High-intensity focused ultrasound for potential treatment of polycystic ovary syndrome: toward a noninvasive surgery

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Objective: To investigate the feasibility of using high-intensity focused ultrasound (HIFU), under dual-mode ultrasound arrays (DMUAs) guidance, to induce localized thermal damage inside ovaries without damage to the ovarian surface.
Design: Laboratory feasibility study.
Setting: University-based laboratory.
Animal(s): Ex vivo canine and bovine ovaries.
Intervention(s): DMUA-guided HIFU.
Main Outcome Measure(s): Detection of ovarian damage by ultrasound imaging, gross pathology, and histology.
Result(s): It is feasible to induce localized thermal damage inside ovaries without damage to the ovarian surface. DMUA provided sensitive imaging feedback regarding the anatomy of the treated ovaries and the ablation process. Different ablation protocols were tested, and thermal damage within the treated ovaries was histologically characterized.
Conclusion(s): The absence of damage to the ovarian surface may eliminate many of the complications linked to current laparoscopic ovarian drilling (LOD) techniques. HIFU may be used as a less traumatic tool to perform LOD. (Fertil Steril® 2014;101:545–51. ©2014 by American Society for Reproductive Medicine.)
Key Words: Polycystic ovary syndrome (PCOS), high-intensity focused ultrasound (HIFU), dual-mode ultrasound arrays (DMUA), laparoscopic ovarian drilling (LOD), infertility

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Polycystic ovarian syndrome (PCOS) is a complex endocrine disorder that is classified as the most common gynecological condition in women of reproductive age (1) and the most common cause of anovulatory infertility (2). It is estimated that about 8%–10% of women worldwide have PCOS (3, 4). The main clinical manifestations of PCOS are obesity, hirsutism, anovulation secondary to hyperandrogenism, and increased incidence of type II diabetes mellitus owing to increased insulin resistance (1).

First-line treatment of PCOS is conservative, including weight loss, an exercise program, and the use of insulin-sensitizing agents like metformin. These measures were found to reduce the risk of type II diabetes mellitus and were associated with a reduction in levels of circulating androgen (1). For treatment of anovulatory infertility, clomiphene citrate is the first-line medical therapy to induce ovulation in addition to the aforementioned measures (1). About 20% of patients do not respond to clomiphene citrate (5). Those patients are eligible for the second-line treatment, which may be gonadotropins or surgery (1). Gonadotropins are expensive, require intensive monitoring, and are associated with a higher incidence of ovarian hyperstimulation syndrome (OHSS) and multiple ovulation (6). The current surgical option is laparoscopic ovarian drilling (LOD), using electrocautery or laser.

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The main rationale behind this surgery is to thermally ablate some of the androgen-producing ovarian tissue to relieve the hyperandrogenism linked to PCOS. The surgery is also thought to enhance the response of treated ovaries to intrinsic gonadotropins through different mechanisms (7). LOD is less expensive than gonadotropins and provides comparable success rates with less incidence of OHSS and multiple pregnancy (6, 8). However, the surgery is traumatic and can be complicated by postoperative pelvic adhesions or accidental bowel injury (9, 10). On this basis, a noninvasive form of thermal therapy capable of producing thermal damage within ovaries while minimizing ovarian trauma may be a new approach for the treatment of PCOS.

High-intensity focused ultrasound (HIFU) is a noninvasive technology used for tissue ablation. Intensified ultrasonic beams can be focused to a point using therapeutic transducers. This causes damage at the focus without significant damage before or after the focal point. HIFU damage is mainly achieved through a thermal effect, although other effects like cavitation and mechanical effects also contribute to the focal damage (11). HIFU is more known in the medical community for its use in ablating body tumors, particularly uterine fibroids and prostate cancer (11–13).

Both ultrasound and magnetic resonance imaging (MRI) are currently used to guide and monitor HIFU therapy. MRI monitoring makes use of shifts in proton resonance frequency in response to focal temperature rise to construct thermal maps. These maps were found to accurately track temperature changes at the focal point and are accepted clinically as indicators of tissue ablation (13, 14). On the other hand, clinical ultrasound monitoring depends on detection of the echogenic changes that develop as a result of bubble activity at the focal point. This bubble activity is attributed to the inertial cavitation and tissue boiling that are commonly encountered during tissue ablation (13, 15). Current clinical ultrasound-guided HIFU systems use two separate transducers, one for imaging and another one for HIFU therapy. The two transducers are spatially aligned along the same axes (11); otherwise any misalignment can cause spatial misregistration between the imaged echogenic changes and the actual ablated tissue.

Dual-mode ultrasound arrays (DMUAs) are advanced transducers that use the same elements for simultaneous imaging and treatment by HIFU. In other words, this paradigm provides a single transducer that does imaging and therapy at the same time. This strategy ensures accurate and complete spatial registration between the imaged and targeted tissue. With a high imaging frame rate, reaching up to 1,000 frames per second, DMUAs can provide sensitive feedback regarding the ongoing ablation process and evolving echogenic changes. Inherent DMUA imaging capabilities are provided through two imaging modes, single transmit focus (STF) and synthetic aperture (SA). Broadly speaking, STF imaging provides precise feedback regarding the ablation process at the focus itself, while SA imaging provides better assessment of the perifocal region owing to an increased field of view. DMUAs have been used for in vivo testing of other potential medical applications (16), and information about the full capabilities of DMUAs is available in the literature (17, 18).

In this pilot study, we hypothesized that HIFU can be used as a less traumatic alternative tool to achieve the same therapeutic outcome as LOD. The main objective of this study was to demonstrate the feasibility of using HIFU, under guidance and monitoring of DMUA, to cause localized damage within the ovarian stroma without damage to the ovarian surface. The secondary objectives were to tune the exposure levels needed to achieve well-localized damage in ovaries and to histologically characterize the damage in the ovarian tissue.

MATERIALS AND METHODS

HIFU Transducer

A 3.5-MHz, 64-element DMUA (Imasonic) with a central fenestration was used in this study. The transducer elements were arranged in two groups, 32 elements each, above and below the central fenestration. Through the central fenestration, a 7.5-MHz linear diagnostic transducer (HST 15-8/20, Ultrasonix) was introduced and spatially aligned with the DMUA. This setup allowed for the collection and comparison of both DMUA and conventional B-mode ultrasound imaging data. This integrated transducer design increased the ability to localize and monitor tissue ablation using multiple imaging modes.

Ovaries

No institutional review board or Institutional Animal Care and Use Committee approval were required for these ex vivo animal experiments. Ex vivo canine and bovine ovaries were obtained from the American Preclinical Services and Lindenfelser's Farm Fresh Meat, respectively. After dissection, ovaries were placed in a holder filled with molten gelatin. Only part of the ovary, sufficient to hold the ovary in place, was immersed in the gelatin, while the ovarian surface through which HIFU therapy took place was kept above the level of the molten gelatin. Gelatin was then left in the refrigerator for 45 minutes to solidify.

Experimental Setup and Ablation Protocols

The tissue holder containing the gelatin-fixed ovaries was attached to a three-dimensional positioning system (Parker Daedal) and placed in a tank of degassed deionized water in front of the integrated DMUA transducer (Supplemental Fig. 1). After identification of the internal anatomical details of the ovaries using both DMUA and conventional B-mode imaging, the tissue holder was adjusted to obtain the best plane to start the treatment (usually the plane showing sizeable ovarian follicles to be used as landmarks during tissue cutting). HIFU was then applied under imaging guidance.

Two ablation protocols were tested in these experiments. The first was a single-shot protocol to produce a single large lesion. The other protocol, the grid protocol, was used to stack smaller lesions side by side in a grid design that was intended to form a confluent large ablation zone. To tune the exposure parameters for both protocols, different exposure times were tested (2 seconds, 1 second, 750 ms, and 500 ms) with an estimated focal intensity range of 4,100–4,700 W/cm^2.