Poster presentation 71005 - Diagnostic Challenges and Prognostic Implications of Liver Findings in Gestational Trophoblastic Neoplasia: A Comprehensive Review (2010-2023)

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Background: Gestational Trophoblastic Disease (GTD) encompasses a range from benign to potentially malignant and malignant diagnoses. Malignant forms of GTD, especially those with metastases to the liver and brain, significantly worsen the prognosis.
Methods: The aim of this study was to analyze cases of patients with GTN with liver findings, from 2010 to 2023 in our center, to assess the incidence of metastases and incidental findings, their impact on morbidity and mortality, and to identify possible diagnostic challenges.
Results: Out of a total of 103 patients (2010-2023) with a malignant GTD, 23 had liver findings, of which 2 had liver metastases. One patient with liver metastases was recorded as having non-gestational choriocarcinoma. Incidental benign findings in the liver were detected in 20 patients, with benign diagnoses. Diagnostic dilemmas arose when a malignant finding was mistakenly interpreted as benign, exemplified by a case of a patient with a hemorrhagic liver cyst initially diagnosed as a metastatic lesion. Despite challenges associated with the diagnosis and management of GTD, all patients managed in our center achieved a negative hCG status, except for one patient with non-gestational choriocarcinoma who died.
Conclusion: The results highlighted the importance of imaging methods in staging for detecting metastases and incidental findings, and underscored the need for careful interpretation of results to minimize diagnostic errors. The study emphasizes the need for ongoing education and research in the field of GTD to improve diagnostic methods and therapeutic approaches.

Oral presentation - 71350 - Additional value of Uterine artery Doppler pulsatility index for ultrasound diagnosis of placental site trophoblastic tumor: prospective cohort study

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Background: Ultrasound (US) diagnosis of placental site trophoblastic tumor (PSTT) is challenging due to lack of pathognomonic features. Differential diagnosis from other forms of gestational trophoblastic neoplasia (GTN) is critical due to major difference in prognosis and treatment. Doppler measurement of uterine artery (UtA) pulsatility index (PI) was proposed for diagnosis and management of GTN. Aim of the present study was to evaluate the addition of UtA-PI Doppler measurement to the standard transvaginal (TV) US assessment, in patients with PSTT as compared to those with other GTN such as invasive mole and choriocarcinoma.
Methods: Prospective monocentric US assessment of GTN cases referred and treated between 2011-2023 at the Trophoblast Unit of San Raffaele Hospital, Milan, Italy. TVUS assessment included: gray-scale analysis for detection of myometrial or endometrial abnormalities, Color-Power Doppler assessment of lesions with scoring and UtA spectral pulsed Doppler for PI measurement. Findings at grey-scale or Color-Power assessment and mean of left/right UtA-PI spectral Doppler were compared in PSTT and other GTN by non-parametric two-tailed statistics.
Results: 71 GTN cases were recruited: 7 patients with PSTT (9.8 %) and 64 with diagnosis of other GTN (90.2 %). None of the US features evaluated significantly differed between PSTT and other types of GTN. However, a significant difference was detected between UtA-PI measurements in GTN and PSTT (median UtA-PI GTN=1.45 vs UtA-PI PSTT= 2.3; p=0.024; AUC 0.758).
Conclusion: This study describes UtA-PI as a novel and effective marker favoring ultrasound differentiation of GTN and PSTT. Greater median UtA-PI observed in PSTT as compared to other GTN (such as invasive mole and choriocarcinoma) suggests a peculiar vascularization pattern, with a potential role in differential diagnosis and management.
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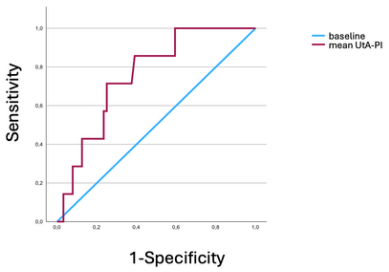
Ultrasonographic characteristics	GTN (%) 64 (90.2%)	PSTT (%) 7 (9.8%)	p-value
Endometrial thickness > 14 mm (N,%)	27/64 (42.1%)	1/7 (14.2%)	0.232
Average endometrial thickness (mm, median, IQR)	15, 7-31.75	25, 10.5-31.25	0.543
Presence of endometrial vascularization (N,%)	32/64 (50 %)	0/7 (0%)	0.112
Presence of myometrial nodule (N,%)	47/64 (73.4 %)	6/7 (85.7%)	0.670
Maximum diameter of the nodule, mm (median, IQR)	35, 22-48	31.5, 19.25-40.5	0.463
Solid myometrial nodule (N,%)	20/47 (42.6 %)	5/7 (71.4 %)	0.504
Cystic or mixed myometrial nodule (N,%)	17/47 (36.2 %)	1/7 (14.2%)	0.669
Vascularized myometrial nodule (N,%)	33/47 (70.2 %)	5/7 (71.4%)	0.723
Theca-lutein cysts (N,%)	16/64 (25%)	0/7 (0%)	0.565
Ut-API right/left (median, IQR)	1.45, 0.8-2.2	2.3, 1.8-3.5	0.024

Table Ultrasonographic characteristics of GTN and PSTT. GTN: gestational trophoblastic neoplasia, PSTT: placental site trophoblastic tumor, IQR: inter-quartile range, Ut-API: uterine artery pulsatility index



Area Under the Curve ROC

Mean left/right UtA-PI

Area	Std.error	Asymptotic sign.	Confidence Interval 95% Lower limit	Upper limit
,758	,078	,001	,604	,911

Figure. ROC curve for the evaluation of Ut-API in the diagnosis of PSTT.

Poster presentation 71377 - The Irish National Gestational Trophoblastic Disease Centre; The first 1,000 registrations.

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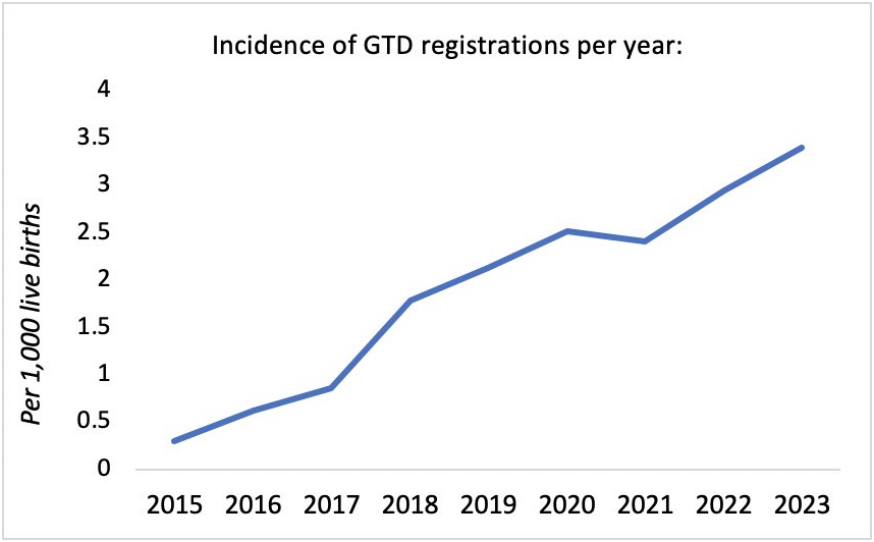
Background: The objectives of this review were to establish the incidence of different presentations of Gestational Trophoblastic Disease (GTD) in Ireland, compare the times taken to spontaneous hCG normalisation and response rates to first and subsequent lines of chemotherapy.
Methods: This retrospective digital data review was conducted in the National GTD centre in Cork University Maternity Hospital. The dendrite database and clinical nurse specialist records were used to collect demographical, clinical, histological and biochemical information. Descriptive and inferential statistical analysis were conducted using Microsoft Excel v16.28 and IBM SPSS Statistics v29.0.2 software.
Results: In Ireland in 2023 there was a GTD incidence rate of 3.4 per 1,000 live births. Overall there were 668 cases of PHM, 296 CHM, 11 patients with a suspicion of a molar pregnancy, 16 choriocarcinomas, 11 atypical placental site nodules and 1 epithelial trophoblastic tumour. The mean age at registration was 33.81 years. There was no statistically significant difference between the time to spontaneous normalisation of hCG levels in PHM (47 days) and CHM (49 days). Fifty-three molar pregnancy patients developed GTN, 17% of CHM and 0.6% of PHM. These were all initially treated with methotrexate. Of these, 31.4% required second line chemotherapy. There was a statistically significant difference between the FIGO scores of patients who responded to first line chemotherapy compared to those who developed resistance ($p<0.001$). Nine of the 16 patients diagnosed with choriocarcinoma had spontaneous hCG normalisation without chemotherapy.
Conclusion: This study is the first to review all GTD registrations with the National Centre in Ireland. The number of registrations has continued to increase annually allowing improved correlation with international studies. We found no significant difference in normalisation times of spontaneously resolving PHM and CHM. To date there has been 100% successful treatment of all patients.


Incidence of GTD registrations per year:
Per 1,000 live births
4
3.5
3
2.5
2
1.5
1
0.5
0
2015
2016
2017
2018
2019
2020
2021
2022
2023

Poster presentation 71393 - Benefits and Challenges of Multi-Disciplinary Team working in a complex case

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Background: A 19 year old patient was admitted to start treatment. Her husband's family brought her to the hospital but left her without any social or financial support.They blamed her for the Molar Pregnancy,telling her that she had 'bad eggs' and it was her fault.Already upset about the 'loss' of pregnancy,she blamed herself and was very concerned about future fertility issues and about being ostracised culturally from her community.She had survived a natural disaster in her home country.Her husband and his family refused her to return home when she was being discharged as they thought they may catch cancer from her.This meant she became homeless.Her visa was a spousal visa,leaving her right to remain in the country in jeopardy.She had no financial support,with no recourse to public benefits.
Methods: A safeguarding concern was raised within the hospital, meaning many teams then became involved in the case. This included the domestic violence team,safeguarding team,teenage and young adult's social work team,a cultural charity,psychology team,complex discharge team and an organisation called IKROW(a women's rights organisation).
Results: Working with different organisations was complex and at times challenging.The communication channel via emails took time.A language barrier with the patient who spoke very little English was challenging for all organisations involved.The teams were able to liaise with the home office for the patient to get support with visa applications.She was placed into a refuge for safety.
Conclusion: A multi-agency approach allowed the patient to be relocated to a place of safety.They could support her with funding and legal paperwork applications.She has re-gained some independence and able to start a new life post treatment.Managing her medical care was often difficult due to the lapses in communication and multiple agency involvement.Multi agency working allows access to complex systems but improved communication channels would make the process more seamless.

Poster presentation 71464 - An Unusual Pattern of Divergent p57 Expression in Products of Conception with Discordant Villi.

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Background: Complete hydatidiform mole (CHM) shows concordant loss of p57 expression in both villous stroma and cytotrophoblast cells. p57 immunohistochemistry is a useful ancillary technique in identifying CHM. Rare cases of discordant p57 expression with loss in either the villous stroma or the cytotrophoblast have been reported, as have cases of divergent p57 expression, where different staining patterns are present between villi or within villi. We present a case with a rare pattern of discordant and divergent p57 expression.
Methods: Ploidy was assessed by flow cytometry and p57 immunostaining undertaken according to standard protocols.
Results: Histological examination of the products of conception showed grossly abnormal chorionic villi across a range of sizes, with a predominance of enlarged hydropic villi. Occasional large irregular trophoblast pseudoinclusions and deep invaginations were noted, but many villi showed no trophoblast overgrowth. Multifocal or circumferential trophoblast growth with cytological atypia was demonstrated in a minor population of villi.

Ploidy studies indicated a diploid conceptus, prompting p57 immunohistochemistry reflex testing, which demonstrated a discordant pattern with positive cytotrophoblast and negative stroma. Strikingly, regions of atypical trophoblast growth showed incomplete p57 staining with focal strips of negative cells interrupting the predominantly p57 positive cytotrophoblast. This unusual discordant and divergent p57 staining pattern suggests the presence of a diandric cell population within the p57 negative foci of cytotrophoblast cells.
Conclusion: p57 immunohistochemistry is an important ancillary tool used in conjunction with histology and ploidy studies to aid in diagnosing molar versus non-molar pregnancies, and is invaluable in cases with equivocal histology. We were able to identify a diandric cell line in a small population of cells comprising the atypical cytotrophoblast, which could not be determined by histological analysis alone. The presence of a diandric cell line in the cytotrophoblast prompted registration and follow-up due to undetermined risk of persistent gestational trophoblastic disease.

Oral presentation 71549 - Investigating the Prognostic Significance of TERT Activation in Epithelioid & Placental Site Trophoblastic Tumours

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Background: Diagnosis of an epithelioid or placental site trophoblastic tumour (ETT/PSTT) more than 48 months from the antecedent pregnancy is associated with significantly poorer survival than when diagnosed within 48 months. However, the cause of this disparity remains unknown. Fusion of the genes LPCAT1 and TERT, resulting in ectopic expression of TERT, has been reported in a total of 3/9 ETTs and 0/2 PSTTs in two studies to date, but no association with interval to pregnancy was investigated. Here we explore the expression of TERT in a large series of short- and long-interval ETTs and PSTTs.
Methods: 32 FFPE ETT/PSTT samples were micro-dissected and underwent transcriptomic profiling using HTG Transcriptome Panel and/or Twist RNAexome sequencing. Gene expression data were normalised using EdgeR, and fusion transcripts were identified using STARfusion.
Results: TERT expression is significantly elevated in long-interval ETTs (9/9 analysed), whilst expression is low or absent in the 8 short-interval ETTs. PSTTs show consistently low TERT expression regardless of interval (12/12), except when the PSTT is a component of a long-interval mixed tumour containing ETT (3/3). Unlike previous studies, we do not observe TERT-LPCAT1 fusions in any sample and further work is ongoing to determine the cause of TERT upregulation.
Conclusion: Expression of TERT, a key enzyme in telomere maintenance, is a mechanism exploited by tumour cells to evade senescence, correlating with poor prognosis in many cancers. In our large series of cases, elevated TERT expression is specifically found in long-interval ETTs and mixed ETT/PSTT tumours. Detection of TERT may act as a prognostic biomarker for long-interval ETTs, potentially to supplement or replace causative pregnancy testing.

Poster presentation 71576 - Centralized Interdisciplinary Management of Trophoblastic Diseases: United We Stand

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Background: We presented two GTN cases in which the clinical management was delayed due to their rarity.
Methods: Case 1. Delay in treatment.
15 y.o. G1A1. In May and June 2023 two seperate D&C was performed due to abortion and retention of material of conception. Although the pathology reports have not been finalized, the patient was considered to have trophoblastic disease due to high serum beta-hCG levels. However, both the medical oncology and pediatric haemato-oncology departments did not initiate the treatment, claiming lack of experience in such a case. In July 2023 a third curettage was performed because of a uterine mass, meanwhile the treatment plan was switched to excision of the mass. The final pathology was "invasive mole", and eventually chemotherapy was given in September 2023. The follow-up was uneventful until March 2024.

Case 2. Delay in diagnosis.
46 y.o. G5P3A2. She had an endometrial biopsy in October 2023 which was reported as choriocarcinoma. However serial serum beta-hCG levels were below 1 mIU/mL. Due to the progressive growth of the uterine mass, the surgery was performed in January 2024 and intraoperative pathology consultation was also reported as choriocarcinoma. However the final pathology was surprisingly reported as "undifferentiated uterin sarcoma" in February 2024. Unfortunately the patient's clinic rapidly detoriated and she was lost in March 2024 before any treatment had started.
Results: Trophoblastic diseases are in the group of rare diseases and present distinct entity by nature in their management algorithm.
Conclusion: Clinicians involved in the management of this disease can reasonably be considered to be less experienced than other common diseases. National and continental scientific consultation networks are needed to make best efforts for diagnostic accuracy and management success. It is possible to achieve our ultimate goal of good clinical practice by sharing knowledge and experience through audio-visual case consultations via instant communication.

Oral presentation 71579 - Use of the Abbott i-STAT®1 Point of Care device for hCG monitoring in early pregnancy

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Background: Serial measurement of human Chorionic Gonadotrophin (hCG) helps guide patient management in early pregnancy. A point-of-care-testing (POCT) hCG solution has the potential to facilitate hCG monitoring at remote locations. This study evaluated use of the Abbott i-STAT®1 for hCG monitoring in early pregnancy.
Methods: Women attending the Early Pregnancy Unit who required a hCG blood test for scheduled care were invited to participate. Following written consent, an additional lithium heparin blood sample was collected in clinic. Whole blood hCG was measured on the Abbott i-STAT®1 analyser in clinic and the remaining sample was sent to the hospital laboratory for hCG analysis on the designated comparator method, the Abbott Architect. Statistical analysis was performed using Analyse-IT software.
Results: Overall, 50 women were recruited to the study, representing miscarriage (n=22), intrauterine (n=7), molar (n=3) and ectopic pregnancy. All hCG results outside the quantitative range (5-2,000 IU/L) of the POCT assay (n=14), although broadly concordant with hCG results determined in the central laboratory, were excluded from statistical analysis. Comparative analysis of the remaining hCG results (n=47) from the i-STAT®1 and Abbott Architect assays demonstrated good agreement across the concentration range assessed (4-2072 IU/L). Spearman correlation was excellent at $r=0.99$, $p<0.0001$. Passing-Bablok linear regression showed good agreement, $y=1.18+0.96x$. Bland-Altman mean difference was -23.70 IU/L (3.5%).
Conclusion: This study adds to limited research on the potential clinical impact of POCT for measuring hCG levels in blood compared to existing laboratory-based testing. The i-STAT®1 hCG results were clinically concordant with those of the central laboratory allowing use of established clinical decision thresholds. This patient-centric approach prioritises patient needs, facilitating shared decision-making during the clinic visit. However, a more extensive prospective verification study, with a larger cohort of women is required before this POCT device could be recommended for routine clinical use in early pregnancy managment.

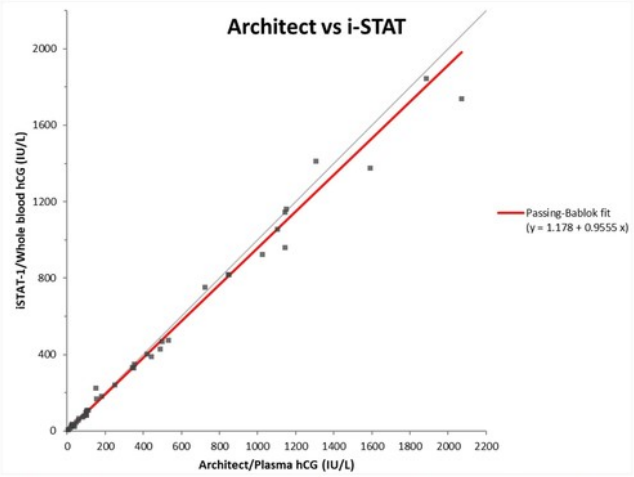

Figure 1: Passing-Bablok Regression analysis for the Abbott i-STAT®1 total β-hCG results compared to the Abbott Architect laboratory reference method

Parameters	Abbott i-STAT®1	Abbott Architect
Sample type	Plasma LH	Serum, Plasma LH
CE Marked	√	√
Minimum Volume	17µL	75µL
Linear Range (IU/L)	5-2,000	1.2-15,000
Hook effect (IU/L)	>300,000†	N/A
Assay Time (Minutes)	10	20
hCG isoforms	‡Total β-hCG	‡Total β-hCG
Test Principle/Detection	2-step ELISA/ECD	2-step ELISA/CMIA
WHO IS	5th (07/364)	4th (75/589)

Table 1: Abbott i-STAT®1 and Abbott Architect laboratory comparator
LH: Lithium Heparin, CE: Conformité Européenne, WHO: World Health Organisation, IS: International standard, ‡Intact hCG and free β subunit, ECD: Electrochemical detection, CMIA; Chemiluminescent microparticle immunoassay, N/A: Not available, ELISA: Enzyme linked immunosorbent assay, †Sowder *et al*. 2015 reported a higher hook effect of 400,000 IU/L

Oral presentation 71598 - Flow cytometry for ploidy of hydatidiform mole

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Background: The prognosis after a triploid partial hydatidiform mole (HM) is significantly better than after a diploid complete HM. Thus, determining ploidy is important. Often the diagnosis HM is only made when the tissue is formalin fixed. A protocol for determining ploidy by flow cytometry of formalin fixed tissue was proposed by Hedley in 1989[1]. However, using this protocol, unequivocal results are not always obtained. In this study we question and optimise the protocol proposed by Hedley.
Methods: Testing the effect of varying steps when isolating nuclei for analysis and controlling the ratio between maternal and placental nuclei. We analyse formalin fixed tissue samples from miscarriages – both non-molar, diploid HMs, and triploid HMs.
Results: The ratio between maternal and placental nuclei, estimated by inspection of slides, was not in coherence with the ratio observed at the flow cytometry results. When we isolated nuclei from triploid HMs from 10, 20, and 30 µm thick tissue sections, results showed that the thinner the sections were, the smaller the signals from nuclei in G2-phases we got. However, signals from sections that were 30 and 50 µm thick were compatible. We discovered that it was possible to mount and dissect 30 µm sections on slides. If the tissue is dissected, sufficient signals from both placental and maternal nuclei are present.
Conclusion: We propose a simple and robust protocol that specifies how to isolate and obtain a sufficient number of placental nuclei. Dissection of tissue sections and thus isolation of placental nuclei has shown to provide more accurate results for determining ploidy on formalin fixed molar tissue.

References (optional):

1. Hedley, D. W. (1989). Flow cytometry using paraffin-embedded tissue: five years on. *Cytometry: The Journal of the International Society for Analytical Cytology*, *10*(3), 229-241.