Infertility treatment by intrauterine insemination in a woman with uterus didelphys — case report

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Abstract

Uterine anomalies are among the most common congenital abnormalities of the female reproductive system, with a prevalence of 2–4% in the general population. The present case report discusses the case of a patient with uterus didelphys who conceived by intrauterine insemination with her husband's semen, and carried the pregnancy until a term delivery by cesarean section. As uterus didelphys is a rare anatomical anomaly, most reports on the subject are based on small retrospective studies or case reports. This results in imperfect sampling and thus often equivocal results. In the context of low prevalence of uterus didelphys in the population and of conflicting reports on the malformation's impact on fertility, couples with this condition who are trying to conceive require highly personalized management.

Key words:

uterus didelphys, infertility, insemination

Introduction

Uterine anomalies are among the most common congenital abnormalities of the female reproductive system, with a prevalence of 2–4% in the general population [1,2]. During embryonic development, the uterus is formed out of the two paramesonephric (Mullerian) ducts. Uterine malformations most commonly result from incomplete fusion of the two Mullerian ducts, which normally occurs between 6 and 22 weeks of gestation. If the Mullerian ducts fail to fuse altogether, a duplex uterus is formed [3]. Clinical symptoms of congenital reproductive malformations, if any, mostly occur at reproductive age, and include recurrent pain or recurrent pregnancy loss. Concurrent congenital urinary tract anomalies are often found.

Currently, the etiopathogenesis of uterine malformations is considered to involve multiple factors, including: abnormal Mullerian regression factor production within the embryonic gonads, local absence of estrogen receptors within the Mullerian ducts, teratogenic factors interfering with the normal development of Mullerian ducts into target structures, abnormal apoptosis resulting from Bcl2 gene mutation, abnormal activity of genes broadly involved in embryogenesis (WT1, PAX2, HOXA7, HOXA13, and PBX1), and abnormal activity of the WNT4 gene that belongs to a family of genes regulating cell and tissue growth and differentiation during development [4,5].

In the currently used classification, developed in 1988 by the American Fertility Society (now: American Society for Reproductive Medicine), didelphic uterus is classified in group III [6]. It is the least common uterine malformation [2,7,9]. In consequence, reports regarding fertility and course of pregnancy in women with uterus didelphys are based on a limited number of cases and thus equivocal [2,7,10]. Hence the need for further analyses and reports on this anatomical anomaly in women trying to conceive, and later, throughout the pregnancy, in order to better establish the understanding of the issue.

The present case report discusses the case of a patient with uterus didelphys who conceived by intrauterine insemination with her husband's semen, and carried the pregnancy until a term delivery by cesarean section.

Presentation of Case

The patient, aged 29, and her partner, aged 31, were consulted in 2016 at the "OVUM" Fertility Center in Lublin, Poland, due to failure to achieve a first pregnancy after 2 years of regular unprotected intercourse. The patients were not treated for other chronic conditions, had normal BMI values, were non-smokers, and were not exposed to any workplace hazards. The patient menstruated regularly, every 28 days, with menstrual pain.

Pelvic examination at the first visit found a vaginal septum and two cervices. Sonogram showed a duplex uterus and 2 normally-sized ovaries. The following tests were scheduled: seminogram, hysterosalpingography, ovarian reserve test, and ultrasound monitoring of the menstrual cycle.

Hormonal tests performed within the next 3 days showed normal ovarian reserve (AMH – 5.15 ng/mL, FSH – 5.71 mIU/mL, LH – 4.32 mIU/mL). Ultrasound examination confirmed ovulation. Hysterosalpingography was performed under anesthesia, following the introduction of a Foley catheter into one cervix, and a Schultze salpingograph into the other. The examination showed a double uterus, with contrast medium freely passing through the fallopian tubes (Fig. 1). Semen analysis in accordance with 2010 WHO guidelines showed a decreased percentage of sperm with normal morphology (2%), while the remaining parameters were within normal ranges (volume – 2.5 mL; count – 41.5 M/mL; percentage of sperm with progressive motility – 61%). Based on the test results, the patients were scheduled for intrauterine insemination (IUI), preceded by gonadotropin ovulation induction. The patient's partner started taking a dietary supplement (FertilMan Plus®: Babystart Limited).

In the first cycle, the patient was administered 75 units of recombinant FSH (rFSH Gonal-F®: Merck-Serono) at the 3rd, 5th, and 7th day of the cycle. At the 11th day of the cycle, sonogram showed 1 follicle sized 20mm in the right ovary, a 20mm follicle in the left ovary, and a 10mm endometrium. Ovulation induction with 250 μg of recombinant human chorionic gonadotropin (rhCG; Ovitrelle®: Merc-Serono) was ordered (before the patient's LH surge). After

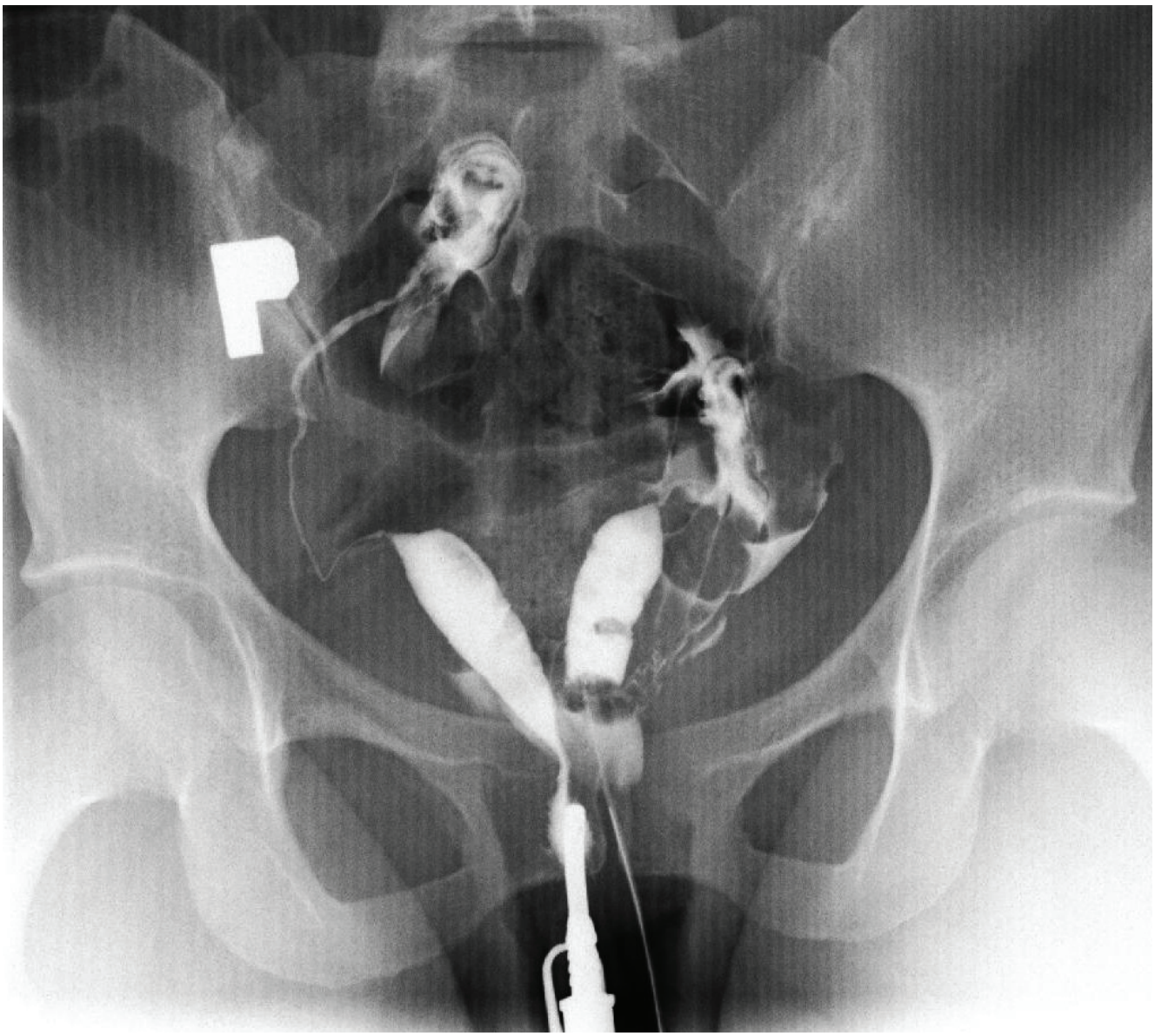

Fig. 1
Uterus didelphys by hysterosalpingography

36 hours, IUI was performed, with 0.3 ml of semen, prepared using the gradient method, introduced into each uterine cavity. Prior to preparation, the semen parameters were as follows: sperm count – 40 M/mL, progressive motility – 40%, normal morphology – 2%. At the time of the procedure, the follicles had not ruptured. In the second phase of the cycle, oral gestagens (Luteina®: Adamed) were administered. Pregnancy was not achieved.

In the second cycle, the patient was administered 37.5 units of rFSH (Ovaleap®: Teva) daily, starting at the 3rd day. At the 11th day of the cycle, sonogram showed a single follicle sized 19 mm in the right ovary and a 11 mm endometrium; rHCG was ordered at the same dose as in the previous cycle (again, before the patient's LH surge). After 41 hours, IUI was performed, with prepared semen introduced into the right uterine cavity. Prior to preparation, the sperm count was 42 M/mL, progressive motility – 50%, normal morphology – 2%. An ultrasound examination prior to the IUI procedure showed that the follicle had burst. The patient started oral gestagen supplementation as in the previous cycle. Two weeks later, pregnancy was found based on a beta hCG test, and continuation of gestagens was ordered.

Between week 6 and 8 of the pregnancy, low-grade bleeding occurred. Otherwise, there were no complications in the course of pregnancy. The patient

delivered at 38 weeks by cesarean section due to the breech position of the fetus. The baby weighed 3100g, was anatomically normal, with the Apgar score of 10 points. Following a 5-day hospitalization, the mother and baby were discharged in good condition.

Discussion

As uterus didelphys is a rare anatomical anomaly, most reports on the subject are based on small retrospective studies or case reports. This results in imperfect sampling and thus often equivocal results. Especially in studies on female patients' fertility, the reproductive potential of the patient's partner should also be included in the analysis as a significant factor. The available reports on concurrent endometriosis in some women with uterus didelphys also indicate that the patients' fertility may be subject to individual variation [8,11,12].

The largest retrospective study on the reproductive impact of uterine malformations was performed by Raga et al. on a group of 3181 patients, and reported decreased fertility and increased risk of miscarriage in the group [2]. The authors also reported a higher prevalence of uterine defects in women with decreased fertility than in those with normal fertility [2]. Similar observations were made by Gruszka et al. in a study on a group of 124 patients with various uterine malformations. The authors found fertility disorders in one in four patients with didelphic uterus, with a 45% risk of miscarriage and a 38% risk of premature birth [7]. Different findings were reported by Heinonen in a study of 49 didelphic uterus cases, where no fertility impairment or increased miscarriage risk were observed. Similarly, Grimbizis et al. report similar prevalence of uterine defects in the populations of fertile and fertility-impaired women, thus questioning the impact of genital malformations on female fertility.

The reproductive potential of women with didelphic uterus seems to be as yet uncertain. However, in analyses of patients' fertility, researchers have disregarded differences in vaginal septum length. The vaginal septum varies in length among patients with didelphic uterus. In the present case, the length was 2.5 cm, but longer septa are found as well. Presumably, with a long vaginal septum, the introduced semen can only effect fertilization if the dominant follicle is on the same side. With a shorter septum, this would likely be of less importance.

Undoubtedly, in couples failing to conceive, fertility is to a larger or lesser extent impaired in both partners. Focusing solely on the first diagnosed abnormality is wrong and may cause the couple to lose precious reproductive time. Even when the fertility treatment process is successful, the question about which component of the treatment contributed the most to this success has no clear answer in most cases.

In the present case, interventions that may have contributed to the pregnancy included the insemination procedures, antioxidant supplementation in the partner, and ovulation induction. However, it is debatable whether the semen prepared should be administered into one or both uterine cavities when bilateral ovulation occurs, if semen parameters are decreased. Administration of the semen into both uterine cavities may result in a decreased number of normal sperm reaching a single ovum, which would decrease the likelihood of pregnancy [18]. Moreover, the possibility of a twin pregnancy developing in both uterine cavities, considering the numerous reports of increased premature birth risk in women with uterine malformations, could decrease the likelihood of a live birth. In the present case, during the first procedure, both uterine cavities were inseminated, which, however, failed to produce a pregnancy. Only the second insemination of one uterine cavity proved effective. Semen parameters were similar in both insemination procedures.

The therapeutic success may have also been partly due to the fact that, by the second insemination procedure, the partner had been taking antioxidant supplements for three months, meaning that the semen used for IUI had been under the beneficial influence of the supplements in the entire cycle of spermatogenesis [14,15]. By the first insemination procedure, only two thirds of the spermatogenetic cycle had been affected by the antioxidant supplement, which may have been insufficient for an increase in semen quality.

Another aspect that differed between the two procedures was the time between ovulation induction before the patient's LH surge and the insemination. With the first procedure, the time was 36h and follicles had not ruptured. With the second, the time was 41h and the follicle had already ruptured. IUI procedures are typically performed 24 or 36 hours after administration of the ovulation inducer [16,17,18]. In clinical practice, the timing of the procedure often depends on individual aspects related to semen collection, liquefaction and preparation. Presumably, the shorter the interval between the procedure and follicle rupture, the higher the likelihood of pregnancy, as sperm waiting for the ovum undergo intensifying DNA fragmentation processes that decrease its reproductive potential [19,20].

In the context of low prevalence of uterus didelphys in the population and of conflicting reports on the malformation's impact on fertility, couples with this condition who are trying to conceive require highly personalized management [21,22,23].The present case report may offer a basis for further discussion regarding the infertility treatment process for couples where uterine malformations are diagnosed. Undoubtedly, the issue of reproductive health in women with didelphic uterus requires further studies.

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Disclosure

The author declare that he have no competing interests.

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