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Tubal muscles determine embryo implantation site; prognosis of ectopic pregnancy at chronic functional disorders

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ABSTRACT

Mammalian oviducts contain smooth muscles and inward-facing ciliated epithelium. Muscular contractions, not ciliary beating, propel oocytes through the oviduct towards the uterus. In crawling gastropods (unique models for studying the functioning of phasic smooth muscles), muscular contractions, propagating along the foot sole, play a principal role in determining the crawling rate. We have described the muscular mechanisms controlling the crawling rate and hypothesize here that the same mechanisms provide embryo transportation through the human fallopian tube. The data collected for gastropods were transferred to the human fallopian tube, using embryo speed and tube length (tonus) instead of crawling speed and sole length. Smooth muscle active states: tonic contraction/relaxation and rhythmic contractions (peristalsis) are involved in ovum transport. The ovum/embryo speed is linearly correlated with the tonus of the longitudinal and/or the circular muscles of the tube. Some known bioactive substances control muscular tonus and we suppose embryo speed through the contraction force of muscle cells involved in peristaltic waves. Other known substances facilitate peristalsis and we suppose that they have no effect on muscular tonus and increase dose-dependently embryo speed through the number of muscle cells recruited in peristaltic waves (at a constant wave frequency). This number depends on the physiological state of the woman. The combination of all possible effects and the ability of muscles to contract rhythmically determine the embryo speed and its implantation site. This hypothesis is the first description of the tubal muscular mechanisms that determine normal and any type of ectopic pregnancy at chronic disorders of tubal contractility. How to predict ectopic pregnancy? We have reason to assume that the intensity of rhythmic uterine contractions reflects that in the fallopian tube. It is known that uterine contractility significantly increases during the preovulatory phase and decreases during the mid-luteal phase. The hypothesis supposes that in women with increased risk of ectopic pregnancy, decreased uterine contractility during the preovulatory phase in comparison with the norm indicates a future tubal/abdominal gestation; increased uterine contractility during this phase and/or the mid-luteal phase as compared to the norm points to a future cervical pregnancy. The optimal methods for recording uterine activity are up to clinicians.

Introduction

Intrauterine and ectopic pregnancy

In humans and other mammals, the wall of the fallopian tube contains both circular and longitudinal smooth muscles [1] and the ciliated epithelium, which faces the lumen of the tube [2]. It seemed that during ovulation, both tissues control ovum transport through the oviduct with subsequent intrauterine implantation. A long-held conception has been that ciliary beating develops the main force to propel egg along the oviduct [3–5]. Only recently it was directly shown that not cilia but phasic muscular contractions (peristalsis) are responsible for egg transport [6].

Ectopic pregnancy occurs when mechanical obstacles such as tubal anomalies, tumors, postoperative scars, and others slow or stop egg transport through the tube. These cases are beyond the scope of this study. This work focuses on functional muscular disorders, leading to ectopic pregnancy, muscle mechanisms, providing embryo transport through the tube, and methods for predicting ectopic pregnancy. All these questions remain unclear.

Model of crawling in gastropods

Studies of visceral smooth muscles and ciliated epithelia typically use a strip of these tissues, leading often to a partial loss of data. Crawling gastropods are unique models for studying the functioning of

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phasic smooth muscles and ciliated epithelium. The locomotor apparatus in the foot sole of these snails contain these tissues [7,8], the functioning of which was studied in an intact snail [9].

Unlike terrestrial snails, which crawl by means of rhythmic muscular contractions (muscular waves), propagating along the foot sole, aquatic gastropods were thought to crawl due to sole ciliary beating (ciliary locomotion) [8]. Recently, it was found that in these snails the sole muscles play an important role in crawling [9–12]. Thus, both aquatic and terrestrial snails, crawl by means of muscular contractions, and the control of crawling rate is also similar [9].

We described the muscular mechanisms that regulate the crawling rate in gastropods over a wide range [9] and hypothesized that the same mechanisms exist in any other phasic smooth muscle, i.e. generating rhythmic activity.

Hypothesis

For instance, these mechanisms exist in the mammalian fallopian tube, where peristaltic waves propel embryo toward the uterus [6]. We transfer the data obtained from gastropods to the human fallopian tube and assume the muscular mechanisms controlling embryo transport through the tube and implantation inside or outside the uterus (Fig. 1). Two types of muscular activity have been known for the myosalpins: continuous tonic contraction/relaxation and rhythmic contractions [13,14]. We assume that these activities play a crucial role in embryo transport.

The ovum rate (embryo speed) linearly correlates with the tubal muscular tonus (Fig. 1a). Bioactive substances control tubal muscular tonus and embryo speed through the contraction force of muscle cells involved in peristaltic waves (Fig. 1b).

Other bioactive substances facilitate muscle contractions but have no effect on muscular tonus. They increase the embryo rate dose-dependently through the number of muscle cells recruited in muscular waves (at constant wave frequency) (Fig. 1b), and this number of cells depends on the physiological state of the female. Thus, the work performed by the muscular wave and determining the embryo rate is the product of the number of muscle cells in the wave and the contraction force of these muscle cells (Fig. 1b).

If the embryo rate is within acceptable limits, intrauterine pregnancy develops (Fig. 1c). If the rate is slower than a certain allowable limit, the fetus is implanted into the tube (tubal pregnancy). On the contrary, if the rate exceeds the allowable limit, the embryo is implanted into the cervical canal (cervical pregnancy). Finally, if the peristalsis is absent or sluggish, the egg is implanted in the ovary (ovarian pregnancy) or in the abdominal cavity (abdominal pregnancy).

Factors affecting muscular activity and determining normal and abnormal pregnancy

Each phasic smooth muscle is under the control of several bioactive substances, which act as neurotransmitters, co-transmitters, neuromodulators, and hormones [15,16]. The substances are different in diverse smooth muscles (heterogeneity). The bioactive substances controlling muscular activity in the human fallopian tube and other mammals have been described in numerous original papers and reviews. A normal pregnancy occurs when the concentrations of all substances, controlling muscular activity and receptor sensitivity, are balanced. Their imbalance causes an ectopic pregnancy. We do not give a comprehensive description of all possible bioactive substances and their effects on the muscles, as well as the different states of the receptors, but adduce a few examples to emphasize the point of view.

Tubal pregnancy, as seen in Fig. 1, develops due to tonic contraction of the fallopian tube. This tonic contraction can be caused by histamine [17], acetylcholine [18], endothelin-1 [19] and stimulation of alpha adrenergic receptors [20]. The stimulation of beta receptors inhibits contractions [20] and nitric oxide (NO) relaxes the smooth muscles of the tube [21].

Some substances affect the rhythmic contractions of the tube and presumably shift the linear relationship along the axis of embryo speed (Fig. 1a). Estrogen [22], 5-HT [23], prostaglandin [24] and NO inhibition increases motility [25]. Interestingly, estrogen receptor alpha (ER*α*) is absent in the fallopian tubes of women with tubal ectopic pregnancy [26]. Progesterone decreases motility [22], as do oxytocin and hCG (human chorionic gonadotropin) [24]. Human oviductal smooth muscle produces prostacyclin [27], which dose-dependently decreases the amplitude of muscular contractions.

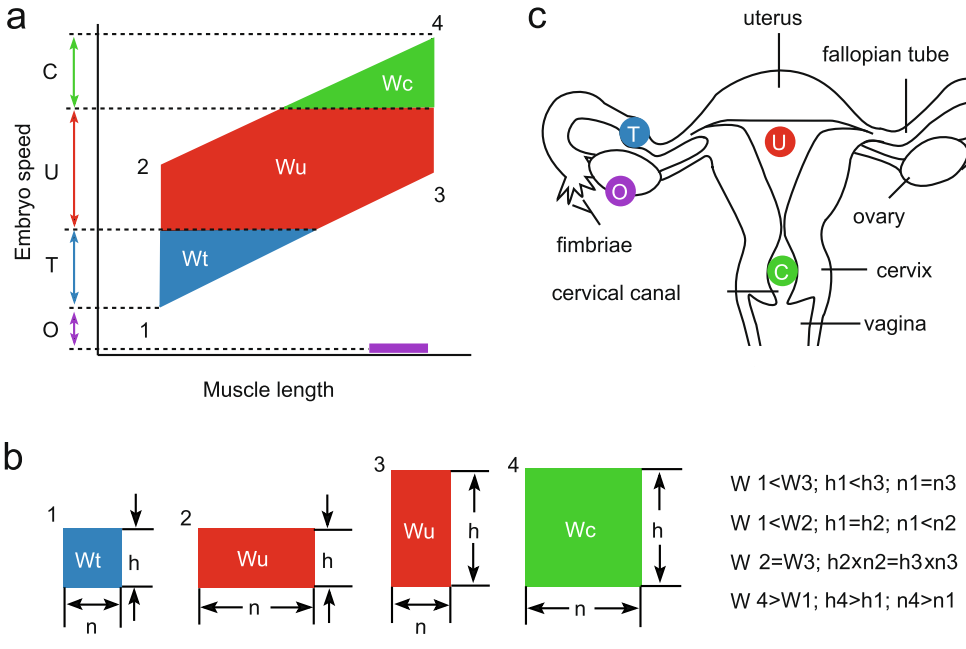

Fig. 1. Schematic representation of hypothetical muscular mechanisms that determine normal and abnormal pregnancy, and the female reproductive system. (a) The plot of the lineal relationship between the length (tonus) of tubal muscles (longitudinal and/or circular) and embryo speed can be shifted maximal upwards (2,4) or downwards (1,3) along the axis of embryo speed or can occupy any intermediate position at a constant wave frequency. The location of the plot depends on the physiological state of the woman. Work (W) produced by a muscular wave for embryo transport at any point in the area Wt (blue) provides embryo speed T and tubal pregnancy, Wu (red) – embryo speed U and intrauterine pregnancy, and Wc (green) – embryo speed C and cervical pregnancy. The horizontal dotted lines between T and U and between U and C are drawn at random. At embryo speed O (purple), the embryo implants in the ovary or in the abdominal cavity. (b) Work (Wt, Wu, Wc) produced by each muscular wave in points 1–4 (a) is the product of the number of muscle cells (n) involved in this wave and the contraction force (h) of these muscle cells. (c) Female reproductive system with an embryo implanted in the ovary (O), the fallopian tube (T), the uterus (U), and the cervical canal (C).

Chronic disorder of tubal tissues (cilia are not meant here and below) can also lead to ectopic pregnancy. Interstitial cells of Cajals (ICCs) are expressed in the human fallopian tube and generate electrical slow waves that determine the propagation of rhythmic muscular contractions along the tube [6]. A significant decrease in the number of ICCs in the fallopian tube may reduce tube motility and slow embryo transportation, thereby provoking ectopic pregnancy [28]. Rhythmic activity is totally disrupted after a Chlamydia infection [6], under the influence of caffeine [29], or as a result of ischemia of the uterine artery [30]. A pathological implantation can also be caused presumably by a violation in the cascade of signals from the receptors to the contractile apparatus in smooth muscle cells [31].

Energy metabolism in tubal smooth muscle cells also plays a crucial role in generating rhythmic contractions. In gastropods, smooth muscle cells of the locomotor apparatus contain giant mitochondria [32,33]. The blockade of mitochondrial respiration by cyanide significantly reduces locomotor activity in aquatic gastropods without affecting the frequency of ciliary beating and completely inhibits muscular waves in terrestrial snails [10,11]. A correlation between the mitochondrial volume and the rhythmic contractility was found in the rat diaphragm in the pre- and postnatal period [34].

How to predict ectopic pregnancy

In clinical practice, the actual task is to determine the pathological pregnancy in the early stages [35,36].

The hypothesis raises a new question concerning the prognosis of ectopic pregnancy at chronic functional disorders in the female reproductive system. It deals with those cases where ectopic pregnancy develops as a result of a violation of muscle control by bioactive substances and/or dysfunction of tubal tissues.

We assumed that the intensity of the rhythmic contractions of the uterus reflects that of the fallopian tubes. First, in the embryogenesis, the fallopian tubes and the uterus have a common origin: both develop from the Müller (Müllerian) ducts of the mesoderm. Second, around ovulation the distal fallopian tube is a trigger zone, from which the peristaltic waves propagate proximally, occupying the uterus and cervix [37]. Third, adequate uterine contractility may facilitate successful intrauterine implantation, while inadequate one may lead to ectopic pregnancy [38].

It has been shown that waves from the fundus to the cervix were most pronounced in the periovulatory phase [39]. After ovulation, the uterus undergoes progressive relaxation, which reaches a maximum during the mid-luteal phase that may assist normal embryo implantation [40]. Quantification of uterine contractions: the amplitude, duration, and frequency during the preovulatory phase and during the mid-luteal phase of the menstrual cycle as it has been previously proposed [39] should be taken as a standard norm and used in clinical practice for women with an increased risk of ectopic pregnancy [41,42], i.e. for those who had previous ectopic pregnancy, extirpation of one of the tubes, Chlamydia infection, adnexal surgery, appendectomy, and use of intrauterine devices. Decreased uterine contractility during the preovulatory phase in comparison with the norm indicates a future tubal/abdominal pregnancy. Increased uterine contractility during this phase and/or the mid-luteal phase as compared to the norm points to a future cervical pregnancy.

Throughout the 20th century, uterine contractility in non-pregnant women has been assessed using a wide range of methods and described [43]. We can add here a non-invasive transabdominal electrohysterography (EHG), which measures the electrical activity of the uterine muscles and their contractions [44,45]. Without having own experience, we rely on clinicians to choose the optimal method (or combination of methods) for recording uterine activity.

How to verify the hypothesis

Use the rat model allowing for the observation of the embryo transport through the fallopian tube [4,6] under the influence of various bioactive substances that control tubal muscular activity. The activity of isolated tube tissues can be investigated in the same way as locomotor activity in gastropods [9–12]. Investigate the mitochondrial apparatus of the smooth muscle cells of the tube in adult rats before and after prolonged sparing ischemia, as well as in juvenile and postmenopausal animals.

Conclusion

I started this work with the study of locomotor mechanisms in crawling gastropods, drew an analogy between the activity of phase smooth muscles propelling the snail and the embryo through the tube, described the mechanisms of intrauterine and ectopic pregnancy in humans, and suggested how to predict ectopic pregnancy at chronic functional disorders. Hope and assume that this work will be supported by clinicians and the prognosis of ectopic pregnancy will finally become a routine practice.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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