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Review Article

The Effect of Chemotherapy in Gestational Trophoblastic Disease on Infertility: A Review on Pathophysiologic Mechanism

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Abstract

Today, young women infertility through chemotherapy has become a global challenge. Chemotherapy destructs the malignant cells by reactive oxygen species (ROS) production and inflammatory factors secretion; these factors can also destruct the ovarian and uterine cells.

Infertility usually happens as a result of ovarian and uterine cells apoptosis, as well as dysfunction in these organs. Signaling pathways activated by chemotherapy lead to increased activation of follicles and depletion of the follicular pool. In addition, excessive secretion of sex hormones leads to follicles activation and infertility in women.

Mesenchymal stem cells (MSC) use have been reported to be a great help in restoring the function of ovarian and uterine cells. On the other hand, they can regulate sex hormone secretion. Finally, the use of MSCs as a suitable treatment strategy can help restore the function of reproductive cells and treat infertility.

Keywords: Chemotherapy; Infertility; Gestational Trophoblastic Disease; Premature Ovarian Failure; Mesenchymal Stem Cell.

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Introduction

Gestational trophoblastic disease (GTD) is a rare disease characterized by disruption of trophoblastic tissue function and cancer formation (1). GTD has several types, the most common is Hydatidiform Mole (HM). Most of the time, HM is benign, but it is invasive in some patients and metastasizes to the other parts of the body (2, 3).

Usually, disease progression is stopped by uterine evacuation; but in some patients, no changes have been observed in the clinical status of the patients despite the uterine evacuation.

Chemotherapy is also used to prevent disease progression to the malignant gestational trophoblastic neoplasia (GTN) (3, 4).

Methotrexate (MTX) and actinomycin D (Act-D) are the main chemotherapy drugs, that are prescribed for GTD patients to prevent GTN (5). Although the use of these drugs reduces the GTN development chances and increases the patients survival; the drugs side effects can affect subsequent pregnancies (6).

Recent studies have shown, that chemotherapy can cause infertility in women, by affecting the uterus and ovulation (7). Therefore, in this review article, we investigated the effects of prophylactic

chemotherapy on the future pregnancies of GTD patients.

Oxidative stress and infertility

Reactive oxygen species (ROS) production is one of the main mechanisms of chemotherapy drugs to prevent cancer cells proliferation (8). Although this method prevents the proliferation of cancer cells, but it can cause infertility by affecting the uterus function (9). The Hedgehog signaling pathway (HH) is one of the regulator pathways of ROS production. It increases the activation of glioma-associated oncogene homolog1 (Gli-1). Gli-1 enhances mitochondrial membrane integrity by inducing the dynamin-related protein-1 (Drop-1) expression. Therefore, It prevents ROS production by enhancing mitochondrial membrane integrity (10, 11).

Gli-1 activation also increases the expression of some antioxidant factors such as glutathione peroxidase (Gpx) and superoxide dismutase (SOD). Also, in the cross-state, activation of Gpx and SOD increases Gli-1 activation. In addition to Gli-1, Metallothionein (MT2A) also affects SOD expression. The results show that MT2A expression prevents SOD activation (12-14). Nuclear factor erythroid 2-related factor 2 (Nrf2) is one of the critical transcription factors, that play an antioxidant role by increasing SOD expression.

Therefore, it can be concluded, that Gli-1 probably enhances the SOD gene transcription through Nrf2 expression (15). Nrf2 is also one of the upstream factors of the Notch signaling pathway, which can activate it (16). Notch plays a vital role in placental formation, decidualization, and blood vessel formation by VEGF secretion (17). It also increases the secretion of Matrix metalloproteinase 9 (MMP9) by activating the AKT/P38/MAPK pathway. MMP9 is involved in the extra villous trophoblastic process (EVT), and causes the placental formation and maternal communication with the fetus (18). On the other hand, ROS production has been shown to activate the ADAM17, which leads to the expression of involved genes in uterine fibrosis by Notch activation (19).

Finally, due to the vital role of Nrf2 in the SOD activation as well as Notch pathway, Nrf2 expression monitoring during chemotherapy can prevent infertility in HM women by inhibiting ROS overproduction.

Inflammation and infertility

Inflammation and inflammatory cytokines secretion are other cytotoxic mechanisms of chemotherapy against malignant cells (20). Although inflammation induction prevents the formation and proliferation of malignant cells in GTD patients, it can lead to infertility in women (21).

The NF-kB factor is at the forefront to induce and spread inflammatory responses; it increases during the process of chemotherapy and Radiotherapy in women (22). Its activation leads to increased production of TNF-α and expression of inducible nitric oxide synthesis (iNOS) and cyclooxygenase2 (COX2). iNOS expression increases the production of nitric oxide (NO) and the inflammatory cytokines secretion (23, 24).

TNF-α production reduces Insulin-like growth factor 1 (IGF-1) levels, which activates the ERk/P38 and PI3K/AKT pathways and prevents ovarian cell apoptosis (25). Following, by increasing the production of inflammatory cytokines, TGF-β as an anti-inflammatory cytokine also increases; it prevents them from spreading by suppressing inflammatory responses. It has been proved, that TGF-β increases TNF-α production and COX2 expression by activating the ERK/P38/JNK pathway (23, 26, 27).

Poly (ADP-ribose) polymerase 1 (PARP-1) is another factor, which activates the ERK/P38/NF-kB pathway; Although PARP-1 inhibits iNOS, it can produce NO by activating eNOS. Silencing the information regulator 1 (SIRT1) is an inflammatory inhibitor, which inactivates the NF-kB; SIRT1 expression decreases following TNF-α production (28, 29).

Another study found that SIRT1 increases NO production by activating PI3K/AKT (30). Wnt/beta-catenin is another molecular pathway, that activates the PI3K/AKT/NF-kB inflammatory pathway (31). Other studies have shown that miR-1275 (a type of non-coding RNA) plays an anti-inflammatory role. This miR prevents inflammation by targeting the Wnt/beta-catenin pathway (32). Recent researchers have identified another type of noncoding RNA,

which is called Long non-coding RNA (LncRNA); they are more than 200 nucleotides in length. LncRNAs play essential roles to control the cellular processes, including inflammation and apoptosis, by regulating miRs expression (33); evaluating miRs expression or inducing them to prevent infertility during chemotherapy may be a useful treatment strategy in the future (Table 1).

Finally, according to the pivotal role of ERk/P38 and PI3K/AKT pathways in inflammation due to NF-kB activation, targeting the cited pathways can prevent inflammation-induced infertility in women.

Table 1. Summary of potential LncRNA, involved in the inflammation induction.

LncRNA	MiR	Up/Down regulation	Mechanism	Ref.
LncRNA NLC1-C	miR-320a	Down regulation	Increase COX-2 and ERK/NF-kB pathway activation	(34, 35)
LncRNA MALAT1	miR-200c	Down regulation	Reduce IL-8 secretion by targeting the NF-kB signaling	(36, 37)
LncRNA-h19	miR-124-3p	Up regulation	Increase IL-6 secretion by NF-kB signaling activation	(38, 39)
LncRNA HOTTIP	miR-128-3p	Up regulation	Cause TNF-α secretion, that leads to increase the IL-6, IL-1 and MMP9 secretion	(40, 41)
LncRNA PTENP1	miR-590-3p	Down regulation	Inhibit TNF-α secretion by reduced activation of NF-kB signaling	(33, 42)
LncRNA LOXL1-AS1	miR-18b-5p	Up regulation	-Cause inflammation by activating the PI3K/AKT and inflammatory cytokines	(43, 44)

Abbreviations: LncRNA: Long non-coding RNA; COX-2: Cyclooxygenase-2; NF-kB: Nuclear Factor kappa-light-chain-enhancer of activated B cell.

Premature ovarian failure

Premature ovarian failure (POF) is one of the leading causes of infertility in young women. So far, many factors have been mentioned in relation to POF incidence, including environmental and genetic factors. Recently, chemotherapy has been considered a significant cause of POF (45, 46). Eventually, chemotherapy leads to POF in young women with GTN and cervical cancer. Many signaling pathways associated with POF, have been identified to be influenced by chemotherapy (47, 48); they activate follicles and eventually, the follicular pool depletes.

Two main involved pathways in the follicle activation include PI3K/AKT and Hippo. The PI3K/AKT pathway leads to mTOR activation, which activates the 40s ribosomal protein S6 (RPS6) and eukaryotic translation initialization factor 4E (EIF4E); it increases the follicles activation (49). mTOR also causes myeloid-derived suppressor cells (MDSCs) to accumulate in the ovary. Excessive accumulation of MDSC increases ROS production (50, 51).

Studies have suggested that using Melatonin as an antioxidant will reduce ROS and prevent POF; it reduces mTOR and PI3K/AKT activity by interacting with MT1. Given that, mTOR causes the accumulation of MDSCs inside the ovaries and leads to ROS production; probably Melatonin prevents the accumulation of MDSCs in the ovaries by inhibiting mTOR (52-54).

PI3K/AKT also activates FOXO3a. FOXO3a plays an essential role in the Dormancy of follicles; it inhibits the cell cycle of follicles by increasing P27 expression (55, 56). On the other hand, it has been shown, that GADD45 expression has increased in

POF patients under chemotherapy (57). According to the GADD45 role to stop the cell cycle by inhibiting CDC2/cyclinB1, and since FOXO3a also stops the cell cycle of follicles, it can be argued that FOXO3a inhibits follicles proliferation by inducing GADD45 expression.

Finally, targeting PI3K/AKT and mTOR pathways as the main pathways for POF can be a good strategy to prevent infertility in young women undergoing chemotherapy. Many efforts are being made to treat POF and many strategies have been used to prevent and treat patients. One of these is the use of mesenchymal stem cells (MSCs), which are used to treat many diseases due to their potential differentiation. In POF, MSCs regenerate the follicles pool by inducing proliferation and repair of damaged ovarian tissues. MSCs also reduce granulosa cell apoptosis, follicular atresia, and ovarian microenvironment improvement. They improve ovarian function through a variety of pathways (Table 2).

The use of MSCs has been shown to inhibit PI3K/AKT signaling, as well as immune cells stimulation prevention. On the other hand, these cells can increase the function of ovarian cells by reducing the apoptosis of granulosa cells. Finally, the use of MSCs as a new treatment can provide new approaches to prevent infertility in young patients (Table 2).

Table 2. Summary of MSCs application for POF treatment.

Authors	Source Stem Cell	Mechanism	Outcome	Ref.
Zheng et al.	Umbilical cord	-Reduce FSH secretion -Reduce caspase 3 expression -Increase NGF and TrkA expression	-Restore ovarian tissue - Inhibit POF progression	(58)
Liu et al.	Human amniotic mesenchymal stem cells	-Increase FSHR, VEGF and IGF expression -Restore the H2O2 function	-Restore ovarian function by angiogenesis and hormone secretion	(59)
Yin et al.	Umbilical cord	-Increase HO-1 expression -Activation of JNK/Bcl-2 signaling pathway -Increase T regulatory cell	-Restore ovarian function by reducing inflammation and apoptosis	(60)
Huang et al.	Fetal liver	-Increase the expression of MT1, JNK1, AMPK	-Restore the ovarian function by inhibition of apoptosis and ROS production	(61)
Yang et al.	Bone marrow	-Increase miR-144-5p -Reduce PI3K/AKT activation by PTEN inhibition	-Increase ovarian function by granulosa cell apoptosis	(62)
Guo et al.	Menstrual blood	-Upregulation of CDC2, CyclinB1 -Down regulation of GADD45b	-Restore the ovarian function by increased proliferation of granulosa cells	(63)

Abbreviations: POF: Premature ovarian failure; FSH: Follicle-stimulating hormone; NGF: nerve growth factor; TrKA: high-affinity nerve growth factor receptor; VEGF: Vascular endothelial growth factor; IGF: Insulin growth factor; HO-1: *Heme oxygenase-1*; PTEN: Phosphatase and tensin homolog.

Conclusion

Finally, it can be said that chemotherapy improves the clinical condition of cancer patients, especially young women; also, it increases the incidence of infertility. Based on this fact, it can be said that identifying the molecular pathways involved in the apoptosis of ovarian and uterine cells, can be used

as a prophylactic and therapeutic strategy for infertility. Also, since MSCs can repair damaged cells and regulate sex hormones secretion, and ultimately restore ovarian function, they can be used to treat infertile patients (caused by chemotherapy).

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Ethics

This article does not contain any studies with human participants or animals.

Conflict of Interest

The authors declared that they have no conflict of interest.

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