Rising frequency of gestation trophoblastic disease in patients without known traditional risk factors

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ABSTRACT:
Objective: To explore emerging nutritional, environmental, and sociodemographic determinants of GTD in a local population.
Methodology: This descriptive cross-sectional study was conducted at the Department of Obstetrics and Gynecology, Peoples University of Medical and Health sciences for Women, Shaheed Benazirabad. During 6 months 50 women aged 18–40 years, with histopathologically confirmed GTD and gestational age less than 12 weeks, were enrolled using non-probability consecutive sampling. Structured proformas covering traditional risk factors and extended variables, including socioeconomic status, education, contraceptive history, subfertility, environmental exposures, dietary habits, and access to prenatal care was used to collect data.
Results: Showed only 16% of participants had a prior GTD history, and the majority belonged to lower socioeconomic (48%) and low-education (52% with primary education) groups. Notable non-traditional contributors included nutritional deficiencies—42% had low protein intake, 24% had inadequate beta-carotene and vitamin A intake, and 30% had zinc and selenium deficiencies
Conclusion: In conclusion, a serious public health concern is the rising incidence of GTD in women who do not have traditional risk factors.

Key words: Pregnancy Complications, Neoplastic, Trophoblastic Neoplasms, Gestational Trophoblastic Disease, Hydatidiform Mole, Hydatidiform Mole Invasive.

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Introduction:

Gestational trophoblastic disease (GTD) encompasses a diverse group of disorders originating from abnormal proliferation of trophoblastic tissue following conception. This spectrum includes benign conditions such as hydatidiform mole and malignant forms like choriocarcinoma, placental site trophoblastic tumor, and epithelioid trophoblastic tumor[1]. Globally, GTD is traditionally associated with specific risk factors, including extremes of maternal age (<20 or >35 years), a prior history of molar pregnancy, and certain ethnic backgrounds, particularly among women of Southeast Asian, African, or Latin American descent[2–4]. These well-established associations have guided screening and diagnostic approaches in clinical practice for decades.

However, recent studies have noted a concerning rise in GTD cases among women without these classical risk markers[5]. This shift challenges current risk models and suggests that existing screening criteria may no longer be sufficient in identifying all at-risk individuals. Reports from both international and local studies indicate an increasing incidence among patients with average maternal age, no reproductive history of molar gestation, and belonging to low-risk ethnic groups[6]. This trend implies an evolving etiological landscape influenced by non-traditional risk factors such as nutritional deficiencies, exposure to environmental toxins, and socio-economic disparities[7].

Locally, a growing body of research has begun to highlight these non-conventional contributors to GTD. Studies conducted in South Asian populations suggest that factors like folate and vitamin A deficiency, rural residency, low educational attainment, and exposure to pesticides or industrial pollutants may play a role in disease onset[8–10]. These findings underscore the need for comprehensive investigations aimed at uncovering the multifactorial causes of GTD in women outside the known high-risk categories.

Rationale for the Study: Even with the accumulation of observational data, there is still a crucial knowledge vacuum about the exact mechanisms underlying the increased incidence of GTD in women who do not have typical risk factors. The creation of context-specific management, screening, and prevention measures has been hampered by this disparity. Examining these new trends can serve as a basis for updating existing risk categorization models and putting into practice customized public health initiatives that target modifiable factors including access to reproductive healthcare, food, and exposure to toxins.

Objectives:

To determine and examine non-traditional risk variables

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linked to the occurrence of GTD.

Methodology:

This descriptive cross-sectional study was carried out at the Department of Obstetrics and Gynecology, Peoples University of Medical and Health Sciences for Women (PUMHS), Benazirabad from July 7, 2023, to December 6, 2023. Prior ethical approval from the PUMHS Ethical Review Committee was obtained and informed written consent obtained from all participants. To ensure an adequate sample size and to capture a broader range of cases, retrospective data from the preceding one year were also included in addition to the six-month prospective study period, as the initial timeframe alone was insufficient to meet the study objectives." Participants were recruited using a non-probability consecutive sampling technique from both the Outpatient and Emergency Departments of the gynecology unit. Women between the ages of 18 and 40 years, with a gestational age of less than 12 weeks and a parity of 1 to 4, were included in the study if they had a diagnosis of GTD confirmed through ultrasound and later verified via histopathology. Women with multiple gestations, ectopic pregnancies, or miscarriages were excluded to avoid confounding variables. Data were collected using a structured proforma administered by trained research staff, who conducted brief orientations to ensure consistency and clarity in responses by explaining the terminology and significance of each item. The proforma captured a comprehensive set of variables, including sociodemographic factors (age, parity, ethnicity—Sindhi, Punjabi, Balochi, Pathan, or other—socioeconomic status, and education level), reproductive and contraceptive history (prior GTD, use of oral contraceptives, IUCDs, barrier methods, subfertility history, and access to antenatal care), lifestyle and environmental exposures (smoking, pesticide, chemical, and radiation exposure), dietary patterns (low beta-carotene and vitamin A intake, folate, zinc and selenium deficiency, high preservative consumption, and low protein diets), pregnancy outcomes (previous normal pregnancy or abortion), and blood group typing. Data were entered and analyzed using SPSS version 20, with categorical variables (e.g., blood group, contraceptive use, environmental exposure, and dietary deficiencies) presented as frequencies and percentages, and continuous variables (e.g., age, gestational age) summarized using means and standard deviations. Associations between GTD and non-traditional factors were assessed using bivariate analysis (Chi-square tests), and multivariate relationships were explored through logistic regression, adjusting for potential confounders. Data from the structured proforma that included both traditional risk factors for gestational trophoblastic disease (GTD) and a broader range of sociodemographic, lifestyle, and dietary variables was entered into SPSS version 20. Descriptive statistics such as frequencies, percentages, means, and standard deviations were computed. Cross-tabulations and visual analyses were employed to highlight associations and emerging trends.

Results:

The study population (n=50) comprised women aged 18 to 40 years, with a mean age of 29.9 ± 6.8 years, mostly within parity range 1 to 4. Nearly half (n=24, 48%) belonged to a low socioeconomic status (GTD n=19) and 38% to a middle-income group (GTD n=9) while in patients with higher socioeconomic status 2 patients present with GTD. Among all 52% patients had primary-level education only. Ethnic distribution showed a predominance of Punjabi (28%), Sindhi (24%), and Balochi (18%) backgrounds. While 72% had access to antenatal care, 28% had limited or no prenatal follow-up.

Among traditional risk indicators, only 16% had a prior history of GTD, and blood groups A (30%) and AB (28%) were the most prevalent. In terms of non-traditional factors, 38% reported oral contraceptive use, 8% had used IUCDs, and 42% had used barrier methods. Subfertility history was noted in 28%, and only 18% reported smoking. Environmental exposure was common, with 26% exposed to pesticides, 8% to industrial chemicals, and 6% to radiation, while 30% reported no toxin exposure. Nutritional risk factors were also evident: 24% had low beta-carotene and vitamin A intake, 16% had low folate intake, and 30% experienced zinc and selenium deficiencies. High preservative consumption and low protein diets were each reported by 42% of participants, reflecting inadequate dietary quality in a large portion of the study group. These findings emphasize a significant contribution of non-traditional and modifiable factors to the rising incidence of GTD in women previously considered low risk.

The descriptive findings revealed several noteworthy trends:

- A disproportionate frequency of GTD in women with low education and poor nutrition, especially those with high preservative intake and low protein diets.
- Environmental exposure (notably to pesticides) was more prevalent among rural residents and correlated with low prenatal care coverage.
- Surprisingly, a significant number of GTD cases occurred in women with no known traditional risk factors, reinforcing the study's hypothesis and underscoring the importance of investigating emerging contributors.

Discussion:

This study investigated the prevalence and contributing factors of gestational trophoblastic disease (GTD) in women who lacked classical or traditional risk markers. Our findings demonstrated that a considerable proportion of GTD cases occurred in women with no prior molar pregnancy, no advanced maternal age, and no recognized high-risk ethnic background. Instead, a wide range of non-traditional factors emerged, including low socioeconomic status, poor nutritional intake (particularly low protein and micronutrient deficiencies), environmental toxin exposure, and lack of adequate prenatal care. The study found that only 16% of participants had a prior history of GTD, a figure significantly lower than in previous studies that often cite a recurrence rate of 6.5% , which rises to 33.3% for those who have their second or third recurrence.[11] This supports the evolving understanding that GTD can present in previously low-risk groups.

Our observation that 48% of patients belonged to a low socioeconomic group, and 52% had only primary-level education, aligns with earlier studies linking GTD with low-resource settings.[12] These findings echo reports from developing nations like the Philippines and Thailand, where similar socioeconomic gradients were observed.[13] Dietary deficiencies, especially in beta-carotene, folate, zinc, and protein, were prominent in our cohort. These nutrients are essential for cellular repair and trophoblastic function. Previous studies from Southeast Asia have associated low vitamin A and protein intake with molar pregnancy risk. [14-16] The high rate of low protein diet (42%) and high preservative intake (42%) in our patients aligns with these findings. Environmental exposure—particularly to pesticides (26%) and chemicals (8%)—was a significant risk in rural women. Studies in agricultural regions of Vietnam and China have

demonstrated similar associations, attributing exposure to persistent organic pollutants to increased GTD incidence.[17,18] Interestingly, despite 72% of women having access to prenatal care, the diagnosis of GTD was delayed in many cases, suggesting gaps in clinical vigilance or resource availability. This points to a need for more specific GTD screening protocols in early antenatal care.

Implications for Public Health:

These findings have important ramifications for preventative measures and public health. First, the results emphasize how important it is to go beyond traditional models of GTD risk assessment and incorporate sociodemographic status, environment, and diet. Public health officials ought to think about integrating micronutrient supplements (such as vitamin A and folic acid) and dietary screening into maternal health initiatives.

Second, environmental health interventions should target rural communities exposed to pesticides. Campaigns to raise awareness about reproductive poisons and the dangers of agricultural labor should be given top priority.

Third, more diagnostic capabilities are needed in the prenatal care system, particularly in the early stages of pregnancy. Better results and earlier referrals can result from teaching medical staff to spot unusual symptoms of molar pregnancy.[19,20]

In comparable resource-constrained environments, maternal health outcomes and early GTD identification can be greatly enhanced by refocusing attention on these modifiable non-traditional risk variables.

Prospective Research Paths.

This study identified a number of research gaps, including the following:

- Future studies should examine gene-environmental interactions, specifically how environmental toxins may epigenetically influence trophoblastic tissue behavior;
- The role of microbiome changes and endometrial receptivity in GTD pathogenesis also warrants investigation; and
- Prospective cohort studies that assess nutrient levels biochemically rather than relying on self-reporting are necessary.

It would be beneficial to do longitudinal studies that monitor pregnancy outcomes and recurrence risk in women who present with non-traditional GTD.

Conclusion:

The study demonstrates a shifting epidemiological pattern in GTD, stressing the increasing importance of modifiable non-traditional risk variables. These findings have significant implications for maternal health policies, emphasizing the importance of incorporating dietary assessment, environmental risk awareness, and reproductive health education into prenatal care. Screening strategies must be updated to cover at-risk women in rural and underserved areas. Additional study is required to better understand gene-environment interactions and develop context-specific preventative strategies.

References:

1. Braga A, Coutinho L, Chagas M, Soares JP, Callado GY, Alevato R, Lozoya C, Sun SY, Araujo Júnior E, Rezende-Filho J. Molar Pregnancy: Early Diagnosis, Clinical Management, and the Role of Referral Centers. Diagnostics. 2025; 15(15):1953. doi:10.3390/diagnostics15151953
2. Lurain JR. Gestational trophoblastic disease I: epidemiology, pathology, clinical presentation and diagnosis of gestational trophoblastic disease, and management of hydatidiform mole. Am J Obstet Gynecol. 2010 Dec;203(6):531-9. doi: 10.1016/j.ajog.2010.06.073. Epub 2010 Aug 21. PMID: 20728069.
3. Mota, M., Beltrão, M. , Bacha, E. , Filho, E. , Jesus, M. , Mascarenhas, N. , Silva, T. , Souza, M. , Borges, V. and Braga, S. Updates in the Diagnosis of Gestational Trophoblast Disease. Health. 2023. 15(1) 48-58. doi: 10.4236/health.2023.151004
4. Joneborg, Ulrika. Epidemiology of Gestational Trophoblastic Disease. Hematology/Oncology Clinics. 2024; 38 (6) p1173-1190. doi: 10.1016/j.hoc.2024.07.003
5. Emmanuel Ifeany Obeagu, Getrude Uzoma Obeagu. Molar Pregnancy: Update of prevalence and risk factors. Int. J. Curr. Res. Med. Sci. 2023; 9(7): 25-28 doi:10.22192/ijcrms.2023.09.07.005
6. Gillespie AM, Lidbury EA, Tidy JA, Hancock BW. The clinical presentation, treatment, and outcome of patients diagnosed with possible ectopic molar gestation. Int J Gynecol Cancer. 2004 Mar-Apr;14(2):366-9. doi: 10.1111/j.1048-891X.2004.014223.x. PMID: 15086739.
7. Vo TM Sr, Hoang TT, Tran HM, Nyamakope K. Gestational Trophoblastic Neoplasia Rate and Its Related Factors in Women With a Partial Hydatidiform Mole at Tudu Hospital, Vietnam. Cureus. 2024 Aug 22;16 (8):e67495. doi: 10.7759/cureus.67495. PMID: 39310541; PMCID: PMC11416125.
8. Capobianco G, Tinacci E, Saderi L, Dessole F, Petrillo M, Madonia M, Virdis G, Olivari A, Santeufemia DA, Cossu A, Dessole S, Sotgiu G and Cherchi PL. High Incidence of Gestational Trophoblastic Disease in a Third-Level University-Hospital, Italy: A Retrospective Cohort Study. Front. Oncol. 2021; 11:684700. doi: 10.3389/fonc.2021.684700
9. Liu Y, Ma S, Huang X, Bo Y, Fu W, Cao Y, Duan D, Dou W, Zeng F, Wang X, Gong M, Zhang X, Lyu Q, Zhao X. Dietary intake and serum concentrations of vitamin A and vitamin E and pre-eclampsia risk in Chinese pregnant women: A matched case-control study. Front Nutr. 2023 Mar 30;10:1049055. doi: 10.3389/fnut.2023.1049055. PMID: 37063333; PMCID: PMC10101204.
10. Huang XM, Liu YH, Zhang H, Cao Y, Dou WF, Duan DD, Chen HN, Bo Y, Amoah AN, Fu WJ, Zhao XL, Zeng FF, Chen YM, Lyu QJ. Dietary and serum vitamin D and preeclampsia risk in Chinese pregnant women: a matched case-control study. Br J Nutr. 2022 Jul 14;128(1):84-92. doi: 10.1017/S0007114521002956. Epub 2021 Aug 6. PMID: 34353401.
11. Nguyen TV, Le LH, Nguyen GT, Vo TM. Late Ultra-High-Risk Recurrence of Gestational Trophoblastic Neoplasia Seven Years Posttreatment. Cureus. 2024 Dec 9;16(12):e75415. doi: 10.7759/cureus.75415. PMID: 39791039; PMCID: PMC11710945.
12. Ghosh, J, P. Agarwala · A. Kapoorb · D.S.J. Philip · V. Choudhary · J. Bajpai et al. Clinical, socioeconomic characteristics, treatment and reproductive outcomes of patients with gestational trophoblastic neoplasia at a tertiary care hospital in India Gynecologic Oncology, 2020. 159, Supplement 1, S1-358159, 348 -349. doi: 10.1016/j.ygyno.2020.05.650
13. K. Roque Perez, M.A. Galvez Nino, M.W. Castro, H.D. Vallejos, R.E. Ruiz et al. Impact of nutritional factors in response and survival of patients with gestational trophoblastic neoplasia Annals of Oncology; 2022. Vol

33- (S5). doi: 10.1016/j.annonc.2022.04.066
14. Hidayat YM, Darmadi A E, Rachmayati S, Kusumah WP, Djuwantono T, Pramatirta AY, Suardi D. Efficacy of Oral Vitamin A in Reducing β-hCG Levels in Low-Risk Gestational Trophoblastic Neoplasia Patients. Asian Pac J Cancer Prev. 2020 Nov 1;21(11):3325-3329. doi: 10.31557/APJCP.2020.21.11.3325. PMID: 33247691; PMCID: PMC8033137.
15. Ferraz L, Ramos CAB, Braga A, Velarde LGC, Elias KM, Horowitz NS, Lopes PF, Berkowitz RS. Association between antioxidant vitamins and oxidative stress among patients with a complete hydatidiform mole. Clinics (Sao Paulo). 2020;75:e1724. doi: 10.6061/clinics/2020/e1724. Epub 2020 Jul 6. PMID: 32638907; PMCID: PMC7330716.
16. Banaei, M., Alamolhoda, S. H., Beheshti Nasab, M., Mohamadkhani Shahri, L., Bayat, F. Relationship between level of vitamins and Hydatiform Mole in Women: A Systematic Review Study. The Iranian Journal of Obstetrics, Gynecology and Infertility, 2020; 23(5): 95-104. doi: 10.22038/ijogi.2020.16619
17. Eysbouts, Y.K, J. Bultenb, P.B. Ottevangerc, A.G. Siebersb, F.C.G.J. Sweep et al. Trends in incidence for gestational trophoblastic disease over the last 20 years in a population-based study. Gynecologic Oncology, 2016; 140, (1). pp 70 – 75. doi:10.1016/j.ygyno.2015.11.014
18. Banaei M, Ghamsari SR, Roozbeh N. The Role of Vitamins Deficiency in the Development of Hydatidiform Moles: Mechanism and Function. Dis Diagn. 2023;12 (1): 55-56. doi: 10.34172/ddj.2023.428
19. Joneborg U, Coopmans L, van Trommel N, Seckl M, Lok CAR. Fertility and pregnancy outcome in gestational trophoblastic disease. Int J Gynecol Cancer. 2021 Mar;31(3):399-411. doi: 10.1136/ijgc-2020-001784. PMID: 33649007.
20. Jin-Kai L, Fang J, Yang X. Prognosticating gestational trophoblastic neoplasia: from FIGO 2000 to future models. EClinicalMedicine. 2024 Nov 7;77:102890. doi: 10.1016/j.eclinm.2024.102890. PMID: 39583749; PMCID: PMC11582452.

Author's contribution

Aqsa	Conceived idea, literature Review.
Bakhtawar Solangi	Developed Proforma
Saima Soomro	Write introduction
Farah	Data Collection
Samina Gaffar	Manuscript draft writing
Ambreen Channa	Data collection/ grammatical review
Raishem Baloch	Proof read manuscript