

Review of Researches on Non-genetic Factors of Embryo Termination

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Abstract: Embryo termination is a common gynecological disease with an incidence of 10% ~15%, which occurs mainly in the 12th week of pregnancy. After embryo termination, there are generally no obvious discomfort symptoms, so early diagnosis is difficult and timely and effective treatment cannot be carried out, which seriously endangers the physical health of women and threatens their health. In order to clarify the factors and pathogenesis that cause embryo termination, many experts and researchers at home and abroad have conducted studies on embryo termination. Based on this, the relevant research on non-genetic influencing factors leading to embryo exposure will be reviewed from the perspectives of uterine microbiota, endocrine factors, immune factors and social psychology. The aim is to provide references and ideas for further exploration of mechanisms and intervention measures related to embryo exposure, thereby providing reference to research and improvement of maternal health.

1. Introduction

Embryonic arrest refers to the stage of pregnancy due to certain factors that cause the embryo to stop growing and developing, is a stage of miscarriage, usually occurs in about 8-12 weeks of pregnancy, but in the mid-pregnancy may also occur^[1]. The causes of embryo termination are complex and varied, and studies have shown that, in addition to genetic factors, immunological factors, infectious factors, environmental factors, endocrine factors and psychosocial factors, the causes of its development are still unknown in 50% of the patients, for example, endocrine imbalance in females, maternal immunity, microbial anomalies, delay in the age of childbearing, poor living habits, increased stress and poor living environment, etc. All of them can increase the incidence of embryo termination^[2]. In this paper, we review the progress of research on the non-genetic influences on embryonic arrest, with the aim of providing a reference for the prevention of embryonic arrest during pregnancy and the maintenance of the physical and mental health of the pregnant mother.

2. Impact of uterine microecology on embryo termination

In order to deeply explore the influence of vaginal microecology on the pregnancy outcome of URIF patients with repeat in vitro fertilization, Shen Yaqian^[3] statistically analysed the results of the vaginal microecology examination of URIF patients who underwent the first (basic) vaginal

microecology examination and the vaginal microecology examination of URIF patients before repeat embryo implantation after the diagnosis of URIF, and analysed the relationship between the results of vaginal microecology of different statuses and the clinical pregnancy rate of URIF patients. Their findings showed that intrauterine microecology plays a key role in maintaining intrauterine homeostasis and the normal physiological function of the endometrium. And there exists a close connection and constraint between intrauterine microbiota and microecology, which plays an important role in maintaining intrauterine microecological balance, and dysregulation of the uterine microbiota will trigger intrauterine microecological disorders, which will lead to adverse pregnancy outcomes such as embryo implantation failure, embryo sterilisation and recurrent miscarriages^[4].

In terms of specific influencing factors, Luan Zonghui et al^[5] concluded that the microecological flora of the uterine cavity are interrelated and constrained by each other to maintain the balance of the microecology of the uterine cavity, and that normal microecological flora in the uterine cavity, such as *Lactobacillus*, have a protective effect on pregnancy, but their specific flora composition and their relationship to embryonic termination are still debated. Luo Wei^[6] applied Meta-analysis to explore the structure of bacterial and fungal biomes in the reproductive systems of normal early pregnancy women and patients with early pregnancy embryonic arrest by high-throughput sequencing technology, compared the differences, and searched for the characteristic bacteria, so as to reveal the correlation between embryonic arrest and changes in the structure of the bacterial flora. The results of their study showed that embryonic termination is closely related to microflora dysbiosis, and the current study confirmed that the colonies associated with embryonic termination include *Chlamydia trachomatis* and *Mycoplasma urealyticum*. Moreno et al.^[7] found that the comparative analyses of endometrial and vaginal specimens from 13 fertile women revealed that the microecology of the uterine cavity consisted of 54 bacterial communities, and that the predominant genus of the vaginal and uterine cavities was *Lactobacillus*. Li W et al.^[8] study also pointed out that the microbiota of normal women of childbearing age is dominated by vaginally secreted *Lactobacillus*, which accounts for more than 95% of the vaginal microbial content, and therefore the number and type of *Lactobacillus* is an important criterion for evaluating whether or not there is an imbalance in the microbiota in the uterus.

Another important cause of embryo termination is the infection of pathogenic microbiota (especially inflammatory reaction) in the reproductive tract of the pregnant mother during pregnancy, whose chorionic and amniotic structures can be destroyed, which is toxic to the endometrium and the normal development of the embryo. Wang R et al.^[9] explored the effect of *Mycoplasma urealyticum* (UU) infection on pregnancy outcomes during pregnancy, and the experimental results showed that the adverse pregnancy outcomes in the experimental group were significantly lower than those in the control group ($P < 0.05$), and the study pointed out that *Mycoplasma urealyticum* is an important factor that leads to infertility and adverse pregnancy outcomes in women, including premature rupture of membranes, spontaneous abortion, preterm delivery of foetuses, and low birth weight of foetuses, which seriously affects the lives of foetuses and maternal. It seriously affects the life and health of the foetus and the mother. Xing Lizhi^[10] analysed the differences in the number of various flora in the vaginal secretions of two groups of women by using fluorescence quantitative PCR, and the results showed that the expression of *Gardnerella vaginalis* and *Atopobium* in the embryonic arrest group was higher than that of the normal pregnancy group, which was statistically significant ($P < 0.05$), and concluded that the increase of anaerobic bacteria, such as *Gardnerella vaginalis* and *Atopobium*, may increase the incidence of embryonic arrest.

In terms of the mechanism of influence, Benner et al.^[11] believe that the microecology of the uterine cavity plays an important role in endometrial immunity, which interacts with epithelial immune cells and acts on the endometrium in the pre-metamorphosis and post-metamorphosis periods through the relevant molecular immune regulation to impair endometrial tolerance and implantation

disorders, which in turn affects reproduction. Li Wisdom et al.^[12] found that the expression of MMP-2 and MMP-9 in the placenta of patients with early termination of pregnancy was significantly elevated, whereas its specific inhibitor, TIMP1, was significantly reduced; meanwhile, at the time of embryo implantation, the bacteria enhanced the infiltration of trophoblast cells, causing them to undergo excessive hydrolysis, necrosis and detachment, and ultimately resulting in embryo sterilisation.

In summary, most scholars and their studies agree that the balance of the microflora of the uterine cavity and the microecology of the uterus during pregnancy is very important for the development of the embryo, especially the balance of the microflora in the female reproductive tract.

3. Impact of endocrine factors on embryo termination

Xiao Fang Zeng^[13] By studying the correlation between chlamydial and mycoplasma infections and serum chorionic gonadotropin (β -HCG) and progesterone (P) levels and embryonic arrest in pregnant women, it was pointed out that chlamydial and mycoplasma infections of the reproductive tract, serum chorionic gonadotropin levels, and low levels of progesterone are all factors affecting the arrest of embryonic development in pregnant women. Zhao Chan^[14] tested the endocrine hormones of the observed women and found that serum PRL was higher in the embryonic arrest group than in the control group. After analysing the reasons, it was believed that hyper PRLemia was triggered by pituitary gland function abnormality or occupying lesion, which inhibited the synthesis and release of hypothalamic gonadotropin, caused follicular development disorder, and interfered with the development of embryo, which led to the embryonic arrest. Among them, Gao Yang et al.^[15] believe that chorionic gonadotropin is a glycoprotein synthesised and secreted by syncytiotrophoblast cells, and its main function is to maintain the menstrual corpus luteum and induce its enlargement into the gestational corpus luteum, which in turn promotes the secretion of steroid hormones, the development of chorionic villi, and the formation of the placenta. At the same time, chorionic gonadotropin adheres to the surface of trophoblast cells and acts as an immunoprotective agent, preventing maternal lymphocytes from attacking the embryo.

Li Zhonghui et al.^[16] tested and compared the serum β -HCG and P levels of early normal pregnancy group, miscarriage and pregnant women with embryonic arrest, and found that the serum β -HCG and P levels of patients with embryonic arrest were significantly lower, this result shows that embryonic arrest is associated with low β -HCG levels and low P levels. Duo Xiaoling^[17] believes that progesterone is also a natural steroidal progesterone, whose main function is to maintain normal pregnancy necessary to help pregnancy, so that the uterine lining to accommodate the embryo bedding, while inhibiting uterine contraction, to promote the normal development of the embryo. If there is insufficient progesterone secretion due to luteal or placental insufficiency caused by various reasons, the mother cannot maintain a normal pregnancy and embryonic termination occurs. Wu Xiaorong^[18] explored the correlation between serum human chorionic gonadotropin, progesterone, and oestradiol levels in early pregnancy and miscarriage and embryonic arrest, and found that compared with pregnant women in the miscarriage group, pregnant women in the embryonic arrest group showed significantly lower levels of serum hCG, PROG, and E2.

In addition to the above hormones that have a direct relationship with female pregnancy, thyroid hormones and other hormones can also indirectly affect the outcome of pregnancy. Lu Xixi^[19] explored the correlation between serum thyroid hormone levels and VEGF expression in chorionic tissue of patients with embryonic foetal termination. The study showed that serum T3, T4 levels and VEGF levels of patients in the embryonic foetal termination group were lower than those of the normal pregnancy group, and the differences were statistically significant ($P < 0.05$), therefore, it can be concluded that the decrease in the levels of thyroid hormones may affect the expression of VEGF

in chorionic tissue, which is one of the possible causes of embryonic foetal termination. Han Hua et al.^[20] also found that the levels of follicle-stimulating hormone, luteinising hormone, free triiodothyronine and free thyroxine were lower than those of normal pregnant women in pregnant women with embryonic foetal termination, and concluded that the blood flow parameters of the uterine artery, the suprahypophyseal artery and the levels of a number of serum hormones in the early stages of pregnancy were lower than those of pregnant women with normal pregnancies in pregnant women with embryonic foetal termination.

Endocrine factors play an important role in embryo termination in pregnant women, with decreased serum β -HCG and progesterone levels strongly associated with embryo termination, in addition to decreased thyroid hormone levels which may be a potential cause of embryo termination by affecting the expression of VEGF in chorionic tissue.

4. Influence of immunological factors on embryo termination

Immunological factors are one of the most important causes of embryonic arrest in early pregnancy. Cui Shihong et al.^[21] reported that the normal expression of IL-6 and MMP-2 in the chorionic villus tissue in early pregnancy plays a role in maintaining early embryonic development, and pointed out that after a woman is pregnant, the embryo is a foreign body relative to the mother, so when the embryo is rejected by the mother, the pregnant woman may not feel any discomfort, but the immunological maladaptation between the mother and the fetus will cause the mother to reject the foetus, which affects the embryo's development, and an excessive rejection reaction of the mother can lead to embryo abortion. Excessive maternal rejection can lead to embryonic termination. Liu Bingbing et al.^[22] pointed out that B cells, T cells, natural killer cells, macrophages and stromal cells in the uterine metamorphosis and trophoblast can secrete a variety of cytokines that are closely related to the occurrence of embryonic termination. Zhang Fengmin et al.^[23] explored the correlation between anti-reproductive immune antibodies and embryonic foetal termination in vivo, and found that the positivity rates of anti-sperm antibodies, anti-endometrial antibodies, anti-cardiolipin antibodies, anti-ovarian antibodies, anti-human chorionic gonadotropin antibodies, and anti-toxoplasma gonorrhoeae antibodies in patients with embryonic foetal termination were significantly higher than that of normal expectant mothers. Different immune molecules have different results in influencing the occurrence of pregnancy outcomes in pregnant women. Wang Juan et al.^[24] analysed the sera of recurrent miscarriage (RSA) patients for three types of antibodies, ACA, ANA and BA, and compared them with normal pregnant women, and found that ACA, ANA and BA were significantly higher in RSA patients than in normal pregnant women.

Immunological factors play a key role in early pregnancy embryonic arrest, and an in-depth understanding of the role of immunological factors in embryonic arrest is important for improving the diagnosis and treatment of early arrest.

5. Psychosocial effects on embryo termination

There may be no obvious symptoms in early pregnancy, and pregnant women's lack of understanding of the immune factors that cause cessation of development, coupled with insufficient attention to obstetric examination in early pregnancy, may lead to failure to detect embryonic cessation of development in a timely manner, which in turn increases the risk of treatment. At present, with the rapid development of society, work pressure and social competitiveness gradually increase, pregnant women come into contact with factors that lead to embryonic foetal arrest gradually diversified, in addition to physiological factors, pregnant women's own habits, past history, exposure to objects, psychological state, etc. will have a certain impact on the state of development of the embryo.

With regard to external environmental factors, Zhang Xiaofen^[25] points out that, with the acceleration of modernisation and industrialisation, the incidence of embryo termination caused by environmental factors is increasing, with heavy metal pollution in the environment being an important cause of embryo termination. In addition, pregnant women who use pesticides, herbicides or insecticides for occupational reasons have a much higher chance of embryo termination. For example, a study by Cai Xiaoru et al^[26] found that the percentage of cases with a history of miscarriage, alcohol consumption, smoking history, use of radioactive electrical appliances >6h/d, sleep deprivation, and psychological depression was higher than that of the control group, suggesting that embryonic termination can be affected by factors such as those listed above. Wang Ying^[27] discussed the risk factors of environmental behaviors in life and work of patients with embryo termination. She found that older age, inhalation of second-hand smoke in 3 months before pregnancy or during pregnancy, use of hair dye, and room decoration may be related to the occurrence of embryo termination. High education level, good health condition before pregnancy, active access to eugenic knowledge, happy emotional state during pregnancy, and harmonious relationship with family members during pregnancy can reduce the occurrence of embryo termination. The incidence of foetal termination may be reduced by a high level of education.

In terms of personal life, Zhao et al.^[28] used multifactorial Logistic regression to analyse the risk factors for embryonic arrest and found that perming and dyeing of hair in the third month before or during pregnancy, smoking or passive smoking, and comorbid anxiety were independent risk factors for the occurrence of embryonic arrest. Li Jun^[29] found that the use of emergency contraceptive pills during conception, recent exposure to toxic and harmful substances, active or passive smoking, and TORCH infection were the high-risk factors for the occurrence of embryonic foetal abortion in early pregnancy.

In terms of psychological factors, Feng Xiaoyue et al.^[30] studied 215 patients with embryonic termination, and the results showed that the differences in the comparison of seven aspects, namely, age, number of deliveries, number of cesarean sections, number of previous embryonic termination, number of previous abortions, history of hysteroscopic surgery, and uterine malformations, were all statistically significant ($P < 0.05$). Among them, excessive anxiety or stress during pregnancy is one of the main factors leading to embryonic termination. Yan Cuiyan et al.^[31] assessed the psychological occurrence of anxiety and depression status in women with embryonic foetal termination and found that the occurrence of anxiety in women with embryonic foetal termination was higher than that in women with voluntary abortion, and that the level of literacy and whether or not it was a planned pregnancy were the influencing factors for the occurrence of anxiety status in women with foetal termination. Wang Zhenqing et al.^[32] showed that the total score of anxiety in patients with recurrent immune-type embryo termination was higher than that of the domestic norm ($P < 0.01$), and the dimensions and total score of social support were lower than that of the domestic norm ($P < 0.01$), and anxiety and depression were negatively correlated with the dimensions of social support as well as with the total score of social support ($P < 0.01$), and concluded that the anxiety of patients with recurrent immune-type embryo termination, depression were overall at a high level and correlated with the level of social support.

Psychosocial factors, heavy metal pollution, chemicals such as pesticides and herbicides, the habits of pregnant women, past history and environmental behaviour are important causes of embryonic termination. The above study also pointed out that the level of social support was negatively correlated with the level of anxiety and depression, and that patients with recurrent immune-type embryonic termination had overall high levels of anxiety and depression.

6. Conclusion

Embryo termination can cause harm to the physical and mental health of pregnant women. If left untreated, it usually leads to adverse consequences such as uterine infections, endometritis, anaemia, etc., which will affect the next pregnancy, and pregnant women will also suffer from a greater psychological burden and have a fear of conceiving again, so it is crucial to adopt appropriate methods to avoid the occurrence of embryo termination^[33]. Factors leading to embryo abortion are complex and diverse, including microbiological, endocrine, immune, environmental and personal factors. In order to reduce the incidence of embryo abortion, couples should undergo a physical examination and genetic counselling prior to conception to identify potential high risk factors for pregnancy^[34]. If there is no problem in the pre-pregnancy examination, women should pay attention to good protection before and during pregnancy to avoid germs infection and exposure to harmful chemicals or radioactive substance exposure to reduce the risk of embryonic termination^[35]. Therefore, it is recommended that both husband and wife should prepare for pregnancy beforehand. Correcting bad habits in life such as staying up late for a long time, smoking, drinking, etc., and maintaining a good psychological state and avoiding excessive tension, anxiety, etc., can improve the quality of sperms and eggs and form a good uterine environment, which not only reduces the risk of embryonic termination, but also prevents foetal abnormalities, and promotes eugenics^[36]. In addition, the family members of pregnant women should pay attention to the physical and mental health of pregnant women in time, avoiding conflicts with pregnant women and making them too emotional, which will affect the balance of endocrine in pregnant women. At the same time, society should also care for pregnant women, do not give pregnant women excessive workload, in public occasions friendly treatment of pregnant women, do not make pregnant women subjected to external malice^[37]. Public service campaigns can be carried out appropriately to explain pregnancy health care knowledge to pregnant women, provide prenatal care guidance and psychological counselling, and help pregnant women understand how to scientifically and reasonably regulate their own emotions and state of mind, so that they can spend their pregnancy in good health.

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