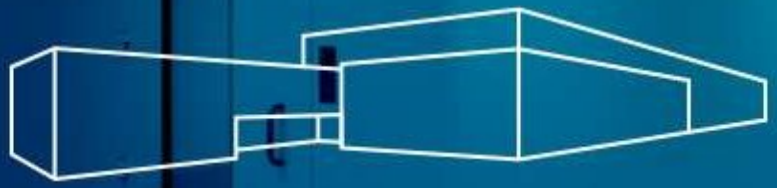
Les clés du succès : l'innovation contraceptive, ophtalmologique, immunitaire ou exosomiale

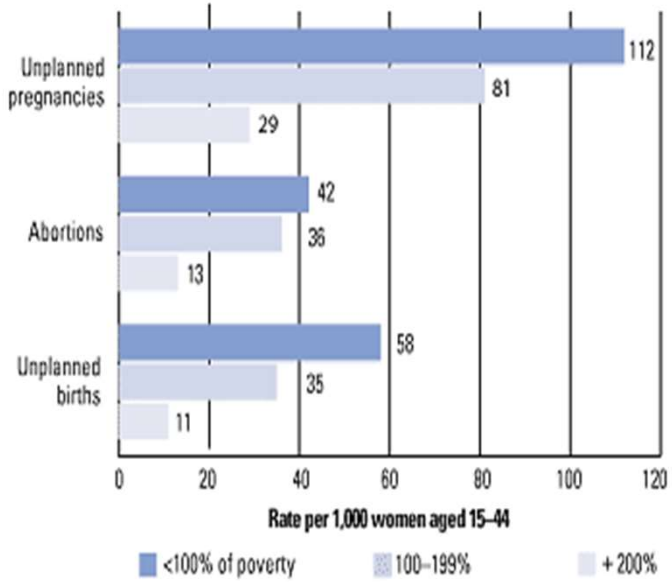


Jean-Michel Foidart

Professeur extraordinaire honoraire Université de Liège

Verviers, 30 janvier 2023

Efficacité Contraceptive : une affaire de santé publique



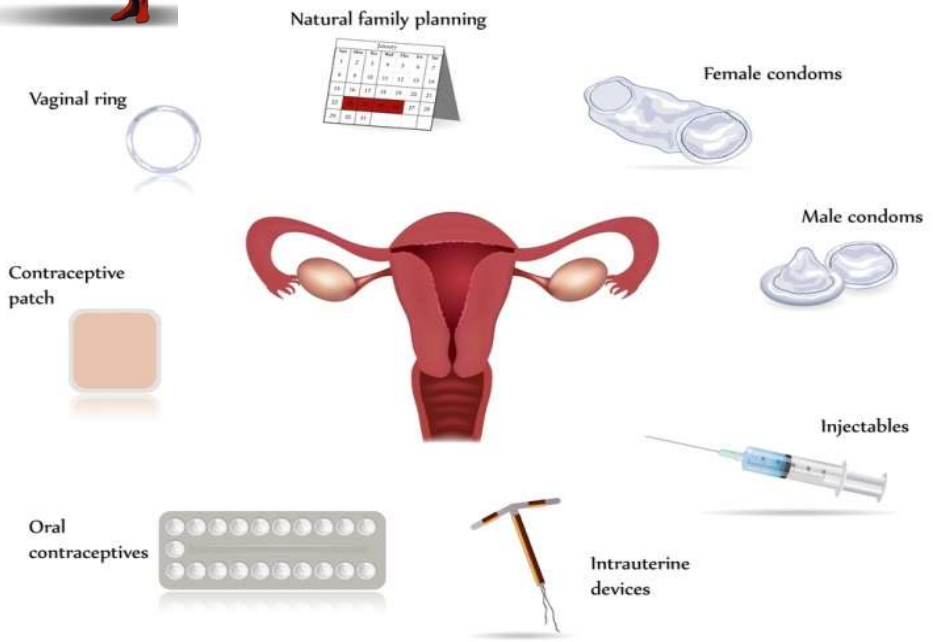
Près de la moitié des 6,7 millions de grossesses aux États-Unis chaque année ne sont pas désirées (Finer, 2014).
Les conséquences néfastes sur la santé des grossesses non désirées sont bien documentées et les grossesses non désirées ont un impact disproportionné sur les femmes pauvres aux États-Unis.

Le taux de grossesses non désirées chez les femmes pauvres en 2008 était de 137/1 000 femmes, contre 26/1 000 chez les femmes à revenu élevé (Finer, 2014).

En 2008, les femmes pauvres avaient un taux de naissances non désirées près de 6 fois plus élevé que celui des femmes à revenu plus élevé (Finer, 2014).

Les femmes pauvres ont l'un des taux d'avortement les plus élevés (52/1000 femmes), tandis que les femmes à revenu élevé ont un taux d'avortement de 9/1000 (Jones, 2011).

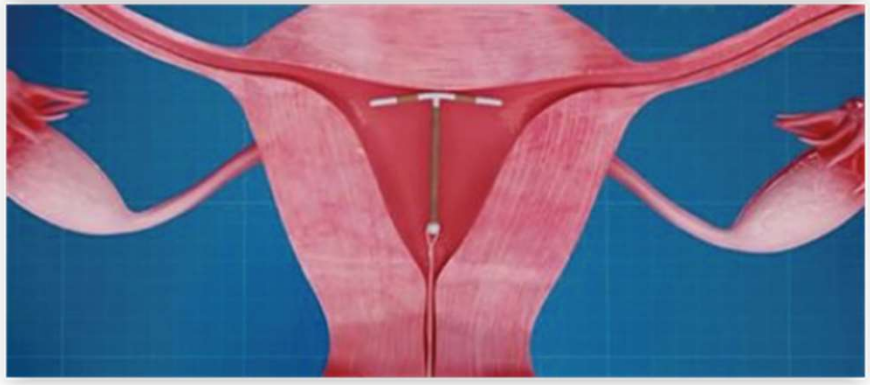
Le bon choix??

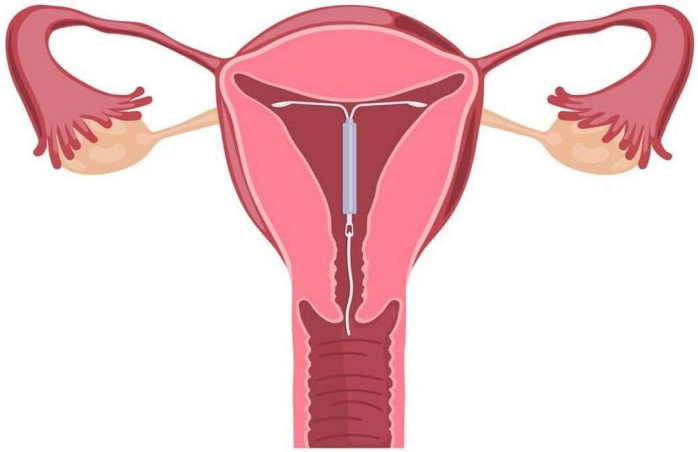


Les femmes disposent d'un choix considérable de méthodes contraceptives efficaces, chaque méthode nécessitant différents niveaux d'implication de l'utilisatrice.

Les méthodes de barrière, telles que les préservatifs, doivent être utilisées à chaque rapport sexuel, et les contraceptifs oraux doivent être administrés quotidiennement.

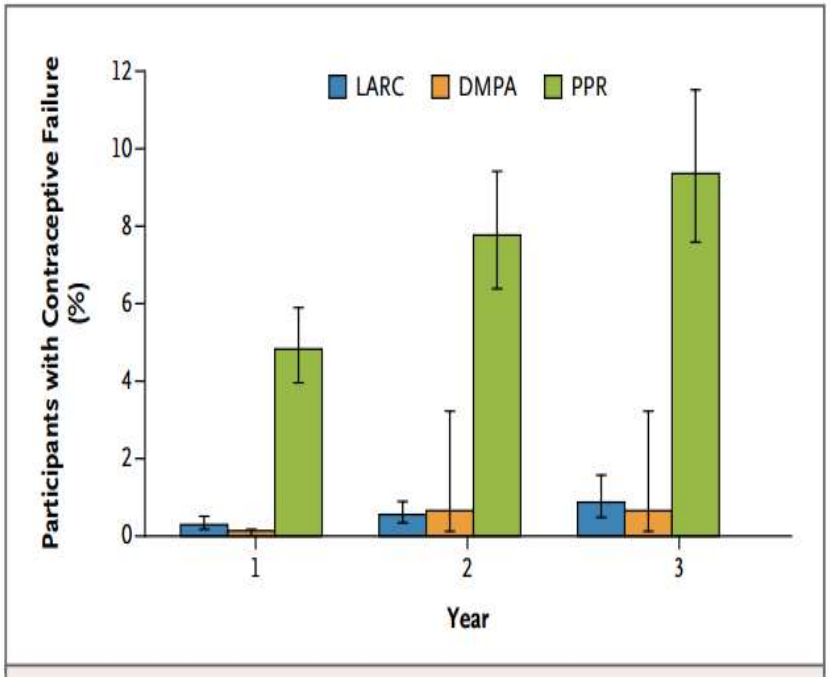
Les contraceptifs réversibles à longue durée d'action (LARC), qui comprennent les dispositifs intra-utérins (DIU), les implants progestatifs seuls et les injections progestatives seules, nécessitent le moins de participation de l'utilisateur.





Les LARC ont les taux d'échec les plus bas des méthodes contraceptives réversibles

Les méthodes contraceptives les plus efficaces ne dépendent pas de l'action régulière de l'utilisateur.

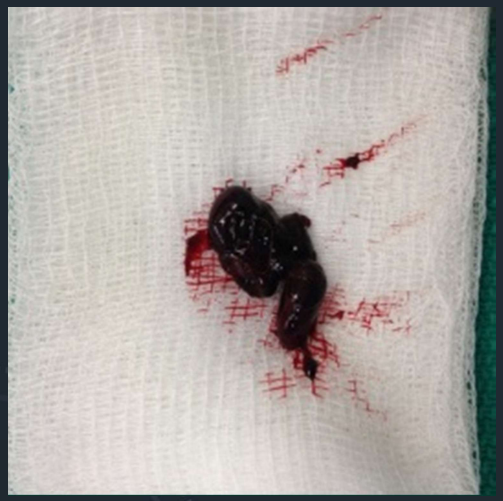


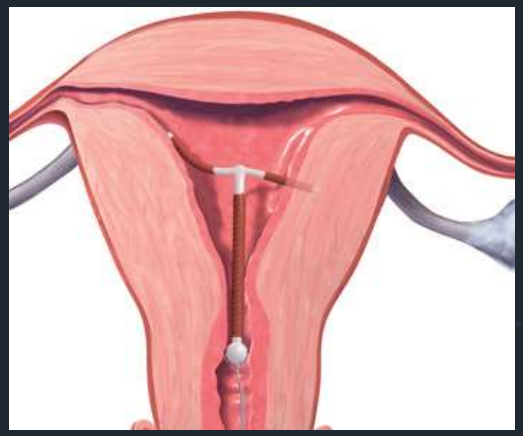
Le taux d'échec de la contraception chez les utilisatrices des LARC est de 0,27/100 années-participantes, contre 4,55/100 années-participantes chez les femmes utilisant d'autres méthodes

Winner B, et al. N Engl J Med 2012; 366(21):1998-2007.

Les effets secondaires des LARC sous-cutanés entraînent une mauvaise adhérence et un faible taux de continuation (33%)

(*Blumenthal et al. Eur J Contracept Reprod Health Care. 2008;13 Suppl 1:29–36).*





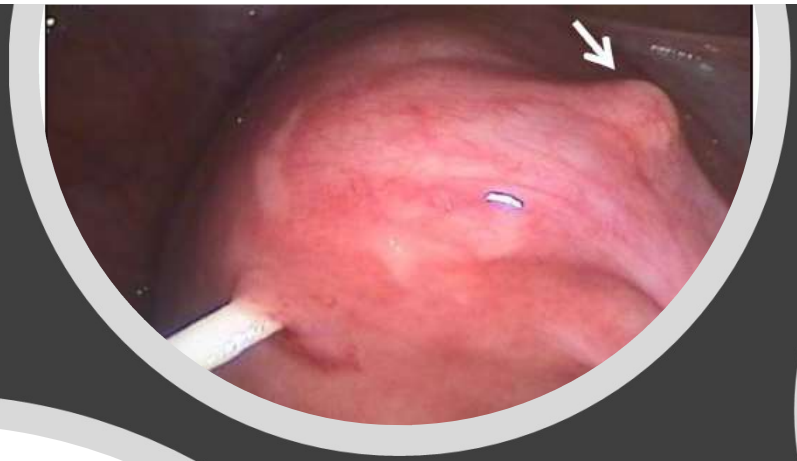
Effets secondaires et pièges actuels avec les DIU au cuivre à éviter lors de la conception d'un nouveau IU LARC

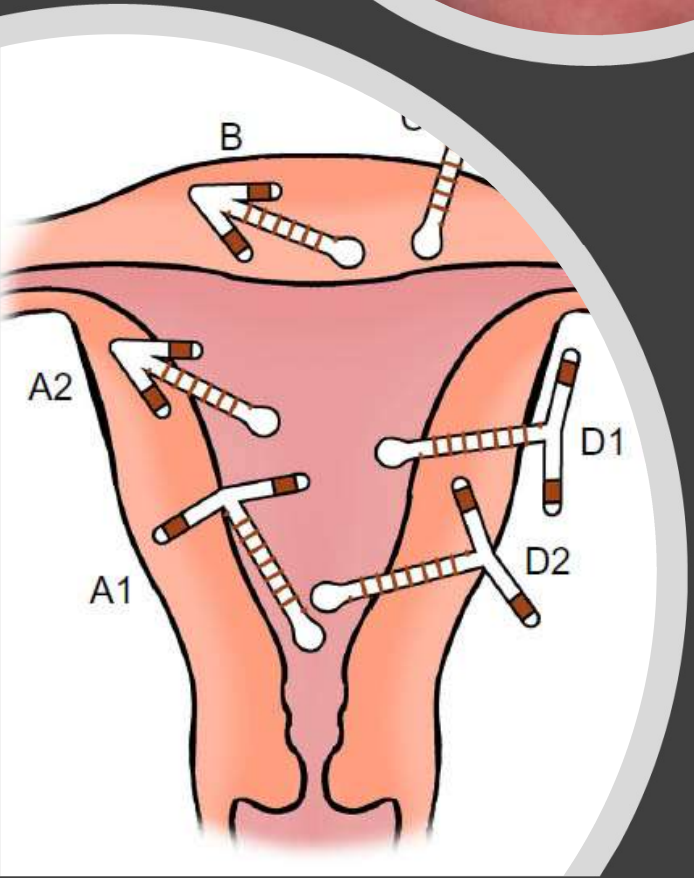
Douleur excessive, saignement, expulsions et/ou retrait

Les femmes nullipares connaissent des taux plus élevés d'expulsion et de retrait de DIU au cuivre pour saignement et/ou douleur par rapport aux femmes multipares.

Les taux d'abandon cumulés sont de un sur quatre à un sur deux sur 5 ans d'utilisation, avec des taux significativement plus élevés chez les adolescentes.

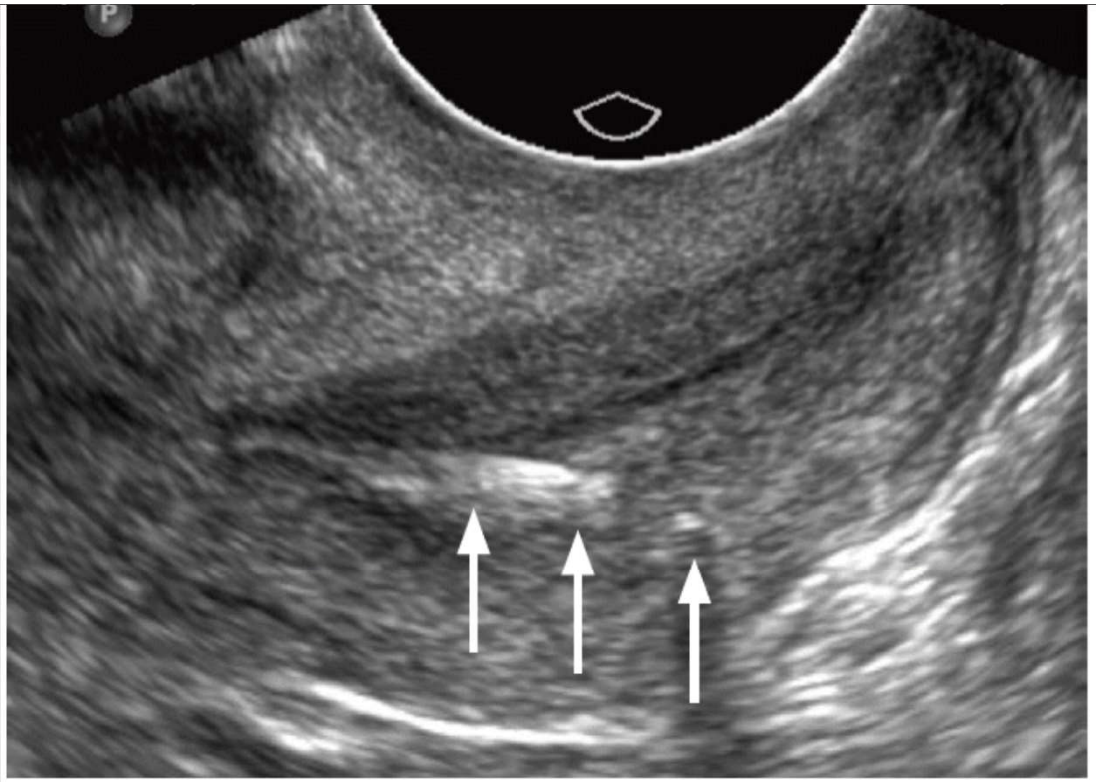
Des taux de douleur et d'expulsion plus élevés ont également été trouvés dans des études avec le SIU-LNG (Mirena) menées chez des adolescentes.

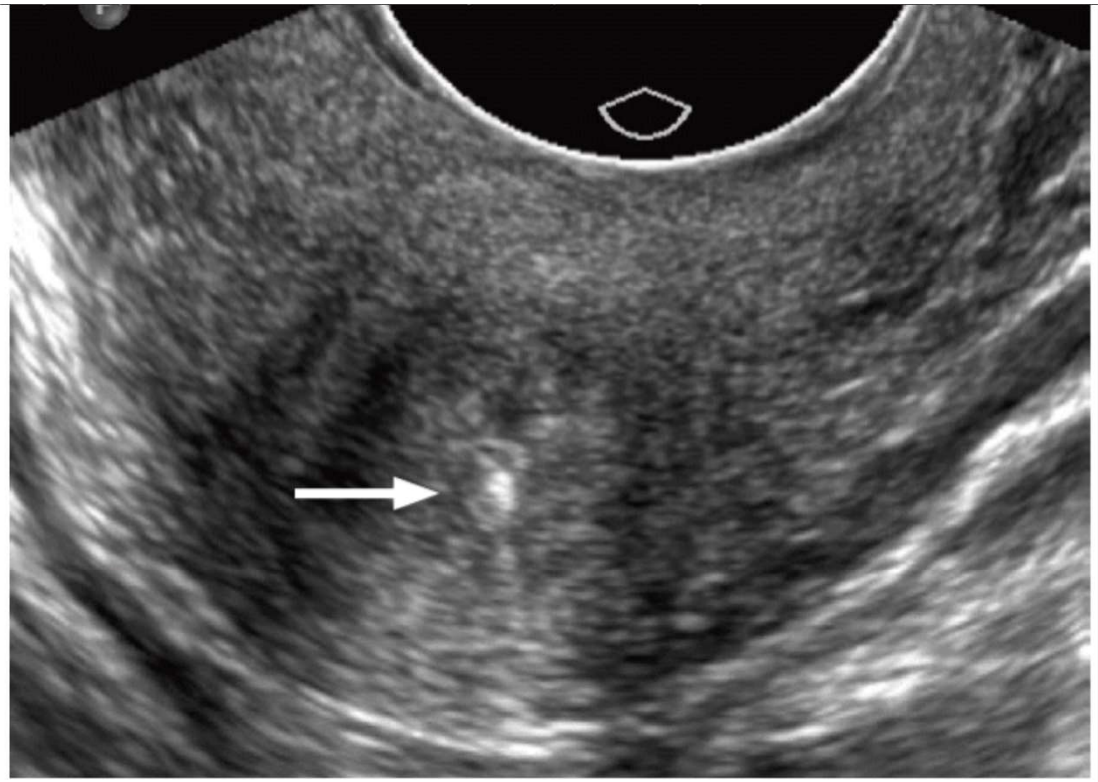




Pièges à éviter lors de la conception d'un nouveau LARC IU

Perforation, expulsion, hémorragie



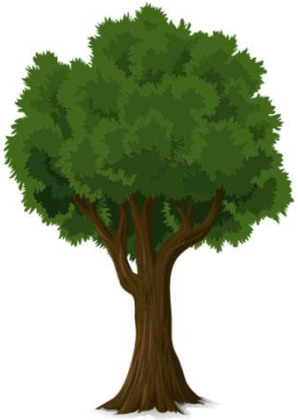


B

Malposition et encastrement partiel

Comment améliorer l'observance chez les femmes nullipares et adolescentes ?



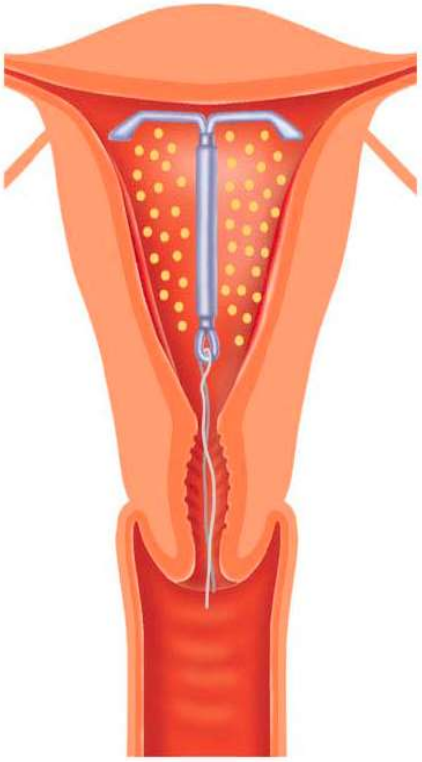



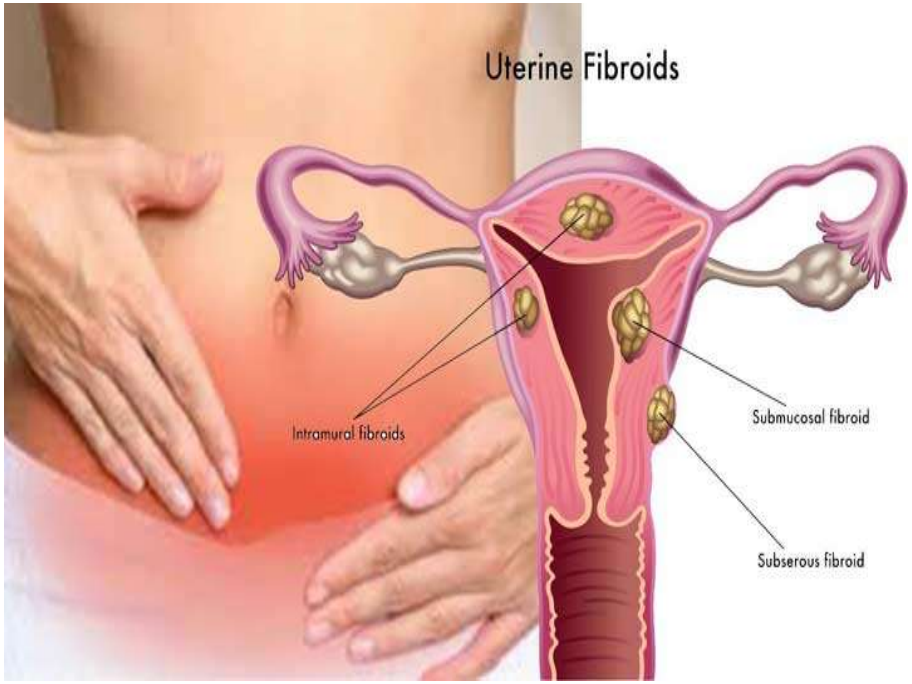
Rigidité versus Plasticité

La propriété viscoélastique du cadre en T détermine la déformabilité et la capacité à s'adapter à la paroi utérine

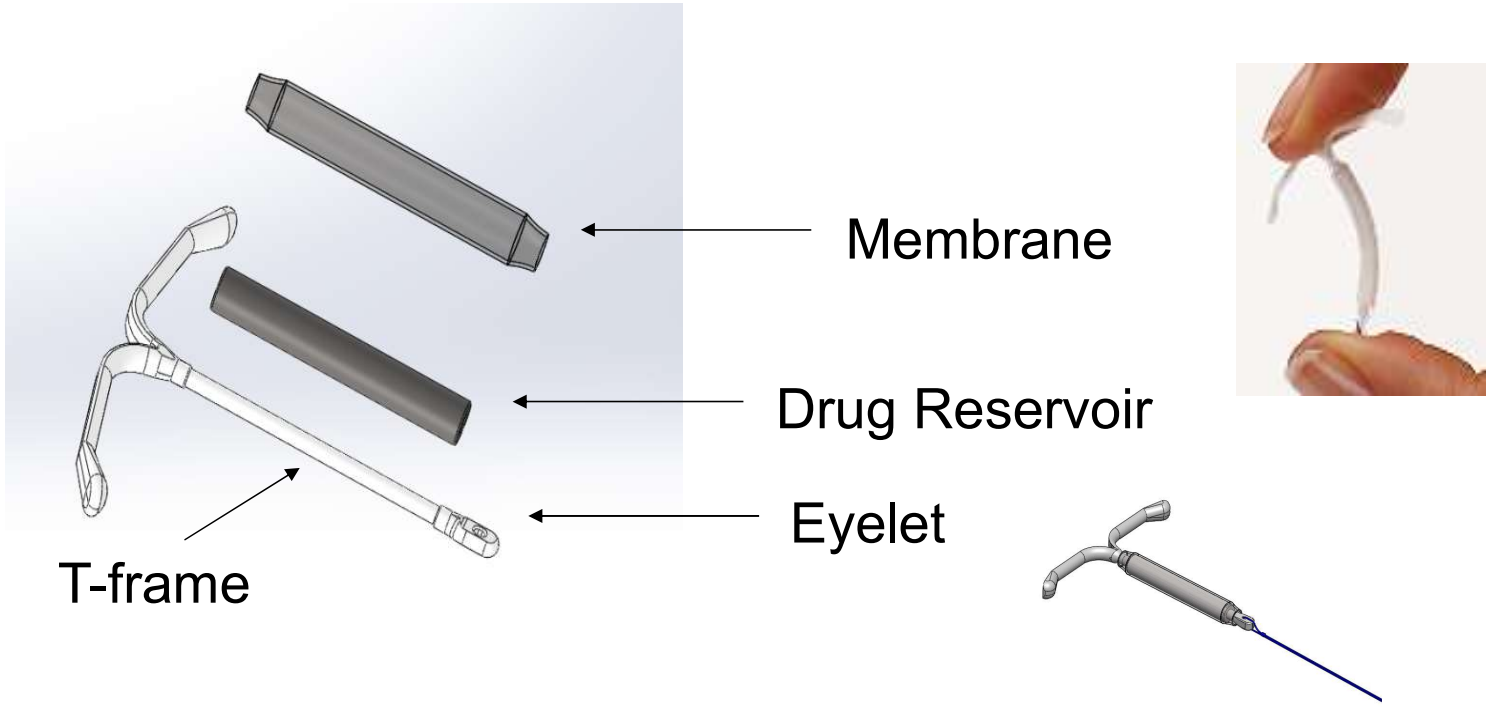
Une collaboration avec les ingénieurs et le Centre SIRRIS

Rigidity versus Plasticity





Conception des caractéristiques mécaniques de Levosert pour améliorer l'observance chez les femmes nullipares et adolescentes



Comment introduire une hormone dans du plastic ?

Quality by design (QbD) - Qualité par conception (QbD)

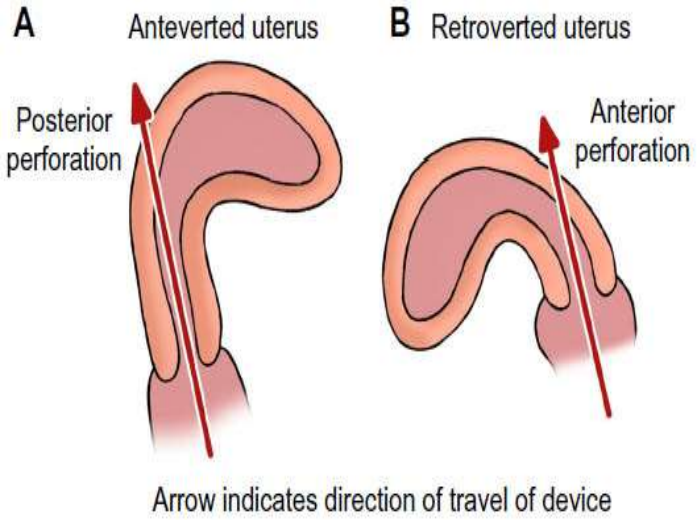
L'objectif de ce concept est que la qualité doit être intégrée à un produit avec une compréhension du produit et du processus par lesquels il est développé et fabriqué, ainsi qu'une connaissance des risques liés à la fabrication du produit et de la meilleure façon d'atténuer ces risques.

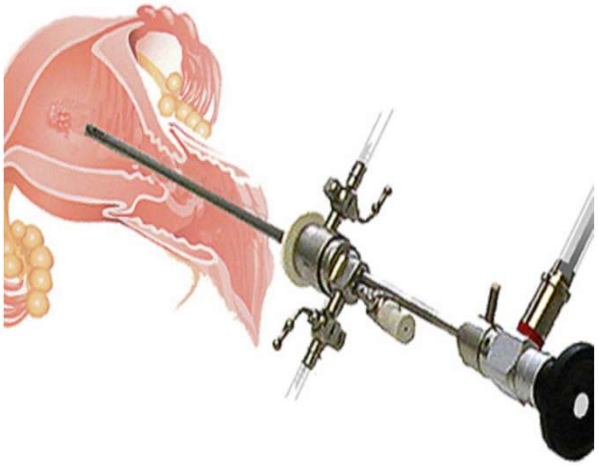
L'initiative QbD (2011) fournit des conseils sur le développement pharmaceutique pour faciliter la conception de produits et de processus qui maximisent l'efficacité et le profil d'innocuité du produit tout en améliorant la fabricabilité du produit.

Manufacturing site

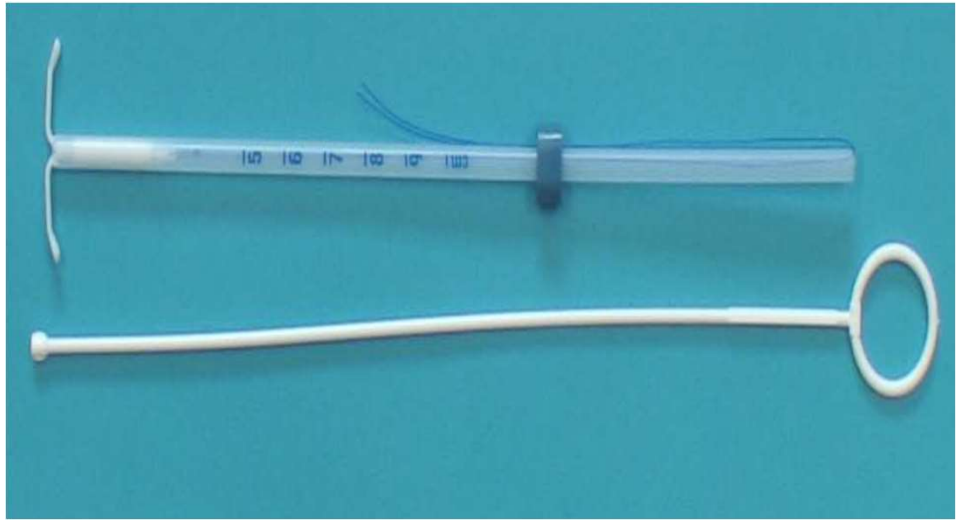
Odyssea Pharma, Grace-Hollogne, Belgium

Les propriétés mécaniques de l'inséreuse sont également cruciales pour éviter la perforation

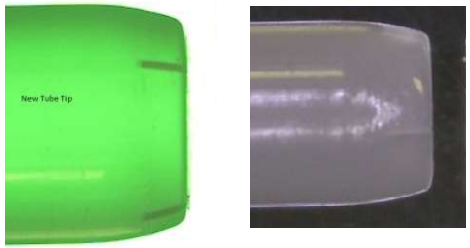




L'insertion est rapide, facile et réussie dans 99 % des tentatives, y compris les jeunes femmes nullipares



Process of the tipping was especially developped to reduce the sharpness of the inserter tube.



Comparison between Levosert and Mirena tips

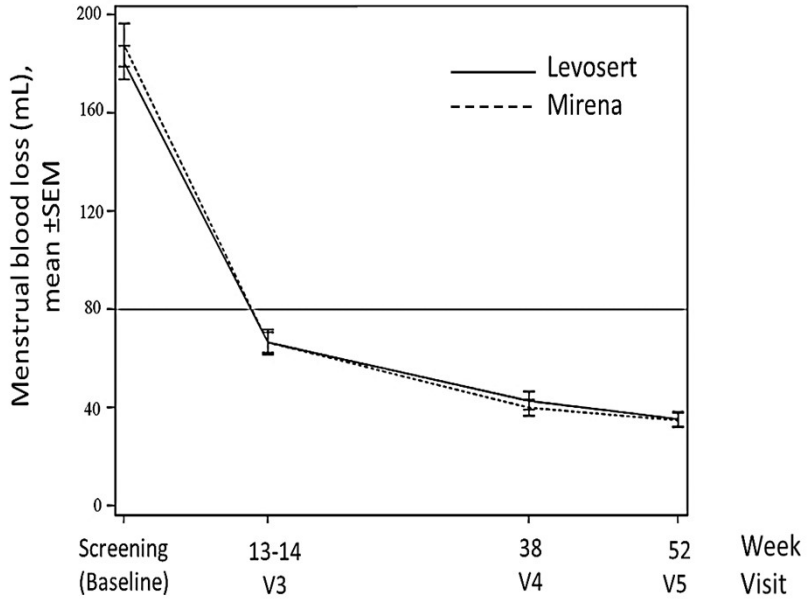
Essai clinique

400 à 450 périodes de règles par vie de femme.

Les pertes menstruelles normales augmentent avec l'âge, en particulier chez la femme en périménopause.

Les ménorragies touchent 10 à 35 % de femmes, affectent la qualité de vie des femmes (hémorragies chroniques, carence en fer, anémie (fatigue, dyspnée, malaise))

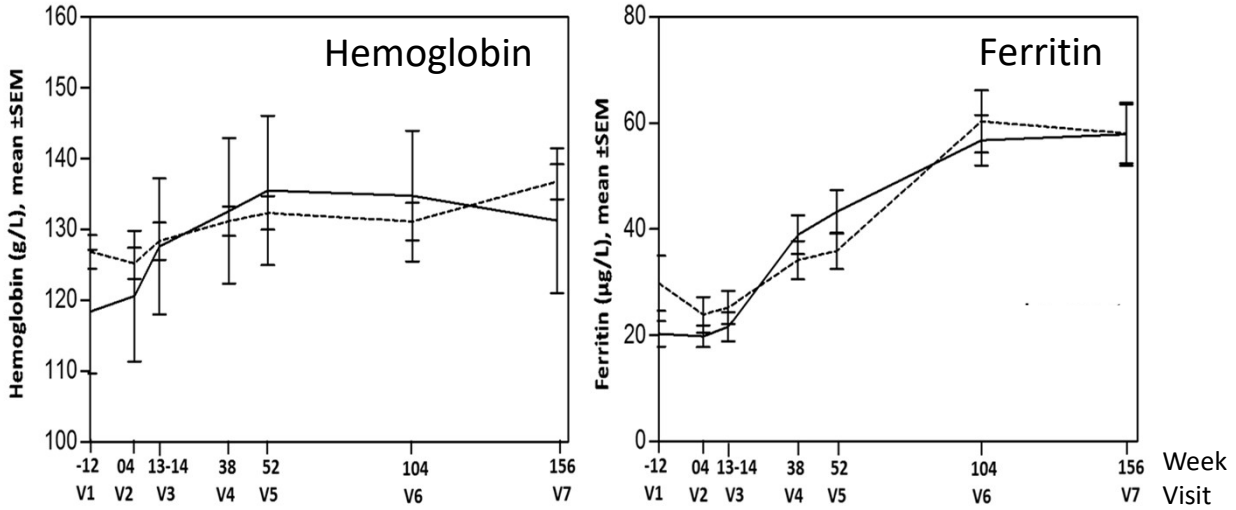
Levosert: Effect on menstrual blood loss



Item	Levosert®	Mirena®	Levosert®-Mirena® difference	
			Estimate (95%CI)	p-value
Menstrual blood loss (mL)				
ITT population				
Baseline, mean ± SD	180.6 ± 81.9	187.7 ± 103.4	−4.1 (−13.5 – 5.4)	0.3972
End of study, mean ± SD	35.4 ± 33.6	34.9 ± 33.5		
Change from baseline, least squares mean (95%CI)	142.3 (135.7 – 148.9)	146.4 (139.6 – 153.1)		

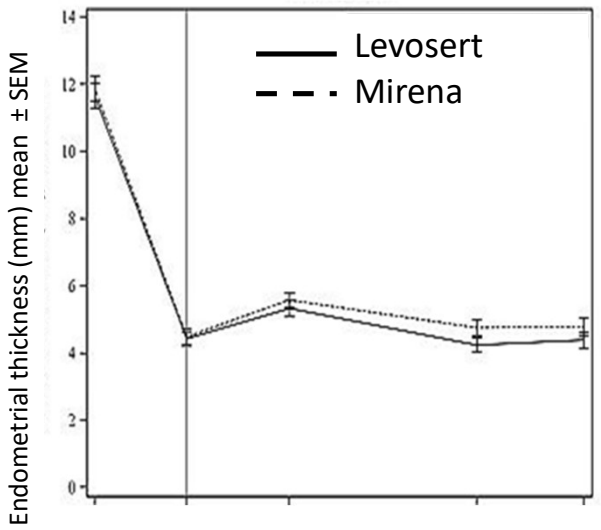
Levosert: Effect on hemoglobin and ferritin levels

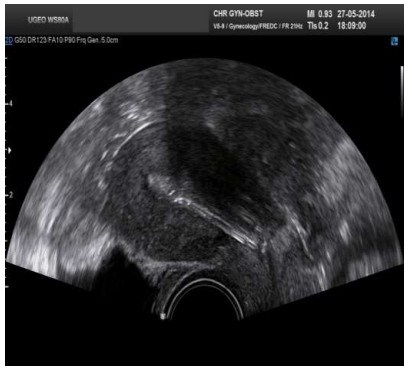
Extension Phase (± SEM; ITT Population)



Levosert Mirena

Effect on endometrial thickness, measured by 2D TVUS





LNG gradually reduces the endometrial thickness and stabilizes the endometrium

Item	*Levosert®*	*Mirena®*	*Levosert®-Mirena® difference*	
			Estimate (95%CI)	*p-value*
Endometrial thickness (mm)				
ITT population				
Baseline, mean ± SD	11.7 ± 4.4	11.9 ± 4.6	0.1 (−0.3 – 1.1)	0.2282
End of study, mean ± SD	4.4 ± 2.7	4.8 ± 3.0		
Change from baseline, least squares mean (95%CI)	7.3 (6.8 – 7.8)	6.9 (6.4 – 7.4)		

Warren Buffett

Warren Buffett en 2015.

Fonction

Directeur général
Berkshire Hathaway

depuis 1970


Our Global Access team is currently attending the International Conference on Family Planning from November 14-17. Stop by our
connect!
Medicines360
› WOMEN
› HEALTH CARE PROFES
MEDICINES360 EMPOWERS WOMEN
Everything we do is fueled by our non-profit mission to close critical gaps in women's healthcare.

Liletta® (levonorgestrel-releasing intrauterine system) 52 mg

IMPORTANT RISK INFORMATION > PRESCRIBING INFORMATION > HEALTHCARE PROFESSIONALS > HELP >

LILETTA®— YOUR LIFE. YOUR JOURNEY. YOUR CHOICE.

Learn more about the LILETTA PATIENT SAVINGS PROGRAM® here >

*LILETTA is an intrauterine system, or IUS, otherwise known as an IUD, intrauterine device

THE FIRST HORMONAL IUS* APPROVED IN THE U.S. FOR UP TO 6 YEARS OF PREGNANCY PREVENTION

DOWNLOAD THE LILETTA PATIENT BROCHURE >

Download the Spanish version >

Tell Me About LILETTA

Understanding My Birth Control Options

How Much Does LILETTA Cost?

US Contraceptive Med 360 L102 study

	Levosert Total
Overall (n)	1751
Age 16-35 years	1600
Age 36-45 years	151

ACCESS IUS (A Comprehensive Contraceptive Efficacy and Safety Study of an IUS) was designed to assess efficacy and safety of a branded levonorgestrel-releasing IUS (LNG20) for up to 7 years of contraception in a diverse population of women.

The study population is the largest phase 3 U.S. study of nulliparous women in which an IUS was assessed for contraceptive efficacy and safety. It is representative of the U.S. population (race, ethnicity and weight/BMI).

Pearl Indices of Long-Acting Reversible Contraceptives

	Pearl Index			
	1 year	Upper 95% CI	3 years (cumulative)	Upper 95% CI
LNG20 IUS	0.15	0.55	0.22	0.44
Mirena[1]	0.19	0.70	NA	NA
Skyla[2]	0.41	0.96	0.33	0.60
Implanon[3]	0.27	0.96	0.38	0.82
LNG-IUS 12 [4]	0.16	0.58	0.45	1.14

[1] Mirena SBA (FDA, 2000); 3-year data are not available. [2] Skyla SBA (FDA, 2012) [3] Implanon SBA (FDA, 2006) [4] European Journal of Obstetrics & Gynecology and Reproductive Biology 210 (2017) 22–28

Manufacturing site

Odyssea Pharma, Grace-Hollogne, Belgium

30 janvier 2023

Mithra
2013-2014

2015-2023
EyeD pharma,
Imcyse, Exo-Biologics

1929:Butenandt and Doisy discover the first estrogen (Estrone)

1930 Estriol

1936 Estradiol

1941Conjugated Estrogens

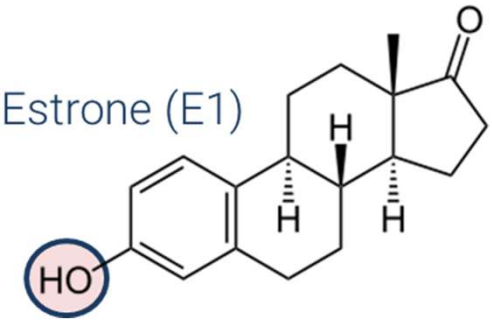
1943 Ethinylestradiol

1 and 7 years later, all natural adult estrogens enter the therapeutic domain

No significant improvement for almost 80 years

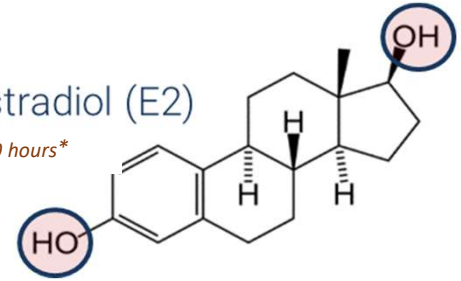
Natural human estrogens

Estrone (E1)

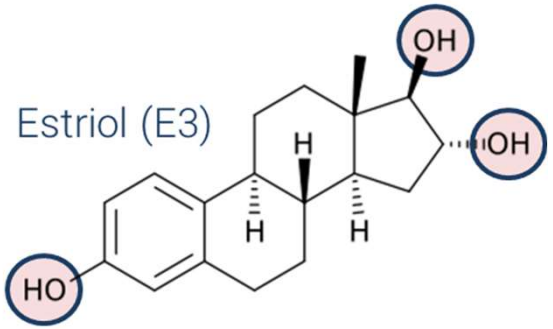


17β- Estradiol (E2)

*Half-life: 2–10 hours**

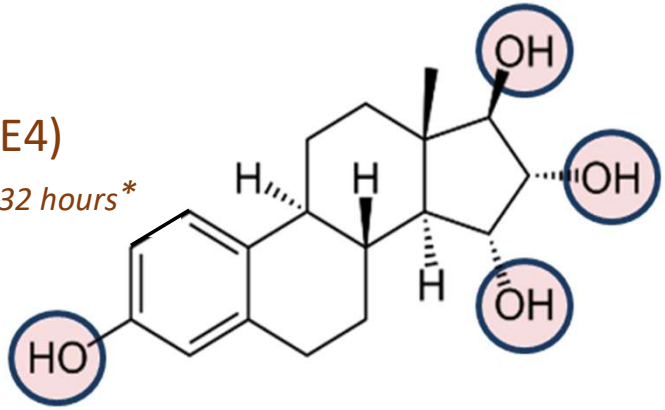


Estriol (E3)



Estetrol (E4)

*Half-life: 24–32 hours**

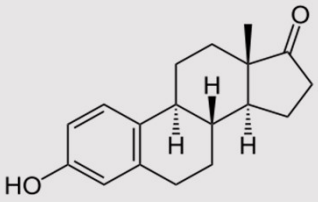


*Extensive variable data / depending on particle size

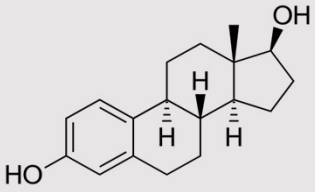
Visser M et al. Climacteric 2008

Propriétés du 4e Estrogène naturel

Estrone, E1

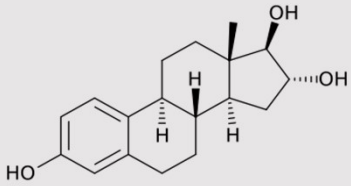


Estradiol, E2

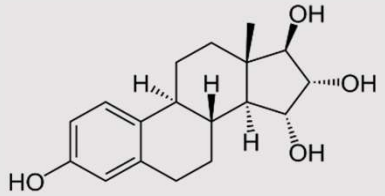


t1/2: 2h

Estriol, E3



Estetrol, E4

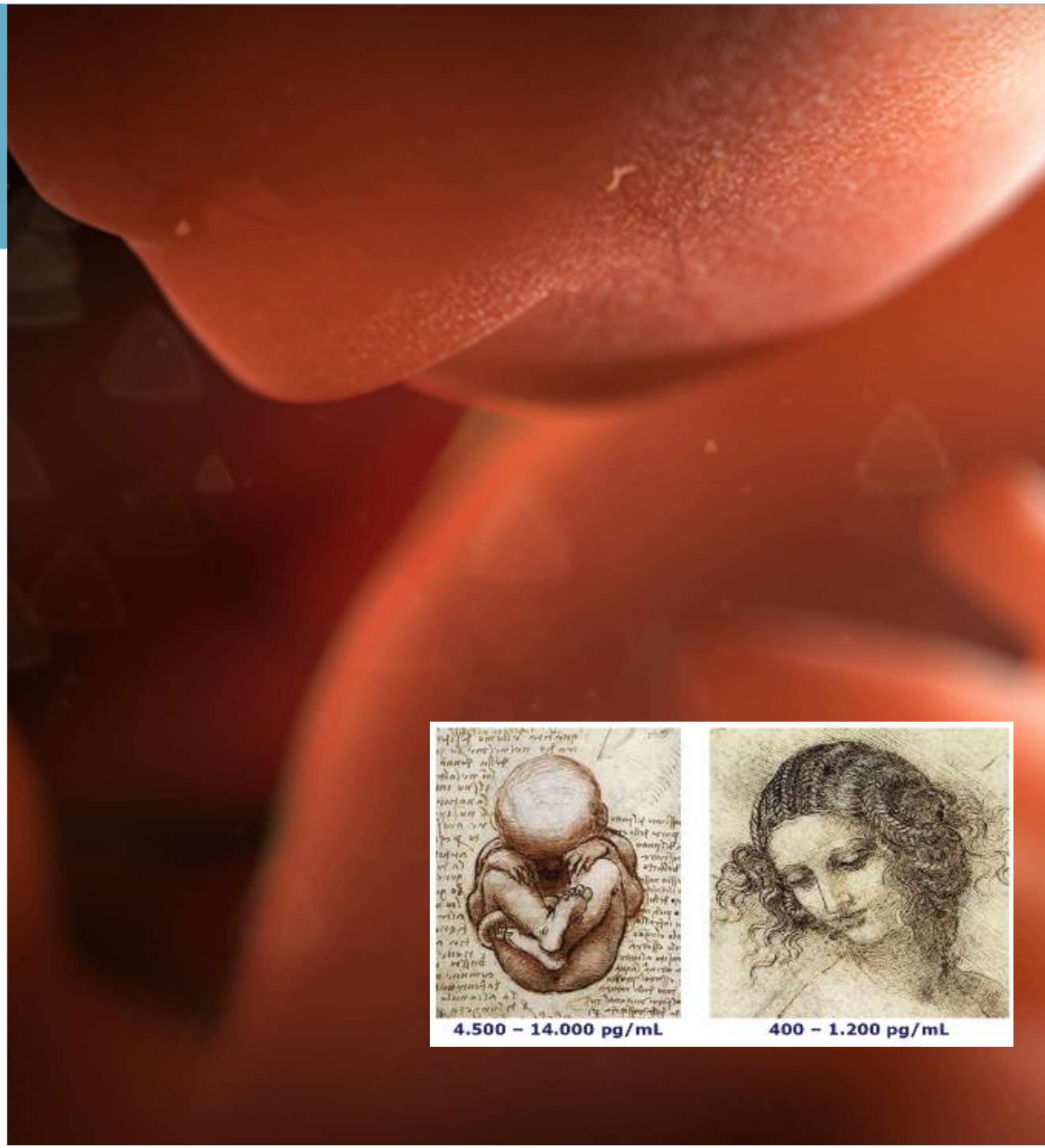


t1/2: 28h

- Découvert en 1965 par E. Diczfaluzy et ses collaborateurs (Karolinska)
- Produit uniquement par le foie fœtal (nécessite la 15- et 16α hydroxylase)
- Spécifique aux primates
- Traverse le placenta
- Les concentrations plasmatiques augmentent avec le temps
- Grande variabilité inter-sujets
- Concentrations lors d'une grossesse à terme :

Estetrol (E4)

- Produit par le foie fœtal humain [1,2]
- Détecté à partir de la 9ème semaine de gestation dans l'urine maternelle [3]
- Taux plasmatiques fœtaux 12 fois supérieurs à ceux de la mère[4]
- Demi-vie longue (24-32h)[5]
- Conçu par la nature, synthétisé à partir d'une source végétale
- Oestrogène naturel à action sélective dans les tissus [6,7]

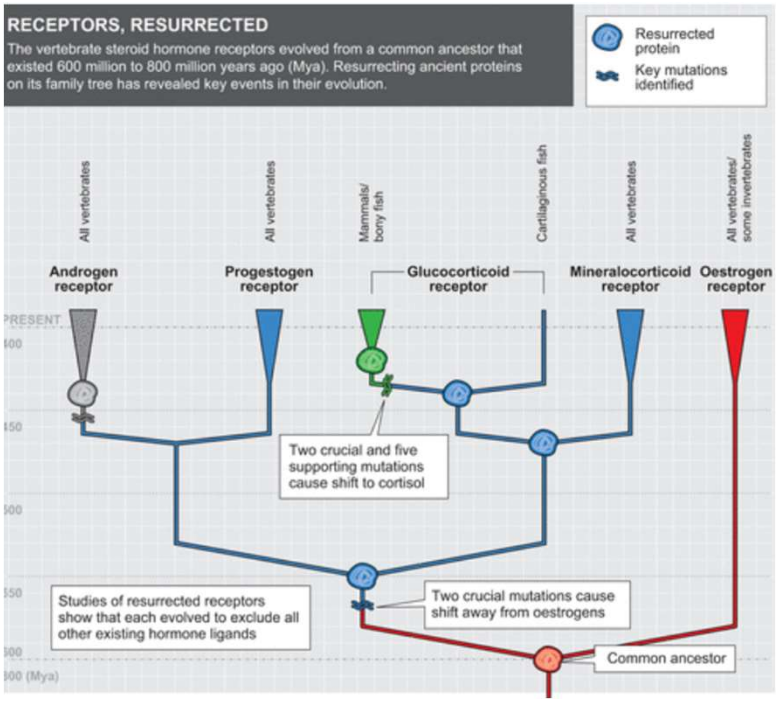


[1]Cantineau R et al. J Steroid Biochem 1985 | [2]Hagen AA et al. Acta Endocrinol 1965 | [3]Heikkilä J. et al. J. Steroid Biochem 1971 [4]Holinka CF et al. J. Steroid Biochem Mol Biol 2008 | [5]Visser M et al. Climateric 2008 | [6]Foidart JM et al. 2019 In: Brinton RD et al. (eds.) 2019. Sex Steroids' Effects on Brain, Heart and Vessels. ISGE Series | [7]Arnal JF et al. Physiol Rev 2017

Estrogens have multiple actions because Estrogen Receptors were the first steroid receptors to appear 600-800 million years ago. They are ubiquitous and pervasive.

Breast
Stimulates epithelial breast cells proliferation but promotes breast cancer

Hemostasis
Increases the synthesis of coagulation factors and the VTE risk



Brain

Body temperature
Memory,prevention of neurodegenerative disorders
Libido, Cognitive function

Uterus

Trophicity
Endometrial proliferation
Angiogenesis

Heart

Heart rate
Healthy lining of blood vessels
Lower Cholesterol

Liver

Cholesterol regulation
Stimulates the synthesis of carrier proteins and angiotensinogen

Bowel

Maintains function
Helps with gut microbiome

Vagina

Lubrification
Reduces bacterial overgrowth

Skin

Collagen production
Reduce moisture loss

Bones

Bone strength

Nerves

Nerve transmission

Joints & Muscles

Anti-inflammatory
Muscle strength
Flexibility
Joint lubrification

Bladder

Reduces risk of infection
Controls bladder function

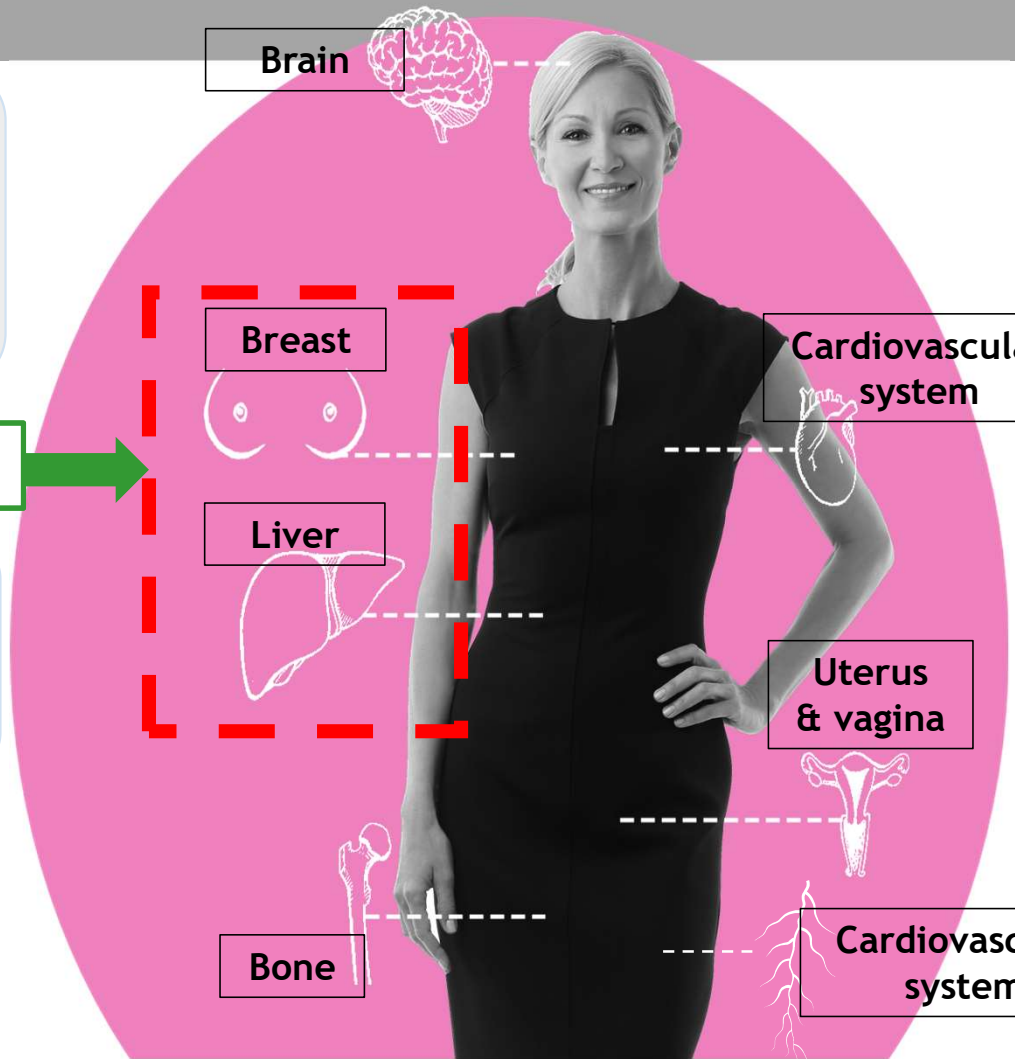
Existing impact

- Uterus
- Vagina
- Bone
- Cardiovascular (heart disease)

Unique impact of E4

- Liver
- Breast
- Cardiovascular (VTE)

Potential impact of E4



Mental Impact

- Quality of life
- Neurodegeneration

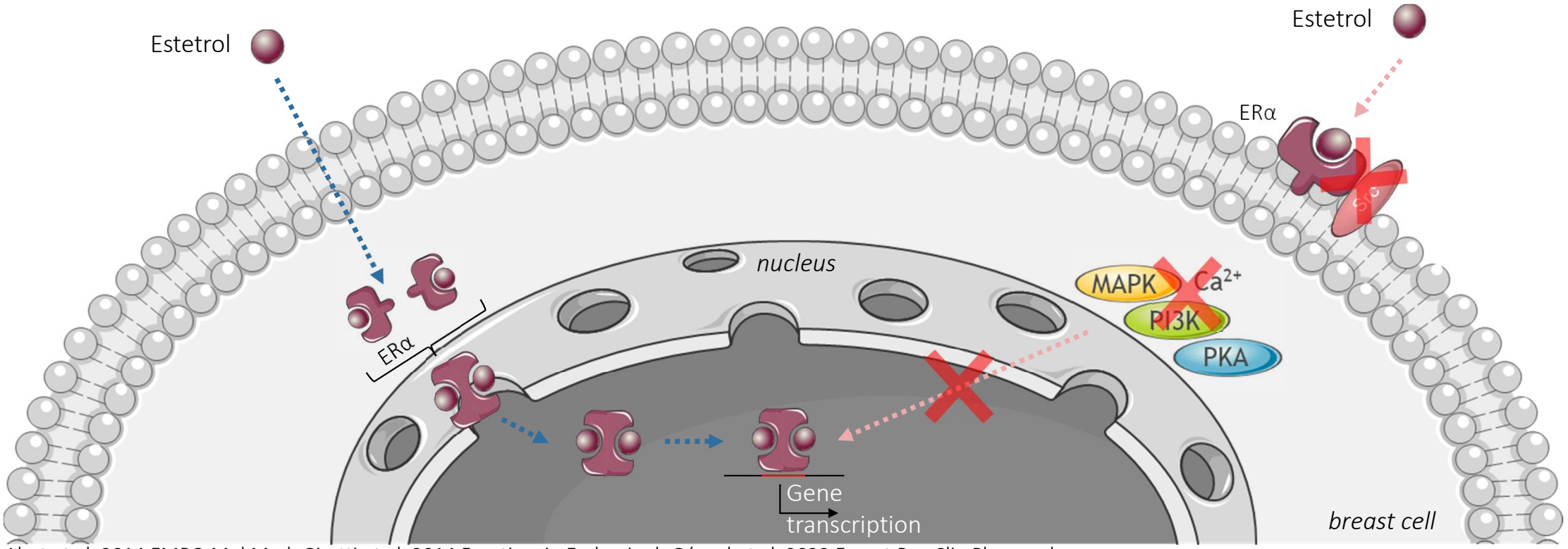
Aesthetic Impact

- Skin
- Hair

E4 has a unique Mode of Action

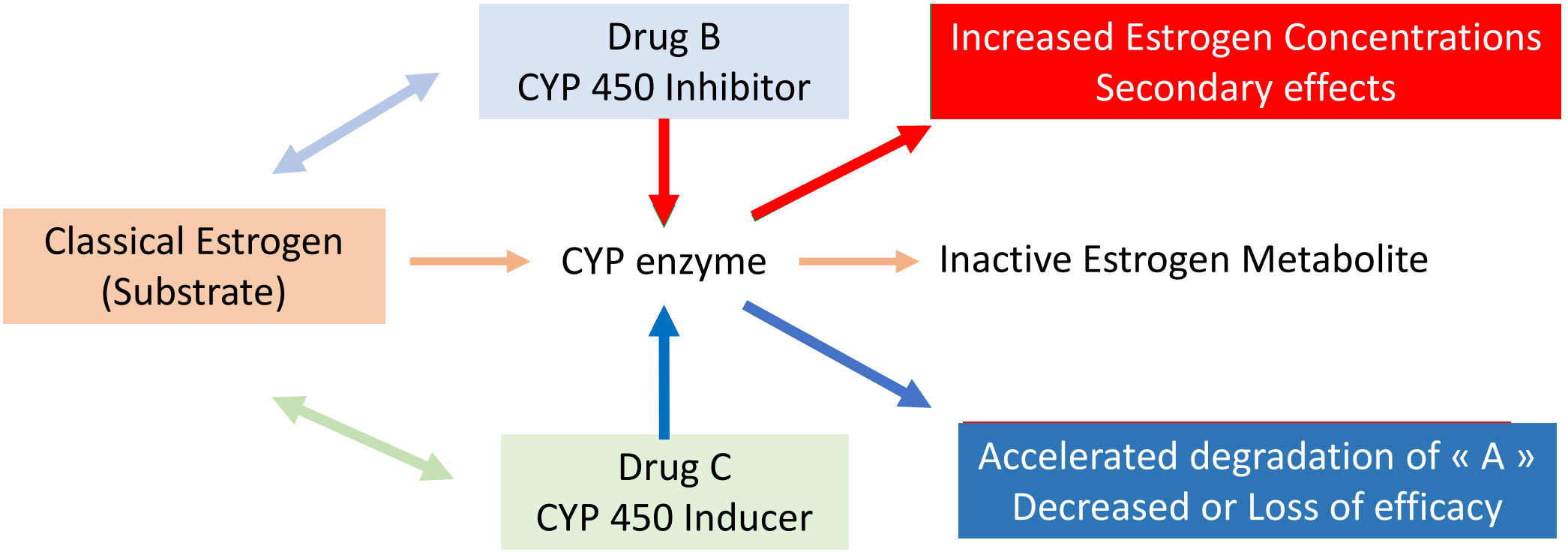
E4-ERα interaction results in:

- Nuclear-initiated steroid signaling (NISS):
- Blockade of membrane-initiated steroid signaling (MISS):



Abot et al. 2014 EMBO Mol Med; Giretti et al. 2014 Frontiers in Endocrinol; Gérard et al. 2022 Expert Rev Clin Pharmcol

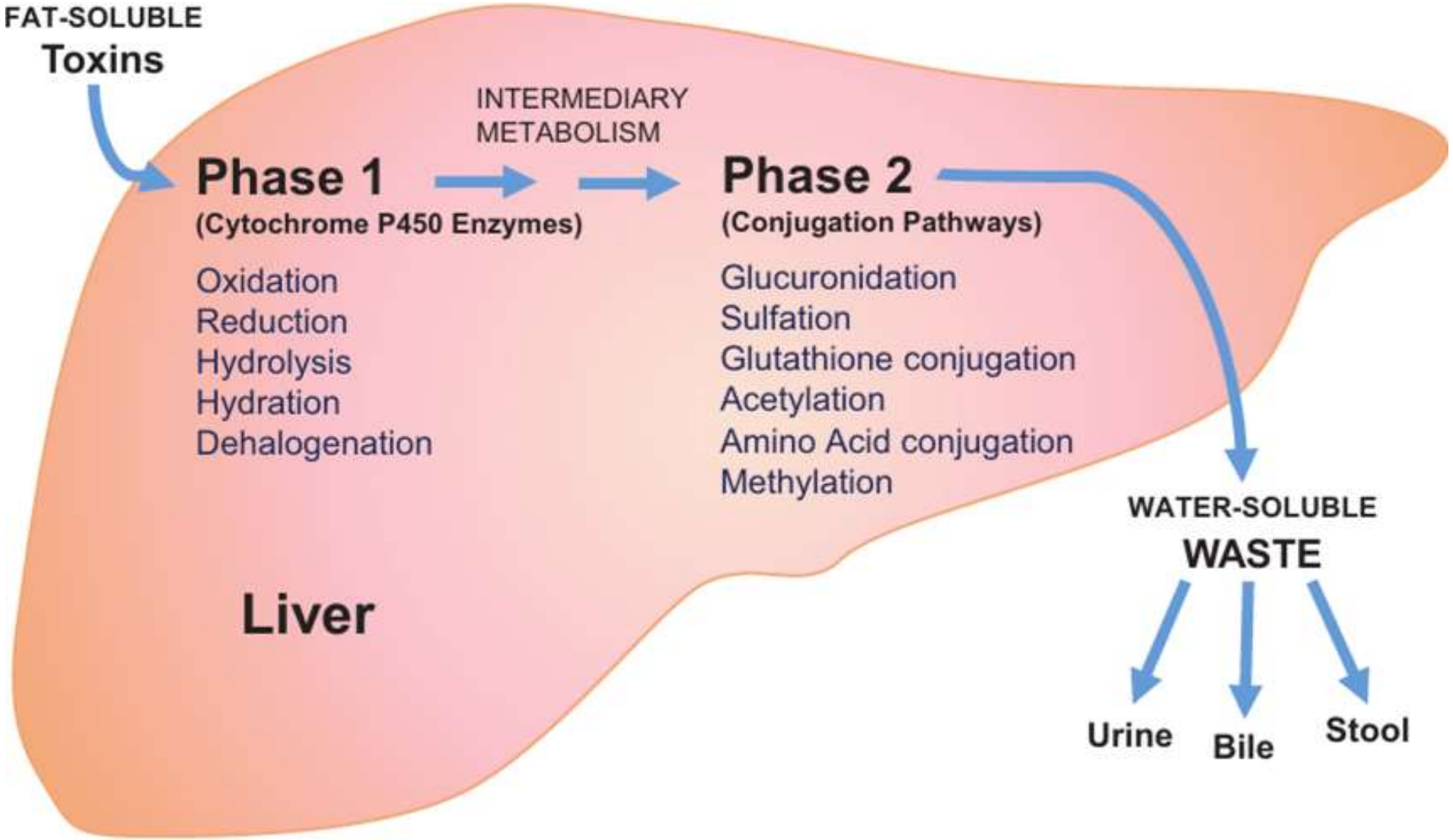
Drug- Drug interaction with classical estrogens (E2, EE, E2 valerate…)



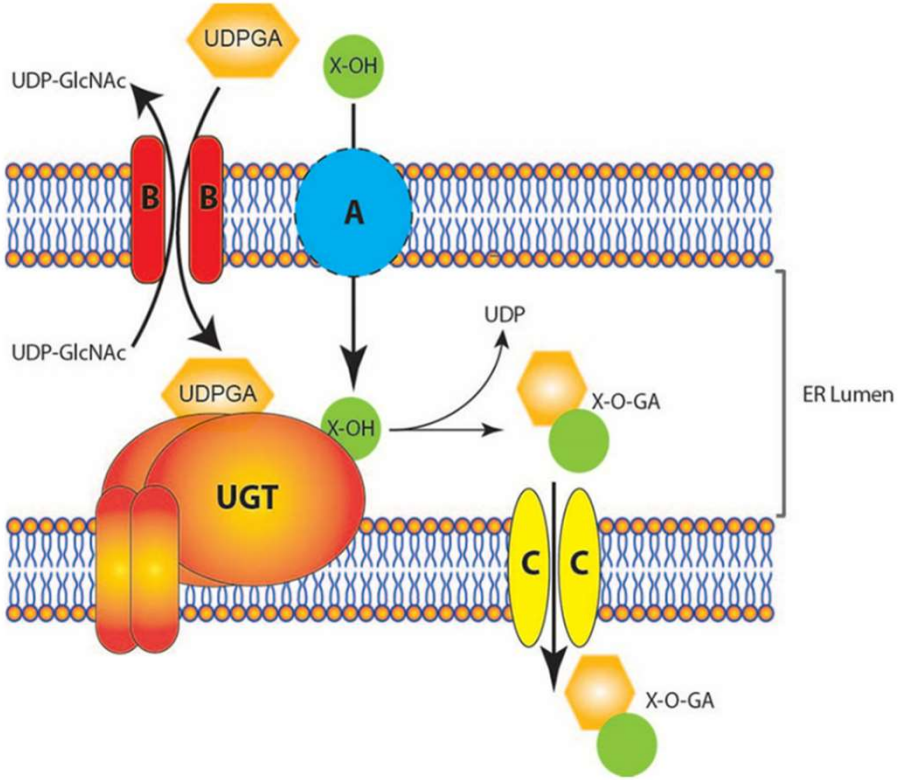
Phase I reactions: Cytochrome P450 enzymes oxidize or reduce drugs.

Drug Interactions

- Estradiol, Ethinyl Estradiol, Testosterone levels are ***INCREASED*** by:
  - Nefazodone
  - Fluvoxamine
  - Indinavir
  - Sertraline
  - Diltiazem
  - Cimetidine
  - Itraconazole
  - Fluconazole
  - Clarythromycin
  - Grapefruit
  - Isoniazid
  - Fluoxetine
  - Efavirenz
  - Paroxetine
  - Verapamil
  - Astemizole
  - Ketoconazole
  - Miconazole
  - Erythromycin
  - Triacetyloleandomycin

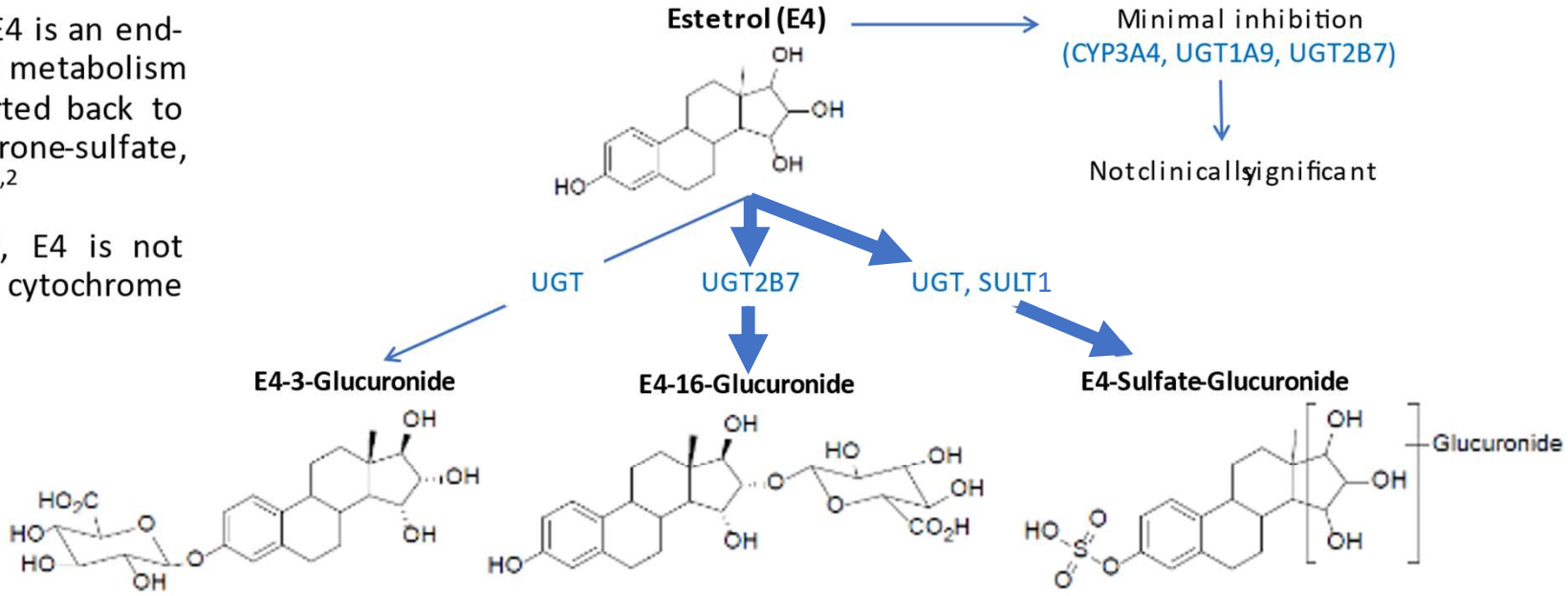

FAT-SOLUBLE
Toxins
INTERMEDIARY
METABOLISM
Phase 1
(Cytochrome P450 Enzymes)
Oxidation
Reduction
Hydrolysis
Hydration
Dehalogenation
Phase 2
(Conjugation Pathways)
Glucuronidation
Sulfation
Glutathione conjugation
Acetylation
Amino Acid conjugation
Methylation
Liver
WATER-SOLUBLE
WASTE
Urine
Bile
Stool

Estetrol is conjugated : sulfo- and glucurono-conjugation



Estetrol (E4): Unique metabolism

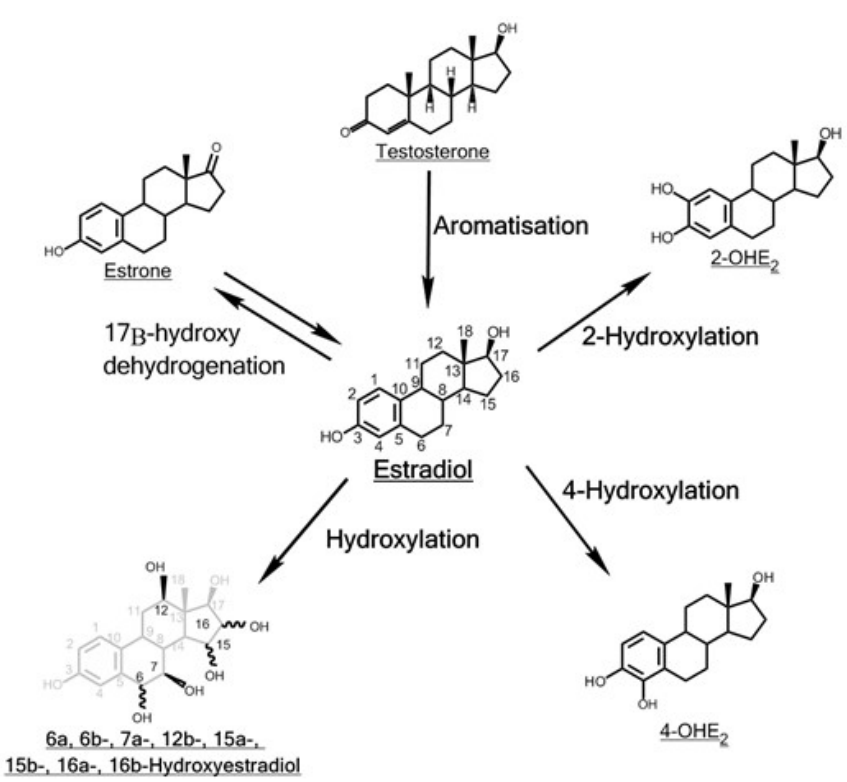
- In contrast to E2, E4 is an end-product of steroid metabolism and is not converted back to estrone, estrone-sulfate, estradiol or estriol[1,2]
- Unlike E2 and EE, E4 is not metabolised by cytochrome P450 enzymes[2,3]

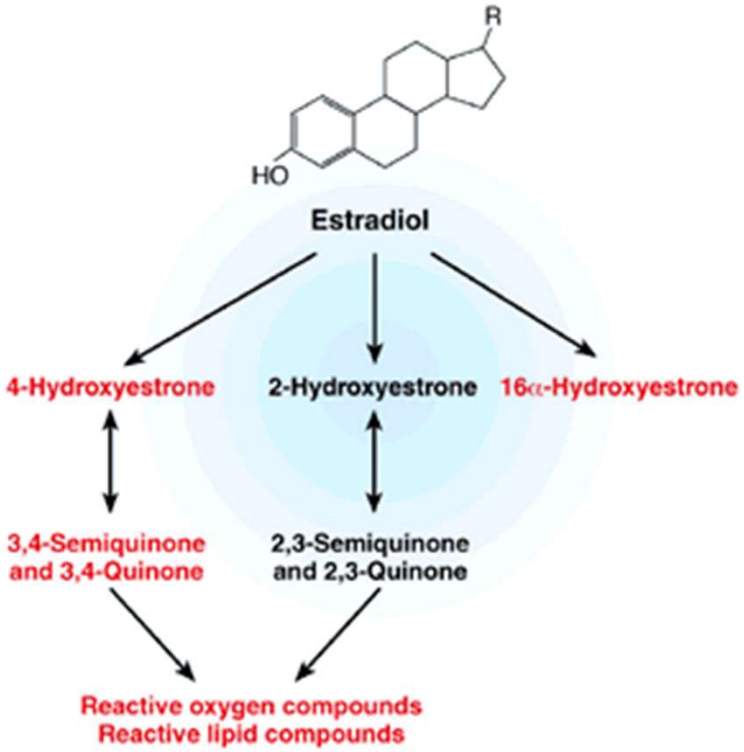


E2, estradiol; E4, estetrol; SULT, sulphotransferase; UGT, uridine 5'-diphospho-glucuronosyltransferase

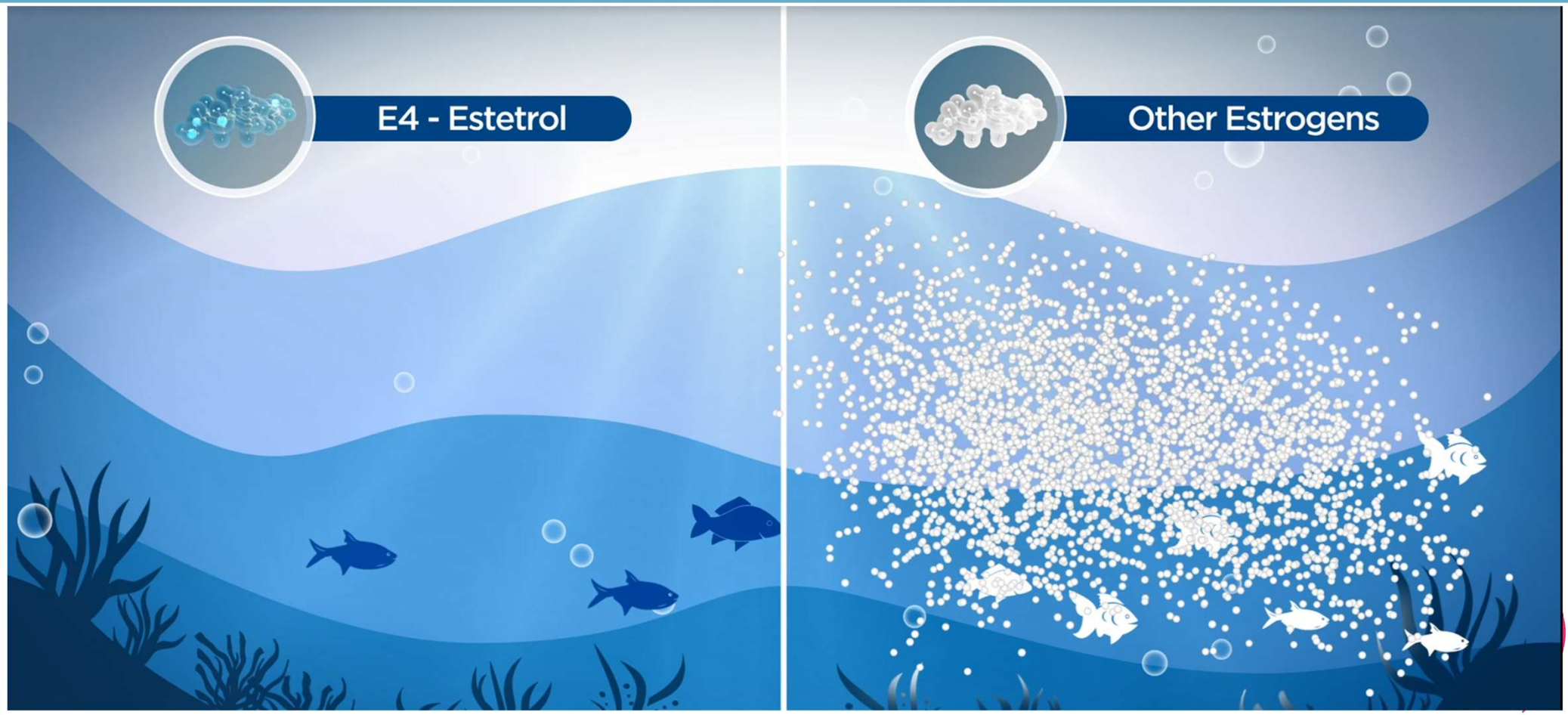
1. Data on file. CSR MIT-Es0001-C105 (QCL114621), July 2016
2. Visser M, et al. Climacteric 2008;11(Suppl.1):64–68
3. Coelingh Bennink HJ, et al. Climacteric 2008;11 Suppl 1:47–58

Carcinogenic metabolites of Estradiol are produced by CYP enzymes





E4 and its impact on environment



Kestemont et al. Contraception, abstract only. Volume 102. Issue 4, P293, October 01, 2020

Why are these male Fish growing Eggs?

- Estrogens (E1,E2 or EE 1ng/L) in lakes[1]
  - reduce eggs production or testicular growth
  - delay sexual maturation
  - feminize populations and promote sexual ambiguity
- E4 does not accumulate in living organisms, surface water, groundwater, or sediment[2]
- Only 2.5% of ingested E4 is released in the urine as biologically active E4[2]

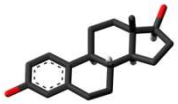
NATIONAL GEOGRAPHIC

85% of male small mouth bass in National wildlife refuges in the Northeastern U.S. have eggs growing in their testes[2]

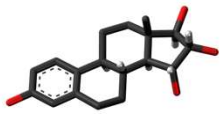
[1]Adeel et al. Environment International. Volume 99, February 2017, Pages 107-119 | [2]Data on file Mithra Pharmaceuticals | [4]Kestemont et al. Contraception, abstract only. Volume 102. Issue 4, P293, October 01, 2020 | | [3]National Geographic, Why Are These Male Fish Growing Eggs? Published February 3, 2016

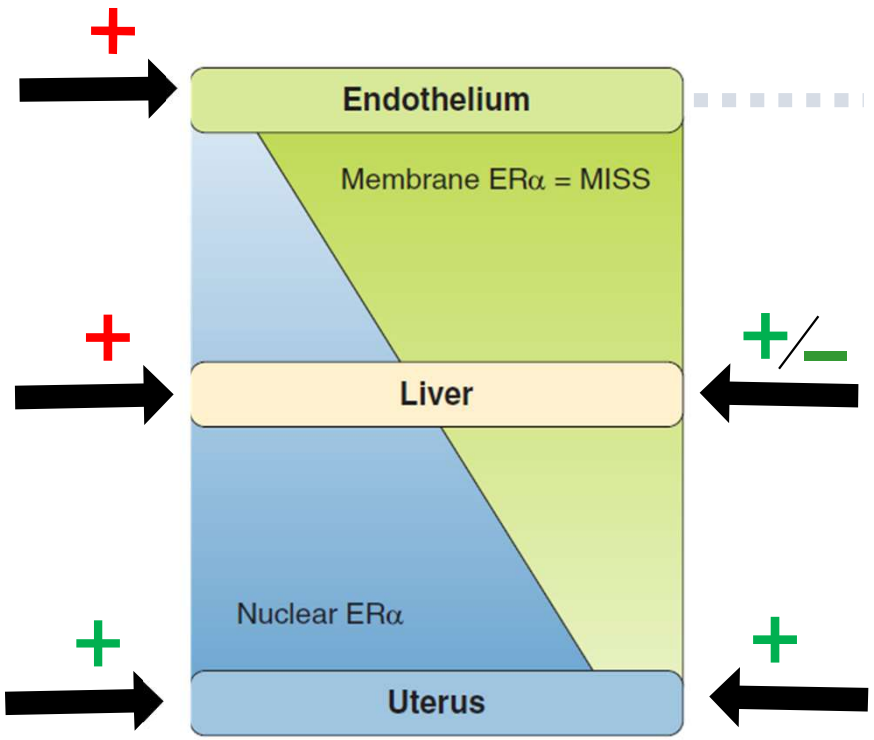
Tissue-specific activity of E4

Estradiol (E2)



Estetrol (E4)



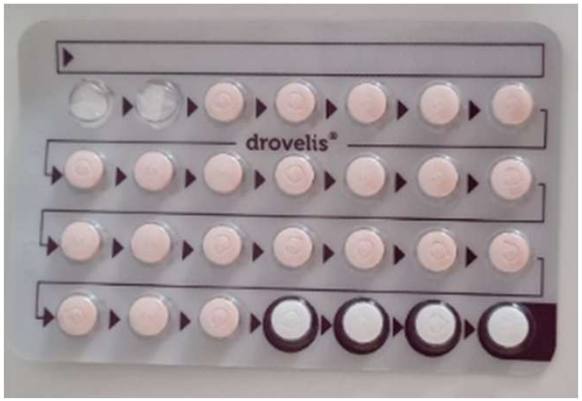


- E2 and E4 exert physiological actions in the uterus, a tissue with dominant ERα **nuclear** activity
- The endothelium with exclusively **membrane** ERα is insensitive to E4
- The liver is more sensitive to E2, depending on both membrane and nuclear ER effects

Estetrol and contraception : In case of forgotten pills

Estetrol has a 70 % bioavailability, (versus 1% for E2, does not bind to SHBG and has a very long half-life (28–32 hours) → prolonged tissue exposure.

Drospirenone has also a long half-life (25-33 hours)



Combined EU and US phase 3 studies

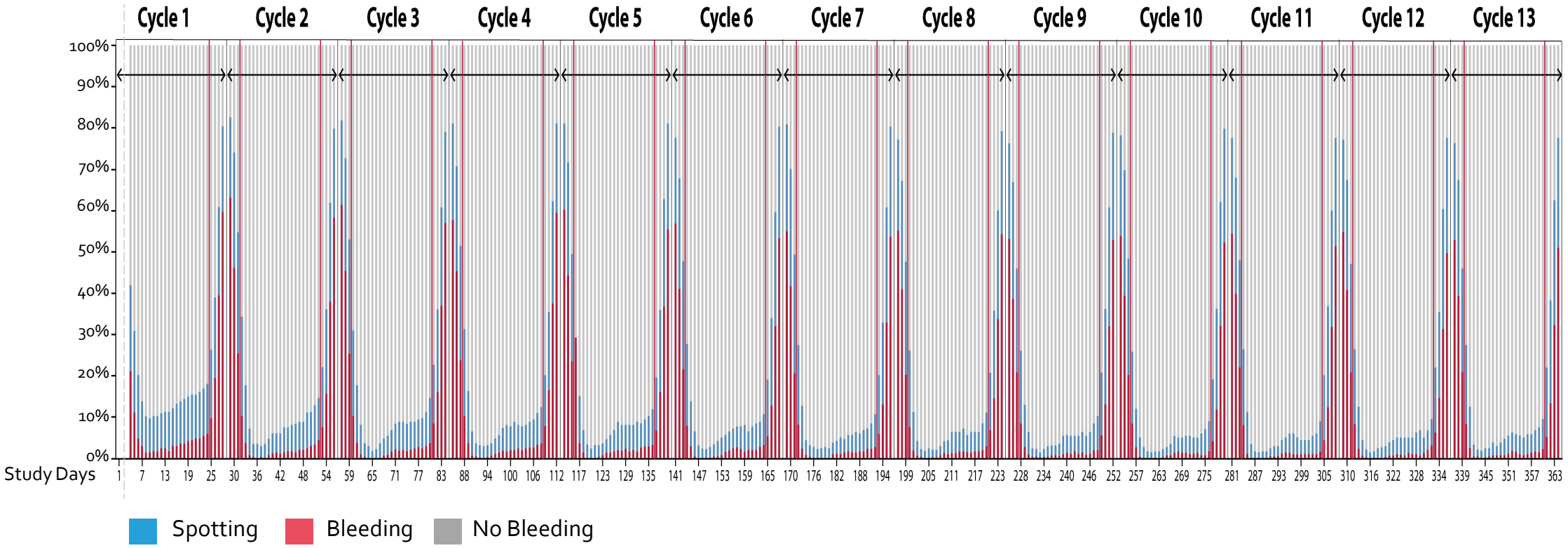
3,027 participants, (26,455 at-risk cycles of use)

Pearl Index of 1.52 (95% CI 1.04–2.16).

Missing active pills	Pregnancies
0	0.09%,
1	0.25%,
2	0.83%,
> 2	1.60%

YO1

E4 15 mg + DRSP 3 mg: regular and predictable bleeding pattern

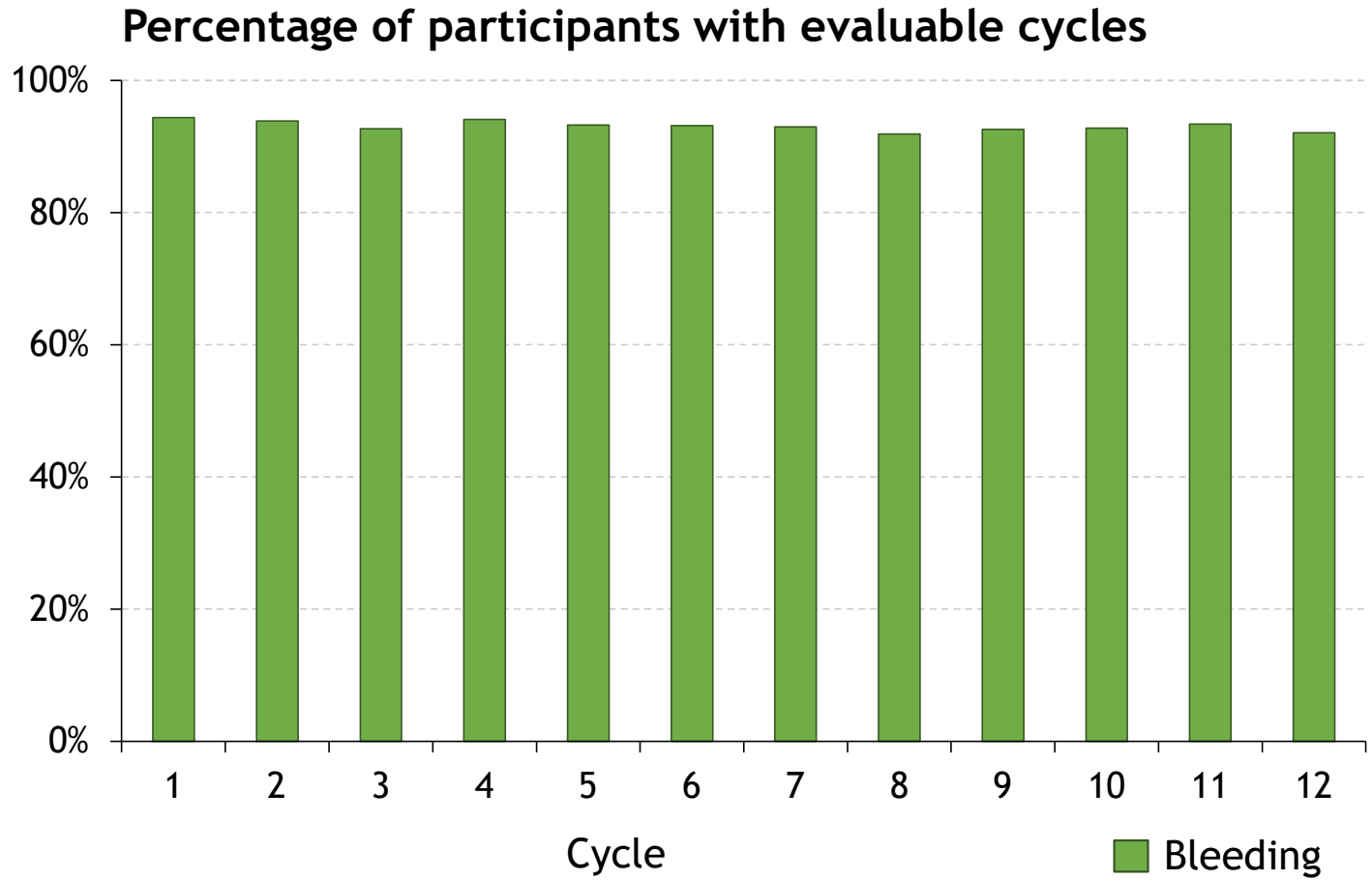


Gemzell-Danielsson K, Estetrol-Drospirenone combination oral contraceptive: a clinical study of contraceptive efficacy, bleeding pattern and safety in Europe and Russia. BJOG. 2022 Jan;129(1):63-71.

Diapositive 51

YO1 Dear Prof Foidart, could we remove EU/RUS from title? see footnote/reference
Yvonne Oligschlager; 03-05-22

>92% of participants with E4 15 mg + DRSP 3 mg had a stable and regular scheduled bleeding pattern – EU/RUS Phase 3

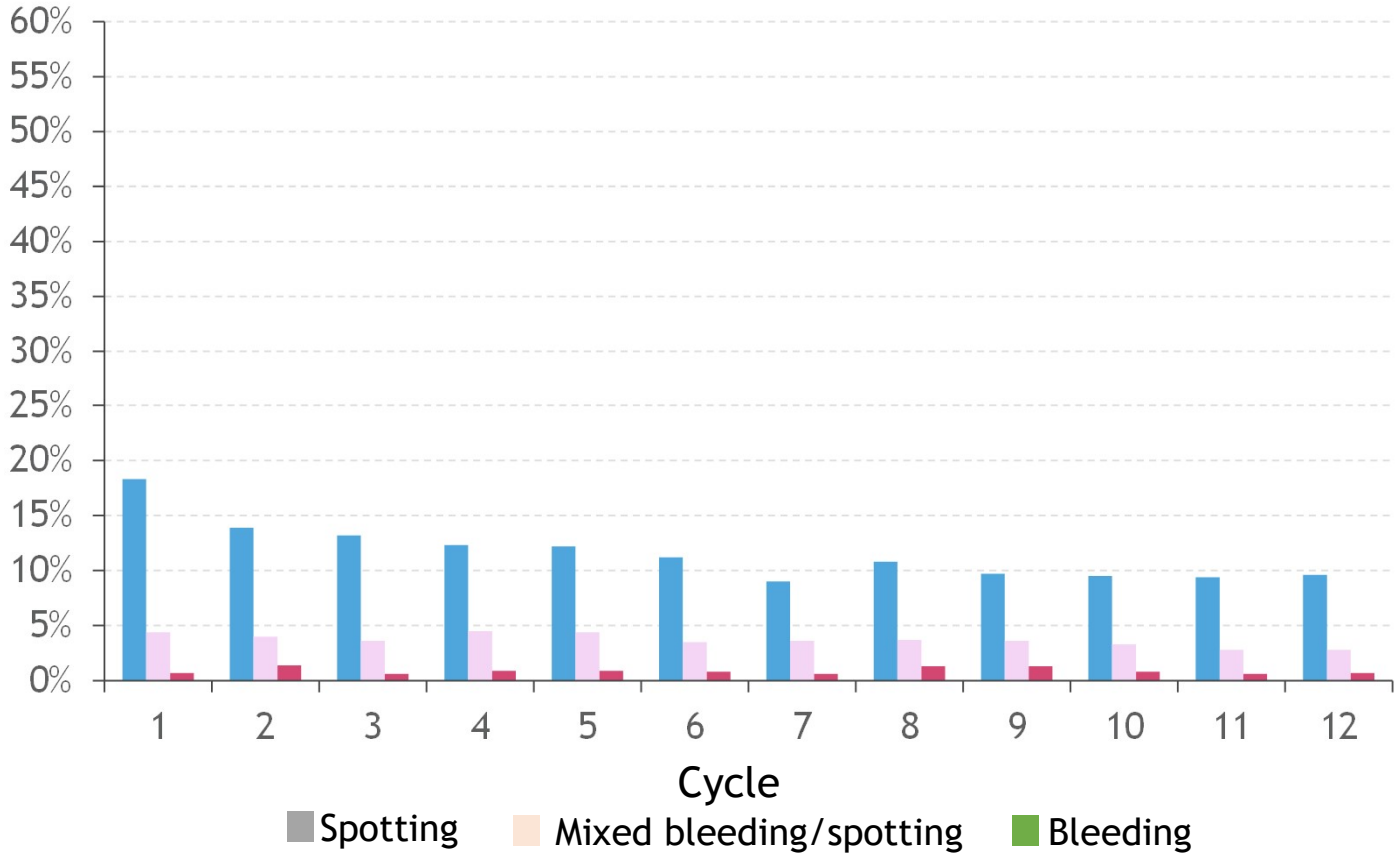


- Over 92% of participants had scheduled bleeding
- Median episode length was 4 – 5 days
- Absence of withdrawal bleeding
  - Occurred at least once during study: 38%
  - Occurred at least twice during study: 15%
  - Occurred during 10-12 cycles: <1%

Gemzell-Danielsson K, Estetrol-Drospirenone combination oral contraceptive: a clinical study of contraceptive efficacy, bleeding pattern and safety in Europe and Russia. BJOG. 2022 Jan;129(1):63-71.

Predictable bleeding pattern with minimal unscheduled bleeding in women with E4 15 mg + DRSP 3 mg – Phase 3

Percentage of participants with evaluable cycles



- Proportion with only scheduled bleeding:
  - Cycle 1: **76.5%**
  - Cycle 12: **87.0%**
- **Most** participants (75%) with unscheduled bleeding/spotting had episodes ≤2 cycles/year
- Median duration unscheduled bleeding/spotting: 3 days
- **Most** participants (66% – 78%) reporting unscheduled bleeding reported spotting-only

Gemzell-Danielsson K, Estetrol-Drospirenone combination oral contraceptive: a clinical study of contraceptive efficacy, bleeding pattern and safety in Europe and Russia. BJOG. 2022 Jan;129(1):63-71.

Combined Oral Contraceptives and Hemostasis

Recent concepts…

- Estrogen induces hypercoagulability
- Progestin has impact as well

Procoagulant

Clotting factors ↑
Protein S ↓
Antithrombin ↓

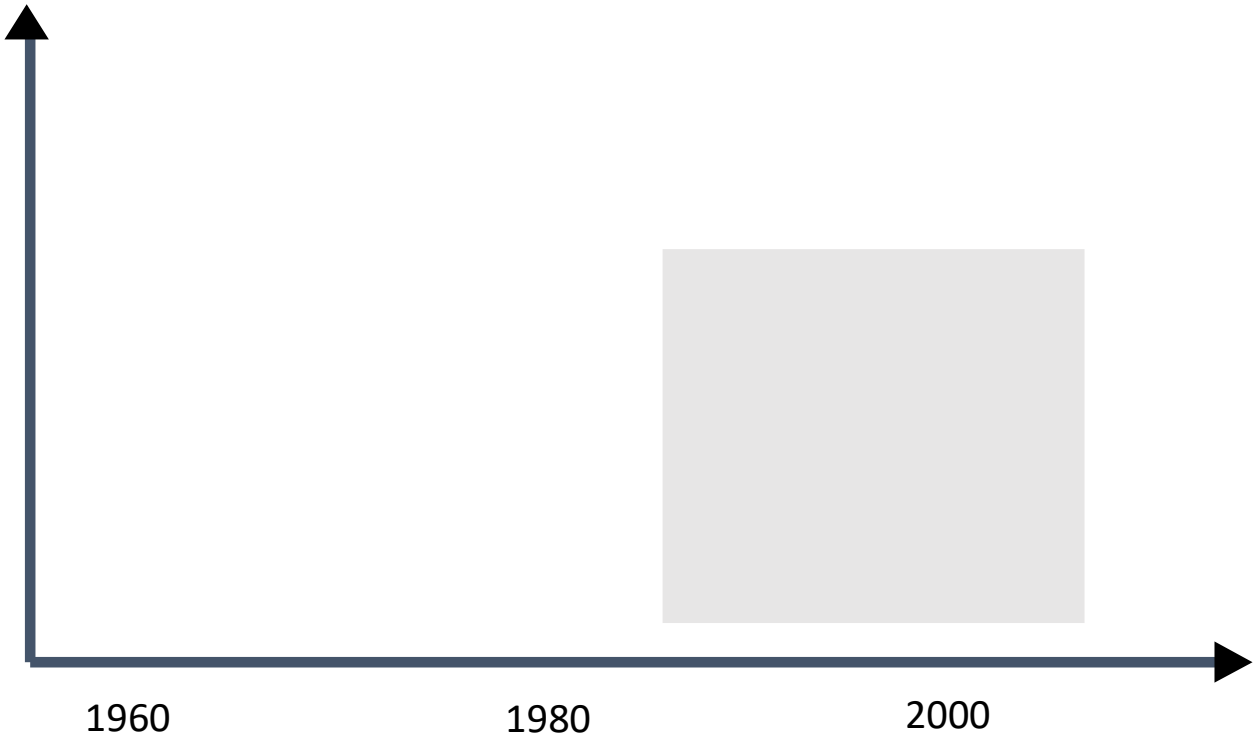
Anticoagulant

Protein C ↑
a_1-Antitrypsin ↑
Plasminogen ↑

Unbalanced hemostasis

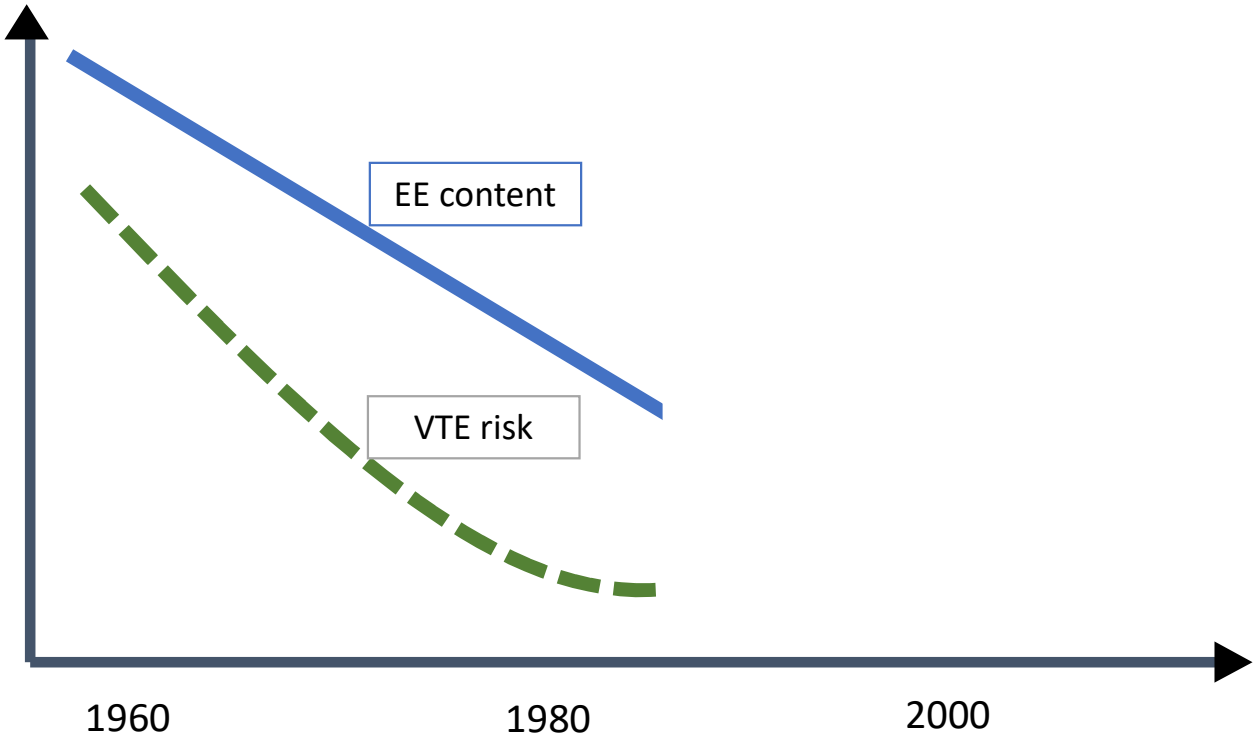
Evolution of a Blockbuster

Mestranol
(150 mcg EE)/
Norethynodrel



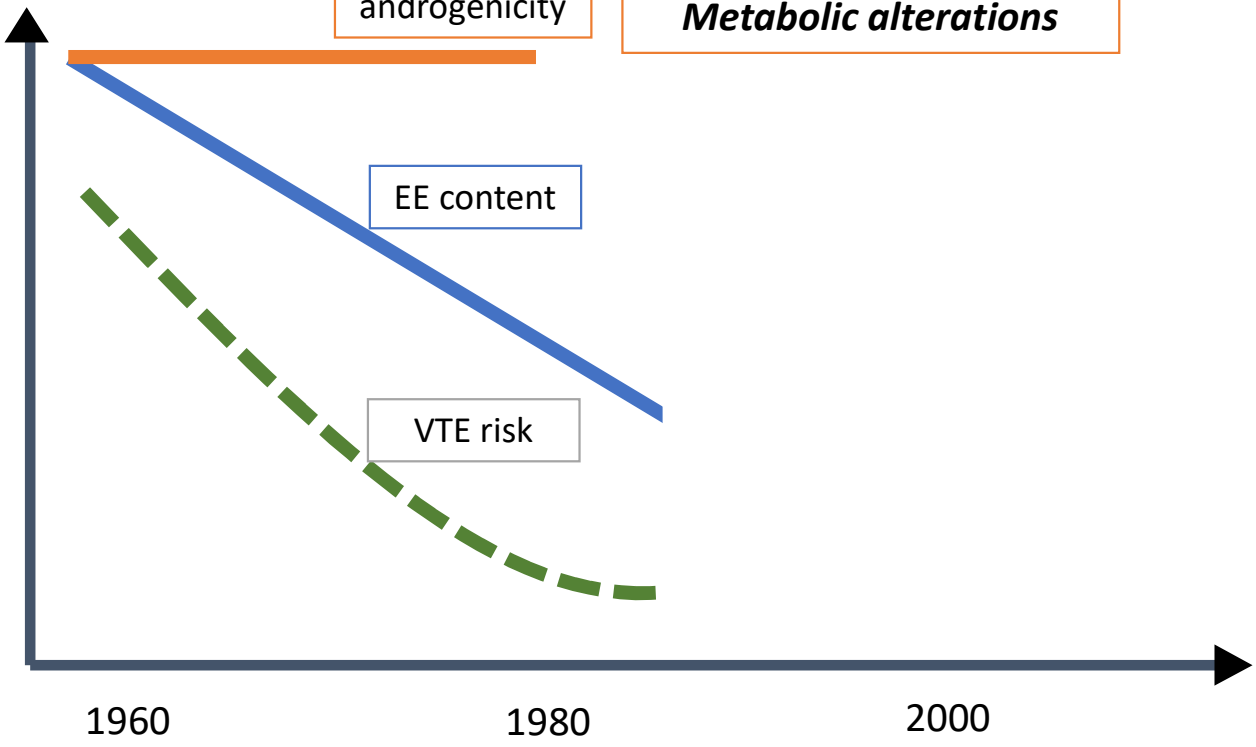
Evolution of a Blockbuster

Mestranol (150 mcg EE)/ Norethynodrel



Evolution of a Blockbuster

Mestranol
(150 mcg EE)/
Norethynodrel



Levonorgestrel (LNG)
- Androgenic

Acne, hirsutism, mood alteration, weight gain, Metabolic alterations

Evolution of a Blockbuster

Mestranol (150 mcg EE)/ Norethynodrel

Progestin androgenicity

Levonorgestrel (LNG)
- Androgenic

Acne, hirsutism, mood alteration, weight gain, Metabolic alterations

EE content

VTE risk

1960

1980

2000

★Drospirenone (DRSP)
- Anti-androgenic
- Anti-mineralocorticoid

Improvement of acne, hirsutism, no HBP, no weight increase, improvement of mood, Metabolic neutral

Evolution of a Blockbuster

Mestranol
(150 mcg EE)/
Norethynodrel

Progestin androgenicity

Levonorgestrel (LNG)
- Androgenic

Acne, hirsutism, mood alteration, weight gain, Metabolic alterations

EE content
20 mcg/d

VTE risk

1960 1980 2000

★Drospirenone (DRSP)
- Anti-androgenic
- Anti-mineralocorticoid

Improvement of acne, hirsutism, no HBP, no weight increase, improvement of mood, Metabolic neutral

VTE risk and Estrogenicity of a COC

Sex hormone binding globulin

Non-user

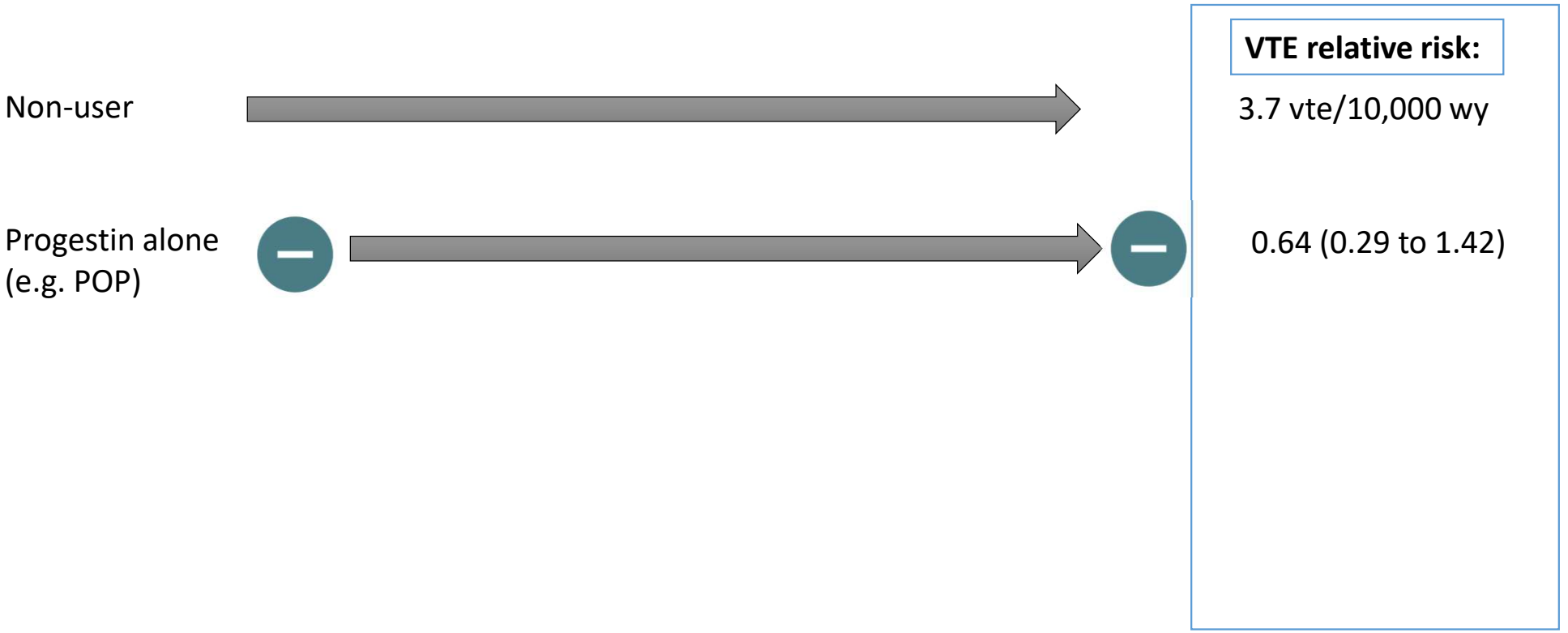
VTE relative risk:

3.7 vte/10,000 wy

Lidegaard O et al. British Medical Journal, 2011;343 (Oct 25): d6423

VTE risk and Estrogenicity of a COC

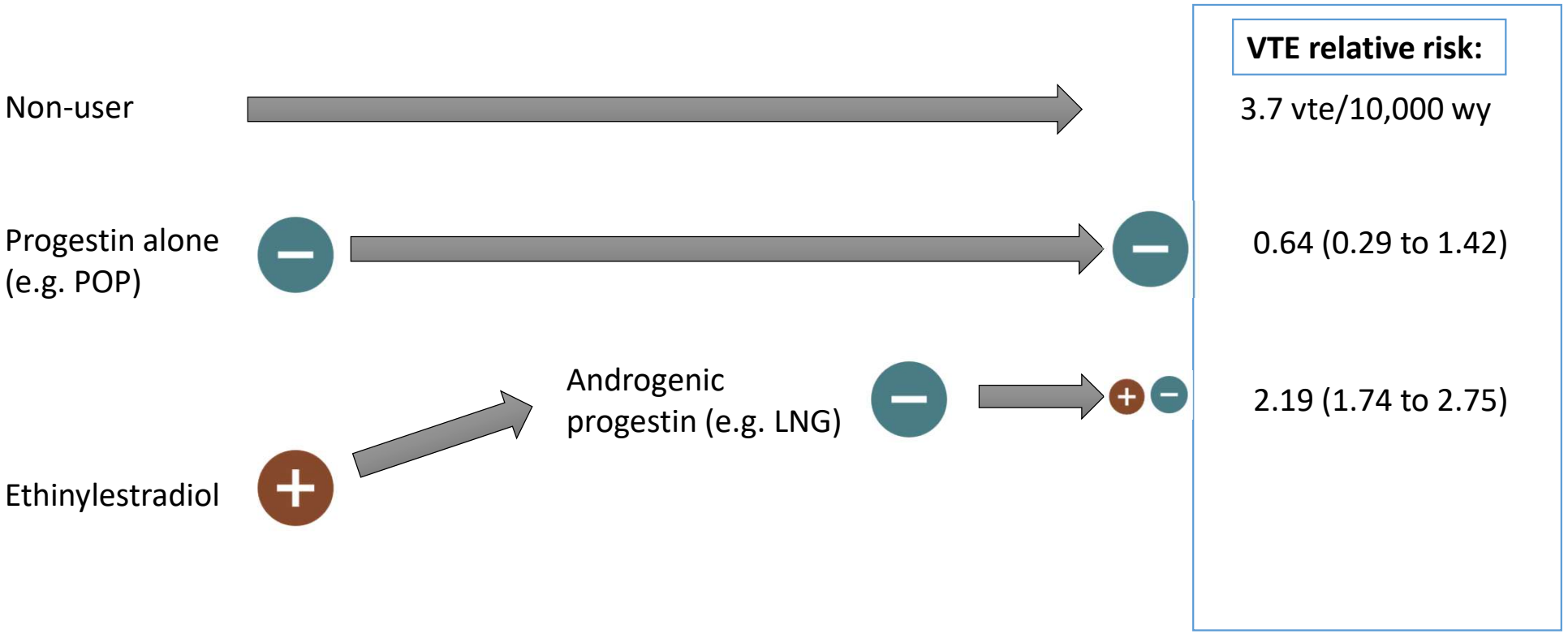
Sex hormone binding globulin



Lidegaard O et al. British Medical Journal, 2011;343 (Oct 25): d6423

VTE risk and Estrogenicity of a COC

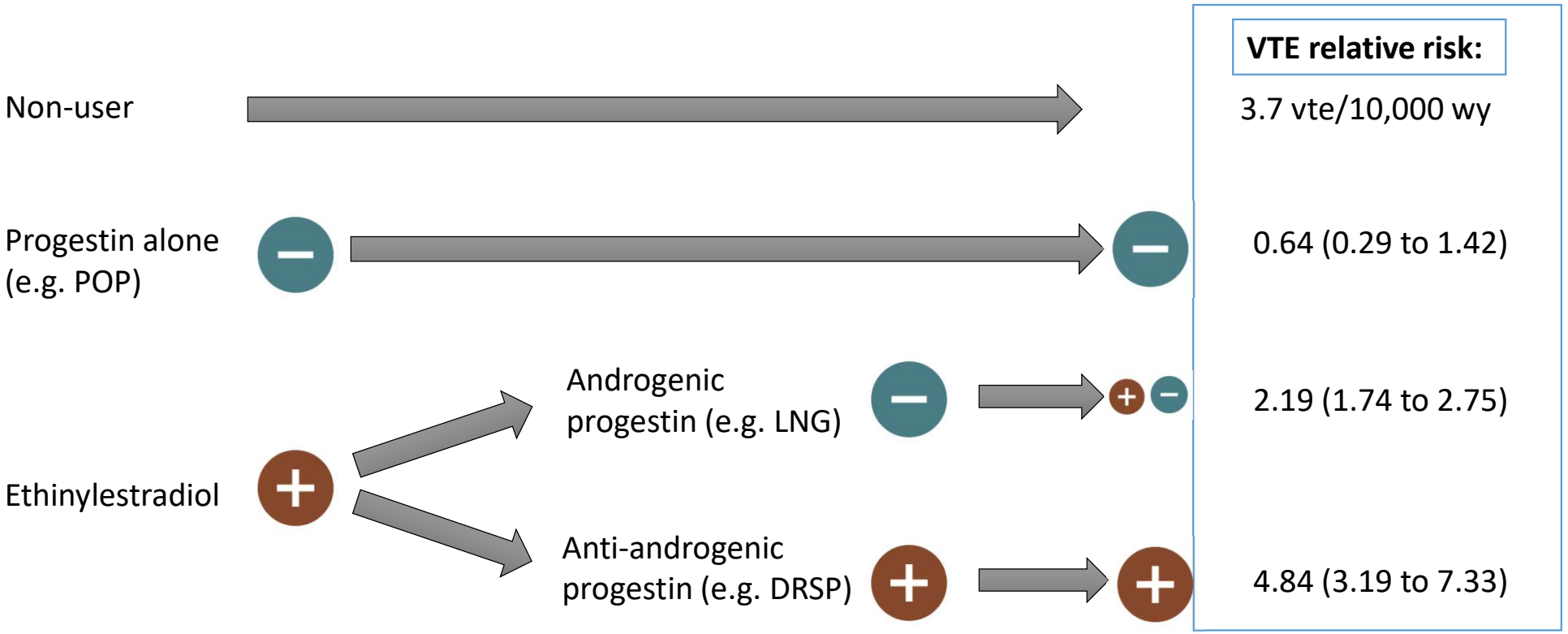
Sex hormone binding globulin



Lidegaard O et al. British Medical Journal, 2011;343 (Oct 25): d6423

VTE risk and Estrogenicity of a COC

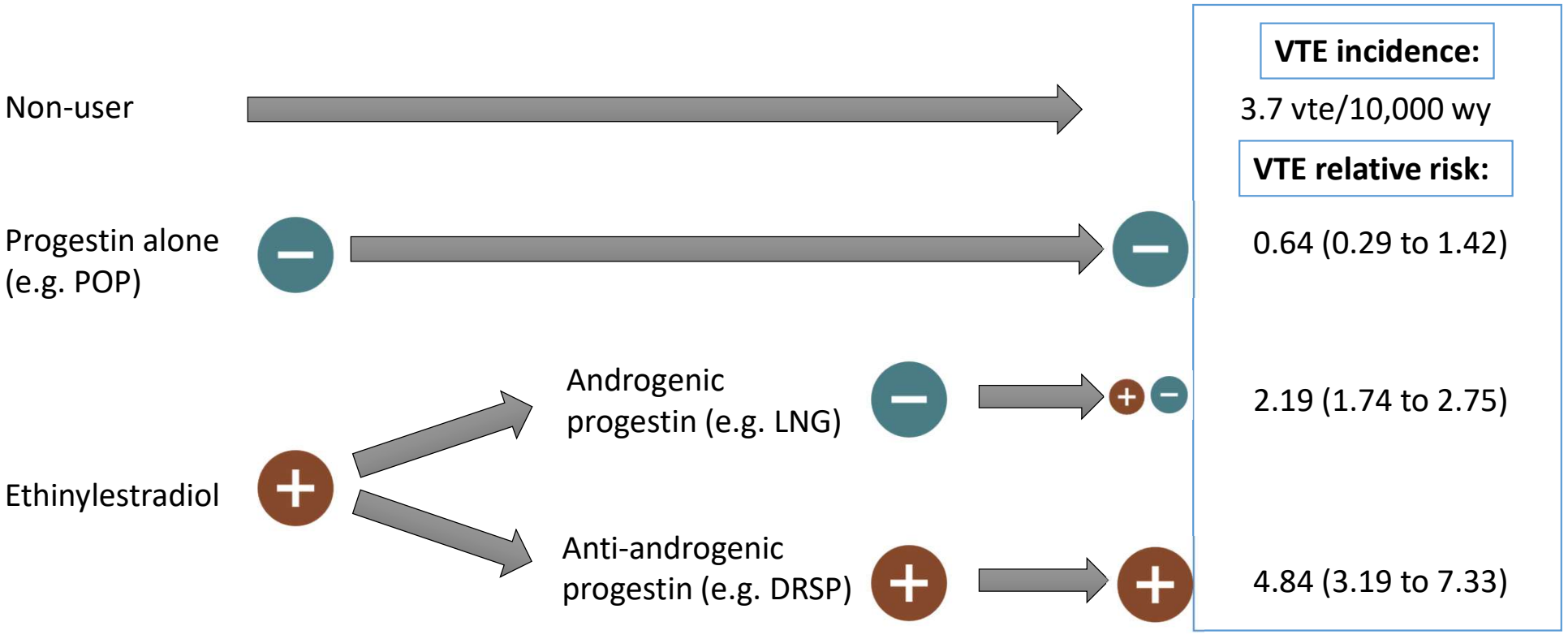
Sex hormone binding globulin



Lidegaard O et al. British Medical Journal, 2011;343 (Oct 25): d6423

VTE risk and Estrogenicity of a COC

Sex hormone binding globulin

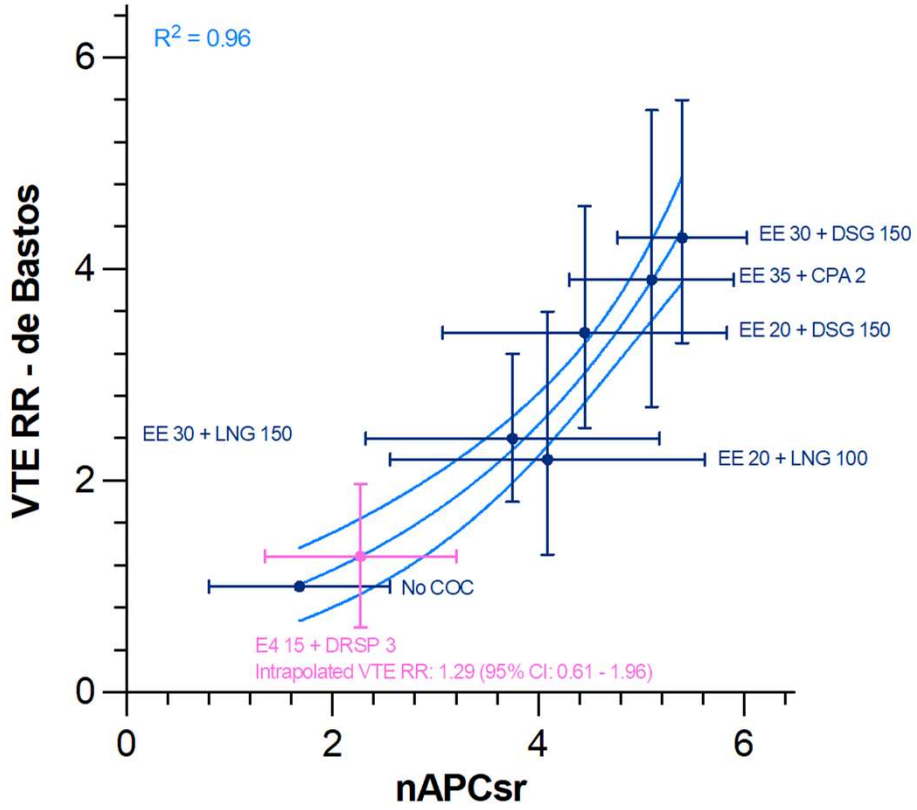


SHBG:

- **Hepatic production proportional to the estrogenicity**
- **Suggested as surrogate marker of the VTE risk**

Lidegaard O et al. British Medical Journal, 2011;343 (Oct 25): d6423

The ETP-based APC resistance assay



Douxfils J, Klipping C, Duijkers I. Contraception. 2020 | Morimont, L., Dogné J-M., and Douxfils J. Thrombosis Research 2020 |E4: Estetrol 15 mg | E4/DRSP: Estetrol 15 mg/drospirenone 3 mg | EE/LNG: ethinylestradiol 30 µg/ levonorgestrel 150 µg | EE/DRSP: ethinylestradiol 20 µg/ DRSP 3 mg | APC: activated protein C APCr: activated protein C resistance | HPP: healthy pooled plasma | nAPCsr: normalized activated protein C sensitivity ratio | COC: combined oral contraceptive | ETP: endogenous thrombin potential

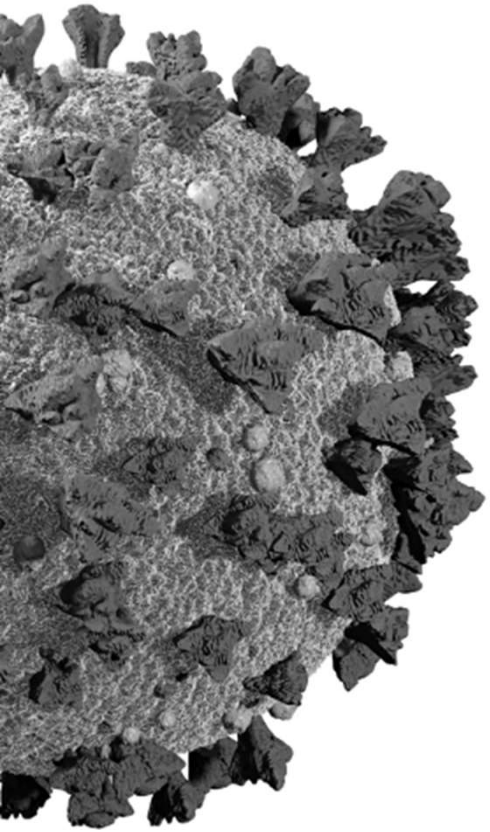
Venous thromboembolic (VTE) risk – EU/RUS Phase 3

Contraceptive	EE 10 µg/ NETA 1 mg[3]	EE 13 µg/ SGA 150 µg[4]	EE 30 µg/ LNG 120 µg[5]	E4 15 mg/ DRSP 3 mg[2]	E4 15 mg/ DRSP 3 mg[1]
Type of contraceptive	COC	Vaginal ring	Patch	COC	COC
Country	US	US	US	US/CAN	EU/RUS
Number of subjects	1,683	1,188	2,031	1,524	1,553
• BMI > 30 kg/m^2	18%	Unknown (mean BMI 24.4 kg/m^2)	35%	23%	13%
• VTE cases	3 (0.18%)	4 (0.34%)	4 (0.20%)	0	1 (0.06%)

Large phase 4 studies needed to confirm the phase 2 and 3 findings that suggest E4/DRSP use is associated with low clinical thrombosis risk

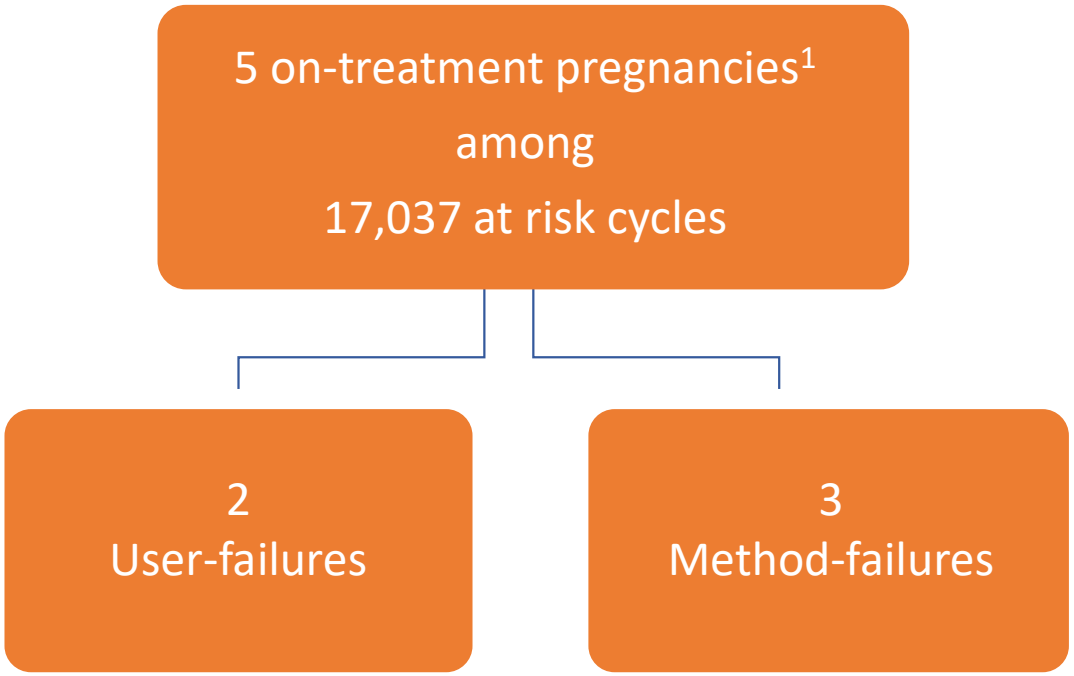
[1]Gemzell Danielsson et al., BJOG 2021 | [2]Creinin et al., Contraception 2021 | [3]Archer et al., Obstet Gynecol.2013 | [4]Gemzell Danielsson et al., Contraception 2019 | [5]Nelson et al., Contraception 2021

Hemostasis in Covid-19 patients



- Would you administer Estrogens to aged patients (60-85 years old) with diabetes, hypertension, CHD, and acute DVT and PE?
- We administered 15 mg E4/d for 21 days to such a high risk population of covid patients with severe comorbidities and in a few ongoing DVT.
- No clinical nor haemostatic changes versus placebo were observed !

Pearl Index (18–50 years) – EU/RUS



Pearl Index[1]
0.38
(95% CI: 0.12, 0.89)

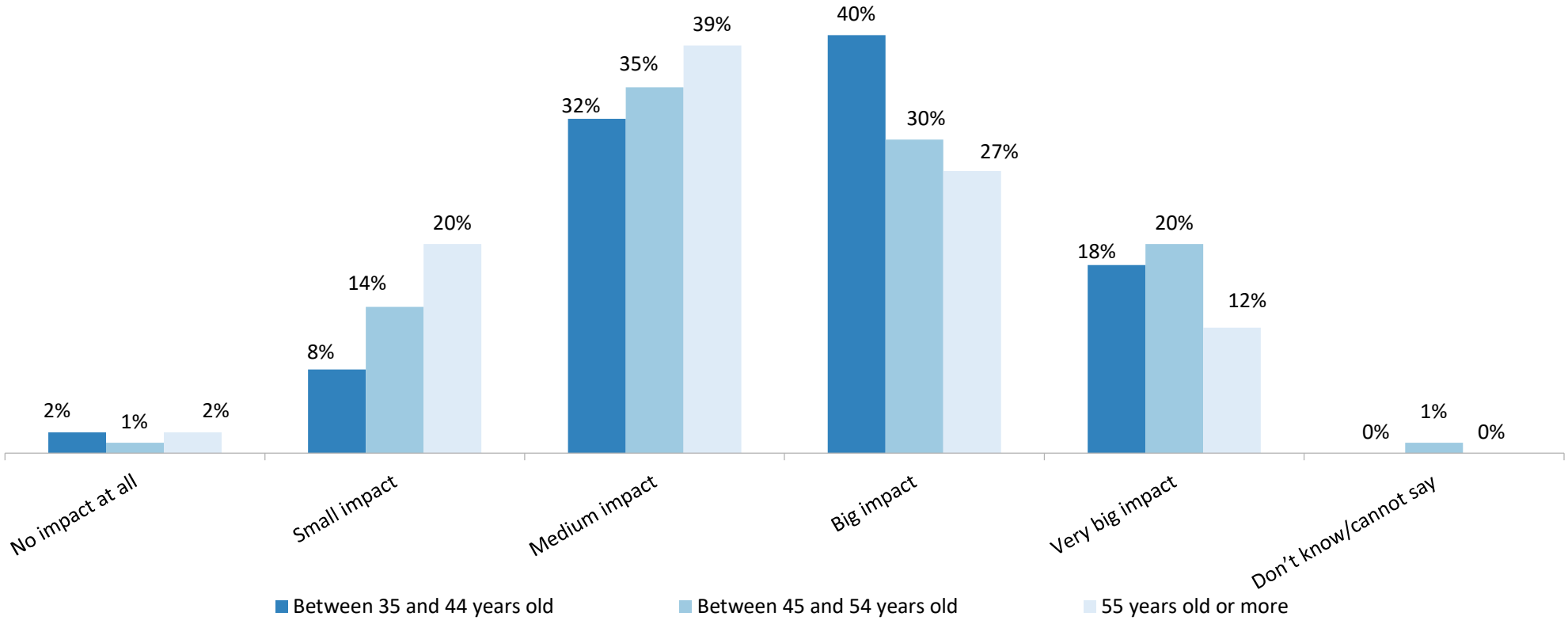
Method-Failure Pearl Index[1]
0.23
(95% CI: 0.05, 0.67)

[1]No other methods of birth control used (EMA definition)

EMA: European Medicines Agency

Trial C301 EU/RUS | Data on file Mithra Pharmaceuticals; EudraCT 2015-003150-40

…and impacts Women's QoL across all age groups

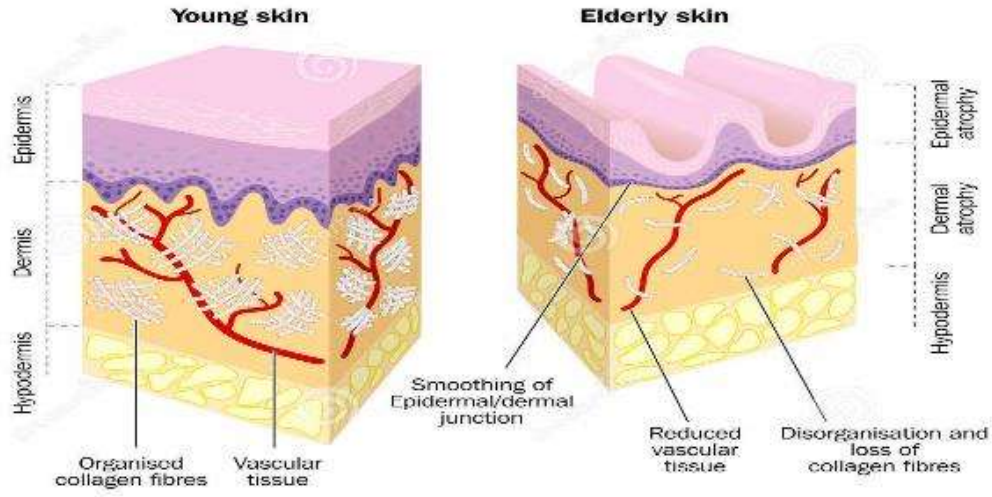


Source: Berenberg . Q6: How much of an impact have these symptoms on your daily life? BASE: (Between 35 and 44 years old: N = 176; Between 45 and 54 years old: N = 742; 55 years old or more: N = 1082)

ENTRACTE

Postmenopausal estrogen-deficiency is associated with a dramatic reduction in skin health

HT slows down this aging process but requires a chronic treatment

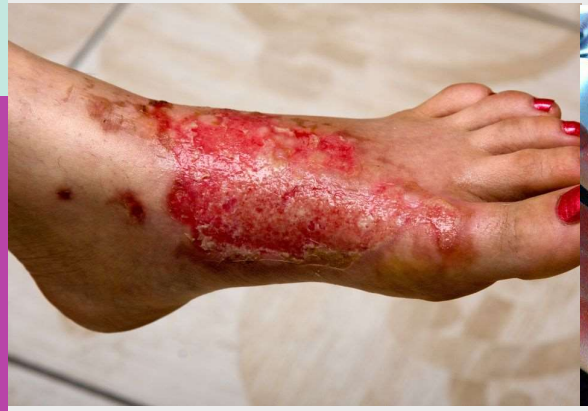


Biological aging is the skin's process of aging after menopause. It becomes more lax in tone, the expression lines become deeper from muscles moving the same underneath the skin over many years, the skin becomes more dry and there is a generalized overall thinning.

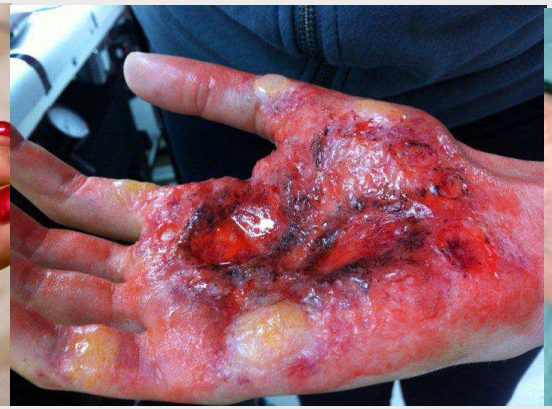
Decreased estrogen slows down mitotic activity in the epidermal basal layer, reduces the synthesis of collagen elastin and proteoglycans. Skin atrophy, hyperseborrhea, increased pilosity on the cheeks and upper lip, loss of scalp hair, increase in degeneration of elastic tissue, atrophy and dryness of the vaginal mucosa are all features of menopause-related aging.

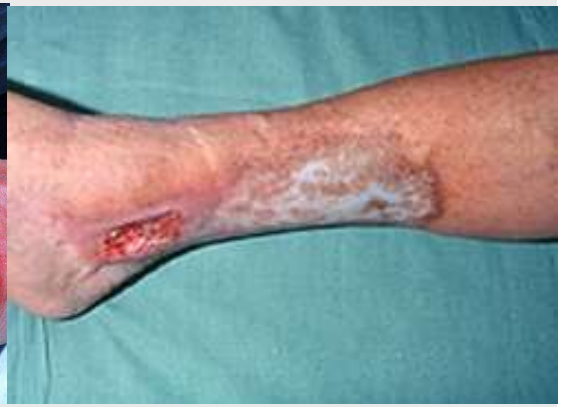
Acceleration of wound healing

Burn
Ulceration

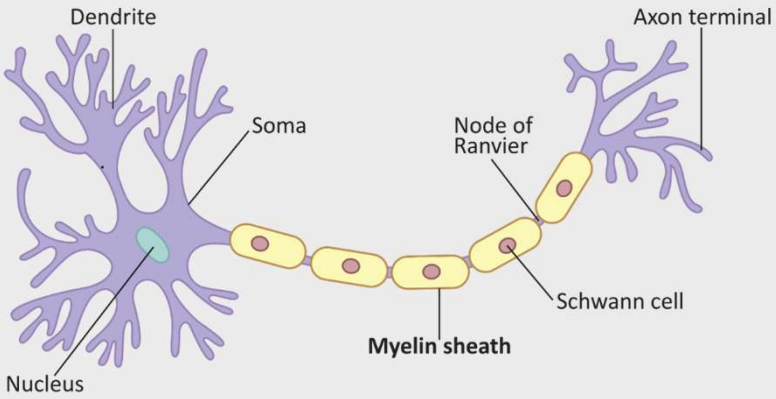


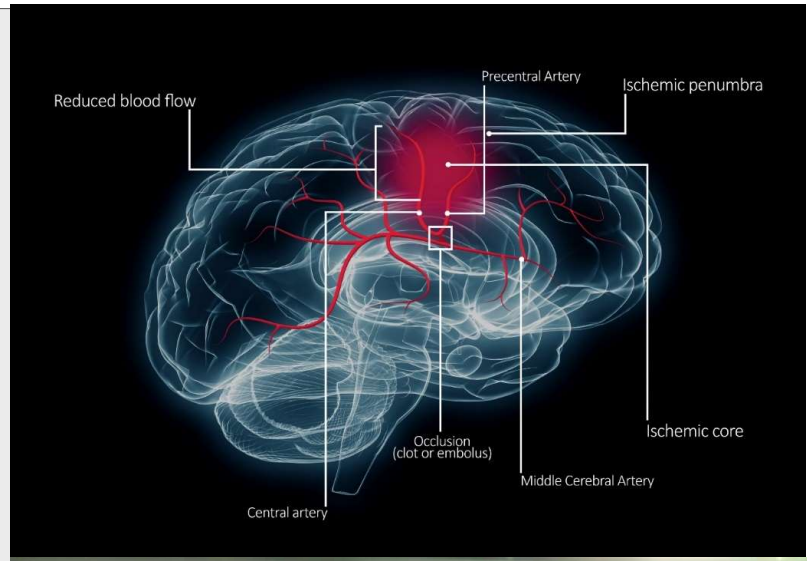
War Wound



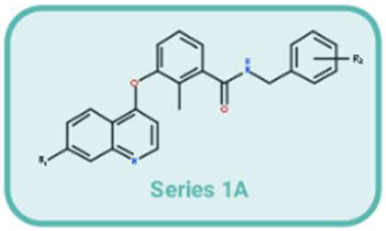
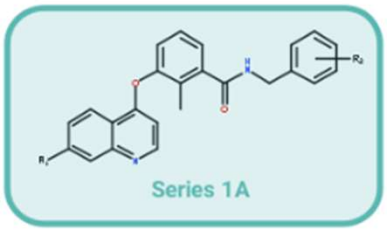
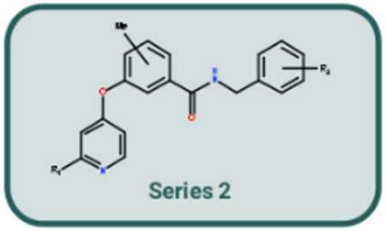
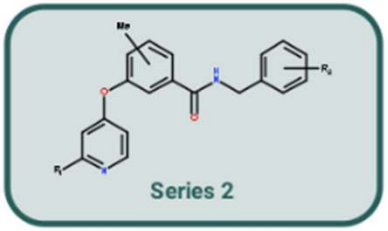
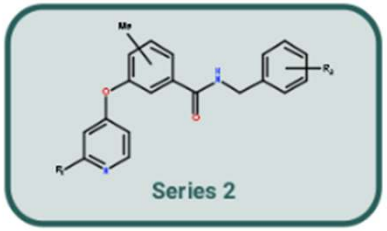
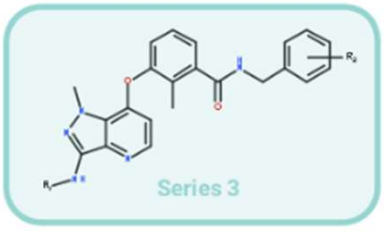
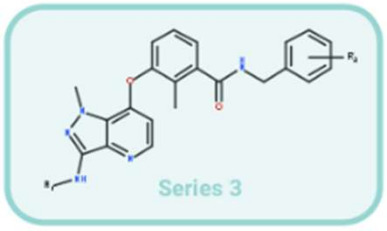
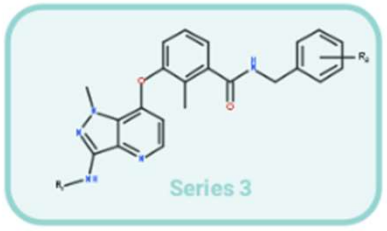
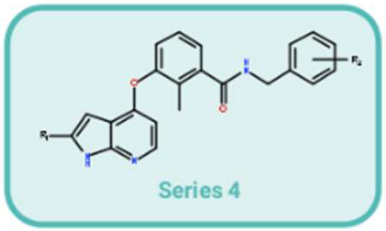
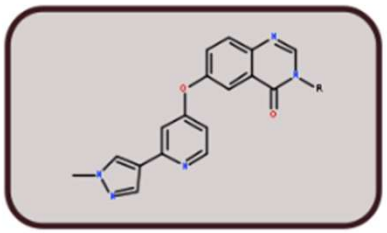


Neuroprotection

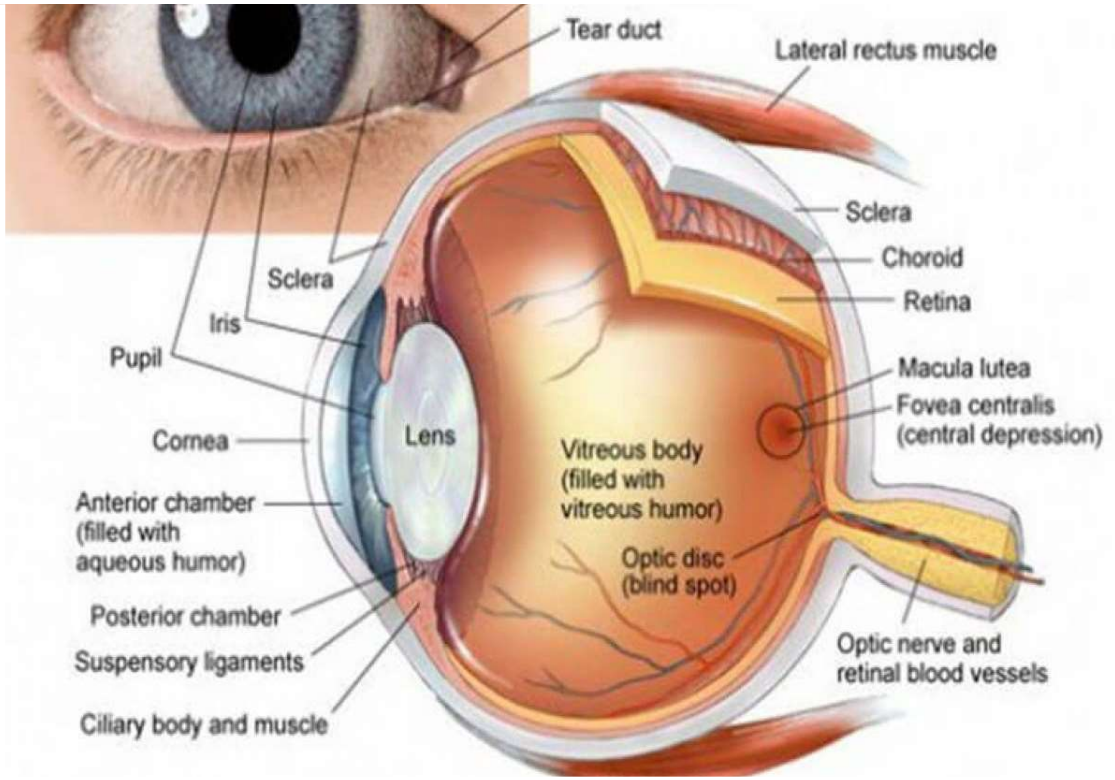





mithracdmo

CSF1R inhibitors	CSF1R/PDGFR inhibitors	PDGFR inhibitors
 Series 1A	 Series 1A	
 Series 2	 Series 2	 Series 2
 Series 3	 Series 3	 Series 3
 Series 4		

E4, major breakthrough in science, at the heart of multiple academic collaborations

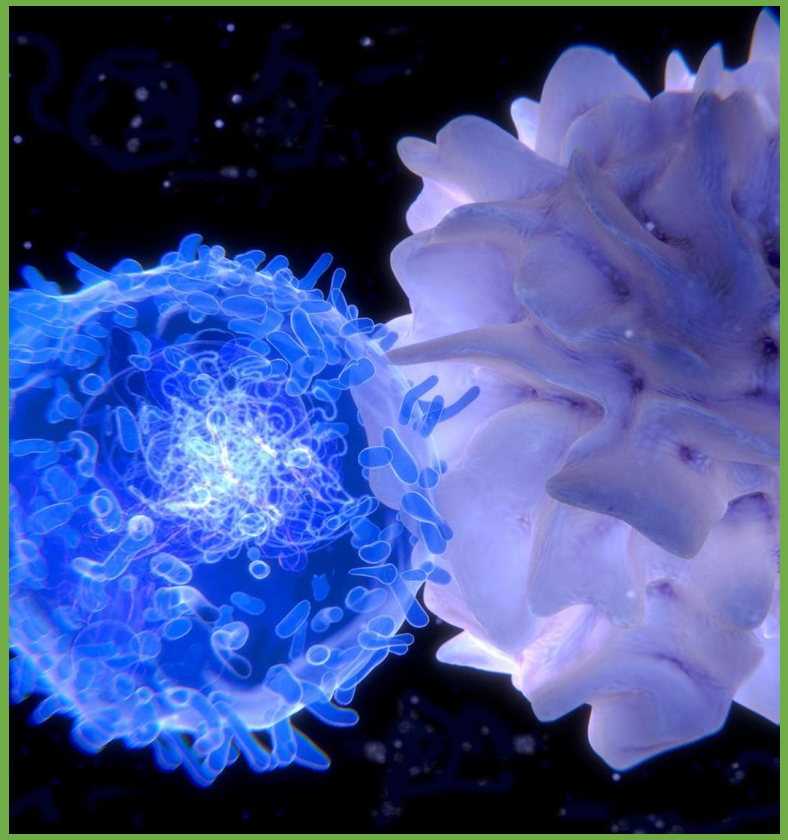


Implant intra-occulaire EYED- PHARMA

Eyed Pharma

Imcyse
2014-2023

Imcyse
specific active
immunotherapeutics

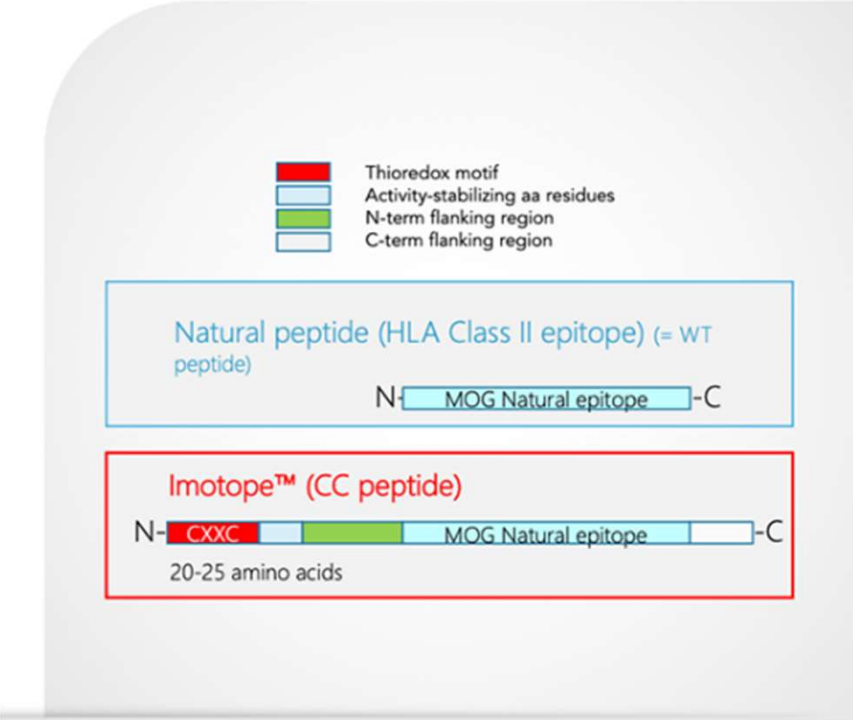


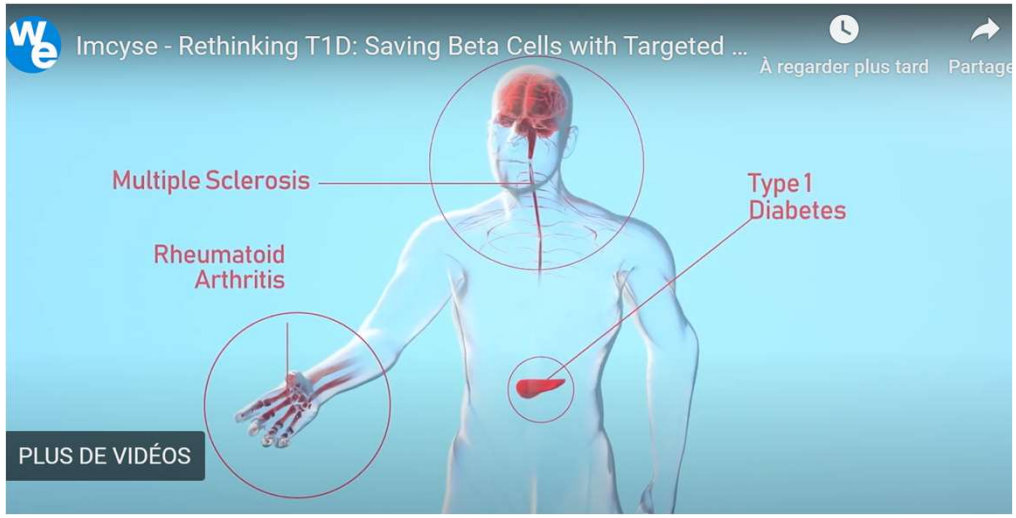
Imotopes™

to prevent, stop and potentially cure autoimmune diseases

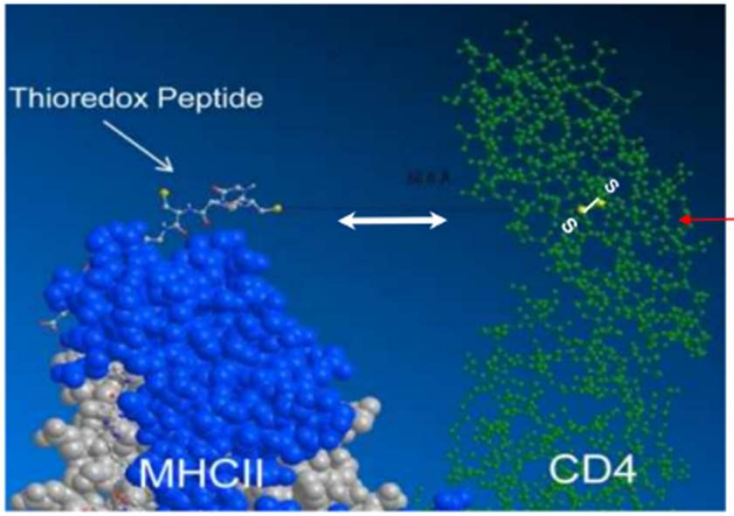
Imcyse
specific active immunotherapeutics

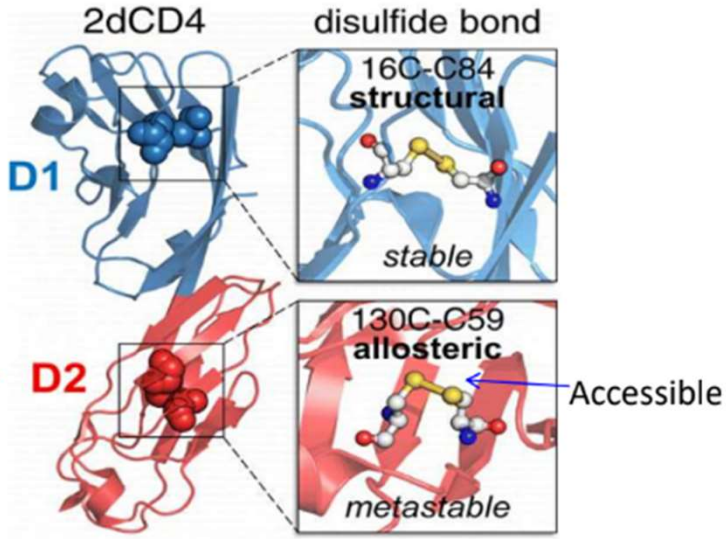
Epitopes modifiés





Impact of an Imotope on CD4 molecule ?





Denis Bedoret former CEO of MasterCells

Imcyse
specific active
immunotherapeutics

EXO Biologics

Discovering the power of exosomes

Company Presentation – Dec 2022

Exosomes or “extracellular vesicles” are inter-cells messengers produced by all cells

Our Mission

Provide innovative exosomes therapies for unmet medical needs

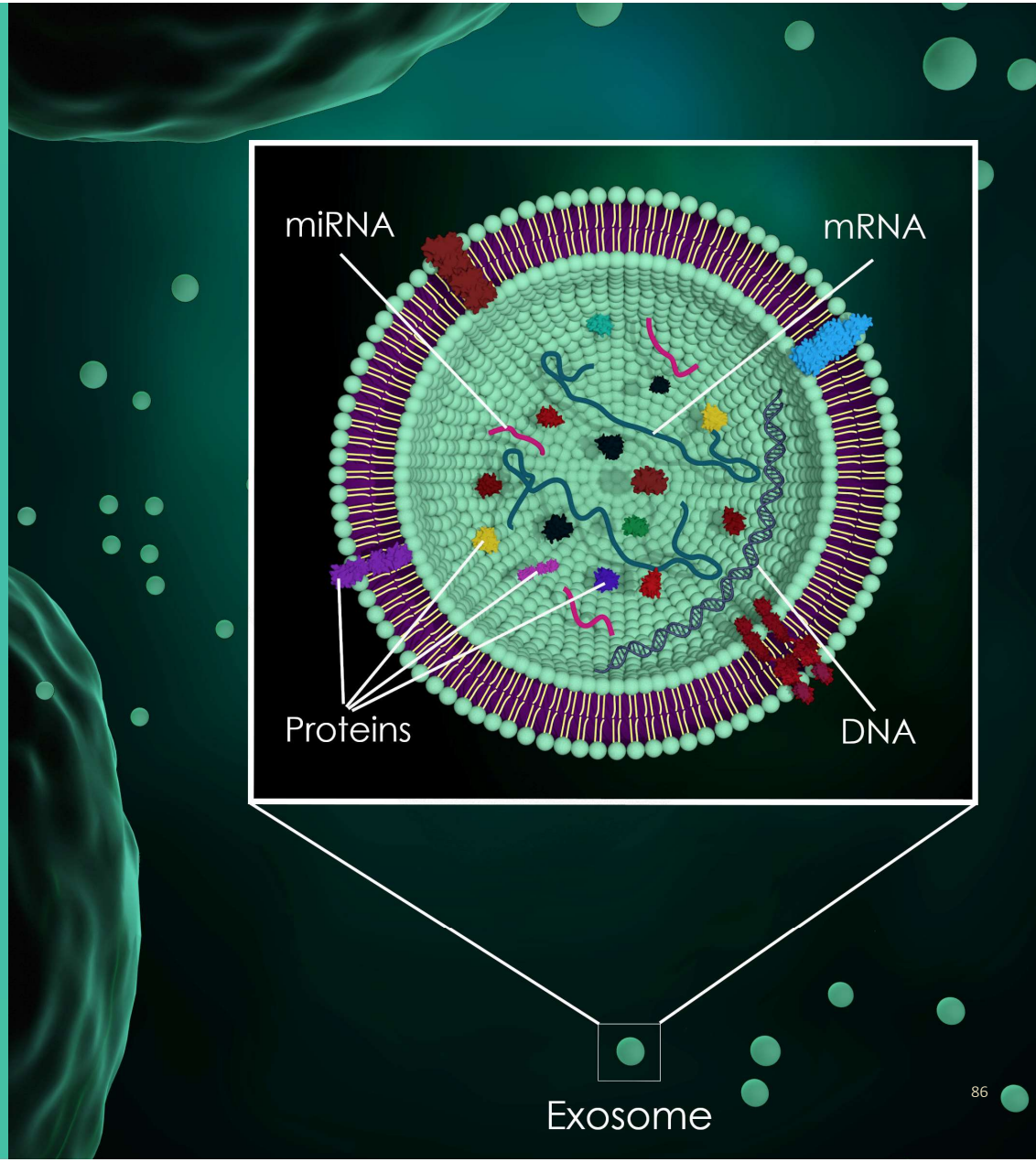
EXTENSIVE EXOSOMES EXPERIENCE (12 YEARS)

EARLY MOVER, CLINICAL STAGE

PLATFORM TECHNOLOGY

DEDICATED MANUFACTURING SITE

EXO Biologics



1- Multifactorial disease - Bronchopulmonary dysplasia

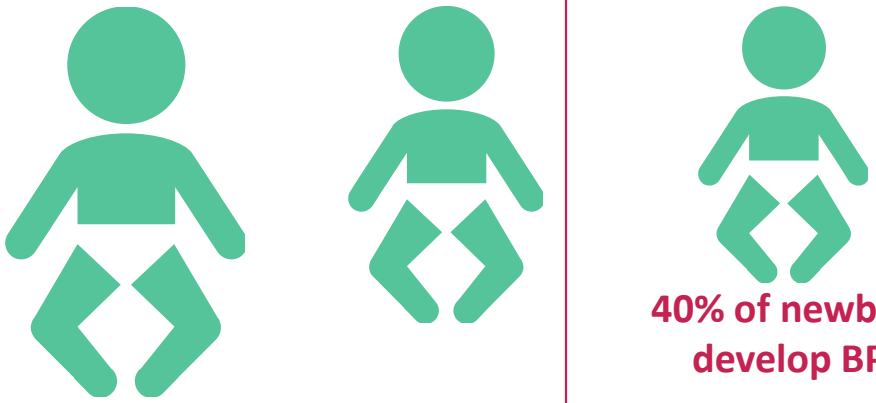
High medical need

A chronic lung disease caused by **damage to the delicate tissue of the lung**

8 million
US & EU newborns

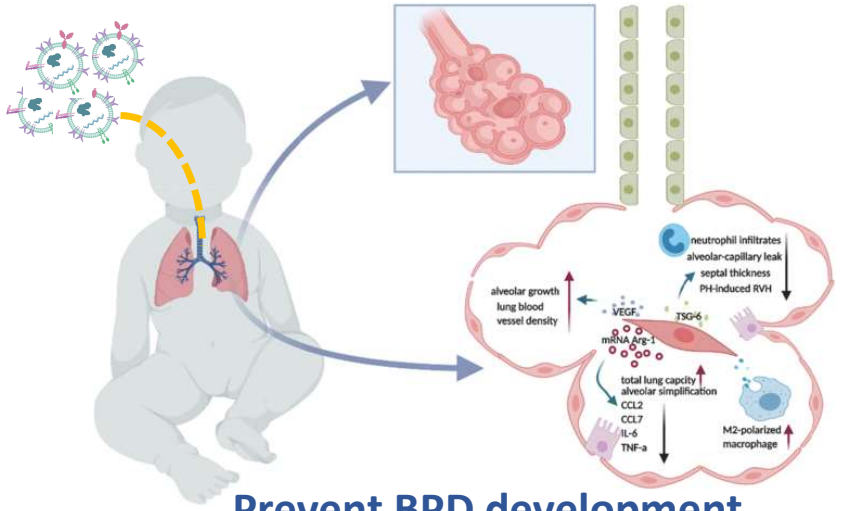
800K
Born premature

80K
Extremely preterm



40% of newborns develop BPD

Yearly Cost due to BPD in US & EU- 12 billion $



Prevent BPD development
Via multiple anti-inflammatory pathways

EXO yearly net sales revenue

800M $

EXO Biologics

1. Airway Therapeutics; 2. World Health Organization; 3. Health Care and Societal Costs of Bronchpulmonary Dysplasia; 4. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5819643; 5. https://adc.bmj.com/content/93/Suppl_2/pw100

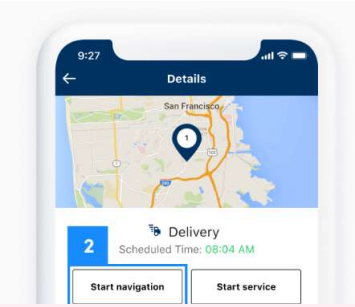
3- Contract Dev & Manufacturing

GMP “State of the art” Exosomes Manufacturing Facilities

- Based in LegiaPark (Liège, Belgium)
- Surface - 1500 m²
- GMP qualification expected by Q4 2023
- Go-to site for Exosomes manufacturing
- Fully dedicated exosomes environment

EXO Biologics

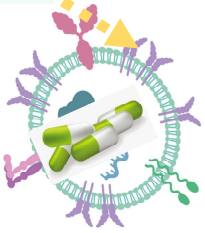
2- Drug Loading and Targeted Delivery

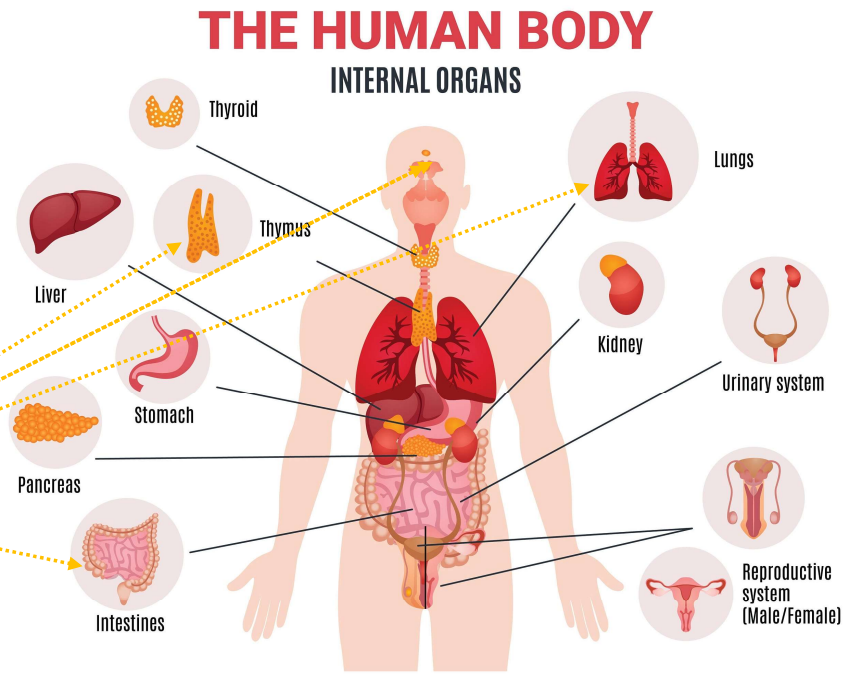


Drug requires targeted delivery to the site of action

EXO Bio has the vehicle with accurate GPS

Loading of
- **RNAs**
- **Proteins**
- **Chemicals**





EXOSOMES as targeted drug delivery carriers

EXO Biologics

Major recent deals with large pharma up to 1B$ milestones payment in this TOP field

Conclusions

La recherche fondamentale est nécessaire et essentielle aux progrès des connaissances. Il faut l'encourager

La recherche appliquée doit s'appuyer sur les connaissances nouvelles et valoriser les acquis des nouvelles technologies en partenariat avec les universités.

Le développement est affaire de science mais aussi de business et l'universitaire doit rester un scientifique et pas un businessman. Le chercheur ne doit pas être entrepreneur et vice-versa.

Les partenariats universités-industrie doivent être professionnalisés et la Wallonie doit créer son WIB à l'image du VIB

Verviétois agissez !!!