

## **Gestational Trophoblastic Disease in Ayder Comprehensive Specialized Hospital, Mekelle City, Northern Ethiopia: A Five Year Review Study**

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### **Abstract**

**Background:** When the regulatory mechanisms fail, gestational trophoblastic diseases result in tumors that are highly invasive, metastatic, and very vascular. Virtually all malignant gestational trophoblastic disease is curable if detected early and treated promptly and aggressively.

**Objective:** To review the experiences with gestational trophoblastic disease at Ayder Comprehensive Specialized Hospital, Mekelle City, Northern Ethiopia, over a five year period.

**Methods:** A chart review was carried out on cases of Gestational trophoblastic disease seen at Ayder Comprehensive Specialized Hospital, Northern Ethiopia, between January 1, 2009 and December 31, 2013.

**Results:** Forty-five cases of gestational trophoblastic diseases were identified over the study period. Over the five-year period, there were 5,185 deliveries at Ayder Comprehensive Specialized Hospital, giving a ratio of 1 case of gestational trophoblastic disease for every 115 deliveries (equivalent to 868 cases per 100,000 deliveries). Numerous deficiencies in the clinical care of these patients were documented. Review of hospital charts revealed that patient histories were often incomplete, laboratory investigations were not obtained in a systematic fashion, specimens for pathological evaluation were not routinely sent, follow-up was poor and generally inadequate, and documentation of findings in the chart was often inexplicably incomplete.

**Conclusion:** The incidence of gestational trophoblastic disease appears to be extraordinarily high in northern Ethiopia. This study revealed numerous deficiencies in clinical practice which have prompted us to create a regional trophoblastic disease center in Mekelle to coordinate care throughout the region.

**Key words:** gestational trophoblastic disease, molar pregnancy, hydatidiform mole, choriocarcinoma, developing countries, Ethiopia.

## **Introduction**

Gestational trophoblastic disease (GTD) refers to a spectrum of neoplastic disorders arising from placental tissue following either normal or abnormal fertilization events [1]. Normal trophoblastic tissue invades the endometrium at implantation to access the uterine vasculature in the process of creating the placenta. As Seckl and colleagues note, however, “in gestational trophoblastic disease the regulatory mechanisms fail, resulting in tumors that are highly invasive, metastatic, and very vascular” [2].

The incidence of hydatidiform mole varies considerably around the world, with incidence rates of 66 – 91 cases per 100,000 pregnancies reported in Europe, 83 – 121 cases per 100,000 pregnancies in the United States and Canada, with much higher rates (81 – 1,299 cases per 100,000 pregnancies) reported from Asia and the Middle East (320 – 580 cases per 100,000 pregnancies) [1]. In Europe, North America and Latin America, rates of choriocarcinoma are much lower than the rates of molar pregnancy, ranging from 2 -7 cases per 100,000 pregnancies, with rates in Asia remaining much higher (5 – 202 cases per 100,000 pregnancies) [1]. Up to 20% of patients with a molar pregnancy will develop malignant sequelae requiring chemotherapy [3, 4]. This is less likely if the patient has a partial as opposed to a complete hydatidiform mole [5]. Therefore, all women with a molar pregnancy should be followed carefully after evacuation of the uterus to ensure that a potentially fatal malignant consequence of their initial pathology does not develop.

Virtually all malignant GTD is curable if detected early and treated promptly and aggressively [2, 6]. Women who die from this disease generally do so because they present late for care, receive an initial misdiagnosis, or undergo inadequate chemotherapy, which leads to tumor resistance and a subsequent fatal outcome [5]. Meticulous, well-documented follow-up is therefore critical for proper disease management. The logistic challenges presented by these cases can be challenging in parts of the world where healthcare systems are poorly developed, management is inadequate, and infrastructure is incompletely developed

For years, the “conventional wisdom” of clinical medicine in Ethiopia has been that GTD is confined mainly to the northern part of the country, and our own clinical impression gained from working in this region is that significant numbers of GTD cases are seen at Ayder Hospital. We, therefore, undertook this study to determine the incidence of GTD in our patient population and to examine the quality of care that such patients receive, with a view of improving clinical practice.

## **Materials and methods**

Ayder Comprehensive Specialized Hospital (ACSH) is a tertiary care hospital located in the city of Mekelle in the Tigray Region of northern Ethiopia. It serves a population of approximately 8 million people, who live mainly in rural areas and earn their living by subsistence agriculture. Transportation is often difficult and female literacy is only

53.2 % in this patient population [7]. ACSH is the main teaching hospital affiliated with the College of Health Sciences at Mekelle University. The Mekelle University School of Medicine is a young institution, having only graduated its first class in 2010. Residency training in obstetrics and gynecology did not begin until January, 2013. In spite of this, Ayder is already the second-largest hospital in Ethiopia, with 500 beds, 96 of which are devoted to obstetrics and gynecology. The hospital has averaged 1,000 deliveries per year since it opened.

In order to assess the incidence of GTD at our institution, we carried out a retrospective chart review of all cases with this diagnosis between January 1, 2009 and December 31, 2013. With the intention of determining the quality of care and the burden of GTD, we reviewed hospital records of all obstetrics and gynecological related ones in five years period followed by thorough review with the

**Table 1: Presenting Signs and Symptoms in 45 Cases of Gestational Trophoblastic Disease in Patients from Ayder Comprehensive Specialized Hospital, Mekelle City, Northern Ethiopia.**

| Presenting sign or symptom* | No. | %    |
|-----------------------------|-----|------|
| Vaginal bleeding            | 37  | 82.2 |
| Passage of vesicles         | 9   | 20.0 |
| Lower abdominal pain        | 19  | 42.2 |
| Big for date                | 14  | 31.1 |
| Hyperemesis gravidarum      | 12  | 26.7 |
| Hyperthyroidism             | 8   | 17.8 |
| Hypertension                | 10  | 22.2 |

\*Patients often presented with more than one sign or symptom.

The average duration of amenorrhea prior to presentation was 4 months (range 1 – 7

months). Thirteen patients (28.9%) identified GTD. Relevant clinical information was retrieved using an extraction format. Criteria were employed to include or exclude from the GTD identified charts. Ethical approval for this chart review was obtained from the Institutional Review Board at ACSH. Initial chart review identified 51 cases of suspected GTD.

### Results

In five years period (2009 – 2013), there were 5,185 deliveries giving an incidence of one case of GTD for every 115 deliveries (868 per 100,000 deliveries). The average patient age was 32.4 years (range 18 to 50 years). Average patient gravidity was 4.9 (range 1 to 14) and average parity was 3.7 (range 0 to 12). The majority (31 patients, 68.9%) of patients were from rural areas and the rest (31.1%) from urban areas. Clinical signs and symptoms at initial presentation are given in Table 1.

months). Thirteen patients (28.9%) presented during the first trimester and 32

patients (71.1%) presented in the second trimester of their pregnancies. Physical findings at presentation included gestational size greater than dates in 14 cases (31.1%) and hypertension in 10 cases (22.2%). Eighteen patients were suspected of having hyperthyroidism on the basis of clinical findings and this was confirmed in 8 cases (17.7% of the total cases) by thyroid function testing. Pelvic ultrasonography was performed on 43 patients (95.5%) and in each case an ultrasound diagnosis of GTD was made. Theca-lutein cysts were documented in 6 cases (13.3%). All patients had a chest x-ray and in 2 cases (4.4%) pulmonary metastases were present. One patient had a CT-scan of the head after a histopathological diagnosis of choriocarcinoma was returned and the scan was negative for cerebral metastases. Based on liver function tests, no patient had suspected hepatic metastases. The average hematocrit at presentation was 33.4 g/dl (range 9 to 48 g/dl) and in 15 cases (37.8%) the presenting hematocrit was less than 33 g/dl. Sixteen cases (35.6%) were blood group A, 11 cases (24.4%) were group B, 11 cases (24.4%) were group O, and 4 cases (8.9%) were blood group AB. Quantitative beta-human chorionic gonadotrophin (B-HCG) levels were drawn on only 36 patients. Total B-HCG levels were measured using the Architect Total B-HCG Assay™ (Abbott Ireland Diagnostics Division, Longford, Ireland), a two-step immunoassay using chemiluminescent microparticle immune-assay technology. The average B-HCG level at presentation was 273,524 mIU/ml (range 3,266 to 1,612,193 mIU/ml).

Twenty-eight cases (62.2%) were treated with suction dilatation and curettage and 15 patients (33.3%) including one case of choriocarcinoma underwent hysterectomy, while treatment was unknown in 2 cases. Two patients with a clinical diagnosis of GTD based on classic ultrasound findings were admitted to the hospital with hyperemesis gravidarum, but left against medical advice and did not undergo treatment. What subsequently happened to them is unknown. Blood transfusions were required in 15 cases (33.3%). The average transfusion was 2.9 units (range 2 to 6 units). Post-operative hospital stays averaged 10.3 days (range 3 to 33 days). Eight patients underwent chemotherapy. In 7 cases, single-agent methotrexate was given and in one case with a histopathological diagnosis of choriocarcinoma the patient underwent multi-agent chemotherapy with etoposide, methotrexate, actinomycin-D, cyclophosphamide, and vincristine (EMACO).

Intensive reviewing was done on 51 charts of which 6 were excluded employing criteria (Table 2). Histopathological examination of surgical specimens was not systematically obtained. In 22 cases (48.9%) histopathology was not obtained. Among the specimens that were examined (23 cases), there were 9 cases of complete mole (20%), 10 cases of partial mole (22.2%), 3 cases of invasive mole (6.7%), and 1 case of overt choriocarcinoma (2.2%).

**Table 2: Characteristics of Excluded GTD Cases among Patients from Ayder Comprehensive Specialized Hospital, Mekelle City, Northern Ethiopia.**

| Case | Passage of Vesicles | Hyperemesis | Theca Lutein Cysts | Hypertension | Ultrasound Diagnosis | Serum B-HCG(miu/ml) | Pathology Report                |
|------|---------------------|-------------|--------------------|--------------|----------------------|---------------------|---------------------------------|
| 1    | No                  | No          | No                 | No           | Partial mole         | 25                  | Retained products of conception |
| 2    | No                  | No          | No                 | No           | Partial mole         | Unknown             | None                            |
| 3    | No                  | No          | No                 | No           | Partial mole         | Unknown             | None                            |
| 4    | No                  | No          | No                 | No           | Partial mole         | Unknown             | None                            |
| 5    | No                  | No          | No                 | No           | Partial mole         | Unknown             | None                            |
| 6    | No                  | No          | Yes                | No           | Partial mole         | 52                  | None                            |

Follow-up of patients with GTD was poor and unsystematic (Table 3). Only 25 of 45 cases (56%) returned for any follow-up. The follow-up that did occur was short-term only: 12 patients returned one week after discharge and 4 returned 2-3 weeks after discharge. Only 9 patients had follow-up longer than one month. In two cases, persistent disease was suspected in patients who still had positive B-HCG levels at their last clinical visit, after which they were lost to follow-up. Remission of disease (with a negative quantitative B-hCG) was documented in 10 cases, but in only 3 of

these cases did patients have 4 consecutive negative B-HCG levels 6 months after treatment. Three patients with ultrasound examinations positive for GTD left the hospital against medical advice after their initial evaluation and were lost to further follow-up. Three patients were referred to Black Lion Hospital in Addis Ababa for chemotherapy (mainly for family reasons), but they, too, were lost to further follow-up. The medical records of the 45 patients in this series did not document any deaths due to GTD.

**Table 3: Chart Deficiencies Noted during GTD Case Review among Patients from Ayder Comprehensive Specialized Hospital, Mekelle City, Northern Ethiopia.**

| Deficiency   | Number | Percent (%) |
|--|--------|-------------|
| No contact telephone number recorded in chart      | 45     | 100         |
| Ultrasound report missing or not done              | 2      | 4           |
| Serum B-HCG level missing or not done              | 6      | 13          |
| Histopathology missing or not obtained             | 22     | 49          |
| Plan for contraception absent from clinical record | 45     | 100         |
| No documented follow-up of any kind                | 20     | 44          |

## **Discussion**

This study found one case of GTD for every 115 deliveries at ACSH, equivalent to 868 cases per 100,000 deliveries. There are relatively few studies of GTD from other low or middle-income countries. Two recent studies from Turkey found incidences of 1 case per 1,337 deliveries [8] and 1 case per 870 deliveries [9]. The incidence of GTD in our series is much higher; a finding perhaps explained in part by the fact that ACSH is the tertiary care referral hospital for approximately 8 million people in northern Ethiopia and also the institutional delivery rate in the study period was low for the catchment area (10%) [7]. The population of the Tigray Region of Ethiopia is largely rural. Many families make their living through subsistence agriculture in an inhospitable, rugged countryside where transportation networks are poorly developed, complicating follow-up care. Female literacy is low [7] and access to quantitative B-HCG testing—the international standard of care for follow-up of GTD is limited.

Questions could be raised about the accuracy of some of the diagnoses included in this series. Initially we identified 51 cases of GTD from the medical record. Six cases were eliminated after detailed chart review as having insufficient evidence to support the diagnosis of GTD (Table 2). In 22 of the remaining 45 cases, histopathological confirmation of GTD was not obtained. In 96% of the 45 cases in this series, a radiological diagnosis of GTD was made. In the two cases in which an ultrasound was not obtained, subsequent

histopathology demonstrated a complete mole in one case; in the other case the patient had an elevated B-HCG of 57,189 mIU/ml, a clinical presentation consistent with a diagnosis of GTD including a history of the passage of vesicles, and vesicles were noted at the time of uterine curettage. Although a specimen was sent for histopathology, it appears to have been lost. The 22 cases without histopathology were included because of a positive ultrasound diagnosis with classical findings of a “snowstorm” sonogram, and elevated B-HCG values or clinical descriptions consistent with GTD in the operative notes. In spite of these limitations, these 45 cases represent a reasonable “good faith” effort to delineate the local experience with GTD.

This detailed case review was undertaken to evaluate the general clinical impression that a large number of cases of GTD occur in the Tigray Region. We set out to determine how many cases had occurred, to critically review the management of these cases, and to identify opportunities for improvement in clinical care. We confirmed a high incidence of suspected cases of GTD. This case review is therefore part of a larger push within the Department of Obstetrics and Gynecology to evaluate the outcomes of current clinical practice and to impress upon the residents the importance of critical introspection and objective case review as tools to improve the quality of care, whatever the area of medicine in which they are involved.

As a result of this case review, numerous changes in clinical practice have been recommended. We have established a

standard protocol for the evaluation of patients with suspected GTD and have taken steps to correct the deficiencies documented in our medical records. We are placing a summary sheet in each chart on which each element of the evaluation will be recorded. This sheet includes the patient's name, her medical record number, home address, a reliable phone number through which she can be contacted, and other demographic information. Per protocol, each patient with suspected molar gestation will have a pelvic ultrasound, a quantitative serum B-HCG level, chest x-ray, serum electrolytes, liver function tests, thyroid function tests, complete blood count, and blood type. All surgical specimens will be sent to pathology for evaluation and the results will be recorded on the summary sheet. Post-surgical contraception will be discussed and a plan of follow up will be recorded for each patient. Every admission with suspected GTD is seen by a consultant obstetrician-gynecologist and this consultation is noted in the chart. Treatment recommendations have adhered to current FIGO standards for GTD [10].

Approximately 20% of complete hydatidiform moles will go on to develop persistent or malignant disease [3, 4]. A controversial area in GTD treatment is the role of prophylactic chemotherapy in such patients [11-15]. Review of their clinical experience with choriocarcinoma at Mulago Hospital in Uganda in 1970 led to the initiation of a protocol of hysterectomy and prophylactic chemotherapy with methotrexate in women with "high risk" molar pregnancies, which was defined as a

mole occurring in a woman over 35 years of age with a parity of 4 [16]. Subsequent experience with oral methotrexate chemotherapy found it to be safe for the first two courses, with the serious complications the longer therapy persisted [17]. More importantly, however, prophylactic methotrexate did not prevent the development of or death from metastatic GTD [17]. A recent study of post-molar gestational trophoblastic neoplasia from Senegal concluded that prophylactic chemotherapy did not prevent GTN, but rather delayed its diagnosis when it occurred and increased the rate of GTN after normalization of hCG levels [14]. With appropriate management and rigorous follow-up, GTD should be curable in nearly every case [18]. Providing diligent care to these patients in our environment is challenging, but possible. We hope to develop a fastidious system of follow-up for these patients, prior to any consideration of the use of prophylactic chemotherapy. Most importantly, this case series demonstrates the importance of critical self-evaluation in improving the quality of care in resource-poor countries such as Ethiopia. Although access to sophisticated high-technology medicine is often lacking in these environments, each clinician nonetheless retains the capacity for critical self-appraisal, diligent attention to clinical detail, and conscientious follow-up of laboratory results and treatment plans. It is the cultivation of these qualities among their caregivers that will ultimately lead to improved results and better outcomes for patients with GTD and other gynecological disorders.

The strengths of the study are that it is institution based and that it will be used as a benchmark for future studies on the incidence of GTD in our population. Limitations of the study are its retrospective nature, probably skewing of the patient population seen at a referral center, incomplete data, and lack of systematic follow-up and treatment.

### **Conclusion**

Our review of these cases of GTD revealed numerous deficiencies in current clinical practice. Patient histories were often incomplete, laboratory investigations were not obtained in a systematic fashion, specimens for pathological evaluation were not sent as a matter of routine, follow-up was poor and generally inadequate, and documentation of findings in the chart was often inexplicably incomplete. For example, none of the charts of patients who were treated by suction dilatation and curettage made any mention of plans for post-surgical contraception, a major benchmark for adequate care in patients with GTD. Furthermore, due to incompatibilities in cataloguing protocols and case numbering systems we were unable to carry out a search of the reports in the pathology department to link clinical records with pathology specimens or to systematically search the pathology reports for other cases of GTD that we had not already identified. In light of the high incidence of GTD in Tigray and to improve the follow-up of patients documented in this case series, we are developing a regional trophoblastic disease center in Mekelle to coordinate care

throughout the region. This project involves the development of pilot programs to assess the use of a designated liaison nurse on the gynecology service who will follow these patients back to their home communities, interview them on a regular basis by mobile phone or (if necessary) in person, obtain blood samples to follow their B-HCG levels, and to bring worrisome cases to Ayder Comprehensive Specialized Hospital for further evaluation and treatment. We plan to work with the Regional Health Bureau to centralize the care of all patients in the Tigray Region with known or suspected GTD at the center at Ayder Comprehensive Specialized Hospital. This will allow us to gain a much truer picture of the incidence and prevalence of this disease in northern Ethiopia. We also hope that this will serve as a model program that can be used in developing clinical services for other women's health problems.

### **Conflict of interests**

None of the authors has any conflict of interest with respect to this study.

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### **Author contributions**

YB was the principal investigator; YB, HG, and LW designed the study. HG collected data. AY and LW were involved in data analysis. AY, HG, YB, and LW wrote first and final drafts of the manuscript.



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## References

- Altieri A, Franceschi S, Ferlay J, Smith J, La Vecchia C. Epidemiology and aetiology of gestational trophoblastic diseases. *Lancet Oncol.* 2003;4(11):670-8.
- Seckl MJ, Sebire NJ, Berkowitz RS. Gestational trophoblastic disease. *The Lancet.* 2010;376(9742):717-29.
- Curry SL, Hammond CB, Tyrey L, Creasman WT, Parker RT. Hydatidiform mole: diagnosis, management, and long-term followup of 347 patients. *Obstet Gynecol.* 1975; 45(1): 1-8.
- Lurain JR, Brewer JI, Torok EE, Halpern B. Natural history of hydatidiform mole after primary evacuation. *Am J Obstet Gynecol.* 1983;145(5):591-5.
- Seckl MJ, Fisher RA, Salerno G, Rees H, Paradinas FJ, Foskett M, Newlands ES. Choriocarcinoma and partial hydatidiform moles. *The Lancet.* 2000;356(9223):36-9.
- Bagshawe KD, Dent J, Webb J. Hydatidiform mole in England and Wales 1973-83. *Lancet.* 1986;328(8508):673-7.
- Central Statistical Agency [Ethiopia]. 2014. Ethiopia Mini Demographic and Health Survey 2014. Addis Ababa, Ethiopia.
- Oge T, Ozalp SS, Güngör T, Yildirim Y, Sancı M, Dogan A, Ertas IE, Yetimaller H, Dilek S, Celik C. Hydatidiform mole in Turkey: results from six centers. *J Reprod Med.* 2012;57(5-6):259-61.
- Çakmak B, Toprak M, Nacar MC, Köseoğlu RD, Güneri N. Incidence of gestational trophoblastic disease in Tokat province, Turkey. *J Turk Ger Gynecol Assoc.* 2014;15(1):22.
- Ngan H, Seckl MJ, Berkowitz RS, Xiang Y, Golfier F, Sekharan PK, Lurain JR. Update on the diagnosis and management of gestational trophoblastic disease. *Int J Gynecol Obstet.* 2015;131(S2).
- Fu J, Fang F, Xie L, Chen H, He F, Wu T, Hu L, Lawrie TA. Prophylactic chemotherapy for hydatidiform mole to prevent gestational trophoblastic neoplasia. *Cochrane Database Syst Rev.* 2012(10):CD007289.
- Kim DS, Moon HY, Kim KT, Moon YJ, Hwang YY. Effects of prophylactic chemotherapy for persistent trophoblastic disease in patients with complete hydatidiform mole. *Obstet Gynecol.* 1986;67(5):690-4.
- Limpongsanurak S. Prophylactic actinomycin D for high-risk complete hydatidiform mole. *J Reprod Med.* 2001;46(2):110-6.
- Gueye M, Kane- Gueye SM, Ndiaye- Gueye MD, Mbaye M, Diouf AA, Niang MM, Diallo M, Moreau JC. Gestational trophoblastic neoplasia after achieving a nondetectable serum human chorionic gonadotrophin level. *Int J Obstet Gynaecol.* 2014;121(11):1415-20.
- Kashimura Y, Kashimura M, Sugimori H, Tsukamoto N, Matsuyama T, Matsukuma K, Kamura T, Saito T, Kawano H, Nose R, Nose Y. Prophylactic chemotherapy for

- hydatidiform mole five to 15 years follow- up. *Cancer*. 1986;58(3):624-9.
16. Smith P. Choriocarcinoma in Uganda–A Case for Active Prophylaxis. *Aust N Z J Obstet Gynaecol*. 1970;10(2):109-11.
17. Kaye DK. Gestational trophoblastic disease following complete hydatidiform mole in Mulago Hospital, Kampala, Uganda. *Afr Health Sci*. 2002;2(2):47-51.
18. Riadh BT, Abdellatif C, Wissal H, Leila A, Taher M, Abdelhamid K. Clinical analysis and management of gestational trophoblastic diseases: a 90 cases study. *Int J Biomed Sci*. 2009;5(4):321.