Medical Hypothesis
Aberrant alteration of vascular endothelial growth factor-family signaling in human tubal ectopic pregnancy: what is known and unknown?

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Received February 8, 2013; Accepted February 25, 2013; Epub March 15, 2013; Published April 1, 2013

Abstract: More than 98% of ectopic pregnancies occur in the Fallopian tube. Because many facets of tubal ectopic pregnancy remain unclear, prediction, prevention and treatment of tubal ectopic pregnancy are still a major clinical challenge. Compelling evidence suggests that angiogenic growth factors are involved in normal and abnormal implantation. While acknowledging the importance of an intrauterine pregnancy requires the development of a local blood supply and angiogenesis, we hypothesize that the hypoxic- and estrogen-dependent regulation of vascular endothelial growth factor/placental growth factor expression, secretion, and signaling pathways that are possibly involved in the pathophysiology of tubal ectopic pregnancy. Our hypothesis may also lead to a new therapeutic strategy for women with tubal ectopic pregnancy.

Keywords: VEGF, VEGF receptor, fallopian tube, ectopic pregnancy

Introduction

Human ectopic pregnancy (EP) complicates up to 2% of all pregnancies in the western world [1] and it shows a significant number of maternal deaths in the first trimester [2, 3]. More than 98% of EPs occur in the Fallopian tube [1]. It is well known that the primary function of Fallopian tubes is to provide the proper microenvironment for fertilization and to transport the embryo to the uterus for implantation [4]. Because the Fallopian tubes are not accommodated to hold a growing embryo, the implantation and growth of the embryo will cause the Fallopian tube to rupture if the EP is not surgically or medically treated [2]. The etiology of tubal EP is still unknown. A major limitation to understanding the pathophysiology of tubal EPs is that no existing mouse models can establish causative roles for factors implicated in the pathogenesis of tubal EP [1, 5]. Although several risk factors are associated with tubal EP in women [1, 6, 7], no experimental studies have firmly established causative roles for any of the factors implicated in the pathogenesis of tubal EP. Furthermore, clinical evidence points out other factors may be involved in the pathogenesis of tubal EP [1]. In this article and the accompanying figure, we hypothesize that the hypoxic- and estrogen-dependent regulation of vascular endothelial growth factor (VEGF) / placental growth factor (PIGF) expression, secretion, and signaling pathways that are possibly involved in the pathophysiology of tubal ectopic pregnancy.

The expression of VEGF/PIGF and their receptors during the intrauterine and ectopic pregnancies

VEGF is a key regulator of physiological and pathological angiogenesis [8]. Its family consists of VEGF-A (generally called VEGF), VEGF-B, VEGF-C, VEGF-D, VEGF-E, and PIGF [9]. Sequence comparisons indicate that PIGF has 42% amino acid sequence identity with VEGF-A
serum PIGF levels are significantly increased in
ine pregnancy [9]. We have recently shown that
a similar role as VEGF during normal intrauter
gestation [27], and placenta-specific PIGF has
expressed in the human placenta throughout
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a similar role as VEGF during normal intrauter-
ine pregnancy [9]. We have recently shown that
serum PIGF levels are significantly increased in
the middle and late stages of intrauterine preg-
nancy compared to the early stage of intrauter-
ine pregnancy. Although some previous studies
have indicated that serum PIGF levels are ele-
vated in tubal EP compared to intrauterine preg-
nancy [22, 28], we are unable to find a sig-
nificant difference in serum PIGF levels between
women with tubal EP and gestational age-
matched women with intrauterine pregnancy.

Multiple factors regulate the VEGF/PIGF sig-
naling pathways during the onset of tubal EP

Cellular responses to reduced oxygen availabil-
ity (hypoxia) are recognized as critical in normal
development and physiology, as well as are
implicated in pathological processes [29].
Hypoxia-inducible factor (HIF), a critical hypoxia
sensor, is a heterodimeric complex composed of
two alpha subunits (HIF-1α, HIF-2α, and
HIF-3α) and a stable beta subunit (HIF-1β), also
known as aryl hydrocarbon receptor nuclear
translocator (ARNT)) [30]. Hypoxic HIF activity is
controlled primarily through post-translational
modification and stabilization of the HIF-1α and
HIF-2α subunits, and HIF-1β expression levels
constitute important determinants of hypoxia
responsiveness [30]. It is well known that het-
erodimeric complexes of HIF-1α/β translocate
to the nucleus and activate several hypoxia-
associated genes, including VEGF [9]. VEGFs
are synthesized, secreted and activated by a
variety of tissues/cells in vivo [9]. Based on the
results from our and other laboratories, we
hypothesize a working model for regulation and
activation of VEGF isoforms and their receptor
signaling pathways during tubal implantation.
Disruption of the local environment such as a
low oxygen level, possibly due to embryo
implantation in the Fallopian tube, induces ele-
vated levels of HIFs [30]. We propose that
implantation in the Fallopian tube leads to the
coordinated activation of a transcriptional cas-
cade in response to the presence of excessive
hypoxia (Figure 1). As a result, tubal VEGF-A lev-
els are increased and this activates the VEGF
signaling cascades in an autocrine manner. On
the other hand, increased levels of tubal VEGF
causes them to be released into the circulation,
and this leads to activation of the VEGF signal-
ing cascades in a paracrine manner. Both auto-
crine and paracrine regulation may result in
tubal fluid secretion, vascular defects, angi-
ogenic dysfunction, and tubal wall damage.
The VEGF family-signaling in human Fallopian tube

The Fallopian tube is a dynamic, steroid hormone-responsive tissue [4]. 17β-estradiol (E2) is a steroid hormone and contributes to a diverse array of Fallopian tubal functions in vivo [31]. The physiological actions of E2 are mediated by its interaction with estrogen receptor (ER), which exists as two different subtypes, ERα and ERβ [31]. Both ER subtypes are expressed in normal human Fallopian tubes [31-34]. Moreover, ERα is frequently lost in the implantation and non-implantation site (our unpublished data) of the Fallopian tube in women who have suffered from EP [32, 35]. Although the VEGF gene promoter harbors the estrogen response element [35], whether E2 is able to directly regulate VEGF-A expression via the activation of ER signaling in human Fallopian tubes is not fully understood. On the other hand, animal studies suggest that E2 and hypoxia can cooperate to regulate the same target in the Fallopian tube. For example, the expression of erythropoietin, a potent anti-inflammatory cytokine, is increased by both E2 and hypoxia in mouse Fallopian tubes both in vivo and in vitro [36]. Treatment with E2 followed by hypoxic stimulation significantly reduces VEGF-A protein synthesis and release in human endometrial tissues in vitro [37]. Because the C-terminal domain of HIF-1β, a potent coactivator of ER-dependent transcription, is essential for the enhancement of ER transcription [38], E2-dependent regulation of VEGF expression and secretion may occur indirectly through HIF isoforms during implantation in the Fallopian tube.

Conclusions and future directions

Successful reproduction is critically dependent upon normal angiogenesis. However, the pic-
ture of VEGF-family signaling in the Fallopian tube is still unclear with many gaps in our understanding the molecular details of VEGF/PIGF and their receptor interaction under pathophysiological conditions. While acknowledging the importance of an intrauterine pregnancy requires the development of a local blood supply and angiogenesis, our hypothesis emphasizes the importance of the crosstalk between hypoxia and estrogen in the regulation of VEGF-family signaling pathways during the onset of tubal EP. From a disease mechanism perspective, it was necessary to expand upon clinical research on circulating VEGF isoforms to understand the mechanisms by which their synthesis is regulated and to understand their biological functions during tubal implantation. Such research would allow for a better understanding of the actual diagnostic values of VEGF-A and PIGF. Although medical treatment of unruptured tubal EP using methotrexate has been established [2, 3], development of more potent and safer medical treatment is needed due to limited indications and side effects of methotrexate. Further studies assessing the levels of VEGFR activation and inhibition in human Fallopian tube in situ need to be carried out. When the specific VEGF signaling pathways that contribute to the tubal implantation are identified, anti-VEGF therapy may be of great benefit for women who have developed a tubal EP.

Funding

This work was supported by the Swedish Medical Research Council (Grants 5859), the Sahlgrenska Academy Research Council, GöteborgsLäkaresällskap, the Hjalmar-Svensson Foundation, Fred G. and Emma E. Kanold’s Foundation, Fredrik and Ingrid Thuring’s Foundation, Anna Cederberg’s Foundation, Tore Nilson’s Foundation, ÅkeWiberg’s Foundation, Wilhelm-Martina Lundgren’s Foundation, the Wennergren Foundation, Jane and Dan Olsson’s Foundation, and the Royal Society of Arts and Sciences in Gothenburg.

Conflict of interest statement

The authors report no conflict of interest.

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References

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[34] Shao R, Wang X, Weijdegard B, Norstrom A, Fernandez-Rodriguez J, Brannstrom M, Billig H. Coordinate regulation of heterogeneous nuclear ribonucleoprotein dynamics by steroid hormones in the human Fallopian tube and endo-
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