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Demographics of epithelioid trophoblastic tumour and placental site trophoblastic tumour: a 21 year UK population study

P. Savage[a], F. Froeling[a], M. Lythgoe[a], R. Fisher[a], G. Maher[a], M. Winter[b], K. Eremeishvili[a], N. Sarwar[a], X. Aguiar[a], K. Singh[b], B. Hancock[b], R. Coleman[b], J. Tidy[b] and MJ Seckl[a]

[a]Department of Medical Oncology, Trophoblastic Tumour Screening and Treatment Centre, Charing Cross Hospital, Imperial Hospitals NHS Trust, London, United Kingdom; [b]Sheffield Trophoblastic Disease Centre, Weston Park Cancer Centre, Sheffield Teaching Hospitals NHS Trust, Sheffield, United Kingdom

ABSTRACT

Background: Epithelioid and placental site trophoblastic tumours are rare gestational malignancies which have little detailed information on their population incidence or risk related to maternal age.

Methods: We performed a retrospective UK national population-based study examining all of the cases registered between 2000 and 2020 using the databases at the UK's two gestational trophoblastic treatment centres at Charing Cross Hospital in London and Weston Park Hospital in Sheffield. The data obtained was compared with the contemporary UK birth and pregnancy statistics.

Results: Over the 21-year study period, there were 132 cases of ETT or PSST. PSTT comprised 57% of the cases, 30% were ETT and 13% had mixed pathology. The combined incidence of ETT and PSTT was 1:118,736 relative to live births and 1:150,872 compared to total viable conceptions. For women aged under 20 the incidence relative to live births was 1:412,488, increasing to 1:188,292 for women 30–34 years, and 1:1,426 for women aged 45 and above. The median interval from the antecedent pregnancy to the time of diagnosis was 15 months (0–288) for the PSTT patients compared to 24 months (0–336) for patients with a diagnosis of ETT.

Conclusions: ETT and PSTT are both rare diagnoses with little detailed information on their demographics. The data in this study indicates a wide range in the interval from the antecedent pregnancy to diagnosis and confirms a close relationship between increasing incidence and rising maternal age.

PLAIN LANGUAGE SUMMARY

Epithelioid and placental site trophoblastic tumours are two similar but rare tumours arising from the cells of pregnancy. Due to their rarity there is little accurate information on the risk of having these diagnoses and how that risk may change with increasing maternal age. In a 21-year UK wide national study we found a total of 132 cases from a total of approximately 19.9 million pregnancies giving an overall risk of 1:150,872.
The risk increased appreciably with rising maternal age increasing from 1:526,349 in women aged under 20 to 1:10,343 for women 45 and over. Despite the rarity the large majority of patients are cured with modern therapy.

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Demographics; trophoblastic; epithelioid; placental; population

Introduction

The malignancies arising from the intermediate trophoblast cells, Epithelioid Trophoblastic Tumour (ETT) and Placental Site Trophoblastic Tumour (PSTT) are the rarest forms of the gestational trophoblastic neoplasia (GTN), historically comprising less than 0.5% of the total cases (Seckl *et al.* 2010). In contrast to gestational choriocarcinoma which characteristically presents with advanced metastatic disease, ETT and PSTT are frequently localised, generally have a more indolent pace of growth and often have a long interval from the antecedent pregnancy to the time of diagnosis (Palmer *et al.* 2008, Schmid *et al.* 2009).

CONTACT P. Savage savage13561@msn.com Oncology Department, Cardiff University, United Kingdom.

ETT and PSTT are both relatively recently described diagnostic entities. PSTT was originally described in 1981 and ETT in 1998 (Scully and Young 1981, Shih and Kurman 1998). Recent transcriptome studies suggest that ETT and PSTT share a similar pattern of gene expression that is significantly different to that of gestational choriocarcinoma (Cho *et al.* 2020). Earlier studies have suggested an overall incidence for PSTT in the region of 0.3–1.0 cases per 100,000 pregnancies with the rate higher in older women (Lybol *et al.* 2011, Yamamoto *et al.* 2022). However, as a result of the rarity of these diagnoses there is little detailed information regarding the age-related incidence of the intermediate trophoblastic tumours.

In the UK, the care of all patients with GTN has been centralised to two specialist centres for the past 50 years. As a result, the databases at Charing Cross Hospital in London and Weston Park Hospital in Sheffield provide a full nationwide dataset for these rare malignancies thereby avoiding any case-selection bias. Here, to gain a more detailed insight into the demographics of ETT and PSTT, we have undertaken a national 21-year retrospective audit of the UK dataset.

Methods

Clinical data

The electronic and clinical records at the two UK National GTN centres at Charing Cross Hospital in London and Weston Park Hospital in Sheffield were reviewed for eligible patients with a date of diagnosis between January 2000 and December 2020. A total of 7 patients from the database were excluded from the study either as a result of amended pathology or due to being non UK patient. This left a total of 132 patients in the study (Figure 1).

In the study we have recorded the patient's demographics, pregnancy information and disease stage characteristics.

Patients were not involved in the development of this project and there was no specific funding associated with it.

This project was undertaken by Imperial College Healthcare NHS Trust and Sheffield Teaching Hospitals NHS Trust as a service evaluation and so did not require ethics approval or patient consent.

Birth and pregnancy statistics

Data on UK births during the study period was obtained from the published statistics for England and Wales, Scotland and Northern Ireland that cover the full period 2000–2020 (https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/livebirths/datasets/birthsummarytables, https://www.nrscotland.gov.uk/statistics-and-data/statistics/statistics-by-theme/vitalevents/births/births-time-series-data, https://www.nisra.gov.uk/publications/birth-statistics).

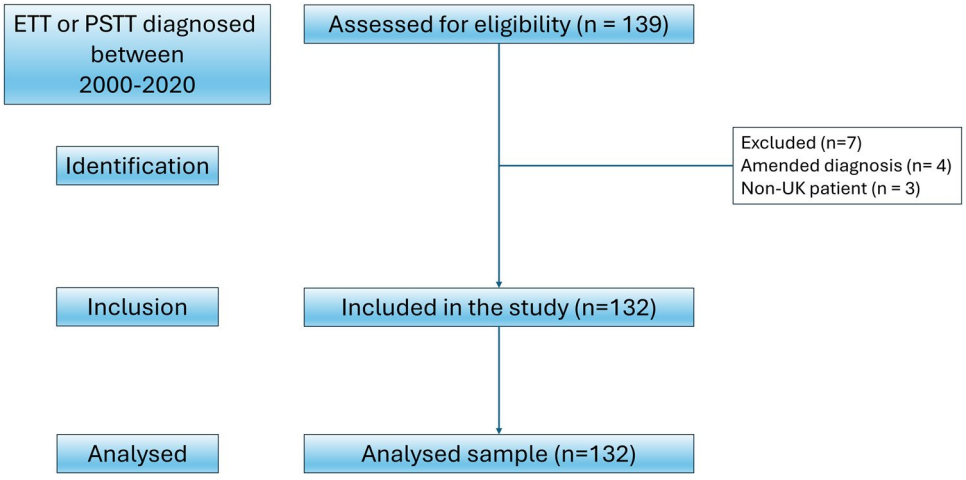

Figure 1. The STROBE flow chart (STROBE, Strengthening the Reporting of Observational Studies in Epidemiology).

The estimates of total viable conceptions (births and terminations but excluding miscarriages) used the birth data combined with the England, Wales and Scotland termination statistics (https://www.gov.uk/government/collections/abortion-statistics-for-england-and-wales, https://www.isdscotland.org/Health-Topics/Sexual-Health/Publications/data-tables2017).

Results

Pathological diagnosis

In the 21-year study period from January 2000 to December 2020 a total of 132 eligible patients with a diagnosis of ETT or PSTT were registered at Charing Cross Hospital in London or Weston Park Hospital in Sheffield.

The breakdown of the histopathological diagnoses of the cases are shown in Table 1. It is apparent that PSTT was the most frequent diagnosis accounting for 56.8% of the cases. Single pathology ETT accounted for 30.3% of the cases and 13% of the cases had mixed histopathology that comprised mixed components of ETT, PSTT and in 9 cases a component of choriocarcinoma.

Age related incidence at the time of diagnosis

During the 21-year study period, the UK national statistics reported a total of 15,673,067 births. As shown in Table 2, this indicates an overall estimated incidence of one case of ETT or PSTT for every 118,736 births.

In Table 2 the number of ETT and PSTT cases diagnosed within each 5-year maternal age group is compared to the relevant birth statistics to give an age-related incidence. The combined incidence of ETT and PSTT cases increases from 1:412,488 for teenagers to 1:1,426 for women aged 45 or over at diagnosis.

Overall, the ratio of ETT to PSTT cases is approximately 1:2; however, there appears to be a trend for the overall proportion of ETT cases to increase with increasing maternal age.

For the 40 ETT patients the median age at diagnosis was 39 years (range 15–53) and for the 75 cases of PSTT the median age was 34 (range 15–64). For the 17 cases of mixed pathology the median age at diagnosis was 36 (range 23–49).

Antecedent pregnancy interval

In Table 3 the estimated interval from the presumed antecedent pregnancy until the diagnosis of PSTT or ETT is demonstrated.

Table 1. Histopathology groupings and diagnosis for the 132 cases of ETT or PSTT diagnosed in the UK 2000–2020.

Histopathology	Number (%)
ETT alone	40 (30.3%)
ETT/PSTT	8 (6.1%)
ETT/Choriocarcinoma	2 (1.5%)
ETT/PSTT/Choriocarcinoma	1 (0.8%)
PSTT alone	75 (56.8%)
PSTT/Choriocarcinoma	6 (4.5%)
Total cases	132 (100%)

Table 2. The number of cases and the maternal age related incidence, compared to the number of live births, for ETT and PSTT in the UK 2000–2020.

Age at diagnosis	Live **births** 2000–2020	ETT number and incidence	PSTT number and incidence	Mixed ETT/PSTT number and incidence	Overall number and incidence
<20	824,976	1 (1:824,976)	1 (1:824,976)	–	2 (1:412,488)
20–24	2,691,706	1 (1:2,691,706)	8 (1:336,463)	1 (1:2,691,706)	10 (1:269,170)
25–29	4,247,767	4 (1:1,061,194)	15 (1:283,184)	3 (1:1,415,922)	22 (1:193,080)
30–34	4,709,833	4 (1:1,177,458)	17 (1:277,049)	4 (1:1,177,458)	25 (1:188,292)
35–39	2,606,652	11 (1:236,968)	15 (1:173,777)	3 (1:868884)	29 (1:89,885)
40–44	554,933	5 (1:110,987)	8 (1:69,367)	5 (1:110,987)	18 (1:30,830)
45 +	37,082	14 (1:2,649)	11 (1:3,371)	1 (1:37,082)	26 (1:1,426)
Total	15,673,067	40 (1:391,827)	75 (1:208,974)	17 (1:921,945)	132 (1:118,736)

Table 3. The interval from the antecedent pregnancy to the time of diagnosis for 132 cases of ETT and PSTT in the UK 2000–2020.

Interval from pregnancy to diagnosis	ETT	PSTT	Mixed	Total cases
<1 month	2	3	1	6
1–3 months	1	4	0	5
4–6 months	1	4	0	5
7–12 months	3	15	4	22
13–24 months	15	32	3	50
25–48 months	4	5	2	11
4–10 years	5	8	6	19
>10 years	9	3	1	13
Not recorded	0	1	0	1
Total	40	75	17	132

Table 4. The number of cases and incidence related to the maternal age at the time of the antecedent pregnancy and compared to the number of viable conceptions, for ETT and PSTT in the UK 2000–2020.

Age at antecedent pregnancy	Viable conceptions 2000–2020	ETT	PSTT	Mixed	Total cases
<20	1,579,046	1 (1:1,579,046)	2 (1:789,523)	0	3 (1:526,349)
20–24	3,881,905	2 (1:1,940,952)	11 (1:352,900)	1 (1:3,881,905)	14 (1:277,279)
25–29	5,198,059	7 (1:742,580)	17 (1:305,768)	6 (1:866,343)	30 (1:173,269)
30–34	5,409,361	16 (1:338,085)	24 (1:225,390)	2 (1:2,704,680)	42 (1:128,794)
35–39	3,069,792	8 (1:383,724)	10 (1:306,979)	7 (1:438,542)	25 (1:122,791)
40–44	724,565	4 (1:181,141)	7 (1:103,509)	1 (1:724,565)	12 (1:60,380)
45+	51,717	2 (1:25,873)	3 (1:17,239)	0	5 (1:10,343)
Not recorded	607	0	1	0	1
Total	19,915,052	40 (1:497,876)	75 (1:265,534)	17 (1:1,171,474)	132 (1:150,872)

Approximately 12% of patients presented within 6 months of the antecedent pregnancy and 29% within the first year. Beyond this point, there is a very wide range of presentation intervals with 24% of patients presenting in excess of 4 years after the antecedent pregnancy.

Overall, for the whole study population, the median interval to presentation was 18 months with a range of 0 to 264 months. However, there is an apparent variation in the median interval to presentation between the tumour types with a median interval of 15 months (range 0–288) for the PSTT patients compared to 24 months (range 0–336) for patients with a diagnosis of ETT and 36 months (range 0–180) for patients with mixed pathology.

Age at antecedent pregnancy and disease incidence compared to viable conceptions

The potentially long interval from the causative pregnancy to diagnosis and the variation in the ratio of births to abortions across the maternal age range are both likely to lead to an overestimate of the ETT and PSTT incidence at higher maternal age particularly when compared to the live birth data.

In Table 4 the incidence, relative to the total number of viable conceptions, related on the estimated age of the patient at the time of the antecedent pregnancy is demonstrated. The overall incidence across the entire age range is 1 case of ETT or PSTT per 150,872 viable conceptions, with the age-related incidence increasing from 1:526,349 in women aged under 20 to 1:10,343 for women aged 45 or over.

Pregnancy number

The pregnancy number of the antecedent pregnancy was available for 129 of the 132 study patients. The results indicate that the diagnosis resulted from the first pregnancy in 20.9% of the patients, from the second in 37.2% and in the 3rd or higher number pregnancy in the remaining 41.9% patients.

Disease stage at diagnosis

The information of the FIGO staging indicated that at diagnosis overall 63% of patients had stage I disease, 8.3% stage 2 and 28% of patients had stage 3 or 4 metastatic disease. The spread of disease stage was similar across ETT, PSTT and the mixed tumours.

Discussion

Summary of findings

This study confirms that intermediate trophoblastic tumours are extremely rare with an overall incidence in the UK of 1 case per 118,736 births or 1 case per 150,872 viable conceptions. PSTT is the more frequent form of intermediate trophoblastic tumour occurring at approximately a 2-fold higher rate than ETT. The PSTT data is in keeping with but slightly higher than other earlier estimates of PSTT incidence, with figures of 1 case in 100,000 deliveries previously reported from the Netherlands (Lybol *et al.* 2011) and 0.3 cases in 100,000 live births from Japan (Yamamoto *et al.* 2022). This current study reports an incidence of approximately 1 in 200,000 for PSTT but with some additional cases with PSTT and mixed pathology. It is likely that these modest differences between studies reflects a degree of diagnostic and classification variation, rather than any more complex biological explanation. Similarly the data on ETT incidence in this study reports a higher figure of approximately 1 case per 400,000 live births compared with the earlier publication estimating a lower incidence of 1 case per 1.4 million live birth. With such a rare and relatively new diagnosis, it is difficult to conclude if these figures reflect a true difference or will become closer with future analysis of larger sample sizes.

The overall incidence of ETT and PSTT is appreciably lower that of non-molar gestational choriocarcinoma which in the same UK population has been reported to occur at a rate approximately two-fold higher with 1 case per 66,775 births or 1 case per 84,226 viable conceptions (Savage *et al.* 2020). In contrast the incidence of molar pregnancy, the most frequent form of gestational trophoblastic tumour, is over 200 times higher with an overall incidence of 1 case per 607 viable conceptions (Savage *et al.* 2013).

The median age at diagnosis for patients with ETT was 39 years and for the patients with PSTT the mean age was 34. However, the data in this study confirms a close association between increasing maternal age and disease risk. The combined overall incidence of ETT and PSTT relative to viable conceptions rises from 1:412,488 in women aged under 20, to 1:188,292 for women aged 30–34 and 1:30,830 for women aged 40–45.

The impact of increasing maternal age on the risk for ETT and PSTT is similar to that previously seen in our earlier report on the demographics of non-molar gestational choriocarcinoma. In choriocarcinoma the disease incidence was 1:223,494 for women aged under 20, 1:80,227 for women aged 30–34 and 1:41,718 for women aged 40–45. In contrast, in molar pregnancy the age-related incidence demonstrates a J shaped relationship with maternal age, with the rate varying from 1:597 at the age of 18, falling to 1:792 at 24 and then rising with increased age to 1:423 at age 40 and 1:101 at age 45.

The differing impact of maternal age on disease risk amongst the varying forms of GTN is likely to reflect the different routes to oncogenesis in these tumours. Molar pregnancies result from an error occurring during fertilisation, whilst choriocarcinoma, ETT and PSTT arise predominantly in initially normal conceptions potentially as an aberration of epigenetic progression in the early post fertilisation phase.

Previous studies have indicated that intermediate trophoblastic tumours may present at a significant interval from the antecedent pregnancy (Schmid *et al.* 2009). The data in this current study shown in Table 3, confirms this finding indicating that 29% of cases are diagnosed within the first year after pregnancy whilst 33% of cases present more than 2 years post-partum. This high incidence of late presentations is similar to that seen in gestational choriocarcinoma where approximately 20% of cases occur later than 24 months (Savage *et al.* 2020). Of note the median interval to presentation appears to be shorter at 15 months for the PSTT patients compared to 24 months for patients with a diagnosis of ETT.

There is little data regarding the pregnancy number and the diagnosis of ETT and PSTT. The data in this study indicate that 20.9% of patients presented with a diagnosis linked to their first pregnancy, 37.2% from their second and 41.9% from their third or higher number pregnancy. These figures are similar to the previous data for gestational choriocarcinoma. The modest excess of cases of intermediate trophoblastic tumours occurring in the higher pregnancy numbers is likely to be a result of the impact of rising maternal age rather than any more complex biological associations.

In contrast to the similar demographic patterns between the intermediate trophoblastic tumours and gestational choriocarcinoma, these malignancies differ in their disease staging. In this current study 72.5% of the ETT cases and 62.7% of PSTT cases had disease limited to the uterus on initial staging,

whilst in gestational choriocarcinoma the tumour is confined to the uterus in 45% of cases (Savage *et al.* 2020).

At present the exact route to oncogenesis in choriocarcinoma and the intermediate trophoblastic tumours is still to be fully documented. However, the role of conventional oncogenic mutations in these malignancies seems to be limited (Cho *et al.* 2020, Savage *et al.* 2019, McNally *et al.* 2024). A recent report examining genetic and epigenetic analysis of a case of gestational choriocarcinoma suggests that defects in the progression of normal epigenetic evolution may be the cause of the malignant phenotype in that diagnosis (Savage *et al.* 2019). ETT appears to frequently be associated with upregulation of TERT gene activity (Oliver *et al.* 2021), as the result of a gene fusion, whilst at present there is little information on the oncogenesis of PSTT.

Conclusion

ETT and PSTT are the rarest of the gestational tumours and to date there has been only limited accurate demographic data available. In this UK population-based study we have reviewed a total of 132 cases from a 21-year study period. The data indicates an overall incidence of 1 case per 1:118,736 live births. In addition to confirming the rarity of these diagnoses, the current results confirm a clear relationship between increasing maternal age and a rising risk for intermediate trophoblastic tumours. This study also supports the findings of earlier reports with regard to the highly variable interval between the antecedent pregnancy and the subsequent diagnosis of an intermediate trophoblastic tumour.

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Authors' contributions

CRediT: **P. Savage**: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing; **F. Froeling**: Data curation, Investigation, Writing – review & editing; **M. Lythgoe**: Investigation, Writing – review & editing; **R. Fisher**: Investigation, Writing – review & editing; **G. Maher**: Investigation, Writing – review & editing; **M. Winter**: Investigation, Writing – review & editing; **K. Eremeishvili**: Investigation, Writing – review & editing; **N. Sarwar**: Investigation, Writing – review & editing; **X. Aguiar**: Investigation, Writing – review & editing; **K. Singh**: Investigation, Writing – review & editing; **B. Hancock**: Investigation; **R. Coleman**: Investigation, Supervision; **J. Tidy**: Investigation, Supervision; **MJ Seckl**: Conceptualization, Investigation, Supervision, Writing – review & editing.

Disclosure statement

None. Completed disclosure of interest forms are available to view online as supporting information.

Ethics approval

All procedures were in accordance with the ethical standards of the institutional research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Informed patient consent was not required. Retrospective data collection was anonymised and routinely collected as part of clinical practice and used for audit purposes.

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Data availability statement

The data that support the findings of this study are available from the corresponding author, [PS], upon reasonable request.

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