gestation.
**Mean embryo score of the transferred embryos**

In order to compare the transferred embryos’ quality between the typical and atypical MRKH patients, the embryo score was determined as follows: four cell embryos = 4 points, three cell embryos = 3 points and two cell embryos = 2 points. Grade I embryos received 4 points, Grade I-II 3.5 points, Grade II 3 points and Grade II–III 2.5 points. The mean score was the sum of the points of the number of cells and grade of each of the transferred embryo divided by the number of embryos. According to this scoring system, two transferred embryos of 4I–II, 4I–II received a mean score of 7.5, two transferred embryos of 4I, 4I–II received a mean score of 8, two transferred embryo divided by the number of embryos. According to this scoring system, two transferred embryos of 4I–II, 4I–II received a mean score of 7.5, two transferred embryos of 4I, 4I–II received a mean score of 8, two transferred embryos of 4I;4I received a mean score of 8, two transferred embryos of 4I received a mean score of 8.

**Statistical analysis**

Results were expressed as means ± SD. Statistical analysis was performed with the JMP statistical package (version 3.2.2. SAS Institute Inc., Cary, NC, USA) using the χ² test. Statistical significance was defined as a P-value of <0.05.

**Results**

The relevant characteristics and COH outcome of ICSI patients with the typical and atypical forms of MRKH are listed in Table I. The mean age of the typical form patients was significantly higher than that of the atypical form patients (32 ± 4.7 and 30 ± 3.1 years, respectively, P < 0.03). The mean number of gonadotrophins needed for stimulation was higher and the duration of treatment was longer in the patients with the atypical form. Serum E2 and progesterone levels on the hCG administration day were similar in both groups. The mean numbers of follicles, oocytes, MII oocytes, fertilizations and cleaving embryos were significantly higher in the typical form patients compared with the atypical form patients. There were no significant differences in fertilization rate, cleavage rate and the mean number of transferred embryos between the two subgroups.

The quality of embryos of the women with each form of MRKH is represented by the mean embryo score. The distribution of the mean score of the embryos which were transferred to the surrogate in the typical and atypical forms of the study patients is shown in Table II.

Of the 20 couples where the female partner had typical MRKH undergoing the complete IVF program, 12 pregnancies were achieved, ending in 10 deliveries: seven singletons, three sets of twins, seven boys and six girls. Seven deliveries were by Caesarean section, due to obstetrical indications or patients’ requests. The remaining three deliveries were by vaginal route. In one surrogate, an emergent Caesarean section was done due to abrupton of the placenta with massive bleeding and disseminated intravascular coagulopathy. The woman was treated in the intensive care unit and the newborn was stillborn. All the three twin sets were delivered by Caesarean section at 35, 36 and 37 weeks of gestation. Two abortions were reported: an inevitable late abortion at 15 weeks of gestation, with suspected cervical incompetence and an early missed abortion. All fetal weights were within normal range for gestational age. No congenital malformations were found among the newborns.

Of the seven patients with atypical MRKH, four pregnancies were achieved: two early missed abortions and two deliveries: one by the vaginal route and the other by a low segment transverse Caesarean section of twins.

The overall clinical pregnancy rate was 17% (17/102) per cycle, with an overall live birth rate of 12% (12/102). The clinical pregnancy rate was similar among the typical (17%, 12/72) and atypical form (17%, 5/30). The abortion rate was higher among the women with

**Table I** The characteristics of patients with MRKH, their response to ovarian stimulation and ICSI outcome—a comparison between typical and atypical forms.

<table>
<thead>
<tr>
<th>Surrogate IVF cycles</th>
<th>Typical form a (n = 72)</th>
<th>Atypical form b (n = 30)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, year</td>
<td>32 ± 4.7</td>
<td>30 ± 3.1</td>
<td>&lt;0.03</td>
</tr>
<tr>
<td>Gonadotrophins (IU)</td>
<td>2925 ± 967</td>
<td>3600 ± 1294</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Gonadotrophin days</td>
<td>11.6 ± 1.6</td>
<td>13 ± 2.3</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>E2 on hCG day (pg/ml)</td>
<td>2703 ± 1760</td>
<td>2711 ± 1278</td>
<td>NS</td>
</tr>
<tr>
<td>Progesterone on hCG day (ng/ml)</td>
<td>1.1 ± 0.6</td>
<td>1.1 ± 0.5</td>
<td>NS</td>
</tr>
<tr>
<td>Follicles, n</td>
<td>12.6 ± 6</td>
<td>8.9 ± 5.4</td>
<td>&lt;0.03</td>
</tr>
<tr>
<td>Aspirated oocytes, n</td>
<td>10.9 ± 6.4</td>
<td>7.8 ± 5.8</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>MII oocytes, n</td>
<td>8.7 ± 5.1</td>
<td>6.7 ± 4.8</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Fertilized oocytes, n</td>
<td>6.0 ± 3.6</td>
<td>4.4 ± 3.3</td>
<td>&lt;0.03</td>
</tr>
<tr>
<td>Fertilization rate (%)</td>
<td>69 ± 24</td>
<td>70 ± 24</td>
<td>NS</td>
</tr>
<tr>
<td># of cleaved embryos</td>
<td>5.7 ± 3.8</td>
<td>4.1 ± 3.3</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Cleavage rate (%)</td>
<td>95 ± 10.5</td>
<td>92 ± 22.7</td>
<td>NS</td>
</tr>
<tr>
<td>Total # of embryos, n</td>
<td>5.4 ± 3.8</td>
<td>4.5 ± 3.4</td>
<td>NS</td>
</tr>
<tr>
<td>Transferred embryos, n</td>
<td>2.5 ± 0.6</td>
<td>2.4 ± 0.6</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are mean ± SE. IVF: in vitro fertilization. NS: non-significant (P > 0.05).

**Table II** The mean score of the embryos of commissioning mothers with MRKHs which were transferred to the surrogate—a comparison between typical and atypical forms.

<table>
<thead>
<tr>
<th>Mean embryo score c (%)</th>
<th>Typical form a (%)</th>
<th>Atypical form b (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>7–8</td>
<td>44</td>
<td>59</td>
</tr>
<tr>
<td>6–7</td>
<td>49</td>
<td>22</td>
</tr>
<tr>
<td>&lt;6</td>
<td>7</td>
<td>19</td>
</tr>
<tr>
<td>7.5–8</td>
<td>24</td>
<td>33</td>
</tr>
<tr>
<td>6.5–7.4</td>
<td>46</td>
<td>40</td>
</tr>
<tr>
<td>&lt;6.4</td>
<td>30</td>
<td>26</td>
</tr>
</tbody>
</table>

aIsolated uterovaginal aplasia/hypoplasia.

bAdditional malformations in the ovary or renal system.

cThe sum of points according to the number of cells and grade of each embryo in the cohort of transferred embryo divided by the number of transferred embryos.
the atypical form 29% (2/7) compared with the typical form 17% (2/12).

The mean clinical pregnancy rate of all age group patients in our IVF unit between the years 2000 and 2010 is 30% (range 27–33%).

Discussion

Many of the articles on MRKH have focused on the technical aspects of forming a functional vagina via laparotomy or laparoscopy (Chapron et al., 1999). With the acquirement of enhanced ART, the reproductive capabilities of the affected women have been investigated and described in a number of reports (Petroza et al., 1997; Corson et al., 1998; Beski et al., 2000; Brinsden et al., 2000; Raziel et al., 2005; Dermout et al., 2010).

In one of the largest series published to date on gestational surrogacy, Goldfarb et al. (2000) compared 15 women who were diagnosed as having MRKH with 51 women who underwent a hysterectomy for various reasons. The patients who had a congenital absence of the uterus had more aspirated oocytes, more mature oocytes, more fertilizations and more embryos for transfer than the patients post-hysterectomy. Those authors suggested that these findings might be due to vascular compromise in the latter group. The MRKH patients were not characterized in that article, but the study results indicated that the reproductive capabilities may differ in different groups of patients who use IVF surrogacy.

Strubbe et al. (1993) divided 91 patients with MRKH on the basis of laparoscopic findings into typical (type A) and atypical (type B) MRKH syndrome, where type B included renal anomalies. They characterized type A by the absence of the vagina and the uterus or only symmetric uterine remnants, normal fallopian tubes and ovaries and type B by asymmetric uterine remnants (aplasia of one or asymmetry of both uterine muscular buds), and asymmetric fallopian tubes (hypoplasia or aplasia of one or both fallopian tubes). Those authors found urinary anomalies in 37% of cases and ovarian anomalies in 15% of cases.

Fedele et al. (2007) analysed the laparoscopic data that had been recorded on 106 patients with MRKHs during laparoscopic creation of a neovagina according to the Vechietti approach. The uterus was absent in all cases. Müllerian remnants were observed in 87% cases, and 26% were cavitated and contained endometrial mucosa. Renal anomalies were found in 30% of patients; of which unilateral renal agenesis was the most frequent (18% of patients). The ovaries were extra-pelvic in 16% of their patients. Similarly, we found renal anomalies in 19% of our patients, of which unilateral renal agenesis was the most frequent. The extra-pelvic position of the ovaries and its relevance to oocyte collection during IVF has already been described by our group (Raziel et al., 2006).

Bearing in mind that MRKH women probably do not comprise an entirely homogeneous group, and based on the recent clinical diagnostic classification of MRKH patients (Oppelt et al., 2006), we compared the reproductive capabilities of the patients with the typical form (confined to the genitalia) with the reproductive capabilities of the patients with the atypical form (in which extra-genital involvement, mainly renal and ovarian, was present). The purpose of this comparison was to determine whether there is a prognostic difference in the reproductive potential of a new patient first diagnosed as having MRKH.

Since all the surrogate mothers had already proven their implantation potential in the past (according to the local law), pregnancies in IVF surrogacy should directly reflect the oocyte-embryo quality of the commissioning women who have MRKH. According to our findings, those women can be divided into those with the typical form who have a better response to ovarian hyperstimulation and a higher number of follicles, oocytes and embryos and those with the atypical form who have a relatively poorer ovarian response. Assigning a newly diagnosed woman to one of these two groups should probably offer her a better prognostic perspective when she embarks on an IVF surrogacy treatment for the first time.

But since our mean clinical pregnancy rate of all age group patients in our IVF unit between the years 2000 and 2010 is 30% (range 27–33%), and among the patients with the mean age of 30–32 years 37%, it is clear that a 17% clinical pregnancy rate among patients with MRKH (either typical or atypical) is unfavourable, certainly in the context of the expected higher rate of pregnancies in surrogate mothers because of former proven pregnancies.

Since the MRKHs has a wide variety of anatomic presentations, and it represents a continuum of embryonic malformations that occur at different stages of embryonic development, it is understandable that the IVF performance is also different between the specific groups of MRKH patients.

Authors’ roles

A.R. (main author) has made substantial contributions to conception and design, acquisition of data, analysis and interpretation of data, drafting and revising it critically for important intellectual content and final approval of the version to be published. S.F. has made substantial contributions to interpretation of data, drafting and revising it critically for important intellectual content and final approval of the version to be published. Y.G. has made substantial contributions to interpretation of data, drafting and revising it critically for important intellectual content and final approval of the version to be published. I.B.A. has made substantial contributions to interpretation of data, drafting and revising it critically for important intellectual content and final approval of the version to be published. D.S. has made substantial contributions to interpretation of data, drafting and revising it critically for important intellectual content and final approval of the version to be published.

References


