Renal effects of hydatiform mole and choriocarcinoma

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Abstract
Molar pregnancy is an abnormal growth of trophoblastic tissue in the uterus. It can be either complete or partial. In complete moles, the development of the fetus is absent, while partial moles contain an abnormal gestational sac. Choriocarcinoma is a malignant form that arises from molar tissue. Hydatiform mole and choriocarcinoma are rare and complicated diseases with numerous pathological conditions that can lead to significant kidney damage. Proteinuria, nephrotic syndrome, preeclampsia, decreased glomerular filtration rate, interstitial inflammation, crescentic glomerulonephritis, and thrombosis of the renal veins are the commonly encountered renal disorders with these diseases. Early intervention and treatment during pregnancy minimize these risks and lessen the risk of chronic kidney disease or end-stage renal failure. A multidisciplinary team approach involving obstetricians, nephrologists, pathologists, gynecologists, and radiologists is necessary for optimal management.

Keywords: Hydatiform mole, Trophoblastic tissue, Choriocarcinoma, Kidney disease, Preeclampsia, Glomerular filtration rate, Proteinuria, Hypertension, Renal failure


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Introduction
Molar pregnancy (hydatiform mole) denotes to the abnormal proliferation of trophoblastic cells within the uterus and is a subcategory of diseases entitled gestational trophoblastic disease. It can be complete or partial. Partial moles encompass an incomplete fetus, whereas complete moles frequently are without a fetus and have double paternal chromosomes (1,2). Though molar pregnancies are unusual, they can have significant kidney effects. Choriocarcinoma is a rare type of cancer that can arise from a molar pregnancy in approximately 3% of cases. In this study, we review the kidney effects of hydatiform mole and choriocarcinoma (3,4).

Search strategy
In this study, a comprehensive search for relevant studies was conducted using various databases, including PubMed, EMBASE, Scopus, and DOAJ, up to April 21, 2023. Specific keywords such as; hydatiform mole, trophoblastic tissue, choriocarcinoma, kidney disease, preeclampsia, glomerular filtration rate, proteinuria, hypertension and renal failure.

Hydatiform mole and kidney disease
In molar pregnancy, the production of human chorionic gonadotropin (hCG) is increased, causing an increase in glomerular filtration rate and proteinuria. Gestational trophoblastic disease and molar pregnancy may result to several pathological circumstances such as pre-eclampsia or eclampsia (4,5). Pre-eclampsia is a serious complication of pregnancy which can lead to kidney injury. Its prevalence is strengthened in molar pregnancies. Meanwhile, proteinuria in molar pregnancy is frequently detectable and can direct to considerable renal injury (5,6).

Additionally, pre-eclampsia enhances the risk of progressing chronic renal failure and finally end-stage kidney failure. In some conditions, nephrotic syndrome is also described in molar pregnancy. High levels of hCG production cause glomerular hyperfiltration, increasing the chances of proteinuria. The presence of proteinuria can lead to damage of the glomerular tissue, consequently causing chronic kidney disease (7). The incidence of proteinuria in patients suffering from these diseases is as high as 70%-80%. The increase in hCG production by the tumor cells can lead to glomerular damage by promoting glomerular hyperfiltration and renal vasodilation. The resulting capillary ultrafiltration helps permeability of proteins through the basement membrane, resulting in proteinuria (8,9). Moreover, hCG can cause direct damage to podocytes in the renal glomerulus, leading to podocyte foot process effacement, proteinuria, and loss of the glomerular filtration barrier function (10). Furthermore, hypertension is common in patients with molar pregnancy and choriocarcinoma (11). In this setting, acute renal failure is rare, and only a few cases have been reported. It may result from a rapidly progressive glomerulonephritis.
leading to extensive renal damage. Previous studies reported that a small number of patients had developed chronic kidney disease, and a subset of these proceeded to end-stage renal disease (12,13).

In general, preeclampsia, high blood pressure, and nephrotic range proteinuria are the frequently findings in molar pregnancy. Likewise, nephrotic range proteinuria, hypoalbuminemia and the resultant edema have significant effects on maternal health. As mentioned kidney failure is rare in molar pregnancy, though some case reports of rapid worsening of kidney function or exacerbation of previous proteinuria described (14,15).

The possible mechanisms for kidney failure in molar pregnancies are renal ischemia (hypoperfusion), reduced glomerular filtration rate, and interstitial nephritis. These modifications and injury of interstitial area may directed to the long-lasting renal damage even after the pregnancy has terminated. It has been hypothesized that the production of free radicals during the metabolism of hCG contributes to the oxidative stress of renal cells, leading to renal dysfunction. hCG can also interfere with the renin-angiotensin system, leading to elevated angiotensin II levels, which causes vasoconstriction and extended the renal injury (16).

**Increased production of other hormones**

There is evidence that other hormones, such as angiotensin II, cortisol, and aldosterone, may also contribute to the renal effects seen in molar pregnancy. These hormones are known to cause renal vasoconstriction, reducing blood flow to the kidneys, leading to ischemia, and renal dysfunction (17,18).

**Immunological abnormalities**

Patients with molar pregnancy and choriocarcinoma often exhibit immunological abnormalities. For example, high levels of anti-phospholipid antibodies, anti-basement membrane antibodies, and complement activation have been reported in some studies. This immune system dysfunction can lead to the activation of complement, the deposition of immune complexes, and subsequent renal damage (19-21).

**Angiogenesis**

Choriocarcinoma and molar pregnancy may also impact angiogenesis or the formation of new blood vessels, which is necessary for normal kidney function. The abnormal trophoblastic cell growth may lead to increased blood vessel formation, leading to abnormal vessel maturation, which can contribute to renal damage (22-24).

**Epithelial-to-mesenchymal transition**

There is evidence to suggest that the transition of renal tubular epithelial cells to mesenchymal cells may play a role in the development of renal fibrosis after experiencing molar pregnancy, choriocarcinoma, or due to the ongoing complications of the disease (25-27).

**Vascular endothelial growth factor**

Both molar pregnancy and choriocarcinoma are associated with high levels of vascular endothelial growth factor, a protein that promotes angiogenesis and increases vascular permeability. Vascular endothelial growth factor production may contribute to the development of proteinuria and glomerulonephritis (28,29).

**Choriocarcinoma**

In rare cases (3%) following molar pregnancy, patients may develop choriocarcinoma. Choriocarcinoma is a modern variant of gestational trophoblastic neoplasia, a severe type of malignancy. Choriocarcinoma accounts for about 1% of all gestational malignancies and displays osteoclastic activity frequently (30-32). Increased hCG levels are observed in 95% of women with choriocarcinoma, causing proteinuria. At this condition, several reports of association of choriocarcinoma with crescentic glomerulonephritis, minimal change disease, membranous nephropathy, focal and segmental glomerulosclerosis, and also renal vein thrombosis exist gave been reported (8,33). Crescentic glomerulonephritis is uncommon that is attributed to the presence of anti-nuclear antibodies and hCG. The high prevalence of crescentic glomerulonephritis and thrombosis in choriocarcinoma patients suggests the possible activation of immune cells, causing both glomerulonephritis and thrombosis (34,35). Though, after treatment, significant improvement in kidney function was observed. Recent studies describe an epigenetic modification like DNA methylation, histone modifications, microRNA expressions could fall under the mechanisms for altered gene expression, responsible for the development of chronic kidney disease and crescentic glomerulonephritis in molar pregnancy after completing their pregnancy term (36-38).

**Management of molar pregnancy**

Management of the hormonal imbalance in molar pregnancy and related complications typically involves the use of medications targeting the renin-angiotensin-aldosterone system (RAAS inhibitors) and the administration of corticosteroids that target inflammation. Other interventions may include anti-
platelet agents, anticoagulation, and therapeutic plasma exchange (39–41).

The multidisciplinary approach to care for patients with molar pregnancies and choriocarcinomas involves the collaboration of healthcare providers from various specialties to ensure prompt and appropriate diagnosis, management, and treatment of the disease. Here are some of the specialists involved in the multidisciplinary team approach for these diseases (42–45):

**Obstetrician-gynecologist**
The obstetrician-gynecologist is responsible for identifying and managing the hormonal, obstetric, and gynecological aspects of the disease processes. They are instrumental in diagnosing and treating the underlying conditions that cause the kidney’s renal system to become impaired, subsequently helping to protect the kidney from further damage (46,47).

**Radiologist**
The radiologist is an essential member of the multidisciplinary team. Their core competence is imaging technology that helps in the diagnosis and interpretation of imaging results, identifying pathological features of the disease (48).

**Pathologist**
The pathologist is responsible for the examination and analysis of tissue samples for any malignant changes. It is critical in diagnosing choriocarcinomas and associated risks (49).

**Nephrologist**
The nephrologist is responsible for identifying and managing the kidney-related complications of molar pregnancies and choriocarcinomas. They are involved in monitoring the patient for the progression of proteinuria, hypertension, and renal failure. They work on the reduction of long-term adverse effects of the diseases like possible end-stage renal disease or fibrosis due to long-term complications (50–52).

**Oncologist**
In cases of choriocarcinomas, medical oncologists, or hematologists are an essential part of the multidisciplinary approach. They assist in the staging, risk assessment, and management of the disease. They must identify the possible cellular and molecular pathways involved in the malignant progression of the disease (53–55).

**Social workers**
Social workers are involved in helping the patient navigate the challenges associated with the disease. Helping the patient with the psychological and financial difficulties that come along in managing the diseases like medical monetary expenses and emotional stresses due to fertility complications. Other healthcare providers: Patients with molar pregnancies and choriocarcinomas may require care from other specialists such as hematologists, genetic counselors, anesthesiologists, and intensive care specialists, according to the patient needs and resources (56–58).

**Conclusion**
In summary, the molecular mechanisms that contribute to the renal effects of choriocarcinoma and hydatiform mole are complex and multifactorial. They range from immune dysfunction and abnormal angiogenesis to alterations in the renin-angiotensin system and hormonal production. Prompt identification and early intervention are critical in preventing permanent damage to the kidneys. Therefore, a multidisciplinary team approach is necessary for the optimal management of renal effects of hydatiform and choriocarcinoma. Hydatiform and choriocarcinoma can lead to several different types of renal disease, including proteinuria, pre-eclampsia, and nephrotic syndrome. Choriocarcinoma can also cause damage to the kidneys.

**Conflicts of interest**
The author declares no conflict of interest related to the subject matter or materials discussed in this paper.

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