HN

SEASON 2

Farah Saeed FS Farah Saeed

Understanding Cancer

Lecture 14

Types of signalling pathway: normal and dysregulated Oestrogen

DR HAFSA WASEELA ABBAS

www.hafsaabbas.com

RECAP:

What you hopefully should understand so far from Lecture 13

- **The Wnt ligands are cysteine-rich glycoproteins that bind to a specific receptor called Frizzled and a protein called LRP.**
- **There are three types of Wnt signalling pathways: β-catenin dependent, β-catenin Independent** And **planar cell polarity**
- **The Wnt ligands can also bind to RYK and ROR receptor families.**
- **The receptor-ligand complex leads to the activation and polymerization of Dishevelled protein.**
- **The activated Dishevelled polymer suppresses and deactivates the destruction complex.**
- **The destruction complex consists of the following: AXIN, APC and two kinases CK1α and GSK3β.**
- **Repressing the complex increases the accumulation of the β-catenin protein that lead to transcription of genes.**
- **Dysregulated Wnt signalling pathway is caused by: Increased Wnt activity, GSK3β mutations And increased β-catenin accumulation**

What will we learn today?

- *What is oestrogen?*
- *Types of oestrogen*
- *The function of oestrogen.*
- *How does the production of oestrogen vary with age?*
- *The menstrual cycle*
- *Follicular phase*
- *Ovulation*
- *Luteal phase*
- *Receptor activation*
- *Signal transduction*
- *Genomic signalling pathway.*
- *Non-genomic signalling pathway.*
- *Cellular response*
- *Dysregulated oestrogen signalling pathway*

GENTLE REMINDER
An ideal way of learning:

Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday

Mini-lectures.

Approximate total time: 1 hour

Divide over 7 days at your **own pace**.

Challenge yourself with a quiz!

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RECAP: How to support your learning?

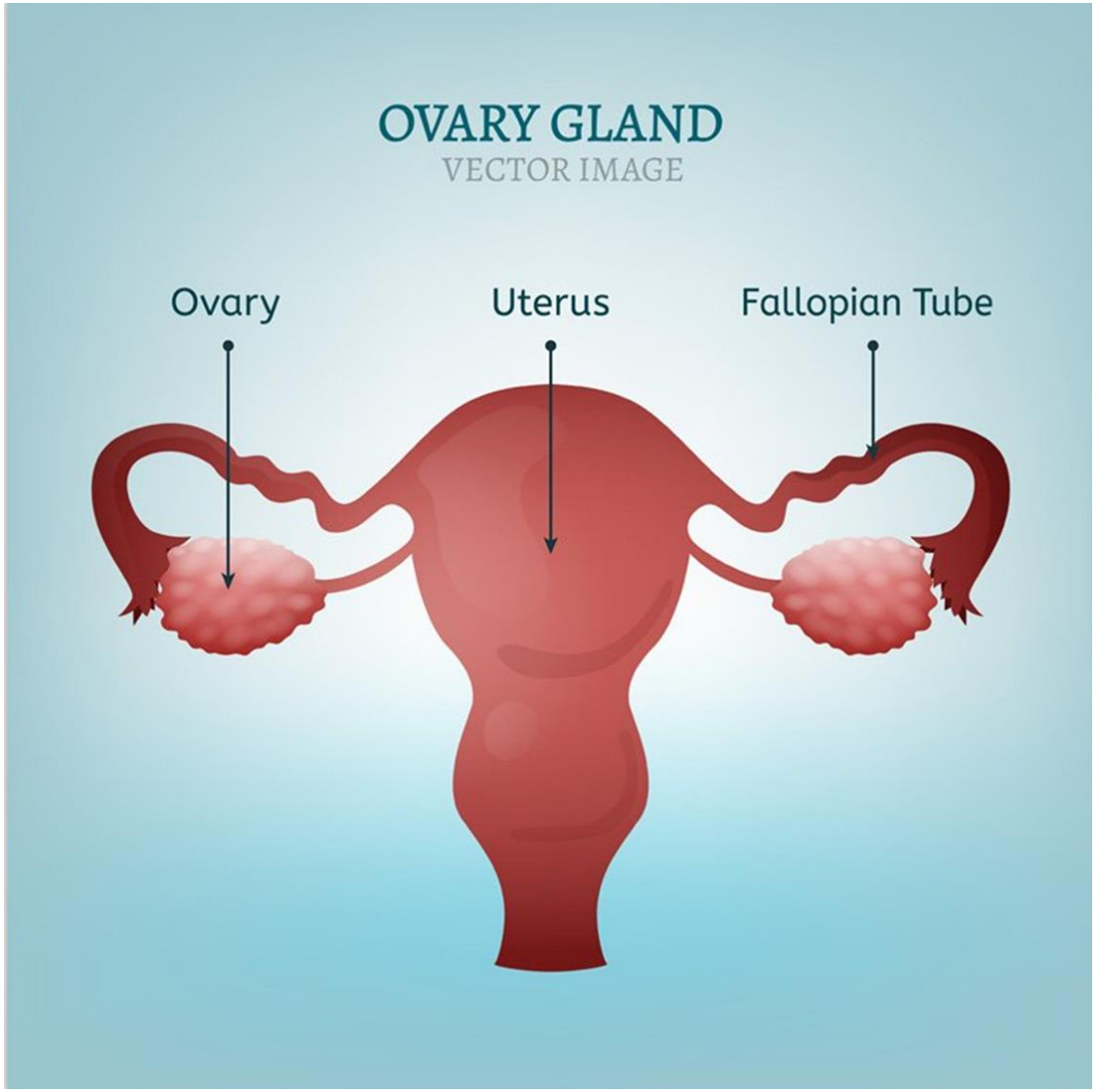
- **Key facts with diagrams by HN designs presented in a simplified way.**
- **Glossary to help understand what key words mean.**
- **Summary doodle revision posters by HN designs.**
- **Quizzes to test your knowledge and reflect.**
- **Reference list for further reading.**

Acknowledgements: Special thanks to my parents, family, friends and colleagues for their support and the respected teachers and health professions who taught me and installed the passion of cancer/oncology.

What is oestrogen?

What is oestrogen?

It is a **steroid hormone** that is produced in the **reproductive organs** of women called **ovaries.**



(Creative Market, 2023a; Rodriguez *et al.,*2019a; Saha Roy, and Vadlamudi, 2012; Williams and Lin, 2013; Manavathi *et al*., 2013)

Types of oestrogen

Types of oestrogen

Oestradiol

- **The main form found in women.**

Oestrone

- **It is produced after menopause.**

Oestriol

- **This form is produced during pregnancy.**

(Rodriguez *et al.,*2019a; Saha Roy, and Vadlamudi, 2012; Williams and Lin, 2013; Manavathi *et al*., 2013)

The function of oestrogen

The function of oestrogen

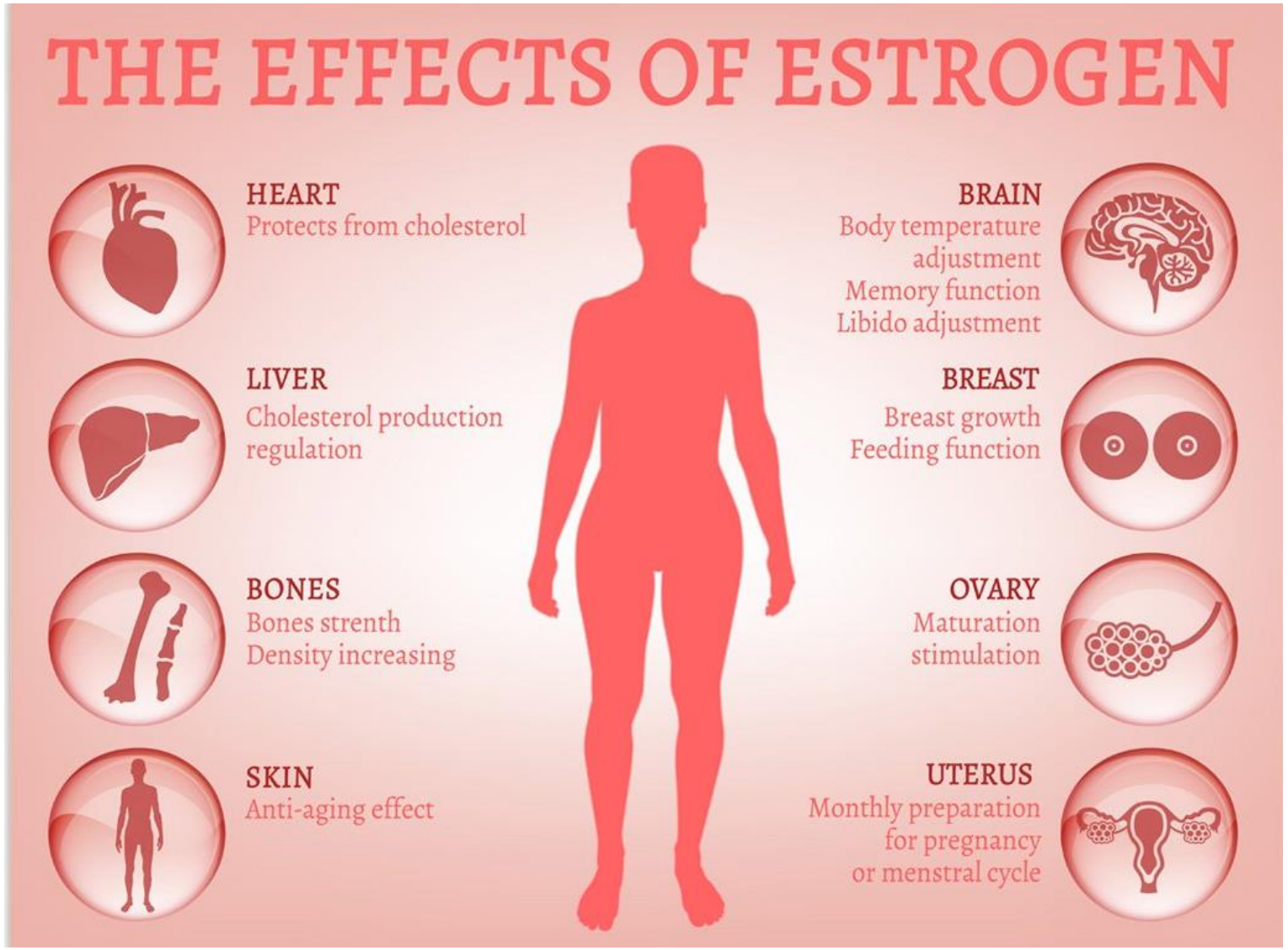
Growth of the womb (uterus)

Period (menstruation)

Pregnancy

Cell-to-cell communication in the breasts.

(Rodriguez *et al.,*2019a; Saha Roy, and Vadlamudi, 2012; Williams and Lin, 2013; Manavathi *et al*., 2013)

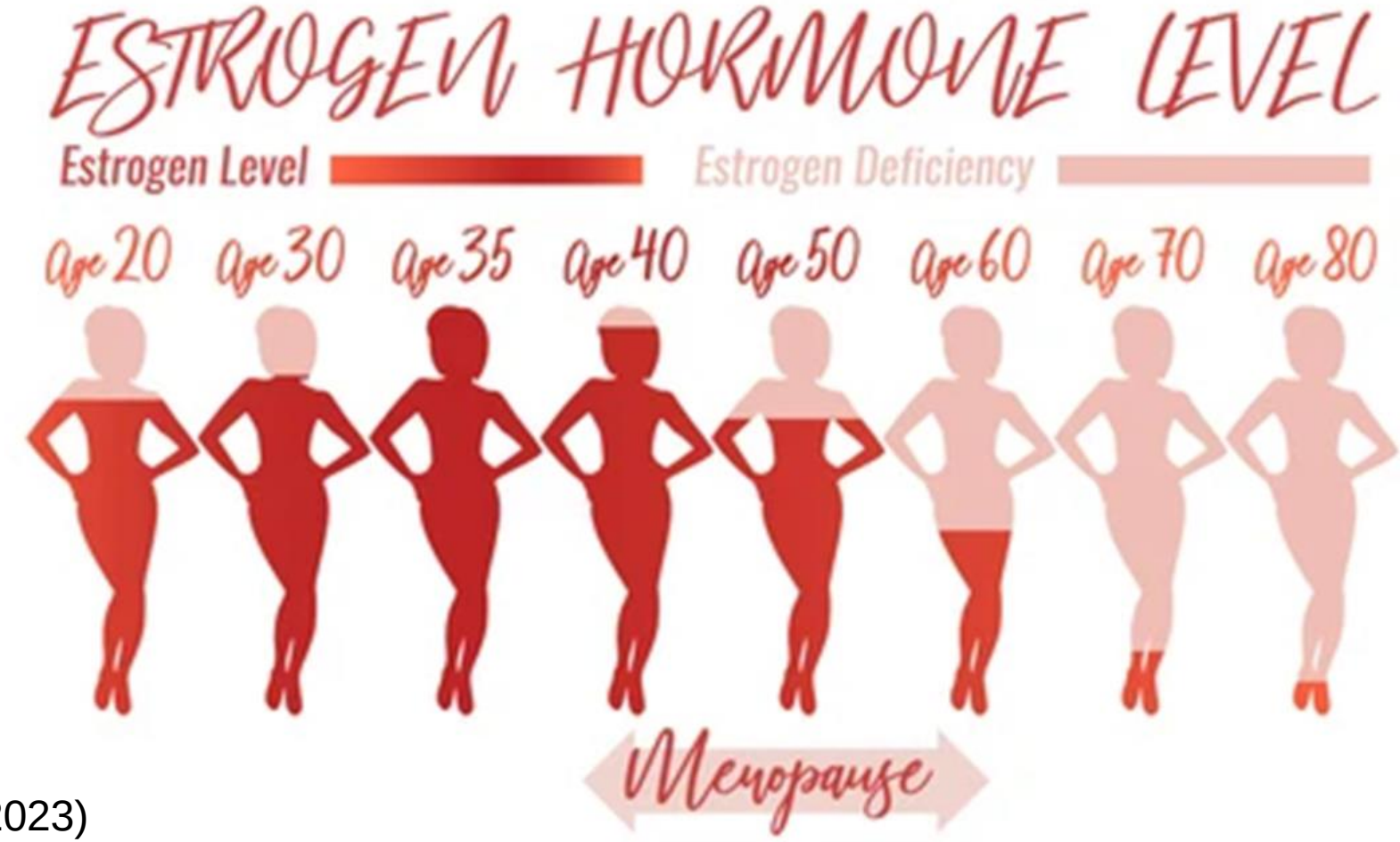


It has many effects on different organs of the body.

(Creative Market, 2023b)

How does the production of oestrogen vary with age?

How does the production of oestrogen vary with age?



(Shutterstock, 2023)

The menstrual cycle

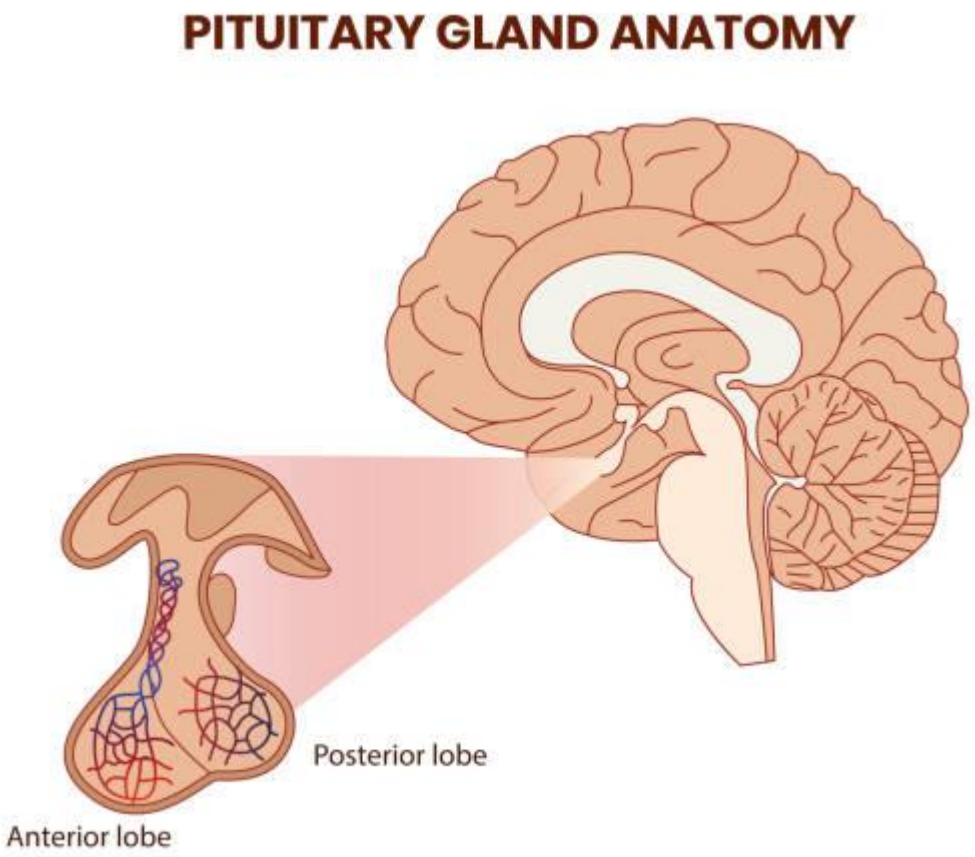
The menstrual cycle

Period (menstruation) is one of the changes that occurs to **females in their teenager years.**

It is the **release of an egg from the ovaries every 28 days** and **changes in the thickness of the womb lining.**

It is controlled by **hormones secreted by the ovaries and the pituitary gland.**

The **pituitary gland is located in the brain.**



iStockPhoto 2023 Pituitary Gland stock illustrations
https://www.istockphoto.com/illustrations/pituitary-gland

(Rodriguez *et al.,*2019a; Saha Roy, and Vadlamudi, 2012; Williams and Lin, 2013; Manavathi *et al*., 2013)

The menstrual cycle

There are three stages that occurs in menstruation:

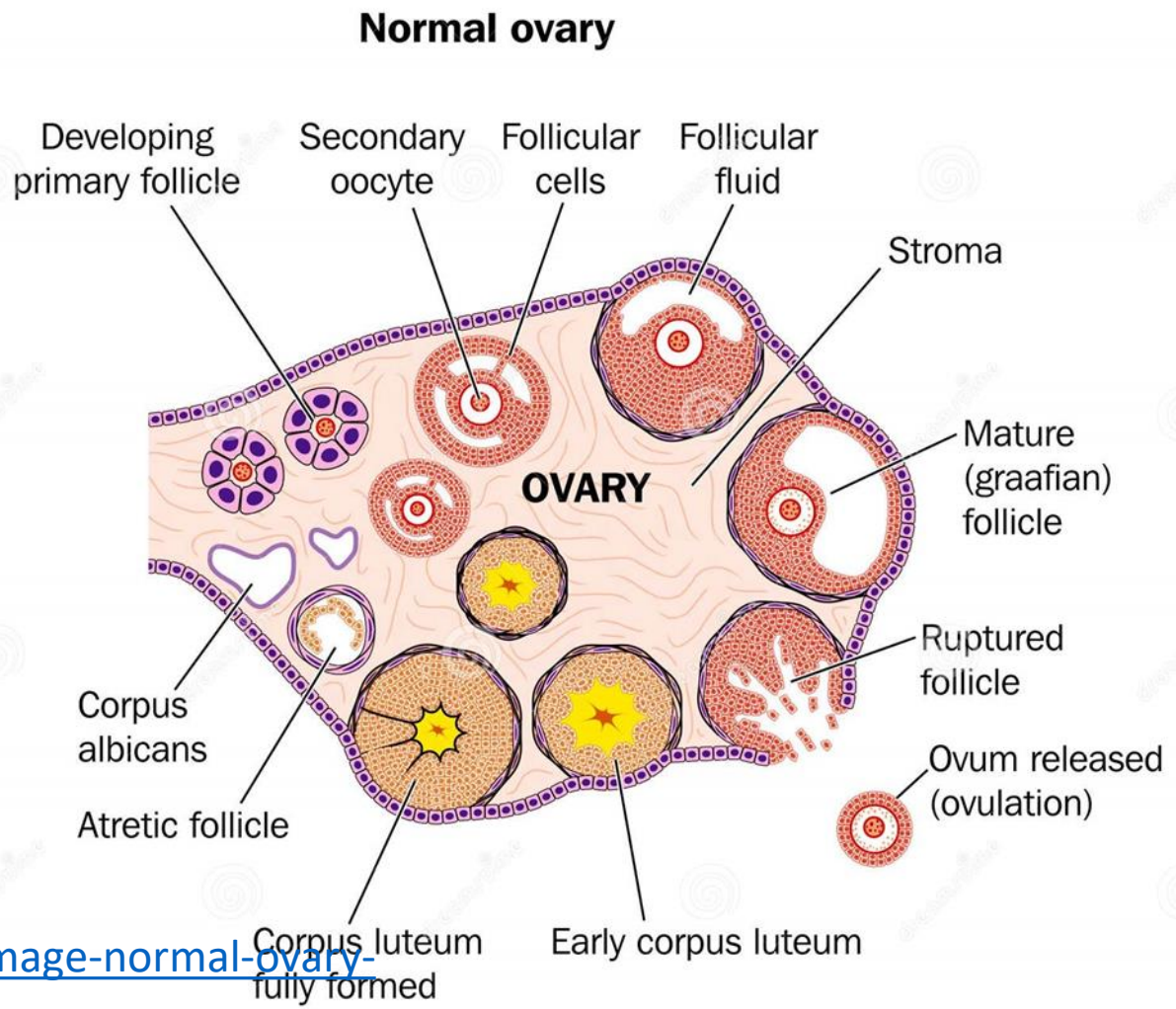
(Rodriguez *et al.,*2019a; Saha Roy, and Vadlamudi, 2012; Williams and Lin, 2013; Manavathi *et al*., 2013)

Follicular phase

Follicular phase

This **during the two weeks** where **the egg grows through different stages** to **become a mature follicle.**

There are low level of oestrogen produced at the start.



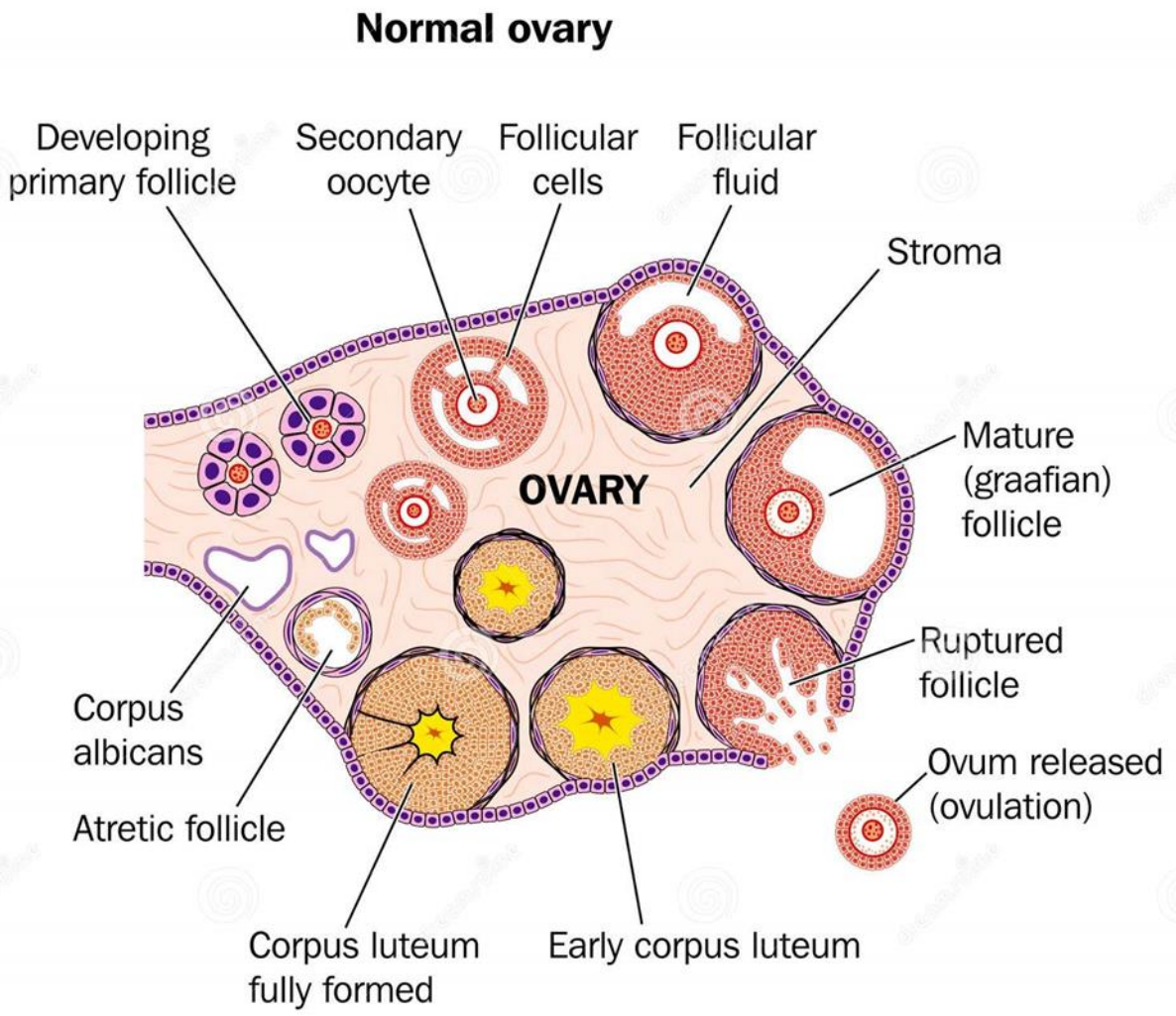
2000-2023 Dreamstime.Normal ovary
https://www.dreamstime.com/stock-image-normal-ovary-image13281711

(Rodriguez *et al.,*2019a; Saha Roy, and Vadlamudi, 2012; Williams and Lin, 2013; Manavathi *et al*., 2013)

Follicular phase

A hormone produced in the **pituitary gland** called the **Follicle stimulating hormone (FSH) stimulates the egg cell to develop the follicles.**

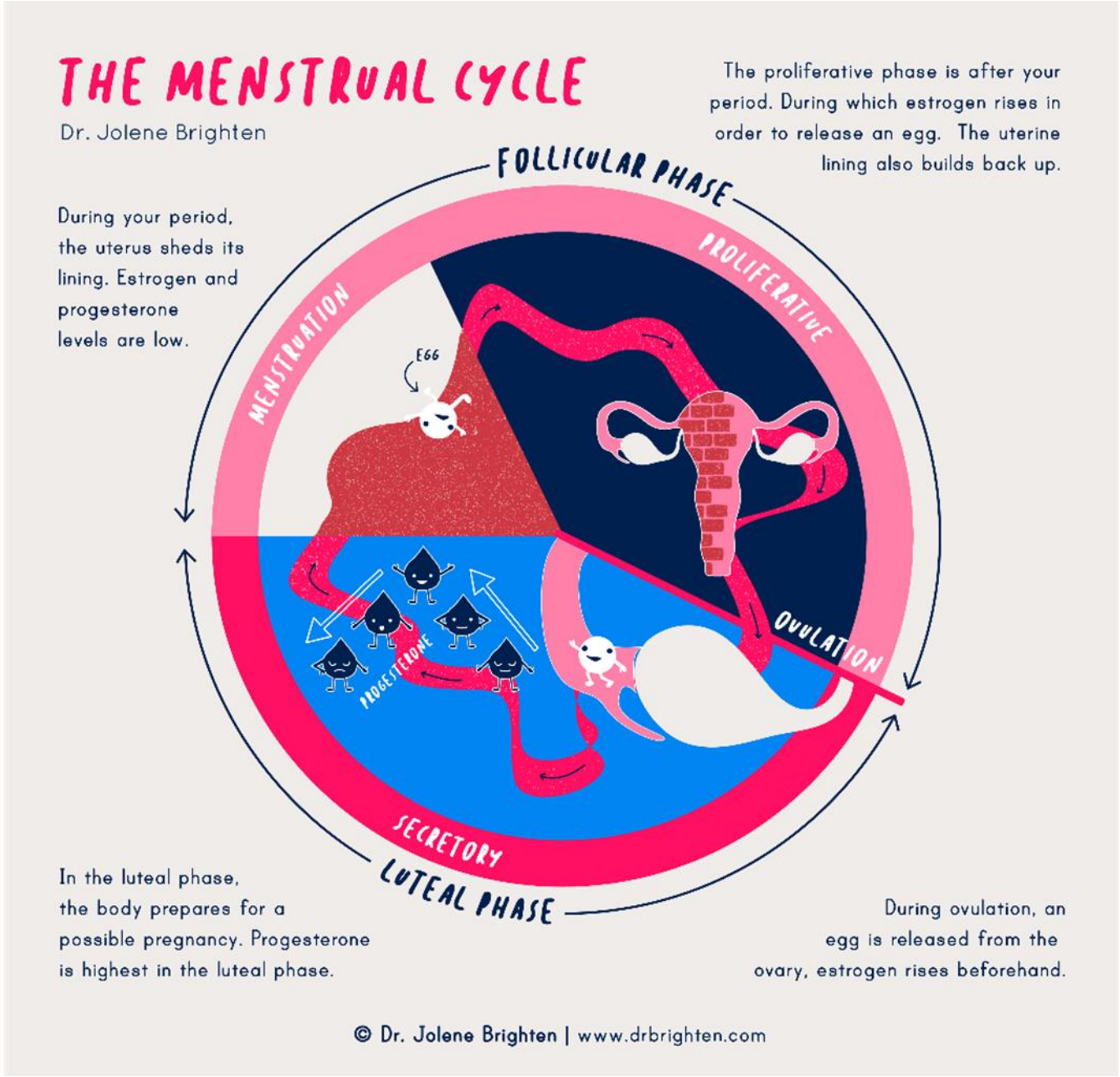
This increases the levels of **oestrogen.**



(Rodriguez *et al.,*2019a; Saha Roy, and Vadlamudi, 2012; Williams and Lin, 2013; Manavathi *et al*., 2013)

Follicular phase

In the **late follicular phase**, **an increase of oestrogen** levels leads to an **increase the need of another hormone secreted in the pituitary gland called the Lutienizing Hormone (LH).**

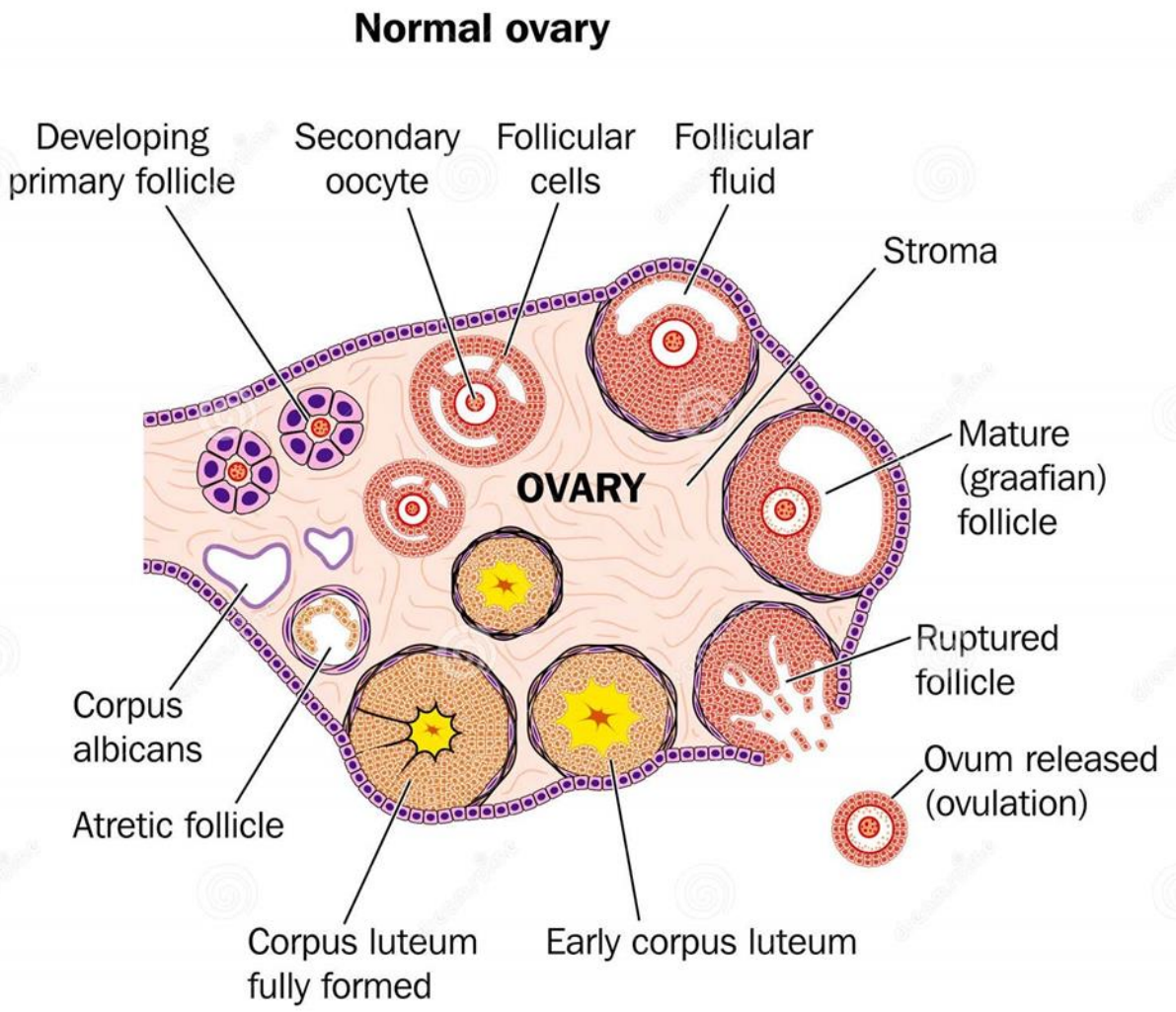


Ovulation phase

Ovulation phase

Day 14 of the 28 days is normally when the mature follicle is released.

This is triggered by the **luteinizing hormone.**

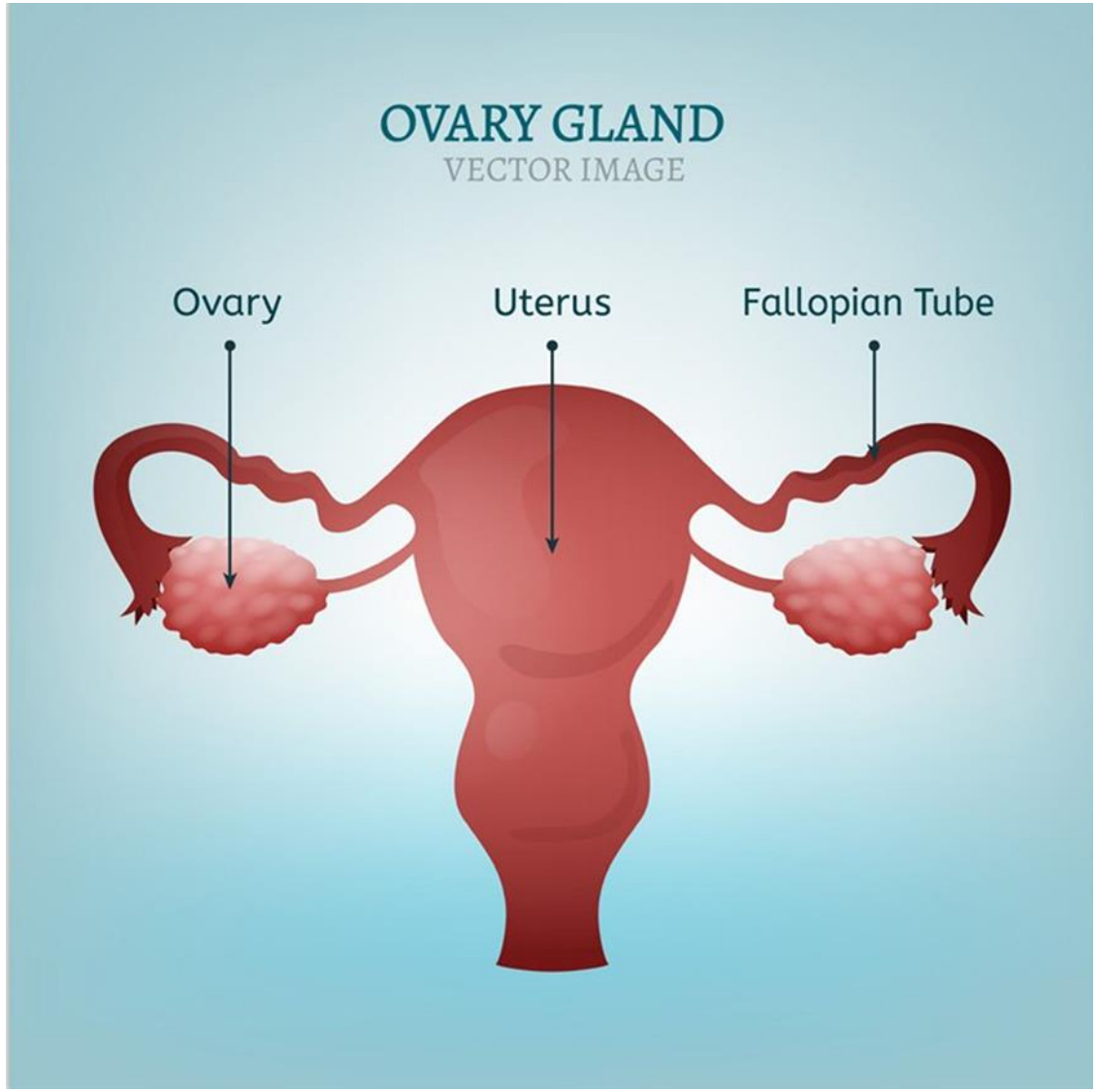


(Rodriguez *et al.,*2019a; Saha Roy, and Vadlamudi, 2012; Williams and Lin, 2013; Manavathi *et al*., 2013)

Ovulation phase

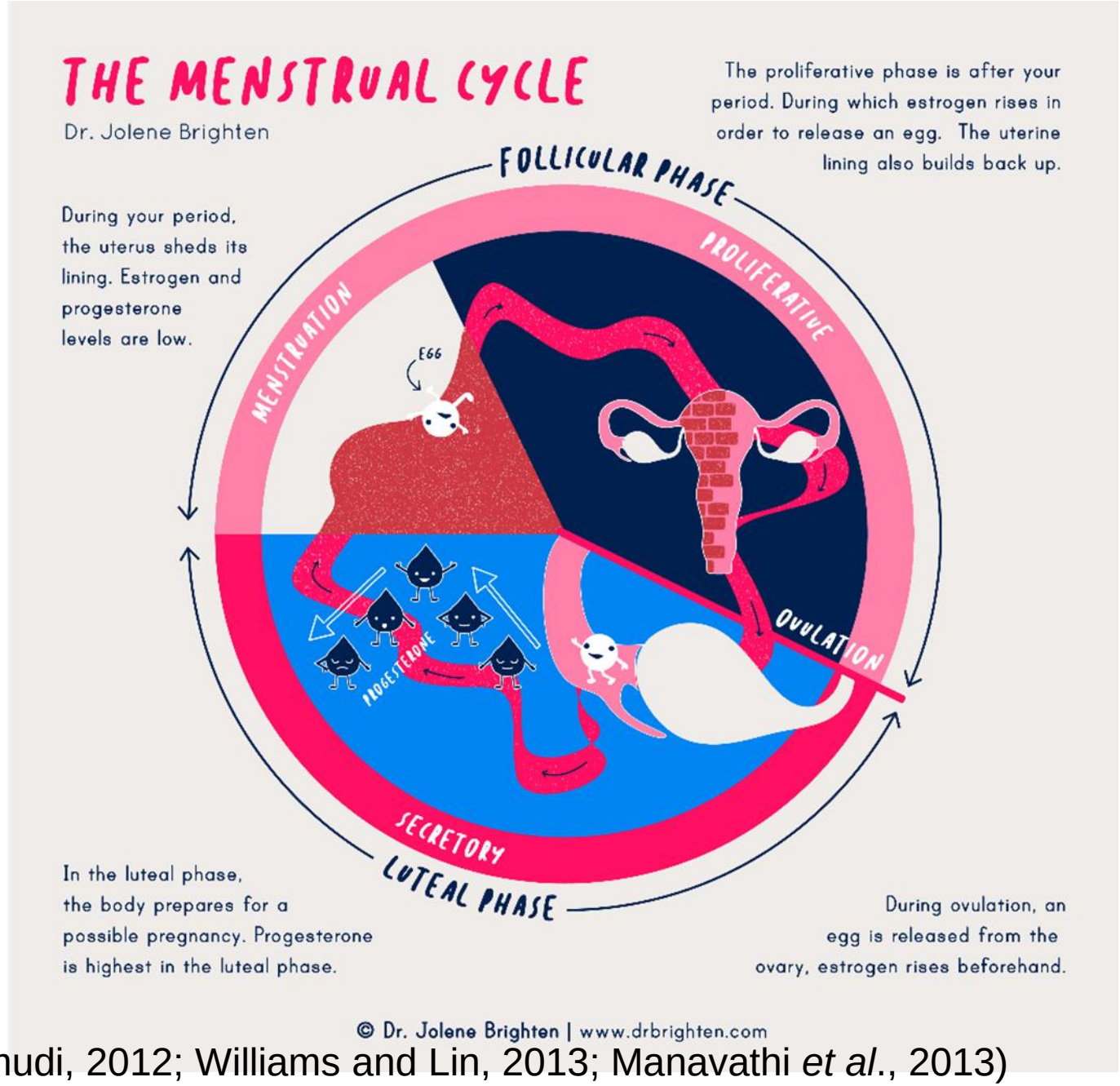
The egg travels through the fallopian tube to the uterus.

It takes three days to reach the uterus.



(Rodriguez *et al.,*2019a; Saha Roy, and Vadlamudi, 2012; Williams and Lin, 2013; Manavathi *et al*., 2013)

Ovulation phase



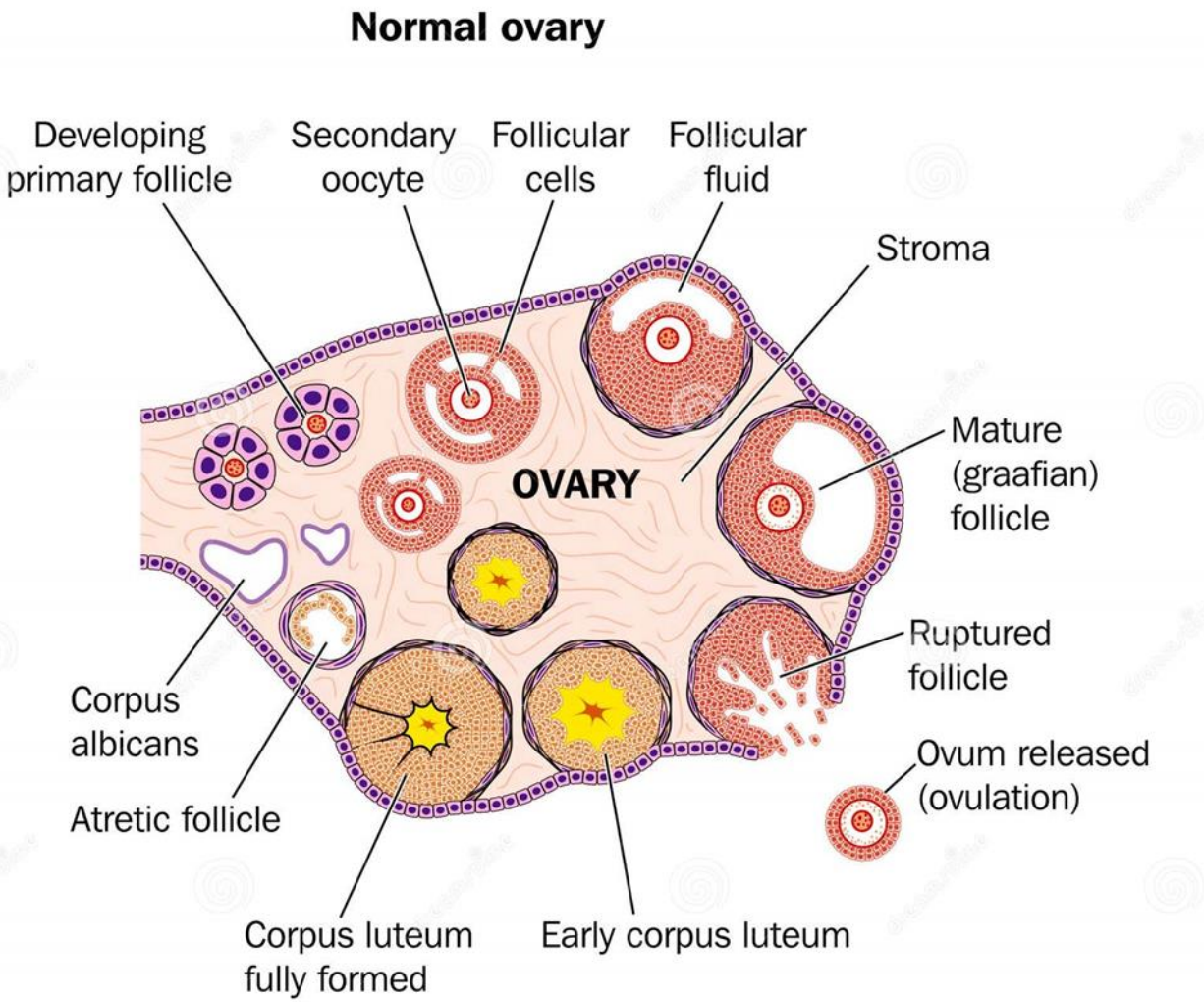
(Rodriguez *et al.,*2019a; Saha Roy, and Vadlamudi, 2012; Williams and Lin, 2013; Manavathi *et al*., 2013)

Luteal phase

Luteal phase

This **is where the corpus luteum secretes the hormone progesterone**.

There are **small amounts of LH produced.**

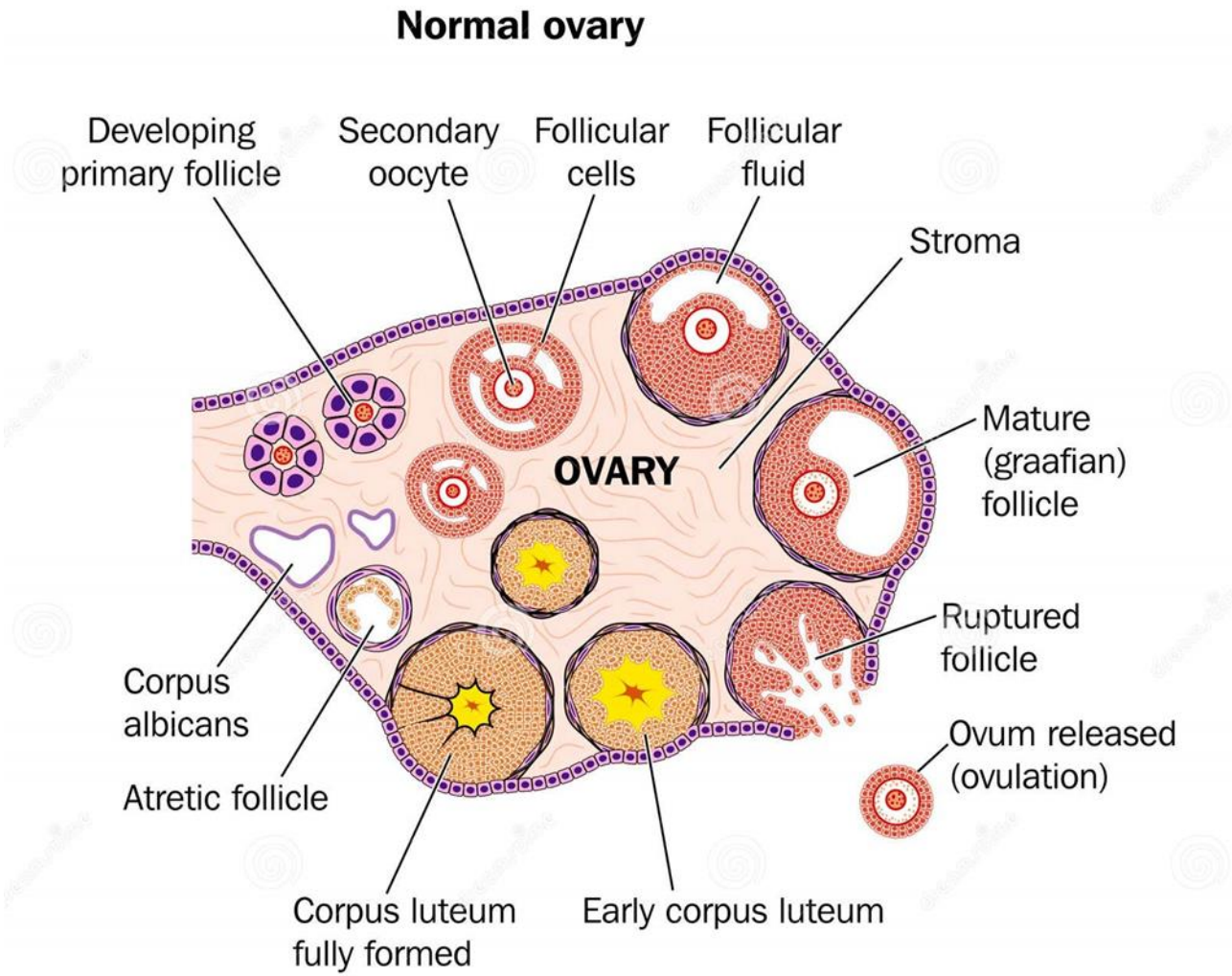


(Rodriguez *et al.,*2019a; Saha Roy, and Vadlamudi, 2012; Williams and Lin, 2013; Manavathi *et al*., 2013)

Luteal phase

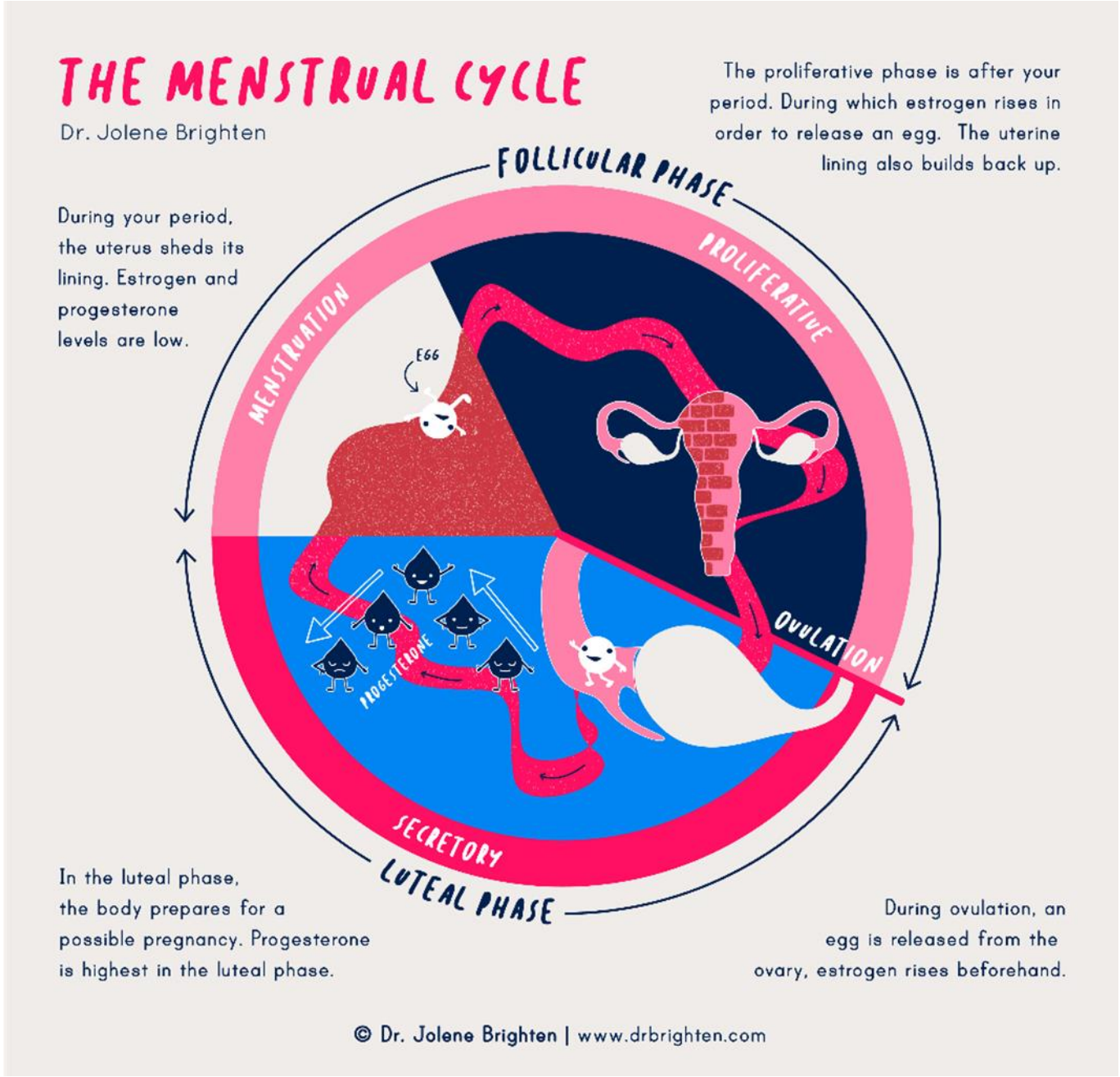
The role of progesterone is to:

- ❑ **To complete the uterine wall**
- ❑ **To increase blood supply**
- ❑ **To store glucose as glycogen.**



(Rodriguez *et al.,*2019a; Saha Roy, and Vadlamudi, 2012; Williams and Lin, 2013; Manavathi *et al*., 2013)

Luteal phase



What happens next?

FERTILISATION WITH THE SPERM TAKES PLACE	FERTILISATION DOES NOT TAKE PLACE
• If yes, the fertilized egg will embed into the wall of the uterus.	• The lining of the uterus is shed. • This causes bleeding which lasts a few days. • The cycle repeats.

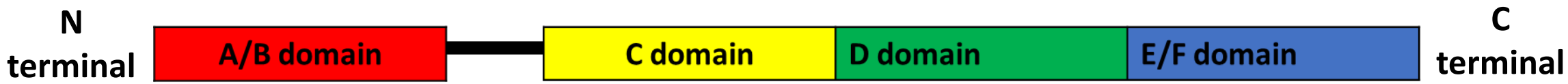
(Rodriguez *et al.,*2019a; Saha Roy, and Vadlamudi, 2012; Williams and Lin, 2013; Manavathi *et al*., 2013)

Receptor activation

Step 1 Oestrogen acts as a ligand where it binds to the oestrogen receptor.

The domains found in the oestrogen receptor

Name of domain	Role of domain	Description
A/B	Activation function 1 (AF-1)	Recruiting cofactors
C	C4-zinc DNA binding domain	Maintain synergy between AF-1 and AF-2 It contains approximately 68 Amino acids
D	Hinge	Recruit and bind to receptor co-modulators
E/F	Two subdomains: ligand-binding domain (LBD) transcriptional activation function 2 (AF2)	LBD binds to oestrogen and recruits cofactors. It has approximately 225 to 285 amino acids. AF2 activate transcription



Types of oestrogen receptors

There are two types of oestrogen receptors:

- ❑ ER*α* (oestrogen receptor alpha)
- ❑ Er*β* (oestrogen receptor beta)

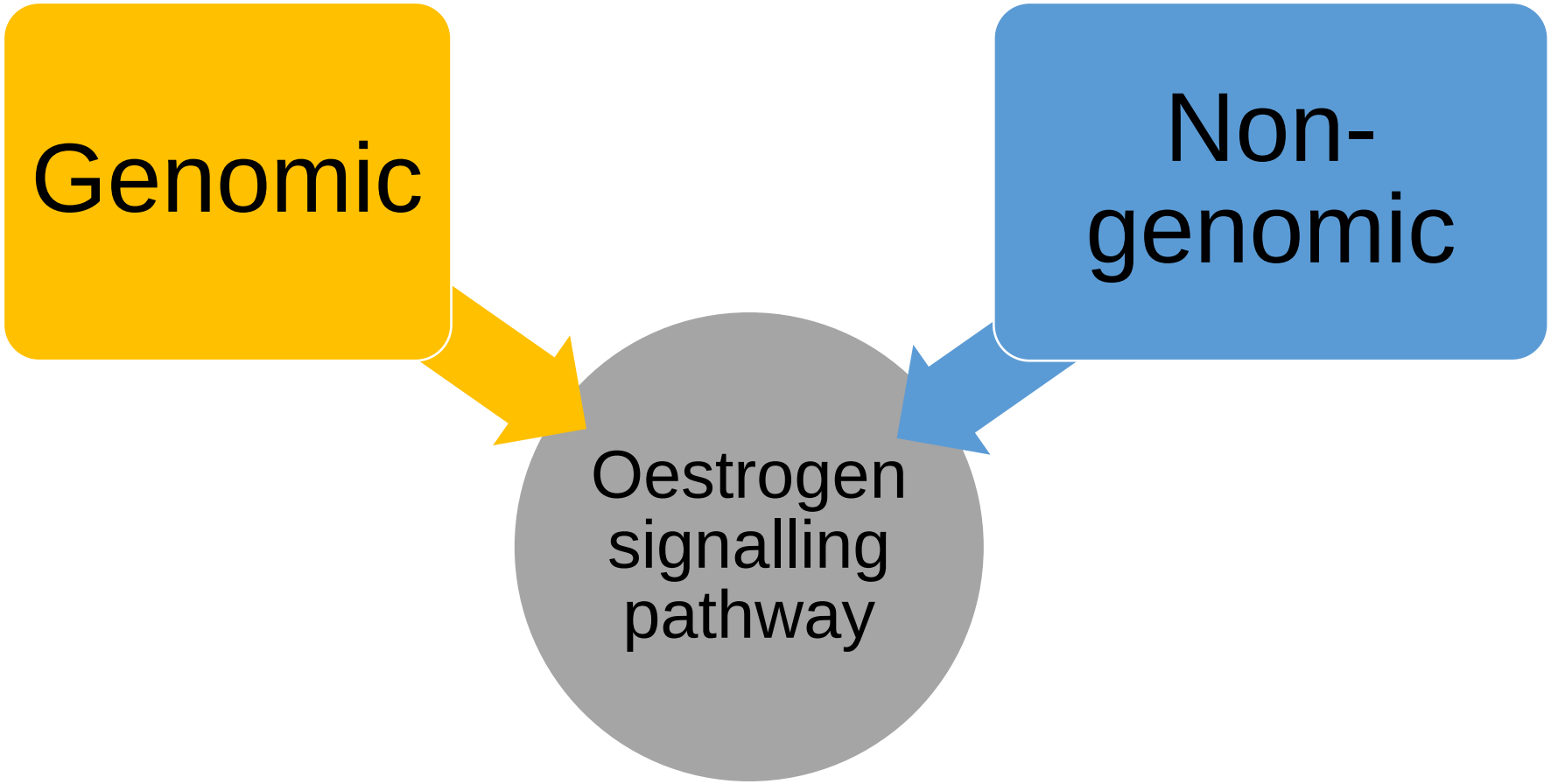
- Both have nearly identical DNA binding domains.
- They have 60% homology in LBD.
- ER*α* is highly expressed in tissues

An G protein coupled receptor bound E2 called *GPER/GPR30.* It found in the endoplasmic reticulum. Some types of oestrogens are strongly associated with their receptor e.g. E2 than E1 and E3.

(Rodriguez *et al.,*2019a; Saha Roy, and Vadlamudi, 2012; Williams and Lin, 2013; Manavathi *et al*., 2013)

Signal transduction

Types of oestrogen signalling pathways



(Lipovka and Konhilas, 2016).

Genomic signalling pathway

Step 2 Activated oestrogen receptor binds to response element in the nucleus.

- The **activated oestrogen receptor** acts as **transcription factor that translocates to the nucleus** and **binds with the genome.**
- The genome contains the **oestrogen response element.**
- **Response elements are the recognition sites found in specific transcription factors.**
- The **oestrogen response element form homodimers and regulate transcription.**

(Rodriguez *et al.,*2019a; Saha Roy, and Vadlamudi, 2012; Williams and Lin, 2013; Manavathi *et al*., 2013)

Oestrogen response elements

Response Element	Transcription Factor	Consensus Sequence
ERE	Oestrogen receptor	5′-GGTCANNNTGACC-3′

- **Oestrogen receptor** can **bind to half of its response element**.

- The **cause of limited binding of the receptor** is because of **the chromatin and processes i.e DNA methylation that habours them.**

(Molecular Biology Web Book, no date)

Other effectors

❑ Coregulatory proteins form a large complex with receptor-ligand complex.

Key examples:

Activators e.g. SRC1 and CBP increase activity of histone acetyltransferase.

Repressors e.g. NCOR and MTA1 associate with histone deacetylases.

Histone deacetylases (HDAC) are enzymes that remove acetyl groups from the amino acid i.e. lysine on a histone protein. The histones wrap around the DNA more tightly and increase gene expression.

Non-genomic signalling pathway

Step 1 The activated oestrogen receptor binds to other signalling pathways to increase response.

cAMP

MAPK

This normally occurs in the uterus.

Step 2 The activation of the IGF-1 receptor

Inside the uterus, the IGF-1 receptor (Insulin Growth Factor) functions as a hormone that manages the effects of the growth hormone (GH) to promote growth of bones and tissues.

(Rodriguez *et al.,*2019a; Saha Roy, and Vadlamudi, 2012; Williams and Lin, 2013; Manavathi *et al*., 2013)

Step 3 Crosstalk with the genomic signalling pathway

This is necessary to construct the templates of RNA to make target proteins.

(Rodriguez *et al.,*2019a; Saha Roy, and Vadlamudi, 2012; Williams and Lin, 2013; Manavathi *et al*., 2013)

Cellular response

Cellular response

Proliferation

Angiogenesis

Tissue development in the breast.

Tissue development in the endometrium.

(Rodriguez *et al.,*2019a; Saha Roy, and Vadlamudi, 2012; Williams and Lin, 2013; Manavathi *et al*., 2013)

Dysregulated oestrogen signalling pathway

Cause 1

Abnormal high levels of oestrogen

- **It increases risk of breast cancer in women before and after menopause.**
- **Lowering oestrogen levels by surgery or drug treatment with oestrogen-blocking drugs lowers cancer incidence.**
- **Oestradiol form of oestrogen can promote or inhibit cancer growth and depends on the state of breast cancer cells on a molecular and cellular level.**

(Lipovka and Konhilas, 2016).

Cause 2

Overexpression of oestrogen receptors.

- **The alpha form of oestrogen receptors is expressed more than the beta form.**
- **It is also present in breast cancer cases because of their dependency on oestrogen.**
- **This affects the transcriptional activity because the oestrogen receptors act as transcription factors.**

(Rodriguez *et al.,*2019a; Saha Roy, and Vadlamudi, 2012; Williams and Lin, 2013; Manavathi *et al*., 2013)

Cause 2

Type I /low-grade endometrial tumours	Type II tumours/ high-grade endometrioid tumours
• High levels of estrogen receptor α are expressed. • They depend on hormones.	• Less expression of the oestrogen receptor. • They have high copy number variation. • Other gene mutations are found of p53. • Worse prognosis.

(Lee and Muller, 2010)

Cause 3

Imbalance of hormones

- **Oestrogens promote growth and outweigh progesterones that prevent growth.**
- **This increases cancer risk.**

(Rodriguez *et al.,*2019a; Saha Roy, and Vadlamudi, 2012; Williams and Lin, 2013; Manavathi *et al*., 2013)

Cause 4

Crosstalk between microRNAs and oestrogen signalling.

- Small microRNAs (miRNAs) regulate gene expression by targeting genes for degradation or by blocking the translation of proteins.

(Rodriguez *et al.,*2019a; Saha Roy, and Vadlamudi, 2012; Williams and Lin, 2013; Manavathi *et al*., 2013)

Cause 5

Lifestyle factors - obesity

- The fat tissue produces oestrogen via the enzyme aromatase.
- Aromatase converts androgens to oestrogen.
- This lowers chances for ovulation to take place, low progesterone levels and increases cancer risk.

Cause 6

Lifestyle factors – Exposure to chemicals

- **Xenoestrogens weakly associate with oestrogen receptors. They can promote oestrogen-like effects and increasing the risk of breast cancer especially during breast development.**
- **Parabens and benzophenones - personal care products.**
- **Polycyclic aromatic hydrocarbons that increase combustion.**
- **Heavy metals in drinking water and air pollution e.g. cadmium, arsenite.**

(Cardona and Rudel, 2021; Open Access Government, 2021)

Summary

- The menstrual cycle is the **release of an egg from the ovaries every 28 days** and **changes in the thickness of the womb lining.**

- There are three phases of the menstrual cycle.

  Follicular phase: This occurs on Day 1 of the period until Day 14. Oestrogen and Follicle Stimulating hormone (FSH) levels rise.

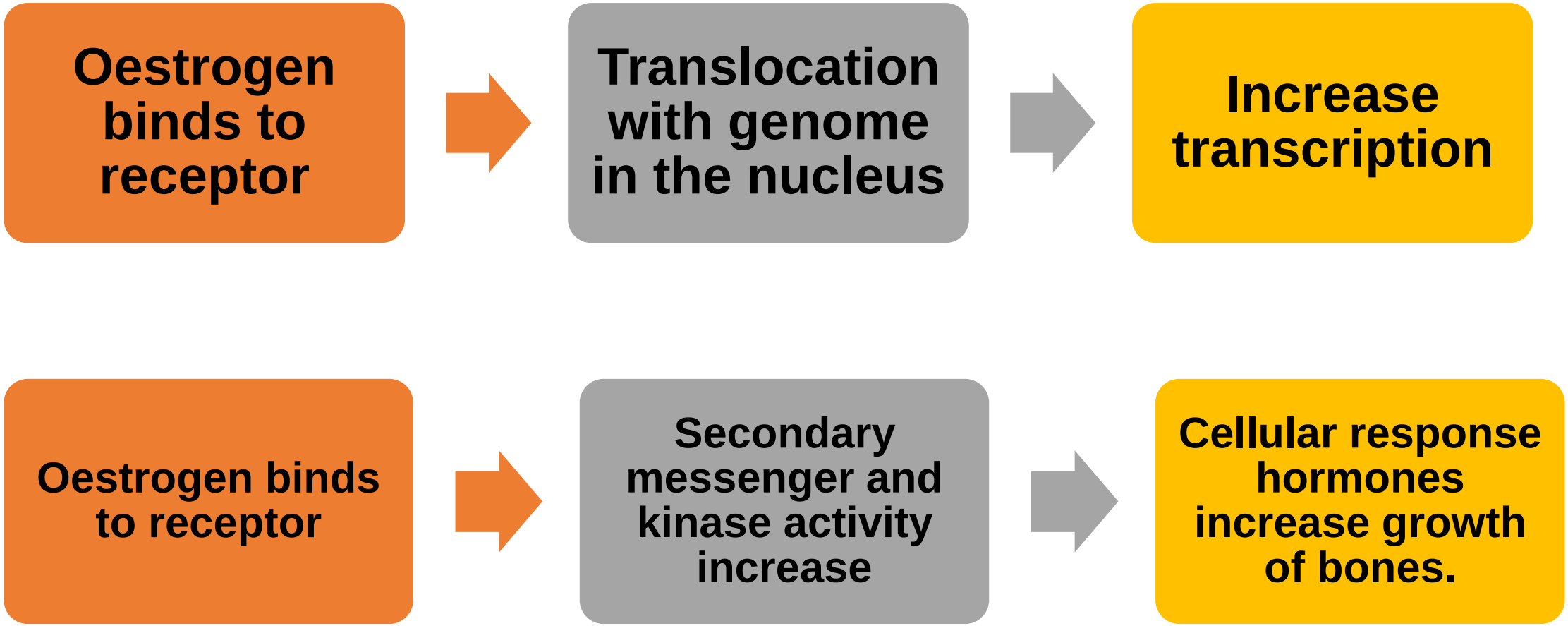
  Ovulation: The release of the egg on Day 14 in most cases. The luteinizing hormone is responsible for its release.

  Luteal phase: Corpus luteum produces progesterone to store glycogen.

- **Oestrogen** has other functions beside**s period e.g. growth of the womb, pregnancy and Cell-to-cell communication in the breasts.**

- Dysregulation of the oestrogen signalling pathway: **overexpression of the receptors, overproduction of oestrogen, imbalance of hormones, coregulatory proteins and lifestyle factors.**

Summary


Oestrogen binds to receptor
Translocation with genome in the nucleus
Increase transcription
Oestrogen binds to receptor
Secondary messenger and kinase activity increase
Cellular response hormones increase growth of bones.

Reference list for further reading

Cardona, B. and Rudel, R.A. (2021). Application of an in Vitro Assay to Identify Chemicals That Increase Estradiol and Progesterone Synthesis and Are Potential Breast Cancer Risk Factors. *Environmental Health Perspectives*, 129(7), p.077003. doi:https://doi.org/10.1289/ehp8608.

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SEASON 2

Understanding Cancer

Lecture 15

Types of signalling pathway: NFKB

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