Undescended ovary and unicornuate uterus: Simplified diagnosis by the use of clomiphene citrate ovarian stimulation and magnetic resonance imaging (MRI)

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BACKGROUND: Although the association between unicornuate uterus and undescended ovaries is well established, little information is available on this entity, suggesting the possibility that many cases are not recognized at all. Consequently, important clinical information is missed in many patients worldwide.

METHODS: During a period of 5 years, eight cases of unicornuate uterus were observed in our infertility clinic. The first three patients received magnetic resonance imaging (MRI) after mild clomiphene citrate (CC) stimulation due to a discrepancy between estradiol levels and follicular growth and because a suspected ectopic ovary could not be visualized on ultrasound. Based on this experience, five consecutive patients were offered MRI after CC stimulation as part of this study.

RESULTS: In five out of eight patients with unicornuate uterus (62.5%) an undescended ovary could be visualized in the upper abdomen. Abdominal ultrasound revealed the ectopic ovary in only two cases. The use of CC stimulation undoubtedly facilitated the diagnosis of the undescended ovary on MRI.

CONCLUSION: It is suggested that MRI after CC stimulation is an excellent non-invasive method to diagnose undescended ovaries in women with a unicornuate uterus.

Key words: ectopic ovary/infertility/MRI/undescended ovary/unicornuate uterus

Introduction

Undescended or ectopic ovaries are characterized by the attachment of the upper pole to an area above the level of the common iliac vessels. Although ovarian maldescent also occurs in patients with a normal uterus, the incidence is reported to be 20% when the uterus is absent (Rokitansky–Küster–Hauser syndrome) and as high as 42% in cases of unicornuate uterus. Bilaterality occurs more often in women with congenital absence of the uterus (Dabirashrafi et al., 1994). Although the term ectopic ovary is commonly used for the condition described here, undescended ovary is probably a more accurate reflection of the underlying pathophysiology.

The incidence of congenital uterine malformations varies between 0.1–5.0% and Müllerian anomalies are found more often in subfertile patients compared with fertile and sterile controls (Acien, 1997; Raga et al., 1997; Grimbizis et al., 2001). Of all Müllerian defects, unicornuate uterus is found in 3–13% of cases (Acien, 1997; Raga et al., 1997; Grimbizis et al., 2001). Unicornuate uterus is caused by a failure of one Müllerian duct to develop (unicornuate uterus without rudimentary horn) or to migrate to its proper location. It is linked to an increase in obstetrical complications such as early miscarriages, ectopic pregnancy, abnormal fetal presentation, intrauterine growth retardation and premature labour (Andrews and Jones, 1982; Heinonen et al., 1982; Donderwinkel et al., 1992; Moutos et al., 1992; Heinonen, 1997; Raga et al., 1997). Despite the well-known association of ectopic ovaries and unicornuate uterus, ectopic ovaries are reported only sporadically, suggesting the possibility that many cases go unrecognized (Verkauf and Bernhisel, 1996).

This is the first report on the use of magnetic resonance imaging (MRI) after ovarian stimulation in the detection of undescended ovaries. We describe four cases of unicornuate uterus in which the diagnosis of ectopic ovary during a routine infertility exploration including hysterosalpingography (HSG), hysteroscopy and laparoscopy was missed.

MRI techniques and methods

Because the cases presented here stretch over a period of 5 years, the imaging technique differed to some degree. All studies were performed on a 1 Tesla MRI unit (Siemens Magnetom Expert, Erlangen, Germany). In the first two cases, axial and coronal turbo spin echo (TSE) T2 weighted images
were obtained (TE = 99 ms/TR = 4600 ms) followed by short tau inversion recovery (STIR) sequences in the coronal, sagittal and axial plane (TE = 60 msec/TR = 6000 ms). Since the stimulated ovary contains numerous fluid-containing follicles, they are easily detected on this sequence. One series of T1-weighted images was obtained in the axial plane using a gradient echo sequence [Turbo Fast Low Angle Shot (TFLASH) with TE = 4.2 ms/TR = 11 ms] focused on the ectopic ovary. This sequence is used to study the signal of the content of the follicles in the latter. Due to technological improvement over the years we performed axial, coronal and sagittal T2-weighted images using a non-breath hold half-Fourier acquisition single-shot turbo spin-echo (HASTE) technique (TR 1400 ms/TE 60 ms) in the last two cases. Also late-echo T2-weighted HASTE images were obtained in the same imaging planes (TR = 1250 ms/TE = 360 ms). The latter has the same imaging capabilities as the STIR images where fluid has very high contrast compared with the surrounding tissue. All patients were examined in the supine position with a four element phased-array torso coil to optimise the signal-to-noise ratio. Slice thickness was 5 mm in all sequences. The centre of the coil was positioned at the umbilicus of the patient. The field of view encompassed the upper border of the kidneys to the bladder base. Neither sedation or i.v.-contrast were applied. Image quality was adequate to detect the ectopic location of the ovary contralateral to the missing uterine horn in all cases. Detection was most adequate on the T2-weighted images, especially on the heavily weighted HASTE series and STIR images.

**Case 1**
A couple with primary infertility for 3 years was referred to our infertility centre for donor-insemination. Investigation of the male partner revealed azoospermia. Genetic testing proved to
be normal. On testicular biopsy the diagnosis of Sertoli-cell only syndrome was made. An infertility work-up of the female, including an endocrinological and immunological evaluation, was normal. An HSG showed an unicornuate uterus with one patent salpinx on the right side (Figure 1a) and this was confirmed laparoscopically. A urological examination including i.v. pyelography (IVP) could not detect any abnormality.

The couple was entered in our donor-insemination programme. Clomiphene citrate (CC) (50 mg for 5 days, days 5–9) for mild ovarian stimulation was used. In the first treatment cycle, we observed a normal bifollicular response with a serum estradiol level of 544 pg/ml on the day of hCG administration. This attempt was unsuccessful. In a consecutive cycle, serum estradiol reached a level of >600 pg/ml, but no ovarian response could be seen on ultrasound. A spontaneous LH surge was noted. In this cycle, we performed no insemination. Because an ectopic ovary was suspected, vaginal and abdominal ultrasound was carried out but could not confirm the diagnosis of an undescended ovary. During the next cycle and following CC stimulation, an MRI examination (Siemens I.O.T. magneton) was carried out on day 12 of the cycle. This confirmed the presence of a unicornuate uterus and revealed a left-sided undescended ovary at the level of the pelvic brim, anterior to the psoas muscle, containing several follicles (Figure 1b–d). A thin cord-like structure continued from this ovary in the direction of the internal inguinal canal. The latter contained a small (15 mm diameter) ‘nodular’ structure at the level of the external iliac vascular axis. This was considered to be a Müllerian remnant or a remnant of the lower gonadal cord. Considering these findings, the diagnosis of an ectopic ovary was made. The right ovary was entirely normal.

**Case 2**

A 26-year-old woman with primary infertility was referred for fertility treatment. An HSG, hysteroscopy and laparoscopy performed in the referring centre had confirmed the diagnosis of a unicornuate uterus with one tube and one normal ovary on the right side. On vaginal ultrasound, only one ovary could be seen. An infertility work-up of the male revealed moderate teratozoospermia with 7% normal forms using strict criteria of sperm morphology (Ombelet et al., 1997a). An IVP showed no abnormalities.

The couple was advised to start with intrauterine insemination (IUI) after CC ovarian stimulation. On day 15 of the first IUI cycle, serum estradiol reached 272 pg/ml with only one follicle of 12 mm diameter visible on vaginal ultrasound. Because of the discrepancy between follicular size and estradiol level an MRI was performed confirming the presence of a left-sided ectopic ovary in the upper part of the pelvis, anterior to the psoas muscle and the iliac muscle. It contained numerous follicles (Figure 2).

**Case 3**

A couple with primary infertility for 2 years was referred for IVF after two unsuccessful IUI attempts with homologous semen. A previous investigation revealed a normogonadotrope anovulation, a unicornuate uterus and only one ovary and tube on the right side. Unilateral tubal patency was documented by HSG and laparoscopy.

A male factor was found with unexplained oligoasthenoteratozoospermia. After the washing procedure, >1×10⁶ motile spermatozoa could be recovered and therefore IUI treatment with CC ovarian hyperstimulation was continued (Ombelet et al., 1997b). During the next IUI treatment cycle a discrepancy between serum estradiol levels and ovarian ultrasound images (follicular growth) was observed. An ectopic ovary was suspected and MRI was carried out after mild ovarian CC stimulation. This confirmed the presence of a unicornuate uterus and a normal right-sided ovary containing numerous follicles. A left retroperitoneal ectopic ovary was seen as a cord-like structure that contained several follicles. Its cranial border reached the left side of the second lumbar vertebra, the caudal part of the cord-like ovary stretched to the internal inguinal canal (Figure 3). The left kidney was absent.
ectopic ovary. In two patients a rudimentary horn was localized ovaries were observed without the presence of an abdominal ultrasound. In three other patients, two normally this patient, the undescended ovary could also be visualized on routine fertility exploration in our centre. Because of the previous experience, MRI after CC stimulation was conducted on routine fertility exploration in our centre. Because of the confusion in terminology, Lachman and Berman (1991) proposed a modification of the terminology for classification of ectopic ovaries. They suggested elimination of the terms supernumerary and accessory ovary. Instead, they introduced usage of the term ectopic ovary, which can be divided in three categories: (i) post-surgical implant, (ii) post-inflammatory implant and (iii) true embryologic.

The embryological mechanism underlying undescended ovaries is uncertain, but could be explained by a lack of caudal descent of the gonads into the true pelvis (Parmley, 1993) or by a retarded differential growth of that portion of the urogenital ridge giving rise to both the gonad and the Fallopian tube (Rock et al., 1986). Ectopic ovaries may be unilateral or bilateral and can be associated with abnormalities of the Müllerian ducts such as unicornuate uterus. The association of unicornuate uterus and urinary tract anomalies including ectopic kidney, renal agenesis, double renal pelvis and horseshoe kidneys is well known (Fedele et al., 1996).

In this study we describe four cases of true embryologic undescended ovaries, with attachment of the upper pole to an area above the level of the common iliac vessels. All four cases were missed by routine fertility exploration. In three cases (reports 1, 2 and 3) MRI was performed after mild ovarian stimulation with CC because a discrepancy between serum estradiol levels and ovarian ultrasound images was found after ovulation induction. The multifollicular growth in the ectopic ovary greatly enhanced MRI diagnosis.

State-of-the-art MRI has proven its value in the detection and characterization of a wide variety of disorders of the female reproductive organs. Ultra-fast cross-sectional T1- and T2-weighted images can be used to assess the normal and pathological ovaries. Usually, MRI is used as an adjunct to ultrasound and/or computed tomography in selected cases. However, while reports documenting the value of MRI in detecting anomalies of the uterus and ovaries are profound in the literature, reports concerning the detection of ectopic ovaries are lacking.

As described in these case reports, we used MRI as the primary imaging tool to detect the location and the appearance of the contralateral ovary in those patients with an unicornuate uterus. MRI was chosen because this technique has a superior soft tissue contrast, has multiplanar imaging capabilities and lacks ionising radiation. MRI was shown to be more sensitive in the detection of an undescended ovary compared with ultrasound.

Discussion
A variety of terms have been used to describe an undescended or ectopic ovary. Supernumerary ovaries include cases in which a third ovary is entirely separated from the eutopic ovary and may be located in the omentum or retroperitoneally. The term ‘accessory ovary’ refers to cases in which excess ovarian tissue is situated near and connected to the normally placed ovary (Wharton, 1959; Printz et al., 1973). Ovarian implant syndrome covers those cases that develop after pelvic surgery or after a history of pelvic inflammatory disease. It has been well established that ovarian tissues may continue to function after transplantation from their original site (Payan and Gilbert, 1987). Because of this confusion in terminology, Lachman and Berman (1991) proposed a modification of the terminology for classification of ectopic ovaries. They suggested elimination of the terms supernumerary and accessory ovary. Instead, they introduced usage of the term ectopic ovary, which can be divided in three categories: (i) post-surgical implant, (ii) post-inflammatory implant and (iii) true embryologic.

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Figure 4. Axial STIR image (TR = 6000/TE = 60 ms). The right ovary was found anterior to the iliac muscle, containing several follicles (arrows).

Case 4
A couple with primary infertility for 6 years as a result of non-obstructive azoospermia was referred after 12 unsuccessful trials with IUI using donor semen. An HSG and laparoscopy showed a unicornuate uterus with one normal tube and ovary on the left side. Abdominal ultrasound was performed but could not detect an ovary on the right side. Agenesis of the right kidney was found on IVP.

Considering our experience with the previous cases of unicornuate uterus, MRI after CC ovarian stimulation was performed. During that cycle one dominant follicle was observed with a diameter of 16 mm in the left ovary. Serum estradiol levels reached 610 pg/ml, again showing a discrepancy between ultrasound findings and serum hormonal level. MRI confirmed the presence of an undescended ovary at the right pelvic brim, anterior to the psoas muscle, containing several follicles (Figure 4).

An IVF cycle was started and on day 14 an oocyte aspiration was performed. Seven oocytes were aspirated from the left ovary. The ectopic ovary could not be observed on abdominal ultrasound. Six out of seven oocytes fertilized and 2 days after oocyte retrieval three fertilized oocytes were transferred laparocopically into the left tube. During this procedure the ectopic ovary with remnants of a tube (1 cm) and fimbriae were seen high up in the abdomen, close to the parietal peritoneum.

Cases 5–8
The next four patients were found to have a unicornuate uterus on routine fertility exploration in our centre. Because of the previous experience, MRI after CC stimulation was conducted in all cases resulting in one extra case of undescended ovary. In this patient, the undescended ovary could also be visualized on abdominal ultrasound. In three other patients, two normally localized ovaries were observed without the presence of an ectopic ovary. In two patients a rudimentary horn was diagnosed on MRI.
A review of the literature revealed one case of a supernumerary ovary in a patient with persistent elevated plasma estrogen levels despite bilateral oophorectomy. The ectopic ovary in that particular patient was diagnosed by stimulation with hCG (Kosasa et al., 1976).

Although the incidence of unicornuate uterus is low, a correct diagnosis is mandatory not only to be aware of the existence of an ectopic ovary but also in considering the reproductive performance when uterine malformations are involved. Early and late abortions as well as preterm delivery are found much more often if unicornuate uterus is involved (Andrews and Jones, 1982; Donderwinkel et al., 1992; Moutos et al., 1992; Heinonen, 1997; Raga et al., 1997). Concerning assisted reproduction, significantly lower implantation rates are described after IVF–embryo transfer in cases of unicornuate uterus (Heinonen et al., 2000).

The knowledge of the existence of an ectopic ovary is also of importance and relevant in the following clinical situations: follicle aspiration techniques in women with unicornuate uterus, exploration of unexplained cyclic abdominal pain due to folliculogenesis, ovulation and cyst formation in the undescribed ovary and medical conditions where surgical castration is indicated.

There are many reasons to promote MRI after mild ovarian stimulation in all cases of unicornuate uterus. Stimulation with CC improves the accuracy of the MRI examination. Therefore we suggest performing routine MRI after CC stimulation in all unicornuate uterus cases. Whether MRI in a non-stimulated cycle is as sensitive as MRI after CC stimulation is doubtful, but has to be investigated.

Continuous refinement of the MRI technique and further improvement of the spatial resolution and increased availability of MRI will progressively increase its application in the detection of undescribed ovaries and other Mullerian fusion defects. Since both intra- and extra-peritoneal locations of an undescribed ovary may occur, the authors suggest that MRI can precede or replace laparoscopic evaluation in this specific patient population (Doyle, 1992).

There are several reasons to prefer MRI above laparoscopy in the diagnosis of undescribed ovaries: (i) the costs (for society) of a laparoscopy are much higher compared with MRI; (ii) in contrast with laparoscopy, MRI is a non-invasive procedure; and (iii) renal abnormalities and extra-peritoneal ovaries (which are probably the most important to diagnose) cannot be evaluated during laparoscopy.

To conclude, MRI after CC ovarian stimulation in all unicornuate uterus cases may avoid otherwise invasive diagnostic techniques and could detect undescribed ovaries more frequently than has been appreciated to date. We described a novel and sensitive tool in the diagnosis of undescribed ovaries, an entity which has probably gone unrecognized until now in many patients at risk.

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