Review Article

Prevalence and Risk Factors of Choriocarcinoma in Saudi Arabia: A Systematic Review

Abstract

Choriocarcinoma is an aggressive trophoblastic neoplasm; its origin could be gestational or non-gestational. Most are gestational, which means they arise from pregnancy, which may be abnormal or normal. This review includes the published literature about choriocarcinoma's prevalence and risk factors. The researchers searched Science Direct, PubMed, EBSCO, Web of Science, Cochrane library, and Scopus. Then they used Rayyan QCRI to screen the study articles by title and abstract and did a full-text assessment. 353 patients who developed the gestational trophoblastic disease were considered in seven studies. Their age ranged from 21 years to 55 years. The decline in prevalence was attributed to the sociomedical improvement in Saudi Arabia. Regarding the case reports, gastrointestinal (GIT) bleeding, including melena and hemoptysis, was recorded in two studies. We concluded that choriocarcinoma manifestations range from silent lesions to symptomatic metastatic conditions. In Saudi Arabia, choriocarcinoma is a very uncommon neoplasm, as the majority of the literature consists of case reports. The reported possible risk factors were lower sociomedical status, multiparous women, abortion, and hypertension.

Keywords: *Choriocarcinoma, Gestational trophoblastic disease, Malignancy, Systematic review*

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Introduction

Choriocarcinoma is an aggressive trophoblastic neoplasm whose origin could be gestational or non-gestational. Most are gestational, which means they arise from pregnancy, which may be abnormal or normal. A complete hydatidiform mole (CHM) is present in more than 50% of cases of gestational choriocarcinoma; the other cases occur as a result of ectopic pregnancies, spontaneous and induced abortions, and normal term or preterm deliveries.[1, 2]

A paternal chromosome complement is a genetic characteristic of gestational choriocarcinoma. Those resulting from a CHM are known as purely androgenetic because they only have paternal genetic material. Although biparental, or containing both maternal and paternal chromosome complements, the intra-placental pattern of gestational choriocarcinoma also has a paternal chromosome complement.[3, 4]

The incidence of choriocarcinoma varies greatly throughout the world. About 1 in 40 people with hydatidiform moles and 1 in 40,000 pregnant women in North America and Europe will develop choriocarcinoma. 3.3 in 40 patients with hydatidiform moles and 9.2 in 40,000 pregnant women, in Southeast Asia and Japan, respectively, go on to develop choriocarcinoma.[5, 6] In China, choriocarcinoma will occur in 1 in 2882 pregnant women.[6] This is associated with a higher risk for Asian, American Indian, and African American women to develop choriocarcinoma.[5]

Studies have indicated that cytotrophoblastic cells act as stem cells and develop into cancerous cells; however, the precise choriocarcinoma pathogenesis is not yet completely understood or explained. Neoplastic cytotrophoblasts undergo additional differentiation to become intermediate trophoblasts and syncytiotrophoblasts.[7] Other gestational trophoblastic neoplasms have a cell mixture that mimics the development of a pre-villous blastocyst.[8]

There are differences between the prognoses of gestational and non-gestational choriocarcinomas, with the latter having a significantly worse prognosis.[9, 10] Nearly 100% of women with low-risk

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gestational choriocarcinomas survive after receiving chemotherapy, and 91% to 93% of patients with high-risk gestational choriocarcinomas survive after receiving multi-agent chemotherapy with or without radiation and surgery. A cumulative score more than 12 or stage IV disease in women are two negative risk factors that increase the likelihood of death.[11]

Choriocarcinoma can cause death if left untreated. Chemotherapy has made it possible for many patients to put their illnesses into remission and be cured of them. Chemotherapy use carries some risks, such as the possibility of nausea, secondary cancers, hair loss, vomiting, fevers, diarrhea, blood transfusions requirement, and infections.[12] As there is a significant lack in the literature investigating choriocarcinoma among the Saudi population, this systematic review includes the published literature about the prevalence and risk factors of choriocarcinoma.

Materials and Methods

In implementing this systematic review, the established guidelines were followed (Preferred Reporting Items for Systematic Reviews and Meta-Analyses, PRISMA).

Study design
This study was a systematic Review.

Study duration
The study period is from November to December 2022.

Study condition
This paper studies the published literature on the prevalence and risk factors of choriocarcinoma in Saudi Arabia.

Search strategy
The researchers did a comprehensive literature search in six main databases, including Science Direct, EBSCO, PubMed, Scopus, Web of Science, and Cochrane Library to find the relevant literature. The search was limited to the English language, and it was customized as required for each database. The following keywords, which were converted into Mesh terms in PubMed, were used to identify the appropriate studies; "Choriocarcinoma," " Trophoblastic neoplasm," " Gestational trophoblastic disease," "prevalence," "risk factors," " hazardous factors," "Saudi Arabia," and "Saudi population." The proper keywords were paired with "OR" and "AND" Boolean operators. The study findings included English, freely available articles, full-text publications, and human trials.

Selection criteria
Inclusion criteria
The participants were selected for addition founded on their applicability to the research, which has the following criteria; male or female patients with choriocarcinoma. We comprised all study designs that met the criteria, including case reports.

Exclusion criteria
All other articles, ongoing studies, and existing studies reviews lacking one of these themes as their primary goal were excluded.

Data extraction
The researchers used Rayyan to find duplicates of the results of the search strategy (QCRI).[13] Then they examined the relevance of the abstracts and titles by limiting the combined search findings based on a series of exclusion/inclusion criteria. The reviewers evaluated the whole texts of the articles that met the inclusion criteria. The authors discussed how to resolve any disagreements. The qualified study was included using a prepared form for data extraction. The data about the study titles, authors, study year, study design, participant number, gender, population type, possible risk factors, the prevalence of choriocarcinoma, and main outcomes was extracted by the authors.

Risk of bias assessment
To assess the level of quality of the included research, the qualitative data synthesis used the non-randomized studies ROBINS-I technique.[14] The reviewers examined and fixed any irregularities in the quality assessment.

Strategy for data synthesis
Summary tables including the data gathered from the eligible researches were prepared to provide a qualitative summary of the included study components and results. After extracting the data for the systematic review, decisions were made on how to best use the data from the included research papers. Studies meeting the full-text inclusion criteria but not providing any data on the prevalence and risk factors of choriocarcinoma in Saudi Arabia were excluded.

Results and Discussion

Search results
Totally 400 research papers resulted from the systematic search, and then 80 duplicates were removed. The researchers did title and abstract screening on 320 studies, and excluded 271 studies. 271 reports were sought for retrieval, and only 10 articles were not retrieved. Eventually, 39 articles were screened for full-text assessment; 10 were excluded for incorrect study outcomes, 15 for unavailable data on diabetes as a risk for cancer, and 7 for the incorrect population type. Seven eligible research articles were included in this systematic review. A summary of the research selection procedure is shown in **Figure 1.**

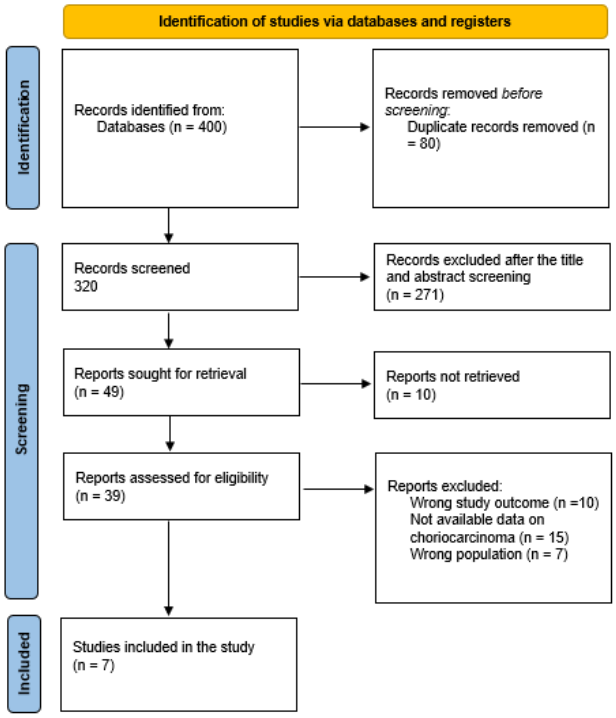

Figure 1. The study selection process is summarized by the PRISMA flowchart.

Specifications of the included studies

The researchers included 7 studies in this review, with 353 patients who developed the gestational trophoblastic disease. 352 of those patients were females, and only one patient was male.[15] Their age ranged from 21 years[16] to 55 years.[17] Two studies were retrospective; one included 289 patients,[18] and the other included 59 patients.[19] Five studies were case reports.[15-17, 20, 21] Four studies were conducted in Riyadh city,[15, 19-21] one in El-Madinah,[18] one in Jeddah,[16] and one in Dammam.[17]

Regarding the study articles, one study reported a (0.7%) prevalence of choriocarcinoma in 2022,[18] and the other reported (5.1%) in 2003.[19] The decline in prevalence was attributed to the sociomedical improvement in Saudi Arabia. Regarding the case reports, gastrointestinal (GIT) bleeding, including melena and hemoptysis, was recorded in two studies.[15, 20] Headache and periorbital fullness were associated with orbital metastasis.[16] Menorrhagia was reported in two cases,[20, 21] and rare skin lesions were reported in two cases.[17, 21] The reported possible risk factors were lower sociomedical status,[18, 19] multiparous women,[17-21] abortion,[20, 21] and hypertension.[20]

Table 1. A summary of specifications of the included research articles

Study	Study design	Country	Population type	Gender	Age	Key findings	ROBINS-I
Almohammadi, 2022[18]	Retrospective study	Madinah	Patients with gestational trophoblastic disease	Females (289)	33.47 ± 9.3	The present study also documents fewer choriocarcinoma incidents: two cases of gestational carcinoma (2.15%) and one case of choriocarcinoma with lung metastasis (0.9%).	Moderate
Khashoggi, 2003[19]	Retrospective study	Riyadh	Patients with gestational trophoblastic disease	Females (59)	40	Two cases of choriocarcinoma were recorded. With the quick sociomedical development of the KSA, the incidence of GTD has decreased.	High
Alshammery *et al*., 2022[20]	Case report	Riyadh	A patient presented with git bleeding (melena) and menstrual irregularities	Female	37	This patient was hypertensive, multiparous, and with two previous abortions. Metastatic choriocarcinoma was detected with histopathology when complications appeared	Moderate
Ahamed *et al*., 2015[16]	Case report	Jeddah	A patient presented with a headache, progressive left periorbital fullness, and blurred vision that had been present for four weeks.	Female	21	Visual impairment and swollen orbits from orbital metastasis in gestational choriocarcinoma patients are uncommon events that call for a high index of suspicion.	High
Althwanay *et al*., 2020[17]	Case report	Dammam	A patient initially manifested as having liver, kidney, and lung metastases along with skin lesions and progressive back pain.	Female	55	She initially manifested as having liver, kidney, and lung metastases along with skin lesions and progressive back pain.	High
Hashim Amer *et al*., 1982[21]	Case report	Riyadh	A patient with a six-year menorrhagia history after a pregnancy that was aborted at five months gestation.	Female	40	Abortion of five months' gestation was recorded. This patient had bullous pemphigoid as a rare skin manifestation associated with choriocarcinoma	High
El-Sharkawy and Al-Jibali *et al*., 2017[15]	Case report	Riyadh	A patient with hemoptysis, weight loss, and abdominal pain for 2 weeks duration	Male	22	This patient had a poor diagnosis and hemorrhagic metastases in the lungs and brain.	High

Choriocarcinoma is a rare malignancy, and its incidence varies greatly throughout the world.[5] This systematic review found that choriocarcinoma manifestations ranged from silent lesions to symptomatic metastatic disease. Choriocarcinoma has a very low prevalence or even rare neoplasm in Saudi Arabia, and most of the literature was case reports. The vast majority of cases were females. There are regional differences have been linked to several highly speculative factors, including ethnic origin, blood type, age, parity, diet and nutrition, contraception, socioeconomic status, immunologic factors, and genetics. Since consanguinity is widespread and hysterectomy is viewed as defeminizing by the Saudi population's sociocultural background, the epidemiologic study of GTD is made all the more fascinating.[5, 6, 19]

Most of the included participants were middle-aged, and only two participants were young.[15, 16] We also found that the decline in prevalence was attributed to the sociomedical improvement in Saudi Arabia. These results are in line with earlier research that suggested a high protein diet, and sociomedical advancements had a significant impact on reducing the prevalence of this disease in developed nations.[22, 23] Other risk factors include having previously had a complete hydatidiform mole (a risk that is multiplied by 100), being older, using oral contraceptives continuously, and having blood type A.[3]

The lymph node, liver, peritoneum, and lung are the most frequent metastasis sites. Patients typically pass away from hepatic failure brought on by disseminated intravascular coagulation, tumor metastasis, and bleeding.[24] The jejunum, followed by the duodenum and the ileum, respectively, is where metastatic disease to the small bowel most frequently occurs. Only 5% of patients[25] who have it metastasize, which is extremely uncommon, present with severe lower gastrointestinal bleeding. Upper abdominal pain, vomiting, intestinal intussusceptions, and a perforated viscus are possible symptoms.[26]

There are many different reasons why lower GI bleeding occurs, but the most frequent ones are neoplasms, vascular lesions, Meckel diverticulum, inflammatory lesions (like Crohn's disease), lymphangiectasia, radiation-induced bleeding, and arteriovenous malformation. LGIB can also be a symptom of small bowel metastasis from melanoma, breast cancer, or Kaposi's sarcoma.[25]

Our study is limited by the lack of investigations and data on choriocarcinoma globally and locally in Saudi Arabia. This implies the rare incidence of the disease and unclear risk factors. Most studies on choriocarcinoma have been case reports. Therefore, the therapeutic modalities, clinicopathology, and prognostic variables are not well established.

Conclusion

According to this systematic review, choriocarcinoma manifestations can range from a silent lesion to a symptomatic metastatic condition. In Saudi Arabia, choriocarcinoma is a very uncommon or even low-prevalence neoplasm, as the majority of the literature consists of case reports. Moreover, females made up the vast majority of cases. The reported possible risk factors were lower sociomedical status, multiparous women, abortion, and hypertension.

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Conflict of interest

None.

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Ethics statement

None.

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