Role of the uterus in fertility, pregnancy, and developmental programming

The extent to which the uterine endometrium contributes to the success of fertility treatments has long been debated. Several uterine conditions have been associated with poor endometrial receptivity and low pregnancy rates (1). Thin endometrium, fibroids, adenomyosis, and endometriosis, for example, can each affect uterine receptivity and limit the ability to conceive. Many of these conditions are commonly seen in the infertile population and many may go undiagnosed. In the absence of obvious defects, the contribution of uterine receptivity to in vitro fertilization success has been controversial; the uterus and eggs are linked in most women undergoing in vitro fertilization making it difficult to discern the relative contribution of the egg versus the endometrium. Oocyte donation can overcome the effect of aging and restore fertility in women no longer producing viable eggs, however it has still been difficult to discern the independent effect of uterine related defects in the infertility population. Gestational carriers have been reported to have higher implantation, clinical pregnancy and live birth rates, suggesting that, in the infertile population, uterine factors are a contributor (2). In this issue Seagal et al. (3) rigorously isolated the effects of the uterine factor in an infertile population compared to healthy fertile women by examining outcomes of oocyte donation cycles in women using their own uterus vs those using gestational carriers. As all used donor eggs, differences in pregnancy rates and outcomes can be attributed to the uterine environment rather than egg quality. Inclusion of large numbers of cycles available through the Society for Assisted Reproductive Technologies (SART) database, gave power to discern the effect of uterine defects on fertility. Data available from SART included pregnancy outcome, birth weight and gestational age at delivery.

Analysis included over 20,000 donor oocyte cycles; of these almost 2,000 were gestational carrier cycles resulting in over 1,000 deliveries while over 18,000 were intended parent recipient cycles resulting in well over 7,000 deliveries. Patients using a gestational carrier had a significantly increased adjusted odds ratio (aOR) of pregnancy (aOR 1.33) and live birth (aOR 1.37). These results were unaffected by adjustment for age, suggesting that uterine defects are not simply a matter of an aging uterus. The fertile population has a 30% to 40% increase in pregnancy rates attributable to lack of uterine implantation defects. A greater understanding of uterine defects and optimal evaluation of the uterus/endometrial receptivity are critically needed.

Not only were pregnancy rates higher in the gestational carrier cycles, pregnancy outcomes were also improved. Among singletons the rate of prematurity was decreased, and birth weight was increased. This suggests that uterine defects influence gestation well after the window of implantation. Poor/shallow implantation and defective decidualization are thought to contribute to fetal well-being, pregnancy complications and prematurity (4). The uterus also plays a vital role in developmental programming; many aspects of adult health and disease are also impacted by fetal exposures and influenced by the uterine environment (5). Long term health outcomes are not tracked by SART and clinically may not be apparent for many decades. While the role of the uterus in fetal programming leading to adult health is well established in animal models, the difficulty in identifying uterine defects and tracking offspring over many years make this data scarce in humans. There is good reason to believe that uterine factor infertility has greater implications than the infertility itself. The long-term health of an individual gestated in an impaired or defective uterus may be compromised.

While the role of the uterus is now better defined in oocyte donor recipients, the same principles likely apply to all infertility patients. Can we identify uterine defects and correct them? Clearly some are amenable to therapy: endometriosis, hydrosalpinxes, polyps, and fibroids can be identified and treated. Thin endometrium, adenomyosis and peritoneal inflammation may be more difficult to rectify, however further efforts to understand how these conditions affect endometrium may lead to enhanced therapies. A thorough uterine evaluation may enhance not only fertility, it may also improve multiple health outcomes in the offspring.

Perhaps pre-conception counseling should always incorporate a uterine evaluation. Implantation defects are likely more common than currently recognized; infertility may represent the most extreme type of implantation defect, in which no pregnancy results. Some fertile women likely have shallow or defective implantation rather than failed implantation. Defective implantation is linked to pregnancy complications and may well be associated with defective developmental fetal programming. Even couples without infertility may benefit from a careful uterine evaluation to avoid unwanted pregnancy complications and to optimize fetal development.

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