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Congenital absence of the uterus and vagina is not commonly transmitted as a dominant genetic trait: outcomes of surrogate pregnancies*

John C. Petrozza, M.D.†‡
Mark R. Gray, Ph.D.†§
Ann J. Davis, M.D.†
Richard H. Reindollar, M.D.†

Department of Obstetrics and Gynecology, Tufts University School of Medicine, Boston, Massachusetts

Objective: To determine the inheritance pattern of congenital absence of the uterus and vagina in affected women undergoing surrogacy IVF with this disorder.
Design: Retrospective study.
Setting: A hospital-based reproductive endocrinology and infertility center.
Patient(s): Women diagnosed with congenital absence of the uterus and vagina undergoing IVF with subsequent transfer of embryos to a surrogate uterus.
Intervention(s): Questionnaires were sent to all infertility treatment centers performing surrogate procedures.
Main Outcome Measure(s): Number, gender, and frequency of congenital anomalies in progeny.
Result(s): Thirty-two of 53 surveyed programs responded (60%). One hundred sixty-two IVF cycles were performed, and 34 liveborn children were delivered (half female). No congenital anomalies were found, except for one male child with a middle ear defect and hearing loss.
Conclusion(s): These results strongly suggest that congenital absence of the uterus and vagina, if genetically transmitted, is not inherited commonly in a dominant fashion.
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Key Words: Congenital absence of the uterus and vagina, surrogacy, in vitro fertilization, Rokitansky-Küster-Hauser syndrome, genetics, inheritance

Congenital absence of the uterus is uncommon (1:5,000) and always associated with absence of the upper portion of the vagina. The uterus is often hypoplastic, consisting of bilateral noncanalized fibrous cords. The vagina can develop only if one or both of the müllerian ducts contacts the endodermal epithelium of the urogenital sinus. The genetics of congenital absence of the uterus and vagina is complex. Almost all patients have a 46,XX karyotype; only a few chromosomal abnormalities have been reported in patients with congenital absence of the uterus and vagina (1). Several familial aggregates of congenital absence of the uterus and vagina and

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† Division of Reproductive Endocrinology.
‡ Reprint requests: John C Petrozza, M.D., Department of Obstetrics and Gynecology, Tufts University School of Medicine, New England Medical Center, 750 Washington Street, Box 036, Boston, Massachusetts 02111 (FAX: 617-636-5906).
§ Program in Cell, Molecular, and Developmental Biology, Program in Genetics, Department of Anatomy and Cellular Biology.

patients with affected siblings have been reported (2), suggesting that congenital absence of the uterus and vagina is a rare autosomal recessive trait. However, because monozygotic twins discordant for congenital absence of the uterus and vagina exist, it is unlikely that every case has an easily explainable genetic cause. Shokeir (3) evaluated 16 Saskatchewan families affected by congenital absence of the uterus and vagina. Ten of these probands had affected siblings or affected paternal relatives, suggesting female-limited autosomal dominant inheritance. However, a survey of 23 American women with congenital absence of the uterus and vagina failed to identify any affected relative, suggesting that either a female-limited autosomal dominant and autosomal recessive inheritance was not likely in this group (4). We surveyed IVF programs that use surrogate pregnancy for patients with congenital absence of the uterus and vagina, for evidence of this disorder or associated stigmata in the progeny of affected women.

MATERIALS AND METHODS

Fifty-three IVF programs in the United States listed in The American Fertility Society and Society for Assisted Reproductive Technology directory as surrogacy centers were surveyed (5). A questionnaire was sent to each center requesting the following: number of surrogacy procedures performed for women with congenital absence of the uterus and vagina, number and gender of births, extent of neonatal physical examination, and number and type of congenital anomalies noted in neonate and early childhood. Programs that did not respond were sent another survey form, followed by a telephone call requesting their participation. Each child was examined by a pediatrician for renal, skeletal, and genital defects. Positive results were followed up by telephone.

RESULTS

Thirty-two (60%) programs responded. Seven programs (22%) reported procedures performed for women with congenital absence of the uterus and vagina. One hundred sixty-two cycles were performed in 58 women with congenital absence of the uterus and vagina resulting in 34 live births (17 female, 17 male). One male child was diagnosed with an unspecified middle ear defect and hearing loss.

DISCUSSION

Until assisted reproductive technologies with surrogacy became available, individuals with congenital absence of the uterus and vagina were unable to reproduce and the mode of inheritance of their disorder remained untested. This survey is the first accumulated data from surrogacy programs to analyze specifically the genetics of congenital absence of the uterus and vagina. These data suggest that this disorder is not inherited in a dominant fashion. If the patients who underwent surrogacy carried a dominant mutation causing congenital absence of the uterus and vagina that is expressed only in females, one would expect 50% of their female progeny to be affected, or 8 to 9 of the 17 female infants should have the manifestations of the disorder.

Only one anomaly was detected in the 34 children of the women with congenital absence of the uterus and vagina: a male with a middle ear defect and hearing loss. The association of ear defects with müllerian tract abnormalities has been observed previously in müllerian anomalies. The ear defects cause auditory deficits in the high frequency range and often can be elicited only with audiometric testing (6). Ossicular deformities have been demonstrated in several patients. Sixty percent of these patients may have renal agenesis. The combination of genitourinary and auditory system defects may be caused by a single developmental defect, including the formation of mesoderm and neural crest cells. These organ systems are formed at 4 to 6 weeks and are completed at 16 to 18 weeks. Any genetic or teratogenic insult during this period may cause a range of müllerian duct or ear defects.

The present findings and earlier reports suggest that congenital absence of the uterus and vagina is a multifactorial disorder with a polygenic mode of inheritance. This pattern is the usual mode of inheritance for anomalies affecting a single organ system or embryologically related systems. It also explains the sporadic reports of families with multiple affected siblings and relatives, our findings of no similarly affected progeny for surrogate women with congenital absence of the uterus and vagina, and a male child reported here with a middle ear defect. Other explanations include recessive gene mutations specific to certain populations (i.e., Saskatchewan) or de novo somatic cell mutations. The phenotypic variation seen for renal, skeletal, and müllerian defects is further evidence for the genetic heterogeneity of congenital absence of the uterus and vagina.

In conclusion, this study suggests that congenital absence of the uterus and vagina is not inherited commonly in a dominant fashion. It is likely a polygenic, multifactorial, or possibly a recessive trait. Perhaps as more surrogate pregnancies occur for

these patients, a clearer presentation of the genetic component of this syndrome may evolve.

REFERENCES

1. Kucheria K, Taneja N, Kinra G. Autosomal translocation of chromosomes 12q and 14q in müllerian duct failure. Indian J Med Res 1988;87:290–2.
2. Sarto GE, Simpson JL. Abnormalities of the müllerian and Wolffian duct systems. Birth Defects 1978;14:37–54.
3. Shokeir MHK. Aplasia of the müllerian system: evidence for probable sex-limited autosomal dominant inheritance. Birth Defects 1978;14:147–52.
4. Carson SA, Simpson JL, Malinak LR, Elias S, Gerbie AB, Buttram VC, et al. Heritable aspects of uterine anomalies. II. Genetic analysis of müllerian aplasia. Fertil Steril 1983; 40:86–90.
5. The American Fertility Society. The American Fertility Society and Society for Assisted Reproductive Technology: clinic-specific outcome assessment for the year 1992. Birmingham: The American Fertility Society, 1994.
6. Letterie GS, Vauss N. Müllerian tract abnormalities and associated auditory defects. J Reprod Med 1991;36:765–8.

Note. Additional references are available upon request.