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Inhibins and Activins as Possible Marker of Ectopic Pregnancy

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1. Introduction

The regulation of reproduction is performed by complex hormonal system: hypothalamus - pituitary - ovary. There are a lot of ovarian peptides, playing an essential role in the regulation of this hormonal system. However, the mechanisms of their action are not exactly elucidated. Within ovarian peptides, inhibins are seemed to be consider as very important. The term "inhibin" was indicated by McCullagh in 1932. He described inhibin as a hydrophilic substance and an extract from male gonads, which inhibits the pituitary gland. However, only 53 years later, the isolation of inhibin from follicular fluid in cows for the first has been performed. Inhibin was characterized as a glycoprotein, consisting of two subunits linked by disulfide bond (Yamaguchi et al, 1991).

Inhibins belong to the superfamily of transforming growth factor β (TGF-β). This family contains about 30 peptides, including activin, Anti-Müllerian Hormone (AMH), epithelial growth factor (epidermal growth factor - EGF) and the subfamily of transforming growth factor-β (TGF-β) (de Kretser et al., 2002).Inhibins (inhibin A, B, total inhibin) play a very important role in the regulation of female reproduction.

Inhibins are glycoprotein substances produced mainly in the ovaries and they take part in the regulation of menstrual cycle. They consist of a glycosylated subunit α combined with disulfide bond with one of two different subunits β (betaA or betaB). The resulting inhibin are properly labeled as inhibin A (alpha betaA) and inhibin B (alpha betaB) (Burger & Igarashi, 1988).

Inhibins play an important role in reproductive functions by regulating pituitary follicle-stimulating hormone (FSH) secretion during the menstrual cycle. This regulation is processed by a feedback mechanism. FSH stimulates the maturation of ovarian follicles, where granulosa cells produce inhibins. Increased levels of inhibins in the peripheral blood subsequently inhibit the secretion of FSH (Muttukrishna et al., 2000).

There are studies about possible use of inhibins in reproductive medicine.

Inhibin A is secreted mainly by the dominant follicles and corpus luteum of the ovary. In addition, the sources of this peptide are also adrenal, pituitary, spleen, bone marrow, placenta and fetal membranes (Petraglia et al., 1999). Recent data indicates the evaluation of inhibin A concentration mainly in the obstetric diagnosis (Florio et al., 2004).

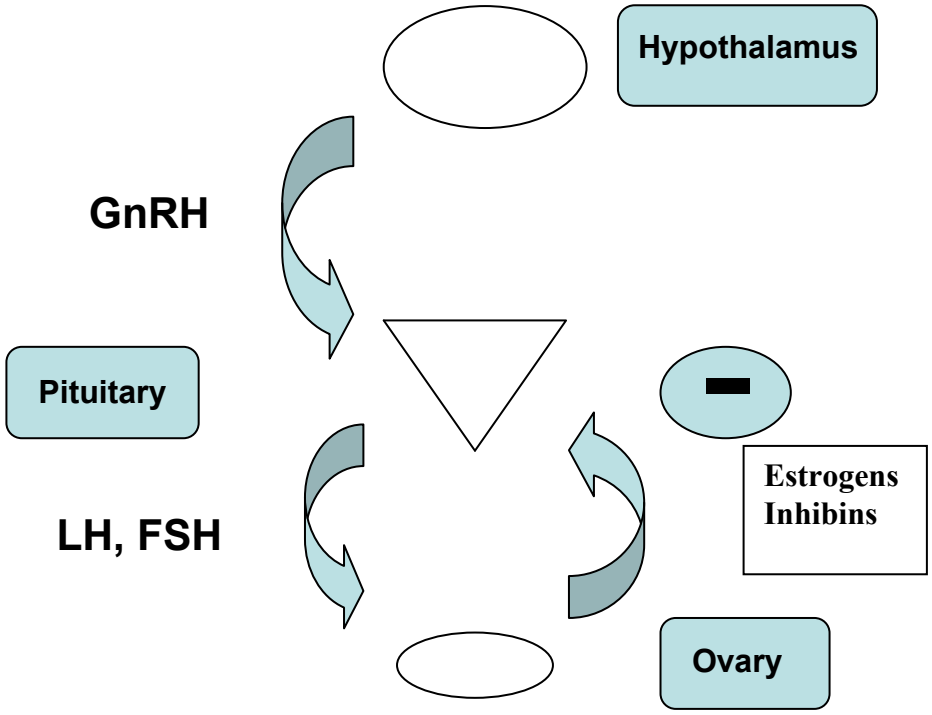

Fig. 1. Role of inhibins in hypothalamic - pituitary – ovarian axis.

According to current knowledge inhibin A can be used in the diagnosis of ectopic pregnancy, mola hydatidosa, threatened abortion, pre-eclampsia and pregnancy associated with Down's syndrome (Meczekalski & Podfigurna-Stopa, 2009).

The concentration of inhibin A in blood serum in the early follicular phase is low. It begins to rise during the late follicular phase, reaching its peak in the middle of the secretion of luteal phase. Throughout the follicular phase of the menstrual cycle inhibin B concentration is higher than the levels of inhibin A in blood serum. Their levels correlate with the concentrations of FSH, luteinizing hormone (LH) and estradiol in the blood serum (Klein et al., 1996).

Inhibin A may be a particular marker of early pregnancy loss (Mattukrishna et al., 2002). Both, single and serial measurements were used to predict subsequent pregnancy loss in women with recurrent miscarriage. There are low serum concentrations of inhibin A at early gestational age in pregnancies destined to miscarry. Its measurement at the time of the first pregnancy test might be able to predict pregnancy outcome (Al-Azemi et al., 2003). Inhibin B is secreted mainly in ovaries and its function is focused on gynecology. Inhibin B is produced by the granulosa cells of early follicles in ovary. The differences in the secretion of inhibin A and B may suggest their different physiological role. Inhibin B seems to play a major role as a marker of follicular growth and could be a potential tool to assess the response to ovulation induction by the action of FSH. It may also play an important role as a prognostic factor in premature ovarian failure and the hypothalamic disturbances (Welt et al., 1997).

In men, only inhibin B is secreted. It is produced by Sertoli cells in the testis, accordingly to the circadian rhythm with a minimum at 10.00 p.m. and the peak from 7.00 to 9.00 a.m. Production

of inhibin B correlates positively with the function of Sertoli cells and the amount of semen. Instead, negative correlation between inhibin B and FSH is recorded (Yamaguchi et al., 1991).
Inhibin B is mainly secreted during the follicular phase of the menstrual cycle. The concentration of inhibin B in serum appears to be growing in the early follicular phase, with a prominent peak occurring after the increase of FSH secretion and gradually decreases in the late follicular phase. Another peak of inhibin B secretion is observed two days after the LH peak, and then its rapid decline, which leads to low levels of inhibin B in the luteal phase (Groome et al., 1996).
Secretion of inhibins changes due to age. In regularly menstruating premenopausal women, in spite of normal levels of estradiol and LH, elevated levels of FSH during the follicular phase of the menstrual cycle was found. This higher concentration of FSH appears for a few years before the onset of menopause, and is accompanied by decreased ovarian reserve and reduced fertility factor. This increased levels of FSH is due to significantly reduced production of inhibin B by a reduced pool of ovarian follicles in the follicular phase. Concentrations of inhibin A, also are reduced in women who are premenopausal. In these patients initially lower the levels of inhibin B in the follicular phase are stated, and only secondly it comes to lower levels of inhibin A. The concentrations of both inhibin A and inhibin B in women during menopause are almost undetectable (Danforth et al., 1998).

	SECRETION
INHIBIN A	dominant follicles and corpus luteum of the ovary Adrenals Pituitary Spleen bone marrow Placenta fetal membranes
INHIBIN B	granulosa cells of early antral follicles

Table 1. Sources of inhibin A and inhibin B secretion in womens' organism.

The measurement of inhibin B can provide useful information about ovarian reserve, and plays an important role in assisted reproductive techniques. Inhibin B can be also regarded as potential marker of diagnosis of premature ovarian failure (POF) and ovarian recovery in hypothalamic disturbances (Meczekalski & Podfigurna-Stopa, 2009).
Both inhibin A and inhibin B can play helpful role in the assessment of ovarian function in patient with Turner syndrome.

	Diagnostic role
INHIBIN A	ectopic pregnancy mola hydatidosa threatened abortion pre-eclampsia pregnancy associated with Down's syndrome
TOTAL INHIBIN	ovarian tumors PCOS

Table 2. Role of inhibin A and total inhibin in obstetrics and gynecology.

Total inhibin is the sum of precursors, subunits of inhibins and molecules. Estimation of total inhibin may play a role in polycystic ovary syndrome (PCOS) and may serve as a potential marker for ovarian cancer (Tsigkou et al., 2007, 2008).
There are requirements of further studies to clarify the use of inhibins in clinical practice of reproductive endocrinology.
Inhibins act indirectly through the antagonistic action to activins, which are dimers with protein molecular weight of about 24,000 Da.
Activins are members of the TGF-β family and they are secreted by the tubal epithelial cells. They are homodimers of inhibin β subunits (β A and β B) and there are distinguished three different glycoproteins: activin A (β A- β A), activin B (β B- β B) and activin AB (β A- β B).
Activins are produced as larger precursor proteins that are subsequently unlinked to excrete the mature C-terminal protein.
Activins regulate their action by binding to a complex of transmembrane serine and threonine kinase receptors. These activin receptors are categorized into two groups: type I receptor group, comprising the activin receptor-like kinase, and type II receptor group comprising the activin type IIA and type IIB receptors (ActRIIA and ActRIIB).
Activin function is regulated by follistatin, which is the binding protein (Refaat et al., 2004). Binding of activin to follistatin is almost irreversible and this harmonized synthesis of follistatin with activin is the main regulator of the local bioactivity of activin.
The activin follistatin complex is most often composed of one activin dimer and two follistatin molecules.
Circulating activin is generally revealed as linked with the long-form follistatin (follistatin-315). The short form of follistatin (follistatin-288) demonstrates high affinity for association with cell membrane proteoglycans. It is said that the affinity of binding activin A, activin B and activin AB to follistatin seems to be similar.
Activins stimulate pituitary FSH secretion and play an important role mainly in the regulation of reproductive, but also in the immunological function.

2. Ectopic pregnancy and serum biomarkers for diagnosis of ectopic pregnancy

Ectopic pregnancy is a situation when fertilized egg has implanted outside the uterus (Walker, 2007). Ectopic means "out of place". The most common site of implantation is fallopian tube (98% of cases), mainly in the ampullary region. Other types of ectopic pregnancy include interstitial, corneal, ovarian, cervical, scar, intraabdominal and heterotopic pregnancy (Condous, 2009).
The incidence of ectopic pregnancy has been increasing in the last decades. The incidence of ectopic pregnancy has increased from 0,37 % of pregnancies in 1948 to approximately 2% of pregnancies in 1992 (Centers for Disease Control). According to the literature from 2002 one in every 80 pregnancy is extrauterines. More than 100 000 cases are reported in each year in United States (Zane et al., 2002). In the developing world the incidence is much higher than in developed countries.
Despite the fact that mortality decreased by almost 90% from 1979 to 1992, ectopic pregnancy remains the leading cause of death during the first trimester of pregnancy with a 9% to 14% mortality rate (Lozeau & Potter, 2005).
Ectopic pregnancy is an increasing health risk for women throughout the world and continues to be the leading cause of maternal death in the first trimester of pregnancy. The

cause of this high mortality is very often because of improper examination delayed diagnosis. The early diagnosis of ectopic pregnancy should be based on the transvaginal sonography. However, in some of women with suspected early ectopic pregnancy, the assessment with the transvaginal sonography is inefficient. In these women, biochemical assessment is used to establish the correct diagnosis.

Measurement of biochemical parameters describing ectopic pregnancy is mainly based on the estimation of serum human chorionic gonadotropin (β-hCG) and progesterone concentrations. None of these markers are efficient in the diagnosis of ectopic pregnancy, that is why new screening methods and algorithms are needed.

Short- and long-term consequences on health related quality of life and psychological issues are important but are rarely quantified.

The most important risk factors include a history of ectopic pregnancy, tubal surgery and pelvic inflammatory disease.

Early diagnosis of ectopic pregnancy is critical for conservation of fallopian tubal integrity and prevent potentially life-threatening abdominal bleeding (Lipscomb, 2010).

Ectopic pregnancy can be difficult to diagnose because symptoms often mirror those of normal early pregnancy. The initial evaluation of patients suspected for to have an ectopic pregnancy contain a quantitative measurements of serum human chorionic gonadotropin test (hCG)and transvaginal ultrasonography (US) (Lipscomb, 2010). The use of above-mentioned traditional tool sometimes cannot be fully helpful (Practice Committee of the American Society for Reproductive Medicine, 2006).

Fewer than 50% of tubal ectopic pregnancies are diagnosed at the patient's initial presentation (Munro et al., 2008). Despite clinical advances in imaging ultrasound is non-conclusive in up to 18% of women whom measurement of serial hCG concentration is necessary guide management. Further difficulties are encountered because serial hCG determination cannot separate arrested intrauterine from tubal ectopic pregnancies (Horne et al., 2010). Decelerated increase in hCG concentration cannot be used to discriminate between a miscarriage and an ectopic pregnancy. If hCG levels are found high, the probability of having ectopic pregnancy is about 30%.

A probability of having ectopic pregnancy in women with unknown pregnancy location and progesterone concentrations higher than 5.01 ng/ml is as high as 30% , whereas with progesterone values below the cutoff the probability of having an ectopic pregnancy is about 3.49%.

Multiple visits and tests currently necessary are a real expense for health service. As an example data from Edinburgh indicates that health services in Scotland are spending up to 1,5 million of British Pounds per year diagnosis and excluding ectopic pregnancy (an estimated 9 million of British Pounds in direct costs alone to health services per year throughout the United Kingdom alone) (Florio et al., 2007).

The aim is to find fast and accurate test to diagnose ectopic pregnancy. It would reduce the number of visit of patients during diagnosis process and it would help to avoid unnecessary laparoscopy.

At present, more than 20 biomarkers have been identified to improve earlier diagnosis of ectopic pregnancy. Some of the biomarkers such as placental protein 14 at first was identified as good marker of ectopic pregnancy but further studies revealed its weak discriminatory value. Some of the biomarkers such as cancer antigen 125, pregnancy associated plasma protein A, estradiol are able to discriminate a tubal ectopic pregnancy from a viable intrauterine pregnancy. Unfortunately, they appeared to be unable to

distinguish the former from a non-viable intrauterine pregnancy (miscarriage) (Katsikis et al., 2006). The problem is also that other biomarkers such us progesterone, creatinine kinase, vascular endothelial growth factor (VEGF) could not be used in clinical practice because the results of study have been conflicting. (Develioglu et al., 2002).

The best serum biomarker should be easy available, cheap, reliable and based on one measurement. It is important particularly for developing countries that it should be a single marker. These countries have the highest morbidity and mortality problems related to ectopic pregnancy. Therefore essential progress can be observed in the work on new candidate biomarkers for ectopic pregnancy diagnosis. New biomarkers can be based on genomic technology. The attention should be paid on recent discovery the inhibin/activin beta B under-expression in the decidualized endometrium of women with tubal ectopic pregnancies. This kind of discovery can indicate that some secreted proteins associated with uterine decidualization can be useful in the diagnostic process of ectopic pregnancy.

Little is known of the mechanism by which the process of embryo transport is coordinated within the tube. Both cilial activity and tubal peristalsis are believed to be necessary for successful transport of the embryo along the tube and to ensure delivery of the embryo at the endometrial cavity at the optimum time for adhesion and implantation. This is critical for the successful establishment of pregnancy and avoidance of ectopic pregnancy. Therefore, we investigated whether epithelium from Fallopian tubes bearing an ectopic pregnancy differs from a normal tube in expression of TGF-β family and related proteins and their receptors.

3. Inhibins in ectopic pregnancy

3.1 Inhibin A in ectopic pregnancy

There are only few reports on the possible role of inhibin A in ectopic pregnancy.

First report about possible role of inhibin levels in ectopic pregnancy comes from 1996.

It was case-control study and included 19 women who had ectopic pregnancy confirmed at surgery and by pathology (Seifer et al., 1996). Control group was composed of 24 women of similar chronological and gestational age with sonographic evidence of an intrauterine pregnancies that are conceived spontaneously**.** Serum total and dimeric inhibin concentrations in women with ectopic pregnancy were < 60% of the concentrations for women with single intrauterine pregnancies. Total inhibin, but not dimeric inhibin-A, was elevated in maternal serum before week 8 of gestation relative to normal menstrual cycle levels. Serum inhibin concentrations are lower in ectopic pregnancy as compared with intrauterine pregnancies that are spontaneously conceived and the relative amounts of dimeric inhibin-A, B, and alpha inhibin subunit in maternal serum may change throughout gestation (Seifer et al., 1996).

Next study related to evaluation of inhibin A as a marker of persistent ectopic pregnancy was published in 1998 (D'Antona et al., 1998). Results of this study suggest that inhibin A will not be a useful marker for ectopic pregnancy but that it may provide a more accurate preoperative assessment of trophoblast viability than hCG, thereby improving management.

Another study (prospective case control study) performed 3 years ago evaluated whether inhibin A concentrations is a clinically useful marker of ectopic pregnancy (Segal et al., 2008). It was confirmed that inhibin A may be reliable marker for diagnosis of ectopic pregnancy.

There is also report that serum inhibin A levels can be used in the prediction of failing "pregnancy of unknown location" but according to authors this marker is not such reliable as serum hCG levels (Kirk, 2009).

The new concept for diagnose ectopic pregnancy is based on the genomic technology. The attention should be paid on recent discovery that there are differences in function of the decidualized endometrium in tubal ectopic and intrauterine pregnancies of similar gestations. Inhibin/activin β_B subunit expression was related to the degree of decidualization of the endometrium and was reduced in tubal ectopic pregnancies.
Serum inhibin levels have been reported to be lower in spontaneously conceived ectopic pregnancies compared with intrauterine pregnancies (Seifer et al., 1996).
Serum inhibin A levels can be used in the prediction of failing "pregnancy of unknown location" (Kirk et al., 2009).
Segal et al (2010) performed a prospective case-control study to determine whether inhibin A concentrations is a clinically useful marker of ectopic pregnancy (Segal et al., 2010). They confirmed that inhibin A may be reliable marker for diagnosis of ectopic pregnancy.
There are also suggestions that inhibin A will not be a useful marker for ectopic pregnancy but that it may provide a more accurate preoperative assessment of trophoblast viability than hCG, thereby improving management (D'Antona et al., 1998)

3.2 Inhibin B in ectopic pregnancy

There are no reports about inhibin B as useful marker of ectopic pregnancy.

3.3 Total inhibin in ectopic pregnancy

Total inhibin is the sum of precursors, subunits of inhibins and molecules. Estimation of total inhibin may play a role in polycystic ovary syndrome (PCOS) and may serve as a potential marker for ovarian cancer (Tsigkou et al, 2007, 2008).
Inhibins act indirectly through the antagonistic action to activin, which are dimers with protein molecular weight of about 24,000 Da.
There is only one report cited above (Seifert et al., 1996) about role of total inhibin in patients with ectopic pregnancy. This study presents that serum total and dimeric inhibin concentrations in women with ectopic pregnancy were < 60% of the concentrations for women with single intrauterine pregnancies.

4. Activins in ectopic pregnancy

The placenta is the main source of activin A during pregnancy. In the maternal circulation serum activin A concentrations are higher than in nonpregnant women and increase throughout pregnancy until delivery. It is thought that activin A plays an essential role in the endocrine physiology of human pregnancy (Petraglia et al., 1987).
As the embryo moves toward the uterine cavity, the uterine tubes are biologically active, providing an environment that assures fertilization and early embryonic development. There is an embryonic maternal cooperation in which the maternal reproductive tract and the embryo changes to provide embryonic and endometrial maturation. Recently, the expression of activin subunits, type II receptors and follistatin by the premenopausal Fallopian tube was demonstrated. It is suggested that activins are combined with follistatin and play a paracrine and autocrine role in early development and transport of embryo (Bahathiq et al., 2002).
Patients with the diagnosis of ectopic pregnancy are characterized by lower serum activin A concentrations than in patients with first-trimester spontaneous abortion and in patients with intrauterine pregnancy. The findings of low activin A concentrations in ectopic pregnancy are quite recent. It is suggested that an impaired secretion of activin A occurs in the presence of problems related to trophoblast invasion and implantation.

Variations in maternal activin A concentrations occurring in trophoblast diseases are believed to be part of the adaptive response of the placenta to adverse environmental conditions (Florio et al., 2001).

Patients with the diagnosis of ectopic pregnancy demonstrate disturbed activin A release in the placenta, which impairs the endometrium vascularization and subsequently trophoblast implantation not in the uterus (Dimitriadis et al., 2005).

Role of the endometrium which is a pivotal source of activin A is essential in the ground of implantation of ectopic pregnancy. During the secretory phase of the menstrual cycle (at the time of blastocyst implantation), activin A is present in the uterine fluid of cycling women in higher concentrations than during the proliferative phase. Activin A is a well-known regulator of the differentiation of proliferative cytotrophoblast into extravillous invasive trophoblast cells of the anchoring villi (Norwitz et al., 2001). The lack of an adequate endometrial secretion of activin A may be related to the lack of appropriate messages to the placenta for a right implantation. Additionally, activin A levels correlate with endometrial thickness. Such an increase of endometrial activin A and secretion at the time of blastocyst apposition may play an important role in embryo implantation (Caniggia et al., 1997).

The probability of having an ectopic pregnancy may be estimated more precisely and more quickly if activin A measurement is performed.

Single activin A measurement may identify patients at risk of ectopic pregnancy with a high sensibility and specificity. Positive predictive value for ectopic pregnancy (approximately 97%) is possible when low serum activin levels are observed. These procedures may select pregnancies at higher risk of ectopic pregnancy earlier and possibly to prevent unnecessary interventions.

Additionally, activins play an important role in inflammation and are involved in the pathogenesis of inflammatory, fibrotic diseases and early scar formation. Activin A expression has been reported to increase in several inflammatory diseases, such as septicemia, inflammatory bowel disease, rheumatoid arthritis and asthma (Phillips et al., 2001).

Nowadays, there is a suggestion that activin A could play an essential role in chlamydial infection. Refaat B. et al in 2009 performed a study about role of activins in the ectopic pregnancy in patients with or without Chlamydia trachomatis infection (Refaat, 2009).

Infection with Chlamydia trachomatis increases the production of tumor necrosis factor alpha (TGF-α) in human cervical tissue, interleukin-1 in human fallopian tube bearing an ectopic pregnancy, and interleukin-6 in serum from women diagnosed with ectopic pregnancy. Activin A has been reported to modulate the function of B lymphocytes, which play an important role in controlling reinfection with Chlamydia trachomatis. Infection with Chlamydia trachomatis is associated with scar formation. Repeated Chlamydia trachomatis infection of pigtailed macaque fallopian tubes produces a Th1-like cytokine response associated with fibrosis and scarring.

There is an increased activin A expression and its related molecules by human tubal epithelial cells in patients with the diagnosis of ectopic pregnancy. It has been suggested that tubal activins may be involved in the immune response to chlamydia-induced tubal chronic inflammation. This impairment in the activin expression by epithelial cells of fallopian tube may result in tubal pathology and subsequently may be the cause of development of ectopic pregnancy (Roan et al., 2008).

Increased expression of activin βA subunit and type II receptors may lead to impairment of tubal motility, an increase in tubal receptivity, and subsequently the development of ectopic pregnancy. It is said that tubal activin A, its type II receptors could be involved in the microbial-

mediated immune response within the fallopian tube, and their pathological expression may lead to tubal damage and the development of ectopic pregnancy (Refaat, 2009).
The intensity of expression of activin-βA subunit, ActRIIA and ActRIIB and follistatin by the epithelial cells of human Fallopian tubes in patients with ectopic pregnancy is increased. However, the up-regulation of the proteins is accompanied by a down-regulation of the mRNA of these molecules. The mRNA of these molecules is rapidly translated and degraded, resulting in rapid turnover of the mRNA, with depletion of these mRNAs due to the prolonged synthesis of large amounts of activin-A, its receptors, and follistatin. (Refaat et al., 2009).
Epithelial cells of the Fallopian tube have been reported to expressed nitric oxide (NO) and NO synthase. Activin-A stimulates the NO production in a concentration-dependent manner in a variety of tissues and cells. NO is engaged in many female reproductive functions and it has a relaxing effect on smooth muscles of the Fallopian tube. Additionally, Perez in 2000 reported in rat oviduct a significant increase in tubal transport of ova after the local administration of NO synthase inhibitors (Perez, 2000).
Increased activin-A expression by the Fallopian tube epithelial cells may stimulate tubal decidualization and trophoblast invasion within the tube. Furthermore, an increase in activin-A expression by the Fallopian tube epithelial cells may increase the production of NO in a concentration-dependent manner, resulting in pathological relaxation of the tubal smooth muscles, failure of propulsion of the early embryo along the Fallopian tube and the development of ectopic pregnancy.

5. Conclusion

Ectopic pregnancy is really an important clinical problem. Particular aspect is referred to precise and fast diagnosis with the use of serum biomarkers. Activins and inhibins can be regarded as such biomarker candidate. So far the number of reports on the role of activins and inhibins in ectopic pregnancy diagnosis is limited.
Majority of studies on inhibin A (but the number is very limited) indicates that this substance can be consider as possible marker of ectopic pregnancy.
New biomarkers can be based on genomic technology. The attention should be paid on recent discovery the inhibin/activin beta B under-expression in the decidualized endometrium of women with tubal ectopic pregnancies. This kind of discovery can indicate that some secreted proteins associated with uterine decidualization can be useful in the diagnostic process of ectopic pregnancy.
During pregnancy, the human placenta is the main source of maternal activin A and serum concentrations of activin A progressively increase throughout pregnancy until delivery. Impaired secretion of activin A is related to trophoblast invasion and implantation. Patients with the diagnosis of ectopic pregnancy are thought to have low serum activin A concentrations.
There is no doubts that further studies on activins and inhibins in the aspect of ectopic pregnancy are required.

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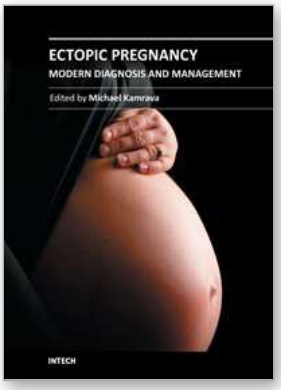

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Ectopic pregnancy is the second major cause of maternal mortality in the United States and a leading cause of maternal morbidity and mortality in the world. This book contains the practical methods to early diagnosis of various forms of ectopic pregnancies and their modern management. Ectopic Pregnancy - Modern Diagnosis and Management is a comprehensive book which guides the reader through all features of ectopic pregnancy, both practical and academic, covering all aspects of diagnosis and management of ectopic pregnancy in a clear, concise, and practical fashion. The book is organized so that it can either be read cover to cover for a comprehensive tutorial or be kept desk side as a reference to the ectopic pregnancies. Each chapter introduces a number of related ectopic pregnancy and its diagnosis, treatment and co-morbidities supported by examples. Included chapters bring together valuable materials in the form of extended clinical knowledge from practice to clinic features.

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