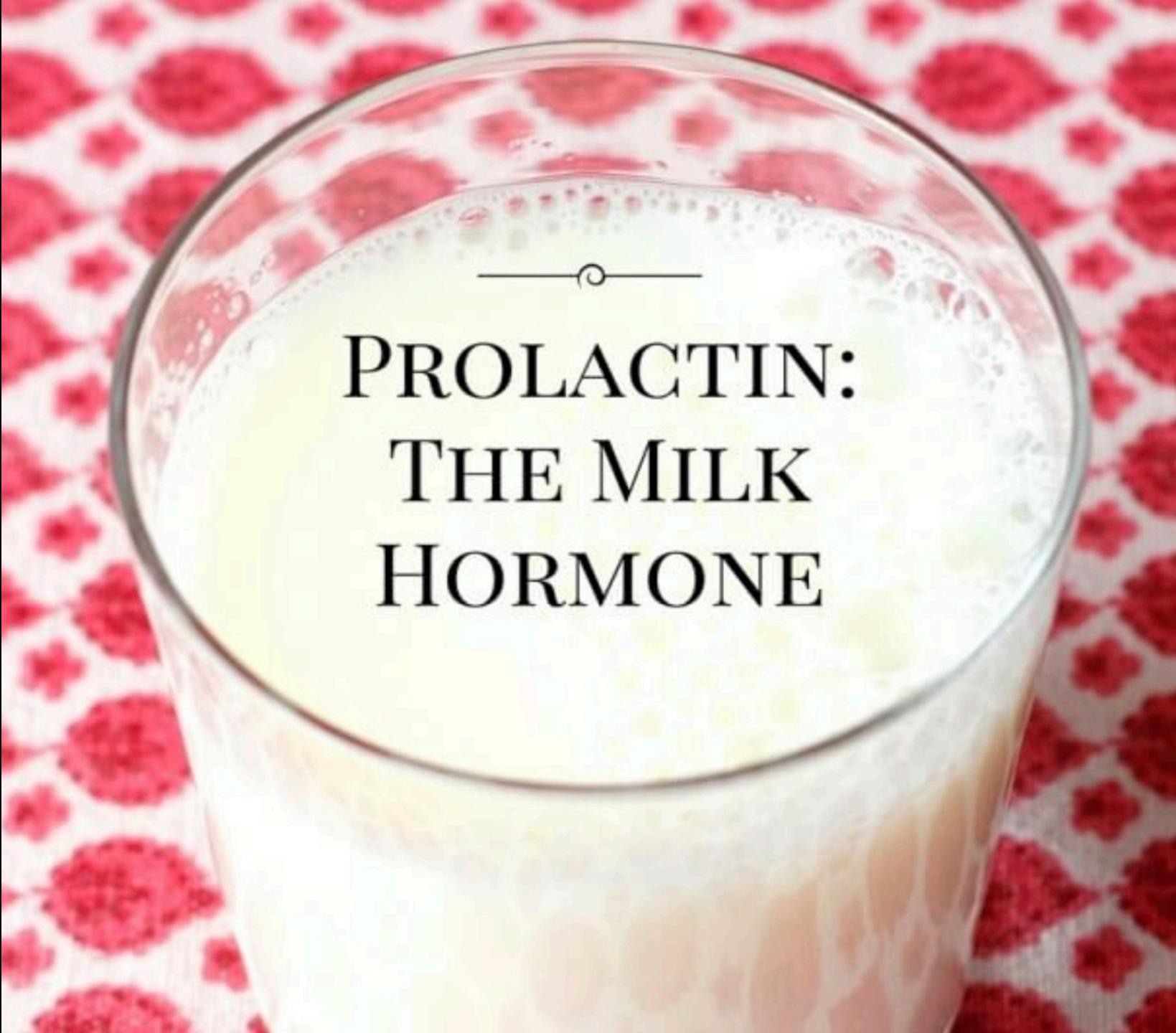


Važnost određivanja makropolaktina u diferencijalnoj dijagnostici hiperprolaktinemije

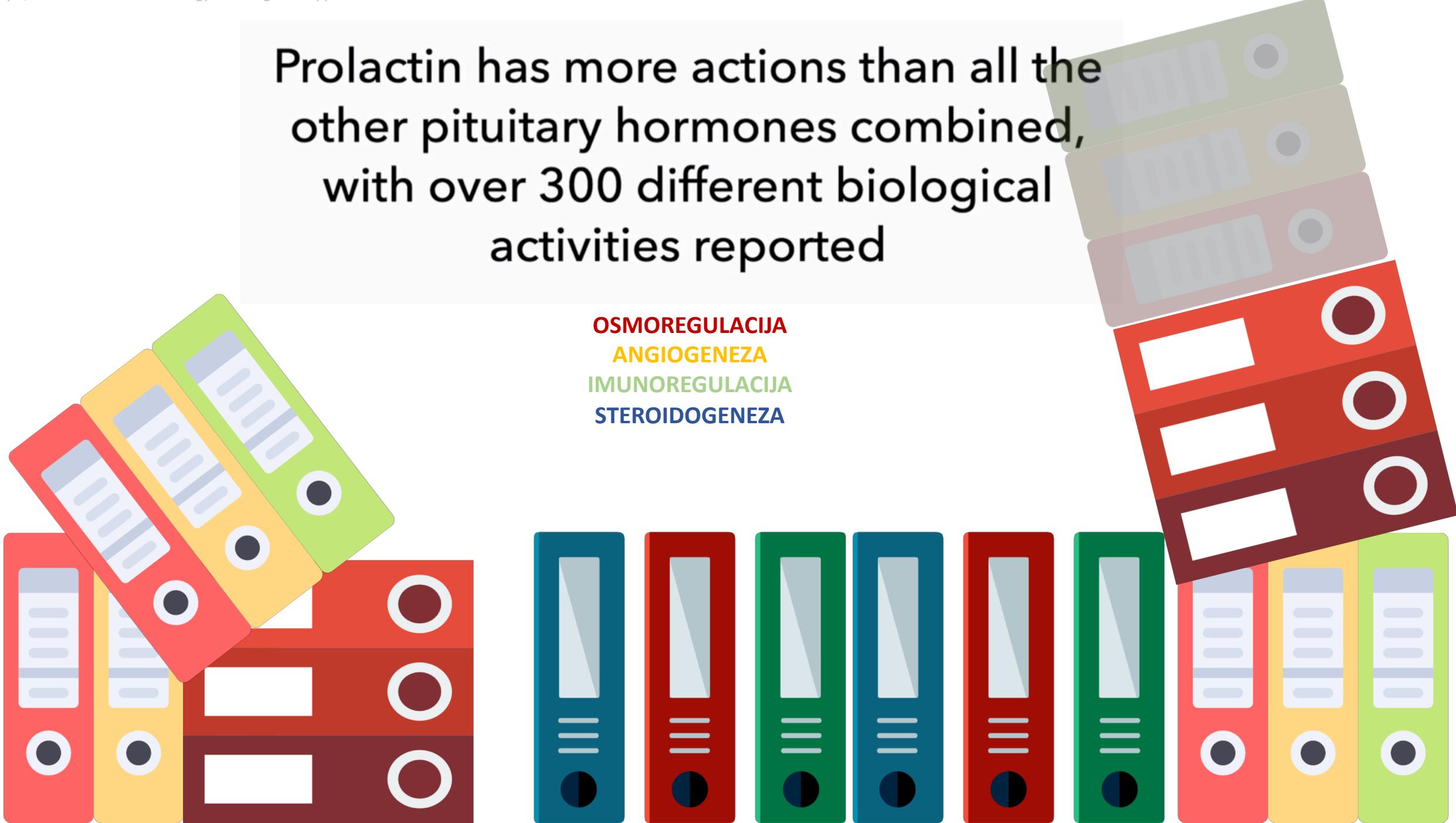
Iva Lukić
Zavod za kliničku laboratorijsku dijagnostiku
KBC Osijek



—

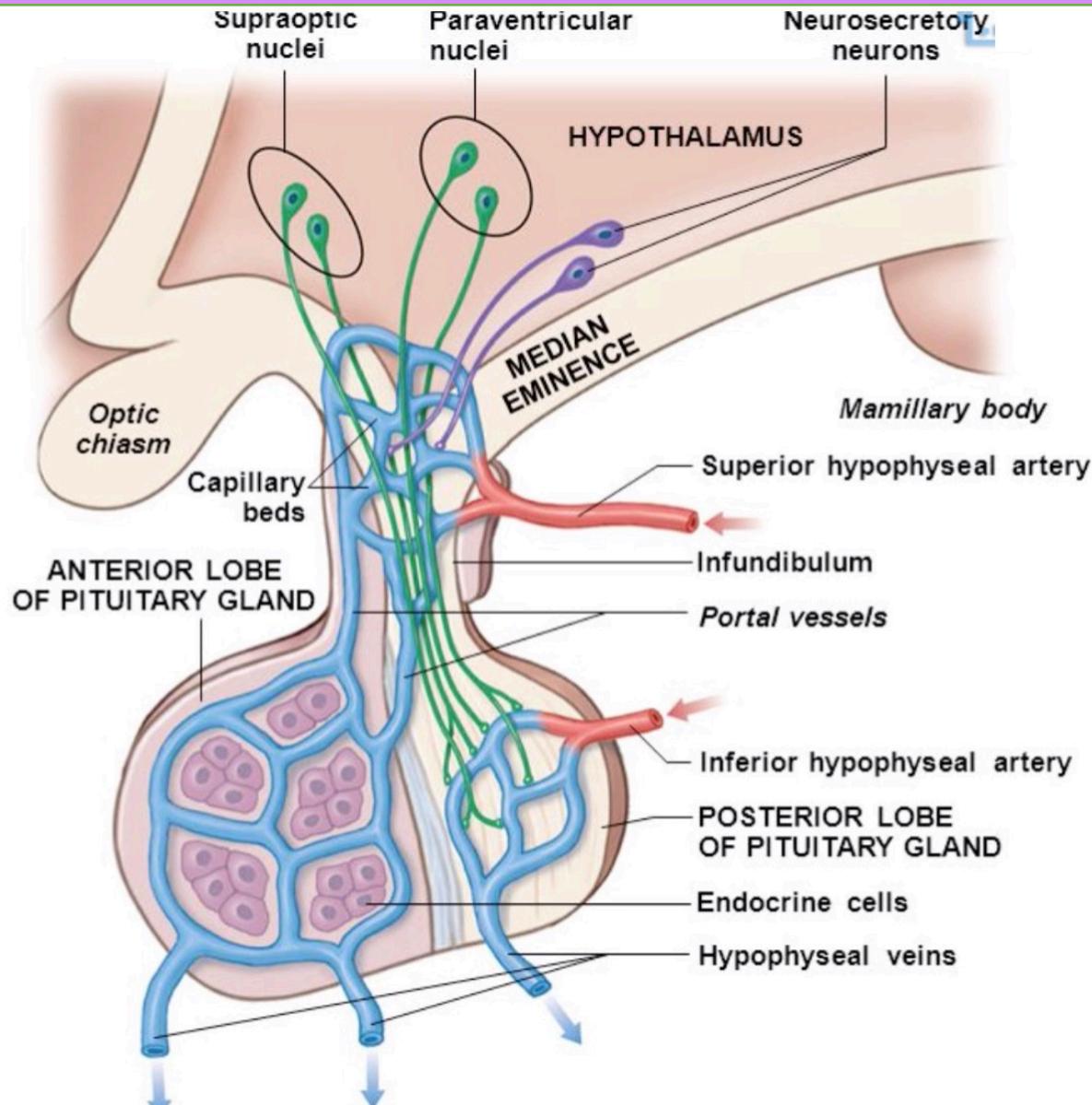
PROLACTIN: THE MILK HORMONE

Prolactin has more actions than all the other pituitary hormones combined, with over 300 different biological activities reported

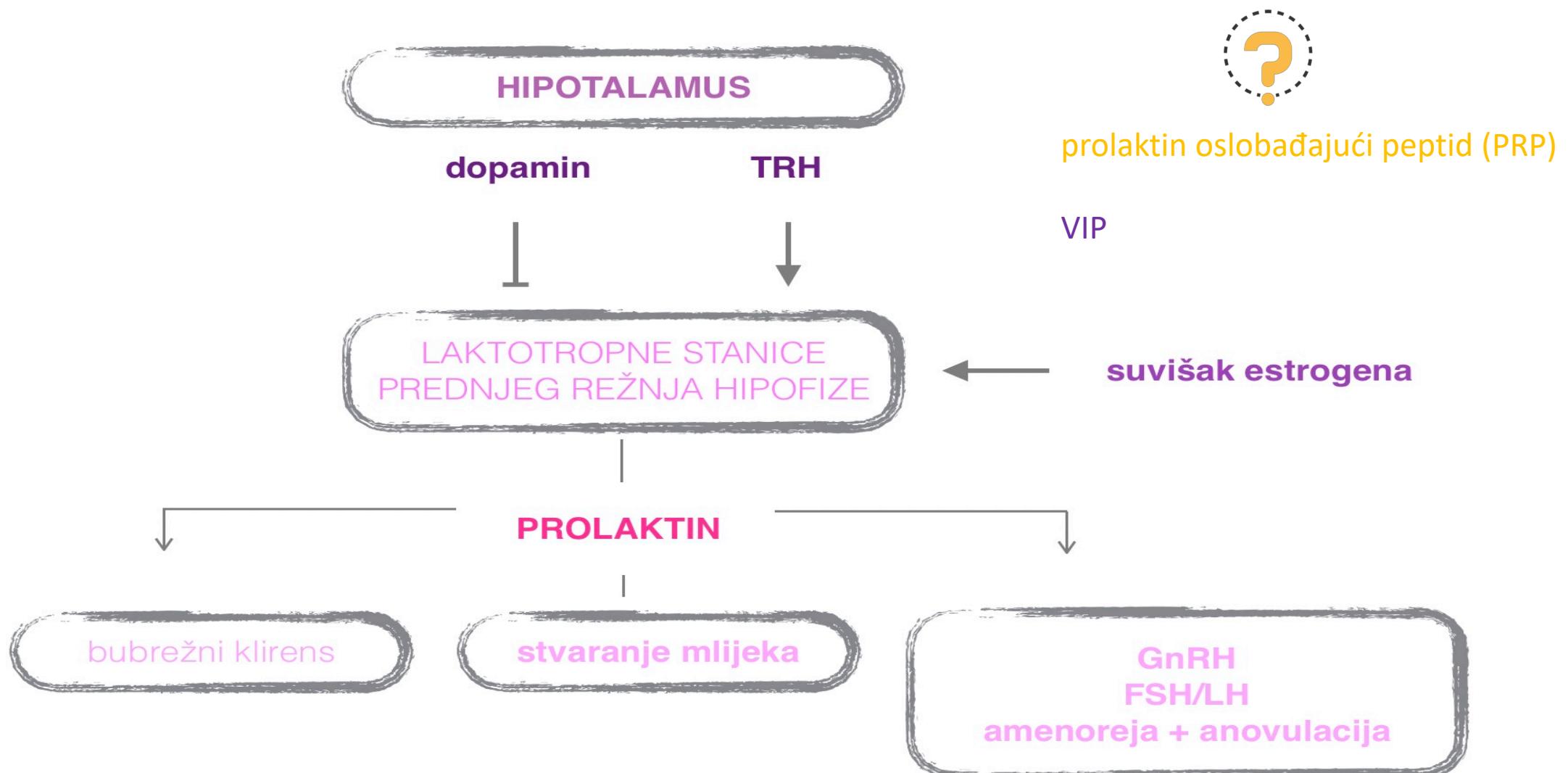


OSMOREGULACIJA
ANGIOGENEZA
IMUNOREGULACIJA
STEROIDOGENEZA

Osovina hipotalamus-prolaktin

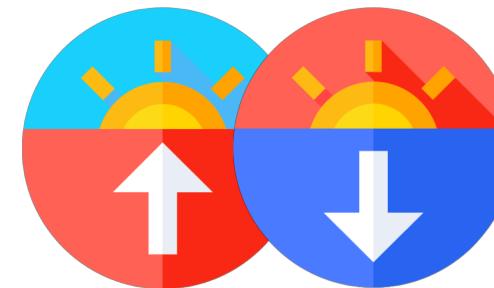
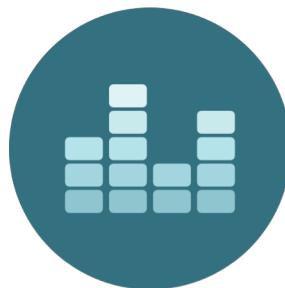


Osovina hipotalamus-prolaktin

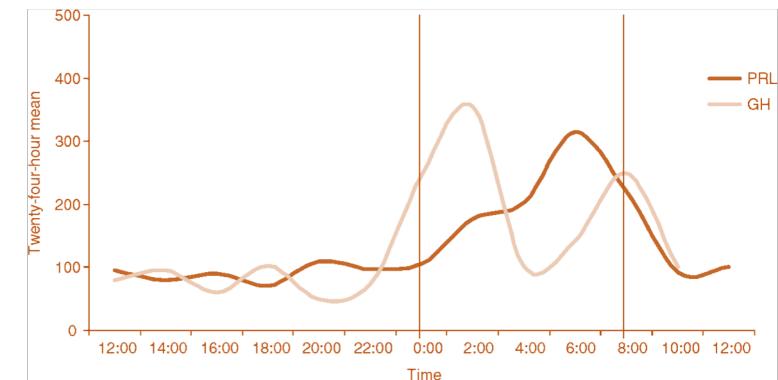


PROLAKTIN

- inhibitorna kontrola dopaminom putem D2 receptora
- sinteza u laktotropnim stanicama adenohipofize
 - preprolaktin 26 kDa
 - prolaktin 23 kDa



- monomer PRL - 85% cirkulirajućeg prolaktina
- big PRL - kovalentno vezani dimeri PRL - 15% ukupnog PRL
- big-big PRL - makropolaktin
- post-translacijske modifikacije (fosforilacija, glikozilacija...)



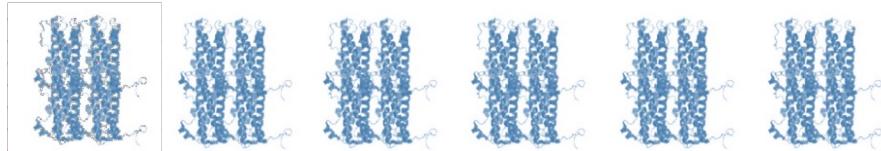
<https://goo.gl/images/3Rg5LY>

Prednji režanj hipofize

The diagram illustrates the different forms of prolactin released from the anterior pituitary gland. It shows a cross-section of the pituitary with red arrows pointing to three main forms: 'Slobodni prolaktin' (free prolactin), ''Big-prolaktin'' (big prolactin), and ''Big-big-prolaktin'' (big-big prolactin). Below the diagram is a table summarizing their characteristics and relative proportions.

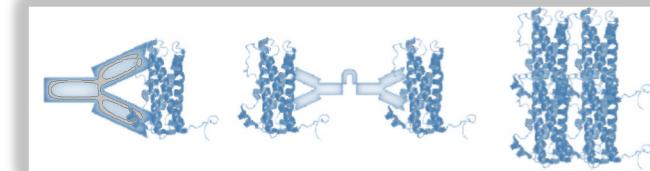
Slobodni prolaktin	“Big-prolaktin”	“Big-big-prolaktin”		
Monomer	Dimer	IgG prolaktin	IgA prolaktin	Agregati prolaktina
23 kDa	40–60 kDa		>100–150 kDa	
Aktivni	Inaktivni		Inaktivni	
60%–90%	15%–30%	0%–8%	0%–2%	0%–3%

Hiperprolaktinemija



vs.

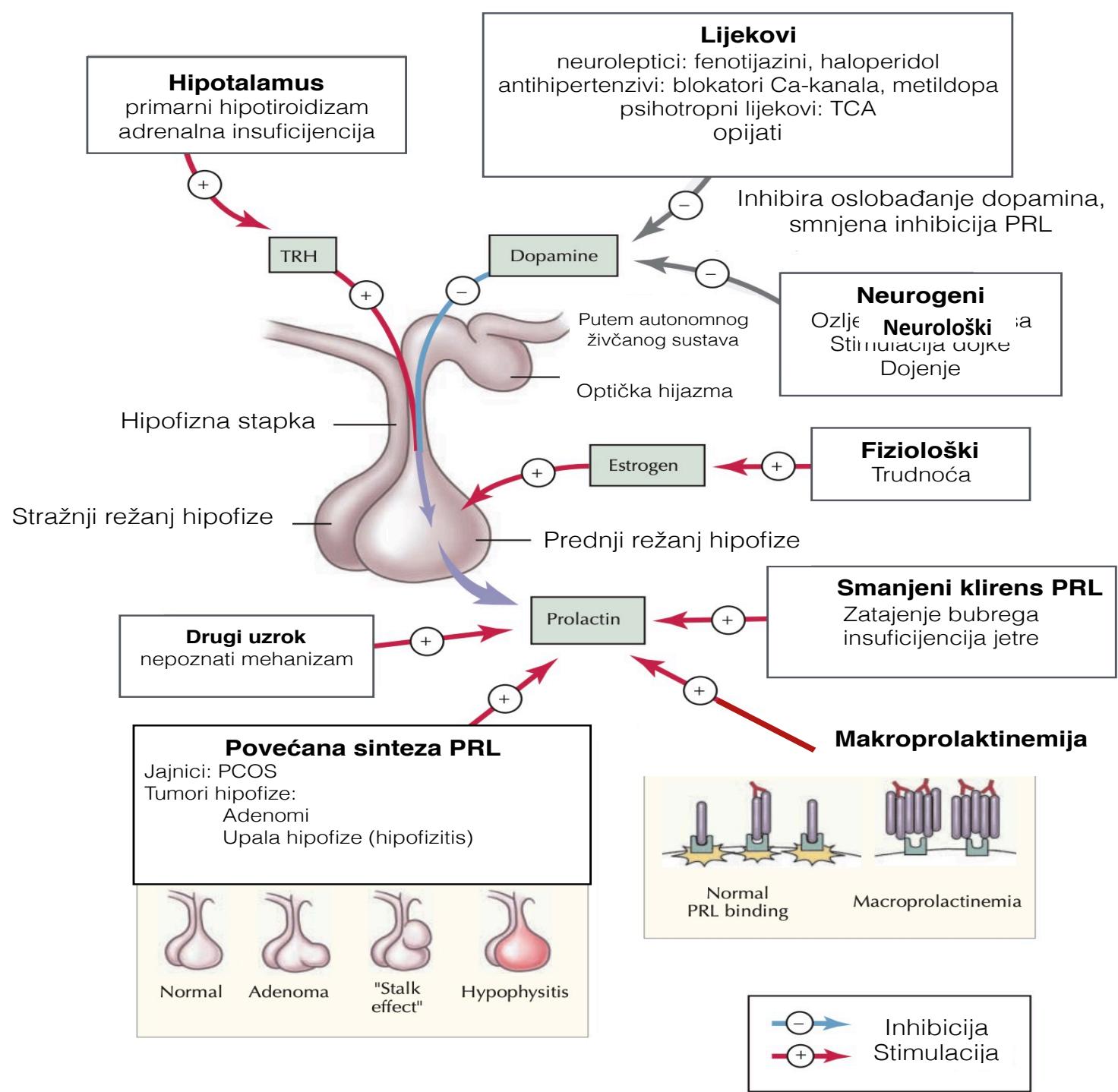
Makroprolaktinemija



- visoka razina mPRL
- poremećaj hipotalamo-hipofizne osovine
- najučestalija manifestacija funkcionalnih adenoma hipofize
- bolesti hipotalamusa, hipofize
- hipotroidizam
- hepatorenalni poremećaji

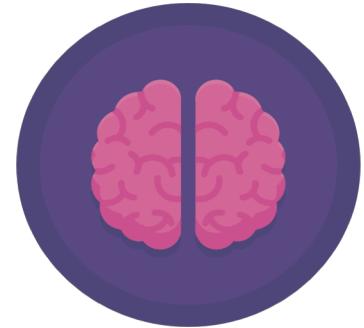
- prolaktin vezan za anti-PRL antitijela (IgG4, IgA, IgM)
- agregati PRL monomera
- nema interakcije sa PRL receptorom
 - nema negativne povratne sprege
- minimalna biološka aktivnost *in vivo*
 - ograničen prolazak kroz kapilarni endotel
 - ALI, moguća disocijacija PRL monomera *in vivo*
- imunoreaktivnost *in vitro*
- Nasumični fenomen?

UZROCI HIPERPROLAKTINEMIJE



Serri et al. Diagnosis and management of hyperprolactinemia.
CMAJ 2003;169(6):575-81

ADENOMI HIPOFIZE



1/3 nije povezana sa hipersekrecijom

- simptomi vezani za intrakranijalnu masu: glavobolja, mučnina, povraćanje, poremećaji vidnog polja

PROLAKTINOM najčešći oblik funkcionalnog tumora hipofize ($\sim 30\%$)
 hormonski aktivni tumor laktotropnih stanica hipofize,
 benigne patologije

- mikroprolaktinom < 10 mm
- makroprolaktinom > 10 mm

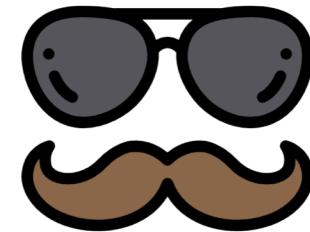
KLINIČKA MANIFESTACIJA HIPERPROLAKTINEMIJE



- Hipogonadizam
- Galaktoreja
- Amenoreja
- Oligomenoreja
- Lutealna insuficijencija
- Anovulacija
- Oslabljen libido
- Hirzutizam
- Virilizacija
- Osteopenija

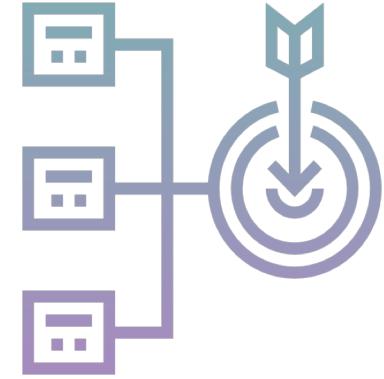


- Insuficijencija hipofize
- Poremećaj vidnog polja
- Pareza okularnog mišića
- Glavobolja



- Oslabljen libido
- Impotencija
- Hipogonadizam
- Ginekomastija
- Galaktoreja

Liječenje hiperprolaktinemije

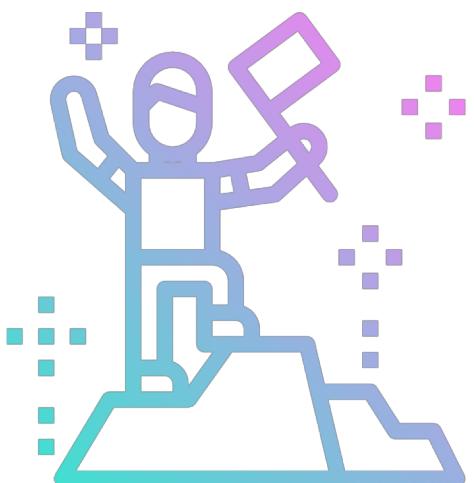


The Endocrine Society's
CLINICAL GUIDELINES

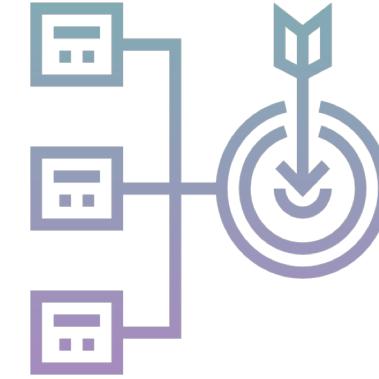
**Diagnosis & Treatment
of Hyperprolactinemia:**

An Endocrine Society Clinical Practice Guideline

Melmed et al. Diagnosis & Treatment of Hyperprolactinemia: An Endocrine Society Clinical Practice Guidelines.
Journal of Clinical Endocrinology & Metabolism, February 2011, 96(2): 273–288



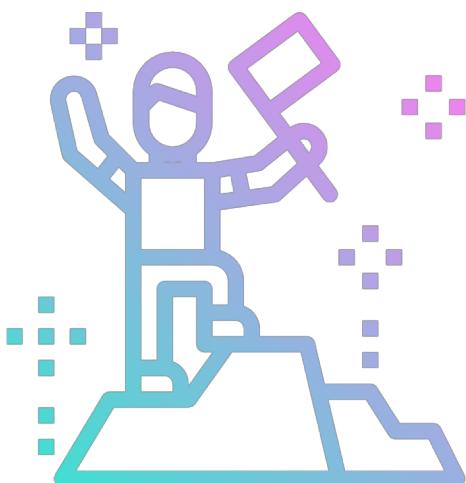
Liječenje hiperprolaktinemije

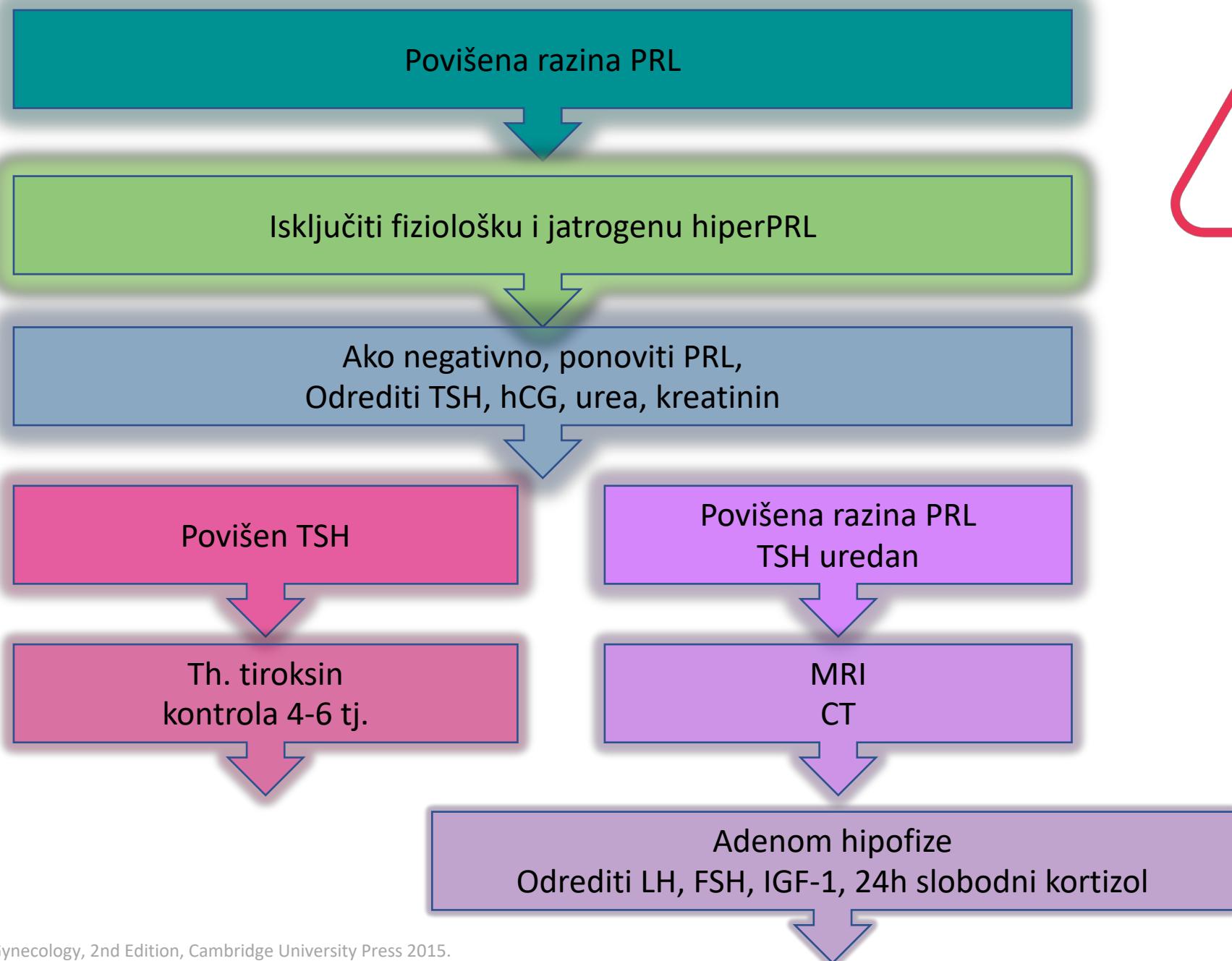
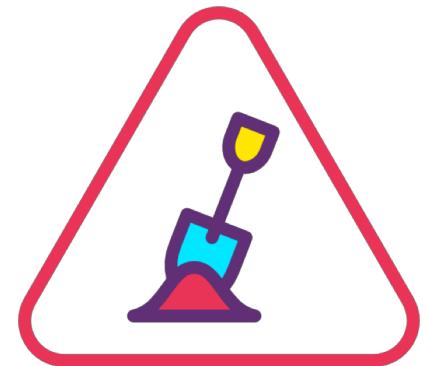


CLINICAL PRACTICE GUIDELINE

Croatian guidelines for the management
of hyperprolactinemia: a viewpoint from a
developing country

Marinković et al. Croatian guidelines for the management of hyperprolactinemia: a viewpoint from a developing country.
Endocrine Oncology and Metabolism (2015) 1; 10-23





LIJEČENJE

Agonisti dopamina

- ▀▀▀ Bromokriptin
- ▀▀▀ Kabergolin
- ▀▀▀ Pergolid

hiperPRL rezistentna na dopamin?
ekstrapituitarni PRL?
kontraindicirana th.?

Antagonisti PRL receptora?

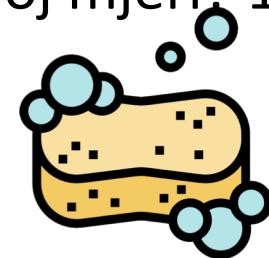
Operativni zahvat

Zračenje



Određivanja makropolaktina

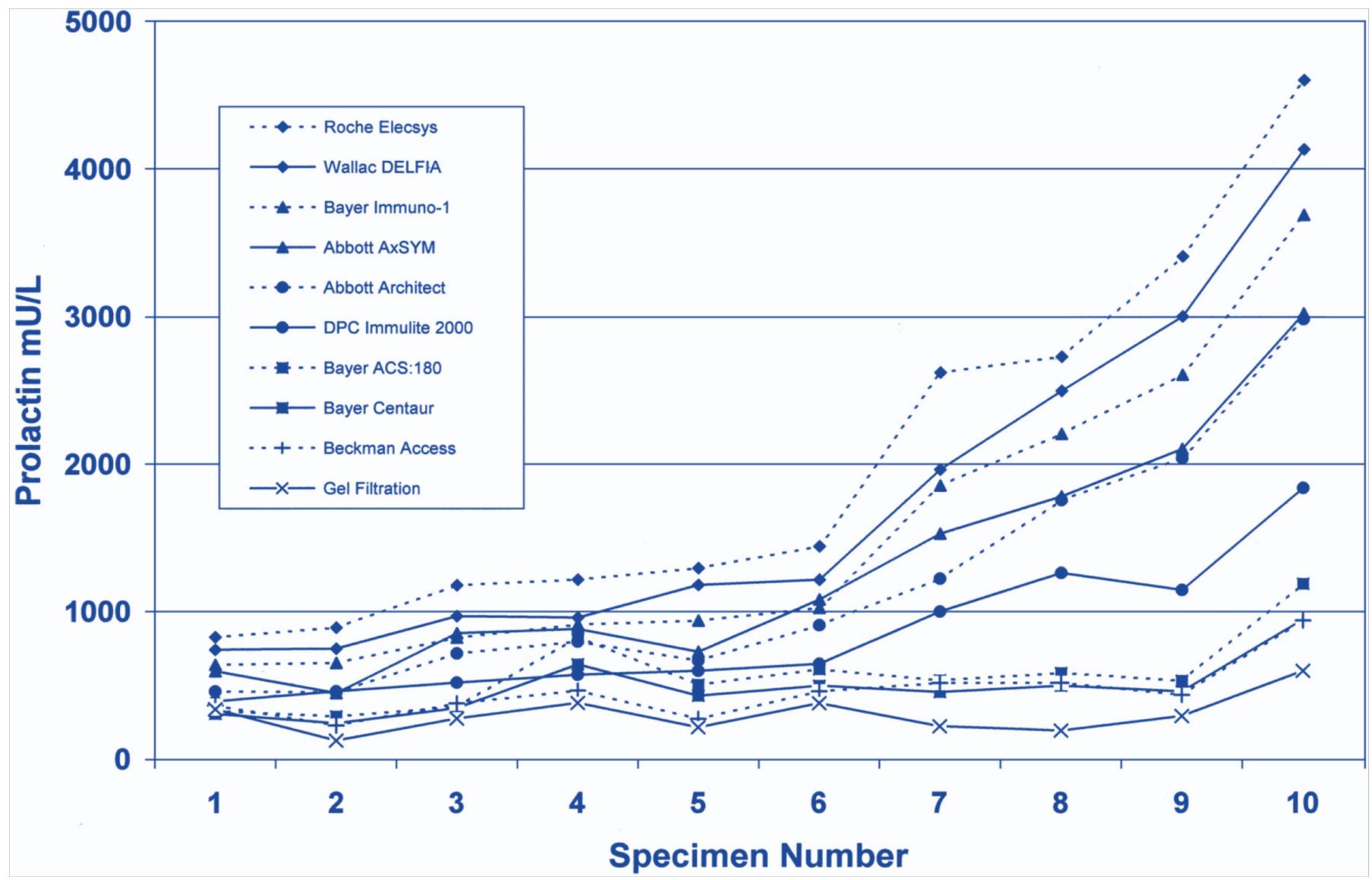
- sve komercijalne imunokemijske metode u određenom stupnju detektiraju makroPRL
 - pseudo-hiperprolaktinemija - križna reaktivnost - u kojoj mjeri? 10%? 50?
- PEG precipitacija kod SVAKE suspektne hiperPRL
- Recovery <40% makropolatinemija
- koprecipitacija mPRL



Beckman Coulter - križna reaktivnost <3%

GFC revealed that total prolactin concentrations obtained with the DxI gave a more accurate reflection of the 'true', or monomeric, prolactin concentration when compared with the post-PEG treated samples analysed on the AutoDELFIA in five of the nine discordant samples. The DxI underestimated prolactin concentrations when compared with monomeric prolactin (GFC) in two of the nine cases. However, in neither case would this have led to misdiagnosis or misclassification of the patient had the DxI prolactin result been reported.

In the interest of patient safety, it is better to accept a small number of false positives. We recommend that prolactin results should be reported directly from the DxI, without prior PEG precipitation, and clinicians should be invited to contact the laboratory if the value seems clinically incongruous. In these cases definitive analysis using GFC should be offered, before imaging is performed. To the best of our knowledge, this is the first study to advocate this approach.



Treba li se makroPRL određivati u svim hiperPRL serumima?

Table 1. Clinical characteristics of 15 patients, with total prolactin levels more than 700 mU/l, retrospectively diagnosed as having macroprolactinaemia; subsequent diagnosis and management

Patient no.	Age (years)	Serum prolactin (mU/l)		Symptoms					Pituitary imaging	Revised diagnosis	DA	
		Not PEG -treated*	PEG -treated†	O/A	G	I	H	NOR			Treatment	Response
1	15	1760	230	Y	N	N	N	NOR	Cyclical mastalgia	N	—	
2	27	1206	344	Y	Y	N	N	MA	OCP-related galactorrhoea	B	Galactorrhoea ceased	
3	26	2240	192	Y	N	N	Y	NOR	PCOS	B	No effect	
4	20	1940	378	Y	Y	Y	N	MA	PCOS	B	Galactorrhoea + menses improved	
5	33	1288	214	Y	N	N	N	NOR	DUB	B	Discontinued early	
6	29	1360	171	Y	N	N	Y	ND	Low body weight	B	No effect	
7	22	1310	236	Y	N	N	N	NOR	Bulimia Nervosa	C	No effect	
8	21	819	302	N	Y	N	N	NOR	Idiopathic galactorrhoea	N	—	
9	38	1590	232	N	N	Y	N	NOR	Paratubular cyst	Y	No effect	
10	55	1530	224	Y	N	N	N	NOR	Menopause	B	No effect	
11	38	3390	248	N	Y	N	N	NOR	Idiopathic galactorrhoea	B	Galactorrhoea improved	
12	40	883	337	Y	N	N	N	ND	Menopause	N	—	
13	28	1037	24	Y	N	N	N	NOR	PCOS	B + C	No effect	
14	32	4021	142	N	N	N	N	NOR	Unexplained miscarriage	B	Became pregnant after 15 months	
15	33	891	194	Y	Y	N	Y	NOR	Infertility related to SLE	C	Became pregnant	

G, galactorrhoea; O/A, oligomenorrhoea/amenorrhoea; I, infertility; MA, microadenoma; ND, not done; PCOS, polycystic ovary syndrome; H, hirsutism; OCP, oral contraceptive pill; DUB, dysfunctional uterine bleeding; SLE, systemic lupus erythematosus; Y, Yes; N, No; NOR, normal.

*Reference range, 105–548 mU/l.

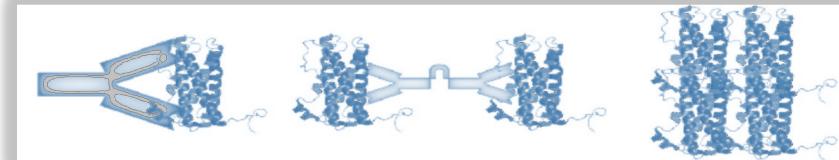
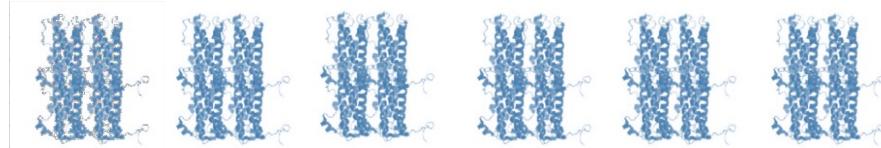
†Reference range, 83–383 mU/l.

Table reproduced from the *Journal of Clinical Endocrinology and Metabolism* 2005, 90(7), 3927–3932. Copyright 2005 The Endocrine Society.²⁷

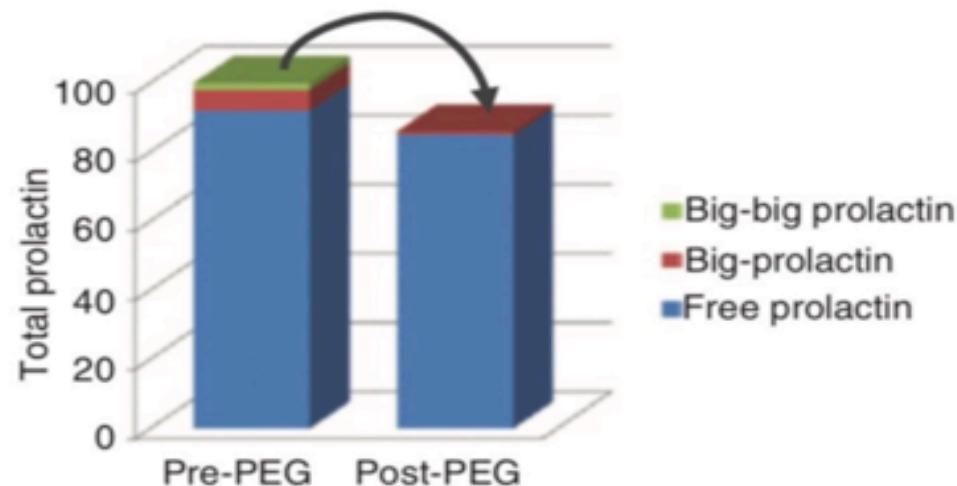
Hiperprolaktinemija

vs.

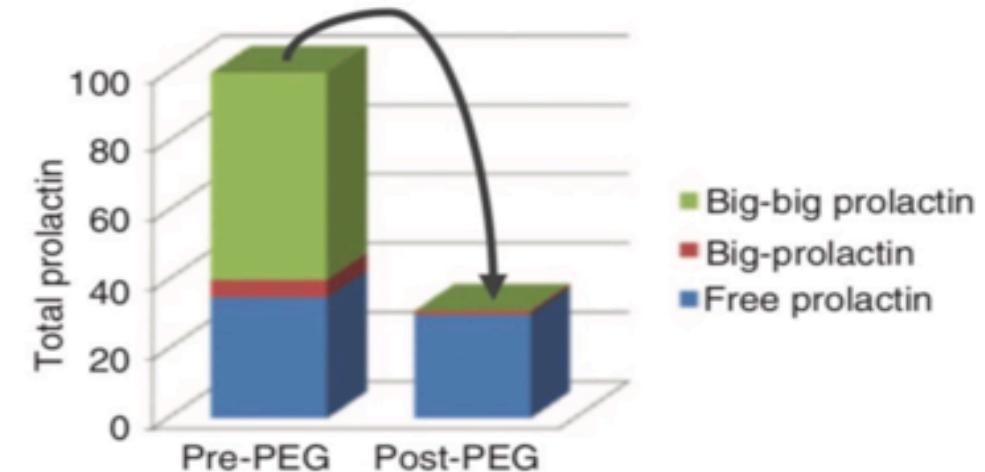
Makroprolaktinemija



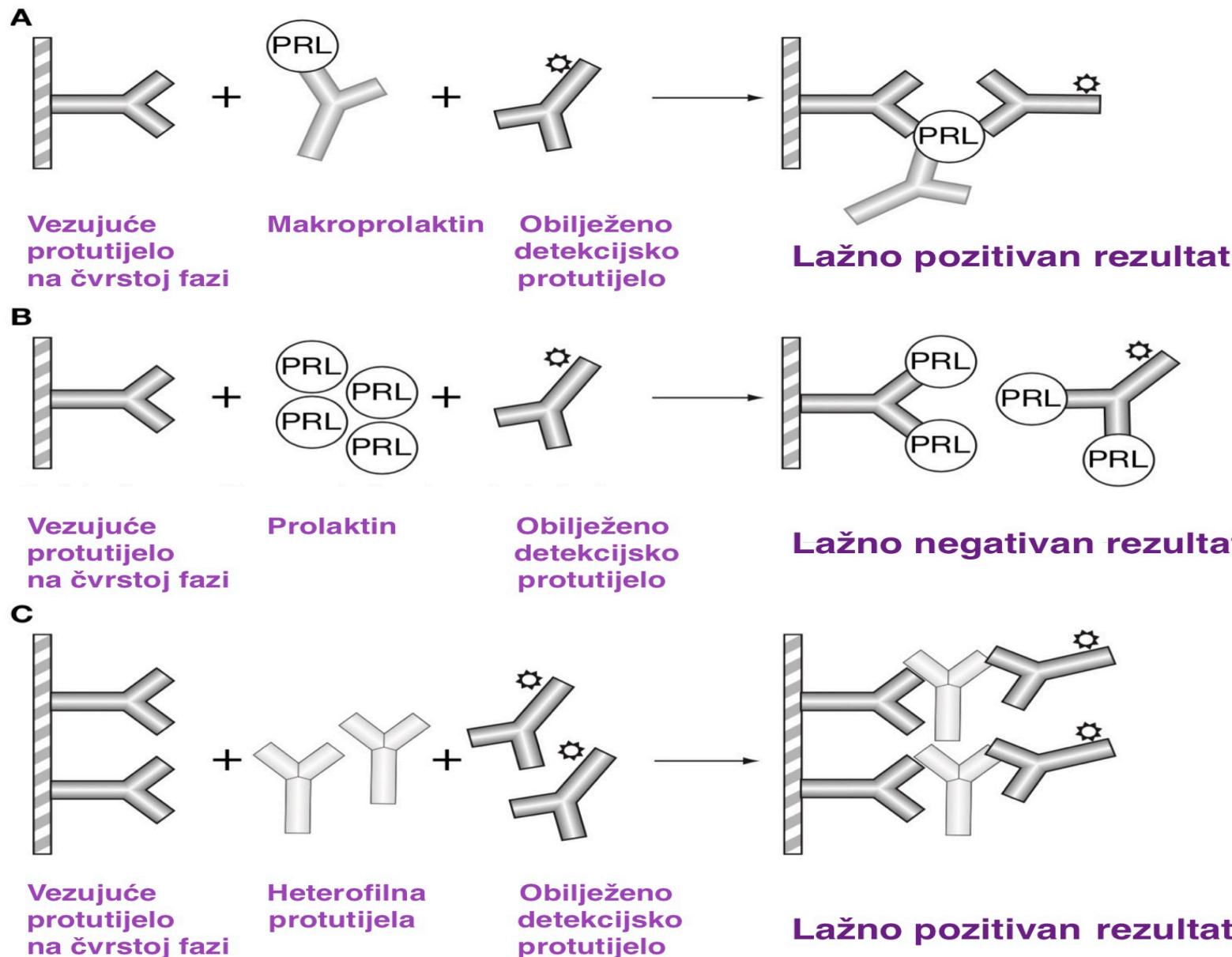
Prava hiperprolaktinemija



Makroprolaktinemija



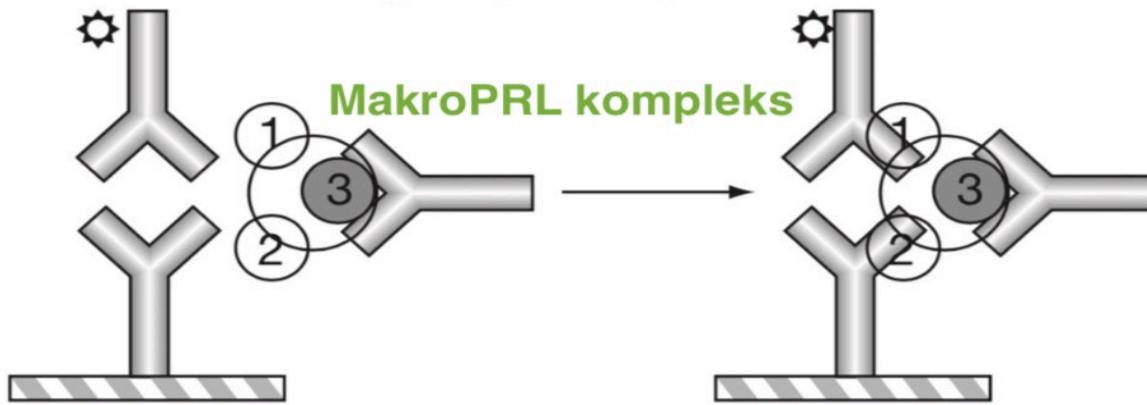
POTENCIJALNI IZVORI INTERFERENCIJE



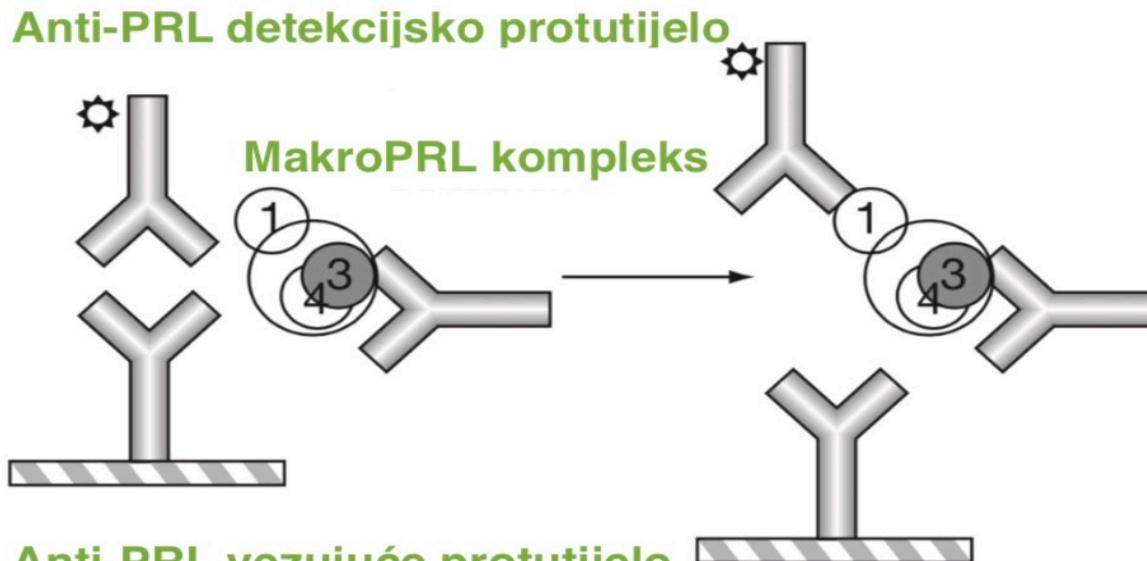
Smith et. al. Technology Insight: measuring prolactin in clinical samples. *Nature Clinical Practice Endocrinology & Metabolism* vol.3, p279–289 (2007)

VARIJABILNOST DETEKCIJE MAKROPROLAKTINA

Anti-PRL detekcijsko protutijelo



Anti-PRL vezujuće protutijelo



Serum Total Prolactin and Monomeric Prolactin Reference Intervals Determined by Precipitation with Polyethylene Glycol: Evaluation and Validation on Common ImmunoAssay Platforms



Luisa Beltran,¹ Michael N. Fahie-Wilson,¹ T. Joseph McKenna,² Lucille Kavanagh,² and Thomas P. Smith^{2*}

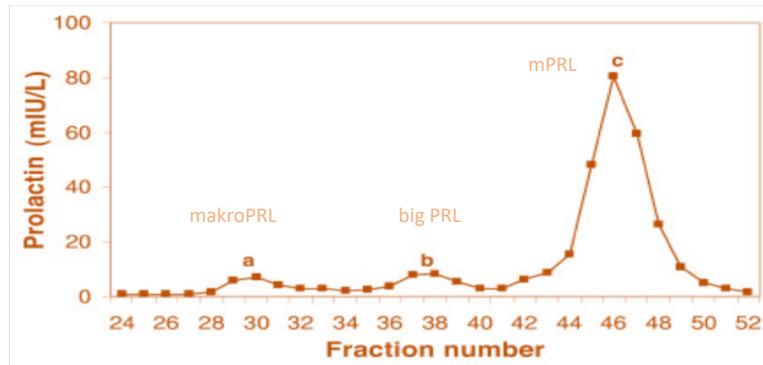
Clinical Chemistry 54:10 1673–1681 (2008)

Table 2. Reference intervals for total prolactin (mIU/L) in serum samples from males and females for each immunoassay platform.

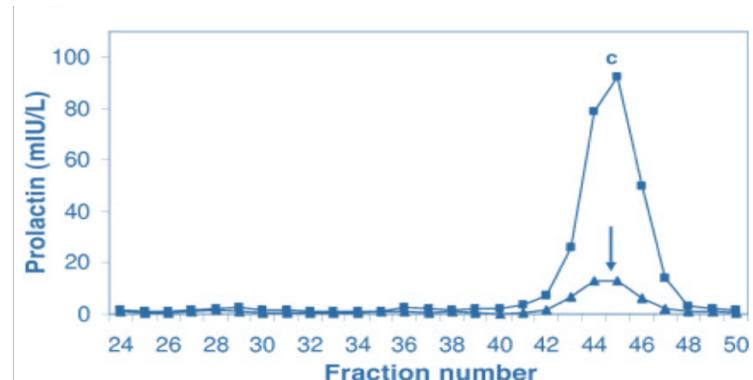
Method	Parametric lower	Estimate upper	Manufacturer's range
Samples from males			
Access	58	277	56–278
Centaur	63	262	45–375
Immulite	70	281	53–360
Elecsys	72	331	86–324
Architect	85	310	54–381
AIA	89	365	97–440
Samples from females			
Centaur	71	348	59–619
Immulite	75	396	40–530
Access	77	408	71–566
Elecsys	88	492	102–496
Architect	98	447	25–629
AIA	105	548	111–780

Table 3. Parametric reference intervals for post-PEG prolactin (mIU/L) in male and female sera for each immunoassay platform.

Analyzer	Male range		Female range	
	Lower	Upper	Lower	Upper
Centaur	61	196	66	278
Elecsys	63	245	75	381
Access	70	301	92	469
Architect	72	229	79	347
AIA	73	247	83	383
Immulite	78	263	85	394



Kromatogram distribucije imunoreaktivnog prolaktina u uzorku seruma



Kromatogram WHO standarda IS84/500 za prolaktin nakon precipitacije PEG-om



<https://goo.g/limages/nQfMLD>