LA SALUTE DI GENERE IN TOSCANA

Presentazione del nuovo Documento ARS

Firenze 11 Maggio 2023

Tematiche al femminile

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UNIVERSITA' DEGLI STUDI DI SASSARI

CENTRO INTERDISCIPLINARE PER LO SVILUPPO RICERCA BIOTECNOLOGICA E STUDIO BIODIVERSITA'

6-7 Ottobre 2004

I° Seminario
di approfondimento

Le donne ed i farmaci

SIF SOCIETA' ITALIANA DI FARMACOLOGIA

FARMINDUSTRIA

A.D. MDLXII
Università degli Studi di Sassari

FONDAZIONE INTERNAZIONALE MENARINI

Genes, Drugs and Gender

Sassari (Italy), October 1st – 2nd, 2009

Il premio **Nobel Louis J Ignarro prende il caffè prima della conferenza magistrale tenuta** nell'aula magna dell'Università di Sassari al convegno "Genes, drugs and gender"

Delibera di Giunta regionale n. 144 del 24.02.2014.

W20 ITALIA 2021 women

2021 Special Commission Equity in Health

W20 ITALIA 2021 women

2023 Global Gender Medicine Board

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Data gap
Physicians training aims at male bodies
Therapy not optimized
Less prevention
Stress
Patient-doctor communication is based on male structures

More cancer
Men have less cancer suppressor genes
More severe infection
More addiction

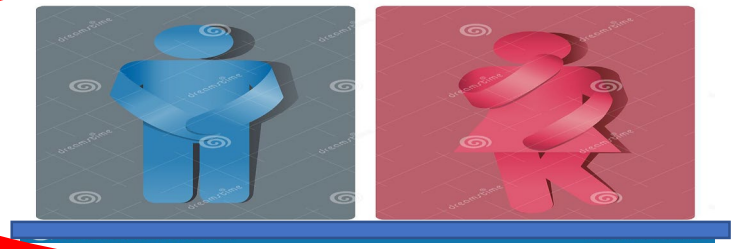
Clinical Trials

The number of women enroll in phase 3 is increased but women are still underrepresented in Phase I trials [Cheng A et al J Women's Health 27:418,2018]. Women's representation remains low in phase 1 clinical trials (≈22%).

Phase	N. Drugs	Women	%	Unknown gender (%)
1	9	788/3600	22	18
2	9	3477/7268	48	12
1+2	29	3034/11881	25	31
3	38	71049/145296	49	7
Totali	38	78 338/168 045	47	9

Modified by Labots G et al Br Clin Pharm J 84: 700; 2018

Beyond the reproductive apparatus, male and female morphology, biochemistry, physiology, diseases, response to treatments are different.



Actually, for example, they are treated with drugs mainly studied in males receiving the same dose of drugs

To become visible it is necessary to adopt:

SEX - GENDER BASED APPROACHES

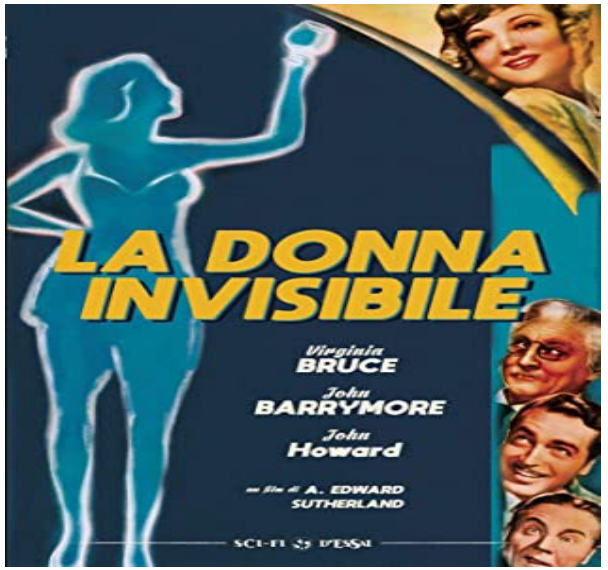
But

76% or not reported

80% or not reported

67% or not reported in RCT

51% of general population



Females are invisible

SPECIFIC WOMEN ASPECTS

- Menstrual cycle (it can varies the drug metabolism)
- The presence of critical periods (pregnancy, puerperium, menopausa ecc.)
- Oral anticonceptionals use
- HRT use

United States General Accounting Office – 2001 Report Washington, DC 20548

Sexual endogenous hormones affect PD

In women, the PK is influenced by changes in the hormonal environment, which occur during the menstrual cycle, pregnancy, menopause, hormonal treatments (such as OC, HRT) drugs, which influence hormonal status [Franconi et al Cells 8, 476, 2019].

Some examples

During ovulation and premenstrually, alcohol blood concentration is higher than in other menstrual phase [Paton A *BMJ* 330:85, 2005]

In premenstrual phase, the dose **of antipsychotics might need to be raised** [Lange B et al Expert Opin. Pharmacother. 18, 351, 2017].

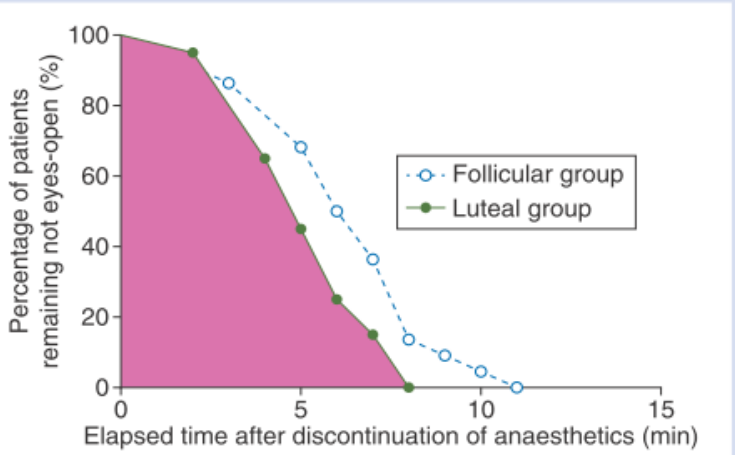


Fig 3 Cumulative percentages of patients remaining unconscious after discontinuation of propofol and remifentanil infusion in the follicular group (unfilled circle and dotted line, empty area) and in the luteal group (filled circle and solid line, shaded area), obtained using the Kaplan–Meier survival analysis. Log-rank differences between the two groups were significant ($P<0.01$).

In the luteal phase, nausea and vomiting are lower than in the follicular phase [Fu F et al Brit J Anaesth *112: 506, 2014*].

Physiological changes during pregnancy: effects on drug disposition

Parameter	Consequences
Delayed gastric emptying and increased gastric pH	Altered drug bioavailability and delayed time to peak levels after oral administration
Increased cardiac output	Increased hepatic blood flow; increased elimination for some drugs
Increased total body water, extracellular fluid	Altered drug disposition; increased V_d for hydrophilic drugs
Increased fat compartment	Decreased elimination of lipid-soluble drugs; increased V_d for hydrophobic drugs
Increased renal blood flow and glomerular filtration rate	Increased renal clearance
Decreased plasma albumin concentration	Increased free fraction of drug
Altered CYP450 and UGT activity	Altered oral bioavailability and hepatic elimination

UGT, uridine diphosphate glucuronosyltransferase; V_d, volume of distribution.

doi:10.1371/journal.pmed.1002160.t001

Enzyme	Effect of Pregnancy [Reference]	Substrate Examples
CYP1A2	Decreased [18]	Paracetamol, propranolol, theophylline
CYP2B6	Increased [21]	Methadone, efavirenz, sertraline
CYP2C8	Increased [22]	Verapamil, fluvastatin
CYP2C9	Increased [23,24]	Glyburide, phenytoin
CYP2C19	Decreased [23,25]	Proguanil, indomethacin, citalopram, escitalopram
CYP2D6	Increased [17]	Alprenolol, codeine, fluoxetine
CYP2E1	Increased [26]	Disulfiram, theophylline
CYP3A4	Increased [27]	Darunavir, citalopram
Uridine 5′-diphospho-glucuronosyltransferases	Increased [28]	Lamotrigine, morphine

doi:10.1371/journal.pmed.1002160.t002

Pariente Get al. (2016) PLOS Medicine 13(11): e1002160. https://doi.org/10.1371/journal.pmed.1002160

Combined oral contraceptives: generators of interactions.

La simultanea somministrazione di un farmaco che induce gli enzimi metabolizzanti gli ormoni aumenta il metabolism o degli ormoni con conseguente:

- *possible gravidanza indesiderata e sanguinamento irregolare*

La simultanea somministrazione di un farmaco che inibisce gli enzimi metabolizzanti gli ormoni con conseguente:

- *aumento il rischio di trombosi*

Poichè in molti studi clinici nelle donne fertili si fa l'antifecondazione bisogna valutare l'influenza dei contracettivi e viceversa sulla risposta farmacologica

Some example of combined oral contraceptives interaction:

Many combined oral contraceptives are mainly metabolized by CYP3A4 (Expert Opin Drug Metab Toxicol. 2022 Jun;18(6):395-411).

- Women taking antiepileptic drugs with strong or moderate metabolic enzyme-inducing properties should avoid any oral contraceptives.

- Women receiving combined hormonal contraceptives may need half of the regularly prescribed daily dosage when using CYP1A2 substrates including clozapine.

- There are no studies exploring the effects of fluoxetine (a moderate inhibitor of CYP2C9 and a weak-to-moderate inhibitor of CYP3A4) or fluvoxamine (a moderate inhibitor of CYP3A4 and CYP2C9) on estrogen metabolism.

Nonpolar and polar amino acid levels and lipds stratified by sex and OC use

	Men (n = 41)	Women (n = 43)	Women OC (n = 26)
Alanine (µM)	255.8 ± 70.0	263.5 ± 62.5	235.8 ± 69.9
Serine (µM)	202.0 (123.0-503.0)	213.3 (123.4-387.0)	211.4 (57.7-1387.0)
Leucine (µM)	220.0 (118.0-481.0) [a, b]	150.2 (49.5-287.3)	138.7 (44.6-281.0)
Isoleucine (µM)	113.0 (57.0-255.0) [a]	73.9 (46.1-136.0)	78.0 (20.0-523.0) [c]
Methionine (µM)	17.6 (14.8-40.6) [a, b]	15.9 (11.3-23.2)	13.8 (9.6-27.9)
Phenylalanine (µM)	66.3 (49.7-109.3)	54.7 (39.3-146.1)	52.3 (41.1-116.5)
Asparagine (µM)	159 (41.0-259.0) [a, b]	82 (46.2-180.7)	84.5 (18.1-268.0)
Tryptophan (µM)	9.0 (2.0-58.0) [a, b]	53.2 (5.0-87.6)	52.0 (1.0-67.5)
Glycine (µM)	204.80 (159.6-351.8)	237.3 (137.9-384.4)	176.7 (112.3-359.9)[c]
Proline (µM)	269.0 (99.0-900.0) [a, b]	216.1 (3.1-566.0)	109.5 (2.9-222.0) [c]
Valine (µM)	251.6 (175.5-467.9) [a, b]	205.0 (171.6-320.7)	208.5 (145.8-313.5)
Tyrosine (µM)	79.5 ± 20.5 [a, b]	71.9 ± 14.3	63.5 ± 18.9
Cysteine (µM)	5.0 (3.0-15.0)	11.2 (2.0-399.0)	10.0 (2.0-17.6)

	Men (n = 41)	Women (n = 43)	Women OC (n = 26)
Cholesterol (mg/dl)	173.5±29.5	184.8±30.4	222.8±41.5
LDL (mg/dl)	103.2±28.3	108.9±22.8	125.8±31.3
HDL (mg/dl)	47.0±9.5	60.8±11.0	73.6±13.7
TG (mg/dl)	68.0 (30.0-155.0)	60.0 (32.0-160.0)	87.0 (48.0-526.0

Ruoppolo M et al Am J Trans Res et al 6,614, 2014

Thank you

Grazie

Grazie

Thank you

Thank you

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