



## Unicornuate uterus and undescended ovary : diagnostic and therapeutic implications

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**OBJECTIVE(S) :** To appraise the association between unicornuate uterus and ectopic (undescended) ovaries with emphasis on diagnostic procedures and therapeutic implications.

**METHOD(S) :** A magnetic resonance image (MRI) after mild clomiphene citrate (CC) stimulation was used to visualize the presence of an undescended ovary in the upper abdomen in 12 cases of unicornuate uterus.

**RESULTS :** Six out of 12 patients with a unicornuate uterus had a concomitant ectopic ovary.

**CONCLUSION(S):** Undescended ovaries are commonly found in women with a unicornuate uterus. The lack of reports on undescended ovaries is fascinating, suggesting the possibility that many cases remain unrecognized. Consequently, important clinical information is missed in many patients. MRI after CC stimulation is an elegant method to diagnose ectopic ovaries.

**Key words:** ectopic ovary, infertility, MRI, undescended ovary, unicornuate uterus

### Introduction

Uterine malformations are the result of major disturbances in the development, formation or fusion of the paramesonephric (mullerian) ducts during fetal life. The unicornuate uterus is caused by the non-development of one mullerian duct or the

failure of the contralateral side to migrate to its proper location. The unicornuate uterus covers a wide range of anatomical entities. Possibilities are a unicornuate uterus with a communicating or non-communicating rudimentary horn, a rudimentary horn without uterine cavity, and the isolated unicornuate uterus. The true prevalence of this uterine malformation is difficult to estimate because data are derived from surveys collected in infertility clinics and anecdotal case reports. The estimated prevalence of a unicornuate uterus is rather low, approximately 0.3% of the whole population, 0.6% of the infertile population, and 0.2% of the fertile population <sup>1</sup>. Of the mullerian defects, however, unicornuate uterus is

found in 3 to 13% of women <sup>1-3</sup>. The presence of a unicornuate uterus is associated with increased obstetric complications like early miscarriage, ectopic pregnancy, abnormal fetal presentation, intrauterine growth retardation, and premature labor <sup>1,4-8</sup>.

Undescended or ectopic ovaries are characterized by the attachment of their upper pole to an area above the level of the common iliac vessels. Although ovarian maldescent occasionally occurs in patients with a normal uterus, the incidence is reported to be 20% when the uterus is absent (Rokitansky-Kustner - Hauser syndrome) and as high as 42% in cases of unicornuate uterus. Bilaterality occurs more often in women with congenital absence of the uterus <sup>9</sup>.

Despite the well-known association of undescended ovaries and unicornuate uterus, ovarian maldescent is reported only sporadically, suggesting the possibility that many cases go unrecognized <sup>10</sup>.

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We describe here the embryological background of mullerian duct anomalies and undescended ovaries. Secondly, we illustrate the association between unicornuate uterus and undescended ovaries. In five patients, the diagnosis of undescended ovary was missed during a routine infertility exploration including hysterosalpingography (HSG), hysteroscopy and laparoscopy. In all cases the diagnosis was eventually made by using magnetic resonance imaging (MRI) after ovarian stimulation with clomiphene citrate (CC) <sup>11-13</sup>.

### **Embryology of mullerian duct anomalies and ectopic ovaries**

During the indifferent stage of duct development, between the 5<sup>th</sup> and the 8<sup>th</sup> week of pregnancy, two pairs of ducts appear and coexist in all embryos, the mesonephric ducts or Wolffian ducts and the paramesonephric ducts, better known as the mullerian ducts. Male differentiation is instigated by the presence of a single factor encoded on the Y-chromosome; female differentiation occurs in its absence. In the absence of mullerian-inhibiting substance which is produced by the sertoli cells in the developing testis, the paired mullerian ducts ultimately develop into the structures of the female reproductive tract. The structures include the fallopian tubes, uterus, cervix, and upper part of the vagina. The ovaries and lower part of the vagina have separate embryologic origins not derived from the mullerian system. Complete formation and differentiation of the mullerian ducts into the different parts of the female reproductive tract depend on completion of three phases of development, i.e. organogenesis, fusion, and septal resorption.

Lateral fusion is the process during which the lower segments of the paired mullerian ducts fuse to form the uterus, cervix, and upper vagina. Bicornuate uterus and didelphys uterus are the result of a failure of fusion. The term vertical fusion occasionally is used to refer to fusion of the ascending sinovaginal bulb with the descending mullerian system. Complete vertical fusion forms a normal patent vagina, while incomplete vertical fusion results in an imperforate hymen. After the lower mullerian ducts fuse, a central septum is present, which subsequently must be resorbed to form a single uterine cavity and cervix. Failure of resorption is the cause of a septate uterus. Ovaries and the lower vagina are not derived from the mullerian system. If both the mullerian ducts do not develop fully, uterine agenesis or hypoplasia is found. A unicornuate uterus is the result of a non-development of one mullerian duct. Depending on the status of the rudimentary horn, four-basic classifications of a unicornuate uterus can be made - (1) no rudimentary horn (2) no cavity (3) communicating and (4) non-communicating. During the third month of fetal life, the ovaries descend from the posterior abdominal wall near the kidneys to the point just inferior to

the pelvic brim. The descent is guided by the gubernaculum, a cord of mesenchyme connected to the lower pole of each gonad. Undescended ovaries are uncommon and mostly associated with an absent uterus (Rokitansky-Kustner-Hausser syndrome) or a unicornuate uterus.

### **Methods and Results**

Three women with infertility having unicornuate uterus undergoing CC stimulation of ovaries for IUI showed discrepancy between estradiol levels and follicular growth. This led to the suspicion of an ectopic ovary. Hence MRI was done which confirmed the presence of ectopic ovary.

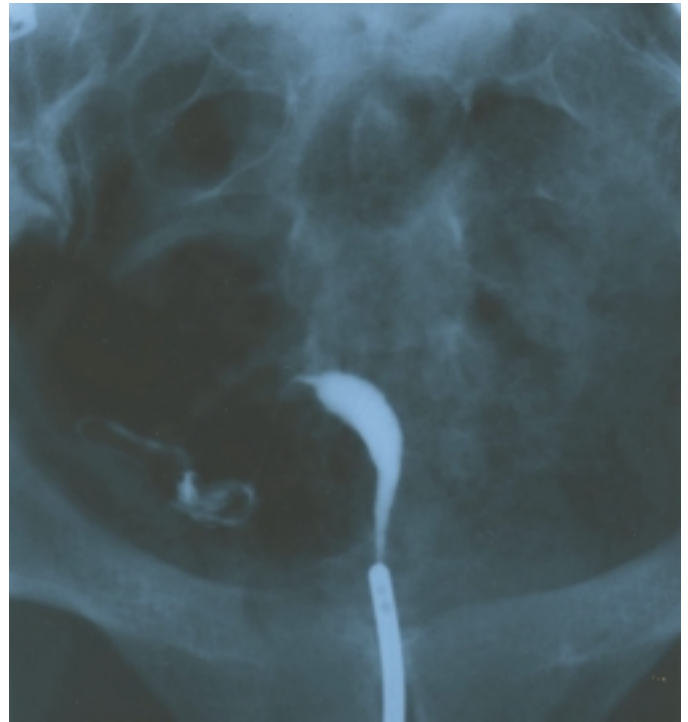
The first couple was referred with a history of primary infertility for 3 years. Investigation of the male revealed azoospermia with high serum FSH levels and bilaterally small testicles. Genetic testing was normal. The diagnosis of sertoli-cell-only syndrome was made by testicular biopsy. An infertility work-up of the female was normal, except for the HSG which showed a unicornuate uterus with one patent tube on the left side. These findings were confirmed laparoscopically. Intravenous pyelography (IVP) revealed no abnormality. The couple was entered in our donor-insemination program. CC (50 mg per day for 5 days from day 5 to 9) was used for mild ovarian stimulation. During the second treatment cycle, serum estradiol levels reached > 600 pg/mL without any ovarian response on ultrasound. Because an ectopic ovary was suspected, vaginal and abdominal ultrasound were 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 the 12<sup>th</sup> day of the cycle. This confirmed the presence of the unicornuate uterus and revealed a left sided undescended ovary at the level of the pelvic brim, anterior to the psoas muscle, containing several follicles. A thin cord-like structure continued from this ovary in the direction of the internal inguinal canal. The diagnosis of an undescended (ectopic) ovary was made. The right ovary was entirely normal.

The second couple was referred with primary infertility. In the referring center, hysteroscopy and laparoscopy were performed confirming the diagnosis of unicornuate uterus with one tube and one normally located ovary on the left side. On vaginal ultrasound, only one ovary could be seen. An infertility work-up of the male revealed moderate teratozoospermia with 7 % ideal forms using strict criteria of sperm morphology <sup>14</sup>. Urological examination with IVP showed no abnormalities. We started with intrauterine insemination (IUI) after CC ovarian stimulation as a first line treatment. On day 15 of the first IUI cycle, serum estradiol levels reached 272 pg/mL with only one follicle of 12 mm

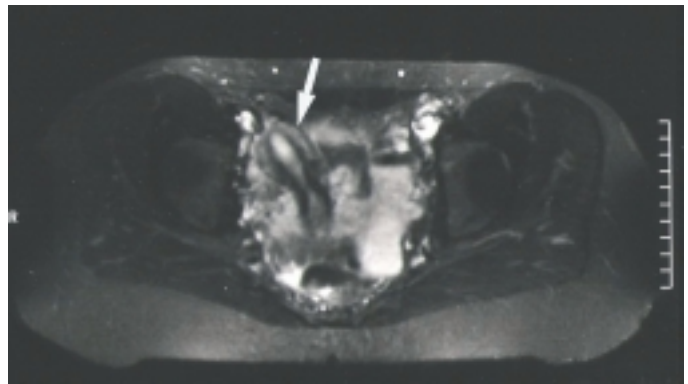
diameter on vaginal ultrasound. MRI after CC ovarian stimulation was carried out because of the discrepancy between follicular size and estradiol level. The diagnosis of a right-sided undescended ovary in the upper part of the pelvis, anterior to the intersection of the psoas and the iliac muscles was made. The ectopic ovary contained numerous follicles, the largest 16 mm in diameter. Ultrasound measurement of follicular growth was continued every other day from day 9 onwards. Because of a spontaneous LH-surge without substantial follicular changes in the normal right-sided ovary (maximum diameter 12 mm), IUI was cancelled and timed intercourse was planned. Serum estradiol levels reached a maximum value of 385 pg/mL. Two days after the LH-surge, some fluid could be visualized in the pouch of Douglas. Ultrasound monitoring was continued until 4 days post-LH-surge. The maximum follicle diameter remained 12 mm although an elevated progesterone level (4.4 ng/mL) could be observed and the endometrium showed typical post-ovulatory pattern. A pregnancy was confirmed two weeks later and after an uneventful antenatal period, a healthy baby boy in breech presentation weighing 3050 g was delivered by cesarean section. This was the first report of an intrauterine pregnancy originating from an ectopic ovary <sup>11</sup>.

The third couple was referred for IVF after two unsuccessful IUI attempts with homologous semen. Previously, the diagnosis of normogonadotropic anovulation, a unicornuate uterus, and only one ovary and tube on the right side was made elsewhere. Unilateral tubal patency was documented by HSG (Figure 1) and laparoscopy. Two consecutive semen samples confirmed the diagnosis of unexplained oligoasthenoteratozoospermia. More than one million motile spermatozoa could be recovered after washing procedure and therefore IUI treatment with CC ovarian hyperstimulation was continued. Once again a discrepancy between serum estradiol levels and ovarian ultrasound images (follicular growth) was observed. An undescended ovary was suspected and MRI after mild ovarian CC-stimulation confirmed the presence of a left retroperitoneal undescended ovary. Its cranial border reached to the left side of the second lumbar vertebra and the caudal part of the cord-like ovary stretched to the internal inguinal canal. The left kidney was absent. The normally located right-sided uterus could be seen on MRI (Figure 2).

The fourth couple had been treated with 12 unsuccessful trials with IUI using donor semen. It was a case of non-obstructive azoospermia. 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 confirmed on IVP. The patient mentioned difficulties encountered during previous IUI procedures. This suggested



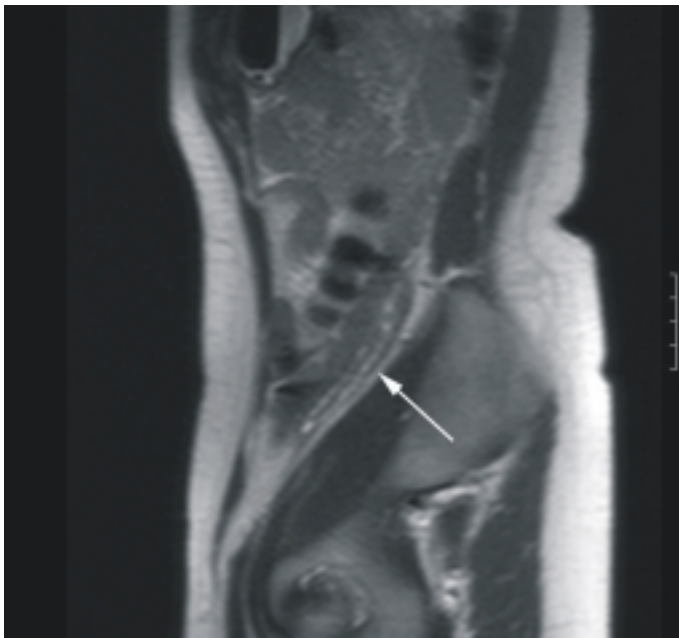
**Figure 1.** A hysterosalpingogram showing a unicornuate uterus with a patent tube on the right side.



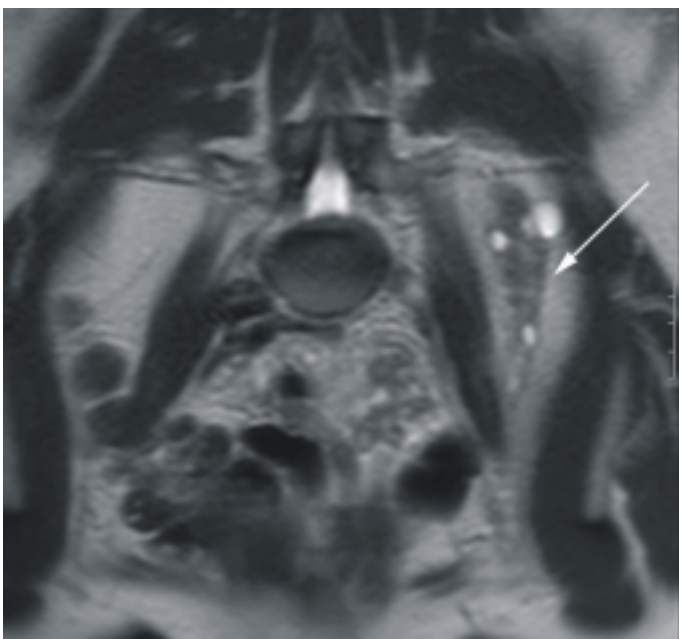
**Figure 2.** MRI showing short tau inversion recovery (STIR) image in the axial plane. A right unicornuate uterus (arrow) is demonstrated. A small amount of fluid is seen in the endometrial cavity.

a problem of cervical stenosis. An attempt to dilate the cervical canal failed. Treatment using in vitro fertilization (IVF) and zygote intra-fallopian transfer (ZIFT) was offered to the couple. Considering our experience with the previous cases of unicornuate uterus, an MRI after CC ovarian stimulation was performed. MRI confirmed the presence of an undescended ovary at the right pelvic brim, anterior to the psoas muscle.

Because of the above described experiences, an MRI after

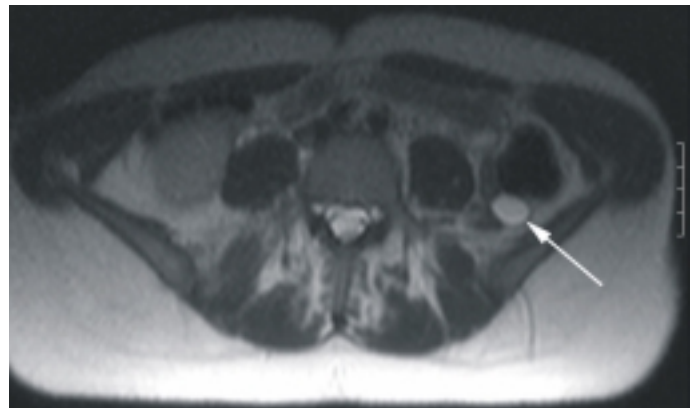


**Figure 3.** T2 weighted image in the sagittal plane. A streak ovary is seen (arrow) and is outlined posterior of the descending part of the colon, anterior to the iliopsoas muscle.



**Figure 4.** T2 weighted image a paracoronal plane, at the level of the cranial pelvic brim. The left, maldescended ovary is seen and has a streaky anatomical configuration. It contains many small follicles (arrow).

CC-stimulation is now being performed routinely in all cases of unicornuate uterus. In the last two years another eight cases of unicornuate uterus presented at our infertility clinic and two more cases of undescended ovary were discovered (Figure 3,4 and 5). In one patient the undescended ovary



**Figure 5.** T2 weighted image in the axial plane. A small hyperintense structure (arrow) is demonstrated posterior of the descending part of the colon, adjacent to the suprailiac part of the psoas muscle. This structure corresponds to a follicle in the undescended ovary..

could also be visualised on abdominal ultrasound.

### MRI: Technics and methods

MRI has already proven its value in the detection and characterization of a wide variety of disorders of the female reproductive organs<sup>15-17</sup>. MRI imaging enables a physician to make an accurate diagnosis of various benign adnexal masses and helps to obviate unnecessary surgery. Ultra-fast cross-sectional T1 and T2 weighted images can be used to visualize normal and pathological ovaries. 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 undescended ovaries are lacking. In our center we use MRI as the primary imaging tool to detect the location and the appearance of the contralateral ovary in patients with a unicornuate uterus. MRI was chosen because this technic has a superior soft tissue contrast, has multiplaner imaging capabilities and lacks ionizing radiation. The latter is especially important in this selected patient population. MRI is also more sensitive, for the detection of an undescended ovary, than ultrasound. Because the presented cases stretch over a period of 6 years, the imaging technics differed to some degree. All studies were performed on 1 Tesla MRI unit (Siemens Magnetom Expert<sup>o</sup>, Erlangen Germany). In the first two cases, axial and coronal turbo spin echo (TSE) T2 weighted images were obtained (TE=99 msec/TR=4600 msec) followed by short tau inversion recovery (STIR) sequences in the coronal, sagittal and axial planes (TE=60 msec/TR=6000 msec). Since the stimulated ovaries contain 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 msec/TR=11 msec) focused on the ectopic ovary. This sequence is used to study the signal of the content of the follicles in the ovary. 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) technic (TR 1400 msec/TE 60 msec) in the later cases. Also late echo T2 weighted HASTE images were obtained in the same imaging planes (TR=1250 msec/TE=360 msec). The latter has the same imaging capabilities as of the STIR images where fluid has very high contrast compared to the surrounding tissue. All patients were examined in the supine position with a four element phased-array torso coil to optimize the signal-to-noise ratio. Slice thickness was 5 mm in all sequences. The center of the coil was positioned at the umbilicus of the patient. The field of view encompassed the area from the the upper border of the kidneys to the bladder base. Sedation and intravenous contrast were not applied. Image quality was adequate in all cases to detect the ectopic location of the ovary. Detection was most adequate on the T2 weighted images, especially on the heavily weighted HASTE series and STIR images.

## Discussion

Different terms have been used to describe an undescended or ectopic ovary. ‘Accessory ovary’ refers to cases in which excess ovarian tissue is situated nearby and connected to the normally placed ovary<sup>18,19</sup>. Ovarian remnant syndrome covers those cases that develop after pelvic surgery or after a history of pelvic inflammatory disease. It has been described earlier as ovarian tissue that may continue to function after transplantation from their original site<sup>20</sup>. Supernumerary ovaries include cases in which a third ovary is entirely separate from the eutopic ovary and may be located in the omentum or retroperitoneally. Lachman and Berman<sup>21</sup> were the first to propose 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: (1) postsurgical implant, (2) postinflammatory implant, and (3) true embryologic ectopic ovary. From an embryological point of view, the presence of ectopic ovaries can be explained by a lack of caudal descent of the gonads into the true pelvis<sup>22</sup> or by a retarded differential growth of that portion of the urogenital ridge which gives rise to both the gonads and the fallopian tube<sup>23</sup>. During the third month of fetal life, the developing ovaries descend from a position near the kidneys to their final position in the true pelvis. We believe that although the term ectopic ovary is commonly used worldwide, undescended ovary is probably a more accurate term, reflecting the underlying pathophysiology. Undescended ovaries may be unilateral or bilateral and can be associated with abnormalities of the mullerian ducts such as unicornuate uterus. The association of unicornuate uterus and urinary tract anomalies including ectopic kidney, renal agenesis, double renal pelvis, and horseshoe kidney is well established<sup>24</sup>. We have described

six cases of unicornuate uterus associated with true embryologic undescended ovaries. In all referred cases the undescended ovary was missed by routine fertility exploration. In the first three cases an MRI was performed after mild ovarian stimulation with CC because a discrepancy between serum estradiol levels and ovarian ultrasound images was found after controlled ovarian hyperstimulation. The multifollicular growth in the ectopic ovary greatly enhanced MRI diagnosis. In the second case we described the first intrauterine pregnancy originating from an undescended ovary more than 15 cm separated from the uterus and the normally located tube<sup>11</sup>. In the third patient, a retroperitoneal location of an undescended ovary was described<sup>13</sup>. This explains why this entity was missed by laparoscopy. Although the prevalence of unicornuate uterus is low, a correct diagnosis is mandatory. It is important to realize that reproductive performance is jeopardized when uterine malformations are involved. Early and late abortions as well as preterm delivery are described more frequently when a unicornuate uterus is involved<sup>1,4,5,7,8</sup>. Concerning assisted reproduction, significantly lower implantation rates are described after IVF-ET in unicornuate uterus cases<sup>25</sup>. Percutaneous oocyte retrieval from an inguinal ovary has been described before, and ultrasound guided percutaneous oocyte retrieval will be possible for most undescended ovaries, especially if the correct diagnosis is made<sup>26</sup>. The knowledge of the existence of an ectopic ovary is also of importance and relevance in the following clinical situations – exploration of unexplained cyclic abdominal pain due to folliculogenesis, ovulation and cyst formation in the undescended ovary, medical conditions where surgical castration is indicated, and counseling about the potentially increased risk of malignant degeneration in retroperitoneal ectopic ovaries. It is possible that a retroperitoneal location of the ectopic ovary may predispose to neoplastic changes in analogy with the undescended testis<sup>19,27,28</sup>. Testicular cancer risk is increased in men with a history of cryptorchidism. This increased risk even applies to the contralateral testis<sup>29-31</sup>. MRI has proven to be the best imaging method to explore an ovary in an anomalous position and to document associated malformations<sup>15-17</sup>. Continuous refinement of the MRI technic, further improvement of the spatial resolution, and increased availability of MRI will progressively increase its application in the detection of undescended ovaries and other mullerian fusion defects. Since both intra- and extraperitoneal locations of undescended ovary may occur, one could argue that MRI could precede or replace laparoscopic evaluation in this specific patient population<sup>32</sup>. Our results indicate that MRI after CC ovarian stimulation in all cases of unicornuate uterus will detect undescended ovaries more frequently than is appreciated so far. This elegant method seems to be superior to ultrasound, computerized tomography, and even laparoscopy. The advantage of investigating the kidney at the same time is another important argument to

promote this novel and sensitive tool in the diagnosis of undescended ovary, an entity which has probably gone unrecognized until now in many patients at risk.

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