

Association between ultrasound findings and serum levels of vascular endothelial growth factor in ampullary pregnancy

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Objective: To assess the association between ultrasound images and serum concentrations of vascular endothelial growth factor (VEGF) in ampullary pregnancies.

Design: Prospective study.

Setting: University hospital.

Patient(s): Fifty patients with ampullary pregnancy.

Intervention(s): Criteria for inclusion in the study were: singleton pregnancy from spontaneous conception; diagnosis of tubal pregnancy in the ampullary region; radical surgical treatment (salpingectomy); and measurement of serum VEGF, human chorionic gonadotropin, and progesterone on the day of surgery. An additional criterion was description of an ectopic mass by transvaginal ultrasound, as follows: [1] ectopic gestational sac containing an embryo with cardiac activity; and [2] tubal ring: a paraovarian formation similar to a gestational sac, not containing a viable embryo (an anechoic structure surrounded by a peripheral hyperechogenic halo); an empty ectopic gestational sac; a sac containing an embryo without cardiac activity; or a vitelline vesicle.

Main Outcome Measure(s): Association between ultrasound images and serum concentrations of VEGF.

Result(s): An association was found between ultrasonographic images and VEGF serum concentrations. Ectopic embryos with cardiac activity were associated with higher levels of serum VEGF.

Conclusion(s): In ampullary pregnancy, higher serum levels of VEGF are associated with the finding of an embryo with cardiac activity on transvaginal ultrasound. Greater production of VEGF likely creates development conditions more conducive to ectopic embryos. (Fertil Steril® 2015;103:734–7. ©2015 by American Society for Reproductive Medicine.)

Key Words: Transvaginal sonography, ampullary pregnancy, ectopic pregnancy, first trimester hemorrhage, VEGF

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The incidence of diagnosis of ectopic pregnancy (EP), defined as the implantation and development of the embryo outside the uterine cavity (1), has increased during the mid-twentieth century, plateauing at

approximately 2 per 100 pregnancies in Europe (2), North America (3), and Asia (4), and representing the fourth most frequent cause of maternal death in the United Kingdom (5). The rising incidence is mainly associated with an

increased prevalence of pelvic inflammatory and sexually transmitted diseases, utilization of in vitro fertilization technologies, increased tubal sterilization practice and subsequent reversal attempts, as well as the use of levonorgestrel as an emergency contraceptive method (6–11). The most common location of EP is in the fallopian tube, with 75%–80% in the ampullary portion (9).

Sonography is used to not only diagnose EP but also triage women into the most-appropriate surgical or nonsurgical management protocol,

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guide percutaneous treatments, and follow up on patients when medical or expectant management protocols are used. Transvaginal sonography (TVS) allows for improved visualization of the endometrial contents and better visualization of the adnexal region.

Vascular endothelial growth factor (VEGF) is an angiogenic factor, and may play a key role in the establishment of a viable pregnancy, participating in the processes of implantation and placentation. The substance serves as a major modulator of vascular growth, remodeling, and permeability in the endometrium, decidua, and trophoblast, as well as vascular development of the embryo (12–18). The secretion and expression of VEGF is dependent on local conditions, and cellular VEGF production is greater in hypoxic conditions (13, 17–20). The implantation environment in the oviduct is very different from that of well-vascularized endometrium, and production and secretion of VEGF seem to be elevated in EP (21, 22).

Our group has already demonstrated that maternal serum concentration of both VEGF and human chorionic gonadotropin (hCG) are associated with the depth of trophoblastic penetration into the tubal wall, and that a TVS finding of an embryo with cardiac activity is associated with deeper penetration of trophoblastic tissue into the tubal wall (23–25). The intent of the present study was to assess the association between ultrasound images and serum concentrations of VEGF in ampullary pregnancies.

MATERIALS AND METHODS

A prospective study was conducted on patients with a diagnosis of tubal pregnancy in the ampullary region who underwent salpingectomy between April 1, 2011 and November 30, 2012. The research project was approved by the ethics committee of the institution.

Criteria for inclusion in the study were: singleton pregnancy, from spontaneous conception; diagnosis of tubal pregnancy in the ampullary region; radical surgical treatment (salpingectomy); and measurement of serum VEGF, hCG, and progesterone on the day of surgery. An additional criterion was description of an ectopic mass with the use of transvaginal ultrasound, as follows: [1] an ectopic gestational sac containing an embryo or fetus with fetal heart beat (FHB); and [2] a tubal ring; a paraovarian formation similar to a gestational sac, not containing a viable embryo (an anechoic structure surrounded by a peripheral hyperechogenic halo); an empty ectopic gestational sac; a sac containing an embryo without cardiac activity; or a vitelline vesicle. The treatment choice (salpingectomy) was based on their clinical state (hemodynamic instability); ultrasound examination (presence of an embryo with heartbeat, and a pregnancy diameter >4.0 cm, as demonstrated by ultrasound); and hCG level (>5,000 mIU/ml). But particularly important were patients' future reproductive wishes: all patients included in this study no longer had reproductive intent. Cases were excluded in which no agreement could be obtained regarding the location of the tubal pregnancy upon surgical description and histologic analysis.

A total of 98 consecutive cases of EP were recorded during the study period. Of these, 43 were not included, for

various reasons. In 2 cases, no TVS image was described; in 12 cases, TVS showed an image described as a solid or complex mass (paraovarian image suggestive of hematosalpinx or pelvic hematoma intermingled with irregular hyperechoic and/or hypoechoic areas); 4 cases were not tubal pregnancies; and 2 cases were tubal but not ampullary pregnancies. A total of 25 patients either received methotrexate or were managed expectantly. Expectant management was offered to all hemodynamically stable women with reproductive desire, an ectopic pregnancy visible on TVS (an ectopic ring or an ectopic mass and/or fluid in the pouch of Douglas), and a plateauing serum hCG concentration of <2,000 IU/l. A plateauing serum hCG was defined as a <50% hCG increase or decrease between day 0 (the day of the first clinical suspicion of an ectopic pregnancy) and day 4. Women with a viable ectopic pregnancy, signs of tubal rupture, and/or active intra-abdominal bleeding, were not eligible for this kind of treatment. Fifty-five patients met the inclusion criteria and were selected to participate in the study. Five cases were excluded because the exact site of implantation of trophoblastic tissue into the fallopian tube could not be confirmed by anatomopathologic examination.

All included patients had had a transvaginal ultrasound examination (using a Voluson 730 Expert equipped with a 7.5-MHz transvaginal probe, GE Healthcare) and were divided into 2 subgroups: [1] embryo with cardiac activity; and [2] tubal ring. A well-trained obstetrician from our department performed all exams.

The fallopian tubes were fixed in 10% formalin and sectioned serially for light microscopic analysis. An average of 10 sections stained with hematoxylin-eosin were analyzed. A single well-experienced pathologist who was unaware of the clinical, laboratory, and image characteristics of the patients performed histologic assessment. The microscopic analysis was carried out to address cases that were ampullary pregnancies.

Multiple logistic regression was performed to verify the association between VEGF and the presence of FHB, controlling for maternal age, progesterone and hCG serum levels, parity, number of gestations, previous EPs, and abortions. For addition of the independent variables to the model, hierarchical forward-stepwise selection was performed based on the likelihood-ratio test. The Student's *t* test was used for comparisons between means of normally distributed data; the Mann-Whitney *U* test was used for nonparametric data. All tests were 2-tailed, and the level of significance was set at 5% for all tests. Statistical analyses were performed on a personal computer with the statistical package SPSS (SPSS, Inc.) for Windows (Version 13.0).

RESULTS

Fifty patients participated in this study. The age of the women ranged from 20 to 43 years (29.3 ± 4.3 years). Twenty-nine (58.0%) were white, and 21 (42%) were nonwhite. With respect to obstetric history, 21 (42%) patients were nulliparous, and 8 (16%) had a history of EP in the contralateral fallopian tube. Twenty-two (44%) cases were included in the embryo-with-cardiac-activity subgroup; 28 (56%) were

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