Reproductive Neuro-Oncology:

Neuro-Oncology in Women (N.O.W.)

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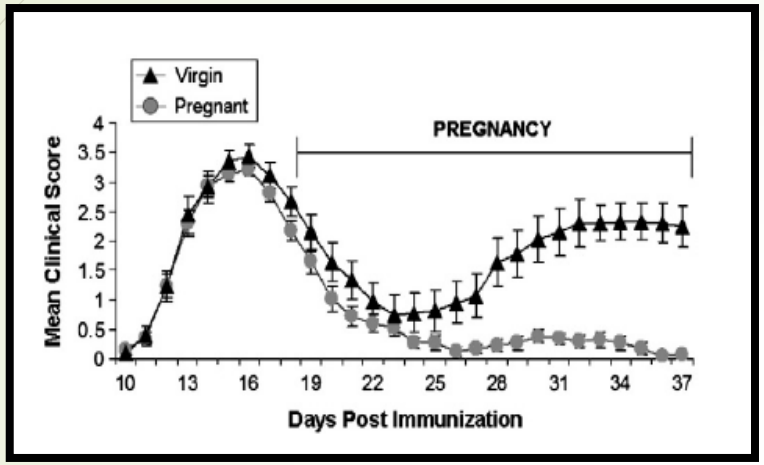
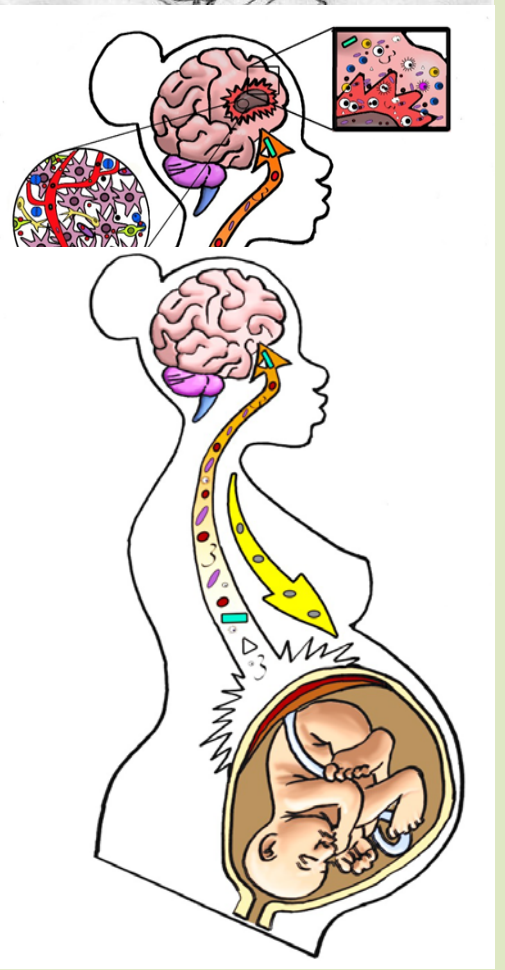
Geisinger Neuroscience & Cancer Institutes

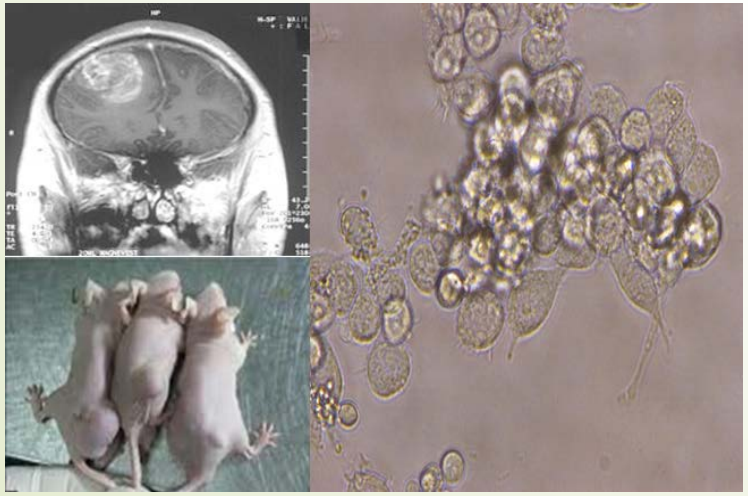
No Relevant Disclosures

Glioblastoma*genesis: In the beginning…*

Clinical Training & Research Background







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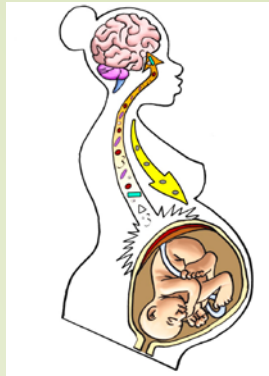
Lecture Overview



- This lecture is formatted as a combination of **cases** and **didactic learning.**
- Topics covered will address brain tumor clinical scenarios and practice points – focused on pregnancy/reproduction:
  - Background and statistics
  - Immune privileged sites
  - Pregnancy and brain tumor progression
    - **Meningioma** (most common benign intracranial tumor) **GBM** (most deadly)
      - Therapies and Surveillance
      - Introduce serum factors and fetal/maternal cell microchimerism
  - Ethical/Social issues with fertility preservation, prevention, and physician responsibility
- Topics **not covered but of great importance** to **N.O.W.** include: Chemotherapy exposure risks (body fluid, caregiver, etc…), social impact of brain tumor in women, parity and birth order considerations, circulating serum factors (cell free DNA, exosomes), and other pregnancy and cancer risks.

Primary CNS post transplant lymphoproliferative disease

BACKGROUND

1

All Cancers & Pregnancy:

- 1 Cancer : 1000 Pregnancies**
- Melanoma >Breast>Leukemia

Most common malignancy in pregnancy

More aggressive during pregnancy

Crosses placenta

Prithviraj, P (2015)

2nd most common

Pregnancy influence on progression vs Metastasis is controversial

BRCA cells migrate away from placental cells

Epstein,S (2014) , Matalon S, (2015)

Very **Rare**

No determined measurable additional pregnancy risk

Vandenbriele, *C* (2010)

2

Brain Tumors & Pregnancy:

- Glioblastoma
- Meningiomas
- Metastatic Brain Cancer

Glioblastoma – pregnancy progression

Rare concurrence. Aggressive disease. mOS ~16 mos. Physician low discussion rate.

Meningioma – pregnancy progression

More common. Usually benign tumor course. Epidemiological overlap. Hormone receptors.

Metastatic Brain Cancer – variable

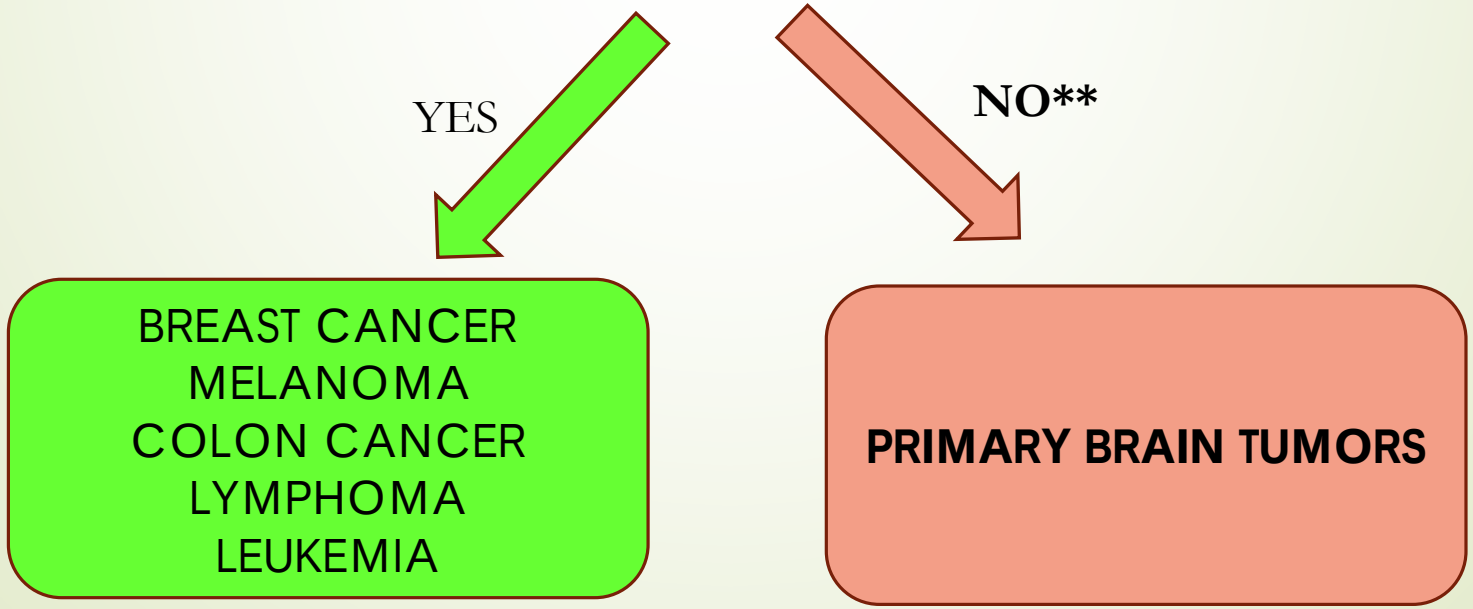
Most common. Longer survival rates. Cancers with hormone receptors. Presumed patho-physiology of metastasis in the brain sanctuary.

Cancer Cell October 2015

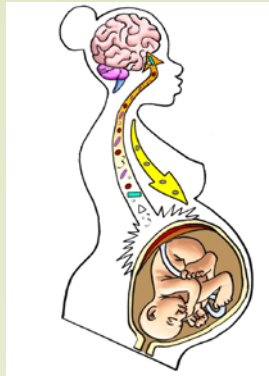
IMMUNE HALLMARKS OF CANCER

Cavallo *et al*. (2011) added : **“Immune Hallmarks of Cancer”**

1. Ability to suppress immune reactivity
2. Ability to evade immune recognition
3. Ability to thrive in a chronically inflamed microenvironment



Hallmarks of Immune Privilege (IP)



- Reduced lymphatic drainage* [Louveau Nature 2015]
- Reduced expression of MHC molecules
- Express neoantigens that induce tolerance in circulating cells
- Express and release immunomodulating factors that limit cell activation/infiltration

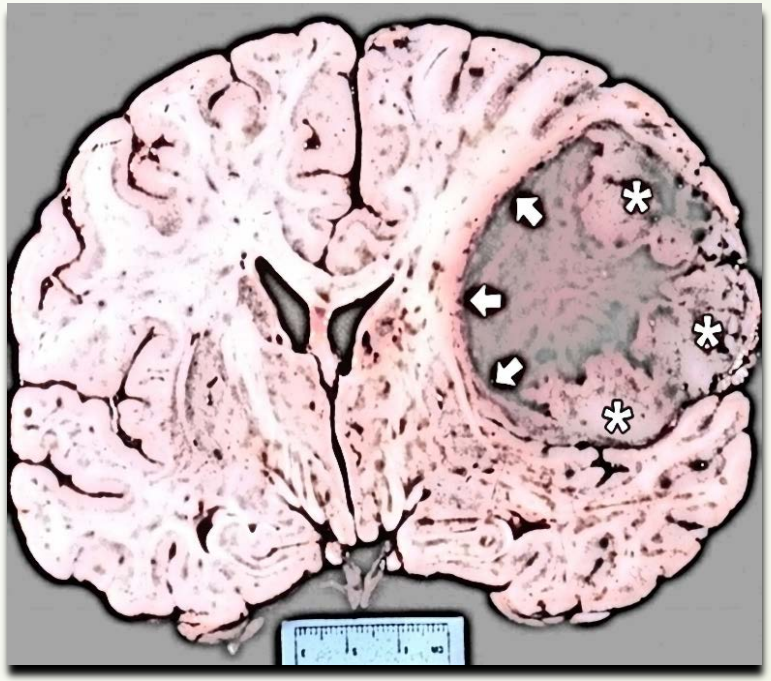
Four IP Compartments

Eye, Testis, **CNS & Gravid Uterus**

- Specialized Structural Barriers
- Tolerates foreign grafts
- Expression of neo-antigens

Shechter, R et al. (2013) *Nat Rev Immunol.*

Pregnancy



Brain Tumor

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Case 1 of 2

50 yo F with recurrent and progressed WHO grade I meningioma. G2P2A0, history of OCPs and use of estrogen/progesterone combined hormone replacement therapy (HRT). Introduced to my clinic in 2017 after 12 years of battling recurrent low grade meningioma.

Surgeries: x 4 (2005, 2008, 2016, and 2017)

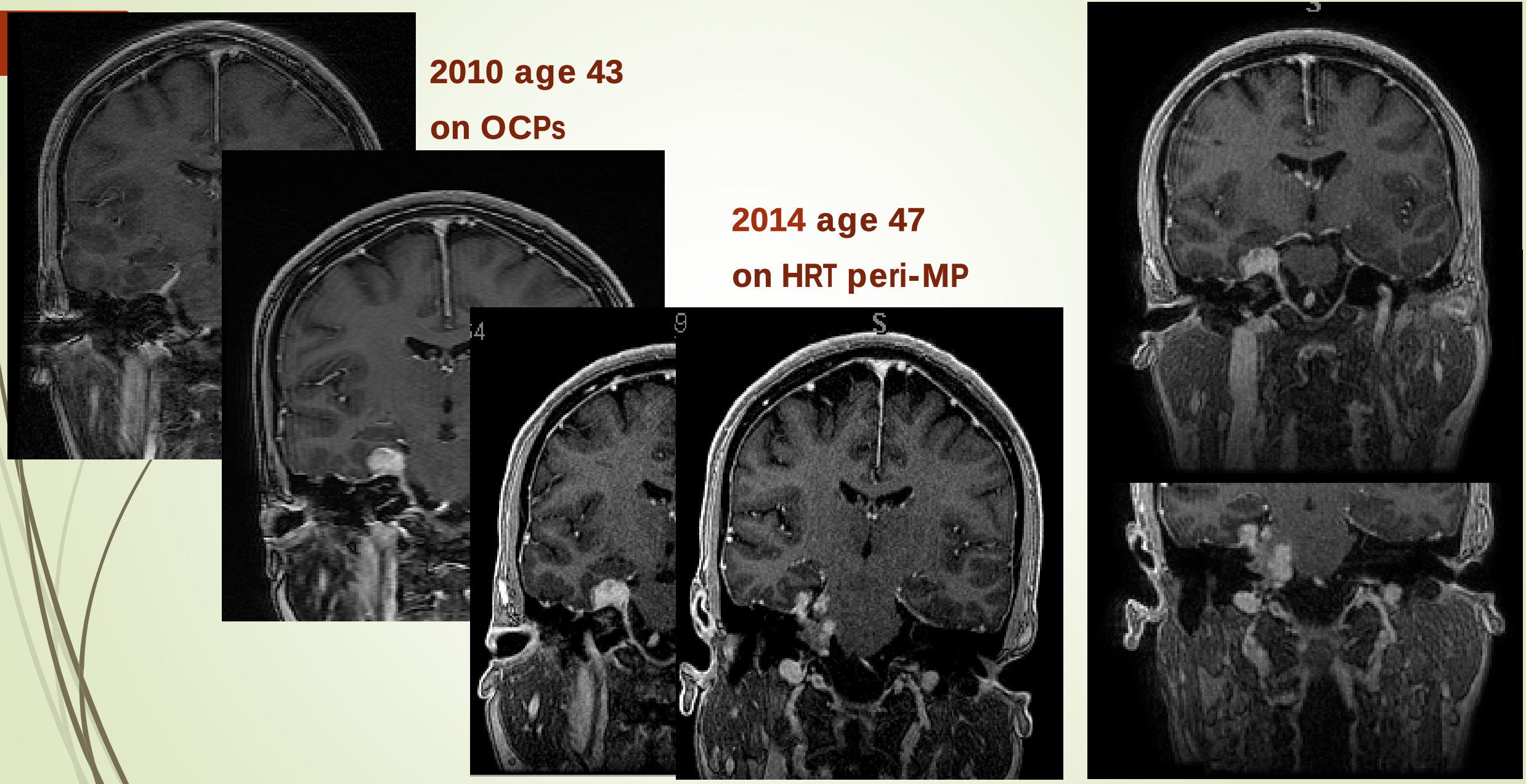
Radiation: x 2 (2008 – SRS and 2016 IMRT)

PE: Tinnitus and hearing loss on right, right facial numbness, double vision, bulbar signs, increased dizziness, right CN VII palsy, left body hemisensory loss, gait instability uses a straight cane for ambulation.

2006 Age 39 OCPs

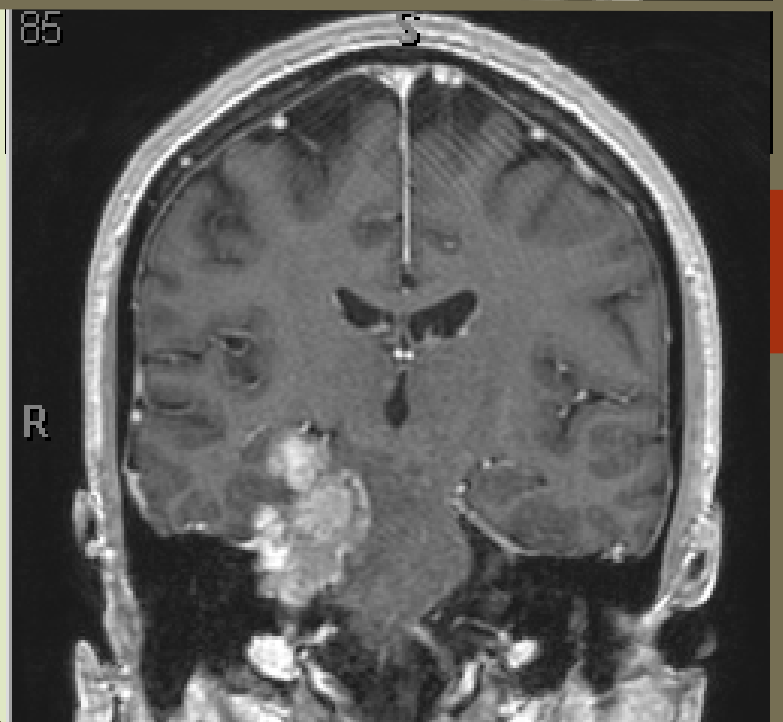
Surgeries: x 4 (2005, 2008, 2016, and 2017)
Radiation: x 2 (2008 – SRS and 2016 IMRT)

2015 age 48 1yr - HRT



2010 age 43 on OCPs

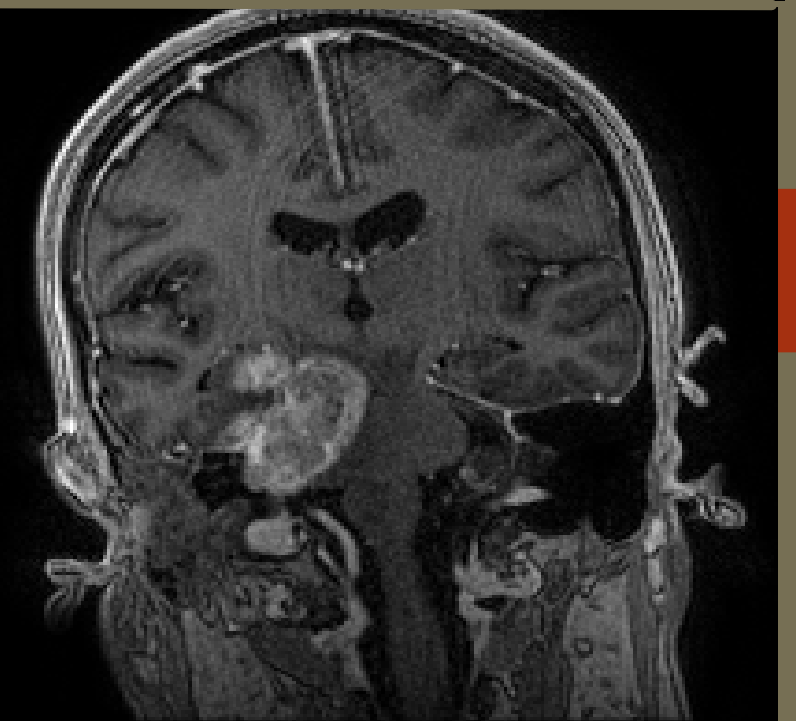
2014 age 47 on HRT peri-MP



2017 age 50 3yr on HRT

Impression: Known residual incisural petroclival components of meningioma **are progressively increased in size with slight worsening of mass effect on the pons and right cerebral peduncle**.

N.O.W.: Patient was discontinued HRT in partnership with her gynecologist and started on Xeloda (Capcitabine) oral chemotherapy and monitored over next year with MRI brain



2018 Age 51 OFF HRT

Impression: Infiltrating predominantly extra-axial mass involving the right middle cranial fossa, cerebello-pontine angle cistern, petrous apex, internal auditory canal, geniculate ganglion of the facial nerve, cochlea and likely cavernous sinus **is without interval change.**

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5518713/

Practice Points To Consider

Meningiomas - 37% of all CNS tumors

Meningioma 2:1 female to male

Increases to ~3x more likely in women between the ages of 35–54

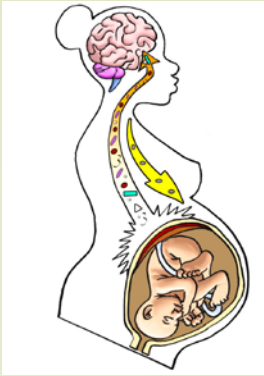
No noted sex-difference for meningioma among children (ages 0-14)

Overall incidence of meningioma increases steadily with age, most significant increase being after age 65

70% express progesterone 20-30% express estrogen <10% express androgen

Meningioma cell proliferation potentially driven by these hormones

Higher risk for diagnosis and tumor progression has been demonstrated in **women on hormone replacement therapy (HRT), also during the post-menopausal stage, and for multiparous women.**



Several large studies have reported an increased risk for meningioma in patients with a history of **ever-use of HRT.** Patients with longer-term use and those exposed to **combined estrogen-progestin** therapies carry and even greater risk.

Accelerated growth of meningiomas has been **associated with pregnancy** as well as during the luteal phase of the **menstrual cycle.**

There is **not currently any verified treatment guidelines** to recommendation to discontinuation of HRT or OCs in patients. Increased guideline directed research is needed in this field.

Recommendation for **closer imaging and clinical surveillance** might be encouraged but is currently not standard of care for patients.

It is debated that there is a significant impact on the risk for development of meningioma for events such as the onset of **puberty, menopause, first pregnancy,** and with use of low dose oral contraceptives.

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Case 2 of 2

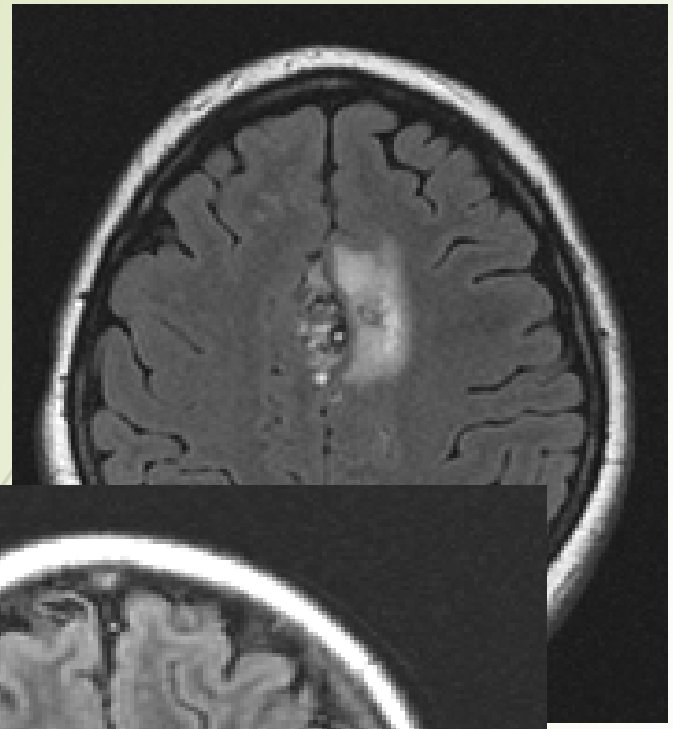
18yo nulliparous RH Latina (Catholic) Fe. Left Frontal, bilateral limbic lobe, & CC on MRI C+ Feb 2015.

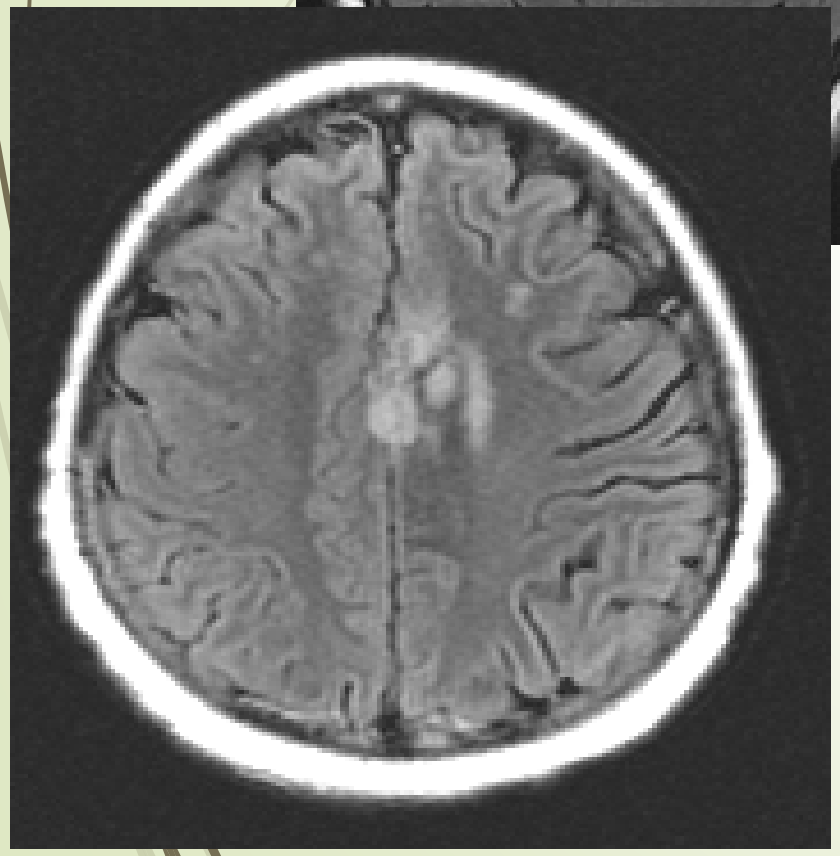
Mar 6, 2015 Subtotal resection – presurgical KPS 90.

Pathology: GB, *IDHwt*

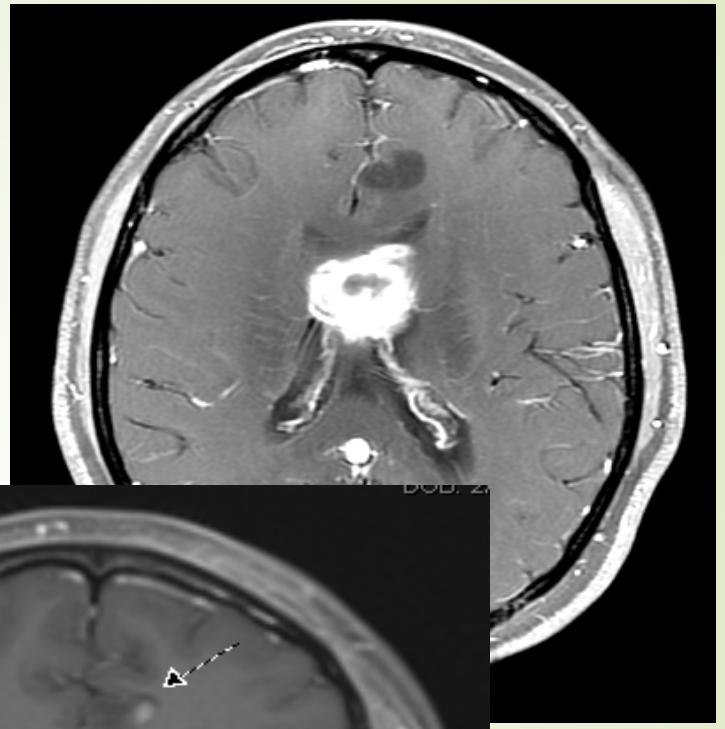
Apr – May Chemoradiation (60Gy – 30fx, TMZ)

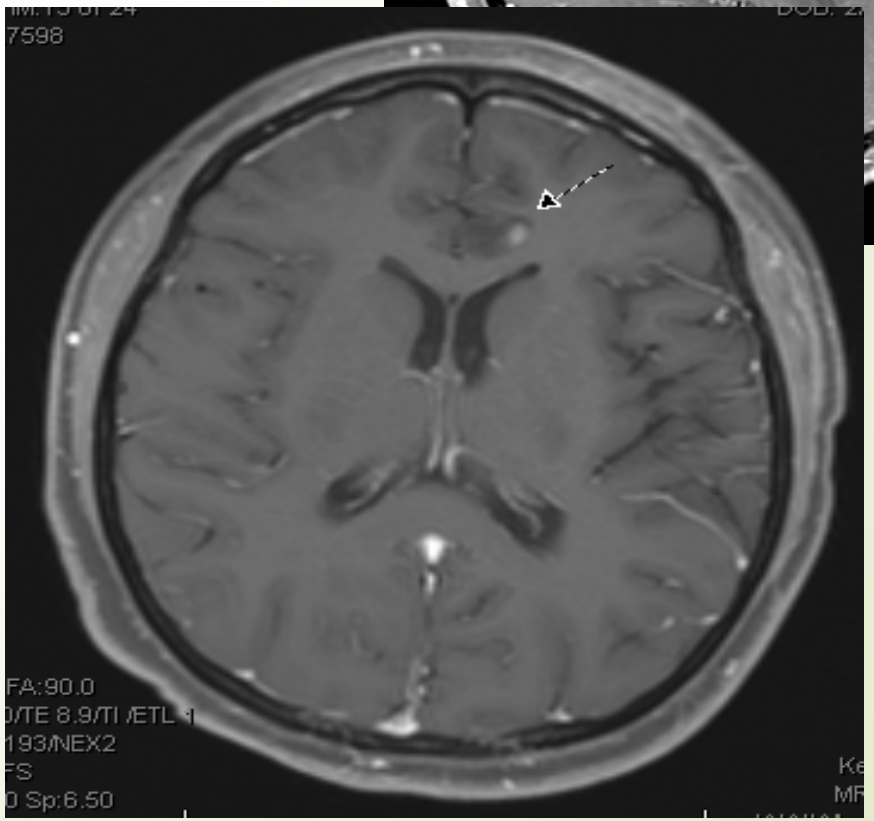
CASE 2





Pre-op



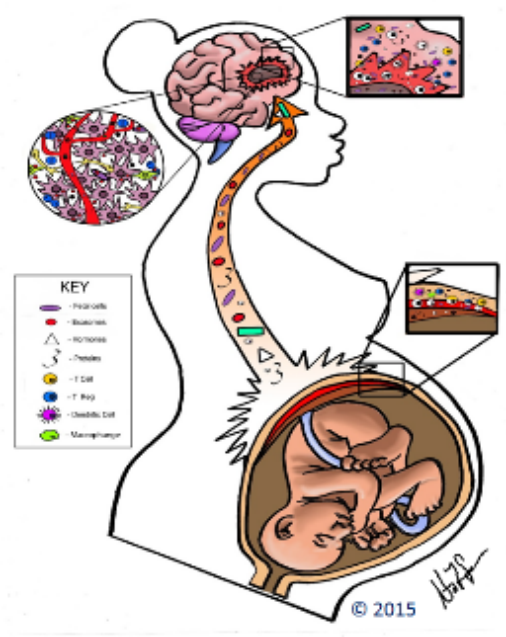


Post-op &
Post RT
May 2015

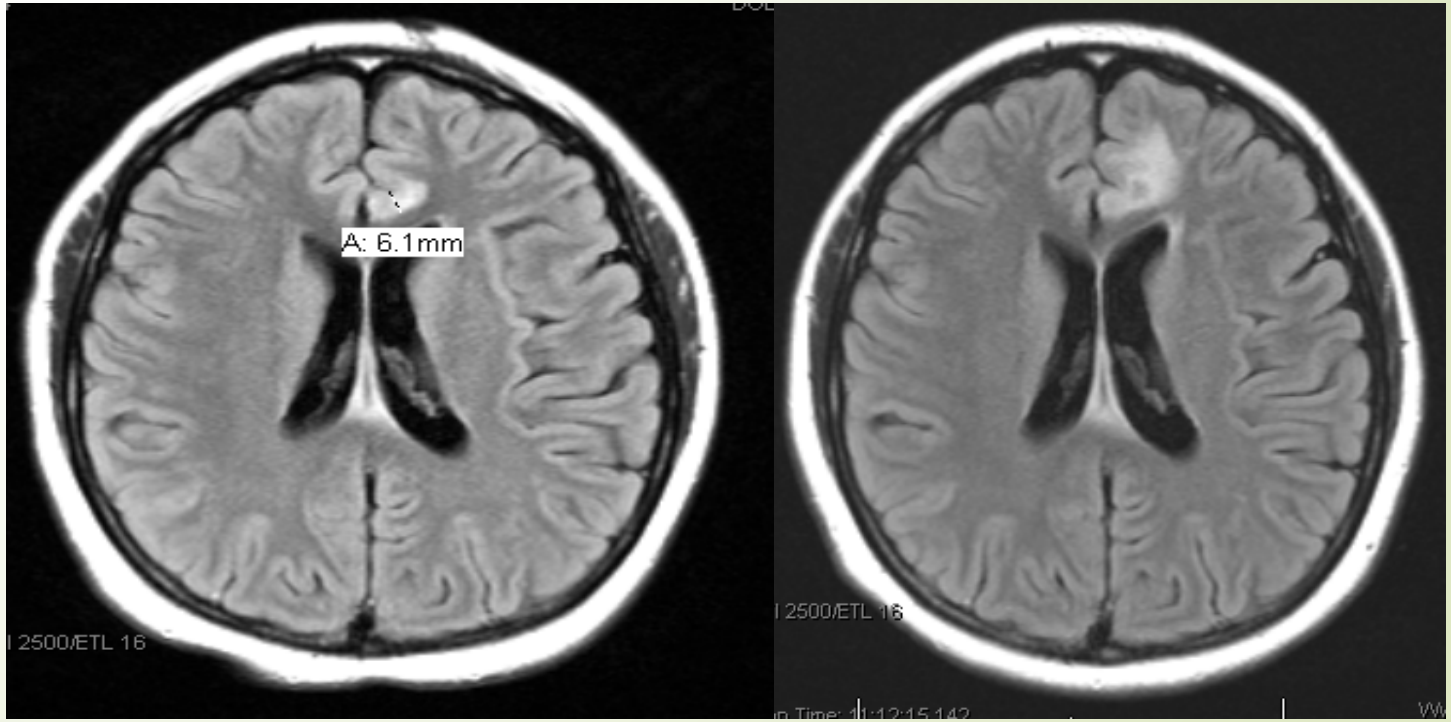
June – Jul Completed 2x adjuvant TMZ of planned 12 cycles

*At visit noted to be 7 wks gestation

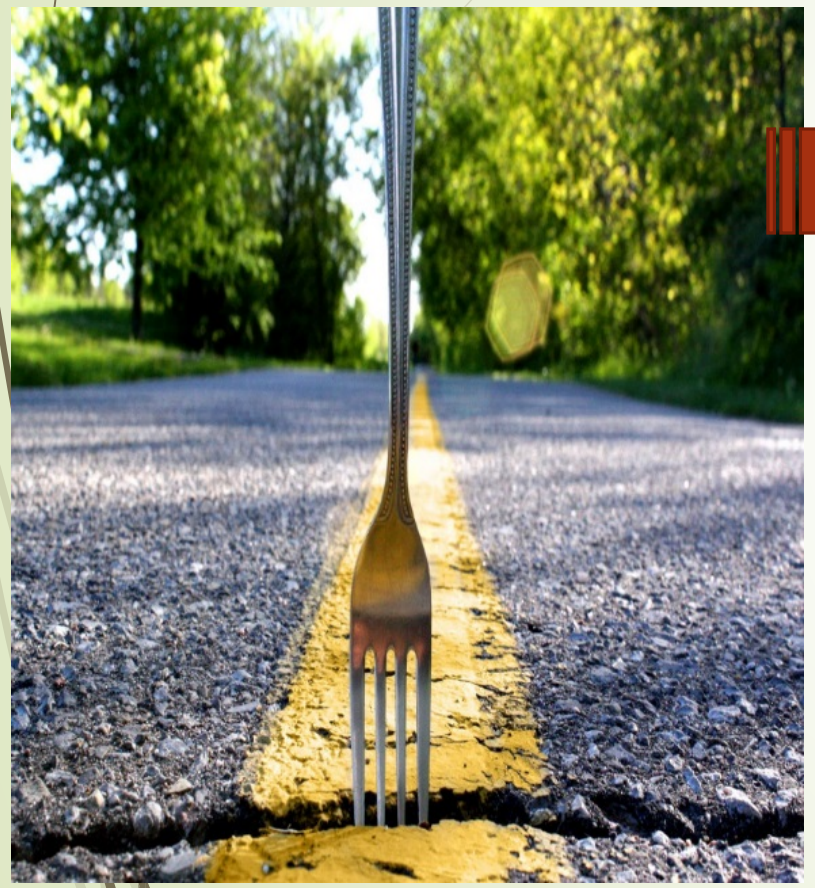
Nov (~16wk) gestation worsening headaches – we obtained a MRI non-Gad which was concerning for progression



New nonC+ MRI



Case 2



Tumor Board

- Law Abortion ≤20wks US/22wks LMP
- Patient wished to continue pregnancy
- Consented for Contrast MRI

Aggressive

Surgery to delay chemo, induce delivery at fetal viability (~28wks)

OR

Terminate Pregnancy @17wks gestation, surgery & resume TMZ

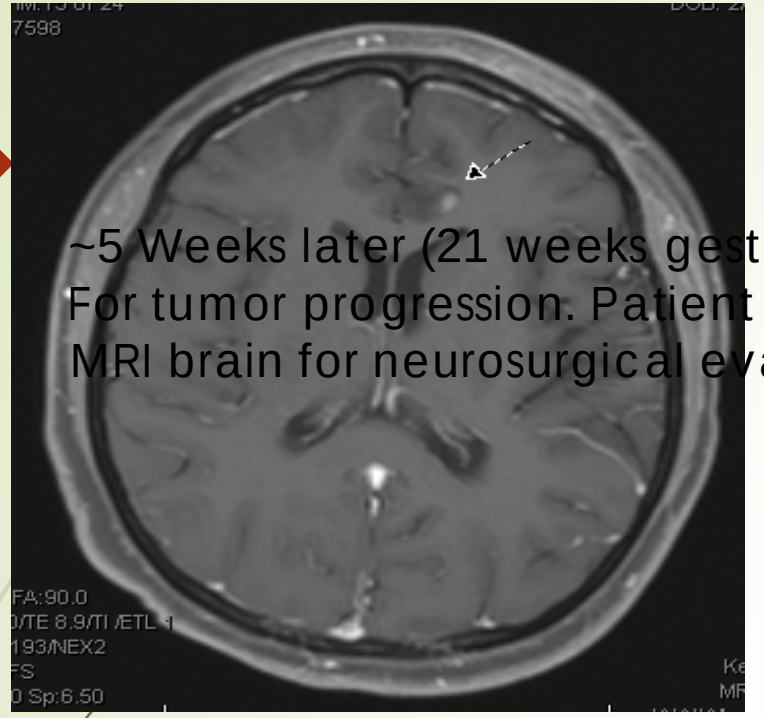
Conservative

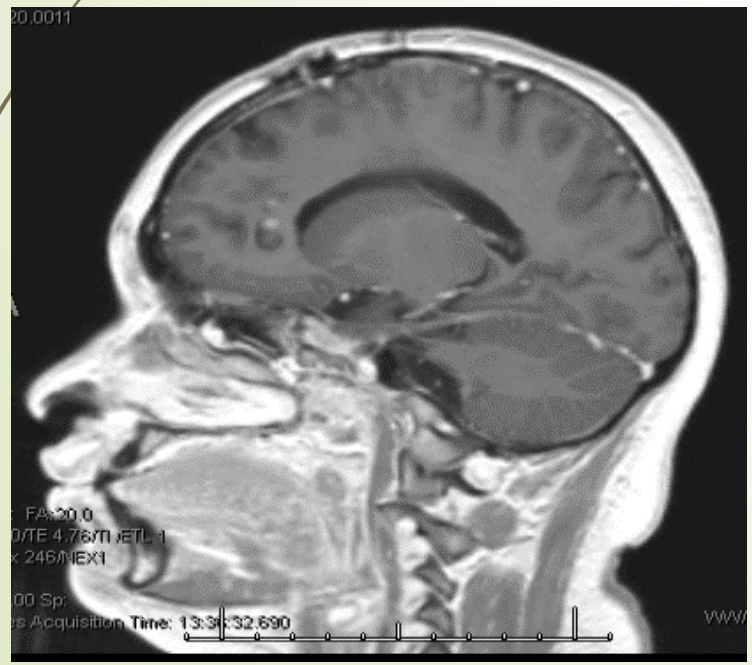
Monitor

Delay surgery and chemo until viability or natural delivery

Then surgery and TMZ.

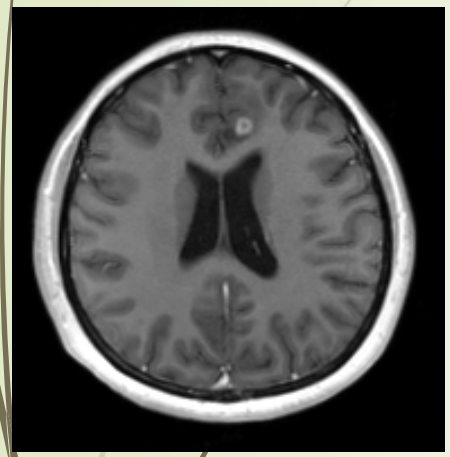
~5 Weeks later (21 weeks gestation) with continued clinical decline and concern For tumor progression. Patient was consented for contrast enhanced MRI brain for neurosurgical evaluation.



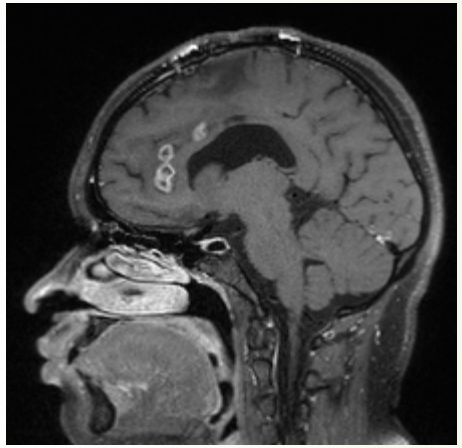


Case 2

Patient underwent Laser Interstitial Thermal Therapy (LITT) ablation of a left frontal proggressed GBM at 21 weeks gestation with female singleton

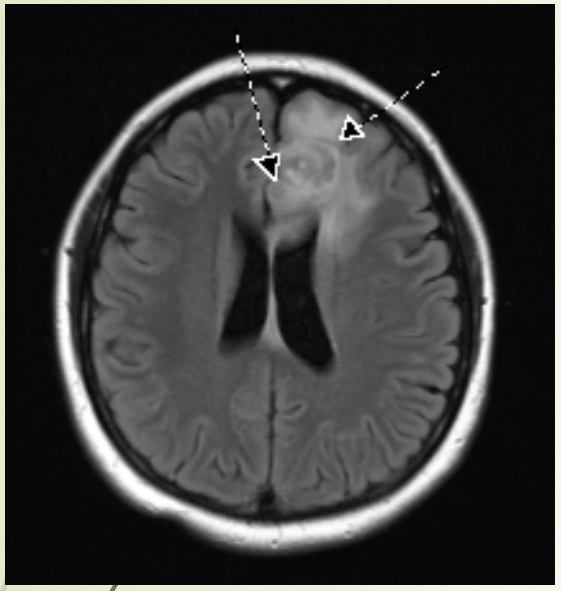


LITT Trajectory



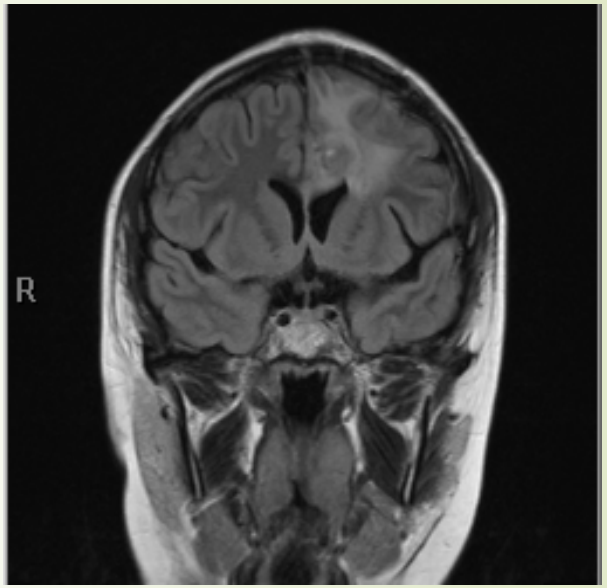
LITT Trajectory

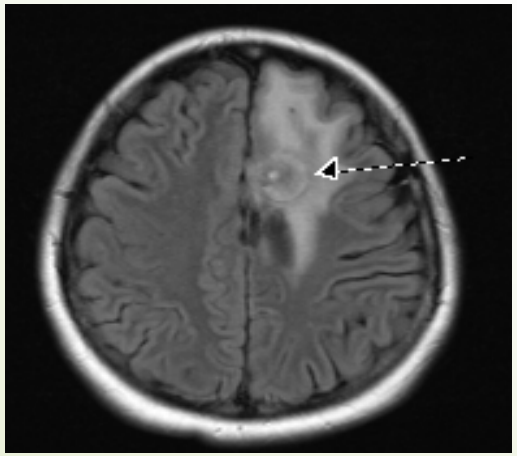
Case 2

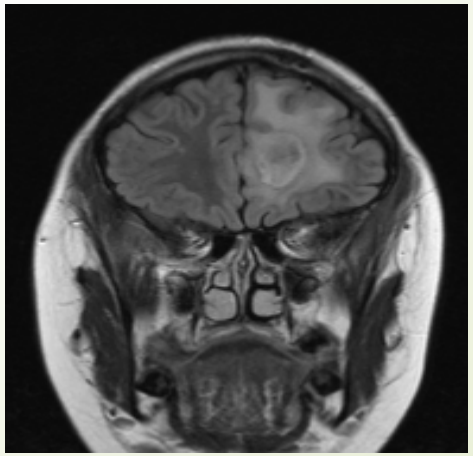


4 weeks s/p LITT
KPS 100%

(27 weeks gestation)
Jan 2016







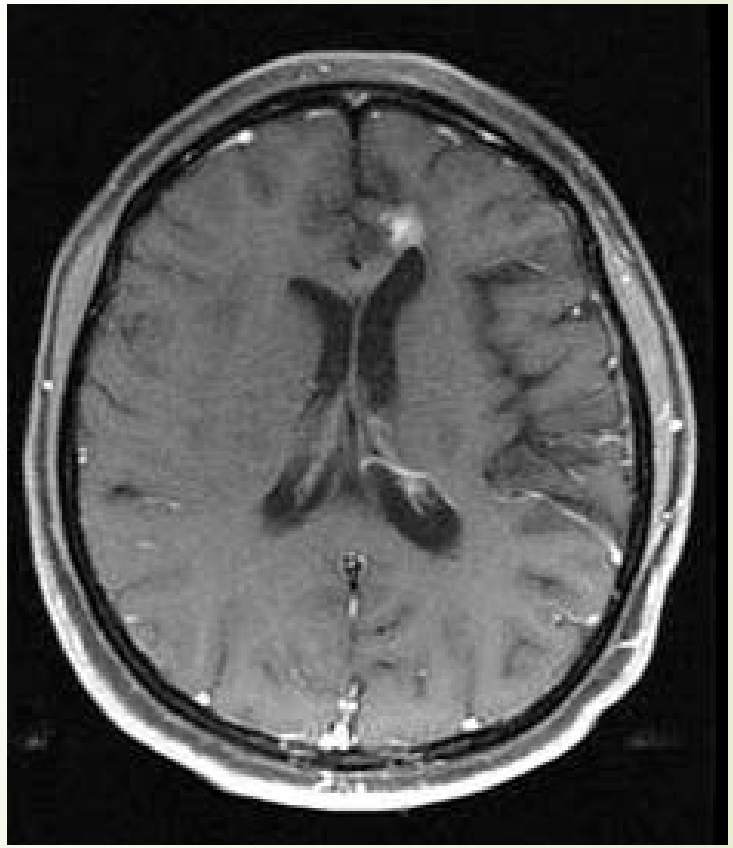
Case 2

- March 2016 - Delivery of healthy baby girl
- April 2016 – Restarted TMZ therapy
- Jan 2017 – Completed 12 cycles of TMZ

CONCLUSION CASE 2

43 months after initial diagnosis of GBM

Imaging, patient, and baby girl remain stable



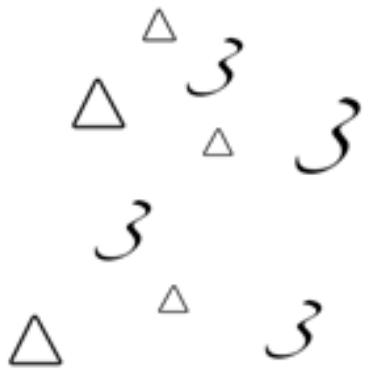
How?

What's Happening During Pregnancy in Our Glioma Patients?

Hormones & Growth Factors

Promote Tumor Signaling Cascades

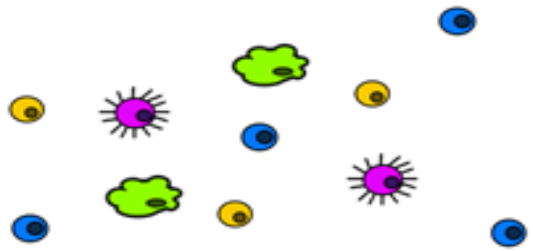
[Pietras 2007]



Pregnancy Serum Factors

Exosomes: Induce T-cell anergy and/or tolerance. [Gatson 2012]

Th2 cytokines; Tregs



Fetal Cell Microchimerism

Emigrate to engraft and differentiate in inflamed tissues [Nguyen 2009, Khosrotehrani 2009]

Bidirectional Microchimerism: Fetal-Maternal > Maternal-Fetal

Multiple Cell Phenotypes

Engraft in multiple tissues including bone marrow.

- Trophoblasts
- **Lymphocytes**
- Erythroblasts
- Hematopoietic Progenitors
- **Mesenchymal Progenitors**

Persist in Maternal Host

Gestational **Day 10-12**

≥51 yrs post partum

- **Y chromosome**

Positive Nulliparous women?

- Miscarriage
- Maternal-Fetal
- Fetofetal transfer
- Exposure to sperm

Immune Modulatory

- Local Immune Tolerance
- Transplant Immunology
- Autoimmunity
- Persist in brain longer in preclinical models

[Dawe 2007]

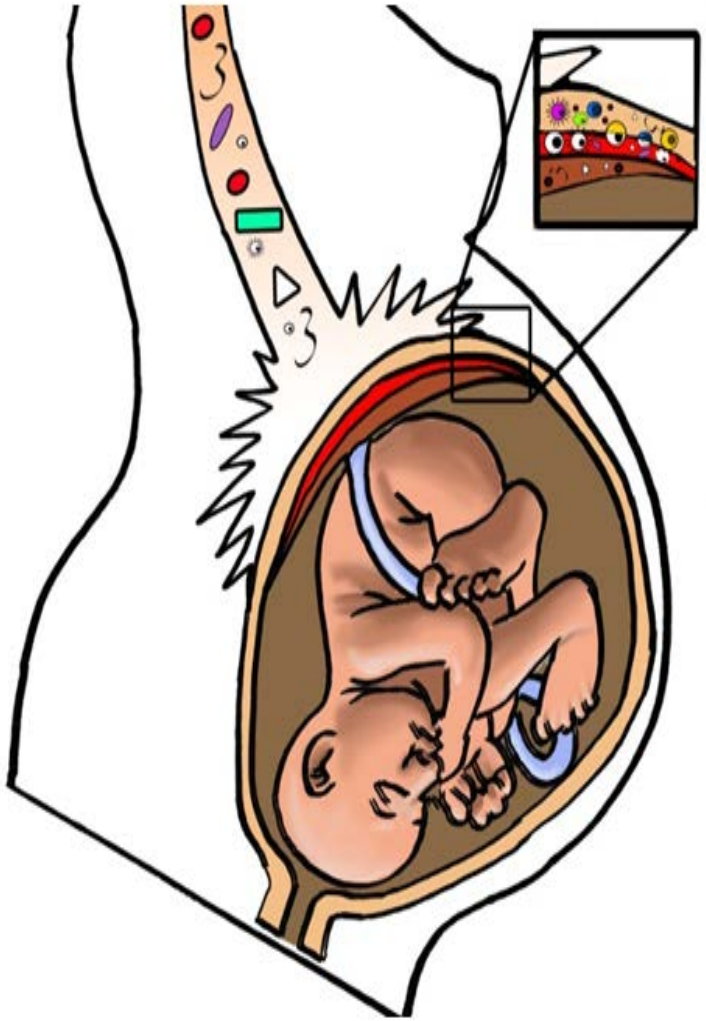
Maternal Host and Fetal Microenvironments

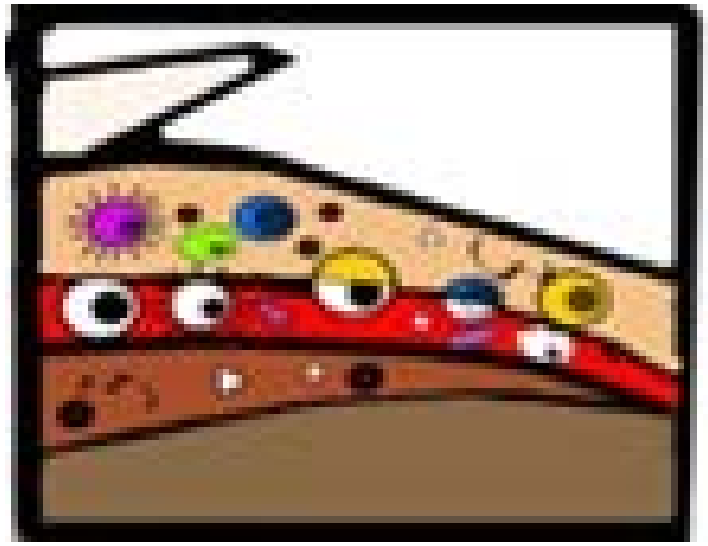
Maternal Host

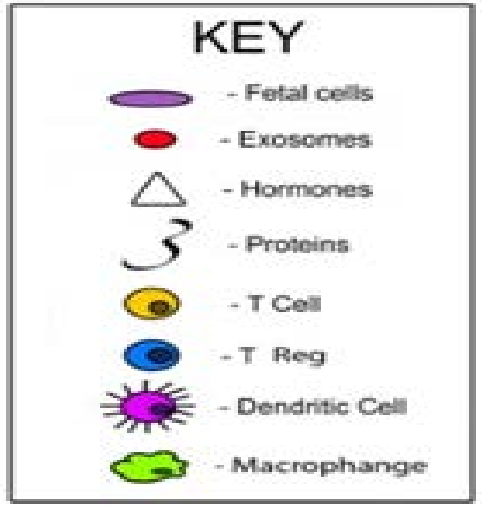
- Immunosuppressed host
- Hypercoagulable state
- Metabolic/Endocrine
- Fetal microchimerism (FMc)

Fetal Microenvironment

- Immune Suppression: *Placentation*
- Hofbauer & Periph Mø
- Maternal Microchimerism (MMc)







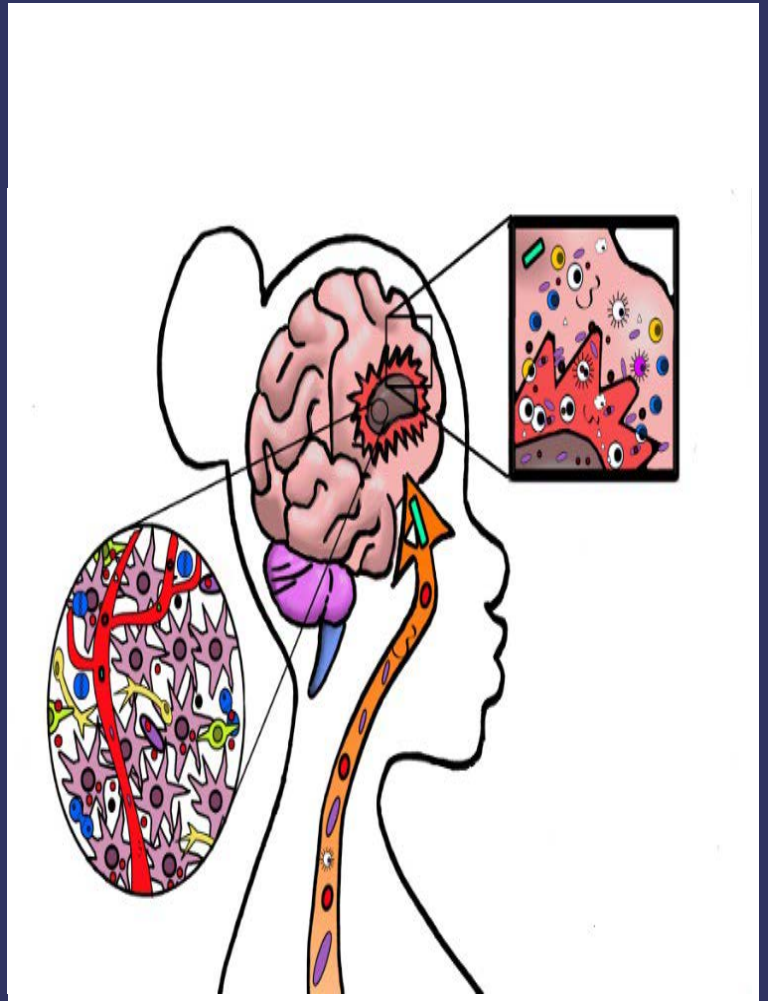
Human Host and Tumor Microenvironments

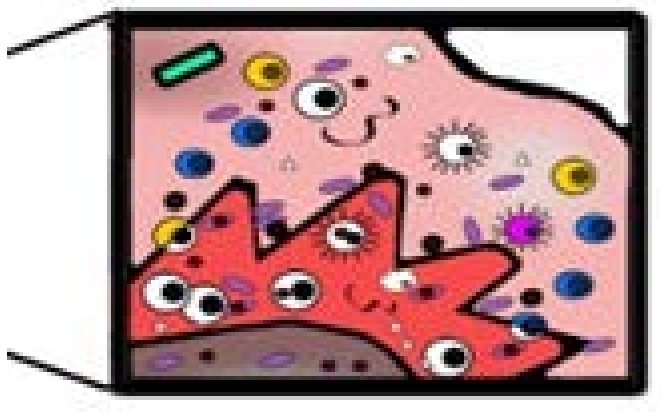
Tumor Host

- Immunosuppressed host
- Hypercoagulable state
- Metabolic/Endocrine
- Circulating glioma cells

Tumor Microenvironment

- Immune Suppression: *Gliomagenesis*
- Microglia & Periph Mø
- Circulating Glioma cells





Pregnancy & Glioma Reviews

Zwinkels *et al.* (2013) Netherlands

Literature review n = 103

Preg → Glioma (73% n=75)

- HGG (56% n=42)

Glioma → Preg (27% n=28)

- LGG (71% n=20)

Overall:

51% progressed **3rd trimester**

50% focal deficits

24% seizure

Yust-Katz *et al.* (2014) MDACC

Retrospective review n=38

Preg → Glioma (40% n=15)

- HGG (60% n=9)

Glioma → Preg (60% n=23)

- LGG (61% n=14)
- WHO grade III (39% n=9)

Overall: (Glioma → Preg)

78% progressed **late or peri-partum**

NR deficits

Stone *et al.* (2015) MSKCC

Retrospective review n= 73

Preg → Glioma (41% n=30)

- 50% presented 3rd trimester

Glioma → Preg (59% n=43)

Prior stable - 32% progressed **during pregnancy**

85% seizure

45% headache

What's Happening During Pregnancy in Our Glioma Patients?

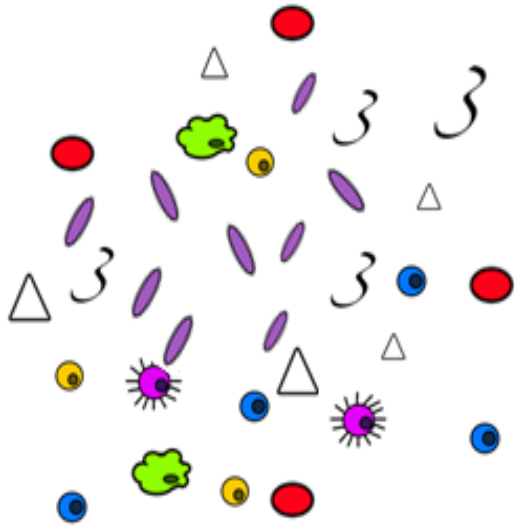
Maybe it's NOT just the **SEED**

Maybe it's NOT just the **SOIL**

But Also

The Rain & Sunshine

MICROENVIRONMENT



Do we discuss fertility preservation/prevention?

How do we minimize toxicity to patients and promote pregnancy maintenance?

Need to develop more multidisciplinary research that aids in our understanding of the tumor microenvironment.

Pioneering Association: Glioblastoma*genesis* and Fetal development

Unique Immune Challenge: Specialized Immune Compartment is a distinguishing feature to better consider when evaluating response to immune-based therapies

Pregnancy is an Age-old Problem:

- 50-60% Unintended/Unplanned

Demonstrated need for Clinical Guidelines: Prospective Clinical Case Studies

Pregnancy and Glioma registry

Multidisciplinary Clinical/Research Teams: Neuro-Onc, MFM/OB, Neurosurg, Rad/RadOnc, Neuropsych, Neuropath

"Necessity is the Parent of Industry"
--Rev J. Rankin (1833)

Identification of biomarkers for early intervention

Development of immunomodulatory treatment approaches

- Spontaneous abortion
- Peri-partum changes

Grant Development Potential

Paradigm-shifting approaches to treatment of brain tumors

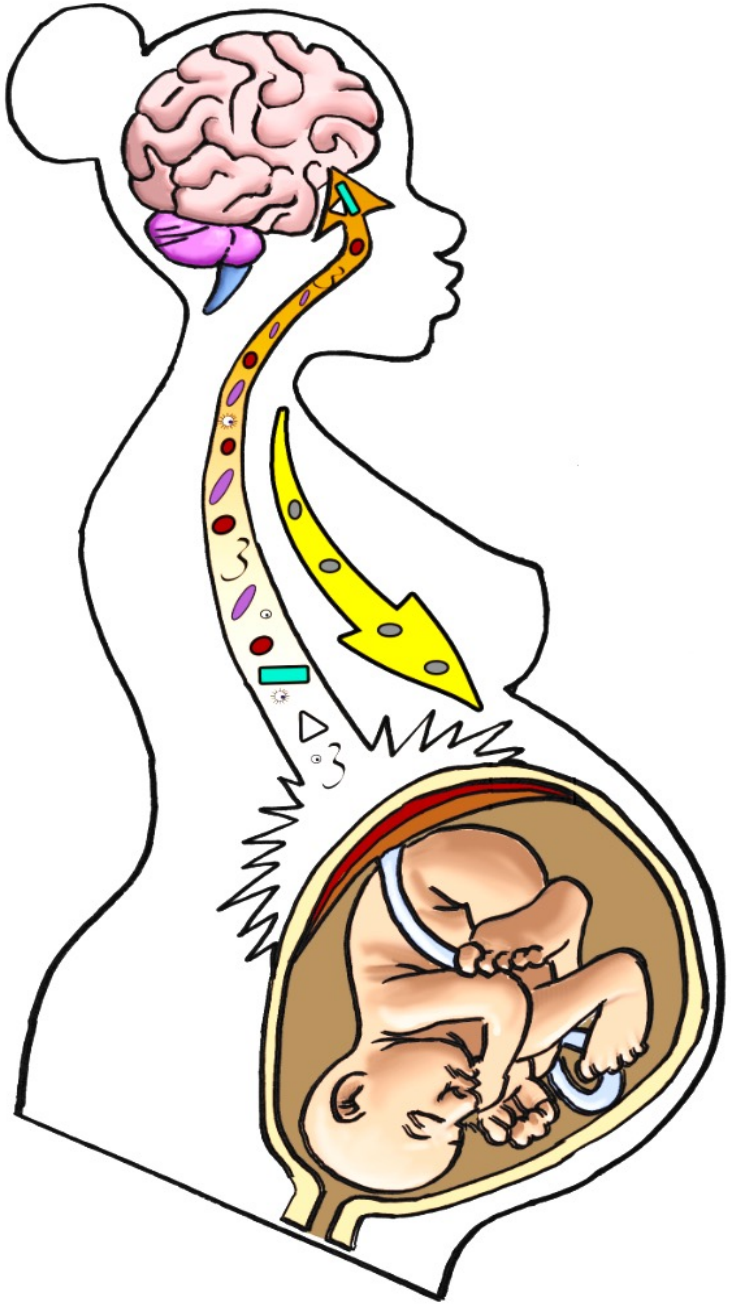
Other Neurology Issues in N.O.W.

Stroke: Pregnancy and Cancer are both hypercoagulable states – more important to consider smoking, use of OCPs, and constantly screen for DVT/PE in these patients.

Seizure: Both primary brain tumor and brain tumor metastases can increase risk for seizures. Patients should understand risks on and off therapy to mother and fetus. Increased vigilance in peri-partum period.

Immunosuppression: Cancer immunosuppressive therapies might increase risk for infection and complicate pregnancy maintenance. Early discussions about pregnancy planning and best selection of therapies conducive to pregnancy is encouraged.

Side-effect considerations on cancer therapies: Determining the overall risk to fetus in patient on chemotherapy has been challenged for obvious reasons. However, many therapies, such as **OPTUNE TTF have never been tested in pregnancy but have categorically made this FDA approved Class 1A Recommendation – contraindicated for use in pregnant women.**



https://oncofertility.northwestern.edu/annual-oncofertility-consortium-conference

Sponsorship opportunities are still available; contact us at oncofertility@northwestern.edu for more information.

This year the Oncofertility Consortium is able to provide *AMA PRA Category 1 Credit™* for the conference.

Northwestern Medicine®
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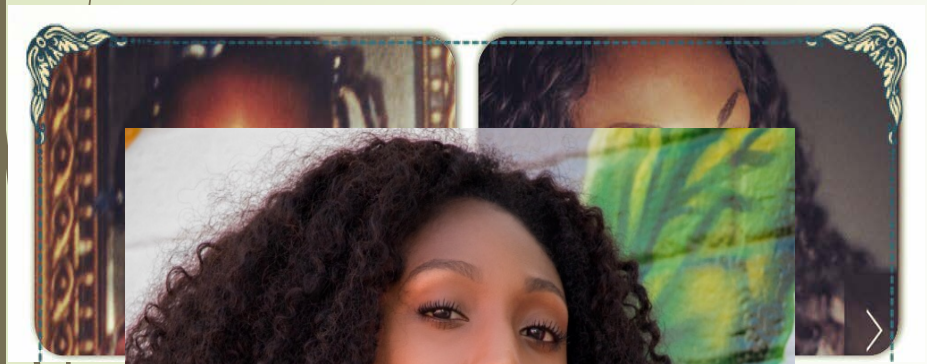
Learning Objectives:

1. Describe the basic science advances in fertility preservation and restoration and global outcomes of pregnancy after cancer
2. Identify ethical considerations for fertility preservation in expanded patient populations such as pediatric and gender and sex diverse patients
3. Recognize alternative communication strategies for discussion fertility treatment

Target Audience:

Healthcare professionals who treat adolescent and young adult patients with cancer and AYA cancer survivors
Research Scientists research ways to mitigate fertility threats to AYA cancer patients

MY CHIMERIC SITUATION



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