WHAT TO EXPECT: PREGNANCY AND THE EYE

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FINANCIAL DISCLOSURES

- Speaker-Carl Zeiss Meditec, Bausch and Lomb, Oyster Point Pharma, Thea Pharma, Alcon, Allergan, Astellas
- Advisory Board-Bausch and Lomb, Carl Zeiss Meditec, Santen, Peripherex, Ocuphire, Ocuterra, Oyster Point Pharma, Allergan, Astellas, Radius XR
- Shareholder-Clearside Biomedical (<0.01% ownership)
- *All relevant relationships have been mitigated*

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OBJECTIVES

1) Evaluate the risks and benefits of prescribing pharmaceutical products in pregnant and breastfeeding individuals
2) Review how pharmaceutical products are evaluated by the FDA in pregnant and breastfeeding individuals
3) Examine commonly prescribed categories of medications used to treat ocular disease and their role in the management of pregnant and breastfeeding individuals

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#1

HOW DO YOU ASK A PATIENT IF THEY ARE PREGNANT?

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IDENTIFYING THE "AT-RISK" PATIENT

- Clues…
  - Of "child-bearing age"
    - 12ish to 51ish
  - Supplementation
- Is pregnancy a medical condition?

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Spoiler Alert

Most teratogenic birth defects are due to alcohol, illicit drugs or ineffective teratogens

Severe birth defects are commonly due to genetic and chromosomal abnormalities

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Spoiler Alert

…Not FDA approved medications

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Background Risk

Every pregnancy begins with a 3-5% risk of a birth defect

and

10-20% risk of miscarriage

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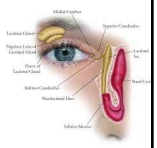
How may topical ocular medications cause systemic effects?



Absorbed via nasal mucosa and nasopharynx

Excess on eyelids and cheeks absorbed through skin

Bypass first pass metabolism

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CONSIDERATIONS DURING PREGNANCY

- Systemic absorption of topically-applied ophthalmic medications is very low
  - How can we decrease it further?
- Pregnant individuals are "complex"…
  - Maternal and fetal well-being

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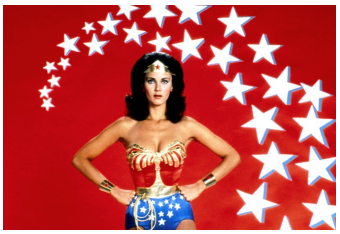

Management of chronic and acute disease states are still needed

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WHAT WE KNOW

- Taking medications during pregnancy is **common**
- About 2/3 of individuals take one or more prescription medication during pregnancy
- Estimated that 50% of pregnancies are unplanned
- Most medications are not well-studied in pregnant people
  - More than 90% of medications FDA approved between 1980 and 2000 had ***insufficient*** data to determine safety during pregnancy

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Every decision you make as a doctor involves a risk: benefit (internal or external) discussion

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Physiological changes

Primarily due to increased levels of estrogen and progesterone

Increased plasma volume
Physiological anemia
Increased cardiac output
Increased oxygen consumption
Physiologic hyperglycemia
Increased insulin resistance
Increased glomerular filtration rate
Slower gastric emptying
Slower bowel transit time

Results in alteration of pharmacokinetics and pharmacodynamics = changes to safety and efficacy

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HOW ARE MEDICATIONS STUDIED IN PREGNANCY?

- Risks and benefits of a drug to both the person and fetus
- Typically, labeling information is based on nonclinical data
  - Often with limited human safety data
- Lack of information makes us (doctor and patient) reluctant to treat the underlying condition
  - *Is that better?*

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HOW ARE MEDICATIONS STUDIED IN PREGNANCY?

- Typically-data is collected in the post-marketing setting, using data from observational studies such as pregnancy exposure registries
  - Cohort studies
  - Case control studies
  - Surveillance methods
- Historically-barriers were put in place in clinical trials to protect pregnant people

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ETHICAL CONSIDERATIONS

- Not just a flip of the switch!
- Complex risk-benefit assessments that vary based on the seriousness of the disease
  - Availability of other treatments
  - Trial design
  - Liability-a legitimate concern
- Whether the investigation will occur in the pre-marketing or post-marketing setting

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Considerations for inclusion of pregnant people in clinical trials?

Responsibility is shifted to people in real life

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ASSESSING **YOUR** PATIENTS

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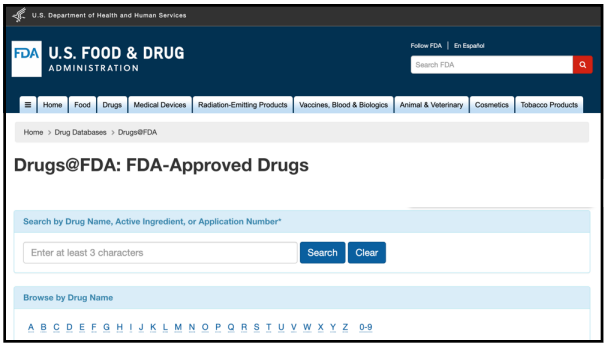

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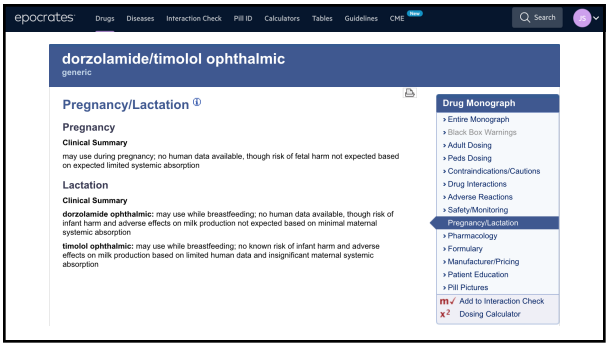

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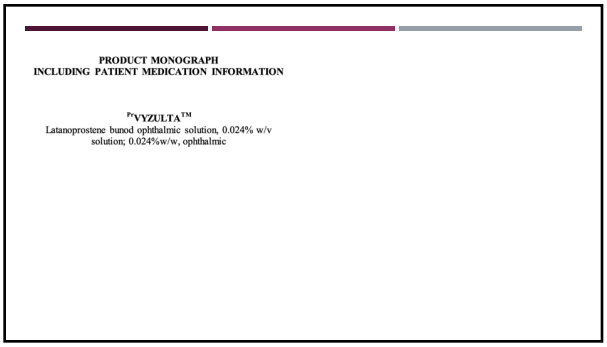

PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

PrVYZULTA™
Latanoprostene bunod ophthalmic solution, 0.024% w/v
solution; 0.024%w/w, ophthalmic

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Special Populations

Pregnant Women
There are no available human data for the use of VYZULTA™ during pregnancy to inform any drug associated risks. However, animal studies indicate that latanoprost acid, the active metabolite of VYZULTA™ readily cross placenta. Therefore, VYZULTA™ should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Latanoprostene bunod was shown to be abortifacient and teratogenic when administered intravenously (IV) to pregnant rabbits at exposures ≥ 0.28 times the clinical dose. No margins of safety were established in the rabbit embryo-fetal development (EFD) study and at a dose level of 0.24 mcg/kg/day the margins of safety were < 1- time the human clinical dose, based on body surface area (BSA). Doses ≥ 20 mcg/kg/day (23 times the clinical dose) produced 100% embryofetal lethality. Structural abnormalities observed in rabbit fetuses included anomalies of the great vessels and aortic arch vessels, domed head, sternebral and vertebral skeletal anomalies, limb hyperextension and malrotation, abdominal distension and edema. Latanoprostene bunod was not teratogenic in the rat when administered IV at 150 mcg/kg/day (87 times the clinical dose). Latanoprostene bunod induced miscarriage and was teratogenic in rats at a dose levels of ≥ 300 mcg/kg/day (> 174 times the clinical dose). The background risk of major birth defects and miscarriage for the indicated population is unknown.

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CASE 1

- 30 year old female presents for comprehensive eye examination due to blurred distance vision with her current glasses and contact lenses
  - Established patient; BCVA 20/20 OD and OS; anterior segment unremarkable. Last DFE 13 months ago-pristine.
- **Now what?**

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CASE 1B

- 30 year old female presents for comprehensive eye examination due to blurred distance vision with her current glasses and contact lenses
  - Established patient; BCVA 20/50 OD and 20/20 OS; anterior segment unremarkable. Last DFE 13 months ago-pristine.
- **Now what?**

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CASE 1C

- 30 year old female presents for an urgent eye examination due to new onset floaters in her right eye
  - Established patient; BCVA 20/20 OD and 20/20 OS; anterior segment unremarkable. Last DFE 13 months ago-lattice degeneration OD and OS;
- **Now what?**

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THE DILATION DILEMMA (IS THERE ONE?)

- Occasional dilation is acceptable-and necessary in certain clinical situations
- What we know:
  - **Systemic** atropine, epinephrine, homatropine, and phenylephrine in the first trimester have been associated with non-life threatening fetal effects
    - Hypoxia, bradycardia
- Tropicamide and cyclopentolates are considered "safer"
  - Avoid atropine, scopolamine, and homatropine when you can due to the long-duration of action (long half life)

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What about a pregnant patient with diabetes mellitus?

Gestational diabetes is <u>not</u> associated with an increased risk of diabetic retinopathy during pregnancy

But diabetic retinopathy often worsens during pregnancy

Anti-VEGF medications will be avoided

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TOPICAL ANESTHESIA?

- Proparacaine & tetracaine
  - **<u>"May use during pregnancy: no human data available, though risk of fetal harm not expected based on expected limited systemic absorption"</u>**
    - *This is typical…and expected…no good quality data that it is unsafe…but also no solid data to show that it is safe*

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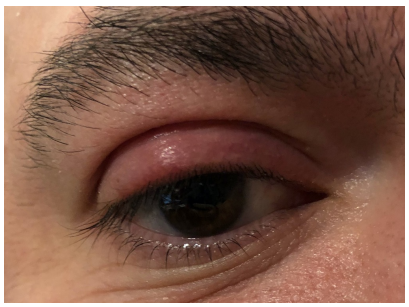

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ORAL ANTIBIOTICS

- Cephalexin, amoxicillin-clavulanic acid, erythromycin, azithromycin
  - Broad spectrum coverage
- *Avoid tetracyclines and fluoroquinolones in pregnant and lactating patients*

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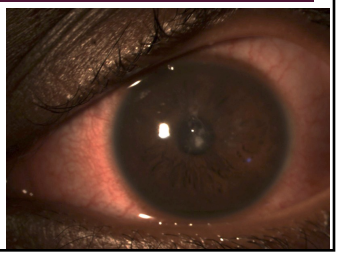
TOPICAL OPHTHALMIC ANTIBIOTICS

- Classically: Tobramycin, erythromycin, polymyxin B, Polytrim, azithromycin
- Topical fluoroquinolones
  - Risk/benefit



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PAIN MANAGEMENT

- Acetaminophen-acceptable for short term use (or is it?!). Used by up to 65% of individuals during pregnancy
  - *There is actual human data!*
- **No aspirin (full strength) or NSAIDs**
- Acetaminophen with codeine are routinely used by obstetrician for short-term pain relief

Pregnancy/Lactation ⓘ

Pregnancy

Clinical Summary

drug of choice for analgesic and antipyretic use during pregnancy; no known risk of fetal harm w/ short-term use based on human data w/ PO form

Lactation

Clinical Summary

drug of choice for analgesic and antipyretic use while breastfeeding; no known risk of infant harm based on human data w/ PO form; no human data available to assess effects on milk production

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Paracetamol use during pregnancy — a call for precautionary action

CONSENSUS STATEMENT

Ann Z. Bauer[1], Shanna H. Swan[2], David Kriebel[3], Zeyan Liew[4], Hugh S. Taylor[4], Carl-Gustaf Bornehag[2,5], Anderson M. Andrade[6], Jørn Olsen[7], Rigmor H. Jensen[8], Rod T. Mitchell[9], Niels E. Skakkebaek[10], Bernard Jégou[11,12] and David M. Kristensen[11,12]✉

NATURE REVIEWS | ENDOCRINOLOGY VOLUME 17 | DECEMBER 2021 | 757

pregnant women should be cautioned at the beginning of pregnancy to: forego APAP unless its use is medically indicated; consult with a physician or pharmacist if they are uncertain whether use is indicated and before using on a long-term basis; and minimize exposure by using the lowest effective dose for the shortest possible time. We suggest specific actions to implement these recommendations. This Consensus Statement reflects our concerns and is currently supported by 91 scientists, clinicians and public health professionals from across the globe.

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DRY EYE DISEASE

- Dry eye patients often experience a worsening of their ocular surface disease during pregnancy
  - Morning sickness, anti-nausea medication
- May lead to contact lens intolerance

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MANAGEMENT OF INFLAMMATION

Pregnant Women:
Lotemax® Gel should not be used in pregnant women, unless the potential benefit to the mother clearly outweighs the risks to the embryo or foetus. Studies in pregnant women have not been conducted. However, studies in animals have shown major reproductive and developmental toxicity when administered orally at approximately40 times the Lotemax® Gel clinical dose. At lower doses (approximately 4 times the Lotemax® Gel clinical dose), maternal toxicity was demonstrated and, although there were no major teratogenic effects, growth retardation and a possible increase in the occurrence of some abnormalities were noted. **See TOXICOLOGY – Developmental and Reproductive Toxicity**.

- Prednisolone acetate generally preferred
  - Risk associated with **oral** prednisone = increased risk of pre-term delivery and low birth weight

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GLAUCOMA THERAPY DURING PREGNANCY

- Approximately 0.5% of women of childbearing age have glaucoma
- IOP naturally decreases during pregnancy-this may be clinically significant (in individuals without glaucoma)
  - Maybe because of increased uveoscleral outflow, decreased episcleral venous pressure, change in corneal biomechanics
    - Estrogen leads to production of nitric oxide
- Options:
  - Monitor without therapy, medications (punctal plugs?!), laser, (surgery?)
- If a pregnancy is being planned-may choose to have SLT or surgery performed early

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GLAUCOMA THERAPY DURING PREGNANCY

- Prostaglandin analogs *(ugh)*
  - Can theoretically increase uterine contractions (premature labor, miscarriage)
    - One human study: 10 women; 1 had a spontaneous abortion (46 year old female)
  - But-are very quickly metabolized and systemic absorption is minimal
    - 67-140x concentration of latanoprost (on label) for induction of abortion
  - *Latanoprostene bunod (Vyzulta) should **probably not** be used during pregnancy (0.28x clinical dose-animal model)*

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Latanoprost Exposure in Pregnancy

Marco De Santis, MD, Angela Lucchese, MD, Brigida Carducci, MD, Anna F. Cavaliere, MD, Lidia De Santis, MD, Annamaria Merola, MD, Gianluca Straface, MD, and Alessandro Caruso, MD

RESULTS: Eleven cases of latanoprost exposure in pregnancy were referred to our Teratology Information Service. One case was lost to follow-up, and one case was complicated by miscarriage. Nine cases had a complete follow-up without congenital anomalies.
CONCLUSIONS: Our series is too small to perform statistical significance; however, we found no evidence of adverse effects of latanoprost on pregnancy or neonatal outcomes. (Am J Ophthalmol 2004;138:305–306.

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Drugs - Real World Outcomes (2022) 9:43–51
https://doi.org/10.1007/s40801-021-00287-y

ORIGINAL RESEARCH ARTICLE

Pregnancy Loss Signal from Prostaglandin Eye Drop Use in Pregnancy: A Disproportionality Analysis Using Japanese and US Spontaneous Reporting Databases

Takamasa Sakai[1] · Chiyo Mori[1] · Honoka Koshiba[1] · Ryuta Yuminaga[1] · Kouichi Tanabe[1] · Fumiko Ohtsu[1]

FAERS: 1997-2018

64 cases of pregnancy loss in individuals using a PGA

Pregnancy loss 15% in *all* reports (not those on PGAs)

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Intraocular pressure–lowering medications during pregnancy and risk of neonatal adverse outcomes: a propensity score analysis using a large database

Yohei Hashimoto ,[1,2] Nobuaki Michihata,[3] Hayato Yamana,[3] Daisuke Shigemi,[2] Kojiro Morita,[2,4] Hiroki Matsui,[2] Hideo Yasunaga,[2] Makoto Aihara[1]

To cite: Hashimoto Y, Michihata N, Yamana H, *et al*. *Br J Ophthalmol* 2021;**105**:1390–1394.

Conclusions IOP-lowering medications during the first trimester were not significantly associated with increase in CA, PB or LBW.

Latanoprost
Timolol

Congenital abnormalities, preterm birth, low birth weight

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GLAUCOMA THERAPY DURING PREGNANCY

- Of all therapeutic agents, brimonidine *theoretically* seems to be safest
  - *Although it should **never** be used during lactation-or near delivery*
    - *Crosses the blood brain barrier and may result in CNS depression*

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GLAUCOMA THERAPY DURING PREGNANCY

- Beta blockers and carbonic anhydrase inhibitors
- Caution with beta blockers while breastfeeding
  - Beta blockers can cross the placental barrier (fetal bradycardia and cardiac arrhythmia)
    - ***Timolol 0.5% QD is equivalent to less than 3% of an oral dose (20mg) of timolol***
- Carbonic anhydrase inhibitors-2nd and 3rd trimester
  - CAI human study: oral acetazolamide (12 women with pseudotumor cerebri)-no adverse effects
  - Have been approved by the American Academy of Pediatrics for use by breastfeeding mothers
    - Limb deformities in animal studies

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Medical IOP management in pregnancy

All prescribing considerations should be carefully discussed with the patient and managing providers

First trimester	Second trimester	Third trimester	Lactation
Brimonidine Beta-blocker PGA ***Caution with topical CAI*** ***No oral CAI***	Brimonidine PGA Beta-blocker CAI	Beta-blocker *CAI* ***Avoid brimonidine and PGA***	Beta-blocker *CAI* ***Avoid brimonidine and PGA***

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What about Latisse during pregnancy?

Relative risk vs. benefit?

Potential risks to the fetus do not outweigh the benefit to the patient

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THE MOST CHALLENGING PART OF PATIENT CARE IS THE PATIENT

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COUNSELING.

- Practice.

- *What are the most common conditions that you encounter?*
- *What's your script?*

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CASE 1C. AGAIN.

- 30 year old female presents for an urgent eye examination due to new onset floaters in her right eye
  - Established patient; BCVA 20/20 OD and 20/20 OS; anterior segment unremarkable. Last DFE 13 months ago-lattice degeneration OD and OS;
- **Now what?**
  - Do you need to check IOP?
  - How do you explain the risks and benefits—and necessity of dilation
    - **Don't sell yourself short.**

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Pregnant individuals need care too.

Always assess the risk of treatment with the potential benefit of treatment

Consider the clinical course of the disease and the risk of lack of treatment

Discuss in detail with the patient and obstetrician, pediatrician, other managing providers

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Pregnant individuals need care too.

The easy part is accessing the data

The difficult part is determining the need for treatment

The most difficult part is communicating that need to the patient

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Thank you

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