A set of conditions connected to pregnancy and caused by trophoblast cells are known as gestational trophoblastic diseases. There are benign and malignant cancers, including invasive moles, choriocarcinomas, placental site trophoblastic tumors (PSTT), and epithelioid trophoblastic tumors (ETT). These cancers are classified as gestational trophoblastic neoplasms (GTN), which are less common but more serious. Most often, monitoring serum human chorionic gonadotropin (hCG) with histological confirmation is used to diagnose GTN. As a differential diagnosis, certain tissue biomarkers have grown in popularity. This has produced more accurate results and various treatment regimens and prognoses for each GTN. The World Health Organization's prognostic score system and the International Federation of Gynecology and Obstetrics anatomical staging system are the foundations for the treatment. Suppose the proper diagnosis is made and the instructions are followed. In that case, choriocarcinoma and invasive mole cases can be cured in 98 percent of instances, whereas PSTT and ETT still have only moderate success rates. The increased understanding of GTN and its characteristics enables medical professionals to rapidly make a differential diagnosis and select the appropriate treatment option, thus improving the overall survival of affected women. Nevertheless, epidemiological data collection and knowledge advancement through basic and translational research are crucial to address issues regarding GTN pathophysiology, their origins, and cellular behaviour.

Keywords: Gestational trophoblastic diseases, human chorionic gonadotropin, treatment.

I. INTRODUCTION

The term "gestational trophoblastic disorders" (GTD) refers to a group of benign and malignant conditions that affect the fetus during pregnancy. Most invasive moles and choriocarcinomas in GTN are caused by prior benign molar pregnancies, which account for 50% of cases, 25% of abortions or ectopic pregnancies, and 25% of term or preterm births. As a result of improper fertilization and placental villi growth, they exhibit an aberrant karyotype. The causes of PSTT and ETT, on the other hand, can be traced back to healthy prior pregnancies or non-molar abortions [1]. Women in Asia are more likely to experience these issues than in the Americas or Europe, where they are rare complications. These disparities in incidence may be caused by subdiagnosis, the availability of pathology knowledge and trained reference centres, epidemiological data collection, or genetic influences. Dependent on the nation, epidemiological data gathering may be limited due to the rarity of the majority of GTN. However, a retrospective national cohort study revealed that the cure rate for GTN is approximately 99%, and the risk factors for lethality were significantly higher when treatment was started outside of reference centres, choriocarcinoma histology, metastatic disease, absence of chemotherapy at the beginning of treatment, and high-risk patients. FIGO/WHO score, according to the International Federation of Gynecology and Obstetrics. In both low- and high-risk situations, the interval between the end of pregnancy and the beginning of chemotherapy is closely related to the development of metastatic illness, with an elevated risk of complications and even mortality [2].

Human chorionic gonadotropin (hCG) surveillance without symptoms is typically used to diagnose postmolar GTN. The FIGO's anatomical staging system and the WHO prognostic index system are crucial to determining the prognosis and directing the selection of the appropriate chemotherapy regimen for GTN treatment. The FIGO criteria for diagnosing postmolar GTN include an hCG plateau lasting for four measurements over three weeks or more, a rise in hCG for three consecutive weekly measurements at a minimum of two weeks or more, and a histologic diagnosis of choriocarcinoma. Additionally, a torax X-ray can detect lung metastasis, count the number of metastases, and assess the risk score. In order to find liver metastases, an ultrasound or CT scan is typically used, whereas MRI or CT scan is the imaging test to find brain metastases [3].

Patients with non-molar GTN typically experience atypical vaginal bleeding, which may be accompanied by haemorrhage symptoms from metastatic sites such as the liver, spleen, intestines, lung, or brain, as well as neurological
signs on by metastases to the brain and spine. For a woman with metastatic disease whose underlying tumour site is unknown, GTN should be considered as a differential diagnosis, and blood hCG testing should be done [4]. Additionally, the current study aims to assemble new and primary aspects of GTN by compiling data on the epidemiology, aetiology, histology, clinical characteristics and recommended therapies for each of these malignancies.

II. CLASSIFICATION

A. Invasive Mole

Hydropic choriocarcinoma villus with cytotrophoblast proliferation and syncytiotrophoblast development enhanced trophoblast invasiveness, and metastatic potential is characteristic of the invasive mole. The chance of having an invasive mole rises with age (>40 years), occurring six to ten times more frequently than choriocarcinoma and particularly following a complete molar pregnancy. The most typical signs are abnormal vaginal bleeding, uterine enlargement, and elevated hCG levels. After a hysterectomy or biopsy of a metastatic lesion, the invasive mole can be identified. Furthermore, before the development of chemotherapy, the mortality rate was around 15%, and invasive moles could develop after an average of 6 months following a previous molar pregnancy. Currently, the cure rate for low-risk patients is over 100%, compared to 90% for high-risk patients [5].

B. Placental Site Trophoblastic Tumour

A monomorphic population of extravillous cytotrophoblast-like cells from the implantation site make up most of the PSTT. Its incidence is roughly 1 in 100,000 births, accounting for only 0.23–3% of all GTN cases, and is higher in Japan, India, and the Middle East. The PSTT can arise from any gestational event, and it typically takes between three and six months after pregnancy for it to manifest, though it can take years. Interestingly, most PSTT instances occur following healthy pregnancies since only 16% and 13% of cases, respectively, show evidence of prior CHM history or abortion [6].

Abnormal vaginal bleeding and uterine enlargement are typical symptoms, followed by amenorrhea and abdominal pain. Small amounts of hCG and placental lactogen are also secreted by the PSTT. In addition to imaging tests, the diagnosis is made through the histological study of curettage, hysterectomy, or biopsy specimens. Additionally, the diagnosis can be confirmed by checking for free hCG, a component of total hCG produced by extravillous cytotrophoblast cells at the site of implantation. The GTN has the highest death rates, ranging from 6.5-27 percent [6]. Due to rarity, chemotherapeutic resistance, and racial and geographic characteristics, there is a significant range in frequencies.

C. Epithelioid Trophoblastic Tumour

Monomorphic extravillous cytotrophoblast cells are the source of the ETT. In contrast to PSTT, ETT cells are derived from the chorionic plate. The ETT can manifest themselves mostly following abortions, with a median onset time of 6.2 years and a range of 1 to 18 years. Furthermore, the lower uterine segment and cervix are the recommended sites for initial lesions for ETT. The Netherlands had the fewest incidences of GTN, and ETT, according to Eysbouts and associates’ (2016) research [7]. Women with ETT exhibit symptoms and indications that are comparable to those of PSTT, but mortality is higher, ranging from 10 to 24.2 percent. The treatment is not yet fully established because ETT is uncommon and has unusual biological activity, although the present methods are comparable to those used with PSTT [6].

D. Choriocarcinoma

Three subtypes of choriocarcinoma can be distinguished: intraplacental, defined by their presence inside the placenta and associated with the development of metastasis in both mother and fetus; non-gestational, derived from germ cells or somatic cells (unrelated to previous pregnancies). And gestational. Compared to the gestational form, the non-gestational type has a worse prognosis and is more resistant to chemotherapy [8].

Most choriocarcinomas develop following molar pregnancies and have significant proliferative, invasive, and metastatic potentials. This cancer exhibits a biphasic morphology with pleomorphic syncytiotrophoblast-like regions and highly proliferative cytotrophoblast-like cells. Tissue-specific trophoblastic cells can develop malignant alterations following extended latent periods, while its reasons are not fully understood. Approximately three months after birth in a full-term pregnancy and 13 months after the molar evacuation, on average, choriocarcinoma development occurs after a molar pregnancy. Choriocarcinoma, however, can develop several years or even decades after a prior pregnancy, an abortion, or another GTD [9], [10].

1 in 40,000 pregnancies in North America and Europe result in choriocarcinoma. However, in Asia, the incidence of choriocarcinoma is 9.2 and 3.3 per 40,000 births, respectively. Risk factors for complete hydatidiform mole (CHM) include Asian ancestry, advanced maternal age, prolonged oral contraceptive use, and advanced maternal age. Vaginal bleeding, elevated hCG levels, and haemorrhage in metastatic areas are all symptoms of choriocarcinoma. The hCG level in the serum, a gold-standard biomarker, is measured during diagnosis and follow-up. Imaging studies and histopathological analyses are also frequently employed for diagnosis [4].

III. DIFFERENTIAL DIAGNOSIS USING HISTOPATHOLOGICAL

The invasive mole manifests as a hemorrhagic lesion with molar villi and extravillous cells resembling cytotrophoblasts, invading the myometrium, and can be found in extrauterine places. Since only invasive moles display them, the presence of molar chorionic villi is crucial for distinguishing it from other GTNs. Intense trophoblastic invasion by cells that resemble cytotrophoblasts alternates with cords made of syncytiotrophoblast-like structures to define choriocarcinoma. Rapid mitotic activity, nuclear atypia, pleomorphism, severe necrosis, bleeding, lack of calcifications, and vascular invasion through tumor thrombi are all linked. The extravillous cytotrophoblasts from the implantation site, which are largely monomorphic, make up
the PSTT, which comprises these cells. In the myometrium, where the extravillous cytotrophoblast invades and separates the muscle fibers, PSTT has various levels of nuclear atypia and a neoplasm that displays an infiltrative tumour boundary. Additionally, PSTT exhibits severe vascular invasion in which cancerous cells and fibrinoid debris take the place of blood vessel walls, with little necrosis or inflammation present inside the lesions. A population of largely monomorphic cells called extravillous cytotrophoblasts of the chorionic type make up the ETT, on the other hand, which is generated by a different population of cells. Few cells invade neighbouring tissues, and it has a well-defined nodular development pattern. Geographic necrosis surrounds islands of cancerous cells in the ETT pattern. The cells combine with a hyaline substance of type IV collagen and adult and oncofetal fibronectins. Vascular invasion and bleeding may not necessarily indicate calcifications [11].

IV. BIOMARKER FOR DIAGNOSIS

The initial biomarker used in the diagnosis and monitoring of the success of GTN therapy is hCG. The glycoprotein known as hCG is made up of two components. All gonadotropins share a common subunit, which is hormone-specific, in charge of hormonal activity and immunoreactivity, and is hyperglycosylated during the first trimester of pregnancy. The two components of the hCG are combined in healthy pregnancies. Around the ninth week, the level of -hCG peaks at 50,000 to 100,000 mIU/mL. The hCG serum level decreases to between 10,000 and 20,000 mIU/mL in the second trimester and stays constant up to the term. However, invasive mole and choriocarcinoma have significantly greater levels of hCG production by GTN (Table 1), while PSTT and ETT have much lower levels [11], [12].

Contrary to healthy pregnancies, the hCG produced by GTN is interestingly destroyed unevenly, resulting in the formation of several fragments, including free -hCG, free notched -hCG, hyperglycosylated -hCG, and -core fragment. For the differential diagnosis of GTN in women with chronically low levels of total hCG, these several hCG subproducts are helpful. After the second trimester, the extravillous cytotrophoblast cells on the implantation site release free -hCG, which prevents these cells' invasion, proliferation, and death. In contrast, the presence of hyperglycosylated hCG is linked to choriocarcinoma, while the presence of 30% free hCG levels can be used to detect PSTT. Additionally, the presence of -hCG in the urine rules out the potential of a false-positive result. At the same time, the presence of hCG in the cerebrospinal fluid can also indicate brain metastases [13].

Although most patients with hydatidiform moles experience spontaneous remission, 15-20% and 0.5–5% of those with complete and partial lesions may develop GTN and require treatment. However, patients who experienced spontaneous remission had hydatidiform moles with higher rates of apoptosis than patients who advanced to GTN, which might have been a sign of malignant change. The same could be said for versican expression, which is eliminated in choriocarcinoma and invasive moles but is highly expressed in healthy tissues and hydatidiform moles with spontaneous remission [14]. Its absence could also serve as a potential marker to anticipate malignant transformation. Several differential biomarkers have been proposed as predictors of hydatidiform mole malignization since differential and early detection are crucial for GTN.

In contrast to other GTN, which had lower proliferative indices of 14 percent in PSTT, 10 percent in ETT, and 5.2 percent in invasive mole, the mitotic activity may be a sign of choriocarcinoma. As mentioned earlier, hCG is a significant biomarker, and both choriocarcinoma tissues and invasive moles exhibit substantial immunoreactivity for hCG. On the other hand, hCG is weakly or completely negative for PSTT and ETT. Invading cells from choriocarcinoma and PSTT express the markers CD146, MUC-4, and HLA-G, whereas ETT alone exhibits strongly expressed HLA-G. For cytokeratin AE1/AE3 and cytokeratin 18, PSTT and ETT are positive, whereas choriocarcinoma is only positive for AE1/AE316. The only GTN that tests negative for -inhibin is choriocarcinoma. Another interesting differential marker is hPL, expressed strongly and weakly by various GTN and PSTT cells, respectively. In contrast to the invasive mole, which has medium protein expression, the PSTT and ETT exhibit significant E-cadherin expression. Additionally, the most accurate marker for ETT has already been identified and is strongly positive for ETT (p63) [6], [15].

V. CURRENT TREATMENTS

The FIGO-adopted anatomical staging system, along with the WHO prognostic system, is used to determine the GTN treatment plan. According to their risk of developing resistance to treatment with a single chemotherapeutic agent, GTN patients are categorized as low risk (stage I to III and score 0 to 6), high risk (stage IV or stage I to III and score 7 or more), and ultra-high risk (score>12). Methotrexate (MTX) or actinomycin D (ActD) is used as the sole chemotherapy drug for low-risk patients, with remission rates that are nearly 100%. When combined with a histological diagnosis of choriocarcinoma and elevated baseline levels of -hCG, a WHO prognostic score of 5 or 6 denotes a potential resistance to chemotherapy with a single agent, necessitating protocols with several agents. Etoposide, MTX, and ActD (EMA) alternate weekly with cyclophosphamide and vincristine in high-risk patients' chemotherapy regimens, which had a 90.6 percent success rate for remission (CO). Ultra-high-risk patients should start their chemotherapy with an induction regimen using low doses of etoposide (EP) and cisplatin, followed by EMA-CO or EP-EMA, which have significantly increased survival for ultra-high-risk patients and prevented early deaths at the time of chemotherapy initiation. The therapy remission rate ranges from 80 to 90 percent for high-risk patients, and for ultra-high-risk patients, it is 67.9 percent [4], [16].

When hCG normalization is attained, the effectiveness of the treatment is evaluated. Patients are deemed therapy-resistant, and second-line therapy should be used if hCG levels remain stable after three cycles. In addition, after the hCG levels in low-risk patients have returned to normal, an additional six weeks of treatment are given. Additional eight weeks are required in high-risk and ultra-high-risk women. After three accurate readings, hCG levels are monitored monthly for a year. In the first year following the completion doi: http://dx.doi.org/10.24018/ejmed.2022.4.5.1403
of chemotherapy, the risk of relapse is around 3%; however, it declines over time to less than 1%. Contraception is advised, and intrauterine devices should not be used until hCG levels are undetectable in the blood. Serum hCG levels should also be measured. Due to the possibility of miscarriage, patients should wait at least six months after the final cycle of chemotherapy before trying to get pregnant. If the patient becomes pregnant after this time, hCG control is halted and restarted for 6 to 10 weeks [17], [18].

Immunotherapy is a novel treatment option for rare cases of resistance or relapse. Strong expression of the programmed cell death ligand (PD-L1) in GTN suggests that the ligand plays a role in tumour immune evasion. Multiple suppressive mechanisms, such as tumour-expressed (PD-L1) signaling to the T-cell inhibitory receptor, control anticancer T-cell activity (programmed death protein 1 [PD-1]). Drug-resistant gestational trophoblastic neoplasia has been associated with the anti-PD-1 medication pembrolizumab. Avelumab, an anti-PD-L1 medication, is another potential medication. It was utilized in the TROPIMMUN phase II trial, demonstrating a positive safety profile and effectively treating around half of the patients with GTN. They were resistant to single-agent chemotherapy [19], [20].

While various GTN exhibit different biological activities and clinical outcomes, PSTT and ETT don’t fit the prognostic scheme outlined above. Since these cancers are typically multicentric, they do not respond satisfactorily to conventional therapies. For choosing the appropriate course of treatment, only FIGO’s anatomical staging is helpful. Hysterectomy is frequently used as a first-line therapy since these tumours are prone to lymphatic spread. Therefore, lymphadenectomy is also advised in cases of deep myometrial invasion and the presence of probable macroscopic nodules. Since chemotherapy alone is ineffective in locally advanced or metastatic illness, curettage, hysteroscopic resection, and chemotherapy may be options for lesions in the uterus. Patients with poor prognoses are advised to undergo adjuvant chemotherapy with several drugs. Therefore, EP/EMA or EP/TP is the preferred protocol in these circumstances [4], [6], [21].

**VI. CONCLUSION**

The GTN are uncommon illnesses that can become complicated if the correct differential diagnosis and course of action are not taken. Controlling the hCG levels is crucial for diagnosis and follow-up. The increase in histological analysis and particular biomarkers is a welcome addition to rare diseases. Applying these protocols and more reference centres is crucial, especially in undeveloped nations with high GTN mortality rates. As a suggestion, it is now important to mobilize multidisciplinary teams globally to develop a global epidemiological and histopathological database to give localized data, diagnoses, cutting-edge treatment regimens, and patient support. Funding for basic research and greater communication with physicians are required to bridge the knowledge gaps surrounding the aetiology and physiopathology of GTN.

**REFERENCES**


