

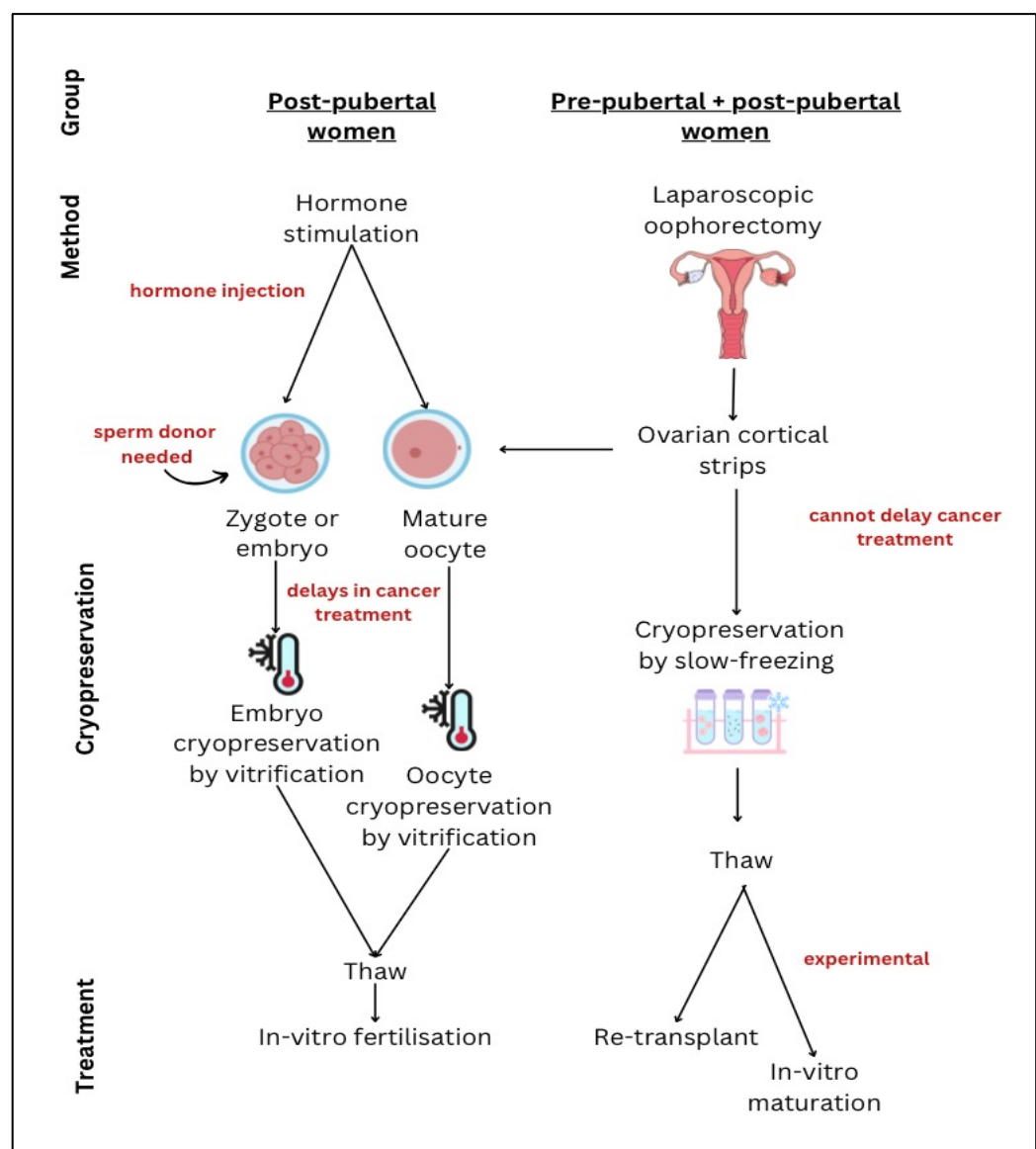
Female fertility preservation in a primary brain tumour cohort

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INTRODUCTION

Fertility Preservation (FP)



Primary Brain Tumours (PBTu's) ^{1,2}

These are the most common types of PBTu's with some 5-year survival statistics (%):

Gliomas

Astrocytomas

- Grade I Pilocytic Astrocytoma
- Grade II Diffuse Astrocytoma (45%)
- Grade III Anaplastic Astrocytomas (>20%)
- Grade IV Glioblastomas (>5%)

Oligodendrogliomas (55%)

Ependymomas (85%)

Mixed Gliomas

Gliomas make up 78% of all PBTu's ³

Medulloblastomas

Pineoblastomas (70-75%)

Germ cell tumours

Patients undergoing **cancer treatment** are often exposed to **gonadotoxic treatment** (radiation and chemotherapy) necessitating discussion of FP.

AIMS AND OBJECTIVES

To analyse prospectively collected primary data on female PBTu patients referred for FP at the Reproductive Medicine Unit, EGA Wing, UCLH, focussing on long-term outcomes.

METHODS

A **retrospective audit** was carried out on **prospectively collected data** between **2017 and 2024** of female PBTu patients from secure databases and EPIC, primarily analysed with **descriptive statistics**.

Baseline data collated included: PBTu type, age at diagnosis, age at FP, time elapsed since FP, chemotherapy regimen, type of FP and number of oocytes/embryos/ovarian tissue cryopreserved per cycle of stimulation (COS).

A systematic literature search was conducted on **6 databases**, identifying **20 eligible full-text studies**. Exclusion criteria included **data not disaggregated by sex**, interventions **not currently used in practice**, and **document-type exclusion** (case reports, review articles, guidelines, protocols).

Standardised search terms included 'fertility preservation', 'brain tumo*', 'treatment'.

5 key themes were identified:

Adverse reproductive outcomes of PBTu treatment (n=8)

Spontaneous pregnancy rates of PBTu cancer survivors (n=3)

Methods and short-term FP outcomes (n=4)

FP counselling (n=4)

FP long-term outcomes (n=1)

Despite 1 study analysing long-term utilisation of stored gametes, the following factors were not mentioned that this study aims to cover:

- Spontaneous pregnancy rates
- Mortality rates

RESULTS

Brain Tumour Type	Grade				Other	Total Patients
	I	II	III	IV		
Anaplastic Astrocytoma			10			10
Glioblastoma				8		8
Diffuse Astrocytoma		6				6
Medulloblastoma				4		4
Glioma			1	2		3
Pilocytic Astrocytoma	1		1		Suprasellar	3
Lumbosacral Myxopapillary Ependymoma		1			Unspecified	2
Oligodendroglioma		1				1
Oligoastrocytoma		1				1
Pineoblastoma				1		1
Anaplastic Oligodendroglioma			1			1
Pilomyxoid Astrocytoma		1				1
Total	1	10	13	15	2	41

Table 1: Number of female patients referred per tumour-type, including grading

- 24/41 (58.5%) underwent a **craniotomy**
- 51.2% (n=21) received **cranial irradiation (CIR)**
- 68.3% followed a regimen including **temozolomide**
- 19.5% had combination therapy: **PCV** or **PACKER**

	Age at Diagnosis (years)	Age at FP (years)	Time elapsed between diagnosis and FP (years)	Age* (years)**	Time elapsed since diagnosis* (years)**
Mean	25.30	26.43	1.13	30.32	5.32
Range	23 (14 - 37)	26 (17 - 40)	7 (0 - 7)	24 (18 - 42)	22 (1 - 23)
Standard Deviation	5.89	6.56	1.77	7.35	5.02

Table 3: Average diagnostic, FP, current ages, and time elapsed between every variable of the PBTu FP cohort.

*Ages as of 10/04/2024; ** excludes 4 patients who have died of Grade II Astrocytoma (n=1), Grade II Oligoastrocytoma (n=1), Grade III Anaplastic Astrocytoma (n=2)

Reasons patients did not undergo FP treatment included:

- Stable ovarian function (n=2)
- Lack of funding (n=2)
- Avoiding treatment delays (n=3)
- Death (n=6)

Patient Number	Tumour Type	Grade	Age at Diagnosis (years)	Age at Death (years)	Time between Diagnosis and Death (years)
1	Glioblastoma	IV	23	26	3
2	Glioblastoma	IV	27	28	1
3	Glioblastoma	IV	29	36	7
4	Glioblastoma	IV	37	39	2
5	Glioblastoma	IV	32	32	0
6	Anaplastic Astrocytoma	III	24	29	5
7	Anaplastic Astrocytoma	III	25	29	4
8	Anaplastic Astrocytoma	III	26	30	4
9	Diffuse Astrocytoma	II	26	33	6
10	Oligoastrocytoma	II	30	35	5
Mean			27.9	31.7	3.7

Table 4: Overview of tumour-type, diagnostic age, and age of death in the 10 deceased patients of the total cohort (n=41).

Brain Tumour Type	Number of Cycles	Number of oocytes retrieved	Total oocytes/embryos stored by stages	Total
Anaplastic Astrocytoma	1	11	11 MII	2
Glioblastoma	2	17	14 MII	1
		23	17 MII, 6 GV	1
		65	57 MII, 1 MI, 4 GV	1
		11, 5	1 MII, 2 embryos	1
Diffuse Astrocytoma	1	7, 9	16 MII	1
		9	4 embryos	1
Medulloblastoma	3	27	19 MII	1
		7, 14, 15	12 MII, 1 MI, 1 GV, 6 embryos	1
Glioma	1	18	13 MII, 5 GV	1
		19	15 MII	1
Lumbosacral Myxopapillary Ependymoma	1	9	8 MII	1
		25	23 MII, 2 GV	1
Oligodendroglioma	1	19	15 MII, 1 MI, 3 GV	1
Oligoastrocytoma	1	8	6 MII, 2 GV	1
Pineoblastoma	1	13	12 MII	1
Anaplastic Oligodendroglioma	1	6	6 MII	1
Total				21

Table 2: Summary of COS cycle number, number of oocytes retrieved, and gametes stored, categorised into tumour sub-types.

NB: 2 FP patients opted for ovarian tissue cryopreservation

Reason for lack of use of stored material	Number of Patients
Progression of disease -> death	4
Anaplastic Astrocytoma	2
Diffuse Astrocytoma	1
Oligoastrocytoma	1
No follow-up	4
Anaplastic Astrocytoma	2
Diffuse Astrocytoma	1
Medulloblastoma	1
Malignancy present	4
Glioblastoma	2
Glioma	1
Medulloblastoma	1
Not currently family planning	4
Anaplastic Astrocytoma	1
Anaplastic Oligodendroglioma	1
Glioma	1
Pineoblastoma	1
Spontaneous pregnancy	2
Diffuse Astrocytoma	1
Lumbosacral Myxopapillary Ependymoma	1
Remission - high AMH/AFC	1
Anaplastic Astrocytoma	1
Waiting for 6 months remission	1
Oligodendroglioma	1
Trying for spontaneous pregnancy	1
Anaplastic Astrocytoma	1
In recovery	1
Medulloblastoma	1
Other Medical Complication	1
Lumbosacral Myxopapillary Ependymoma	1
Total	23

Table 5: Summary of reasoning for lack of cryopreserved gamete use as of 10/04/2024, categorised by tumour sub-type.

No patients have utilised their stored material

DISCUSSION

Temozolomide may be **less gonadotoxic** than combination therapy such as **PACKER** or **PCV** ⁴. Research indicates **minimal permanent ovarian failure risk** due to CIR as 0/14 patients treated with CIR developed primary ovarian insufficiency ⁵. As these are the most common treatment modalities for PBTu's, it questions the rationale for proceeding with FP.

This is supported by the finding that 1 patient from this cohort had a **spontaneous pregnancy** post-recovery and treatment with temozolomide and that 2 women decided not to proceed with FP due to predicted **stable ovarian function post-treatment**.

There remains **low survivorship** in **high-grade cancers** (e.g. glioblastomas) with a **high recurrence risk** post-recovery in **Grade III/IV PBTu's** ⁶.

With 5-year survival rates in the UK around 5% for glioblastomas, ethical issues such as **discarding of cryopreserved gametes**, **post-humous reproduction** and **resource allocation (time and money expenses)** are raised ².

Ethical conundrums are present regarding **balancing oncological priorities** to treat aggressive cancer and **quality of life** improvement through FP.

Strengths:

- Largest number of patients being referred for PBTu
- Diverse range of tumour subtypes
- Good cohort to follow-up long-term
- Ethical Considerations

Limitations:

- Retrospective nature
- Short follow-up duration (4.53 ± 5.14)
- Inconsistent follow-up with regards to ovarian reserve markers and menstrual patterns

CONCLUSION

The systematic review conducted has shown that long-term outcomes post-FP in female PBTu patients are rarely reported, including spontaneous pregnancy and mortality rates.

Patients with low chance of survivorship and high recurrence rate (e.g. glioblastoma patients) may not use their stored materials and those with low levels of gonadotoxicity from common treatment modalities may not need to.

These raise ethical concerns and highlight the importance of shared decision-making.

Further large-scale, multi-centre studies with prospective cohorts, including data from national and international registries, are required to formulate new guidelines and policies as to when patients should be offered FP.

Outcomes of importance to investigate include:

- Associations between **chemotherapy regime** and fertility/pregnancy outcomes
- Correlation between **radiotherapy dosage** and fertility/pregnancy outcomes
- Testing **menstruation** and **ovarian reserve** with **post-treatment AMH levels** can strengthen findings
- **Live birth** rates
- **Mortality** rates (categorised by tumour sub-type)

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