

OVARIAN HYPERSTIMULATION SYNDROME (OHSS)

Maria Giroux, HBSc, MD

Outline

1. Overview
2. Pathophysiology
3. Clinical Presentation
4. Investigations
5. Management
6. Prevention



Binarwan, H., Lubis, H., & Amalia, T. (2015, June 7). Durante operation, uterus with bilateral multiloculated ovary that shows sign of ovarian hyperstimulation syndrome [Digital image]. Retrieved from <https://www.sciencedirect.com/science/article/pii/S1110569016300450>

Sources

SOGC REAFFIRMED GUIDELINES

This guideline was peer reviewed by the SOGC's Reproductive Endocrinology and Infertility Committee in April 2017, and has been reaffirmed for continued use until further notice.

No. 268, Reaffirmed November 2017

No-268-The Diagnosis and Management of Ovarian Hyperstimulation Syndrome

This clinical practice guideline has been prepared by the Joint Society of Obstetricians and Gynaecologists of Canada-Canadian Fertility and Andrology Society Clinical Practice Guidelines Committee, reviewed by the Reproductive Endocrinology and Infertility Committee of the SOGC,* and approved by the Executive and Council of the Society of Obstetricians and Gynaecologists of Canada and the Board of the Canadian Fertility and Andrology Society.

Doron Shmorgun, MD, Ottawa, ON
Paul Claman, MD, Ottawa, ON

Disclosure statements have been received from all members of the committee.

***Joint SOGC-CFAS Clinical Practice Guidelines Committee:** Mathias Gysler, MD (Co-Chair), Mississauga, ON; Robert Hemmings, MD (Co-Chair), Montréal, QC; Anthony P. Cheung, MD, Vancouver, BC; Gwendolyn J. Goodrow, MD, Mississauga, ON; Edward G. Hughes, MD, Hamilton, ON; Jason K. Min, MD, Calgary, AB; Jeff Roberts, MD, Burnaby, BC; Vyta Senikas, MD, Ottawa, ON; Benjamin Chee-Man Wong, MD, Calgary, AB; David C. Young, MD, Halifax, NS.

Key Words: Ovarian stimulation, ovarian hyperstimulation syndrome, gonadotropin, human chorionic gonadotropin

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Women have the right and responsibility to make informed decisions about their care in partnership with their health care providers. In order to facilitate informed choice women should be provided with information and support that is evidence based, culturally appropriate and tailored to their needs. The values, beliefs and individual needs of each woman and her family should be sought and the final decision about the care and treatment options chosen by the woman should be respected.

NOVEMBER JOGC NOVEMBRE 2017 • e479

Shmorgun, D., Claman, P. (2017, November). No-268-The Diagnosis and Management of Ovarian Hyperstimulation Syndrome [Digital image]. Retrieved from <https://www.ncbi.nlm.nih.gov/pubmed/29080733>.

SOGC CLINICAL PRACTICE GUIDELINE

No. 315, November 2014

The Prevention of Ovarian Hyperstimulation Syndrome

This clinical practice guideline has been prepared by the Reproductive Endocrinology Infertility Committee and approved by Executive and Council of the Society of Obstetricians and Gynaecologists of Canada.

PRINCIPAL AUTHORS

Shannon Corbett, MD, Ottawa ON
Doron Shmorgun, MD, Ottawa ON
Paul Claman, MD, Ottawa ON

REPRODUCTIVE ENDOCRINOLOGY INFERTILITY COMMITTEE

Anthony Cheung, MD (Co-chair), Vancouver BC
Sony Sierra, MD (Co-chair), Toronto ON
Belina Carranza-Mamane, MD, Sherbrooke QC
Allison Case, MD, Saskatoon SK
Cathie Dwyer, RN, Toronto ON
James Graham, MD, Calgary AB
Jon Havelock, MD, Burnaby BC
Sarah Healey, MD, St. John's NL
Robert Hemmings, MD, Montreal QC
Kimberly Liu, MD, Toronto ON
Tarek Motan, MD, Edmonton AB
Ward Murdock, MD, Fredericton NB
David Smithson, MD, London ON
Tannys Vause, MD, Ottawa ON
Benjamin Wong, MD, Calgary AB

SPECIAL CONTRIBUTOR

Mathias Gysler, MD, Oakville ON

Disclosure statements have been received from all contributors.

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Corbett, S., Shmorgun, D., Claman, P., Cheung, A., Sierra, S., et al. (November 2014). The Prevention of Ovarian Hyperstimulation Syndrome [Digital image]. Retrieved from <https://sogc.org/wp-content/uploads/2014/11/gui315CPG1411E.pdf>.

Abstract

Objective: To review the clinical aspects of ovarian hyperstimulation syndrome and provide recommendations on its prevention.

Options: Preventative measures, early recognition, and prompt systematic supportive care will help avoid poor outcomes.

Outcomes: Establish guidelines to assist in the prevention of ovarian hyperstimulation syndrome, early recognition of the condition when it occurs, and provision of appropriate supportive measures in the correct setting.

Evidence: Published literature was retrieved through searches of Medline, Embase, and the Cochrane Library from 2011 to 2013 using appropriate controlled vocabulary (OHSS ovarian hyperstimulation syndrome and: agonist IVF, antagonist IVF, meffomin, HCG, gonadotropin, coasting, freeze all, agonist trigger, progesterone) and key words (ovarian hyperstimulation syndrome, ovarian stimulation, gonadotropin, human chorionic gonadotropin, prevention). Results were restricted to systematic reviews, randomized control trials/controlled clinical trials, and observational studies published in English. There were no date restrictions. Searches were updated on a regular basis and incorporated in the guideline to February 2013.

Grey (unpublished) literature was identified through searching the websites of health technology assessment and health technology-related agencies, clinical practice guideline collections, clinical trial registries, and national and international medical specialty societies.

Values: The quality of evidence in this document was rated using the criteria described in the Report of the Canadian Task Force on Preventive Health Care (Table 1).

Summary Statements

1. The particular follicle-stimulating hormone formulation used for ovarian stimulation does not affect the incidence of ovarian hyperstimulation syndrome. (I)
2. Coasting may reduce the incidence of severe ovarian hyperstimulation syndrome. (III)

Key Words: Ovarian hyperstimulation syndrome, ovarian stimulation, gonadotropin, human chorionic gonadotropin, prevention

CLINICAL GYNECOLOGIC ENDOCRINOLOGY AND INFERTILITY

Eighth Edition



MARC A. FRITZ and LEON SPEROFF

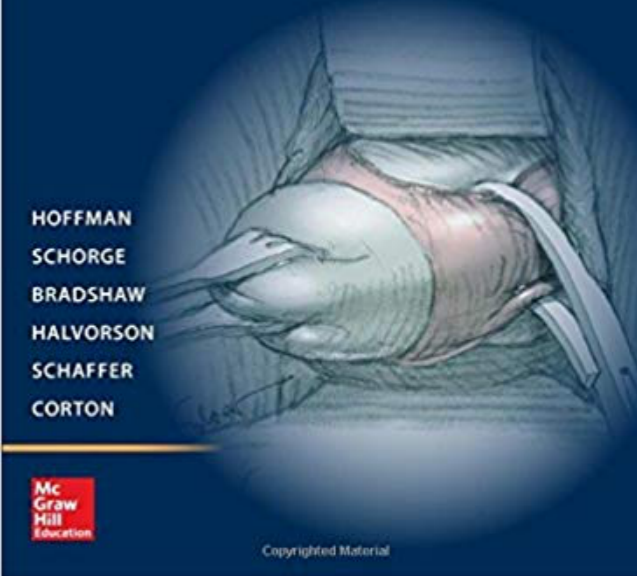
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THIRD EDITION

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Education

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Hoffman, B., Schorge, J., Bradshaw, K., Halvorson, L., Schaffer, J., & Corton, M. (2016, April 22). Williams's Gynecology [Digital image]. Retrieved from <https://www.amazon.ca/Williams-Gynecology-Third-Barbara-Hoffman/dp/0071849084>

Ovarian Hyperstimulation Syndrome

- Complication due to hyperstimulated ovaries

Causes

- Iatrogenic → complication of **supraphysiologic ovarian stimulation** used to mature several follicles
 - Associated with gonadotropin stimulation (FSH)
 - Incidence after gonadotropin superovulation for IVF
 - **Mild OHSS: 20-33%** → little clinical consequence
 - **Moderate OHSS: 3-6%**
 - **Severe OHSS: 0.1-2%**
- Rare with
 - Spontaneous ovulation, after LH surge
 - Clomiphene citrate
 - HCG

Risk Factors OHSS

- OHSS may occur in pts without risk factors
- Most high risk pts do not develop OHSS

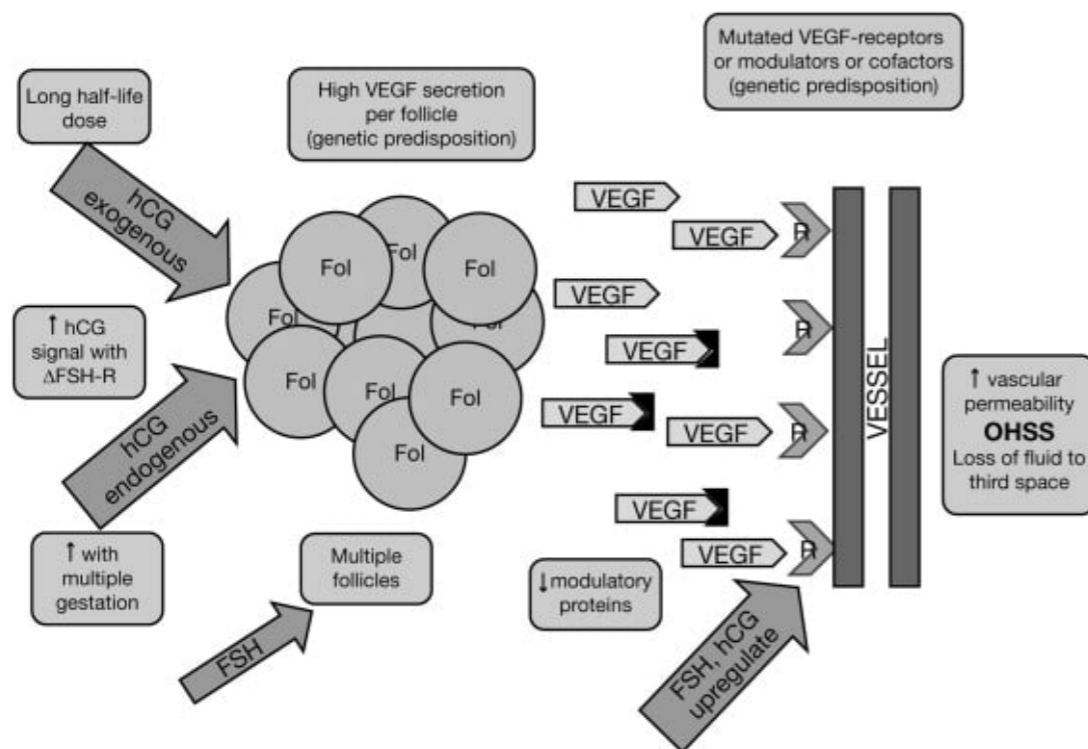
Risk factors:

- <30yo
- Gonadotropin ovarian stimulation (ex. FSH)
- Hx OHSS
- Early pregnancy
- PCOS or high basal antral follicle count on US (ex. >24 antral follicles)
- Large number of small follicles (8-12mm) on US during ovarian stimulation
- Large number of oocytes retrieved (>20)
- High serum estradiol at HCG trigger or rapidly increasing serum estradiol levels
- HCG instead of progesterone for luteal phase support after IVF
- High AMH (>3.36ng/mL)

Pathophysiology

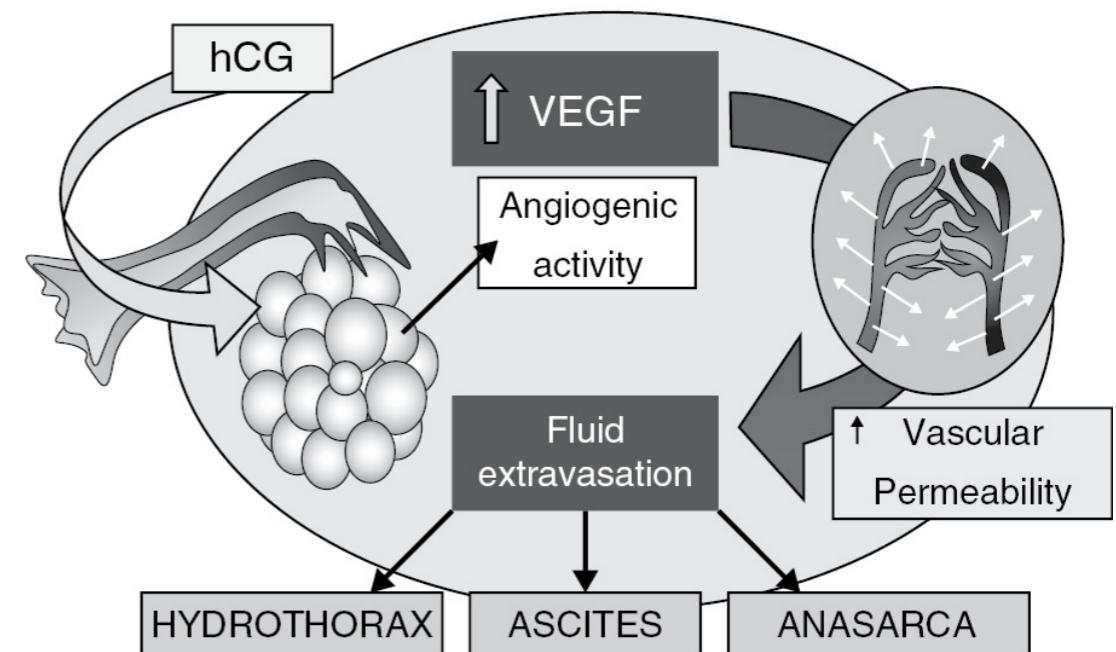
Severe OHSS:

- In order for OHSS to develop, need exposure to exogenous HCG or exogenous/endogenous LH
- HCG has indirect effect on vascular system
 - HCG → granulosa cells in hyperstimulated ovaries release vasoactive peptides (ex. **VEGF**) → **vasodilation** (↑ vascular permeability) → **3rd spacing** (shift of fluid, proteins, electrolytes into peritoneal and thoracic cavities) → hemoconcentration
- Vasodilation may also be due to vasoactive substances produced by corpus luteum



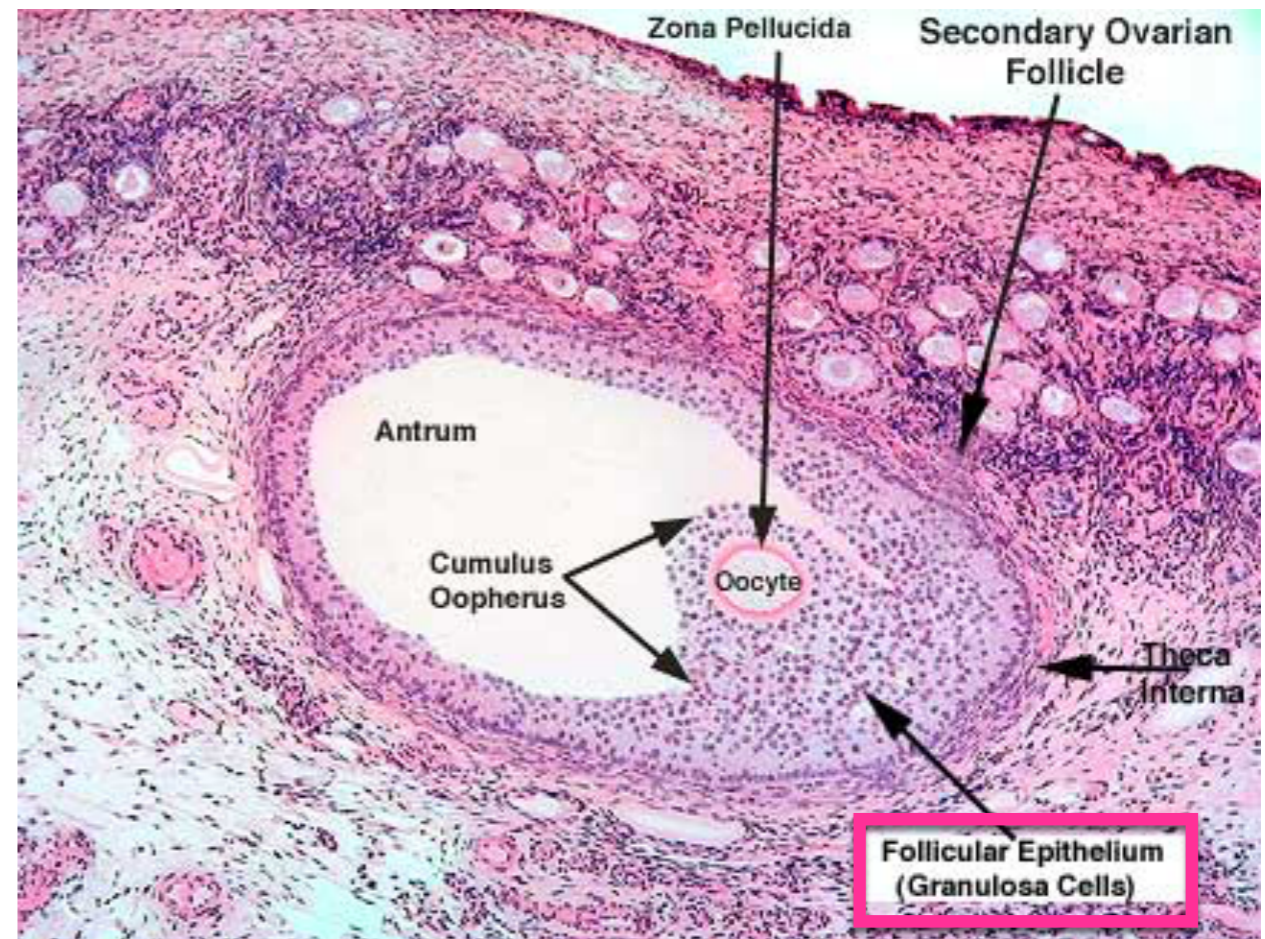
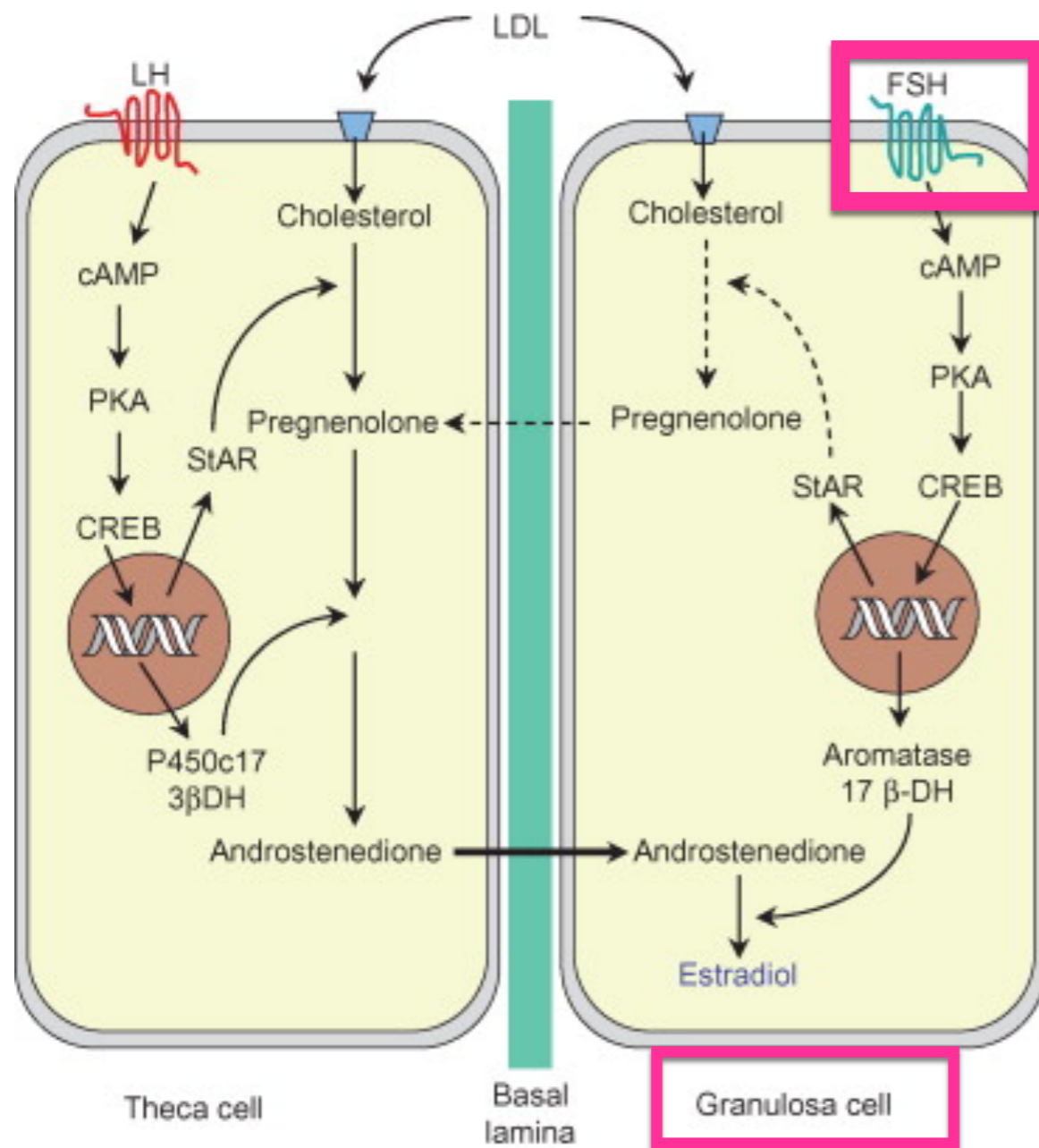
Singh, M. (n.d.). [Pathophysiology of OHSS]. Retrieved from <https://www.mireproductivemedicine.com/ovarian-hyperstimulation-syndrome/>

Pathophysiology:



Rizk, B. (2017, March). Classification and Pathophysiology of Ovarian Hyperstimulation Syndrome [Digital image]. Retrieved from <https://www.cambridge.org/core/books/complications-and-outcomes-of-assisted-reproduction/classification-and-pathophysiology-of-ovarian-hyperstimulation-syndrome/22BCB37B56CF00E38AA3FD1F55F17B71>

Pathophysiology



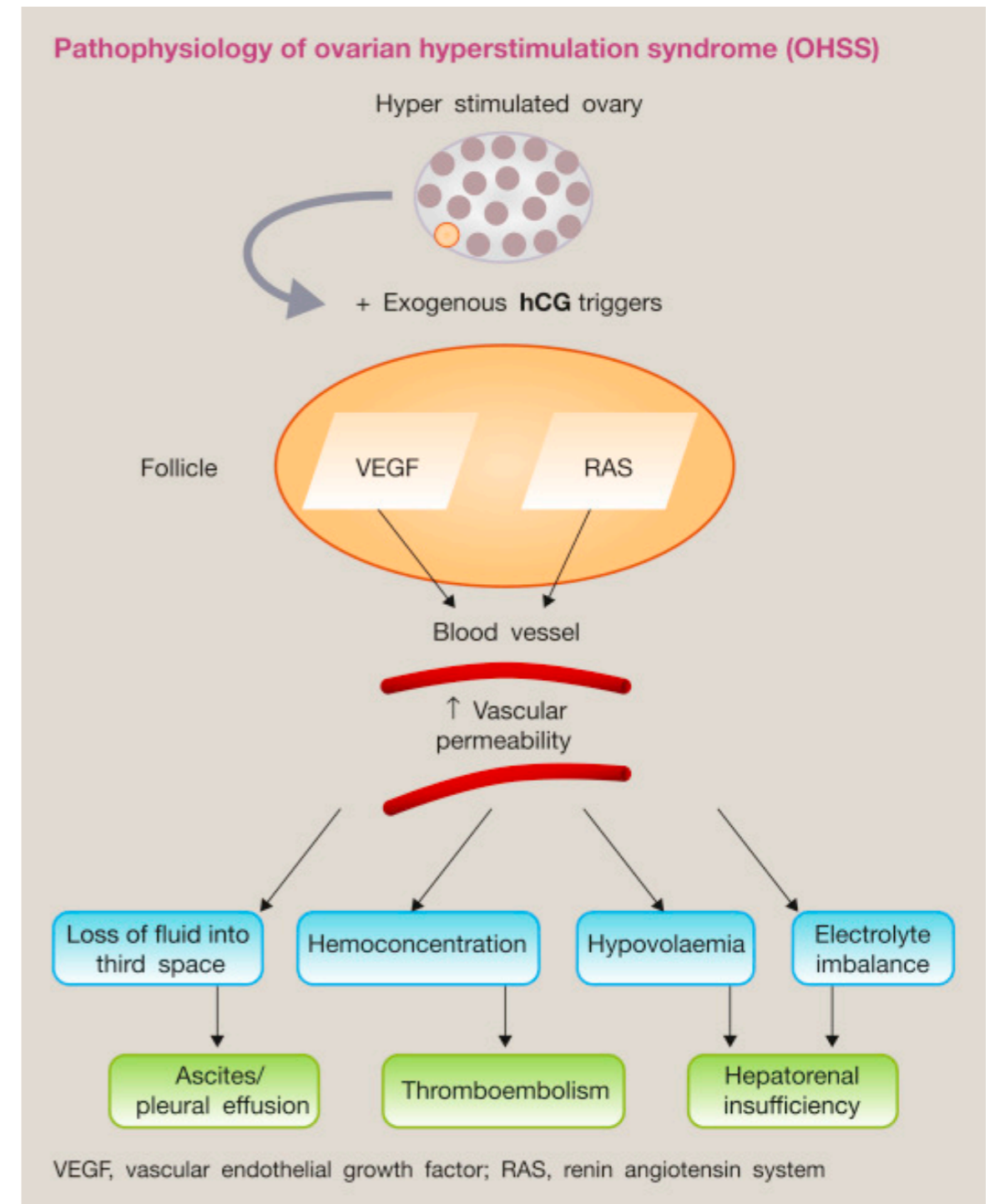
[Digital image]. (2017, August 11). Retrieved from <https://usmlemd.wordpress.com/2007/08/11/theca-and-granulosa-cells/>

Jhingran, A., & Thomas, G. (2010). Theca and granulosa cell cooperation in estrogen synthesis [Digital image]. Retrieved from <https://www.sciencedirect.com/topics/neuroscience/granulosa-cell>

Pathophysiology

Severe OHSS:

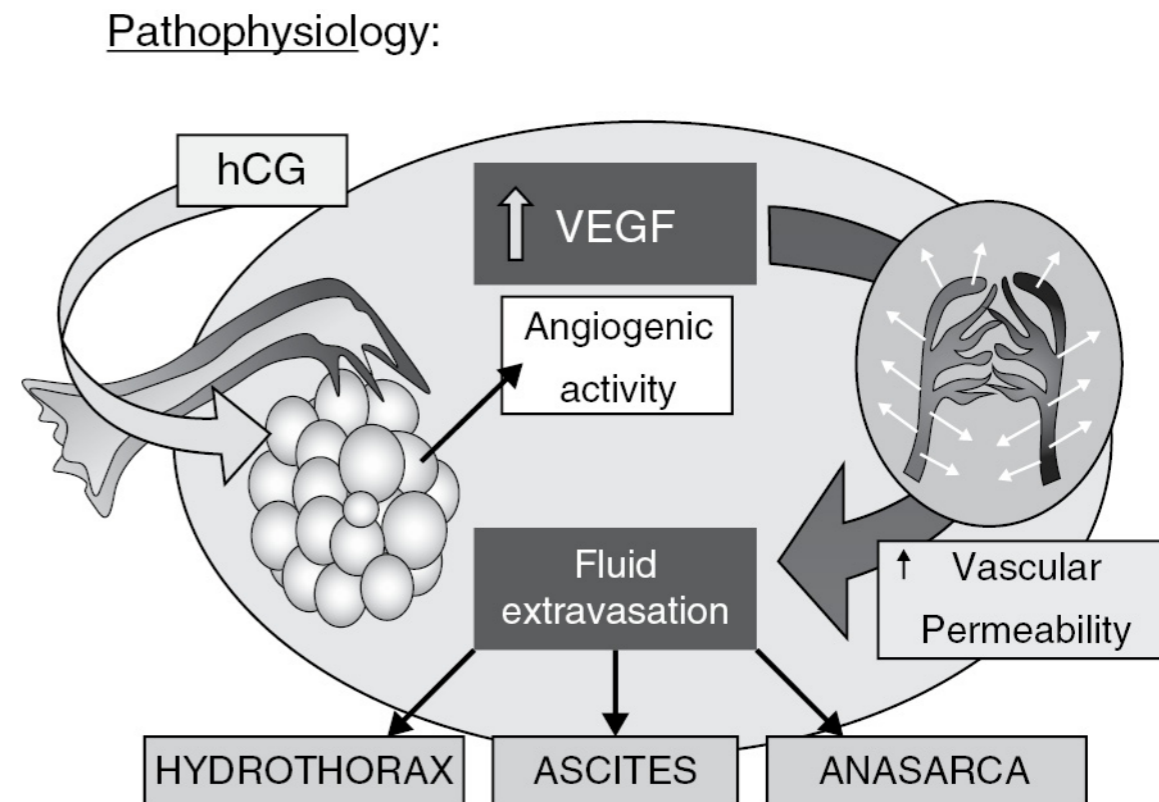
- Intravascular **fluid shifts** into extravascular compartments
 - Pleural effusion
 - Ascites
 - Pericardial effusion (rare)
 - Anasarca
 - Compartment syndrome
 - Increased intra-abdominal pressure → ↓ blood flow to kidneys → oliguria
- **Hypovolemia** (↓ intravascular volume) → dehydration → hemoconcentration → hypercoagulability
 - Renal failure → oliguria, anuria
 - Liver failure
 - Electrolyte imbalances
 - Thromboembolism (VTE)- due to hyperviscosity or increased estrogen



Balakumar, V., Ramalingam, M., & Kay, V. (2017, December). Ovarian hyperstimulation syndrome [Digital image]. Retrieved from <https://www.sciencedirect.com/science/article/pii/S1751721417302038>

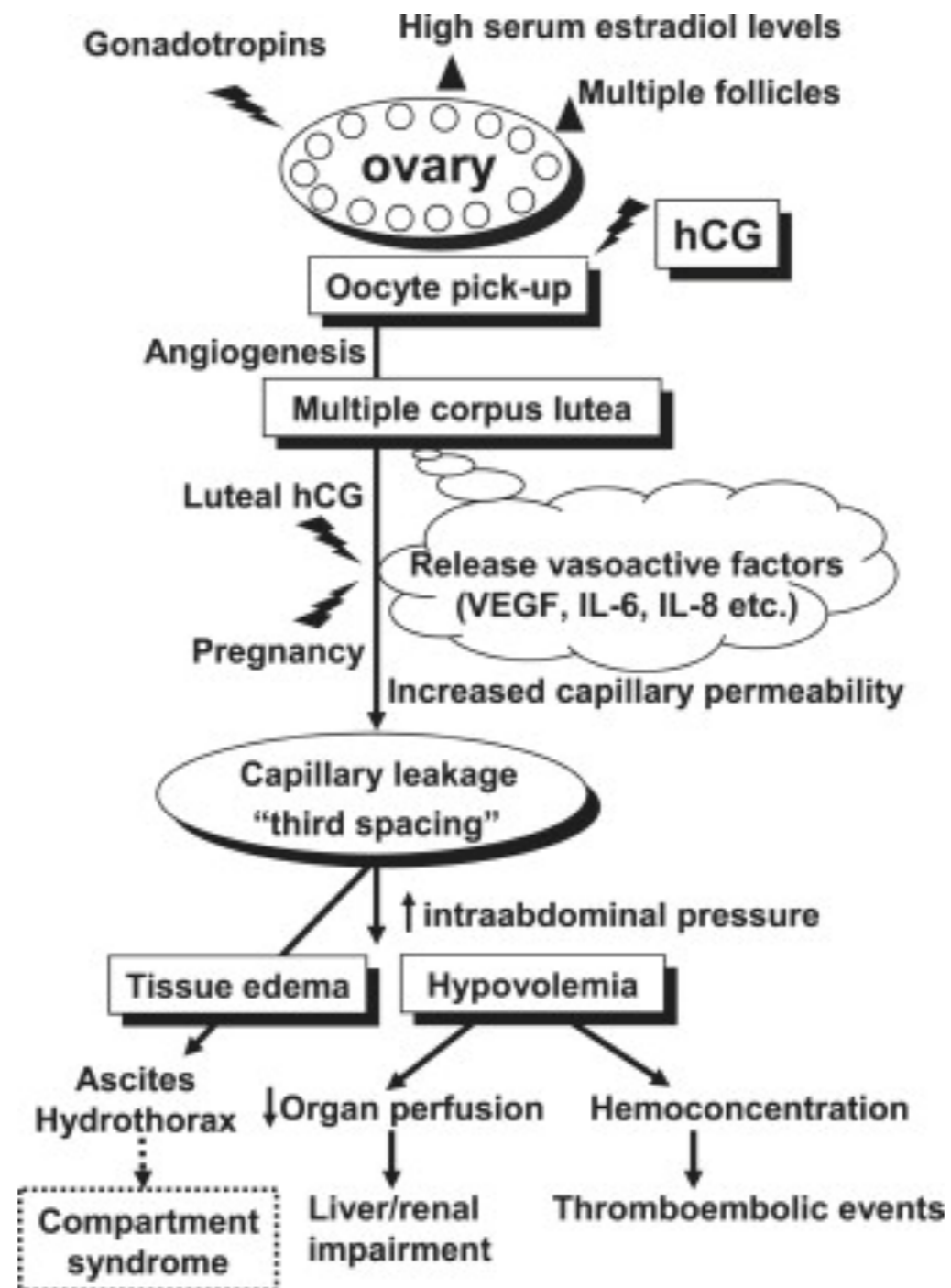
Pathophysiology

- **Most important mediator is VEGF** (vascular endothelial growth factor)
 - Involved in HCG-dependent ovarian angiogenesis and OHSS
 - HCG increases VEGF expression in granulosa cells
 - Serum VEGF levels correlate with severity of OHSS
- Other factors involved
 - IL6
 - Insulin-like growth factor 1
 - Angiotensin 2



Rizk, B. (2017, March). Classification and Pathophysiology of Ovarian Hyperstimulation Syndrome [Digital image]. Retrieved from <https://www.cambridge.org/core/books/complications-and-outcomes-of-assisted-reproduction/classification-and-pathophysiology-of-ovarian-hyperstimulation-syndrome/22BCB37B56CF00E38AA3FD1F55F17B71>

Pathophysiology

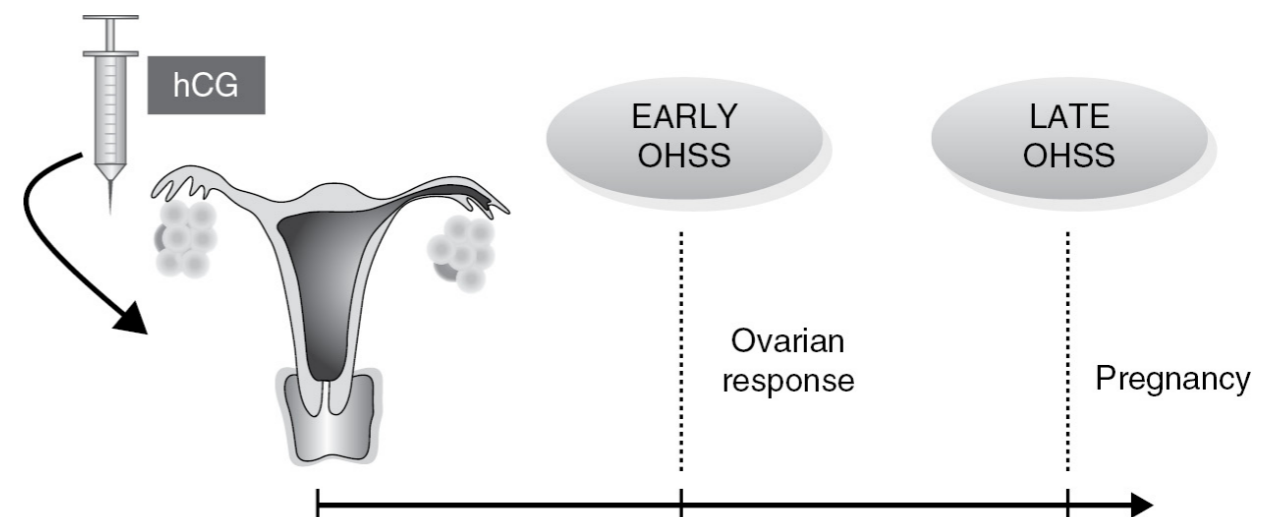


Chen, C., Wu, M., Chao, K., Lien, Y., Chen, S., & Yang, Y. (2011, March). Pathophysiology of ovarian hyperstimulation syndrome [Digital image]. Retrieved from <https://www.sciencedirect.com/science/article/pii/S1028455911000155>

Clinical Presentation

- May develop during ovulation induction, after ovulation, or in early pregnancy
 - Endogenous/exogenous LH surge
 - Then ovulation- either spontaneous or exogenous HCG administration
 - Can develop in early pregnancy due to endogenous HCG
- **Symptoms onset: 24hrs post-HCG**
- **Most severe: 7-10 days post-HCG**
 - Severe OHSS is usually due endogenous HCG from early pregnancy

Early onset	<ul style="list-style-type: none"> • ≤9 days of HCG administration • Milder, resolves in few days in pts who are not pregnant
Late onset	<ul style="list-style-type: none"> • >9 days of HCG administration • Can be very severe if pregnant → may need prolonged hospitalization



Rizk, B. (2017, March). Classification and Pathophysiology of Ovarian Hyperstimulation Syndrome [Digital image]. Retrieved from <https://www.cambridge.org/core/books/complications-and-outcomes-of-assisted-reproduction/classification-and-pathophysiology-of-ovarian-hyperstimulation-syndrome/22BCB37B56CF00E38AA3FD1F55F17B71>

CASE

- 30-year-old G0P0 female with 1yr Hx of primary unexplained infertility
- **Infertility workup:**
 - Normal: day-3 hormone profile, TSH, prolactin, sono-HSG, semen analysis
- **Infertility treatment:**
 - Jan-Mar: 3 letrozole/IUI cycles with antral follicle counts
 - Letrozole 2.5mg days 3-7
 - June: Decided to proceed with IVF with intracytoplasmic sperm injection (ICSI) and elective single embryo transfer (eSET)



Collection of Cartoon Woman Cliparts [Digital image]. (n.d.). Retrieved from <http://clipart-library.com/cartoon-woman-cliparts.html>

OB Hx: nullip

Gyne Hx: Last pap. No Hx STI. Menses regular, last 5 days, dysmenorrhea (uses acupuncture). No galactorrhea, no hot flushes. Previously used OCP and Depo-Provera.

PMHx: healthy

- Medical conditions: none
- Meds: folic acid 1mg PO daily
- Allergies: none
- Surgeries: none

Fx: none

Sx: works as an accountant. No SAD.

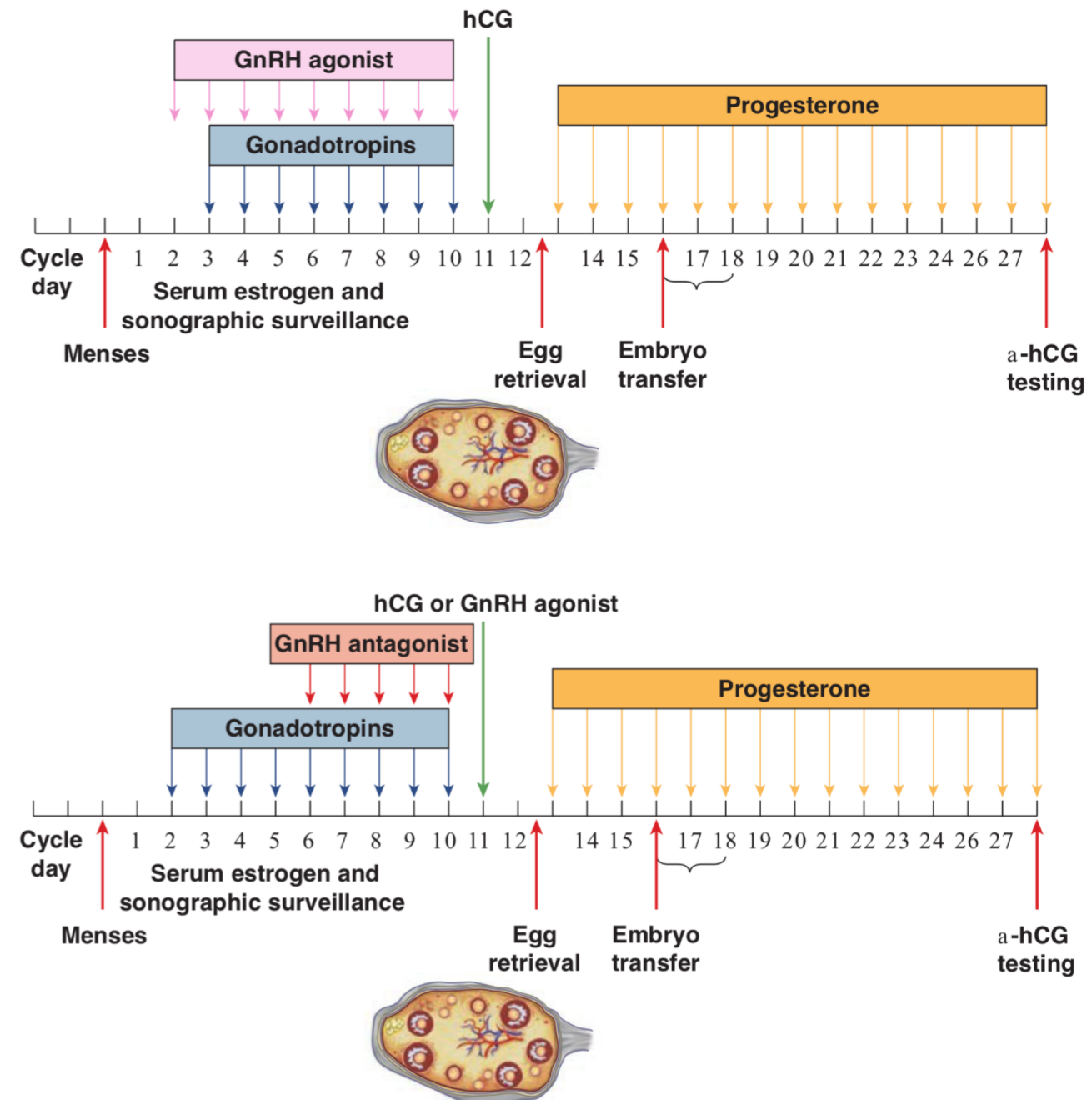
Partner: also accountant, 31yo, healthy, no SAD.



Collection of Cartoon Woman Cliparts [Digital image]. (n.d.). Retrieved from <http://clipart-library.com/cartoon-woman-cliparts.html>

IVF Cycle

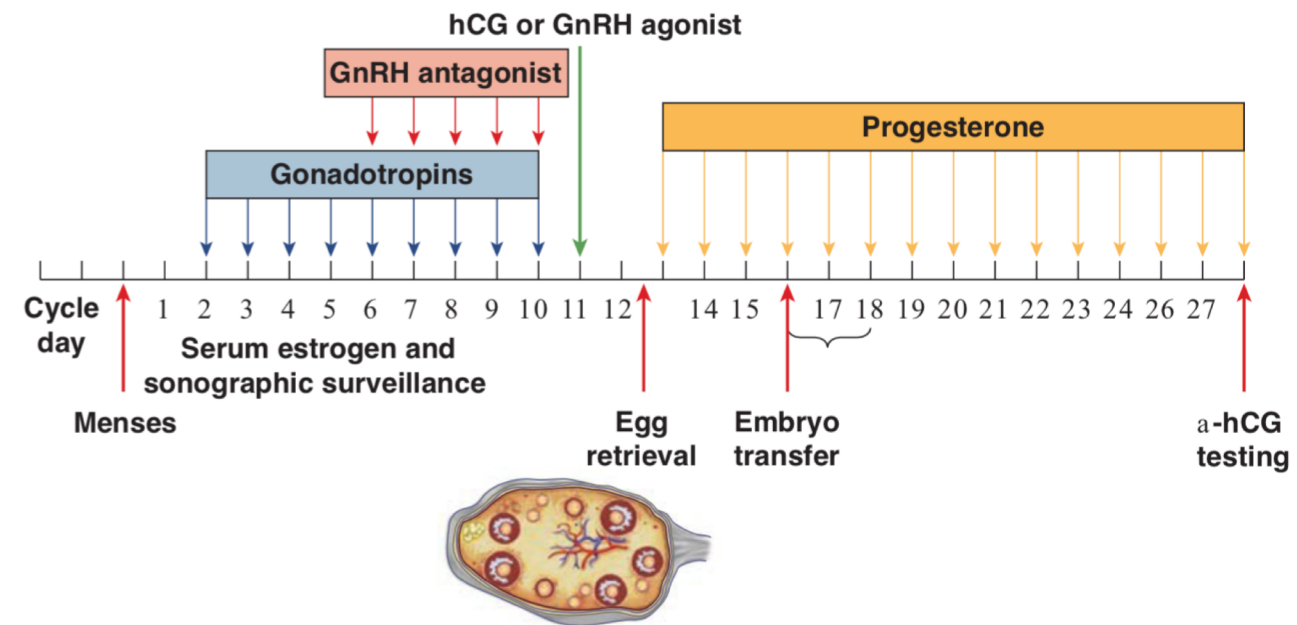
- GnRH agonists and antagonists are used to suppress pituitary gland to prevent endogenous LH surge before follicular maturation → gonadotropins for follicular maturation → HCG to trigger final oocyte maturation → egg retrieval → luteal phase hormonal supplementation



Hoffman, B., Schorge J., Bradshaw K., Halvorson L., Schaffer J., Corton M. (2016). William's gynecology. 3rd ed. New York. McGraw-Hill Education.

IVF protocol:

- LMP June 3
- GnRH antagonist
- Gonadotropins: Gonal-F 150
- LH, FSH: Menopur 75
- GnRH agonist trigger: Decapeptyl
- Carbegoline given on the day of HCG trigger
- **June 17, 2015-** oocyte retrieval
 - **33 oocytes retrieved**
- Intracytoplasmic sperm injection (ICSI) due to low sperm binding capacity
- Plan for elective single embryo transfer (eSET) on day 5 (fresh transfer)
- Luteal phase support: progesterone



Hoffman, B., Schorge J., Bradshaw K., Halvorson L., Schaffer J., Corton M. (2016). William's gynecology. 3rd ed. New York. McGraw-Hill Education.

June 20:

- Presented with abdominal pain, nausea, vomiting
- Has not had embryo transfer



Collection of Cartoon Woman Cliparts [Digital image]. (n.d.). Retrieved from <http://clipart-library.com/cartoon-woman-cliparts.html>

How does OHSS present on history and physical exam?



Brain Thinking Clipart [Digital image]. (n.d.). Retrieved from https://www.clipartmax.com/middle/m2i8i8H7N4d3Z5K9_clipart-of-brain-thinking-black-and-white/

Clinical Presentation

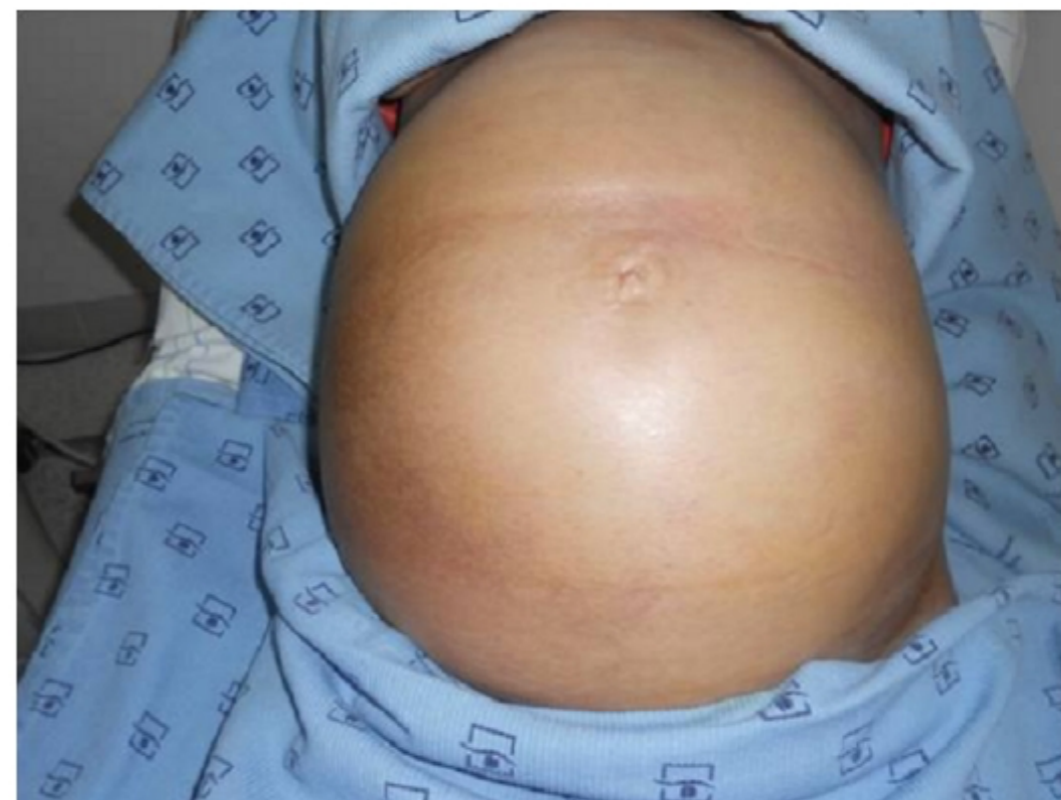
Abdominal bloating is the common initial presentation and 1st sign of impending severe OHSS (due to increased ovarian size and ascites)

History:

- When had ovarian stimulation, when had HCG or spontaneous ovulation, onset of symptoms
- Rapid weight gain
- **GI:** abdo pain, abdo bloating/distension, n/v, ability to tolerate PO intake
- **Cardioresp:** C/P, SOB
- **GU:** urinary output
- **Extremities:** calf pain (VTE), swelling

O/E:

- **Vitals:** ↓ SpO₂, ↑ RR
- ↓/no U/O
- Weight, anasarca, extremity swelling
- **Cardioresp:** crackles, decreased air entry
- **Abdo:** abdo distension, abdo girth at umbilicus, tenderness
- **Ascites:** fluid wave test, shifting dullness
- **Extremities:** swelling, signs of DVT (unilateral calf swelling, palpable cords, tenderness, + Homan's sign)
- **Pelvic exam:** be careful to avoid trauma to enlarged ovaries!



Myriam, R., Chaara, H., Fdili, F., & Melhouf, A. (2011, October). Significant increase in abdominal girth in a patient with ovarian hyperstimulation syndrome in a spontaneous pregnancy with invasive mole [Digital image]. Retrieved from https://www.researchgate.net/figure/significant-increase-in-abdominal-girth-in-a-patient-with-ovarian-hyperstimulation_fig6_221852220

DDx:

- PID
- Intra-abdominal hemorrhage
- Ectopic pregnancy
- Appendicitis
- Ovarian torsion
- Ovarian cyst hemorrhage

Classification of OHSS

Navot et al. (1992), modified by Mathur et al. (2007):

- Once diagnose OHSS, need to classify
- Broad spectrum

Mild	Moderate	Severe	Critical
<ul style="list-style-type: none"> • Abdominal bloating • Mild abdominal pain • Ovarian size <8cm 	<ul style="list-style-type: none"> • Moderate abdo pain • Nausea +/- vomiting • Ovarian size 8-12cm • Ascites on US 	<ul style="list-style-type: none"> • Ovarian size >12cm • Ascites clinically • Pleural effusion • Oliguria (↓ U/O) • HCT >45% (hemoconcentrated) • Low protein (hypoproteinemia) 	<ul style="list-style-type: none"> • Tense ascites • Large pleural effusion • ARDS • Oliguria/anuria • HCT >55% (hemoconcentrated) • ↑ WBC >25,000 • Thromboembolism (VTE)

What investigations would you like to order?



Brain Thinking Clipart [Digital image]. (n.d.). Retrieved from https://www.clipartmax.com/middle/m2i8i8H7N4d3Z5K9_clipart-of-brain-thinking-black-and-white/

Investigations

- **CBC, renal panel**
 - ↑ WBC
 - Due to hemoconcentration, expression of monocyte tissue factor from granulosa cells
 - ↑ HCT (hemoconcentration)
 - Electrolyte imbalances
- **Urinalysis**
 - ↑ urine specific gravity (dehydration)
- CXR if suspect pleural effusion
- Echo if suspect pericardial effusion

	Flags	Results	Ref Range	
CBC - CBC & Auto Differential (F)				
<u>WBC - Leukocytes (F)</u>	H	12.84	4.00 - 11.00	x10e9/L 2015-Jun-20 12:55 PM
<u>RBC - Erythrocytes (F)</u>	H	5.76	3.20 - 5.40	x10e12/L 2015-Jun-20 12:55 PM
<u>Hemoglobin - Hemoglobin (F)</u>	H	167	110 - 160	g/L 2015-Jun-20 12:55 PM
<u>Hematocrit - Hematocrit (F)</u>	H	0.506	0.330 - 0.480	L/L 2015-Jun-20 12:55 PM
<u>MCV - MCV (F)</u>		87.8	79.0 - 99.0	fl 2015-Jun-20 12:55 PM
<u>MCH - MCH (F)</u>		29.0	27.0 - 32.0	pg 2015-Jun-20 12:55 PM
<u>MCHC - MCHC (F)</u>		330	320 - 360	g/L 2015-Jun-20 12:55 PM
<u>RDW - Erythrocyte Distribution Width (RDW) (F)</u>		12.6	11.5 - 15.0	% 2015-Jun-20 12:55 PM
<u>Platelet - Platelets (F)</u>		261	150 - 400	x10e9/L 2015-Jun-20 12:55 PM
<u>MPV - MPV (F)</u>		9.2	7.4 - 10.6	fl 2015-Jun-20 12:55 PM
<u>Neutrophils - Neutrophils (F)</u>	H	10.64	1.50 - 7.50	x10e9/L 2015-Jun-20 12:55 PM
<u>Lymphocytes - Lymphocytes (F)</u>	L	1.14	1.50 - 4.00	x10e9/L 2015-Jun-20 12:55 PM
<u>Monocytes - Monocytes (F)</u>		0.98	0.20 - 1.00	x10e9/L 2015-Jun-20 12:55 PM
<u>Eosinophils - Eosinophils (F)</u>		0.04	0.00 - 0.60	x10e9/L 2015-Jun-20 12:55 PM
<u>Basophil - Basophils (F)</u>		0.03	0.00 - 0.20	x10e9/L 2015-Jun-20 12:55 PM

	Flags	Results	Ref Range	
Electrolytes (4) Creatinine Urea - Electrolytes, Urea & Creatinine (F)				
<u>Sodium - Sodium (F)</u>		136	135 - 146	mmol/L 2015-Jun-20 1:18 PM
<u>Potassium - Potassium (F)</u>		4.1	3.5 - 5.1	mmol/L 2015-Jun-20 1:18 PM
<u>Chloride - Chloride (F)</u>	L	95	100 - 110	mmol/L 2015-Jun-20 1:18 PM
<u>CO2(Total) - Carbon Dioxide (F)</u>		26	22 - 31	mmol/L 2015-Jun-20 1:18 PM
<u>Urea - Urea (F)</u>		4.0	3.7 - 7.0	mmol/L 2015-Jun-20 1:18 PM
<u>Creatinine - Creatinine (F)</u>		85	45 - 90	umol/L 2015-Jun-20 1:18 PM
<u>Anion Gap - Anion Gap (Na, Cl, CO2) (F)</u>		15	8 - 16	mmol/L 2015-Jun-20 1:18 PM

	Flags	Results	Ref Range	
ALT - Alanine Aminotransferase (ALT) (F)				
<u>ALT - Alanine Aminotransferase (ALT) (F)</u>		16	5 - 45	U/L 2015-Jun-20 1:18 PM

Reviewed: 2015-JUN-22 by acase

	Flags	Results	Ref Range	
AST - Aspartate Aminotransferase (AST) (F)				
<u>AST - Aspartate Aminotransferase (AST) (F)</u>		20	10 - 35	U/L 2015-Jun-20 1:18 PM

Investigations

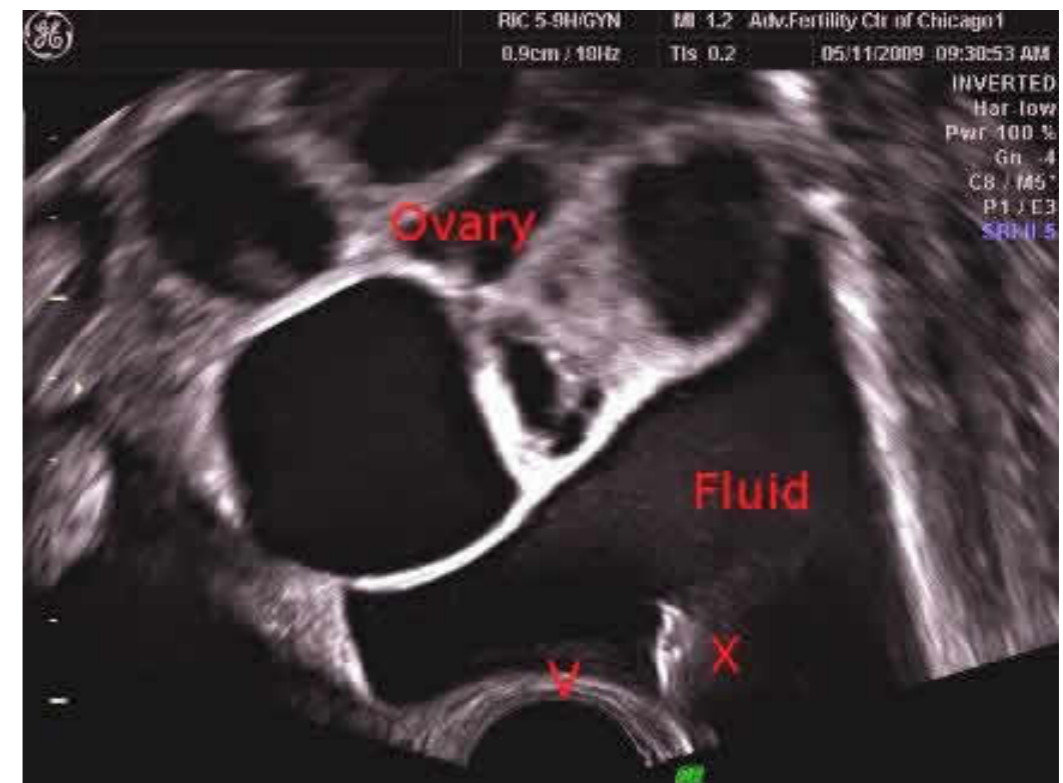
- **TVUS**
 - Early intraperitoneal fluid can be usually seen only with TVUS
 - Transabdominal US is difficult

US findings:

- Enlarged ovaries filled with multiple luteal cysts
 - <8cm- mild OHSS
 - 8-12cm- moderate OHSS
 - >12cm- severe OHSS
- Ascites



Smith, L. (2013, November 12). Ultrasound and Ovarian Hyperstimulation Syndrome [Digital image]. Retrieved from https://link.springer.com/chapter/10.1007/978-1-4614-9182-8_23



Sherbahn. (n.d.). Picture showing paracentesis being done for OHSS [Digital image]. Retrieved from <https://www.advancedfertility.com/ovarian-hyperstimulation.htm>

Ultrasound Findings:

Right ovary:

69.2 x79.2 x67.9 mm

Multiple luteal structures consistent with recent ovarian stimulation

Left ovary:

88.5 x57.6 x59.2 mm

Multiple luteal structures consistent with recent ovarian stimulation

Uterus:

Endometrial thickness: 9.9 mm; D (luteal) pattern

The uterus is anteverted.

Anterior Free Fluid: 44.3 x25 mm

Posterior / cul-de-sac Free Fluid: 36.5 x39.8 mm

What is your impression?



Brain Thinking Clipart [Digital image]. (n.d.). Retrieved from https://www.clipartmax.com/middle/m2i8i8H7N4d3Z5K9_clipart-of-brain-thinking-black-and-white/

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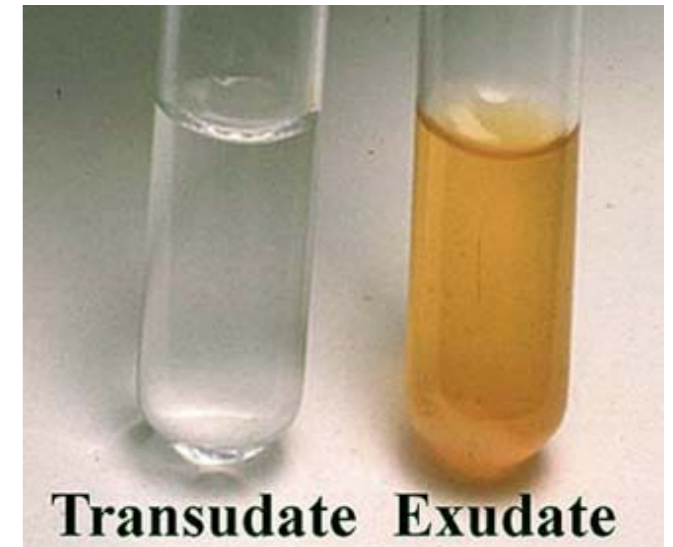
Posterior / cul-de-sac Free Fluid: 36.5 x39.8 mm

Moderate

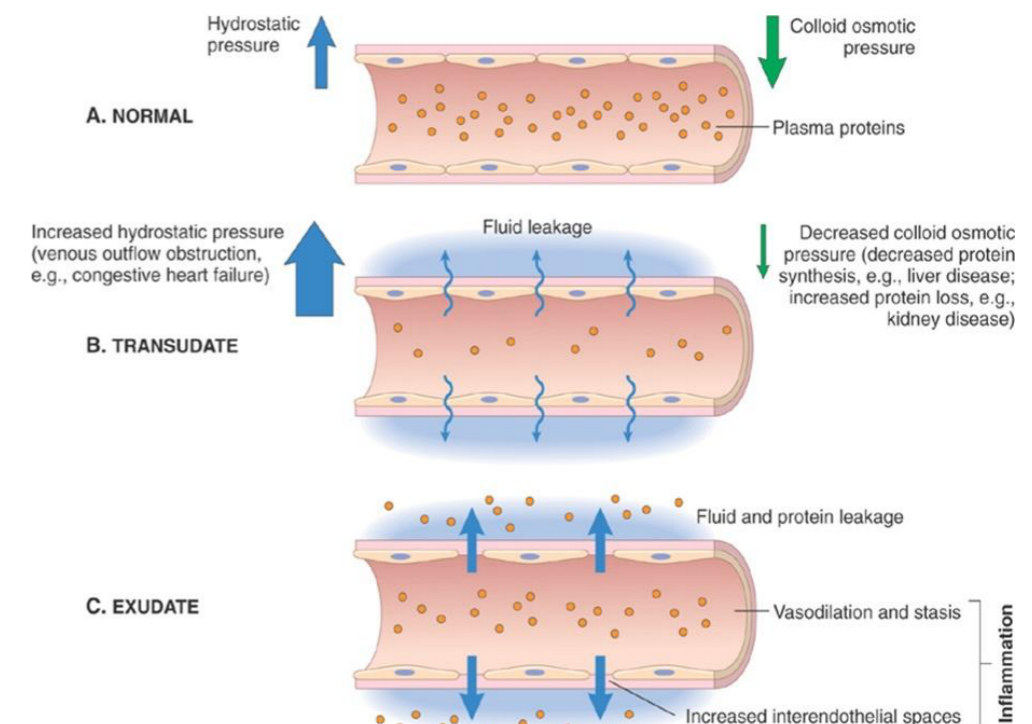
- Moderate abdo pain
- Nausea +/- vomiting
- **Ovarian size 8-12cm**
- Ascites on US

Investigations

- **US-guided paracentesis** → ascitic fluid
 - Clear or straw-colour
 - Extravascular albumin-rich exudate
 - **Exudate**- both fluid and protein leak out of blood vessels → decreased plasma oncotic pressure
 - ↑ albumin, ↓ WBC
 - RBC (from bleeding due to egg retrieval or from paracentesis procedure)



Composition of Edema Fluid [Digital image]. (n.d.). Retrieved from https://vet.uga.edu/ivcvm/courses/VPATS200/01_circulation/edema/edema04.html



Kumar et al: Robbins & Cotran Pathologic Basis of Disease, 8th Edition. Copyright © 2009 by Saunders, an imprint of Elsevier, Inc. All rights reserved.

[Digital image]. (2013, January 3). Retrieved from <http://pathalamus.blogspot.com/2013/01/pleural-disease-inflammation-malignancy.html>

What are the possible complications of OHSS?



Brain Thinking Clipart [Digital image]. (n.d.). Retrieved from https://www.clipartmax.com/middle/m2i8i8H7N4d3Z5K9_clipart-of-brain-thinking-black-and-white/

Complications

- Multidisciplinary management, may require admission to ICU

Pt

- Ovarian torsion
- Ovarian cyst rupture → hemorrhage
- Compartment syndrome
- Hepatorenal failure
- VTE
- Pericardial effusion
- Hydrothorax
- Hyperkalemia
- ARDS
 - From untreated pleural effusion
- Death
 - 8 fatalities have been reported from most severe OHSS
 - Cause: hepatorenal syndrome, thromboembolism, ARDS

MANAGEMENT

Management

- Recommendations based on expert opinions
- Usually self-limiting, resolves spontaneously
- Supportive management until OHSS resolves

Consider:

- Patient's age
- Onset of presentation (early vs late)
- Follicle # and size during ovarian stimulation
- # eggs retrieved
- Peak estradiol level
- Estradiol level at trigger

Pregnant with OHSS

- Need close monitoring
 - Rapid increase in HCG levels → increased risk of progression to severe OHSS
 - Resolution may take longer
- Pregnancy unlikely to be affected by uncomplicated OHSS

OUTPATIENT MANAGEMENT

If used in early stages, can decrease associated complications

Outpatient Management

- **Analgesia:** Tylenol +/- narcotics
 - Avoid NSAIDs with antiplatelet properties
→ can interfere with implantation, compromise renal function in pts with severe OHSS
- **Hydration:** drink 2-4L fluids PO daily to avoid hemoconcentration
- **Avoid exercise, intercourse**
 - To decrease risk of ovarian torsion or rupture of enlarged hyperstimulated ovaries
- Maintain daily communication with MD, pt must know when to seek medical care!
- Severe OHSS: assessment by MD q1-2 days

Indications for outpt management:

- Mild/moderate OHSS
- Severe OHSS, compliant pt

Table 3. Daily communication checklist

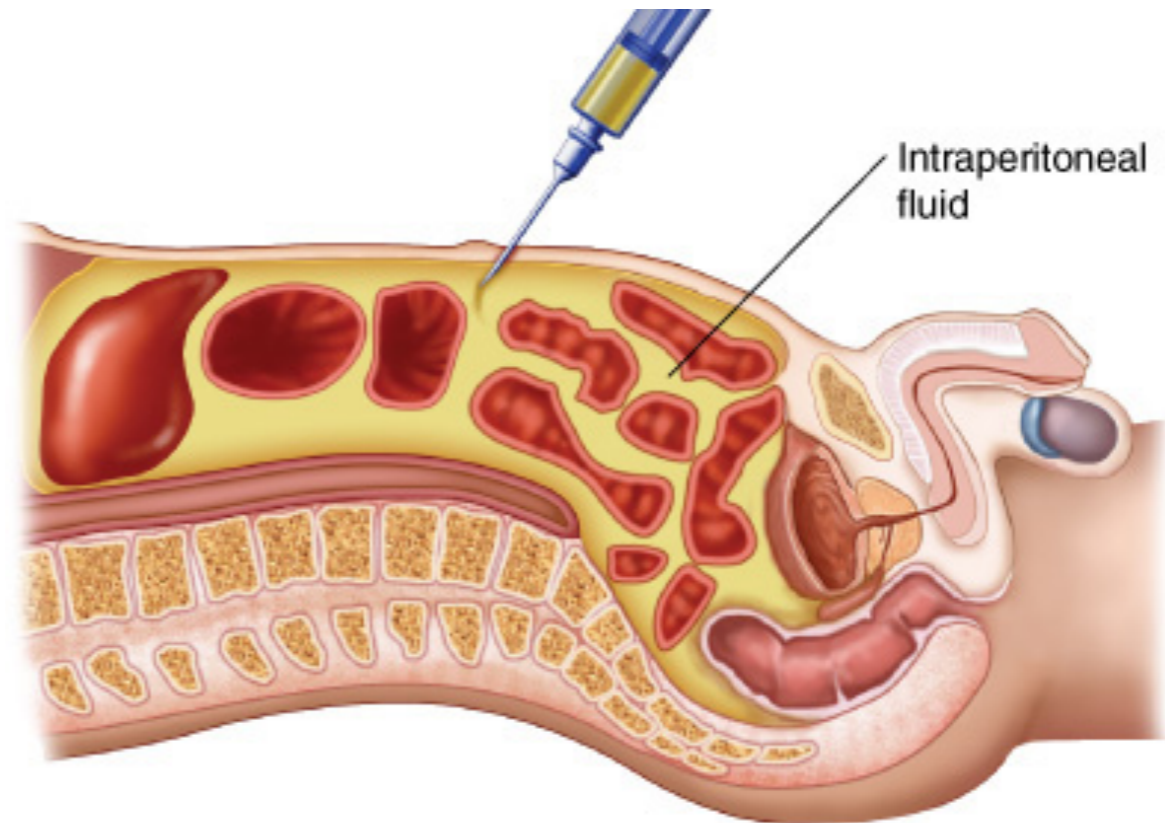
- Is the patient adequately hydrated?
 - Quantitative estimates of oral intake and urine output
- Can she maintain adequate oral hydration?
- What is her weight today?
- What is her abdominal girth measured at the umbilicus?
- Are there any manifestations of severe or critical OHSS? Does the patient have worsening shortness of breath, calf pain, or new neurological deficits?

Shmorgun, D., Claman, P. (2017, November). No-268-The Diagnosis and Management of Ovarian Hyperstimulation Syndrome [Digital image]. Retrieved from <https://www.ncbi.nlm.nih.gov/pubmed/29080733>.

Outpatient Management

US-guided paracentesis:

- Via outpt clinic
- For pts with **tense ascites** resulting in significant pain and/or resp compromise
- Improves
 - Ascites
 - Pleural effusion
 - Oliguria (due to ↓ renal perfusion)
 - Abdominal pain



Source: Hanson CW III: *Procedures in Critical Care*: <http://www.accessmedicine.com>
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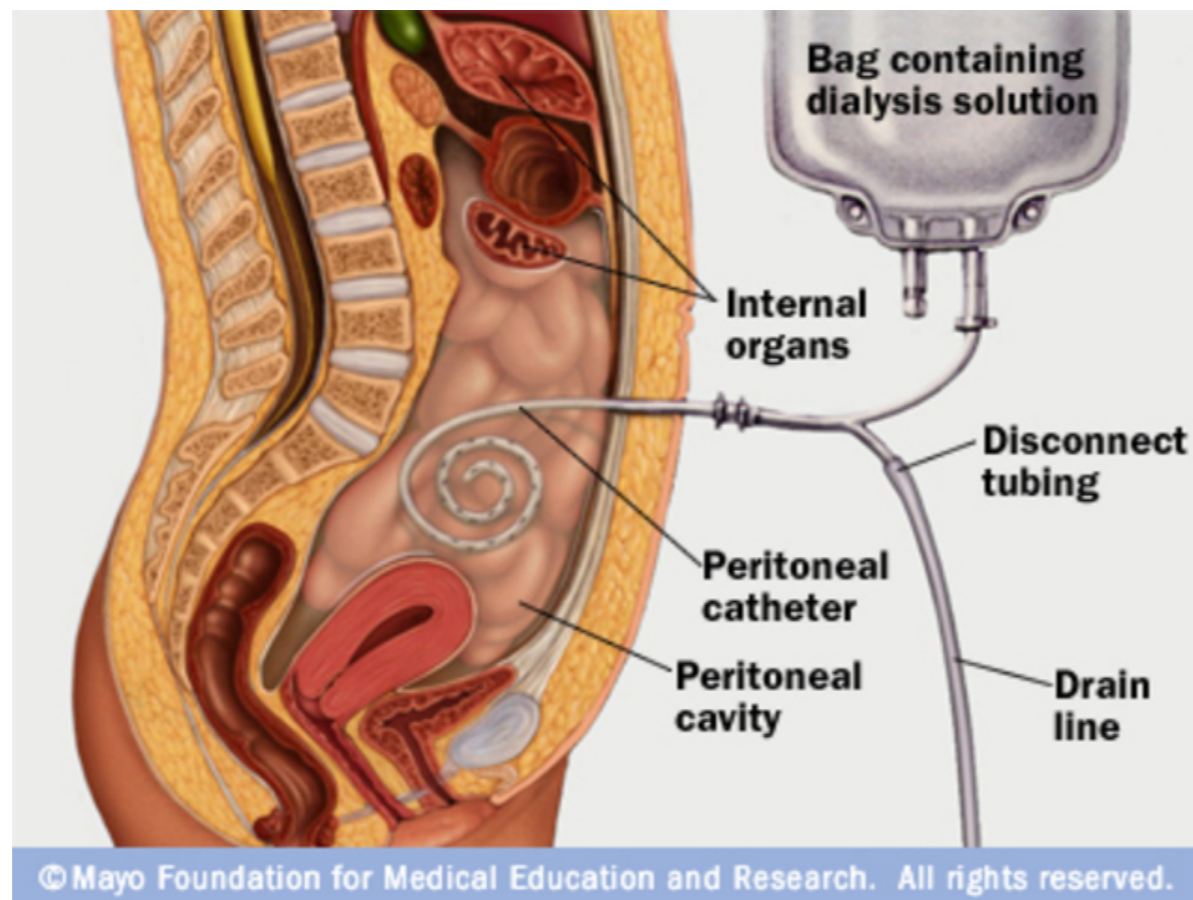
Hanson, C. W. (n.d.). Graphic showing paracentesis aspiration of peritoneal fluid [Digital image]. Retrieved from <https://mhmedical.com/Content.aspx?bookId=414&ionId=41840273>

Outpatient Management

Indwelling pig catheter

- Can insert percutaneous pigtail catheter under US guidance
 - Decreases potential infection from multiple attempts to drain fluid

- Monitor ascites output, urinary output daily
- Clinically resolves when paracentesis ↓, U/O ↑
- **Remove catheter when ascites output <50mL/day**

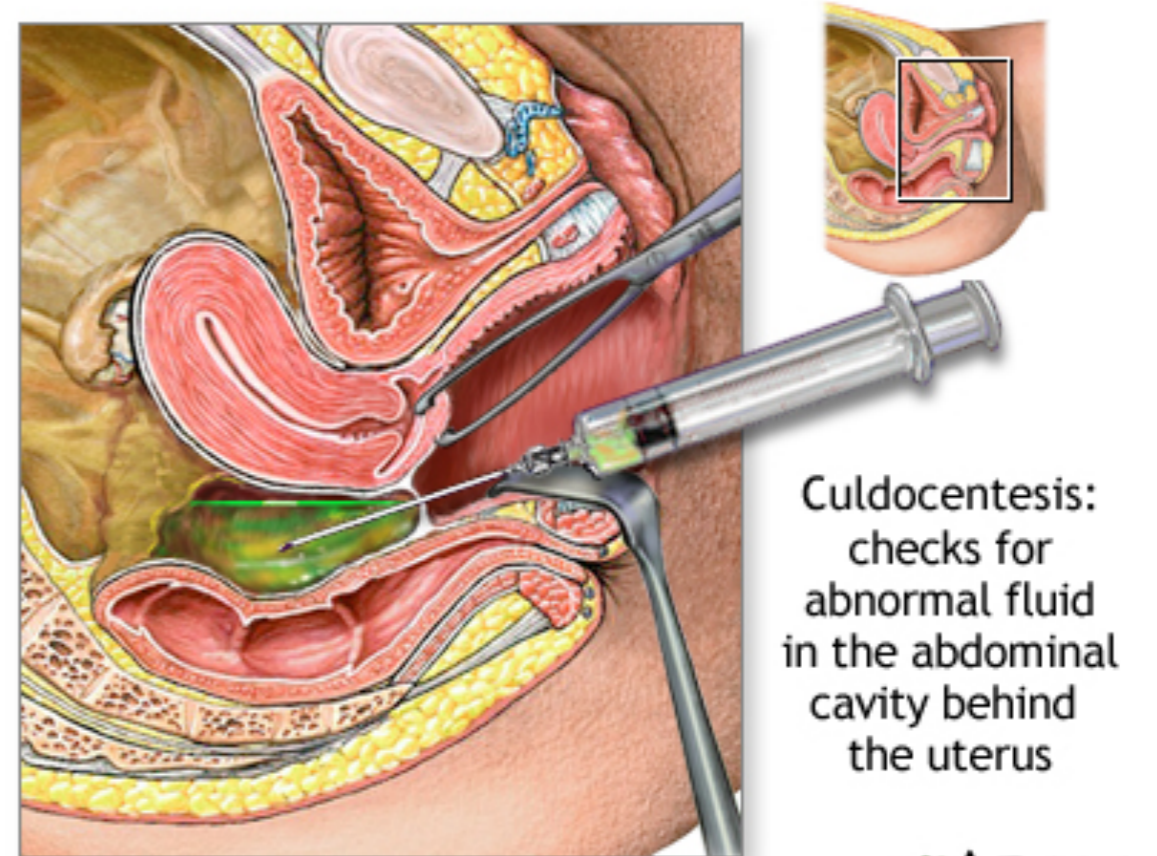


Loh, C. (n.d.). Milestones on the Development of Peritoneal Dialysis [Digital image]. Retrieved from <https://www.timetoast.com/timelines/milestones-on-the-development-of-peritoneal-dialysis>

Outpatient Management

Culdocentesis:

- Aspirate fluid using spinal needle from pouch of Douglas
- Used to
 - Prevent disease progression from moderate to severe OHSS; improve severe OHSS
 - Decrease abdo pain
 - Causes diuresis in pts with oliguria
 - Decrease need for hospital admission



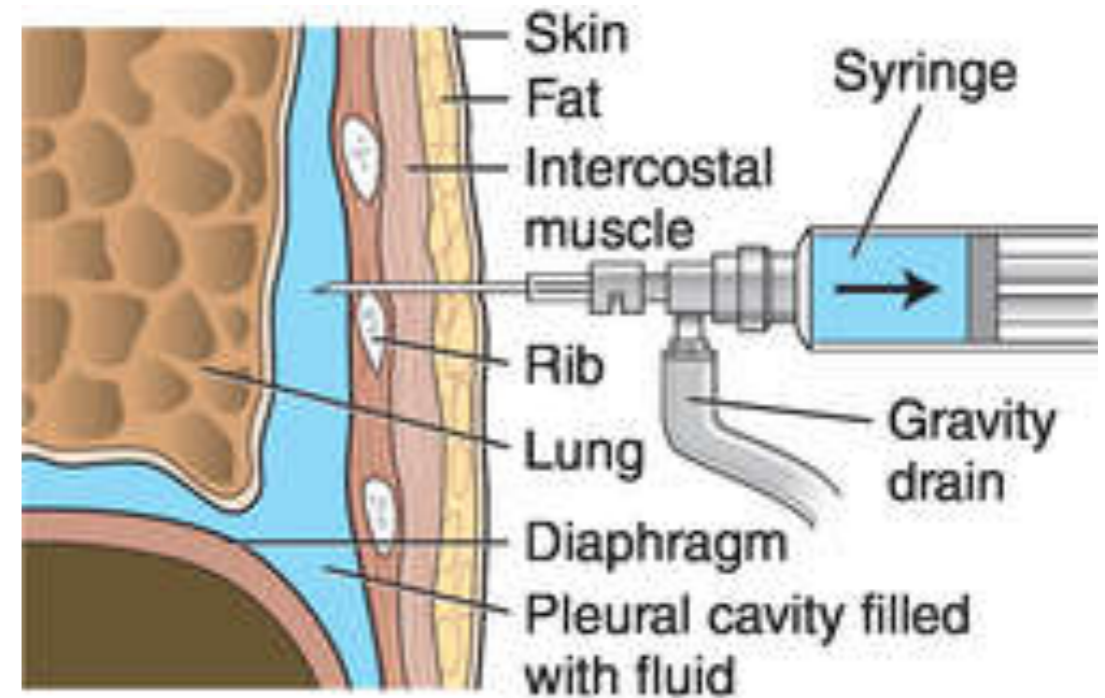
[Digital image]. (2018, January 14). Retrieved from <http://eclinicalworks.adam.com/content.aspx?productId=39&pid=1&gid=003919>

ADAM.

Outpatient Management

Pleuracentesis

- For symptomatic pleural effusions that persist after paracentesis



Thoracentesis [Digital image]. (2012). Retrieved from <https://medical-dictionary.thefreedictionary.com/pleuracentesis>

Outpatient management:

- June 21-24:
 - Daily TVUS showing moderate OHSS with ascites
 - Daily in-office transvaginal paracentesis (US guided) x4
 - June 20-1100mL
 - June 21- 1100mL
 - June 22- 2000mL
 - June 23- 1200mL
 - Daily IV fluids (1L)
 - Labs
 - HCT normalized
 - Albumin low (26)
 - ALT, AST mildly elevated
- Froze 16 embryos (cryopreservation)
- Stopped progesterone for luteal phase support
- Symptomatic improvement
- Once ascites improved on US, did daily labs, continued to monitor symptoms by phone, reassessed in office → OHSS resolved
 - Daily labs: CBC, renal panel, AST, ALT

Conclusion of case:

- Had 7 frozen embryo transfers
 - 2015-2016: conceived 4 out of 5 transfers → 4 1st trimester SA at <10w, no D&C
 - 2017: transferred 2 embryos → C/S at term for singleton breech



Collection of Cartoon Woman Cliparts [Digital image]. (n.d.). Retrieved from <http://clipart-library.com/cartoon-woman-cliparts.html>

INPATIENT MANAGEMENT

Management

- May be admitted for few days-4 weeks
 - Longer hospital stay if pregnant

Indications for inpt management:

- Severe and critical OHSS
- Dehydrated, unable to maintain PO hydration → admit for IV fluids, possible paracentesis
 - ↑ HCT, ↑ urine specific gravity
- Pain despite PO analgesia

Inpatient Management

Fluids:

- Drink according to thirst
- Aggressive IV fluid rehydration with crystalloids
 - NS preferred (RL has risk of hyponatremia)
 - Then maintenance 100-150cc/hr until diuresis
- If persistent hypovolemia despite IV fluids
 - Use colloid fluids: **25% albumin IV 15-20mL/hr over 4hrs,** repeat until hydration improves
- Avoid diuretics

Electrolyte imbalances:

- Treat electrolyte imbalances (ex. Hyperkalemia)

Inpatient Management

Analgesia

- Tylenol, PO/IV opiates
- Avoid NSAID with antiplatelet properties
 - Can interfere with implantation
 - Can compromise renal function

Nausea, vomiting

- Antiemetics

Inpatient Management

Prevention of VTE:

- At risk of VTE due to hemoconcentration and immobilization
- VTE prophylaxis from admission until discharge

VTE prophylaxis:

- Pneumatic compression stockings
- Anticoagulation: LMWH
 - VTE prophylaxis strongly considered for severe OHSS
 - However, no RCT demonstrated that prophylactic anticoagulation prevents VTE in severe OHSS. There are case reports of VTE even with anticoagulation!

Inpatient Management

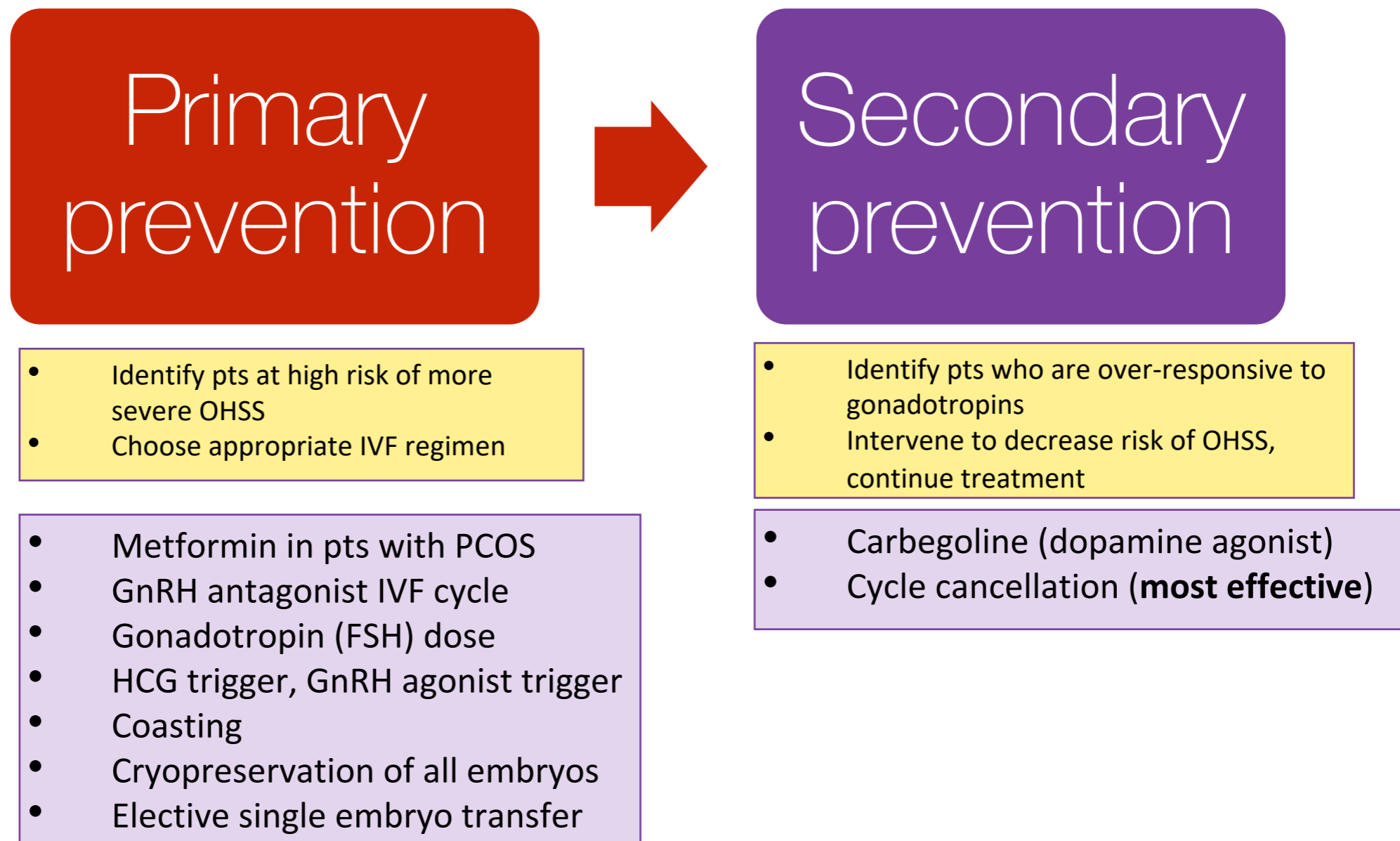
Inpt monitoring:

- Daily
 - Weight, fluid balance, urinary output (N \geq 30mL/hr)
 - O/E: vitals, hydration status, cardioresp exam, ascites, signs of VTE
- Daily labs
 - CBC (Hb, HCT)
 - Renal panel: lytes, creatinine
 - Serum albumin
 - Urine specific gravity
- Weekly labs
 - Liver enzymes

PREVENTION

Prevention of Severe OHSS

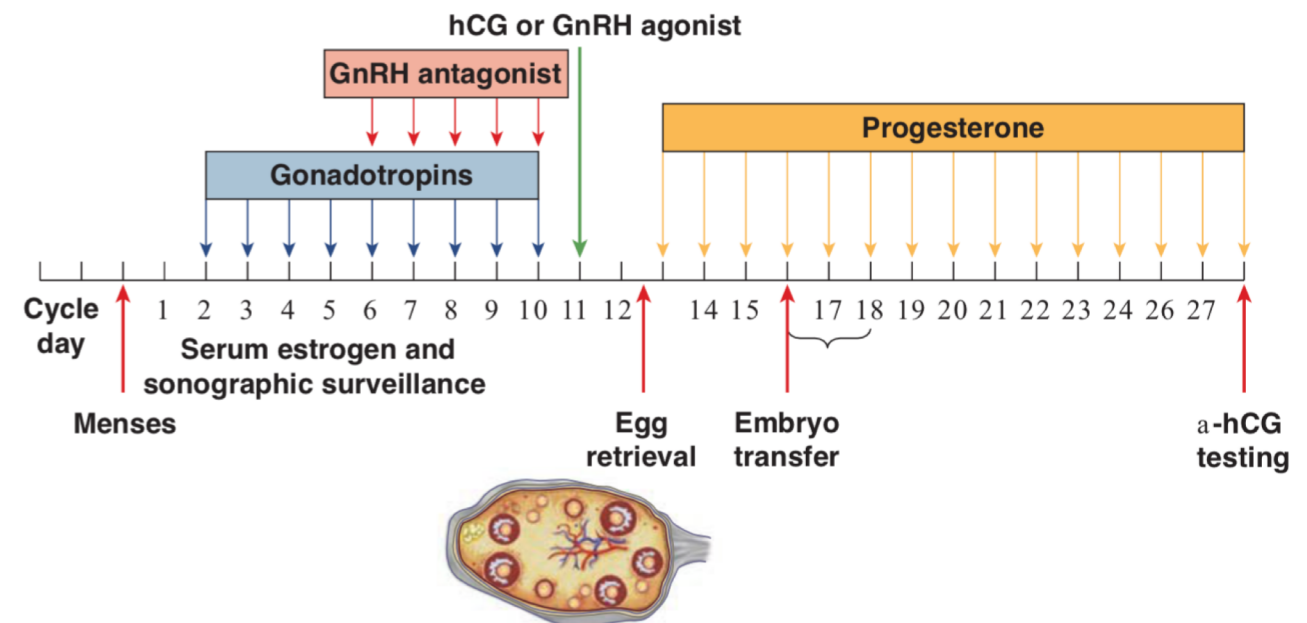
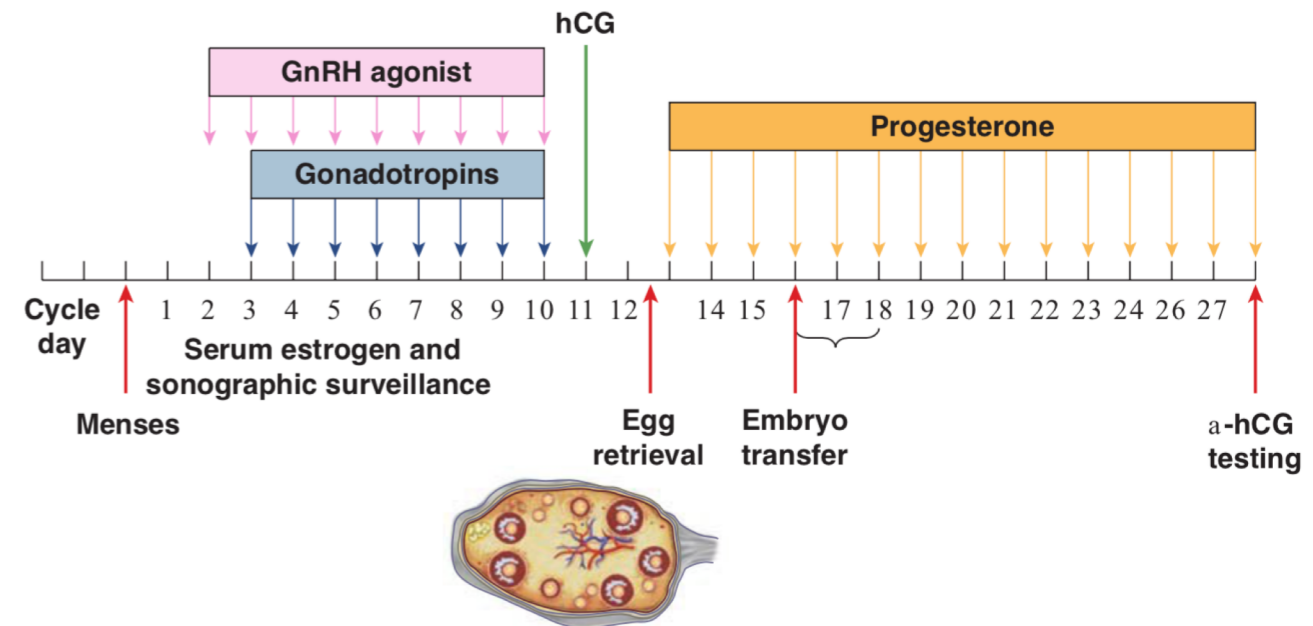
- Controlled ovarian stimulation, knowledge about OHSS pathophysiology, RF, clinical presentation are crucial



IVF Cycle

Metformin:

- Prevents only for pts with PCOS
- Start 8 weeks before gonadotropin stimulation, continue until egg retrieval
- Start Metformin 500mg PO at bedtime
 - Then slowly increase dose to 500mg TID
- Dose is titrated to decrease GI side effects

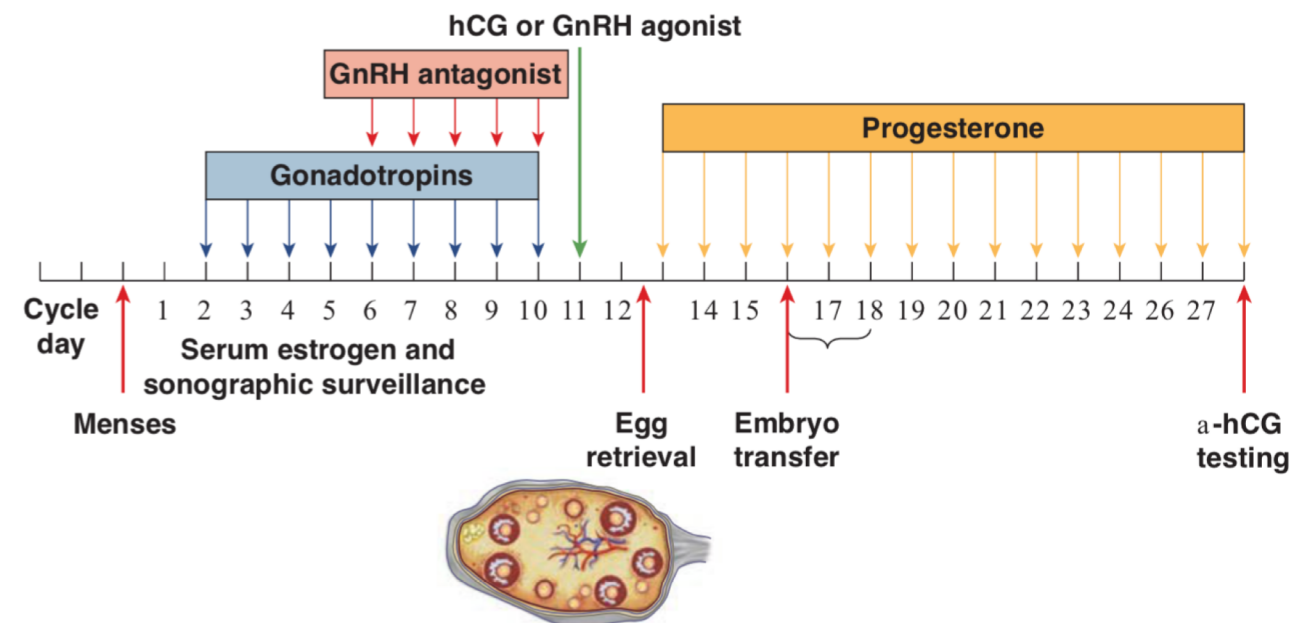
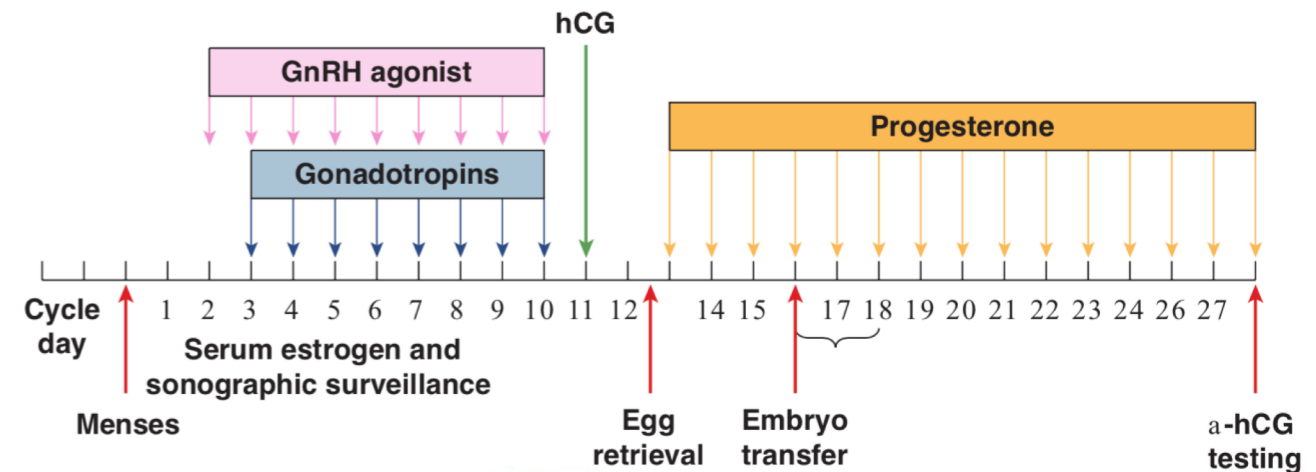


Hoffman, B., Schorge J., Bradshaw K., Halvorson L., Schaffer J., Corton M. (2016). William's gynecology. 3rd ed. New York. McGraw-Hill Education.

IVF Cycle

GnRH agonist/antagonist IVF cycle:

- **GnRH antagonist is recommended** for pts at high risk of OHSS
 - Less risk of OHSS
- No difference in pregnancy or live birth rates



Hoffman, B., Schorge J., Bradshaw K., Halvorson L., Schaffer J., Corton M. (2016). William's gynecology. 3rd ed. New York. McGraw-Hill Education.

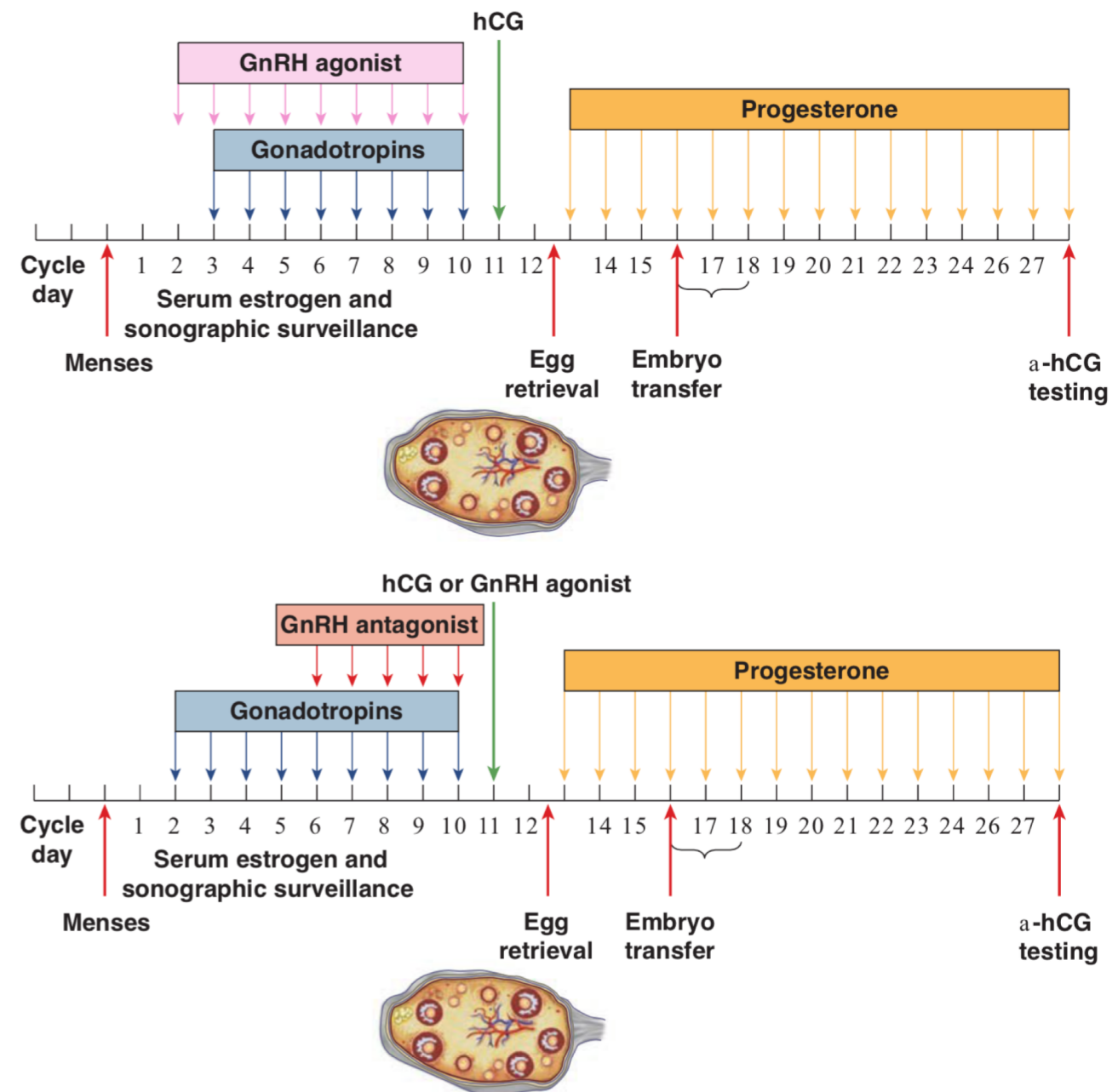
IVF Cycle

Gonadotropins: FSH

- No difference in OHSS rates between recombinant and urinary FSH
- Pts who develop OHSS tend to respond strongly to **lower doses** → need a **lower starting dose**, carefully monitored → **decrease dose** if response is too strong
 - No positive linear correlation between dose of gonadotropin and severity of OHSS

Gonadotropin dose:

- Use clinical judgement for starting dose
- Depends on
 - Age
 - BMI
 - Antral follicle count
 - Previous response

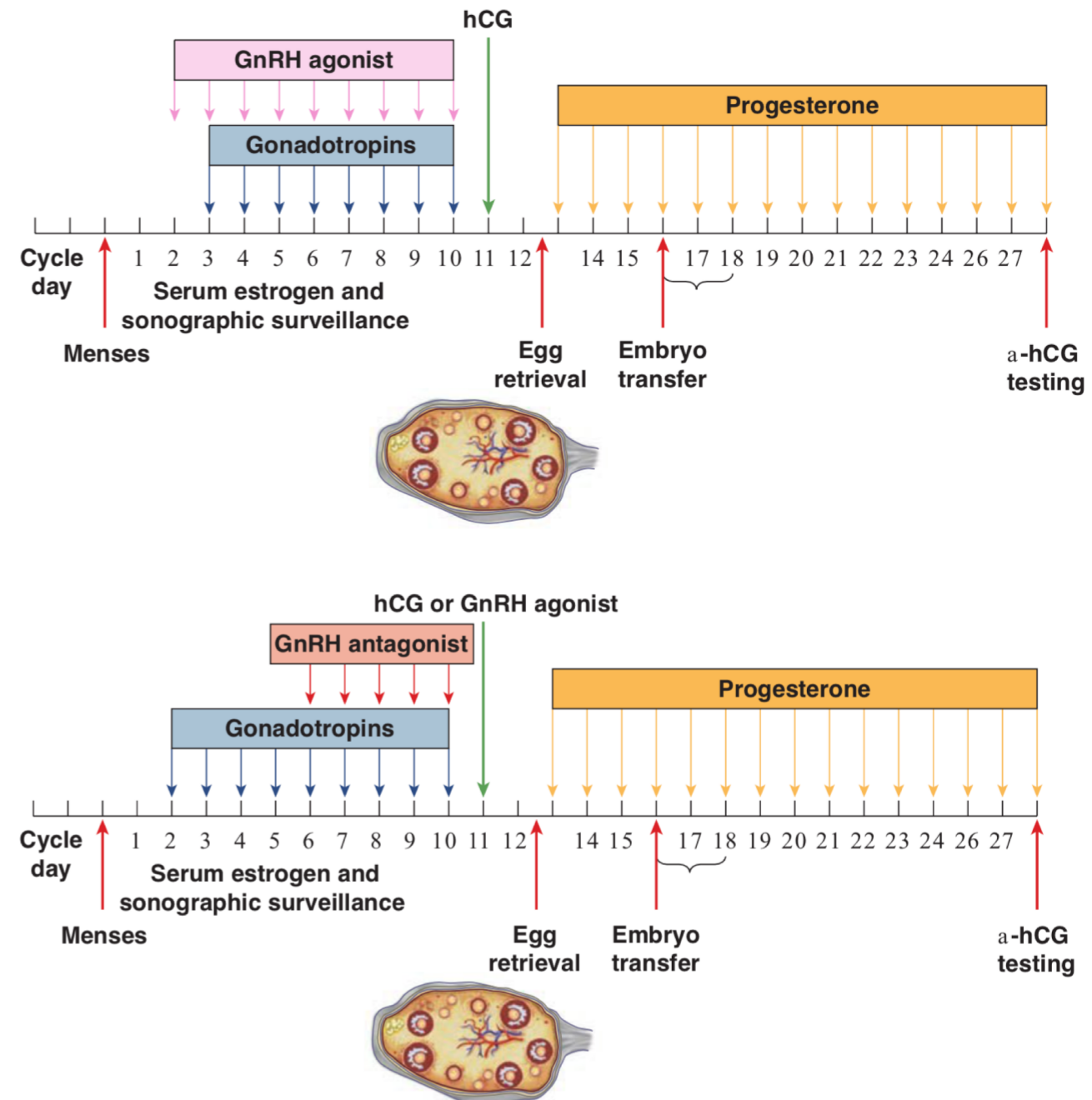


Hoffman, B., Schorge J., Bradshaw K., Halvorson L., Schaffer J., Corton M. (2016). William's gynecology. 3rd ed. New York. McGraw-Hill Education.

IVF Cycle

Coasting

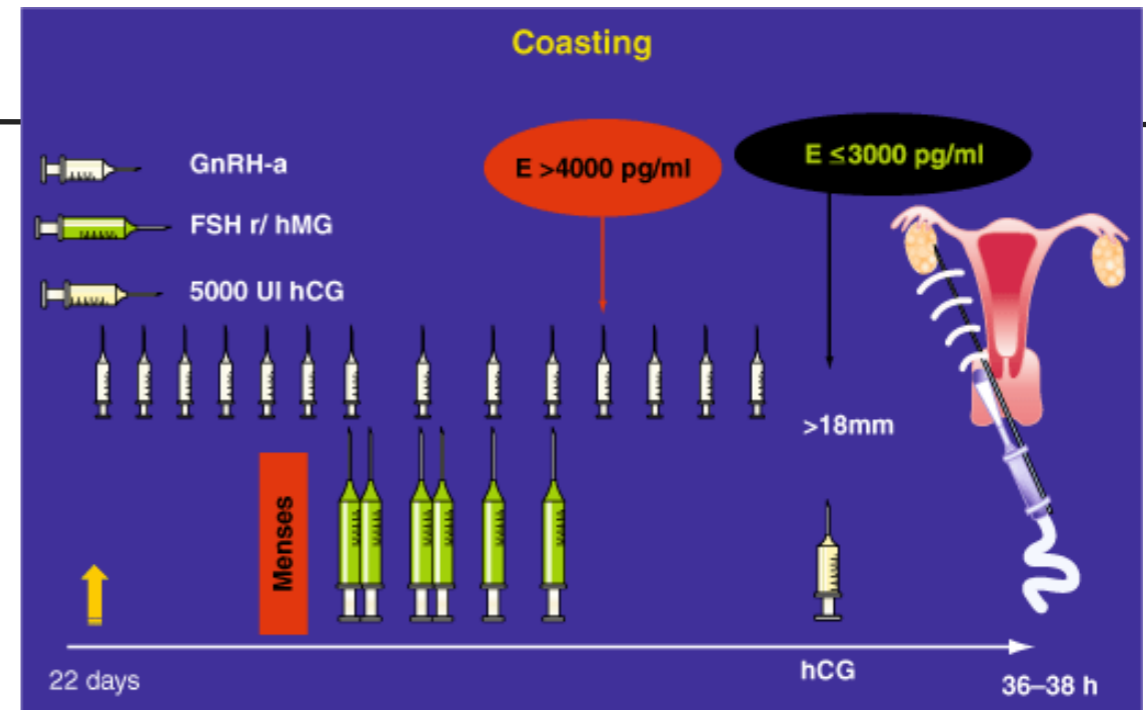
- **Withholding FSH for 1 or more days before HCG trigger injection**
- For pts with very robust response to gonadotropins
- May decrease incidence of severe OHSS
 - Moderate OHSS: 18.7%
 - Incidence of hospitalization for OHSS with coasting: 2.5%
- How it works
 - Give GnRH agonist/antagonist to maintain pituitary suppression
 - **Stop gonadotropins (ex. FSH) once follicles are >12mm**
 - Larger follicles need less FSH than smaller follicles
 - Larger follicles continue to grow and mature, smaller follicles undergo atresia → ↓ production of VEGF
 - Give HCG to trigger oocyte maturation once estrogen levels plateau/drop
 - Then egg retrieval



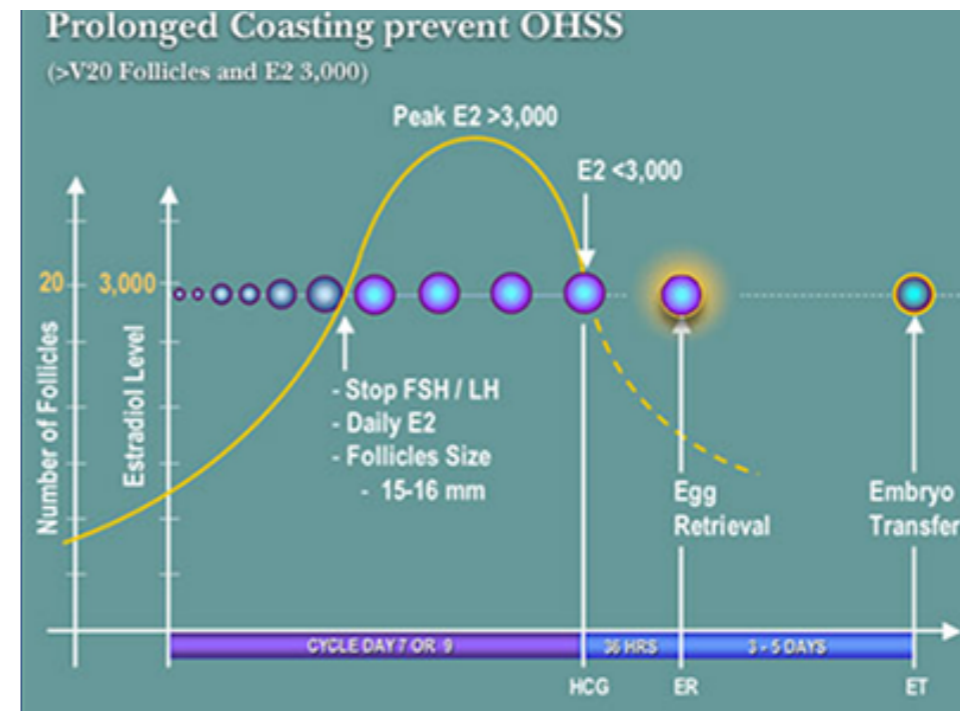
Hoffman, B., Schorge J., Bradshaw K., Halvorson L., Schaffer J., Corton M. (2016). William's gynecology. 3rd ed. New York. McGraw-Hill Education.

IVF Cycle

- Coasting on GnRH agonist alone for **up to 3 days** does not affect pregnancy outcomes
 - Coasting >3 days: ↓ IVF pregnancy rates
 - Consider cycle cancellation if estradiol levels do not decrease by day 4 of coasting
- Similar IVF outcomes for GnRH agonist and antagonist cycles
- Recombinant LH+ urinary HCG vs urinary LH+ recombinant HCG for final oocyte maturation
 - No difference in incidence of OHSS



Rizk, B., Rizk, C., Nawar, M., Garcia-Velasco, J., & Sallam, H. (2010). Ultrasonography in the prediction and management of ovarian hyperstimulation syndrome [Digital image]. Retrieved from <https://www.cambridge.org/core/books/ultrasonography-in-reproductive-medicine-and-infertility/ultrasonography-in-the-prediction-and-management-of-ovarian-hyperstimulation-syndrome/0D635789F101AEBE724546D0F2BF09A7>



Prolonged Coasting Prevent OHSS [Digital image]. (n.d.). Retrieved from <http://login.medscape.com/login/sso/pa?urlCache=aHR0cHM6Ly93d3cubWVkc2NhcGUub3JnL3ZpZXdhcncRpy2xLzgyMjA2MI90cmFuc2NyaXB0&cc=aHR0cDovL2xvZ2luLm1ZHNjYXBILmNvY293b2dpbi9zc28vcGE/dXJsQ2FjaGU9YUhSMGNITTZMeTkzZDNjdWJlXVmtjMk5oY0Y0dWVldzSm5MM1pwWlhaGnuUnBZMnhsThpneU1qQTJNbDkwY21GdWMyTnlhWEIw&cookieCheck=1>

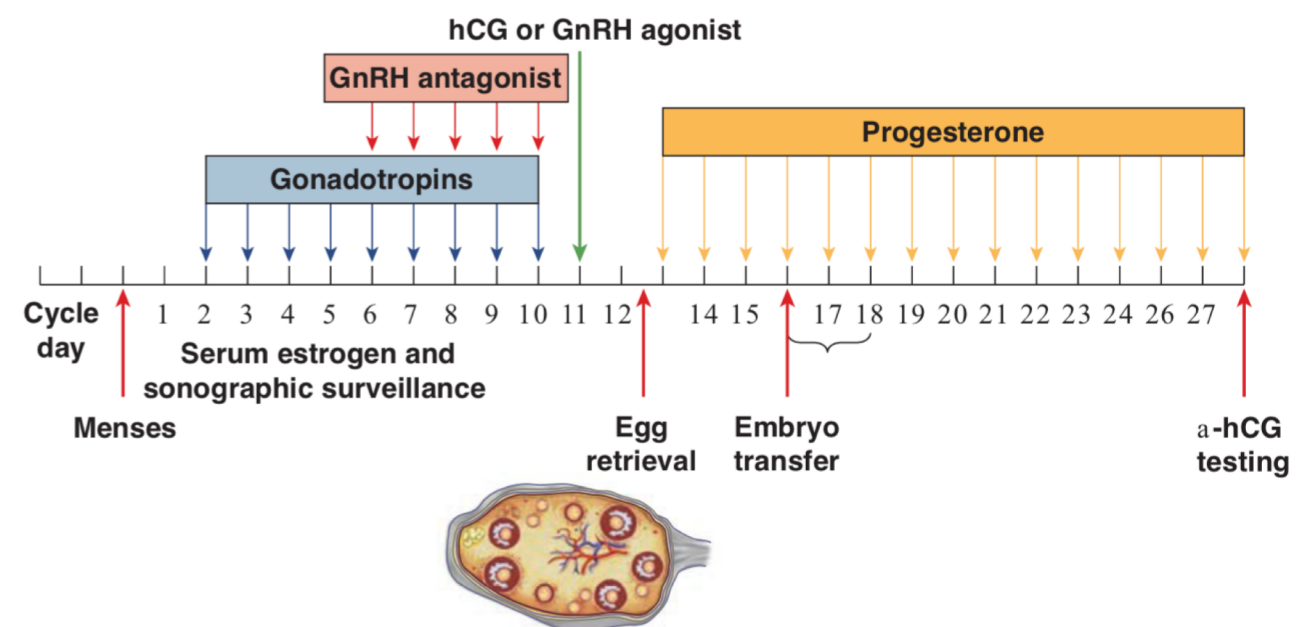
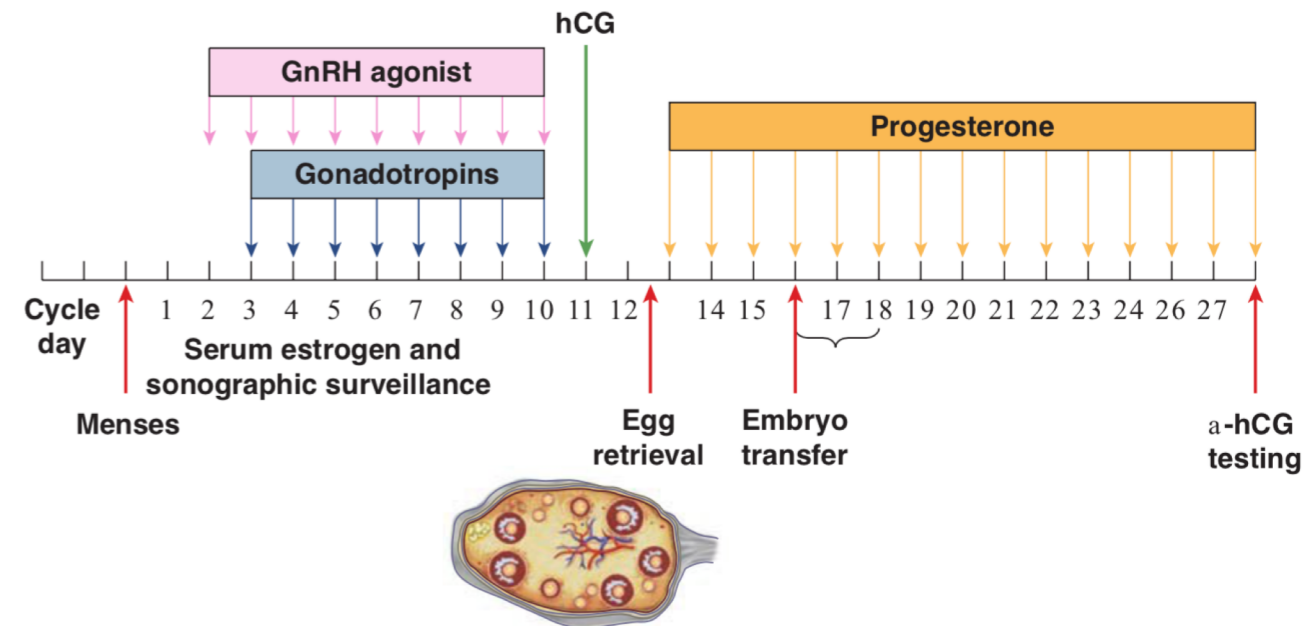
IVF Cycle

HCG trigger

- HCG dosing depends on BMI
- Severe OHSS incidence with HCG trigger: 4.6%
- No clear evidence that decreasing HCG dose decreases rate of OHSS
 - Some evidence that using lower dose of HCG for final oocyte maturation in high-risk population decreases risk of OHSS

Example of HCG dosing used by 1 Canadian fertility centre:

- BMI <28: 5,000IU SC
- BMI ≥28: 10,000IU SC

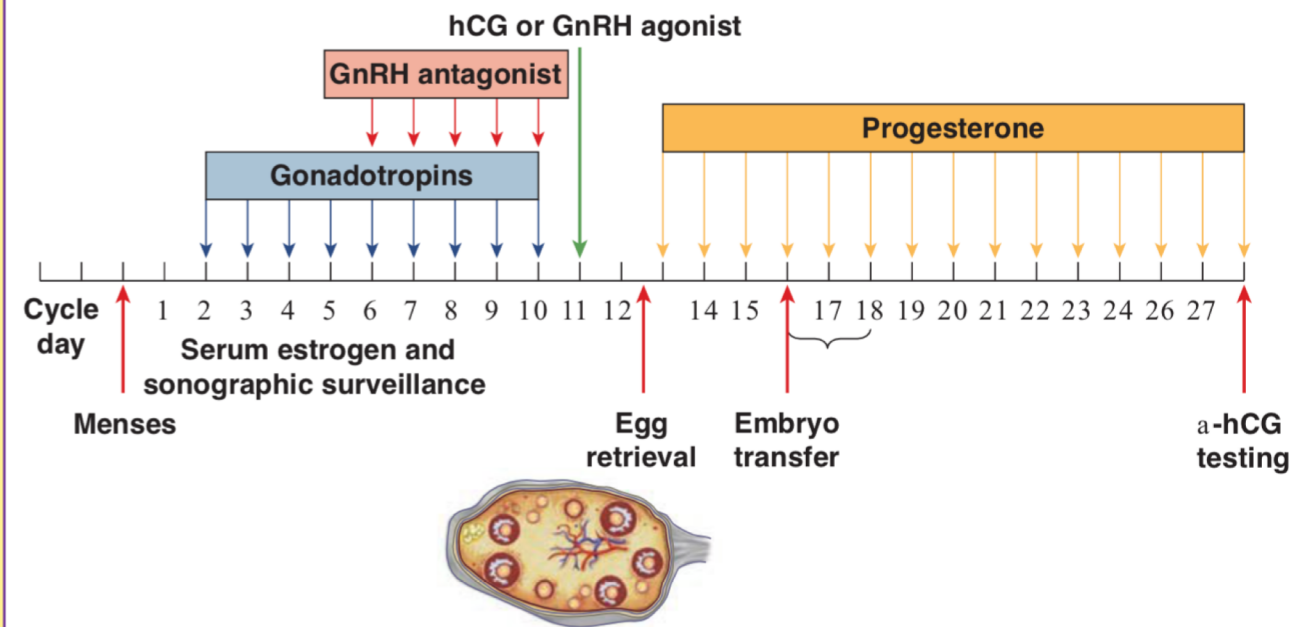


Hoffman, B., Schorge J., Bradshaw K., Halvorson L., Schaffer J., Corton M. (2016). William's gynecology. 3rd ed. New York. McGraw-Hill Education.

IVF Cycle

GnRH agonist trigger (ex. Lupron):

- For IVF: use GnRH antagonist, then GnRH agonist trigger instead of HCG → results in endogenous LH surge
- May prevent early OHSS
 - Decreased risk of severe OHSS in pts with robust ovarian stimulation response
- **Recommend GnRH antagonist protocol with GnRH agonist trigger** for donor oocyte and fertility preservation cycles in which embryo transfer will not occur
- **Less OHSS than HCG trigger (no cases vs 4.6%) with fresh embryo transfer with adequate luteal phase support**
 - GnRH agonist trigger displaces GnRH antagonist from GnRH receptor → induces controlled endogenous LH and FSH surge (endogenous LH has much shorter $t_{1/2}$ than exogenous HCG) → shorter stimulation → less risk of OHSS
- Does not affect embryo quality



Hoffman, B., Schorge J., Bradshaw K., Halvorson L., Schaffer J., Corton M. (2016). William's gynecology. 3rd ed. New York. McGraw-Hill Education.

Lupron 3mg (0.6mL) IM

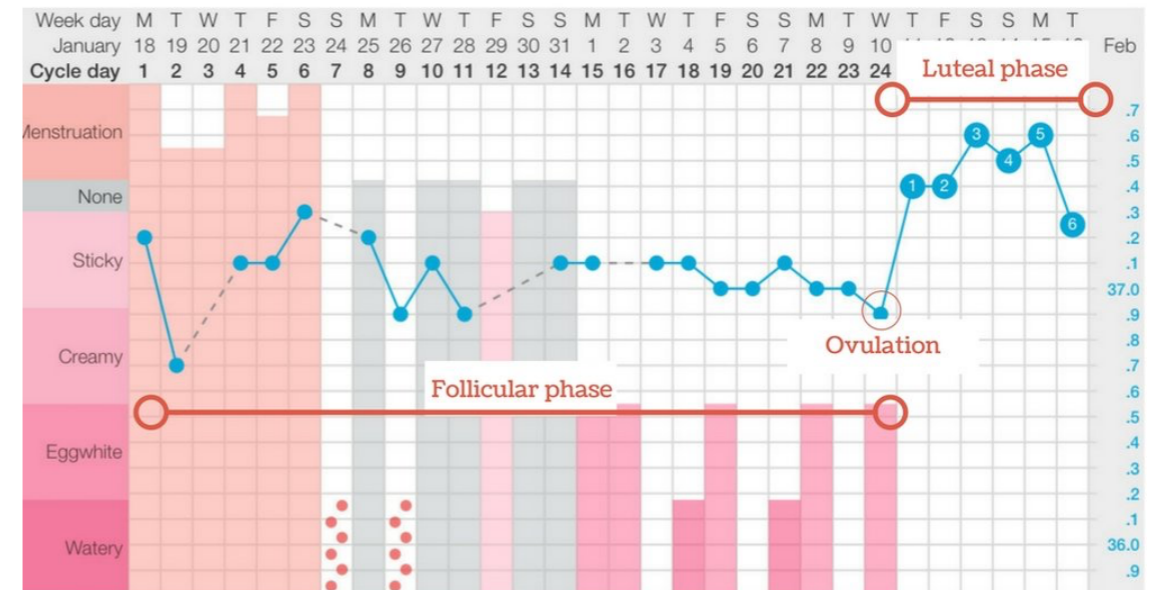
- 1st dose prior to oocyte retrieval
- 2nd dose 10hrs later

IVF Cycle

Risks:

- inadequate luteal phase → need luteal phase support!
 - May have shorter luteal phase and compromised corpus luteum formation, endometrial problems in luteal phase
 - Initial reports: increased early SA, compromised pregnancy
 - Transfer of frozen-thawed embryos: similar SA rates to HCG trigger
 - If embryos are not being transferred into pt during that cycle, no concern for inadequate luteal phase
 - Aggressive luteal phase support: comparable IVF success rates to HCG

SHORT LUTEAL PHASE



Short Luteal Phase [Digital image]. (n.d.). Retrieved from <http://www.thepreggerskitchen.com/short-luteal-phase/>

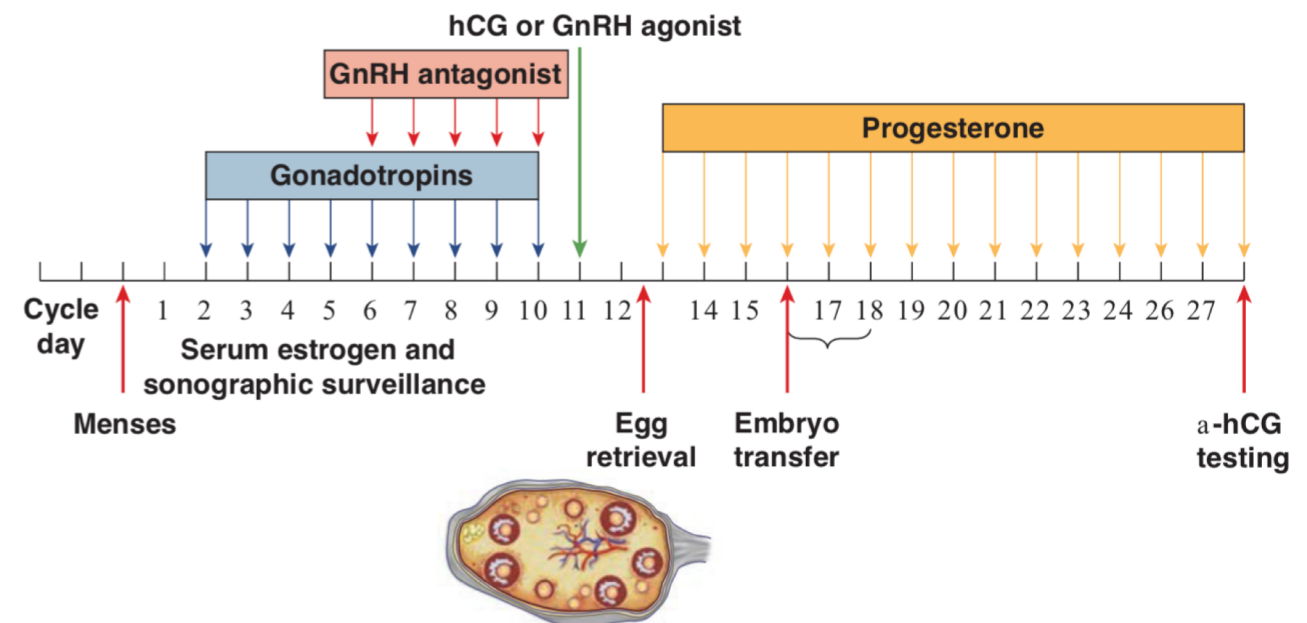
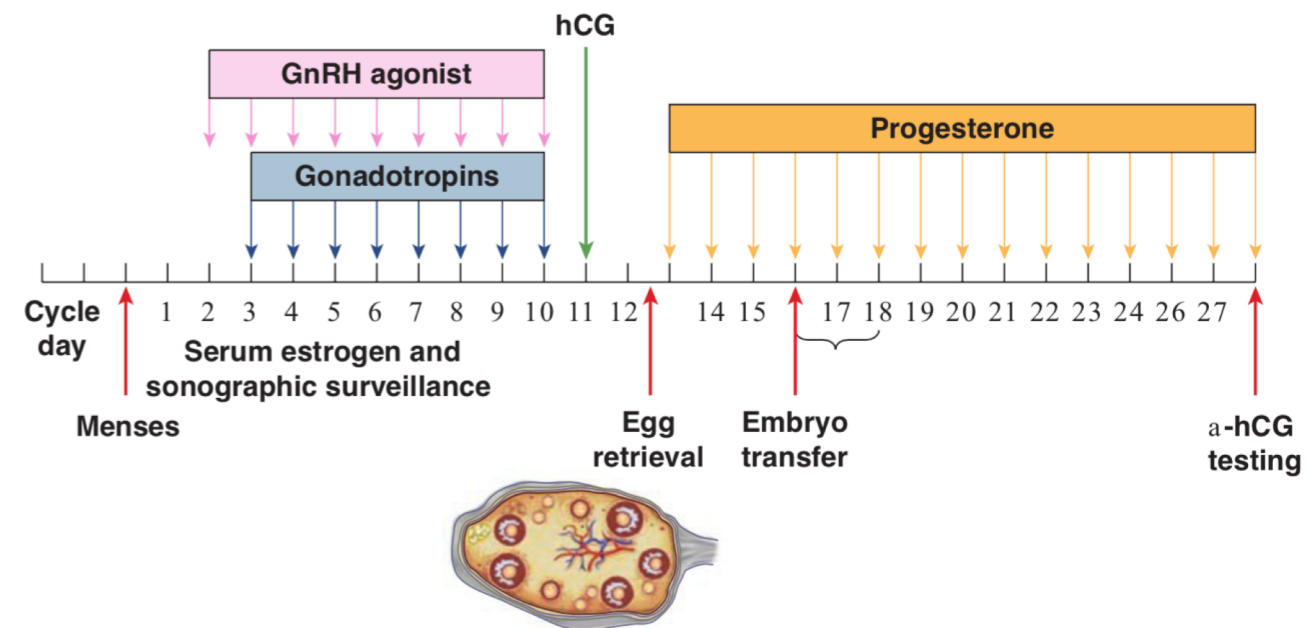
IVF Cycle

Carbegoline

- Decreases risk of severe OHSS when given on the day of HCG trigger
 - Decreases risk of moderate OHSS in pts at high risk for OHSS
 - Decreases risk of early (not late) OHSS
- No adverse effect on pregnancy rates for IVF pts
- Side effect: nausea

Example regimens:

- Ex. Carbegoline 0.5mg 2 times per week for 6 doses, then 0.5mg 2 times per week for 3 doses
- Ex. Carbegoline 0.5mg q3d for 4 doses

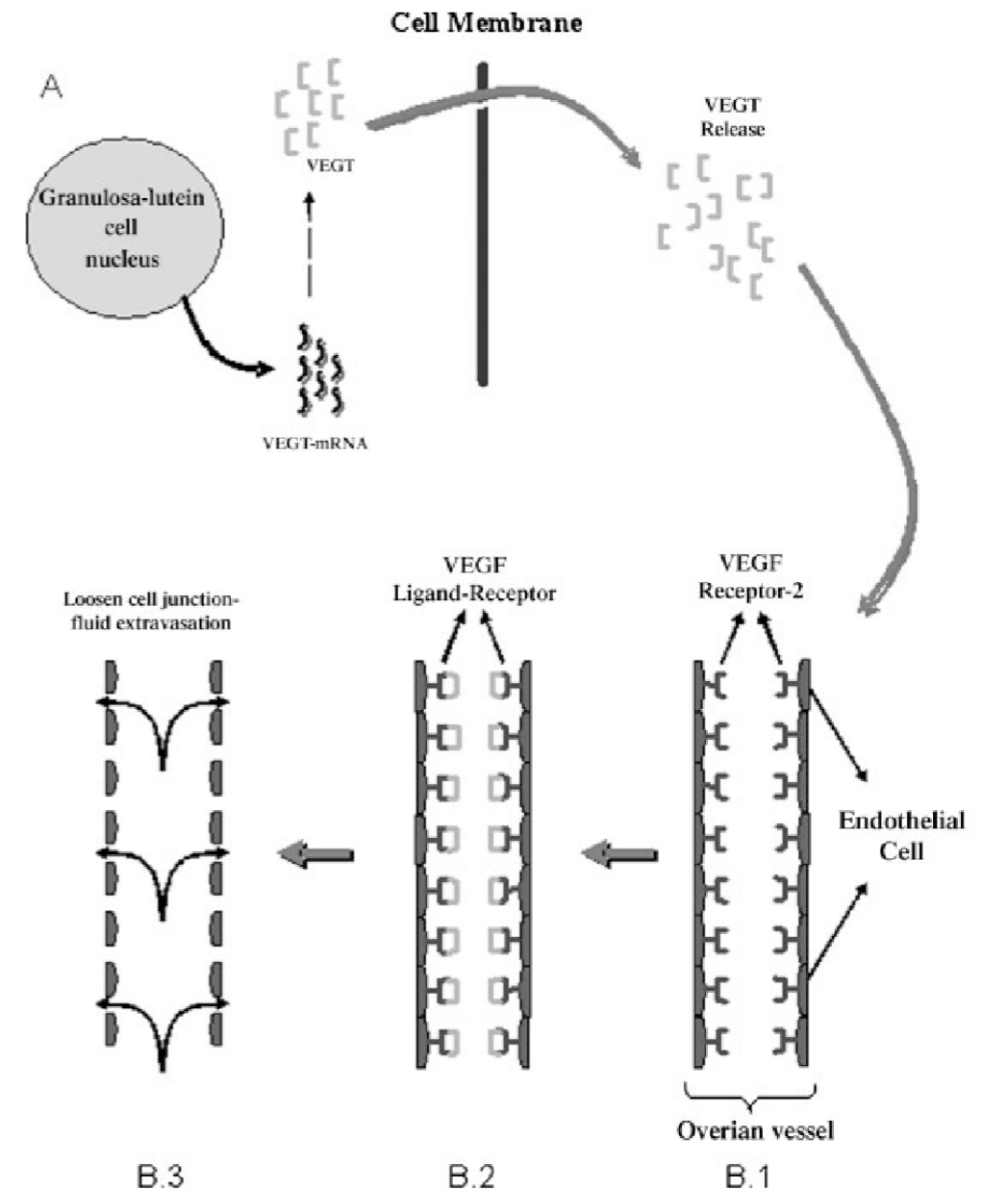
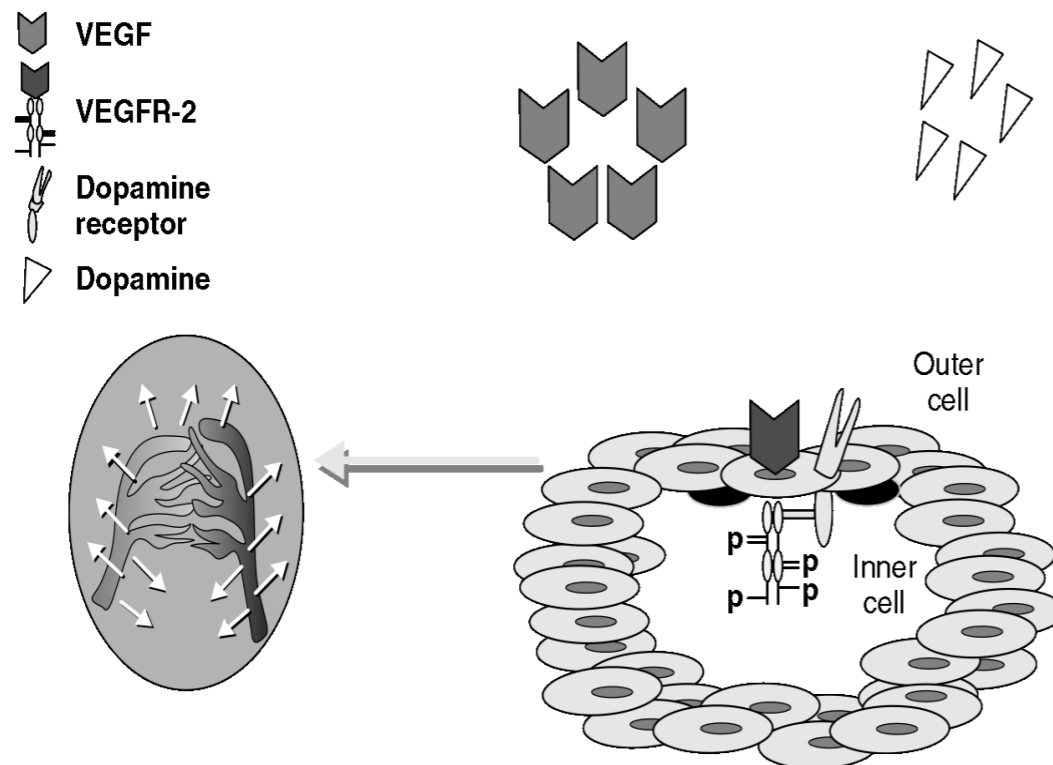


Hoffman, B., Schorge J., Bradshaw K., Halvorson L., Schaffer J., Corton M. (2016). William's gynecology. 3rd ed. New York. McGraw-Hill Education.

Prevention Strategies

Carbегoline

- Dopamine agonist
- Activates dopamine receptors (partial inhibition of phosphorylation of VEGF2 receptor) → internalization of VEGF → blocks VEGF-mediated vasodilation
- Does not affect ovarian angiogenesis



ovarian hyperstimulation syndrome pathophysiology. (A) High amounts of vascular endothelial m

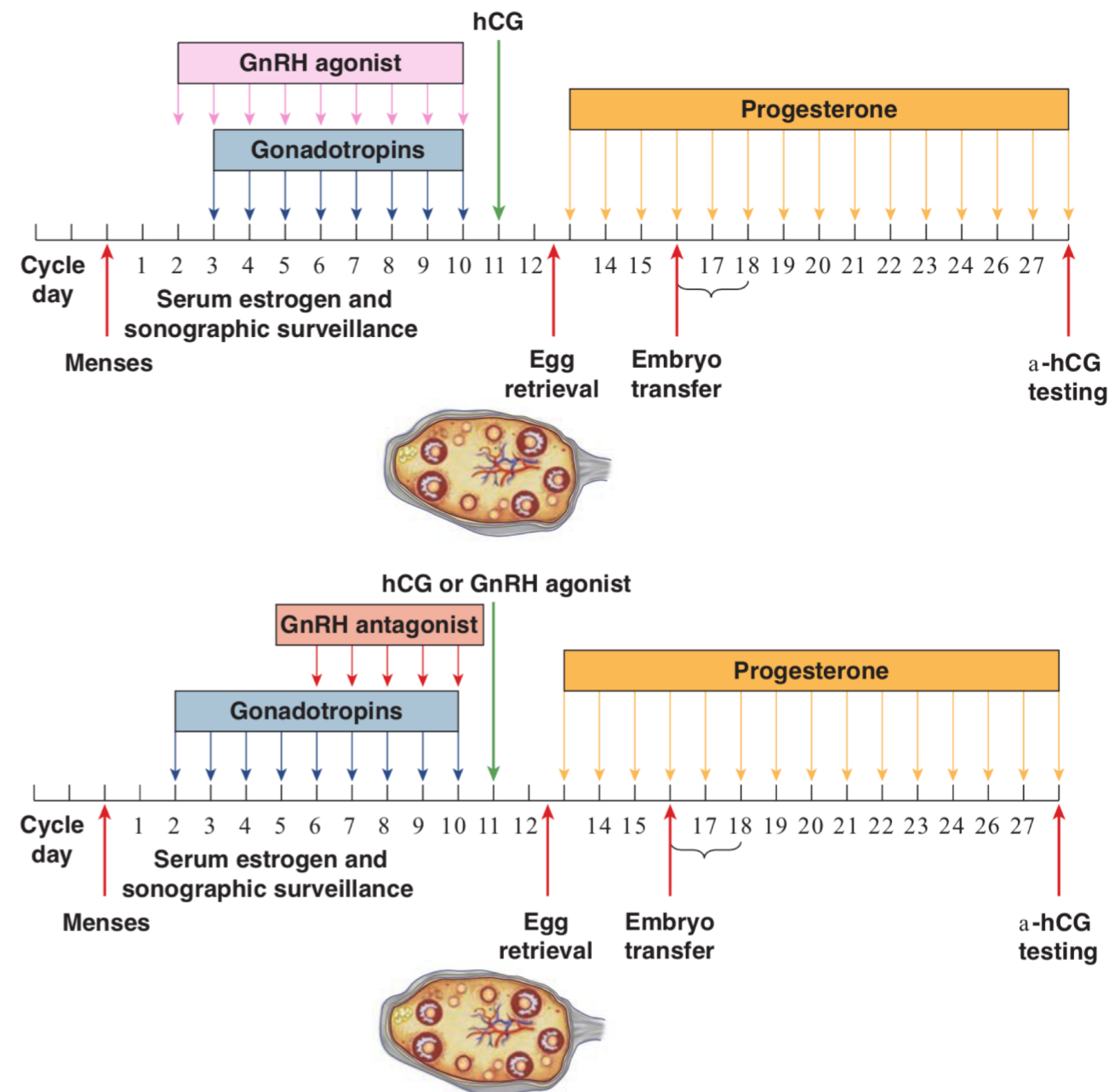
Rizk, B. (2011, August). Ovarian hyperstimulation syndrome [Digital image]. Retrieved from <https://www.cambridge.org/core/books/ovarian-stimulation/ovarian-hyperstimulation-syndrome/22C529660397A0D033B3C050D4D669AE>

Gomez, R., Soares, S., & Pellicer, A. (2010). Ovarian hyperstimulation syndrome pathophysiology [Digital image]. Retrieved from <https://www.semanticscholar.org/paper/Physiology-and-pathology-of-ovarian-syndrome.-Gómez-Soares/f0cc584228e65e4d225ef77c57b0adcaed57c713>

IVF Cycle

Cycle cancellation

- **Withhold HCG trigger if cycle is at risk of OHSS,** consider IVF in the future rather than attempting ovulation induction
- **Most effective method at preventing OHSS!**
 - Especially important when do not have a substitute for HCG to trigger ovulation
- Drawbacks
 - Financial and emotional cost → try other prevention strategies before cancelling cycle

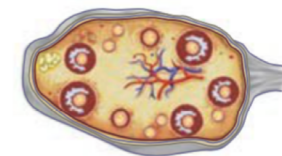
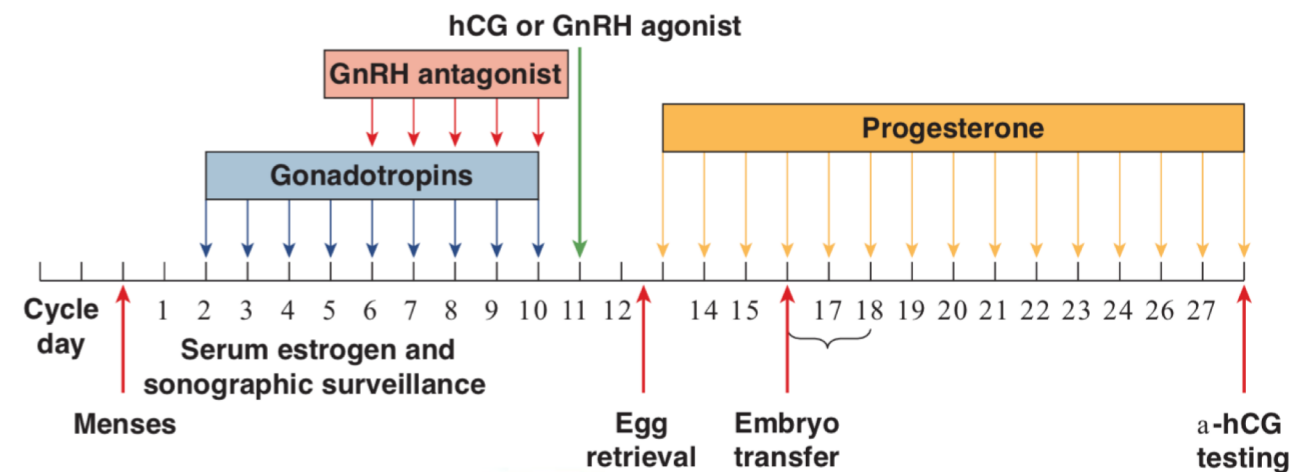
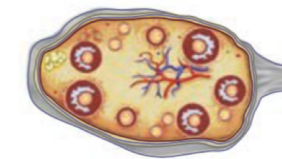
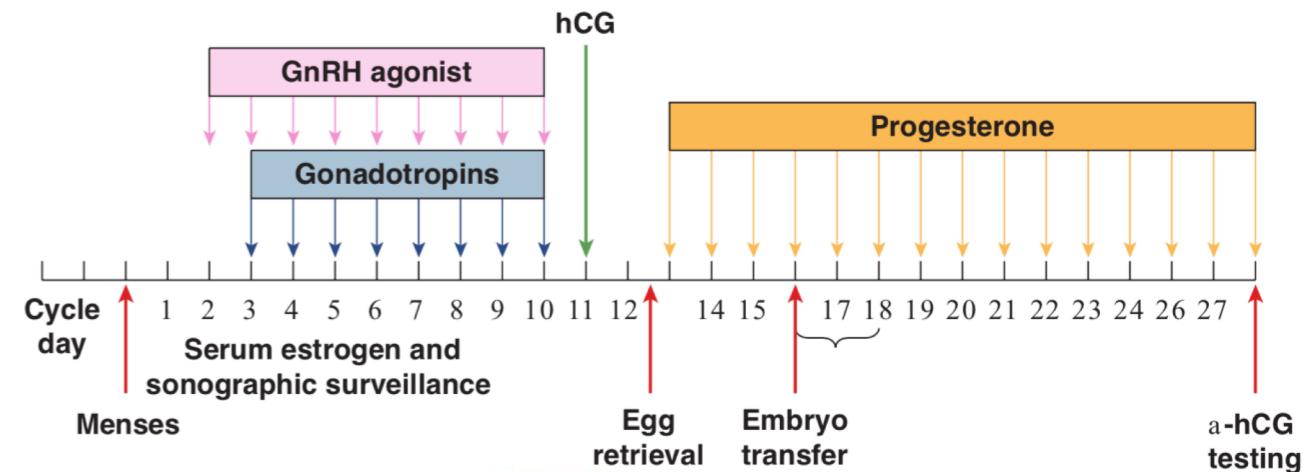


Hoffman, B., Schorge J., Bradshaw K., Halvorson L., Schaffer J., Corton M. (2016). William's gynecology. 3rd ed. New York. McGraw-Hill Education.

IVF Cycle

Prophylactic IV fluids:

- IV fluids at the time of oocyte retrieval **not recommended**
 - Albumin, HES, Haemaccel, dextran
 - Safety of HES has not been established



Hoffman, B., Schorge J., Bradshaw K., Halvorson L., Schaffer J., Corton M. (2016). William's gynecology. 3rd ed. New York. McGraw-Hill Education.

IVF Cycle

Cryopreservation (freezing) of all embryos

- For pts on GnRH antagonist protocol at high risk for severe OHSS
- Prevents possibility of pregnancy in the cycle → decreases incidence of severe prolonged OHSS
 - Pregnancy is associated with prolonged hospitalization for pts with severe OHSS
- Process
 - GnRH agonist trigger → egg retrieval → eggs are vitrified (flash-freezing) → eggs are thawed at a later date → fertilization → embryos transfer later
- Issue: embryo survival, chance of success
 - Comparable to cycle cancellation at preventing OHSS
 - Embryo survival rates have improved with oocyte vitrification → little compromise in success of IVF
- Benefits
 - Higher pregnancy and implantation rates with cryopreservation than fresh embryo transfer after coasting
 - No OHSS cases reported with cryopreservation and then embryo transfer
 - Does not affect pregnancy rates in GnRH antagonist protocols then GnRH trigger

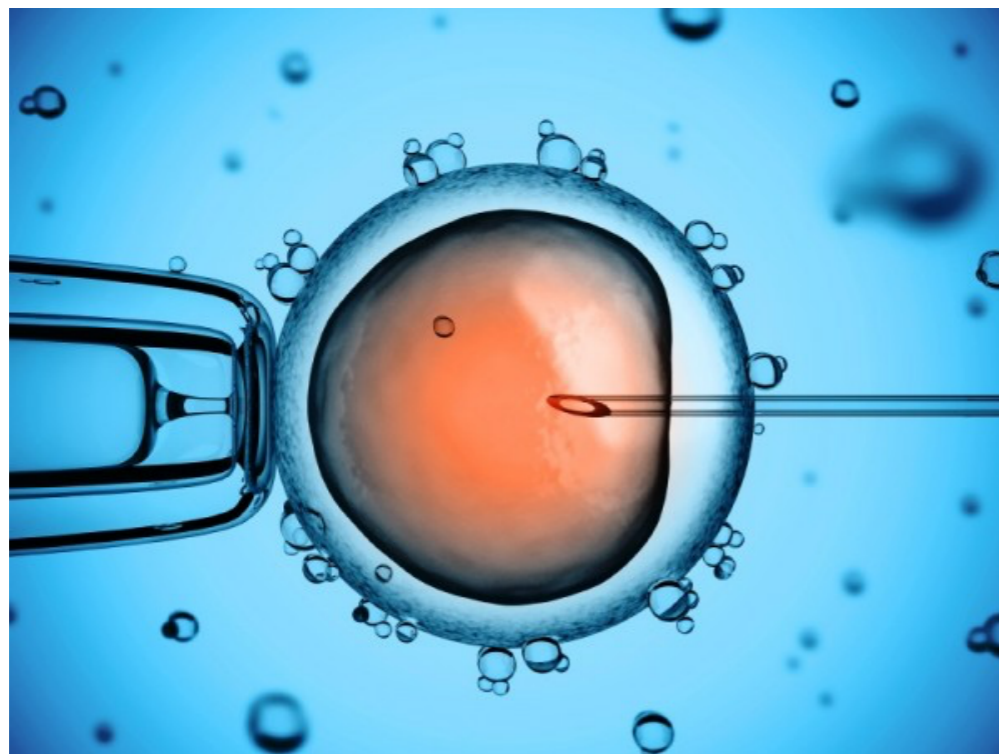


Lane, D. (n.d.). [Digital image]. Retrieved from <https://www.lanefertilityinstitute.com/blog/egg-freezing-embryo-banking>

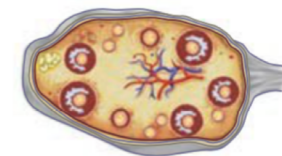
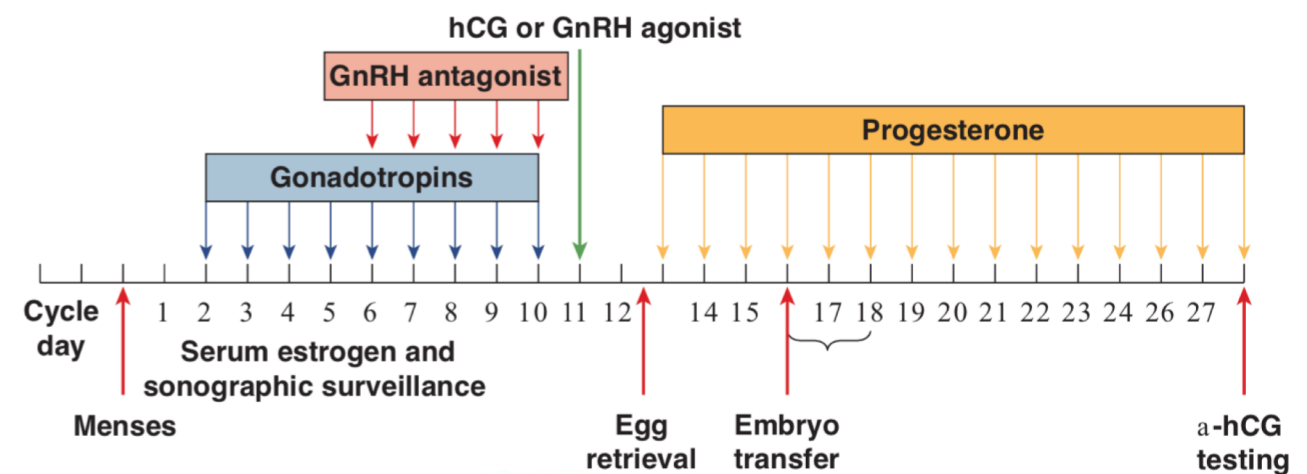
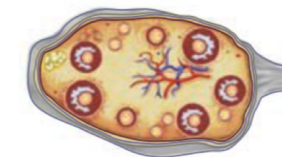
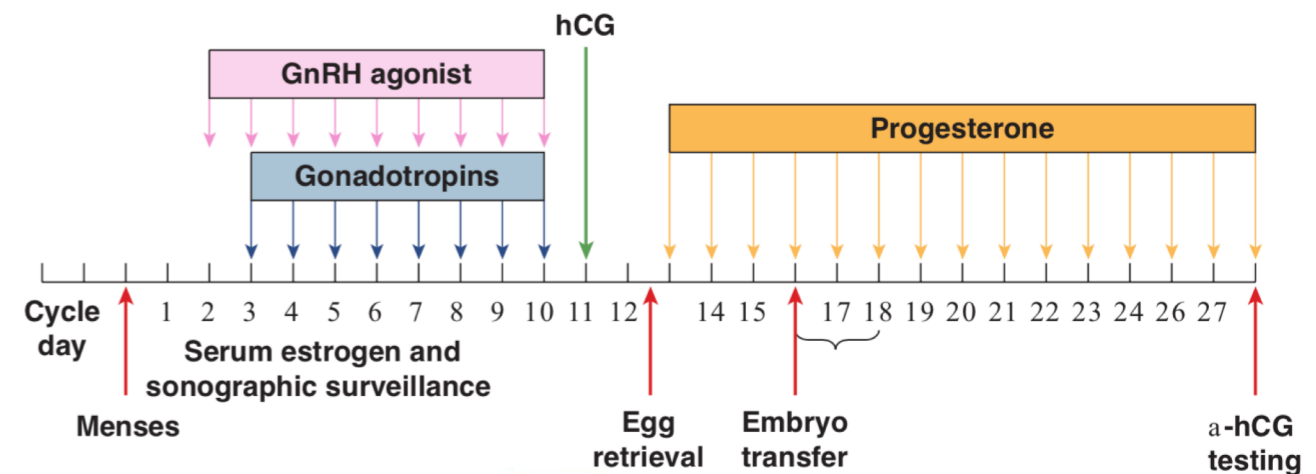
IVF Cycle

Elective single embryo transfer

- For pts at high risk of OHSS
- Decreases risk of multiple gestations, severe OHSS
 - HCG levels are higher in multiples than singleton pregnancy → multiples have higher risk of severe OHSS



Weiss, R. (2015, February 7). Why We Prefer Transferring A Single Embryo [Digital image]. Retrieved from https://www.fertilitycenter.com/fertility_cares_blog/why-we-prefer-transferring-a-single-embryo/



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IVF Cycle

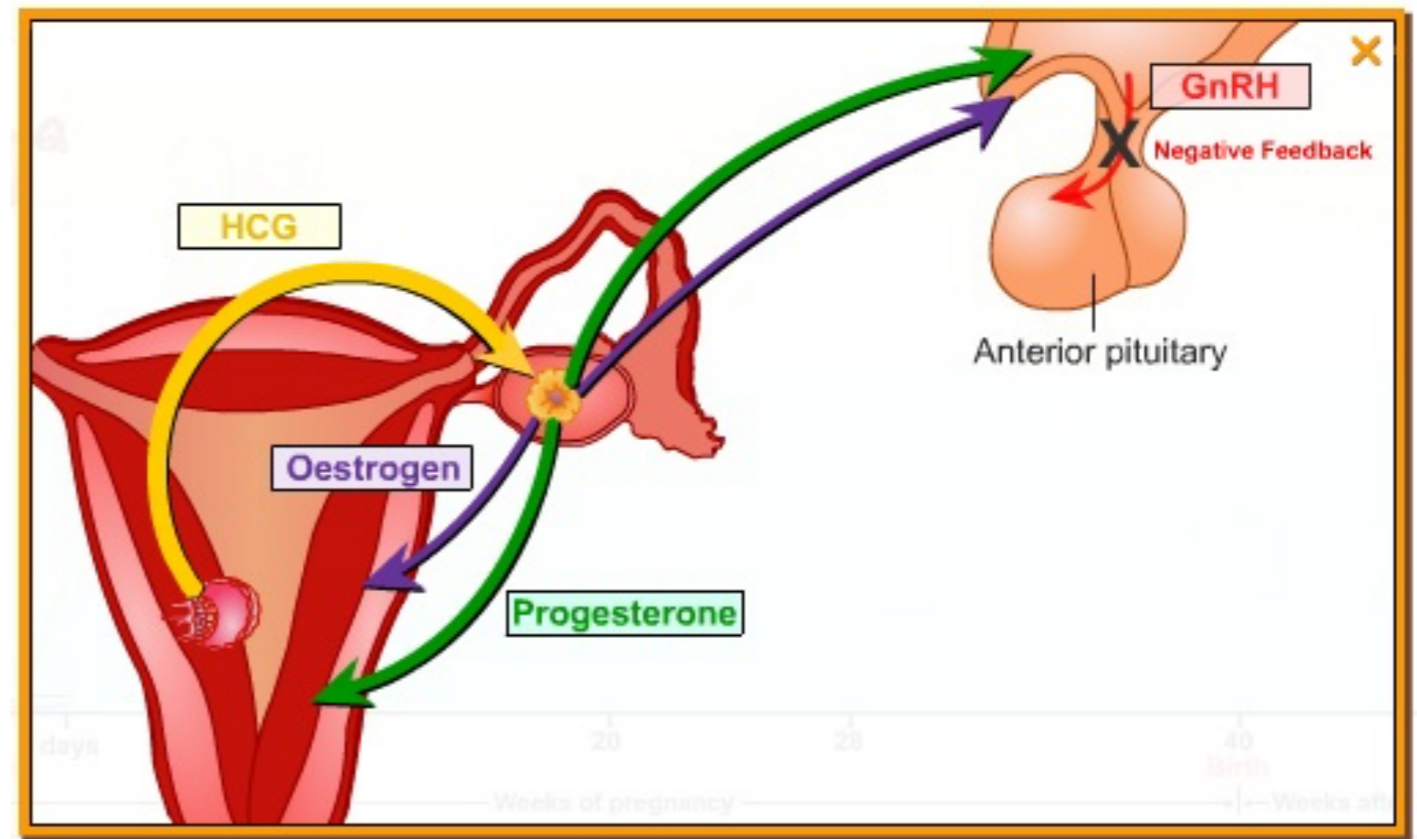
- In early pregnancy, HCG acts on corpus luteum → corpus luteum produces estrogen and progesterone to support pregnancy until placental steroidogenesis is established

Luteal phase support (LPS):

- Needed to maximize chance of pregnancy
- Used in GnRH agonist-triggered cycles

2 approaches:

- 1) Estrogen+ progesterone supplement
 - Allows for corpus luteum to degenerate
 - Decreases risk of OHSS
- 2) Administer HCG on the day of egg retrieval+ standard LPS (estrogen + progesterone)
 - HCG can increase risk of OHSS!

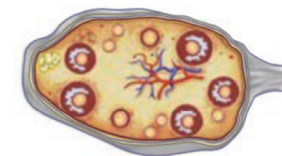
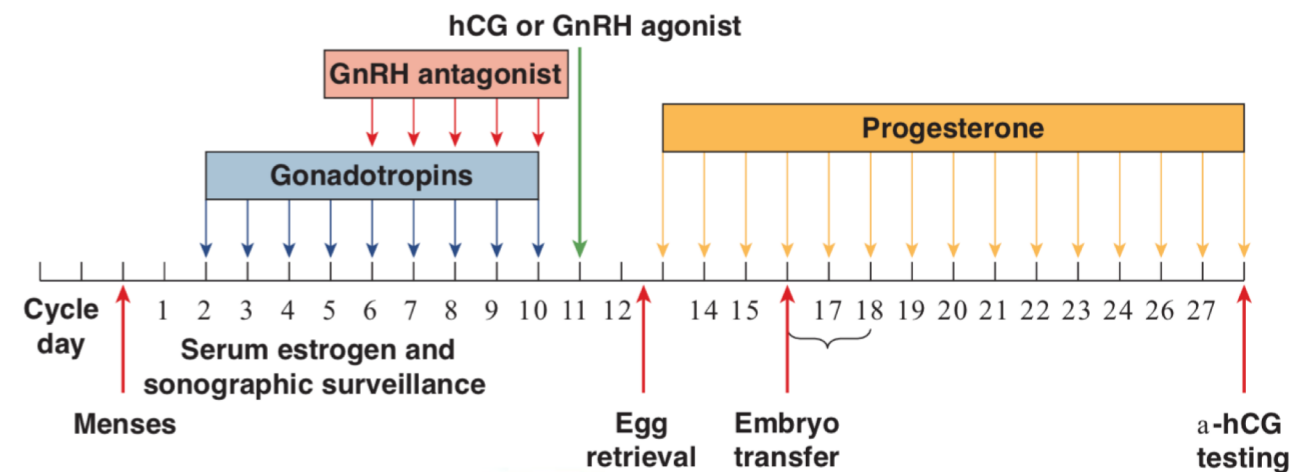
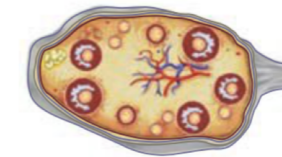
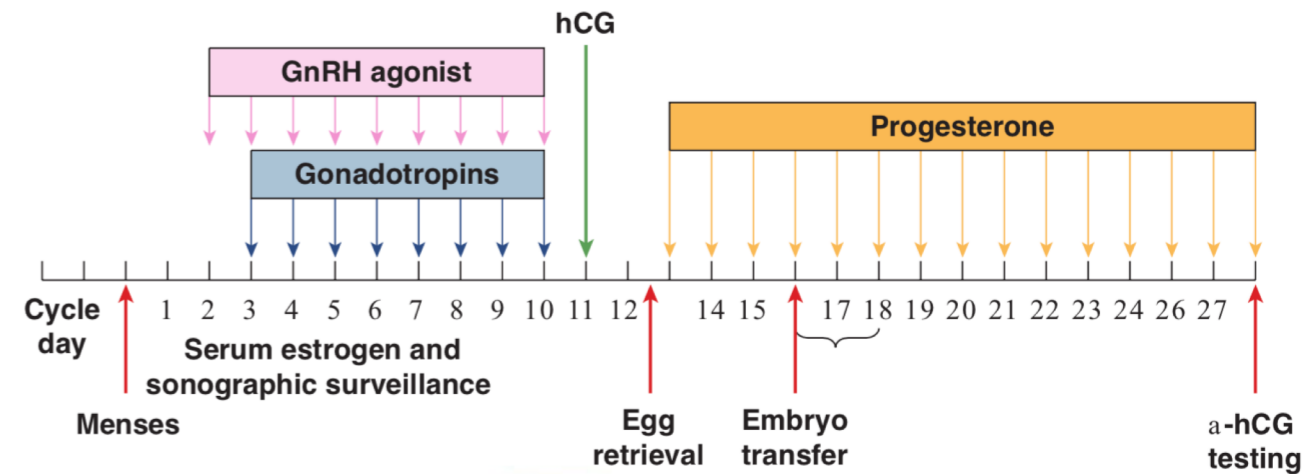


[Digital image]. (2012, September 15). Retrieved from <http://biomhs.blogspot.com/2012/09/hormones-in-reproduction-ii.html>

IVF Cycle

Luteal phase support:

- **Progesterone** should be used instead of HCG
 - Both are equally effective
 - HCG has higher risk of OHSS and may worsen established OHSS



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