ORIGINAL ARTICLE: INFERTILITY

Association of uterine fibroids and pregnancy outcomes after ovarian stimulation–intrauterine insemination for unexplained infertility

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Objective: To investigate the association of non–cavity-distorting uterine fibroids and pregnancy outcomes after ovarian stimulation–intrauterine insemination (OS-IUI) in couples with unexplained infertility.
Design: Secondary analysis from a prospective, randomized, multicenter clinical trial investigating fertility outcomes after OS-IUI.
Setting: Reproductive Medicine Network clinical sites.
Patient(s): Nine hundred couples with unexplained infertility who participated in the Assessment of Multiple Intrauterine Gestations from Ovarian Stimulation (AMIGOS) clinical trial.

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Intervention(s): Participants were randomized to one of three arms (clomiphene citrate, letrozole, or gonadotropins), and treatment was continued for up to four cycles or until pregnancy was achieved.
Main Outcomes Measure(s): Conception (serum hCG increase), clinical pregnancy (fetal cardiac activity), and live birth rates.
Result(s): A total of 102/900 participants (11.3%) had at least one documented fibroid and a normal uterine cavity. Women with fibroids were older, more likely to be African American, had a greater uterine volume, lower serum antimüllerian hormone levels, and fewer antral follicles than women without fibroids. In conception cycles, clinical pregnancy rates were significantly lower in participants with fibroids than in those without uterine fibroids. Pregnancy loss before 12 weeks was more likely in African American women with fibroids compared with non-African American women with fibroids. There was no difference in conception and live birth rates in subjects with and without fibroids.
Conclusion(s): No differences were observed in conception and live birth rates in women with non–cavity-distorting fibroids and those without fibroids. These findings provide reassurance that pregnancy success is not impacted in couples with non–cavity-distorting fibroids undergoing OS-IUI for unexplained infertility.
Clinical Trial Registration Number: NCT01044862. (Fertil Steril® 2016;■:■–■. ©2016 by American Society for Reproductive Medicine.)
Key Words: Intrauterine insemination, ovarian stimulation, pregnancy, unexplained infertility, uterine fibroids

Whether uterine fibroids impair pregnancy outcomes has been a longstanding topic of debate (1–7). Increased rates of implantation failure and early pregnancy loss have been consistently reported in women with submucosal fibroids and intramural fibroids that distort the endometrium (8–10). Historically there has been no consensus regarding the association of intramural and/or subserosal fibroids and pregnancy outcomes in women with a normal endometrial cavity contour. In women with intramural fibroids and a normal uterine cavity confirmed by hysteroscopy, saline sonohysterogram, or hysterosalpingogram, some studies have reported no difference in early pregnancy loss (9, 11), ectopic pregnancy (11), and live birth rates (9, 12) compared with women without fibroids and a normal endometrial cavity. In contrast, other studies have reported lower clinical pregnancy and live birth rates in the presence of intramural fibroids without endometrial cavity distortion (1, 4, 13). Because most studies are from a single center with a small sample size, are retrospective, and vary significantly in the selection of control groups and primary endpoints (clinical pregnancy vs. ongoing pregnancy vs. live birth), it is difficult to interpret contradictory results (2,14–19).

In addition to the notion that fibroids cause anatomic disruption and impair fecundity, there is also the thought that both unexplained infertility and fibroids share common underlying mechanisms (6). Specifically, the pathogenesis of unexplained infertility and fibroids may be mediated by inflammatory pathways, hormonal aberrations, and/or genetic alterations, all of which can negatively impact pregnancy outcomes (6, 20). In couples with unexplained infertility, who do not have an identifiable etiology for their inability to conceive, initial empirical treatment commonly involves ovarian stimulation with intrauterine insemination (OS-IUI) (21–23). It is estimated that approximately 10%–50% of reproductive-aged women have uterine fibroids (24, 25), and an estimated 15% of infertile couples have unexplained infertility (6, 26). The Reproductive Medicine Network's (RMN's) Assessment of Multiple Intrauterine Gestations from Ovarian Stimulation (AMIGOS) multicenter, randomized clinical trial provides an opportunity to evaluate the relationship between non–cavity-distorting fibroids and pregnancy outcomes in couples with unexplained infertility (27). The objective of this hypothesis-generating study was to use the AMIGOS database to investigate the association of non–cavity-distorting uterine fibroids and pregnancy outcomes in couples with unexplained infertility undergoing OS-IUI. Because a higher prevalence and greater severity of uterine fibroids has been consistently observed in African American women compared with other racial/ethnic groups (28–31), this study also sought to investigate whether there are race-specific differences in pregnancy outcomes in couples with unexplained infertility and non–cavity-distorting fibroids.

MATERIALS AND METHODS

Study Design

This secondary analysis included all 900 participants from the AMIGOS clinical trial. AMIGOS was a prospective, randomized, multicenter clinical trial that investigated the rate of conception, live birth pregnancy, and multiple gestations associated with OS-IUI in couples with unexplained infertility (27). The trial was conducted at 12 clinical locations in the United States (clinicaltrials.gov number NCT01044862). Randomized treatment arms included clomiphene citrate (300 couples), letrozole (299 couples), and gonadotropin (Menopur, Ferring Pharmaceuticals; 301 couples). Couples underwent OS-IUI treatment in the assigned arm until four cycles were completed or pregnancy occurred. Study participants were women aged ≥ 18 to ≤ 40 years, with regular menses (9 or more per year), a normal uterine cavity, at least one patent fallopian tube, and a male partner with an ejaculated semen specimen of at least 5×10^6 motile sperm. A complete description of study design, inclusion and exclusion criteria, statistical analyses, baseline characteristics, endocrine assays, and treatment outcomes of participants has been previously reported (27, 32, 33). Institutional review board approval was