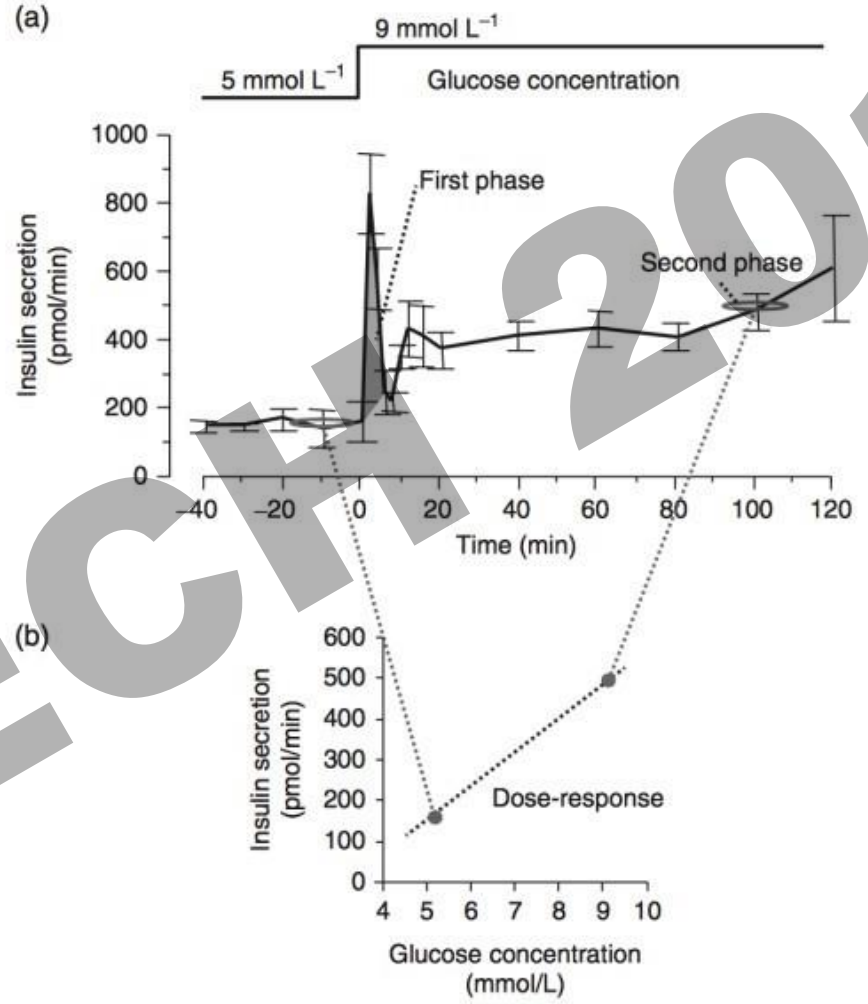
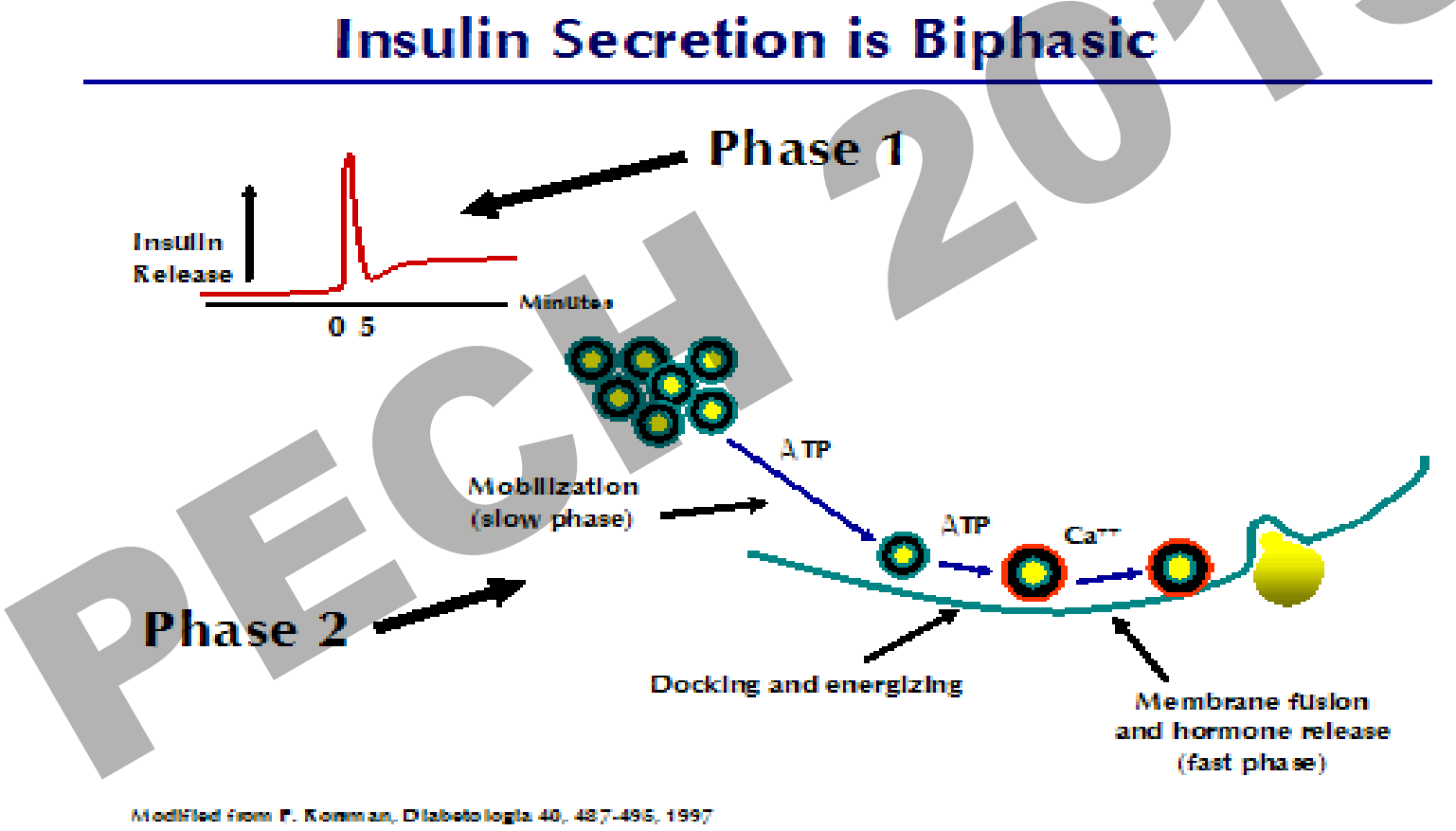
A szénhidrát anyagcsere és a női reproduktív rendszer kapcsolata

Dr Tűű László

Az inzulin szekréció folyamata
Inzulin szekréció a glukóz koncentráció függvényében

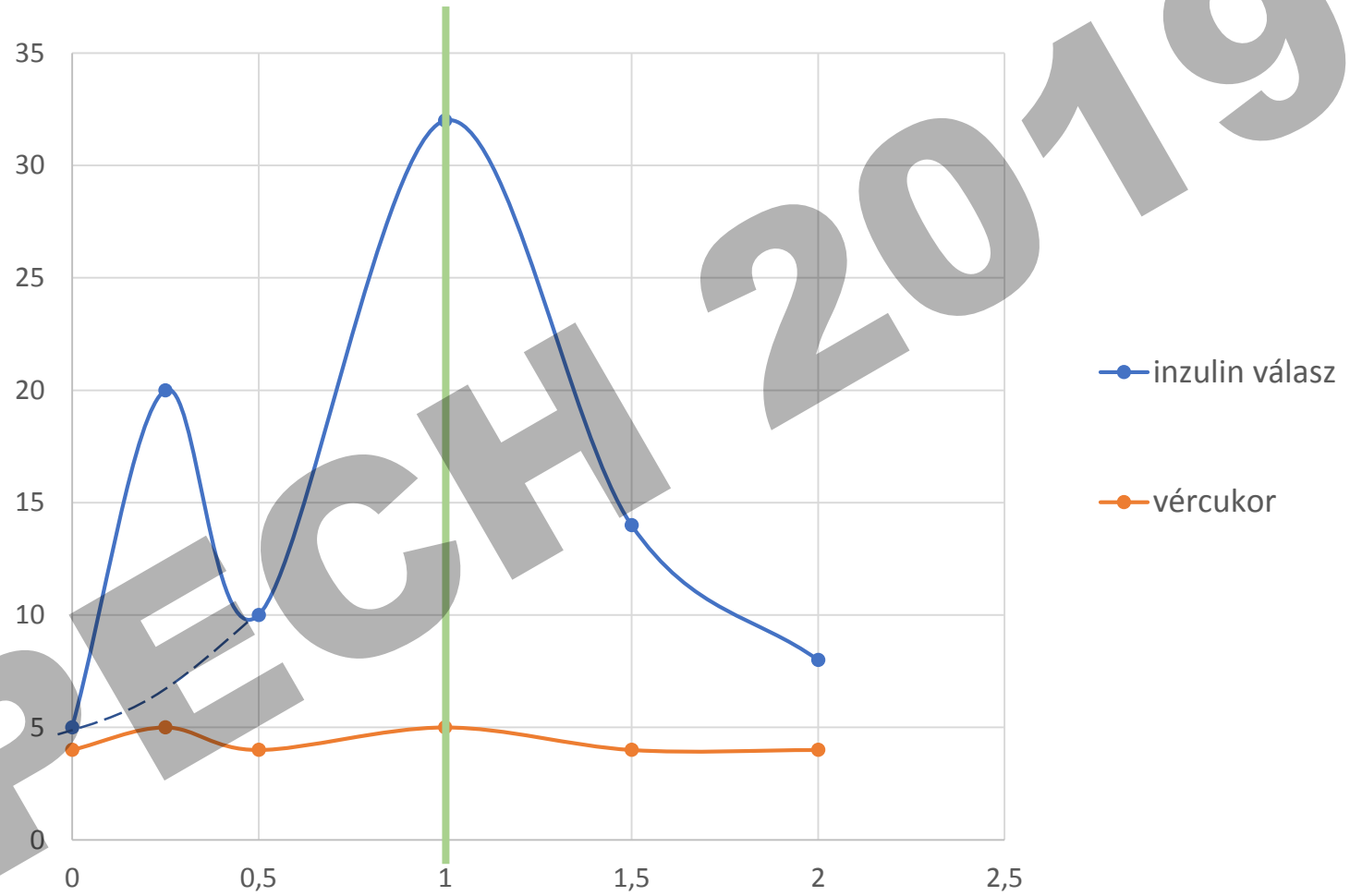


A normál inzulin válasz kétfázisú

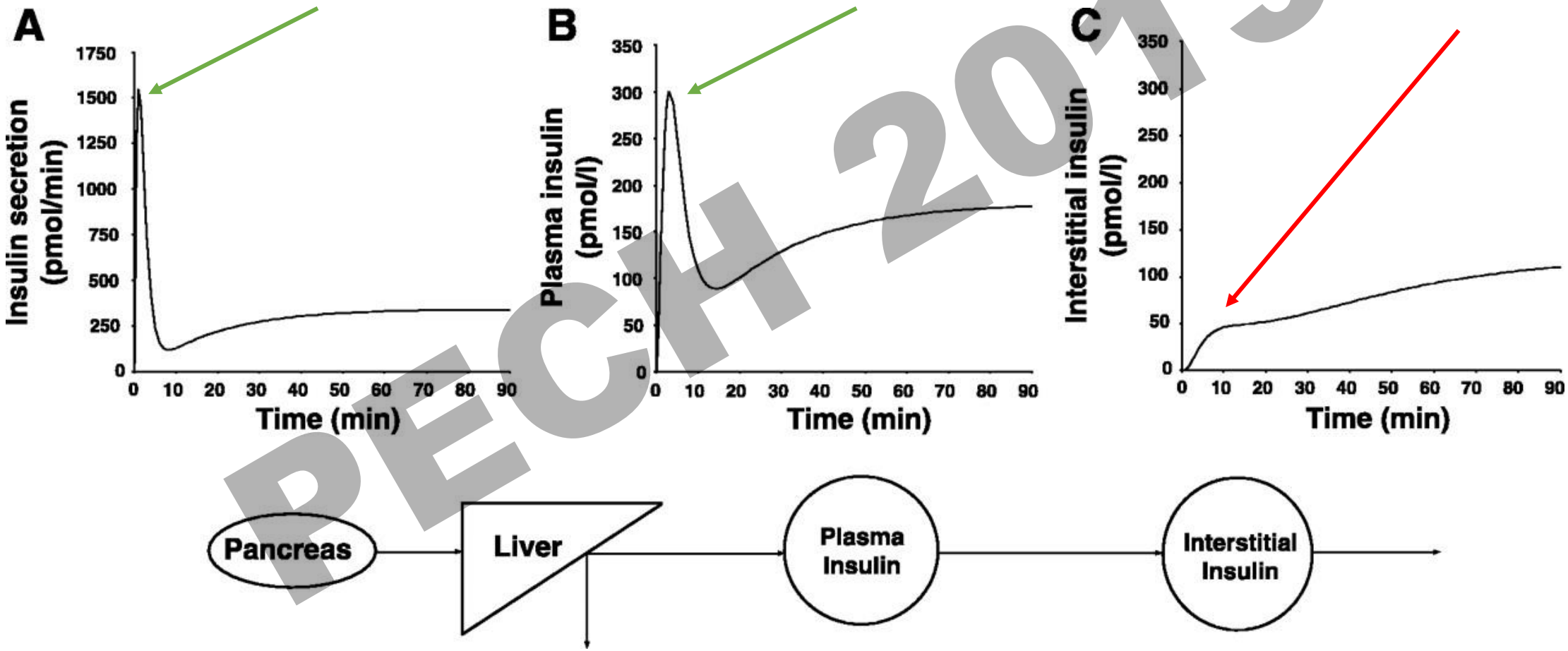


Modified from F. Konman, Diabetologia 40, 487-495, 1997

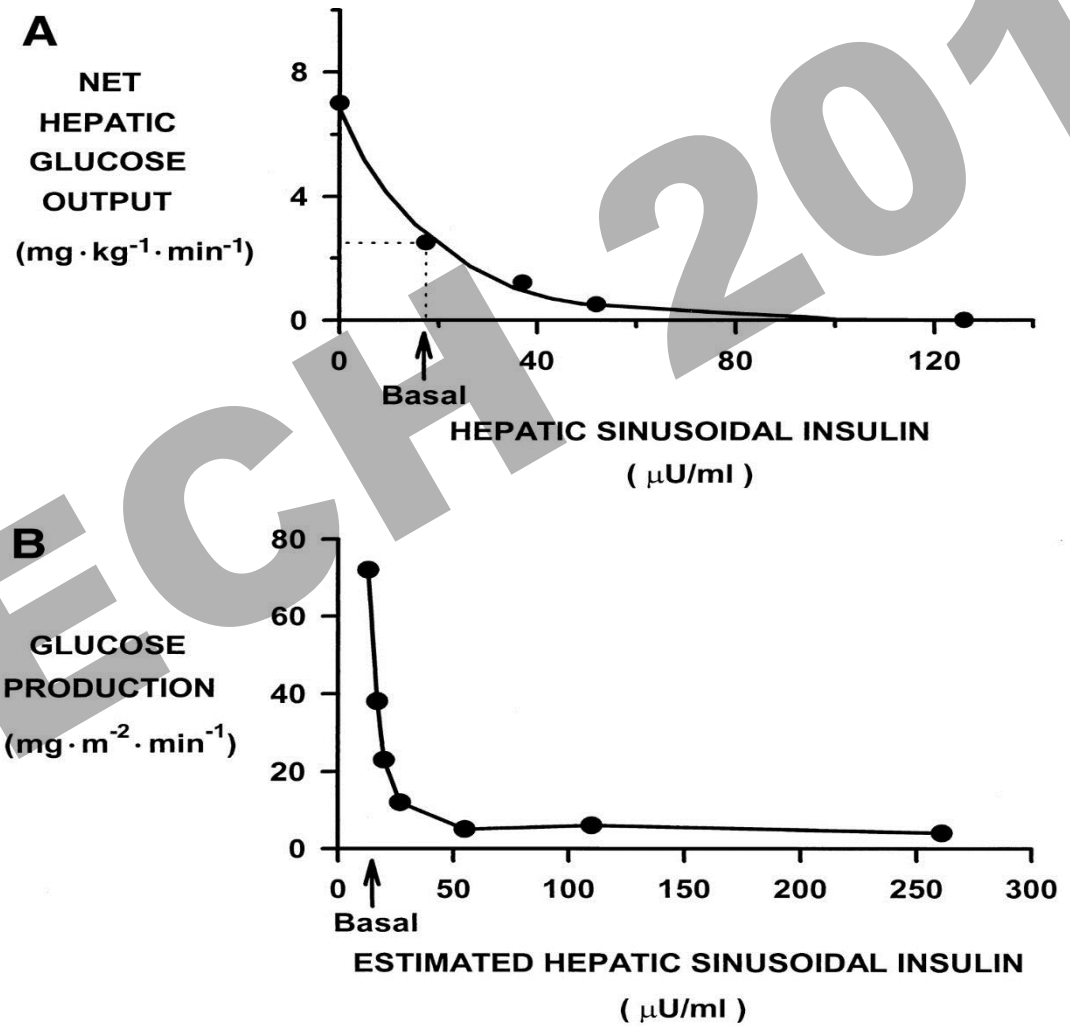
Élettani inzulin görbe



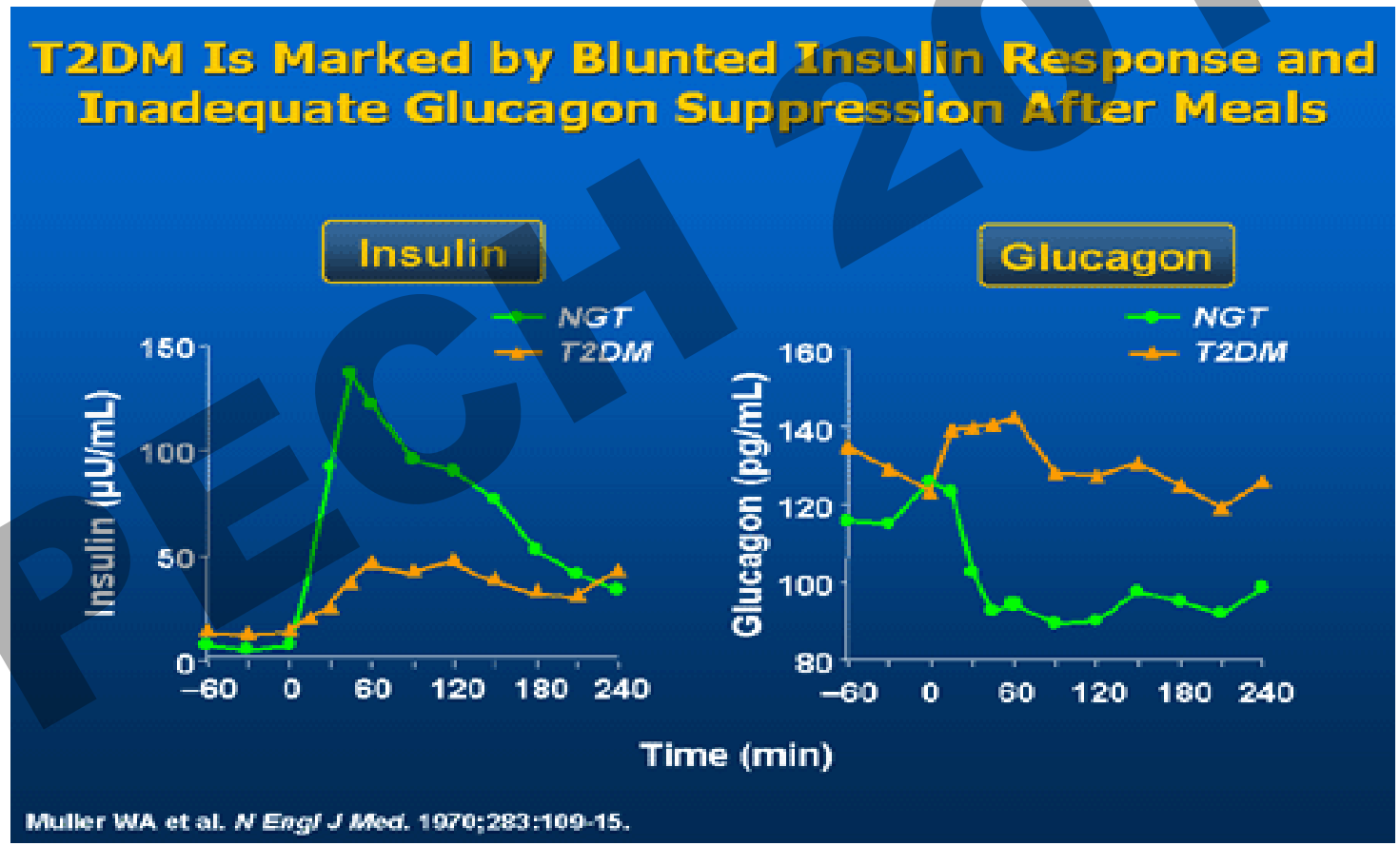
Az inzulin szekréció, a plazma inzulin és az intersticiális inzulin-szint változása étkezés hatására



Korai inzulin csúcs: a hepatikus glukóz produkció szupressziója



A korai inzulin csúcs hatásai: glukagon szupresszió



A béta sejtek %-os aktivitása a vércukor-szint függvényében

Percent activation (PA) of pancreatic β-cells subject to different glycemic stimuli, as extracted from Fig 2 in [1].

Glyc. (mg/dl)	50	100	150	200	300	500
PA	2%	18.75%	43.75%	56.25%	75%	100%
		5,5	8,3	11,1	16,7	27,8

Napi inzulin szekréció egészséges, normál súlyú felnőtt: 0,5 U/ttkg ~30-50 U/nap

Az inzulin hatás, vagy az inzulin szekréció zavara az elsődleges 2-es típusú Diabéteszben?

Insulin secretion and insulin action in non-insulin-dependent diabetes mellitus: which defect is primary?

Reaven GM

Diabetes Care [1984, 7 Suppl 1:17-24]

Defects in both insulin secretion and insulin action exist in patients with non-insulin-dependent diabetes mellitus (NIDDM). The loss of the acute plasma insulin response to intravenous glucose is seen in patients with relatively mild degrees of fasting hyperglycemia, but patients with severe fasting hyperglycemia also demonstrate absolute hypoinsulinemia in response to an oral glucose challenge. In contrast, day-long circulating insulin levels are within normal limits even in severely hyperglycemic patients with NIDDM. The relationship between NIDDM and insulin action in NIDDM is less complex, and is a characteristic feature of the syndrome. This metabolic defect is independent of obesity, and the severity of the resistance to insulin-stimulated glucose uptake increases with magnitude of hyperglycemia. Control of hyperglycemia with exogenous insulin ameliorates the degree of insulin resistance, and reduction of insulin resistance with weight loss in obese patients with NIDDM leads to an enhanced insulin response. Since neither therapeutic intervention is capable of restoring all metabolic abnormalities to normal, these observations do not tell us which of these two defects is primarily responsible for the development of NIDDM. Similarly, the observation that most patients with impaired glucose tolerance are hyperinsulinemic and insulin resistant does not prove that insulin resistance is the primary defect in NIDDM. In conclusion, reduction in both insulin secretion and action is seen in patients with NIDDM, and the relationship between these two metabolic abnormalities is very complex.

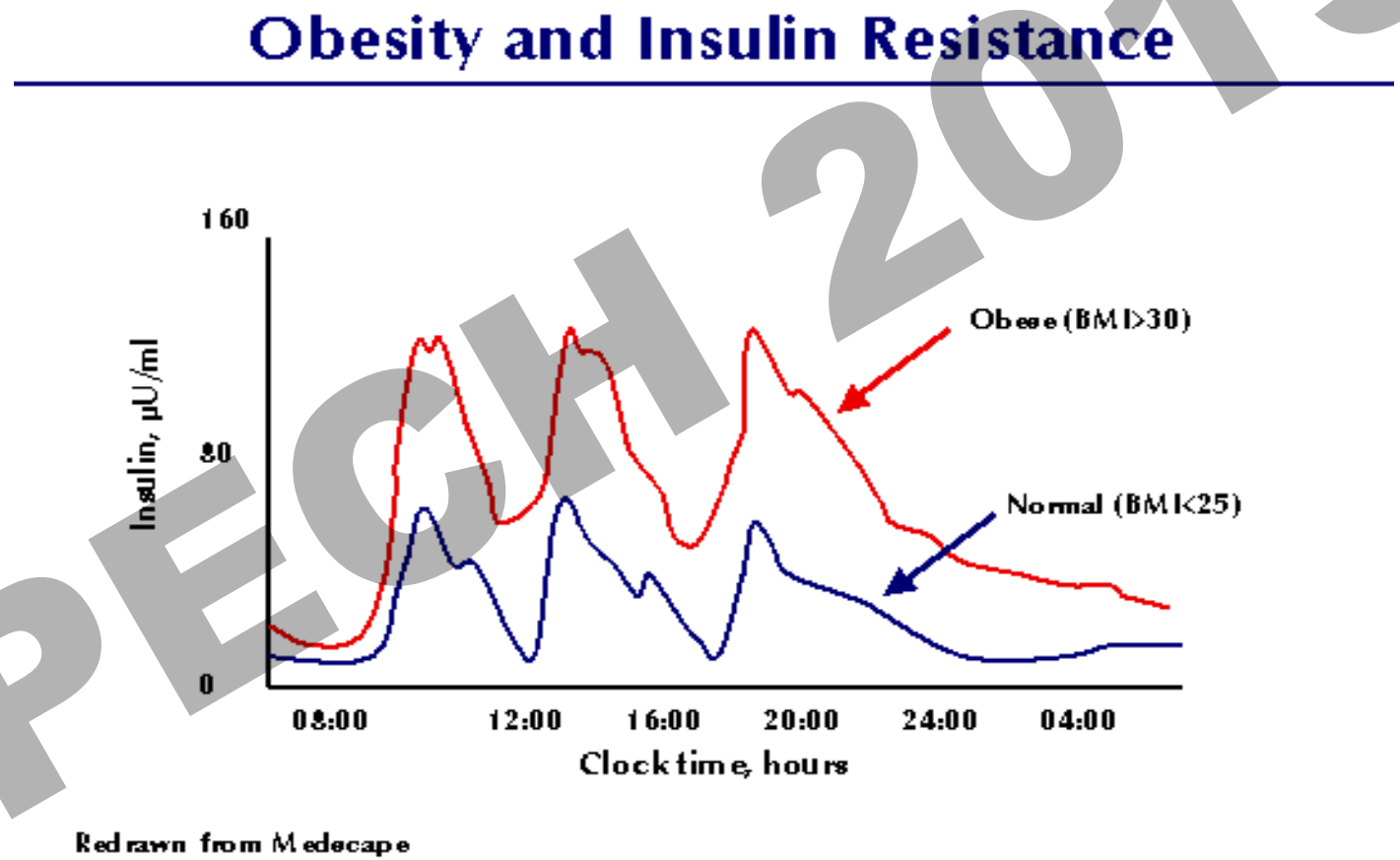
Az inzulin szenzitivitás és szekréció eltérései a prediabetes és a T2 DM alcsoportokban

Table 2.
Overview of the Defects in Insulin Sensitivity and β-Cell Function Observed in the Different Subgroups of Prediabetes and T2D

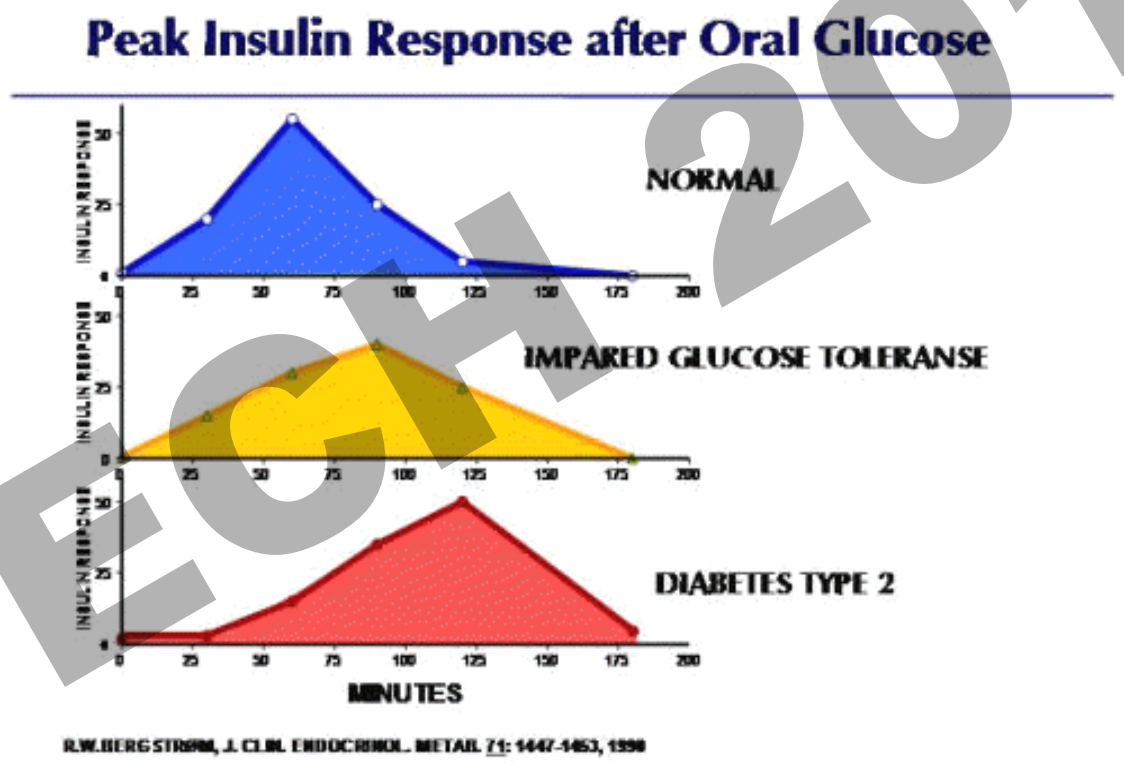
	Absolute Early Insulin Release	Insulin Sensitivity (Glucose-Stimulated State)	Insulin Sensitivity (Fasting State)	Relative β-Cell Function (Glucose Stimulated State)	Relative β-Cell Function (Fasting State)
OGTT definition					
NGT	Ref.	Ref.	Ref.	Ref.	Ref.
i-IFG	↓↓	↔/↓	↓↓	↓	↓↓
i-IGT	↔/↑	↓↓	↔/↓	↓	↓
IFG+IGT	↓	↓↓	↓↓	↓↓	↓↓
F-DM	↓↓↓	↓↓	↓↓	↓↓	↓↓↓
2h-DM	↔	↓↓↓	↓↓	↓↓	↓↓
F-2h-DM	↓↓↓	↓↓↓	↓↓↓	↓↓↓	↓↓↓
HbA1c definition					
HbA1c < 6.0%	↔	↔	↔	↔	↔
HbA1c 6.0%–6.4%	↓	↓↓	↓↓	↓↓	↓↓
HbA1c ≥ 6.5%	↓↓	↓↓↓	↓↓↓	↓↓↓	↓↓↓

↔, unchanged; ↓, mildly decreased; ↓↓, moderately decreased; ↓↓↓, highly decreased; ↑, mildly increased; Ref, Reference.

A szérum inzulin túlsúly esetén



Inzulin válasz változása a CH anyagcsere-zavar kialakulása során



J Clin Endocrinol Metab. 1996 Mar;81(3):942-7.

Beta-cell dysfunction independent of obesity and glucose intolerance in the polycystic ovary syndrome.

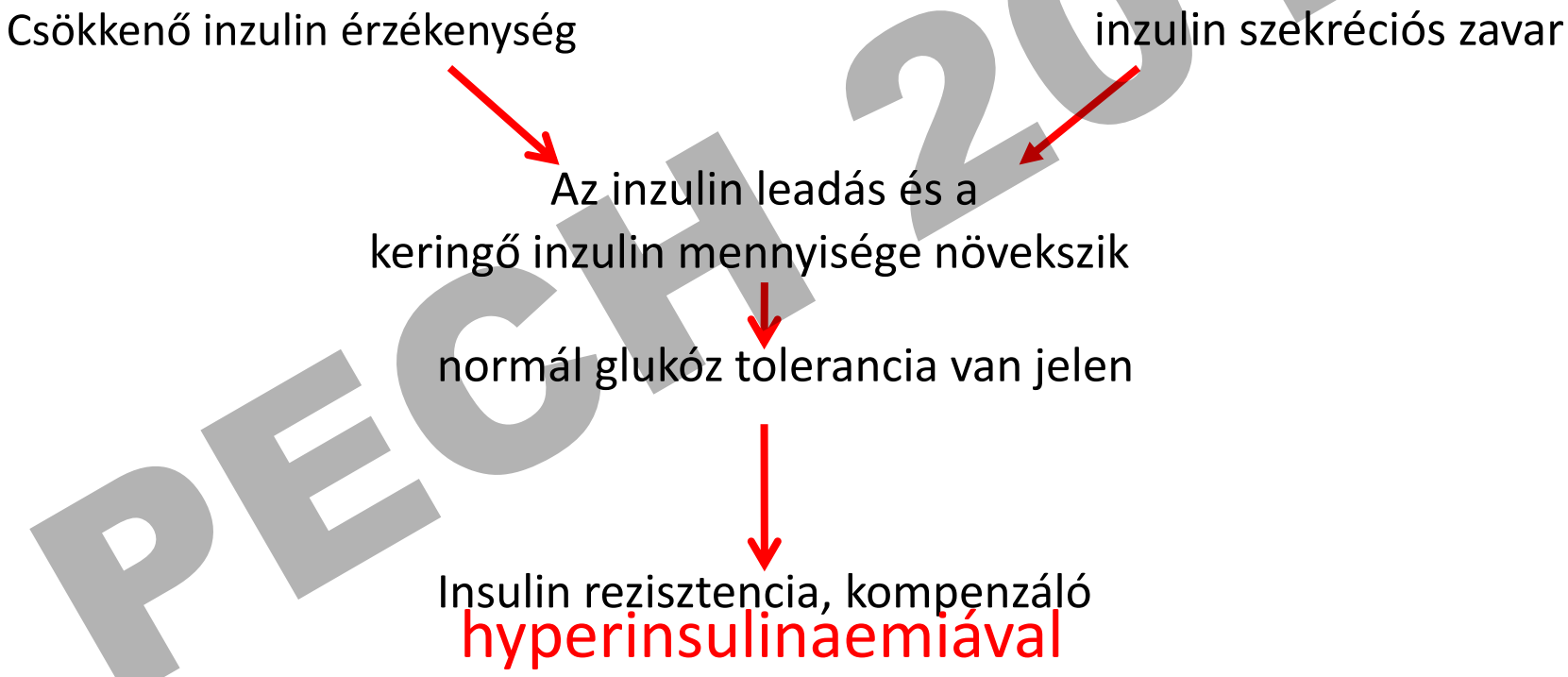
Dunaif A[1], Finegood DT.

Abstract

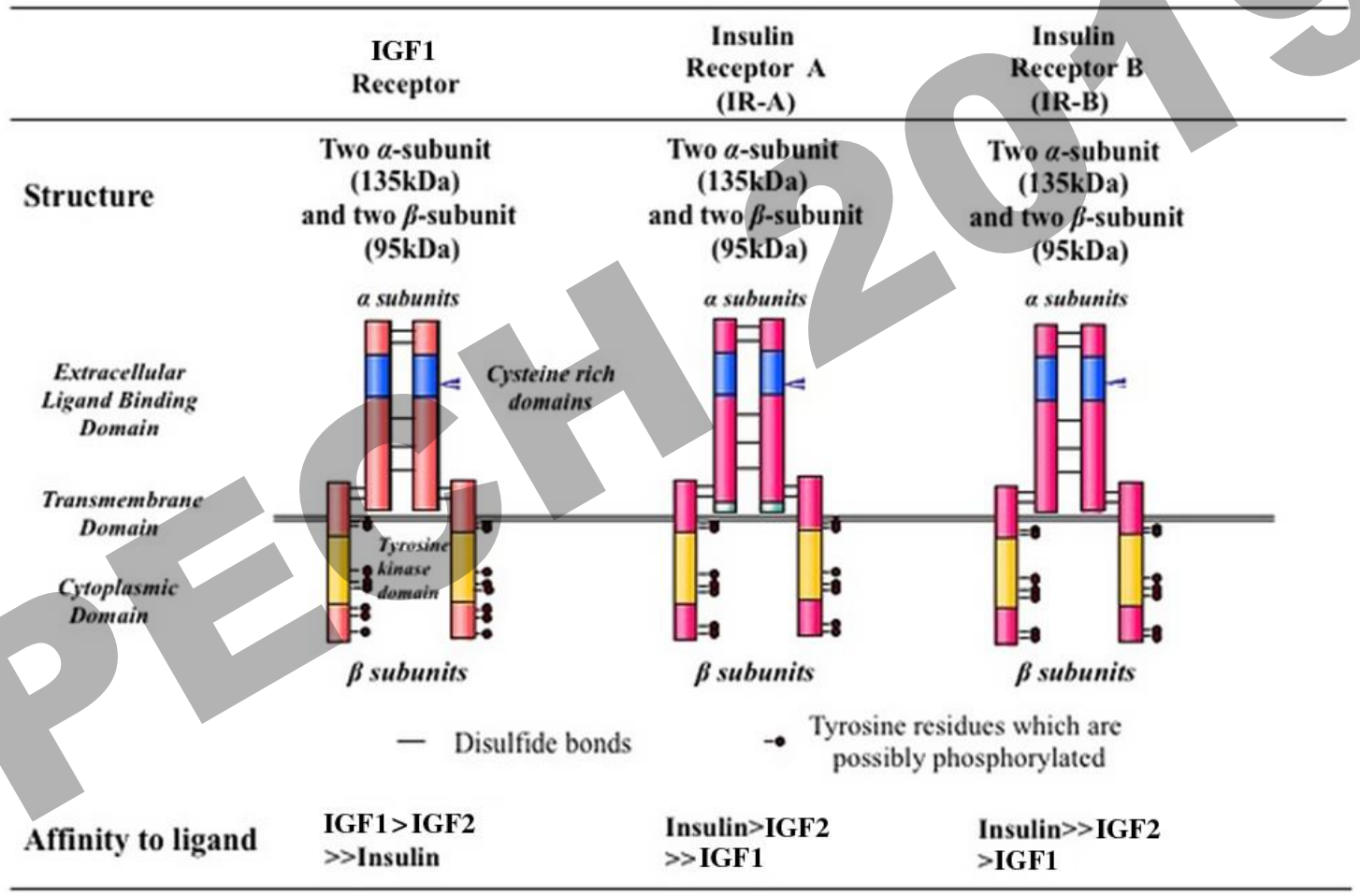
Several distinct groups of subjects at high risk to develop noninsulin-dependent diabetes mellitus (NIDDM) have been found to have insulin secretory defects when beta-cell function is assessed in the context of peripheral insulin sensitivity. We investigated this with a modified frequently sampled iv glucose tolerance test to determine acute insulin responses to glucose (AIRg) as well as insulin action by minimal model analysis in 28 women with polycystic ovary syndrome (PCOS; 15 obese and 13 nonobese) and 29 age- and weight-matched normal women (14 obese and 15 nonobese). No subject, PCOS or control, had fasting hyperglycemia, but seven PCOS women (six obese and one nonobese) had impaired glucose tolerance or NIDDM. The PCOS women had significantly decreased insulin sensitivity compared to the normal women (P < or = 0.001), and the obese women were less sensitive than the nonobese women (P < or = 0.001). The empiric measure of insulin release, AIRg, was significantly increased by obesity (P < or = 0.01), but not by PCOS. However, the disposition index (insulin sensitivity x AIRg) was significantly decreased by both PCOS (< or = 0.005) and obesity (< or = 0.005), suggesting that AIRg was inadequate for the degree of insulin resistance. When the PCOS women with impaired glucose tolerance or NIDDM were removed from the analysis, all of the reported PCOS-related changes in insulin action and secretion remained significant.

We conclude that both obese and nonobese PCOS women have beta-cell dysfunction as well as insulin resistance. However, this was not associated with glucose intolerance in the majority of PCOS women.

Inzulin rezisztencia kialakulásának mechanizmusa

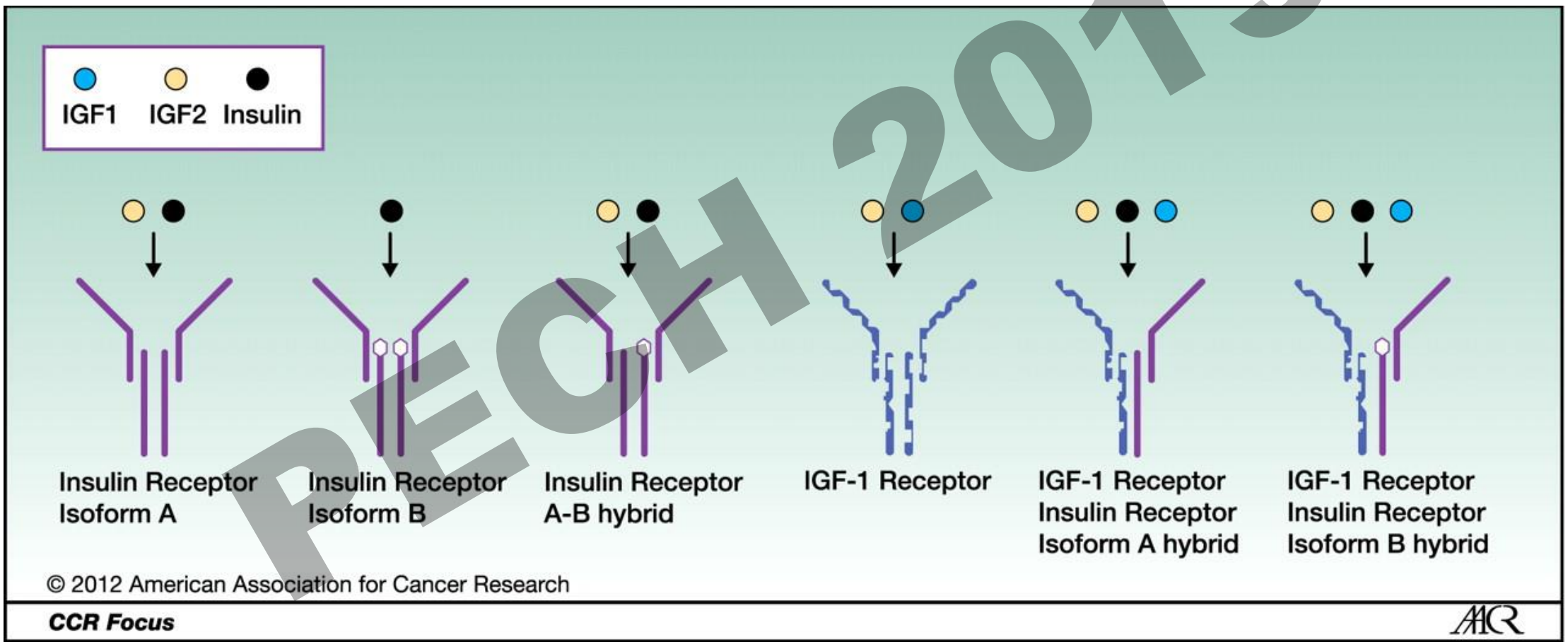


Az Inzulin/IGF-1 receptor család

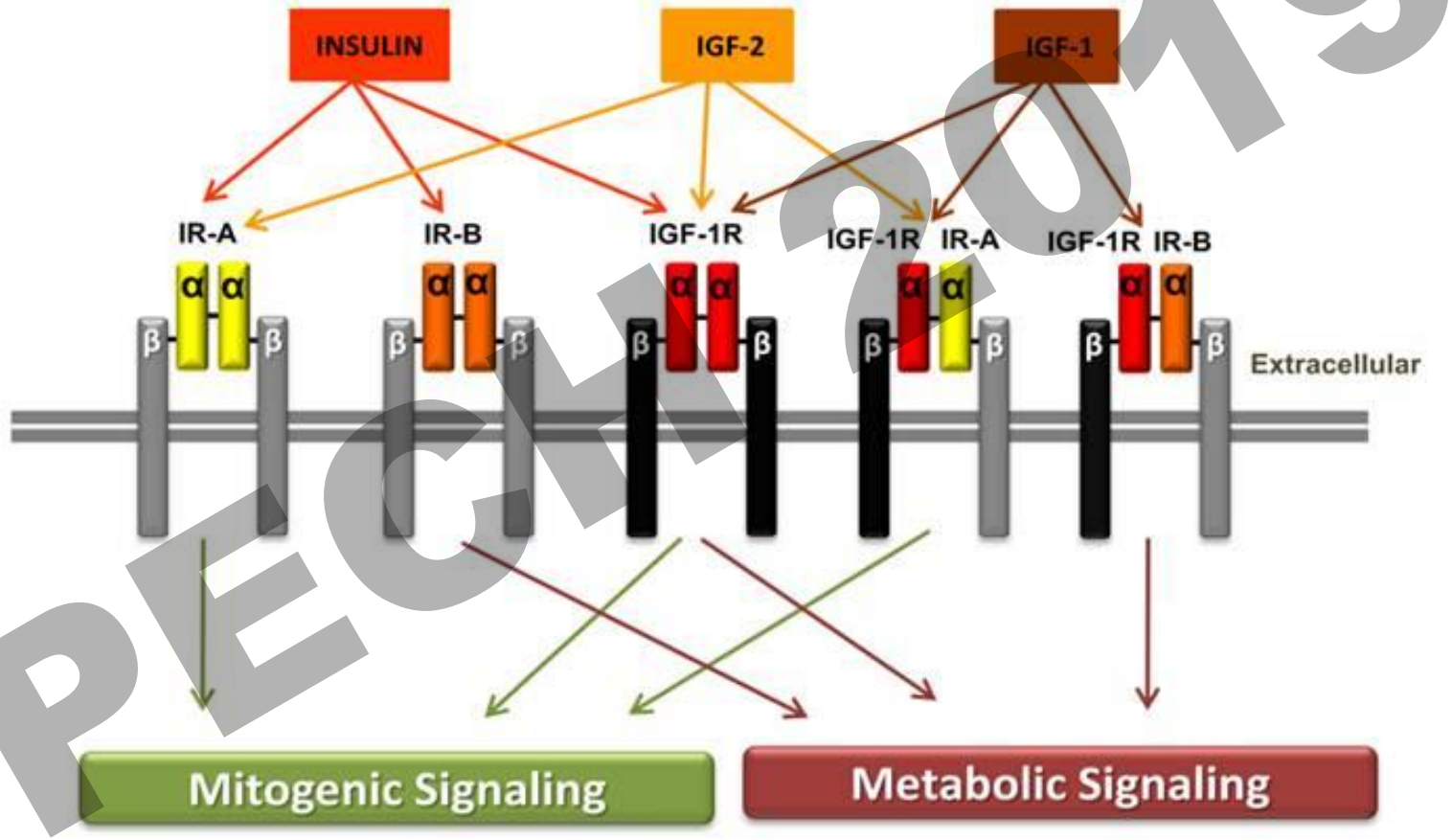


40 YEARS OF IGF1: IGF1 receptor signaling pathways
Fumihiko Hakuno[1] and Shin-Ichiro Takahashi
Journal of Molecular Endocrinology, T69–86, volume 61, Issue:1

Az Inzulin/IGF-1 receptor család

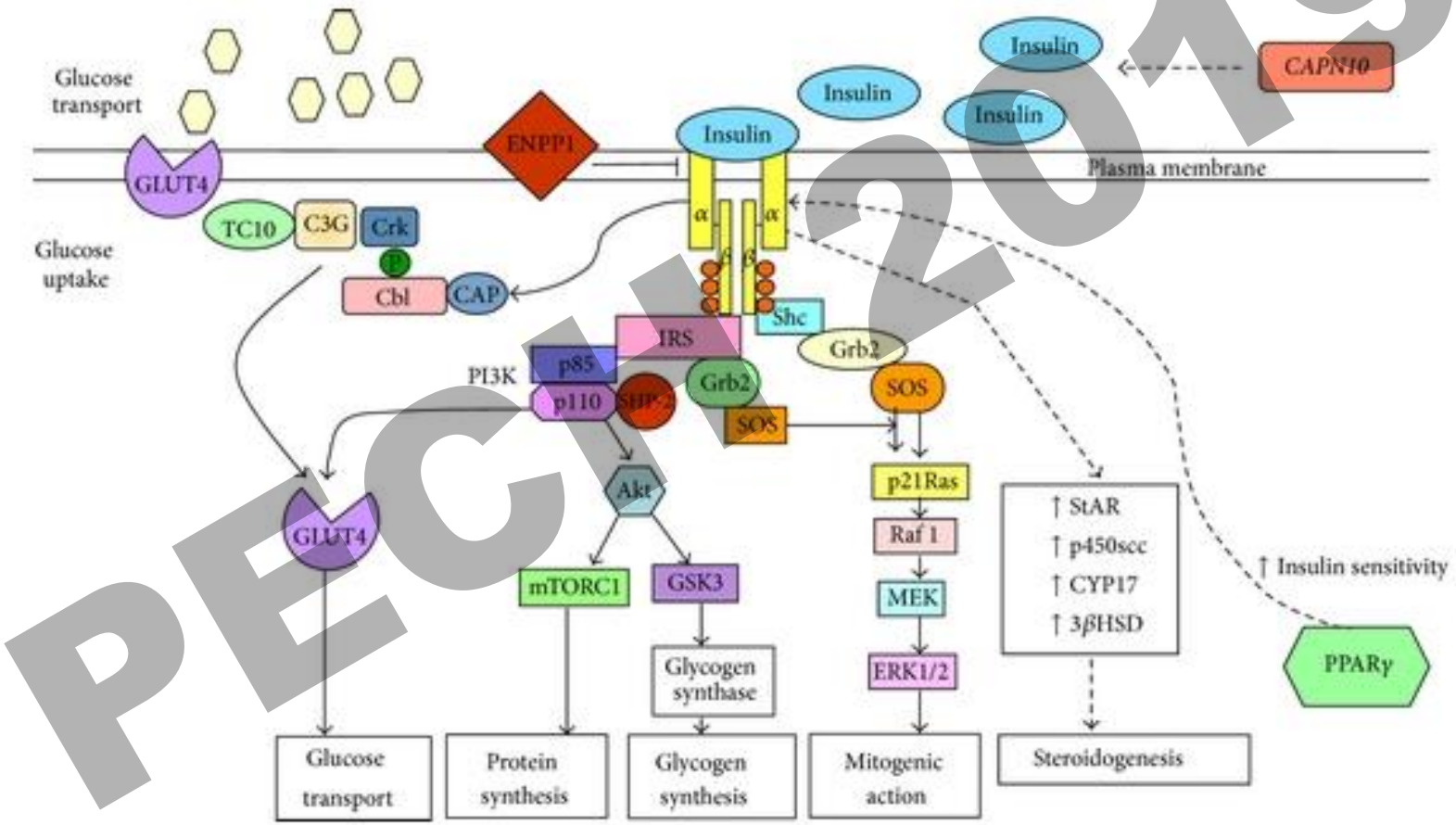


Az Inzulin/IGF-1 receptor család

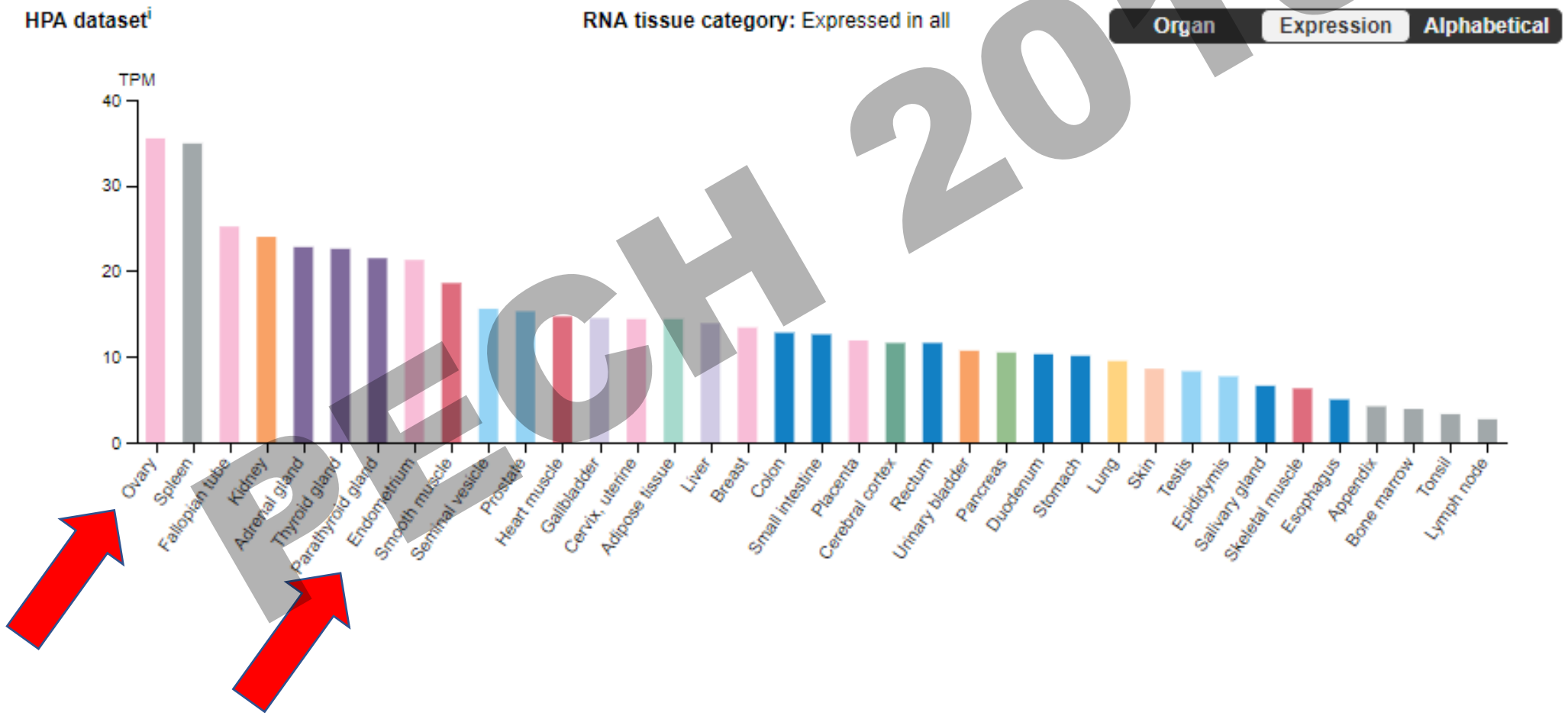


40 YEARS OF IGF1: IGF1 receptor signaling pathways
Fumihiko Hakuno[1] and Shin-Ichiro Takahashi[1]
Journal of Molecular Endocrinology, T69–86, volume 61, Issue:1

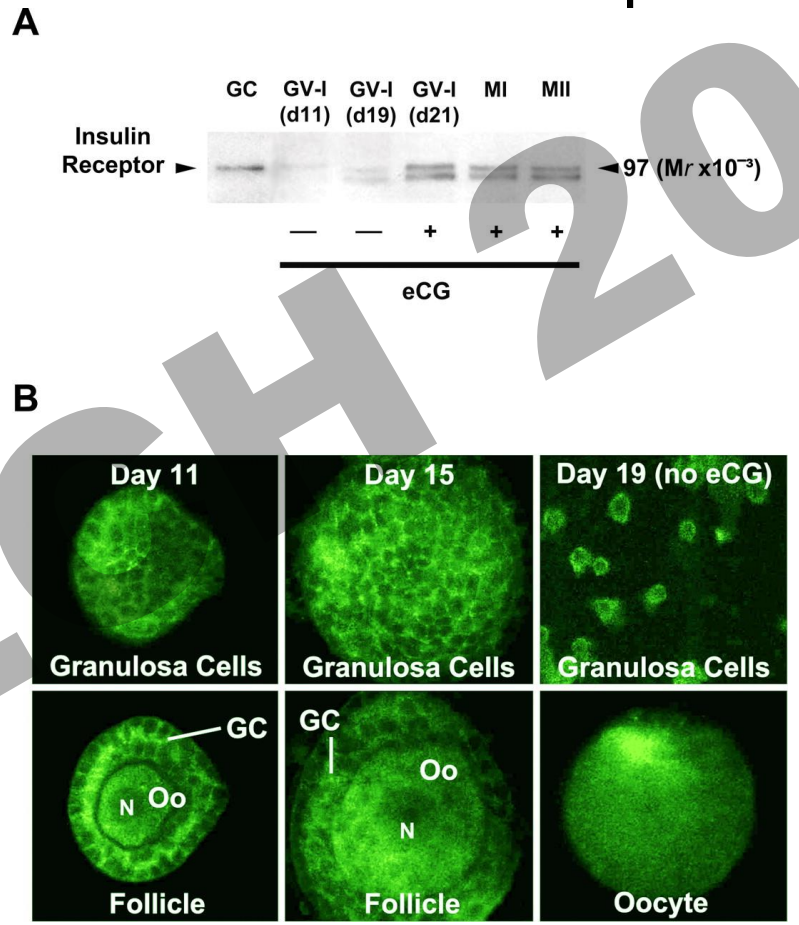
Interaction of insulin with insulin receptor



Inzulin receptor RNA expresszió a humán szövetekben

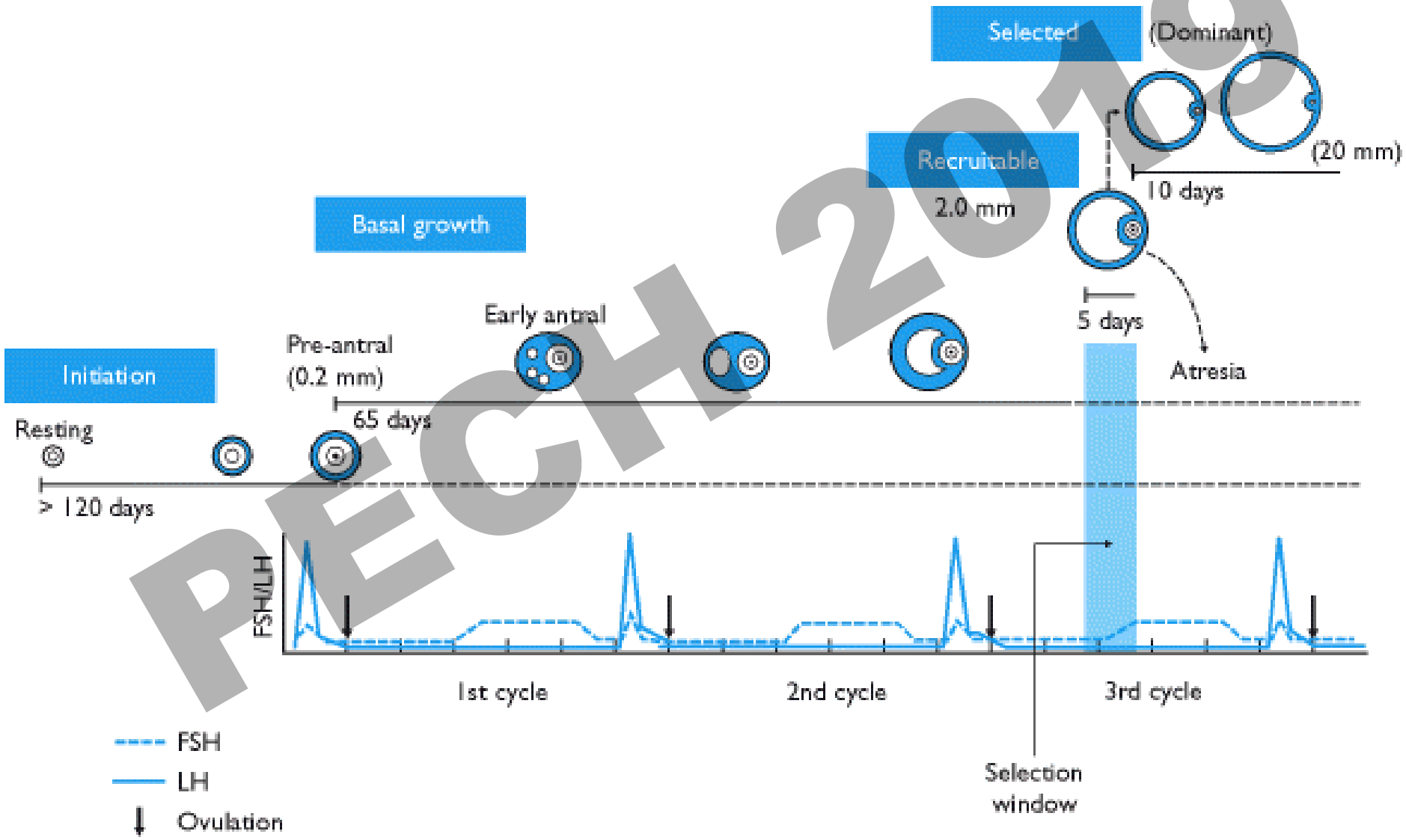


Expression of INSR-β protein in meiotically incompetent (d11) and competent (d19, d21) oocytes at various developmental stages

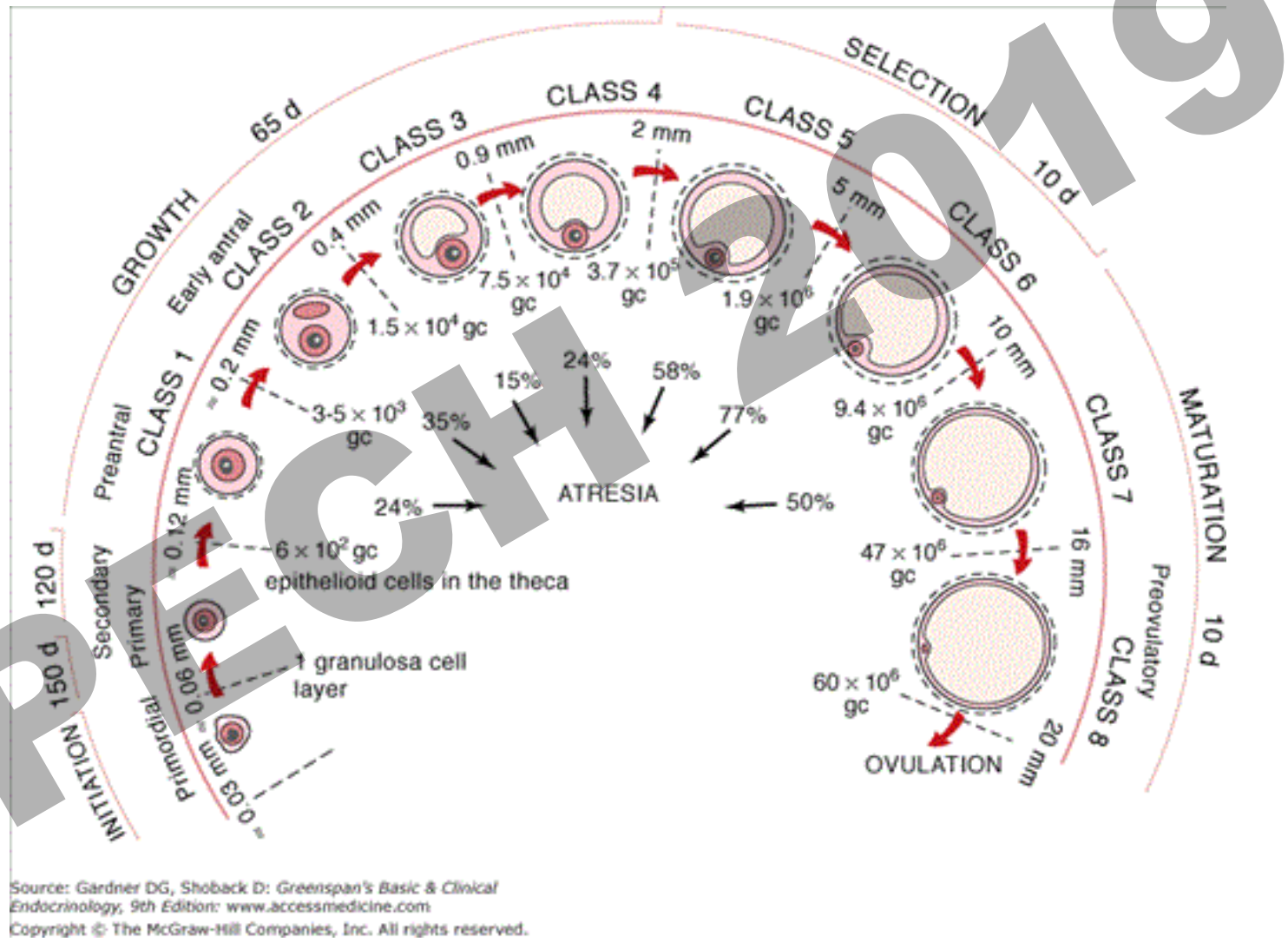


Insulin Signaling in Mouse Oocytes ;Nicole Acevedo, Jun Ding, Gary D. Smith; Biology of Reproduction, 77(5):872-879 (2007)

A follikulogenezis

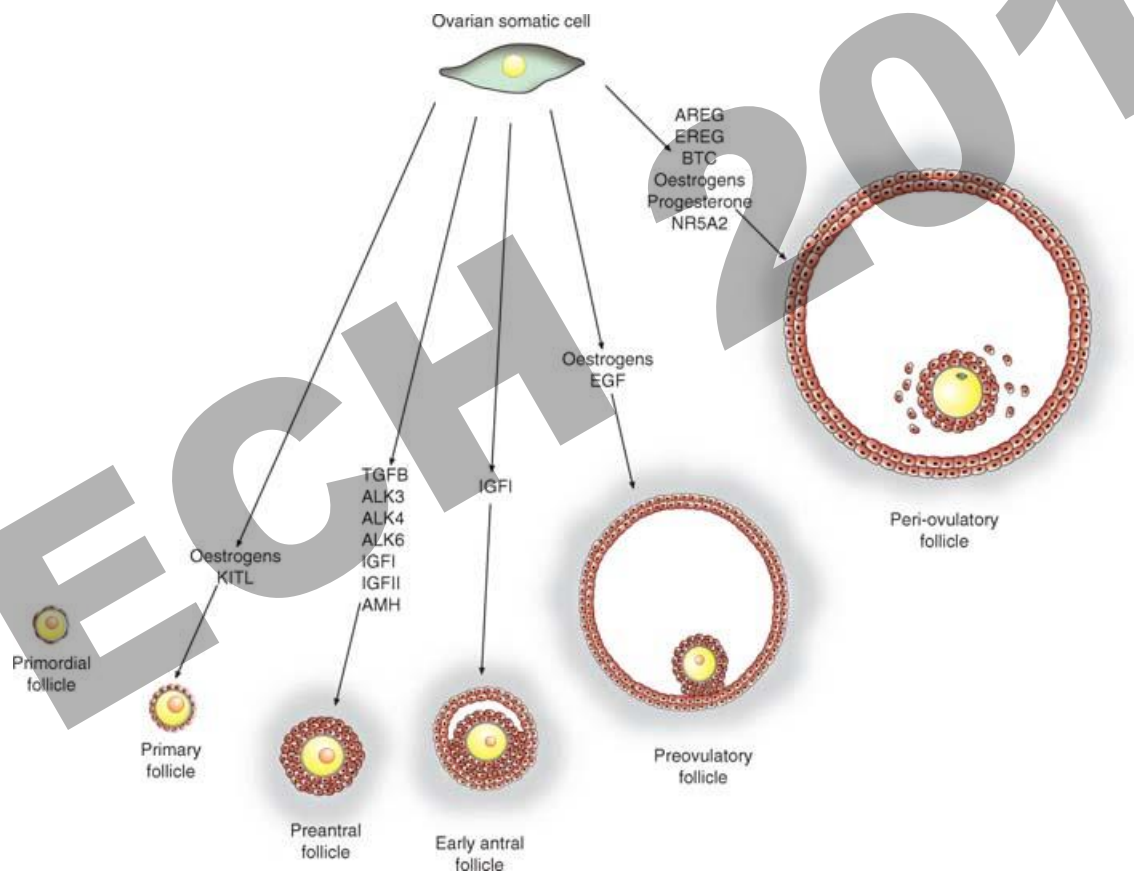


A follikulogenezis



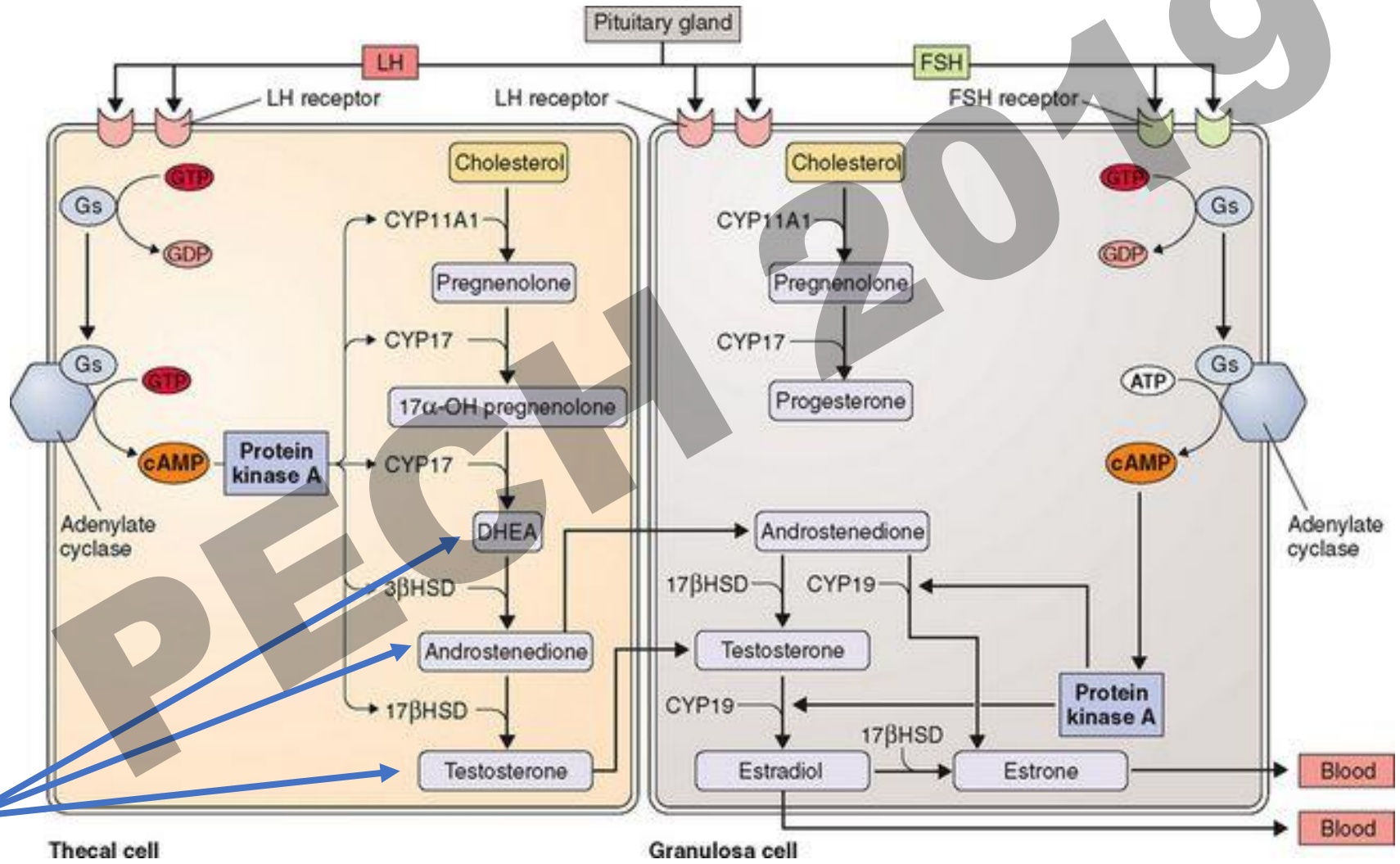
Source: Gardner DG, Shoback D: *Greenspan's Basic & Clinical Endocrinology, 9th Edition:* www.accessmedicine.com

A follikulogenezis



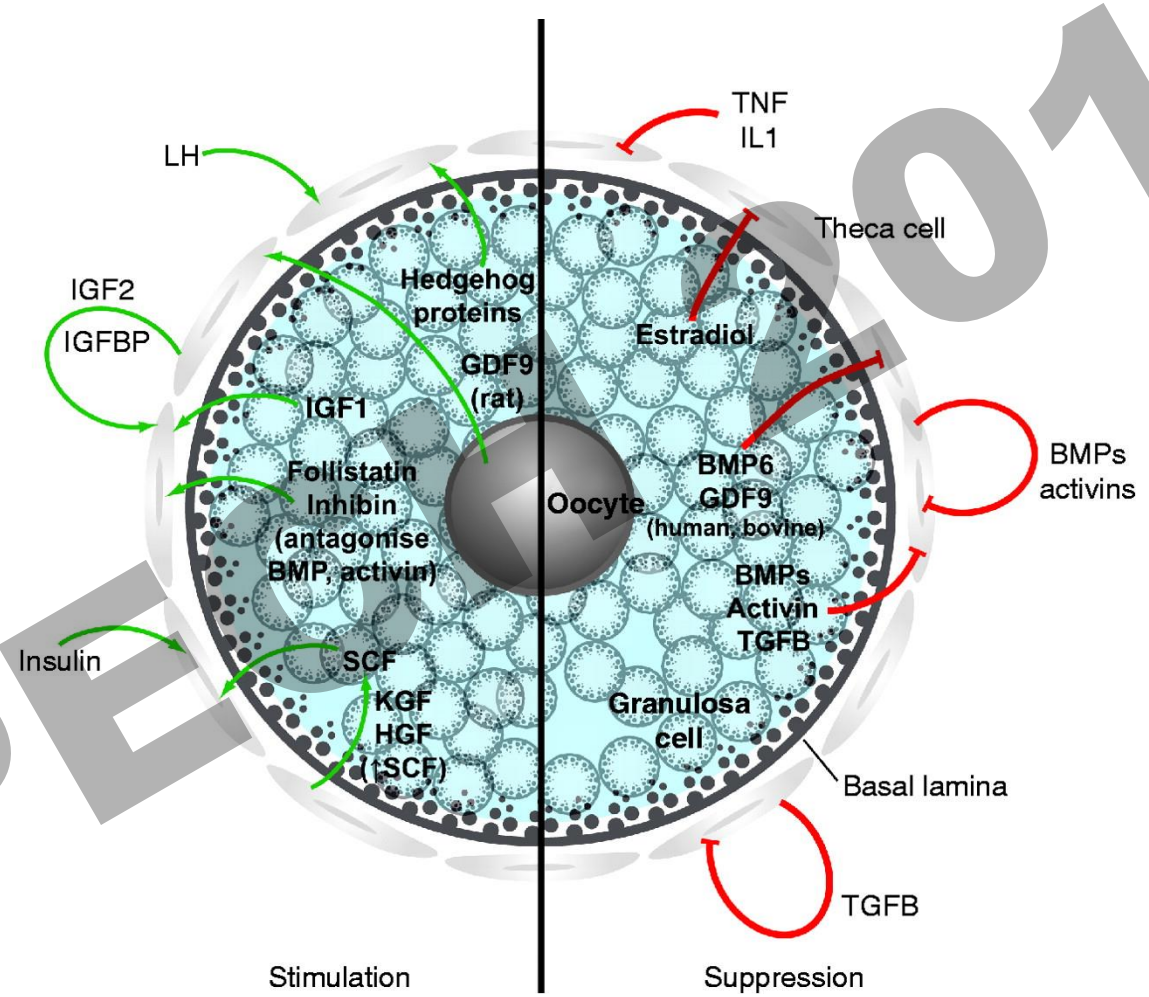
Coordinated regulation of follicle development by germ and somatic cells
Mario Binelli , Bruce D. Murphy ; *Reproduction, Fertility and Development* 22(1) 1-12

Az ösztrogén bioszintézis lépései



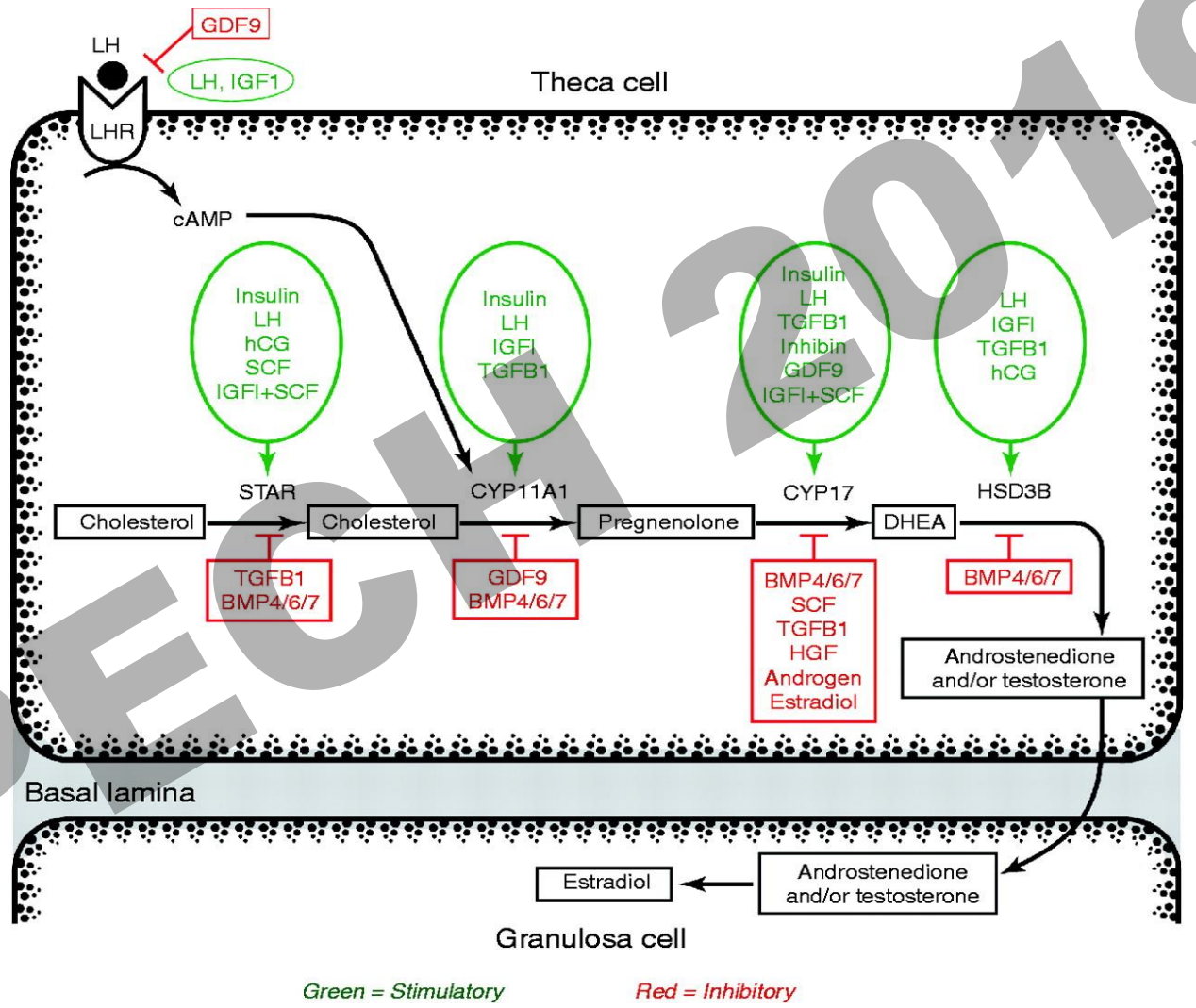
E2 prekurzor

A Theca sejtek steroid produkciójának szabályozása

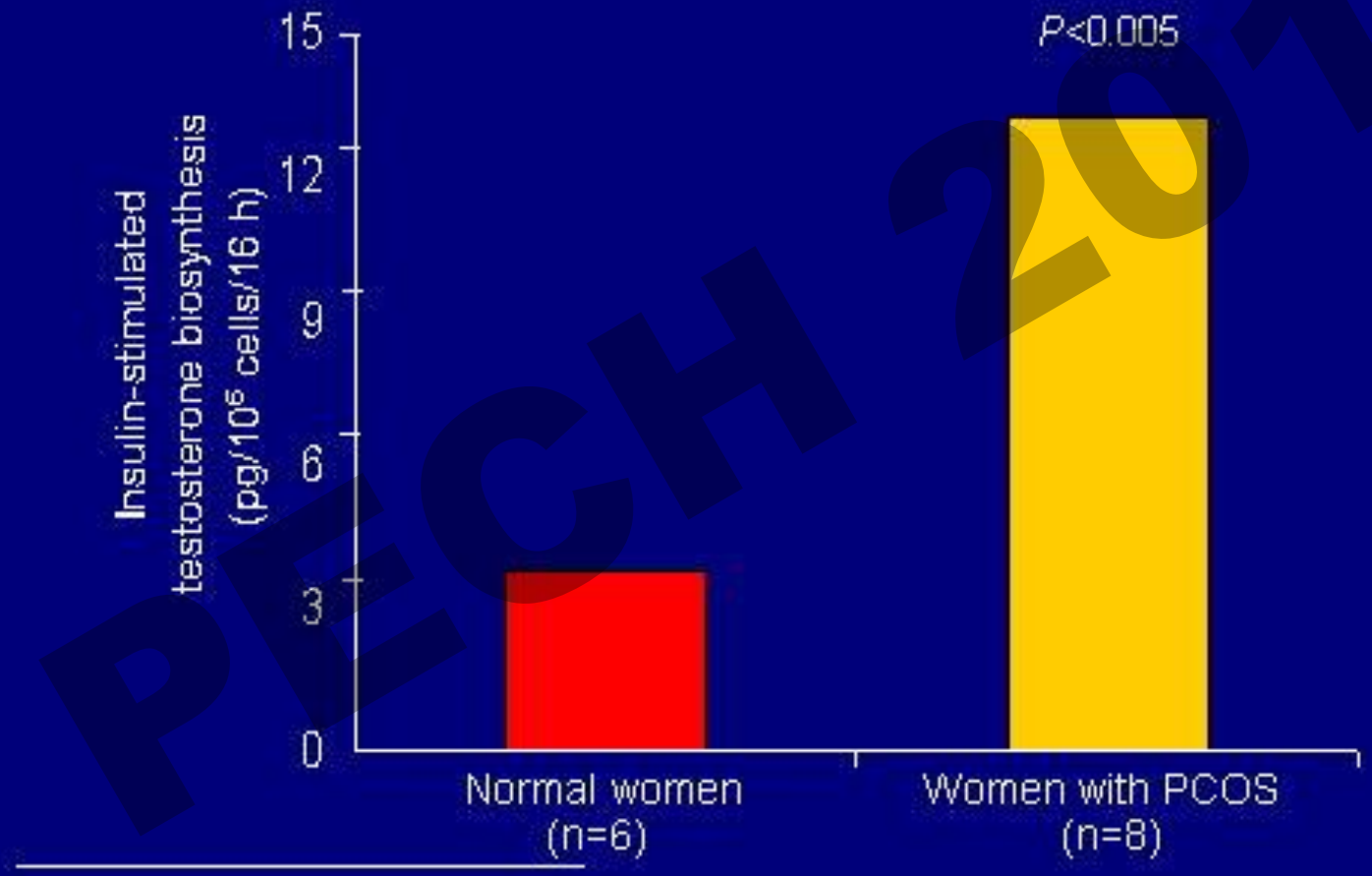


Theca: the forgotten cell of the ovarian follicle; J M Young and A S McNeilly; Reproduction, Volume 140: Issue 4, 489–504

A Theca sejtek steroid produkciója

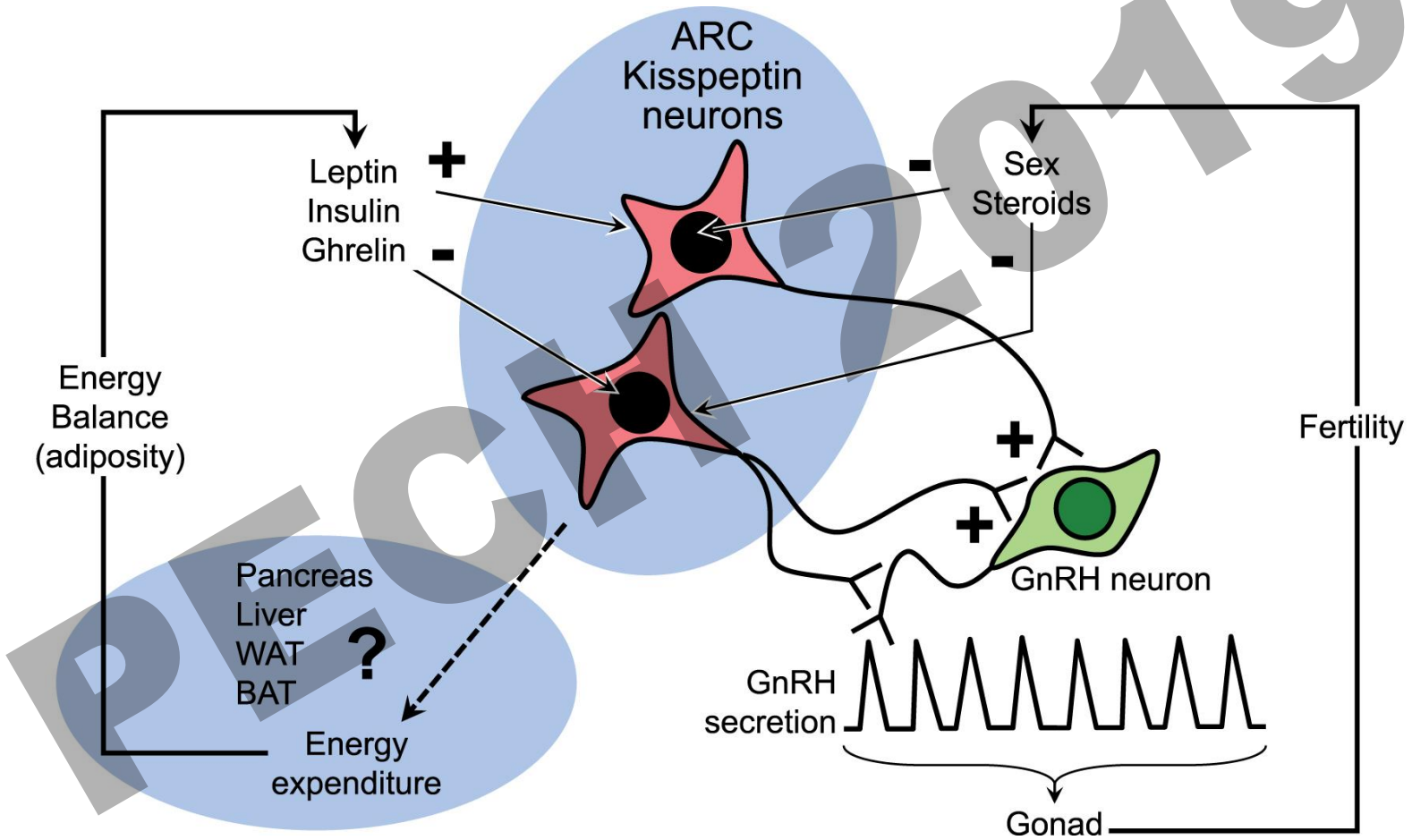


Effects of Insulin (20 µg/mL) on Testosterone Production by Ovarian Thecal Cells



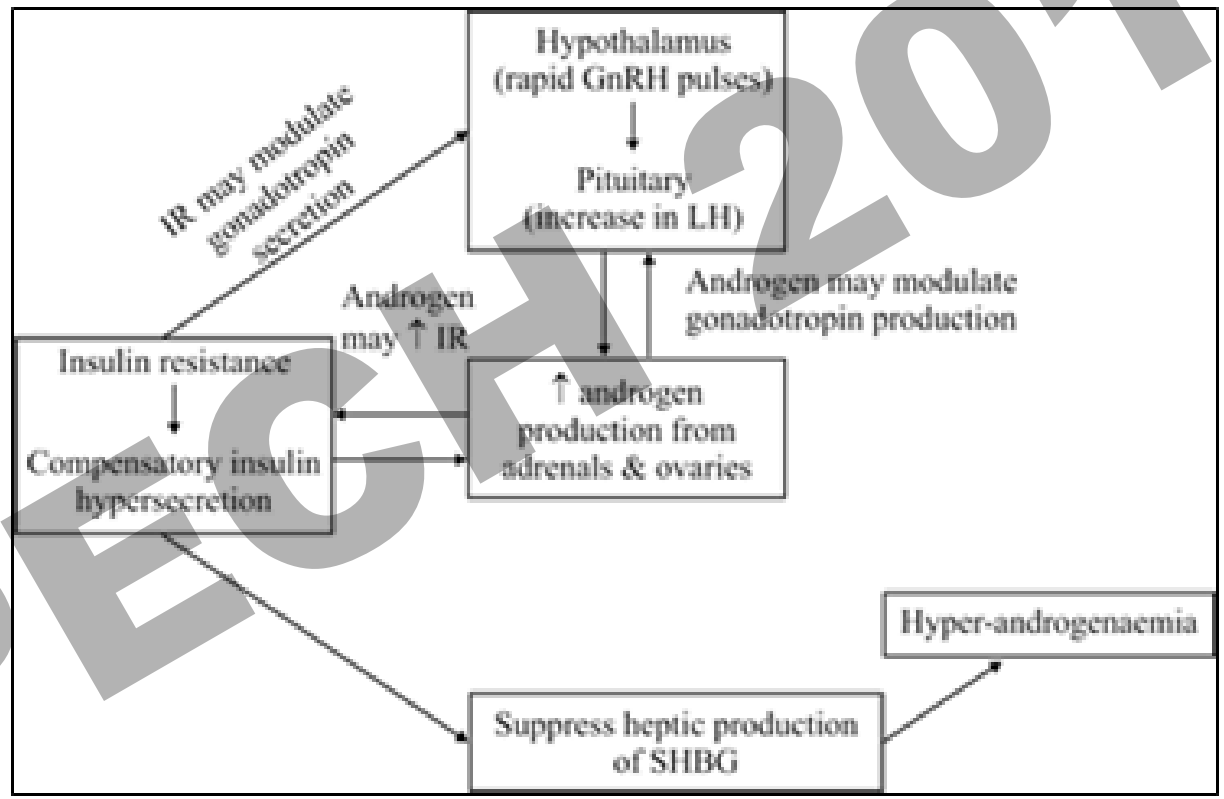
Nestler JE, et al. *J Clin Endocrinol Metab.* 1998;83:2001-2005.

Az inzulin hatása a GnRh szekrécióra



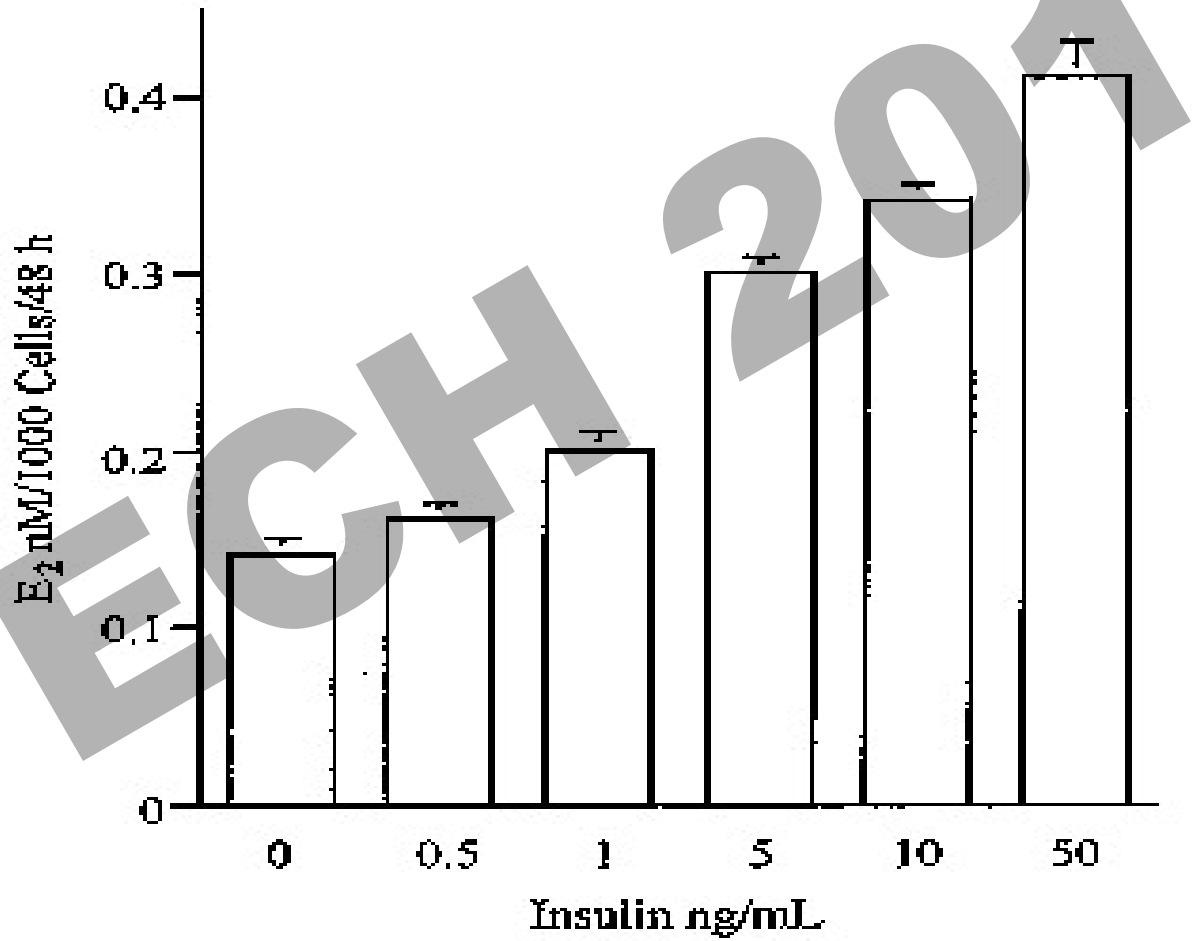
Vaijinath Biradar, Sangeeta Tengli. Myoinositol in PCOS. Journal of Evidence based Medicine and Healthcare; Volume 1, Issue 15, December 15, 2014; Page: 1927-1936.

Az inzulin hatása a GnRh és gonadotropin szekrécióra



Vaijinath Biradar, Sangeeta Tengli. Myoinositol in PCOS. Journal of Evidence based Medicine and Healthcare; Volume 1, Issue 15, December 15, 2014; Page: 1927-1936.

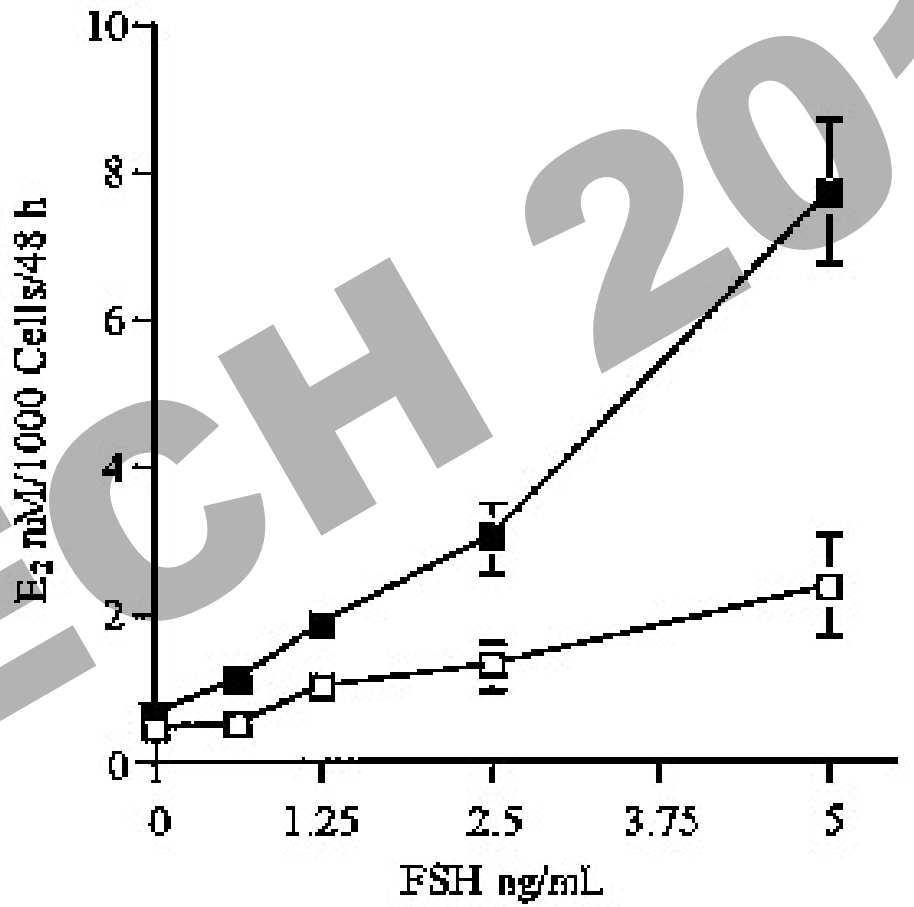
Estradiol (E2) response to insulin in granulosa cells from an 8-mm follicle from a normal ovary



Modulation by insulin of follicle-stimulating hormone and luteinizing hormone actions in human granulosa cells of normal and polycystic ovaries.

Willis D[1], Mason H, Gilling-Smith C, Franks S. ; J Clin Endocrinol Metab. 1996 Jan;81(1):302-9.

Effect of insulin on FSH-induced E2 production in granulosa cells from follicles < 10 mm and anovPCO. Open square = no insulin; and solid square = + insulin



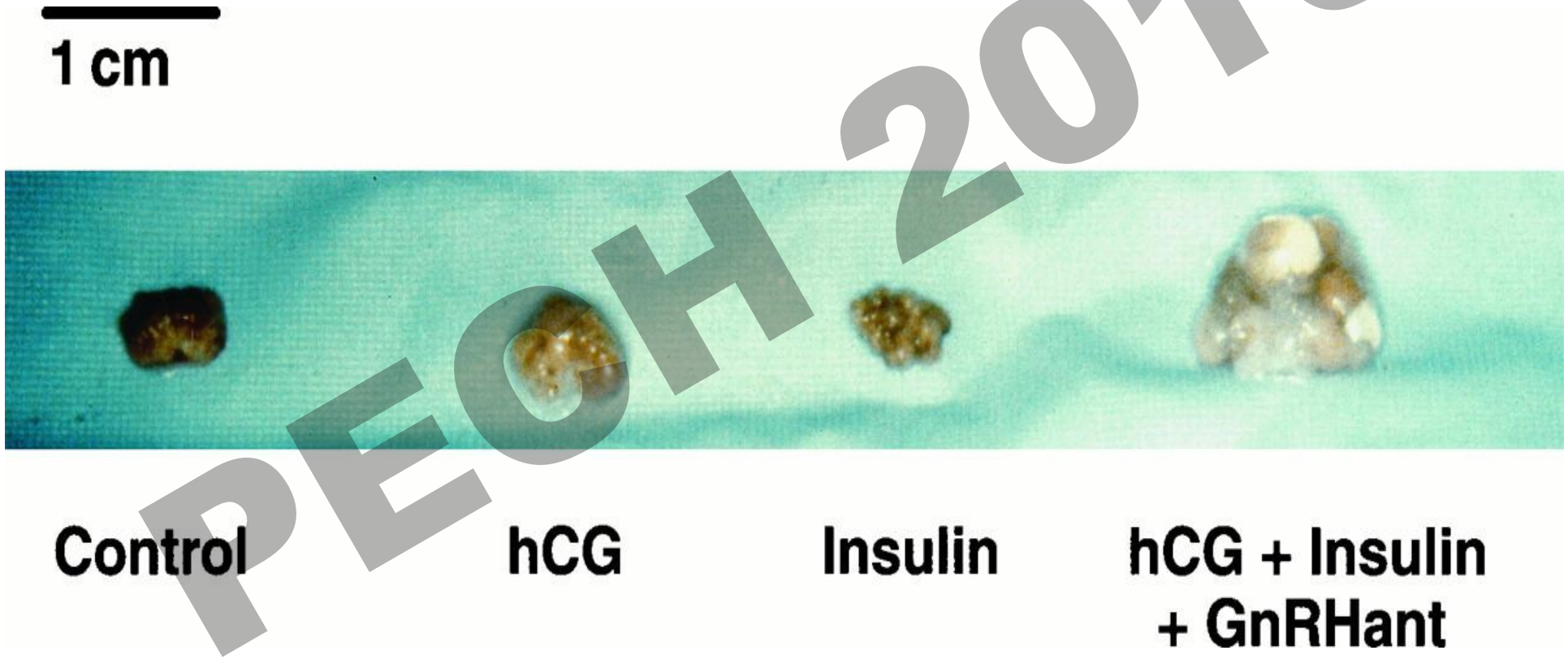
Modulation by insulin of follicle-stimulating hormone and luteinizing hormone actions in human granulosa cells of normal and polycystic ovaries.
Willis D[1], Mason H, Gilling-Smith C, Franks S. ; J Clin Endocrinol Metab. 1996 Jan;81(1):302-9.

Az inzulin petefészek működést befolyásoló hatásai

Közvetlenül stimulálja a steroidogenesist	Ovárium
Stimulálja a 17-hydroxylase-t	Ovárium
Stimulálja, vagy gátolja az aromatázt	Ovárium és zsírszövet
Növeli az LH receptorok számát	Ovárium
Serkenti az ováriumok növekedését, a cisztaképzést synergistaként az LH/hCG- vel	Ovárium
Növeli az IGF-1 receptorok számát	Ovárium
Gátolja az IGFBP-1 termelést	Ovárium és máj
Gátolja az SHBG termelést	Máj
Fokozza a GnRH hatását az LH/FSH szekrécióra	Hypothalamus/hypophysis

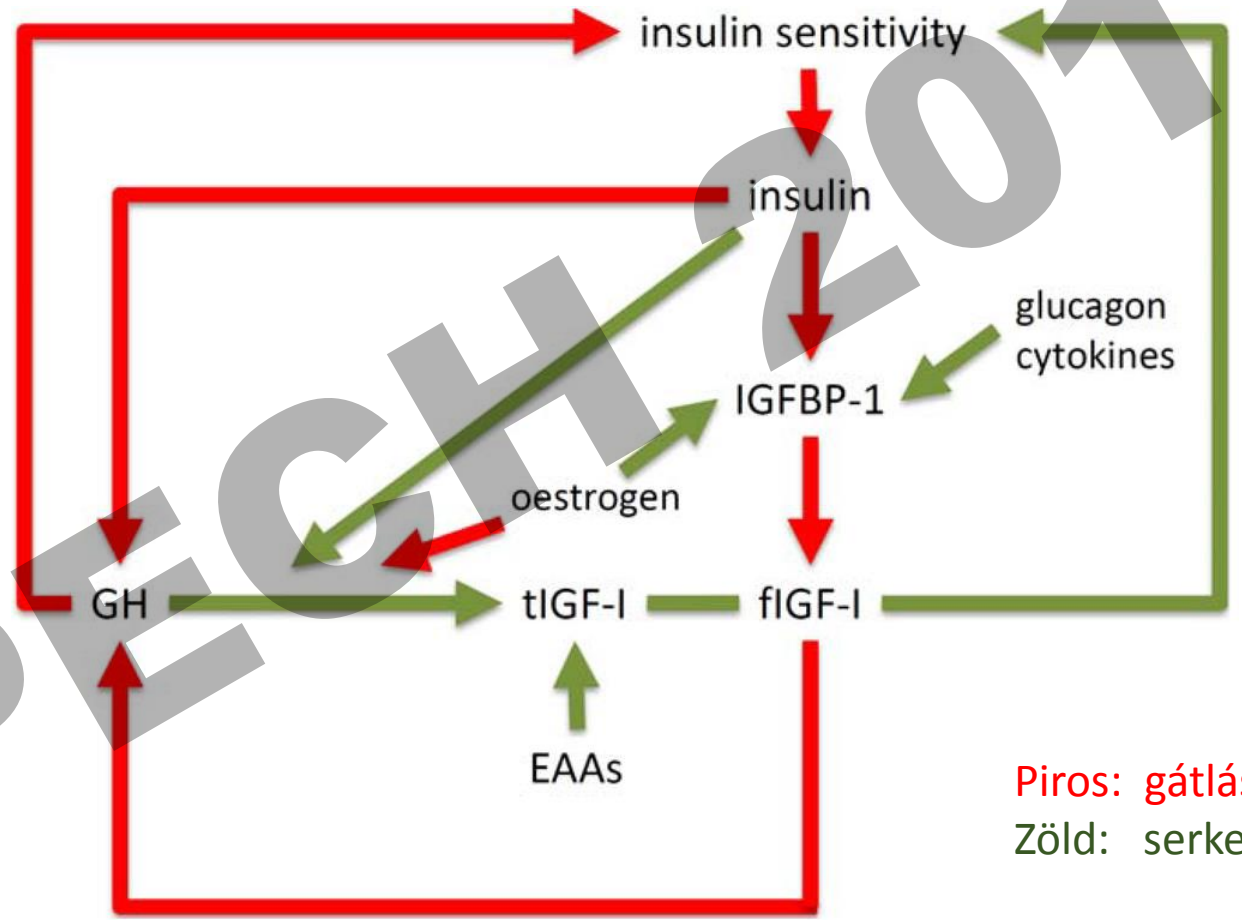
The Insulin-Related Ovarian Regulatory System in Health and Disease LEONID PORETSKY
Endocrine Reviews 20(4): 535–582

Inzulin hatása patkány ováriumon



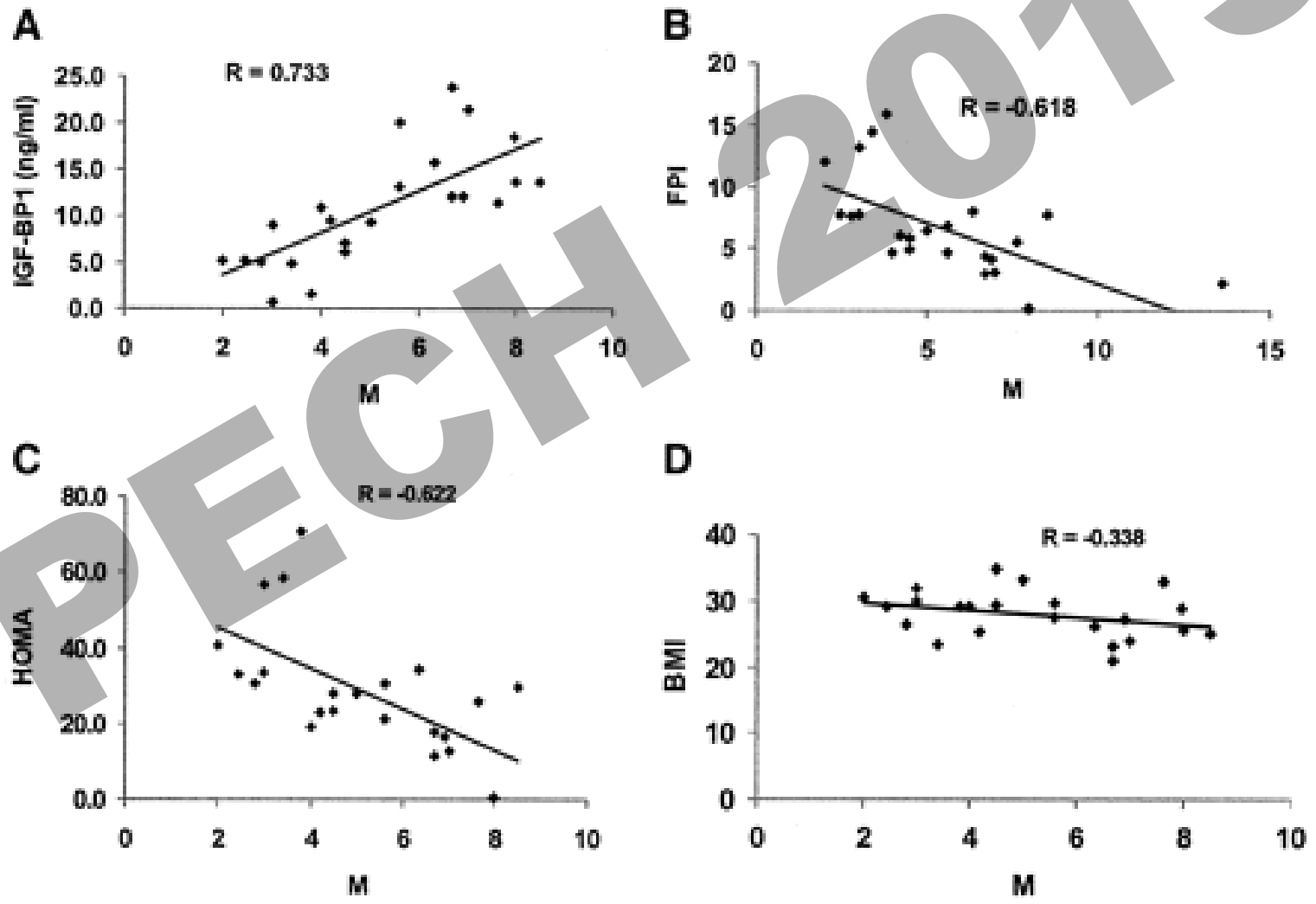
The Insulin-Related Ovarian Regulatory System in Health and Disease LEONID PORETSKY
Endocrine Reviews 20(4): 535–582

Az inzulin és IGF-1 rendszer összefüggései



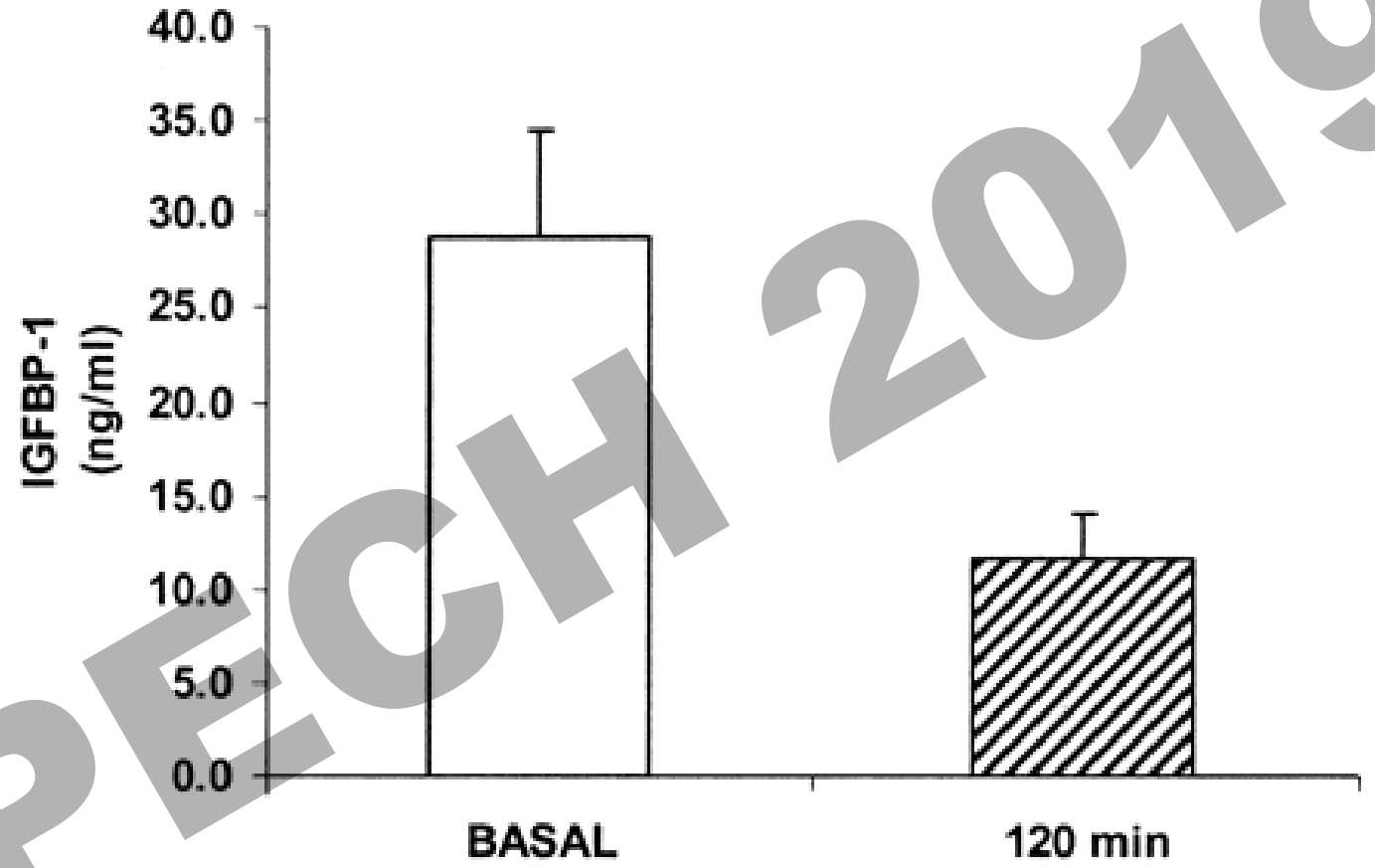
Piros: gátlás/csökkentés
Zöld: serkentés/emelés

IGF-Binding Protein-1 Levels Are Related to Insulin-Mediated Glucose Disposal and Are a Potential Serum Marker of Insulin Resistance



RESEARCH DESIGN AND METHODS:
Twenty-three subjects underwent a euglycemic insulin clamp. Glucose disposal rates (M) were then correlated with measurements of IGFBP-1, fasting insulin levels, homeostasis model assessment (HOMA), and BMI.
RESULTS:
IGFBP-1 levels more strongly correlated with M (R = 0.73) than the other parameters such as BMI or HOMA. The level of this protein decreased in individuals who became more insulin sensitive by exercise training.
CONCLUSIONS:
These studies show a strong correlation between insulin sensitivity and the serum levels of IGFBP-1.

Effect of hyperinsulinemia on IGFBP-1 levels



Insulin-sensitive subjects (*n* = 11) were given oral glucose to increase insulin levels. IGFBP-1 levels were measured at basal and 120 min after glucose administration ($P < 0.01$ initial vs. 120 min). □, basal; ▒, 120 min.

The regulation of insulin-like growth factor binding protein (IGFBP)-1 during prolonged fasting

Cotterill AM[1], Holly JM, Wass JA.

OBJECTIVE:

Insulin-like growth factor binding protein (IGFBP)-1 levels increase overnight, being inversely related to changes in insulin. With prolonged fasting IGFBP-1 levels increase further. In animal studies high IGFBP-1 levels increase plasma glucose levels possibly by regulating the insulin-like actions of 'bio-available' plasma IGF. Following prolonged fasting, there is an increase in insulin requirement. A proportion of this reversible insulin resistance may be due to inhibitory effects of high IGFBP-1 levels on IGF action. This study examined the regulation of IGFBP-1 in the presence of reversible insulin resistance.

SUBJECTS: Nine normal adult volunteers, seven female and two male (mean age 27.6 +/- SD 2.6 years, range 21.7-46.0 years) of normal body mass index were studied.

METHODS: Subjects fasted from 2200 h day 0 to 0900 h day 3 (59 hours), the fast being completed with a 75-g glucose meal. At least one week later, an 11-hour overnight fast was performed, followed by a repeat glucose meal. Blood samples were taken at regular intervals from 0900 h day 1 and for 5 hours during both glucose meal studies via an indwelling cannula.

MEASUREMENTS: Serum levels of IGFBP-1, insulin, GH, glucose, IGF-I and cortisol were measured at varying intervals during the fast and both glucose meal studies.

RESULTS:

Following the initial 11-hour overnight fast IGFBP-1 levels rose from (mean +/- SEM) 32 +/- 5 micrograms/l to reach a maximum of 144 +/- 24 micrograms/l after 32 hours of fasting. IGFBP-1 levels then fluctuated, falling in the morning (93 +/- 8 micrograms/l) and then rising overnight (126 +/- 9 micrograms/l), but not regaining the initial peak levels. The increase of IGFBP-1 from overnight fasting levels was associated with a fall in plasma insulin from 5.7 +/- 0.7 to 2.2 +/- 0.2 mU/l. In comparison, 30 minutes after termination of the fast with the glucose meal, IGFBP-1 levels fell from 120 +/- 11 to 24 +/- 2 micrograms/l within 4 hours. After an overnight fast IGFBP-1 levels fell from 35 +/- 5 to 13 +/- 2 micrograms/l within 3 hours. There was glucose intolerance and increased insulin levels following the glucose meal preceded by the 59-hour fast when compared with the overnight fast. The fall of IGFBP-1 levels after the glucose meal was best expressed, taking into account subject variation, by the following regression equations: Glucose meal preceded by 11-hour fast: log [IGFBP-1] = 1.64-0.255 log [1 h previous insulin] (R2 0.51); Glucose meal preceded by 59-hour fast: log [IGFBP-1] = 1.41-0.265 log [1 h previous insulin] + 0.557 log [current glucose] (R2 0.82).

CONCLUSION:

In man, insulin appears to regulate circulating IGFBP-1 levels in all circumstances, this regulation being unaffected by the resistance to insulin action induced by prolonged fasting. The high IGFBP-1 levels were statistically related to the higher glucose levels and may have directly contributed to the increased insulin requirement observed after prolonged fasting.

IGF-1 mint lokális parakrin szabályozó faktor

Follicular Fluid Insulin-like Growth Factor-I and Insulin-like Growth Factor–Binding Protein-1 and -3 Vary as a Function of Ovarian Reserve and Ovarian Stimulation; J Assist Reprod Genet. 1998 Nov; 15(10): 587–593

Laurel Stadtmauer,[1,2] Andrea Vidali,[1] Steven R. Lindheim,[1] and Mark V. Sauer[1]

Abstract

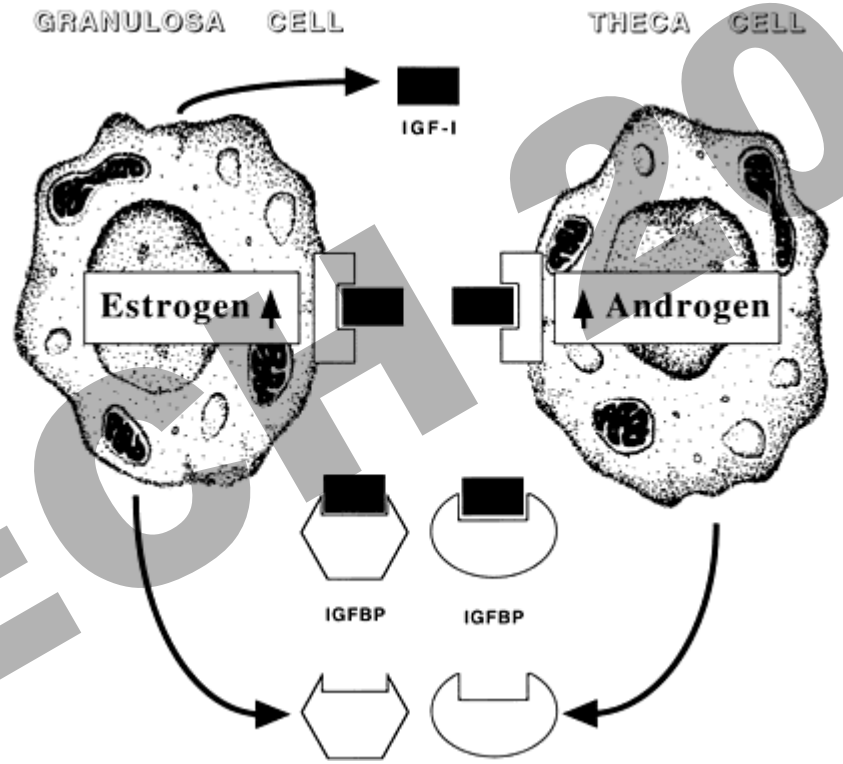
Purpose:*Follicular fluid concentrations of insulin-like growth factor (IGF)-I, IGF-II, IGF-binding protein (BP)-1, and IGFBP-3 in 57 women undergoing in vitro fertilization and embryo transfer were examined to determine whether levels reflected differences in patients' exposure to gonadotropin stimulation and a diminished ovarian reserve.*

Methods:*Preovulatory follicular fluid was obtained from both gonadotropin-stimulated and unstimulated cycles. Subjects were grouped according to normal or decreased ovarian reserve and whether or not they received gonadotropin stimulation.*

Results:*The mean follicular fluid concentrations of IGF-I and IGFBP-1 were significantly lower in the "decreased" ovarian reserve group compared with the "normal" ovarian reserve group, with no change in estradiol or IGF-II levels.* *This resulted in a decreased molar IGF-I: BP ratio and an increased molar IGF-II:IGFBP-1 ratio. In unstimulated cycles, mean follicular fluid concentrations of IGFs did not differ significantly compared with those in stimulated cycles, whereas concentrations of IGFBP-1 and IGFBP-3 were significantly lower, leading to higher molar ratios of the IGFs to the binding proteins.*

Conclusions:*Follicular fluid IGF and binding proteins vary as a function of ovarian reserve and gonadotropin stimulation. This may reflect either differences in oocyte quality or a suboptimal follicular fluid environment.*

The intraovarian insulin-like growth factor-I system



Evron, A, Blumenfeld, Z, *et al*, *Glob. libr. women's med.*, *(ISSN: 1756-2228)* 2015; DOI 10.3843/GLOWM.10288
This chapter was last updated: March 2015

Az IGF-1és IGF-2 ovarialis hatásai

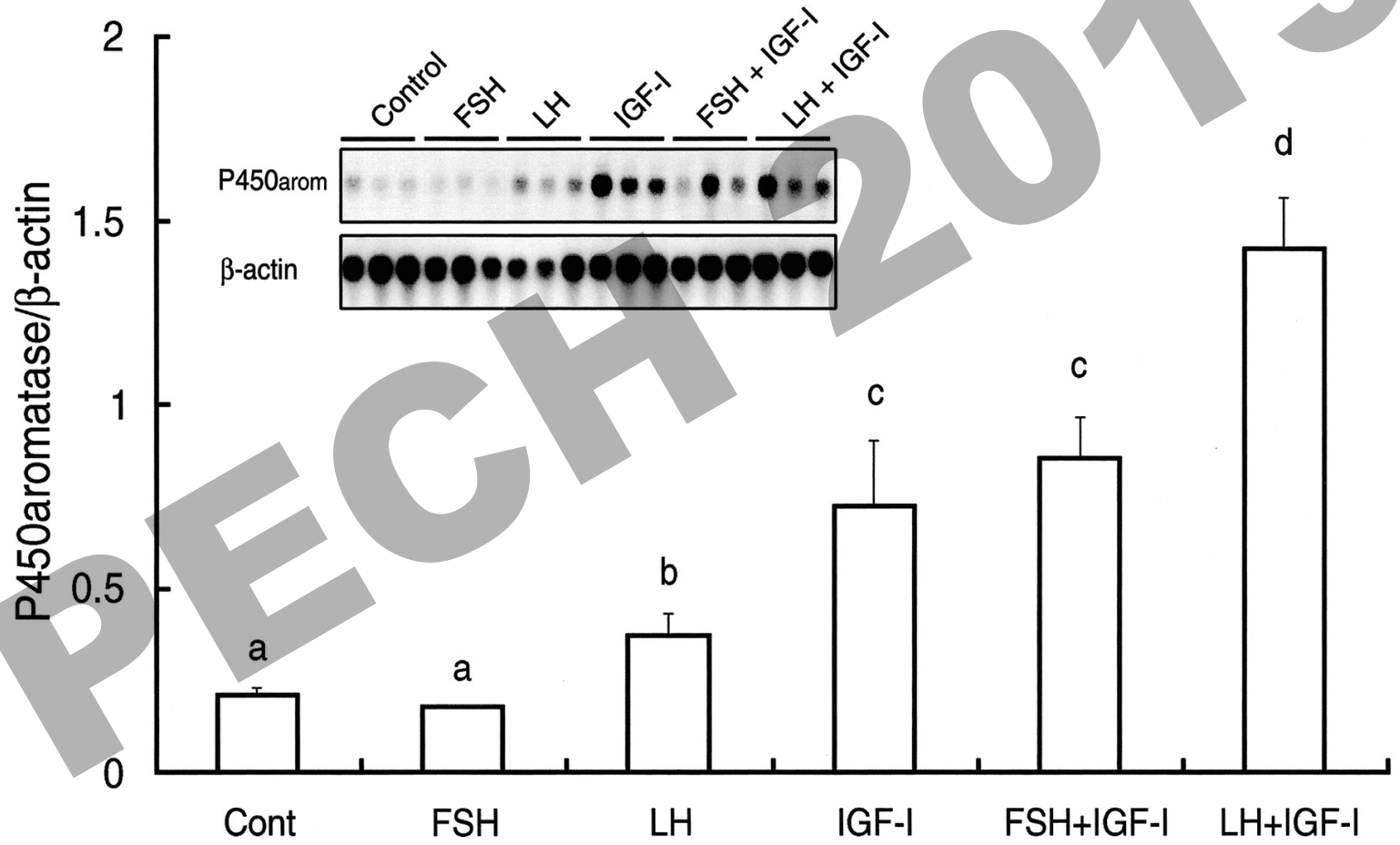
Table 2 Ovarian actions of IGF-I and IGF-II in humans

Granulosa (granulosa/luteal) cells *Promotes:*	*Theca cells/explants* *Promotes:*	*Follicles* *Promotes:*
Aromatase activity and mRNA	Androstenedione production	Oocyte maturation?
Basal E_2 and P secretion	Testosterone production	
FSH-stimulated E_2 and P secretion	DNA synthesis	
DNA synthesis		
Cellular proliferation		
IGFBP-4 proteolysis		
IGFBP-5 production		
?IGFBP-2 proteolysis		
Inhibits:		
IGFBP-1, IGFBP-2 production		

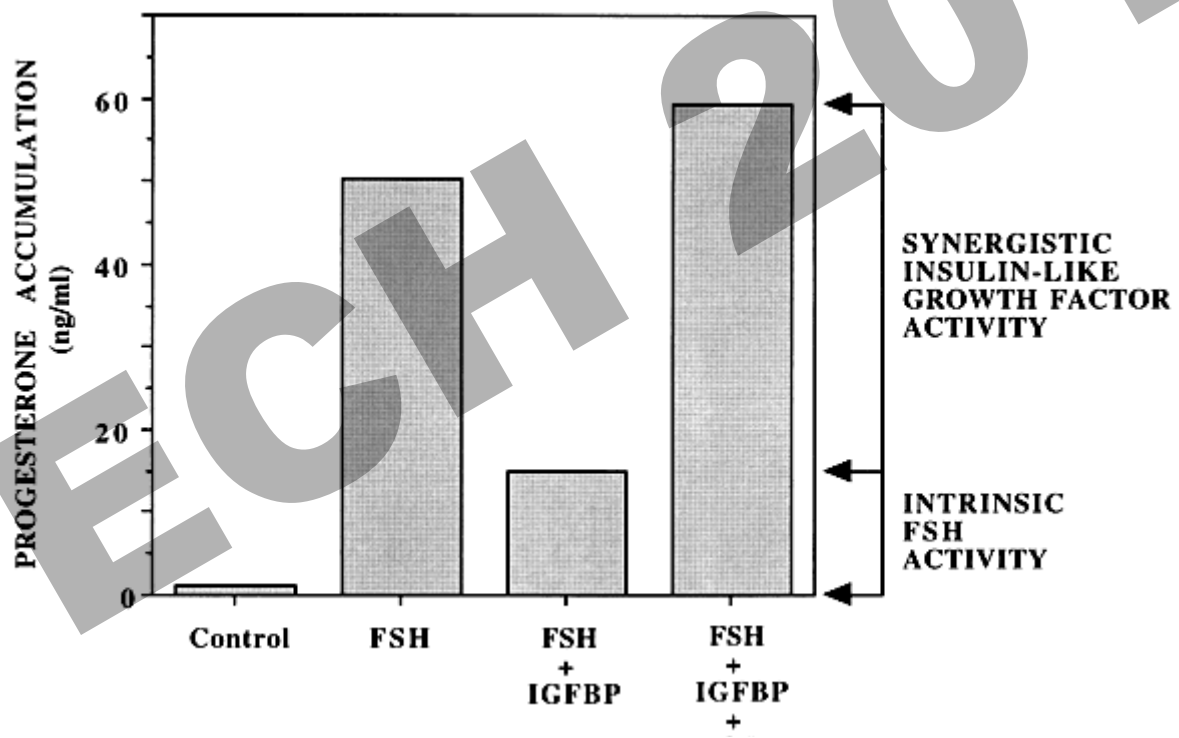
From Poretsky *et al*,[7] with permission.

The Insulin-Related Ovarian Regulatory System in Health and Disease LEONID PORETSKY
Endocrine Reviews 20(4): 535–582

Ovarialis aromatáz aktivitás FSH, LH, IGF-1 hatására

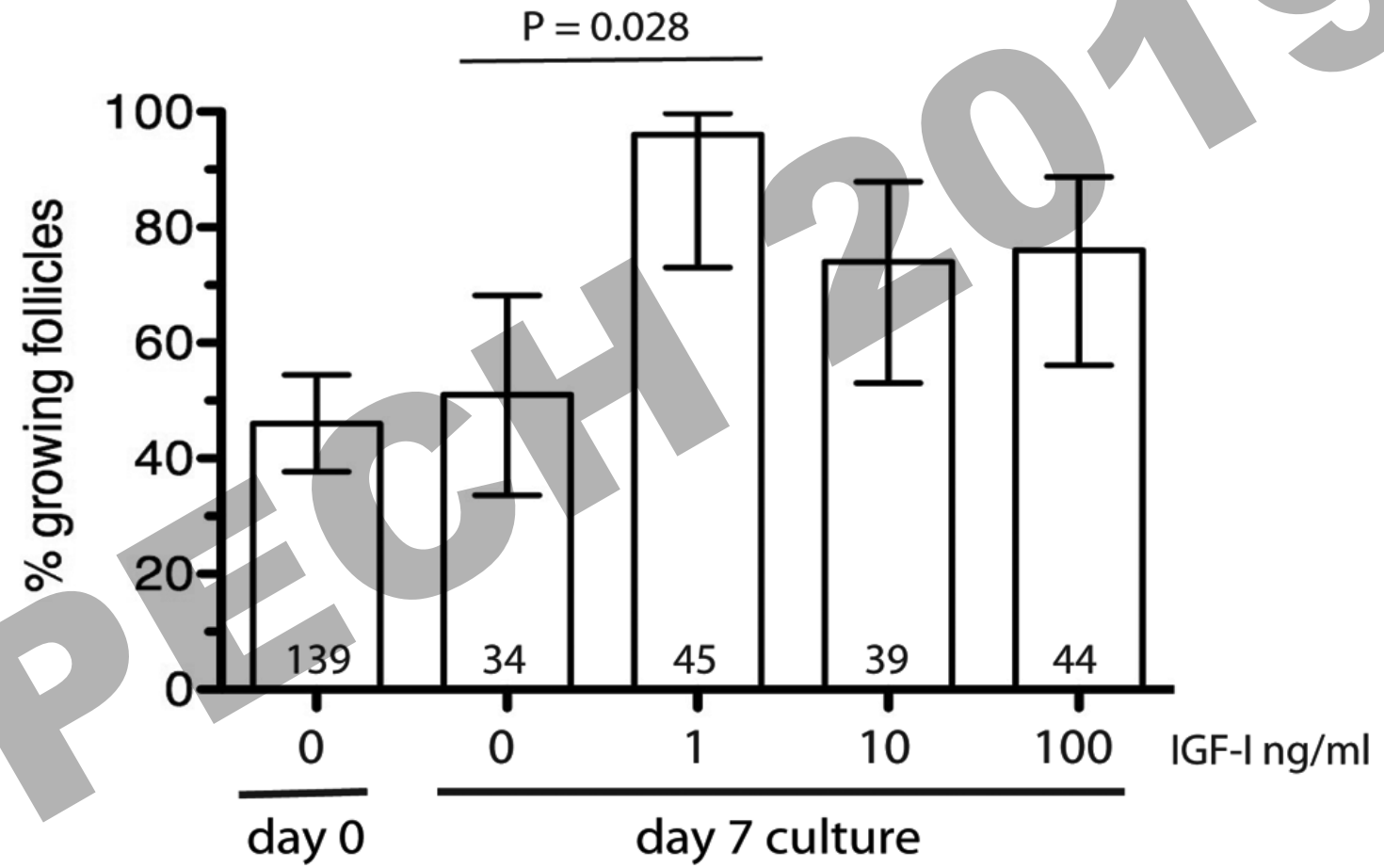


Enhancing effect of insulin-like growth factor-1 on follicle-stimulating hormone-stimulated progesterone accumulation



Evron, A, Blumenfeld, Z, *et al*, *Glob. libr. women's med.*, *(ISSN: 1756-2228)* 2015; DOI 10.3843/GLOWM.10288
This chapter was last updated: March 2015

Effect of IGF-1 on initiation of follicle development. Bars show the mean percentage of healthy growing follicles (with 95% confidence interval) in samples of normal human ovary cortex



Addition of IGF-1 at 1 ng/mL to the culture media significantly increased the proportion of growing follicles compared with samples cultured in the absence of IGF-1. There was no further increase with the addition of higher doses of IGF-1, but the overall difference in response to varying doses of IGF-1 was significant (*P* = .047). Numbers in the bars indicate the total number of follicles analyzed in each group.

Role of Insulin-like Growth Factors in Initiation of Follicle Growth in Normal and Polycystic Human Ovaries Sharron A. Stubbs, Lisa J. Webber, Jaroslav Stark, Suman Rice, Raul Margara, Stuart Lavery, Geoffrey H. Trew, Kate Hardy, and Stephen Franks ; J Clin Endocrinol Metab, August 2013, 98(8):3298 –3305

A follikuláris folyadék IGF-1 koncentráció összefüggése az embryo minőséggel

Parameter (rate %)	High FF IGF-1 (*n*=60) (>59.25 ng/mg protein)	Low FF IGF-1 (*n*=60) (≤59.25 ng/mg protein)	*P* value
Mean age (years)	32.81±3.83	31.77±4.51	0.14 NS
FF E2 (pg/ml)	284631±15486	189972±67400	0.0411*
Total number of eggs retrieved	378	372	NS
Fertilization (no.) %	(313) 82.80±17.65	(292) 78.49±19.49	0.0320*
Cleavage (no.) %	(297) 78.57±17.82	(259) 69.62±19.77	0.0010**
Blastocyst formation (no.) %	(169) 44.71±15.13	(70) 18.82±2.75	<0.0001***
Top/grade 1 embryos (%)	61.19±23.08	25.19±10.29	<0.0001***
Average/Grade 2 embryos (%)	26.19±18.67	40.00±19.54	0.0060**
Poor/Grade 3 embryos (%)	12.69±9.14	34.81±23.76	0.0007***
Total no. of embryos transferred (D3+D5/6)	125 (68+57)	126 (108+18)	NS
Mean no. of embryos transferred	2.08	2.1	NS
Clinical pregnancy rate (no.) %	(23/60) 38.33	(12/60) 20.00	0.0272*
Twin pregnancies (no.) %	(4/23) 17.39	(1/12) 8.33	0.4819 NS
Implantation rate (no.) %	(27/125) 21.6	(13/126) 10.32	0.0152*

All values are represented as mean±SD statistical significance was obtained by student's *t* test. *P*<0.05*=Significant;<0.01**=Highly significant;<0.0001***=Extremely significant; NS=Non-significant; n=Number of patients; E2=Total estradiol levels. D3 represents cleavage stage embryos which were graded by Veeck's criteria on the basis of blastomere size/shape/eveness and % fragmentation. D5/6 represents blastocyst stage embryos that were graded as per Gardner grading system. Embryos meeting the maximum positive criteria of morphological evaluation were considered top/grade 1 followed by average/grade 2 and poor/grade 3. Implantation rate=Total no. of gestational sacs×100/total no. of embryos transferred. IGF-1=Follicular fluid insulin like growth factor-1; FF=Follicular fluid

Follicular fluid insulin like growth factor-1 (FF IGF-1) is a biochemical marker of embryo quality and implantation rates in *in vitro* fertilization cycles
Bindu N Mehta, Natachandra M Chimote,[1] Meena N Chimote,[2] Nishad N Chimote,[3] and Nirmalendu M Nath[4]
J Hum Reprod Sci. 2013 Apr-Jun; 6(2): 140–146.

Follikulus folyadék IGF-1 szint vs. embrió minőség, terhesség

FF IGF-1 (ng/mg protein)	Embryo quality	Clinical pregnancy
Pearson *r* (95% CI)	0.3894 (0.23-0.53)	0.5972 (0.48-0.70)
P value	<0.0001***	<0.0001***
R^2	0.1516	0.36

Pearson *r* correlation coefficient was obtained. *P*<0.0001***extremely significant;
FF IGF-1=Follicular fluid insulin like growth factor-1; CI=Confidence interval

Follicular fluid insulin like growth factor-1 (FF IGF-1) is a biochemical marker of embryo quality and implantation rates in *in vitro* fertilization cycles
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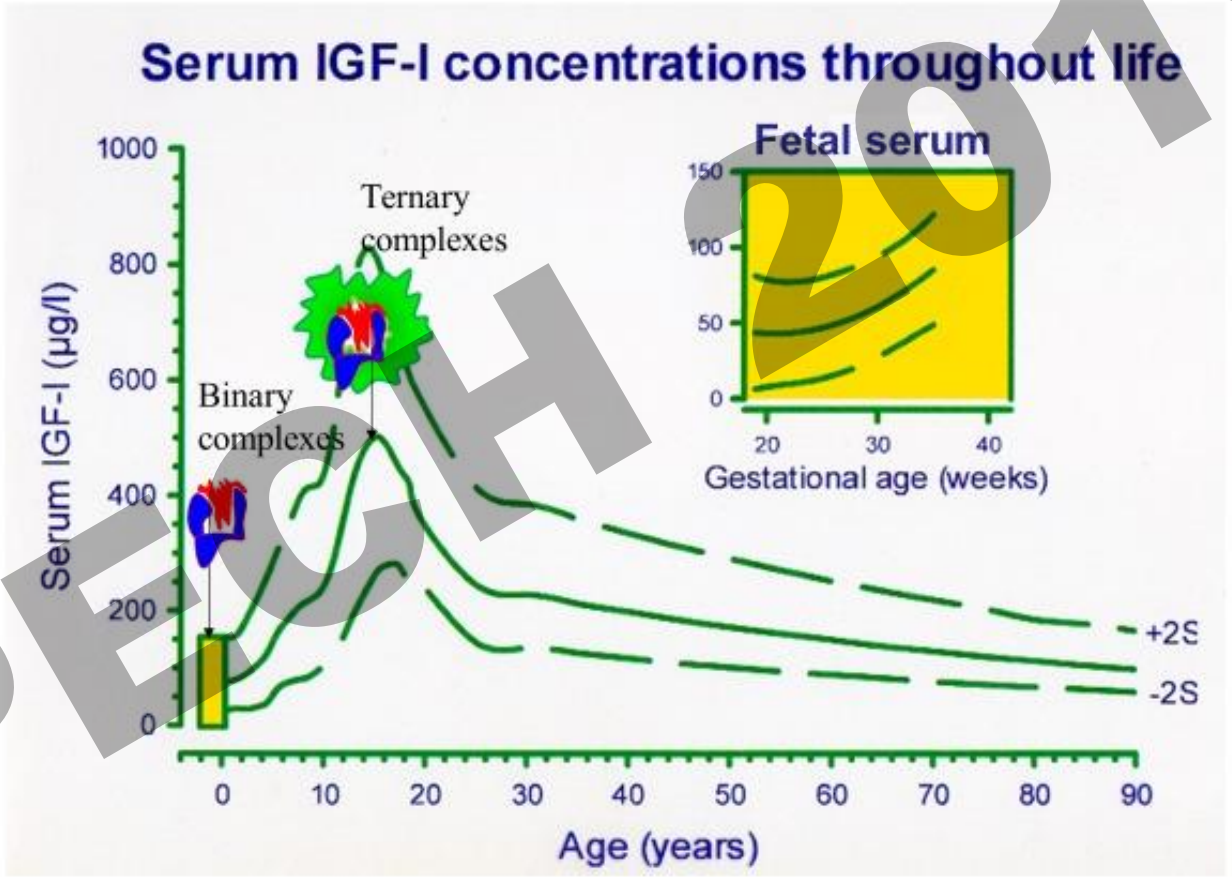
Effect of supplementation of SCF and/or IGF-1 in preantral follicle culture *in vitro*

Variable	None	SCF	IGF-1	SCF + IGF-1
No. of mice	3	3	3	3
No. of preantral follicles isolated	60	60	60	60
No. of follicles survived at day 9-11 (% per isolated)	46 (76.7)	43 (71.7)	48 (80.0)	49 (81.7)
No. of follicles with antrum formation	35	35	45	46
% per survived	76.1[a]	81.4	93.8	93.9[a]
% per isolated	58.3	58.3	75	76.7
No. of oocyte (% per antral follicle)	35	35	45	46
Degenerated	10	8	11	7
GV	8	10	7	11
GVBD	10	15	16	14
MII	7	2	11	14
% per total oocyte	20	5.7[a]	24.4	30.4[a]
% per isolated follicle	11.7	3.3	18.3	23.3
MII derived from GV	0	1	0	0
MII derived from GVBD	3	3	2	4
Final no. of MII oocyte	10	6	13	18
% per total oocyte	28.6	17.1	28.9	39.1
% per isolated follicle	16.7	10	21.7	30

Effects of hCG, stem cell factor (SCF), and/or insulin-like growth factor (IGF) supplementation in growth medium were investigated.

A szérum IGF-1 koncentráció változása az életkor előrehaladtával



Pediatric Implications of Normal Insulin-GH-IGF-Axis Physiology
Peter Bang, MD, PhD, MSci.

Improved controlled ovarian hyperstimulation in poor responder in vitro fertilization patients with a microdose follicle-stimulating hormone flare, growth hormone protocol

M.D. William Schoolcraft..A. Terry Schlenker. Author links open the author workspace.B.S. Marsha Gee.
B.S. John Stevens..M.S. Lyla Wagley.
The Center for Reproductive Medicine, Englewood, Colorado, USA

Objective:
To assess the efficacy of a novel protocol-microdose GnRH agonist (GnRH-a), FSH, and GH, for the stimulation of IVF patients who were canceled previously on a standard luteal GnRH-a, FSH, GH protocol.

Design:
Prospective evaluation using the patient's previous IVF stimulation attempt as historic controls.

Participant(s):
Thirty-two patients who had prior ovulation induction cycles canceled using luteal phase GnRH-a suppression followed by exogenous gonadotropins and GH.

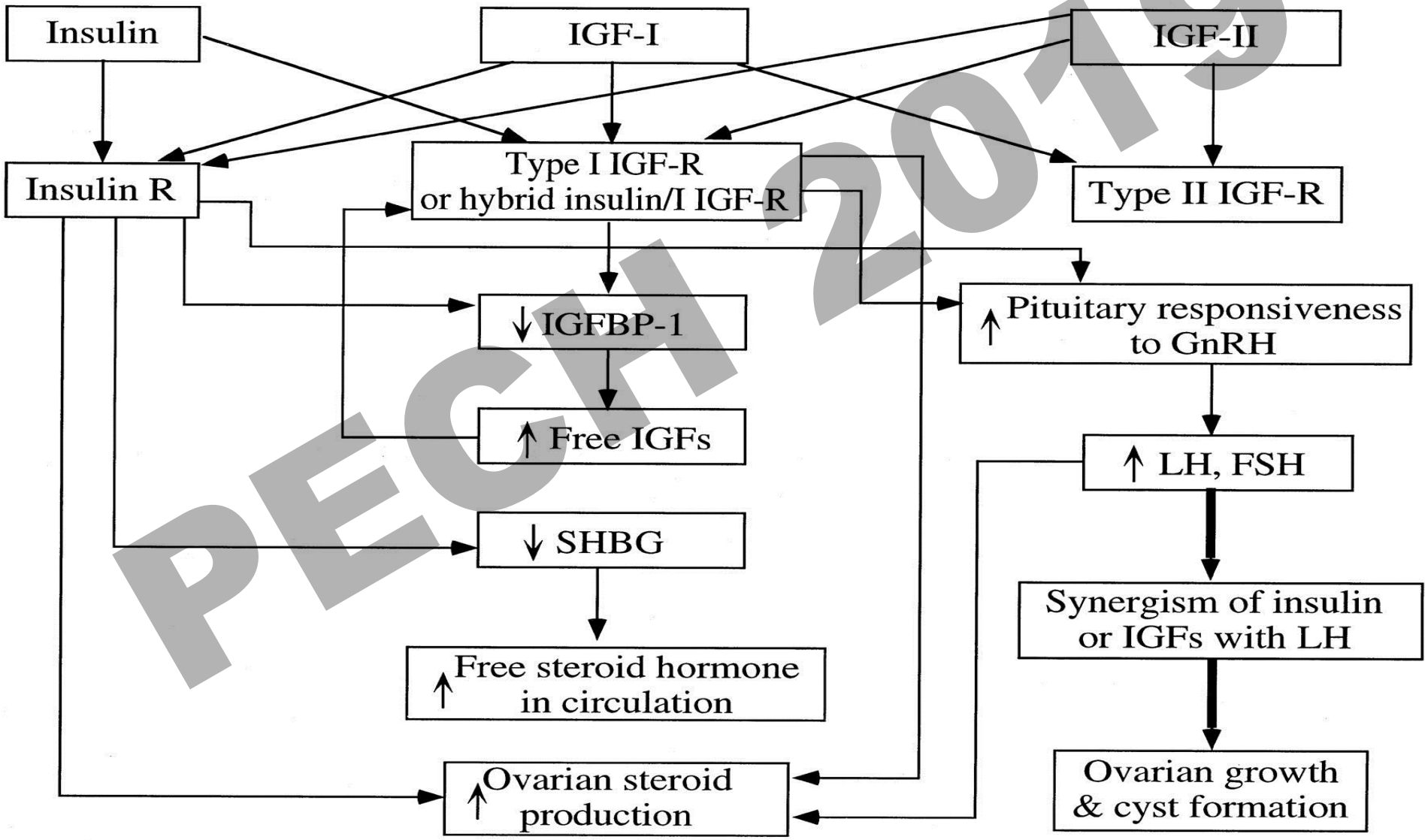
Intervention(s):
Precycle treatment with oral contraceptives followed by follicular phase administration of 40 μg leuprolide acetate every 12 hours beginning on cycle day 3 and FSH supplemented with GH beginning on cycle day 5.

Main Outcome Measure(s):
Paired analysis of E_2 day 5, number of follicles, ampules of FSH required, and cancellation rate. The number of oocytes, embryos, embryo quality, implantation rate, and pregnancy rate (PR) were determined for completed cycles on the microdose GnRH-a, FSH, GH protocol.

Result(s):
Controlled ovarian hyperstimulation was superior during microdose GnRH-a, FSH, GH stimulation when compared with the prior luteal GnRH-a cycle. Specifically, there was a higher E_2 response, more oocytes, fewer cycle cancellations, and no premature LH surge or luteinization. The microdose GnRH-a, FSH, GH protocol produced an average of 10 oocytes and a 50% ongoing PR.

Conclusion(s):
The microdose GnRH-a, FSH, GH protocol is superior to standard protocols for the treatment of patients with decreased ovarian reserve undergoing controlled ovarian hyperstimulation for IVF.

A keringő inzulin/IGF-1 hormonrendszert érintő hatásai



PCOS vs. kontroll egyének anyagcsere és hormonális paraméterei

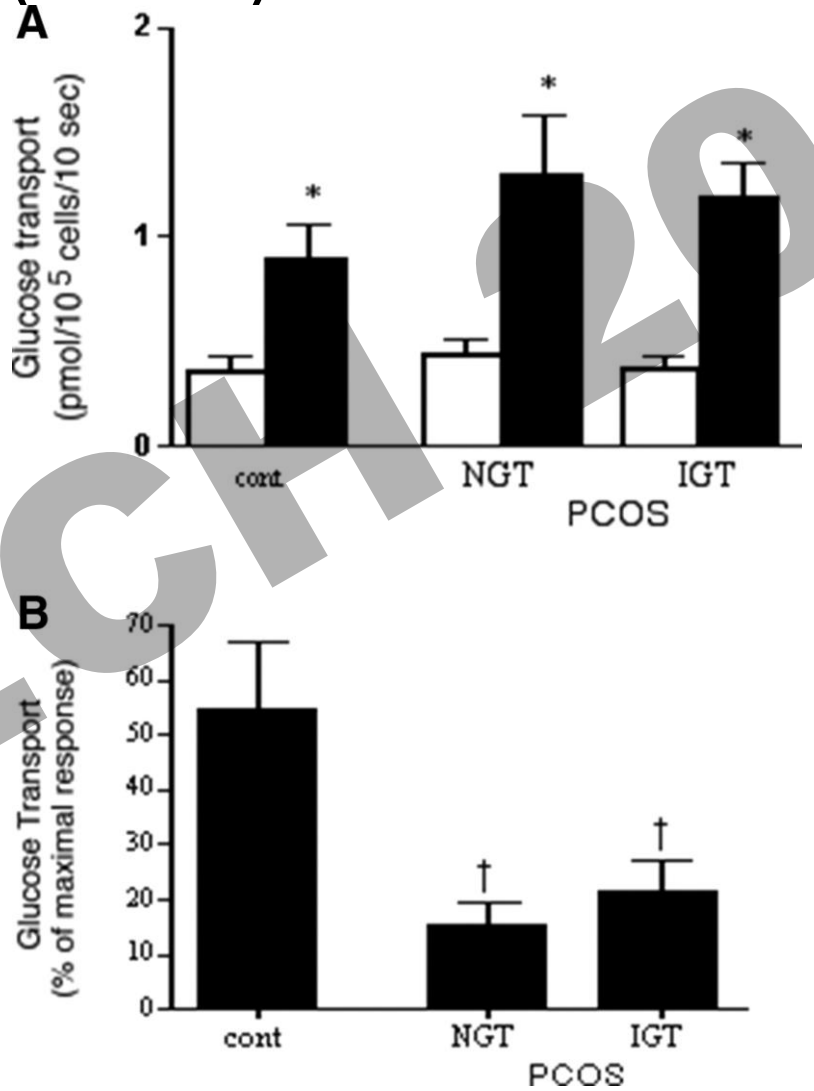
	PCOS (n = 50)	Control (n = 50)	*P*-value
Age (years)	23 ± 5	22 ± 4	0.185
Body mass index (kg/m^2)	20.4 ± 1.6	20.5 ± 1.8	0.785
Percentage of fat (%)	30.6 ± 4.4	31.1 ± 3.9	0.576
Fat mass (kg)	16.4 ± 3.1	16.9 ± 3.2	0.759
Sex hormone-binding globulin (nmol/l)	59.9 ± 20.2	101.8 ± 42.8	<0.001
Total testosterone (ng/dl)	84.7 ± 17.2	43.2 ± 13.8	0.094
Free testosterone (ng/dl)	1.07 ± 0.32	0.37 ± 0.16	<0.001
Free androgen index	5.5 ± 2.1	1.7 ± 0.8	<0.001
Fasting glucose (mg/dL)	84 ± 7	84 ± 6	0.951
Post-load 2-h glucose (mg/dL)	94 ± 12	91 ± 18	0.311
Fasting insulin (mIU/L)	5.70 (1.81–8.03)	3.41 (0.14–6.75)	0.066
Post-load 2-h insulin (mIU/L)	28.65 (17.71–47.25)	19.82 (11.06–30.46)	0.007
HOMA-IR	1.17 (0.38–1.58)	0.74 (0.03–1.36)	0.091
HOMA-M$_{120}$	6.95 (3.60–10.73)	4.44 (2.31–7.29)	0.005
ISI-Stumvoll (μmol/kg. min). (pmol/L)$^{-1}$	0.106 (0.095–0.114)	0.113 (0.103–0.123)	0.010
HOMA-F (mIU/mmol)	95.34 (21.09–148.99)	68.70 (2.07–121.70)	0.097
Ovarian volume (cm^3)	9.4 ± 3.6	4.6 ± 1.4	<0.001
Ovarian follicle no.	9.7 ± 2.7	6.1 ± 1.7	0.001

Plus-minus values are mean ± SD.

Values before parentheses are medians, and values in parentheses are interquartile ranges. PCOS, polycystic ovary syndrome; HOMA-IR, homeostasis model assessment of insulin resistance; ISI, insulin sensitivity index; HOMA-F, homeostasis model assessment β-cell function.

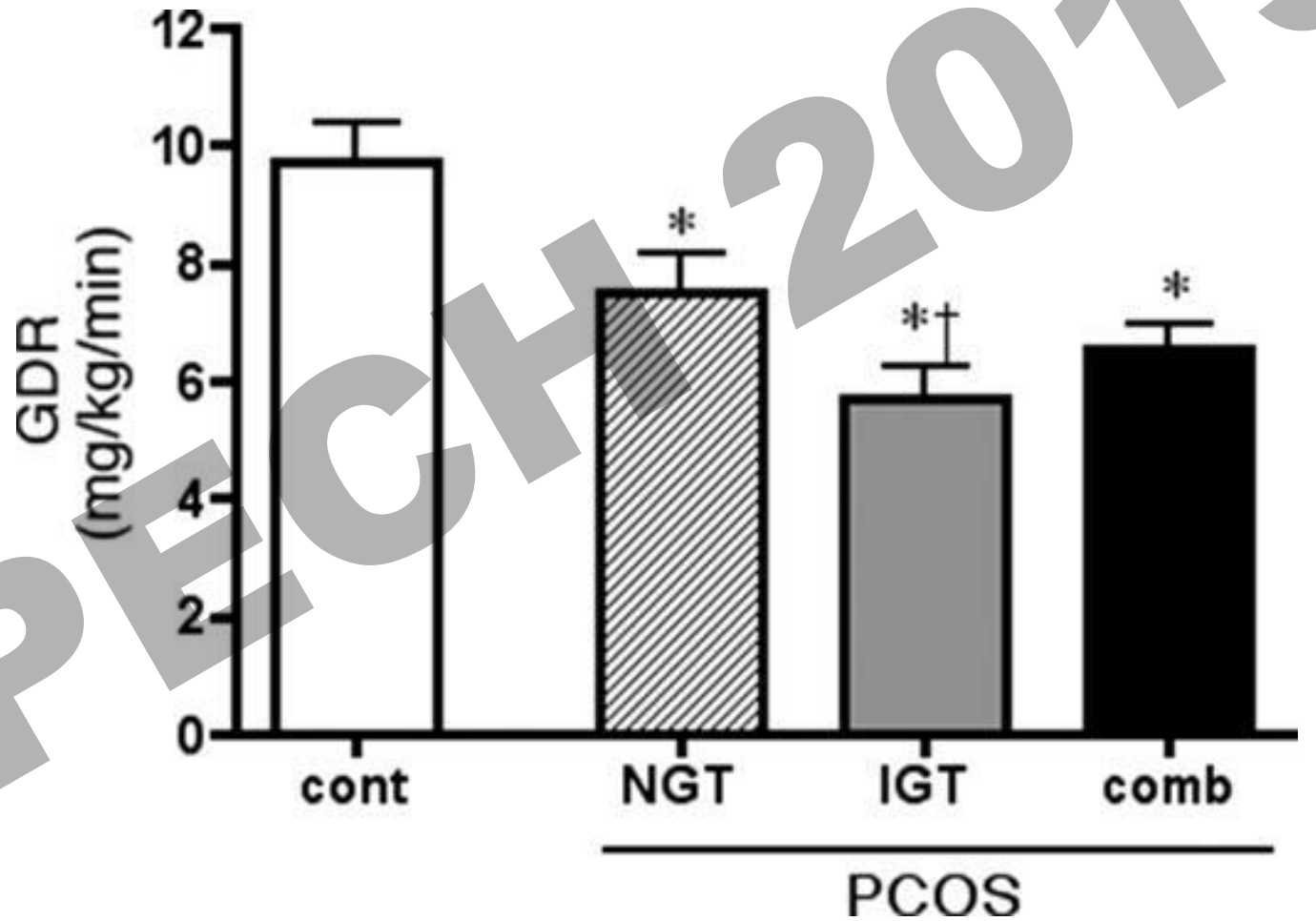
https://doi.org/10.1371/journal.pone.0178120.t002

Glucose transport in adipocytes isolated from control (cont) and PCOS subjects

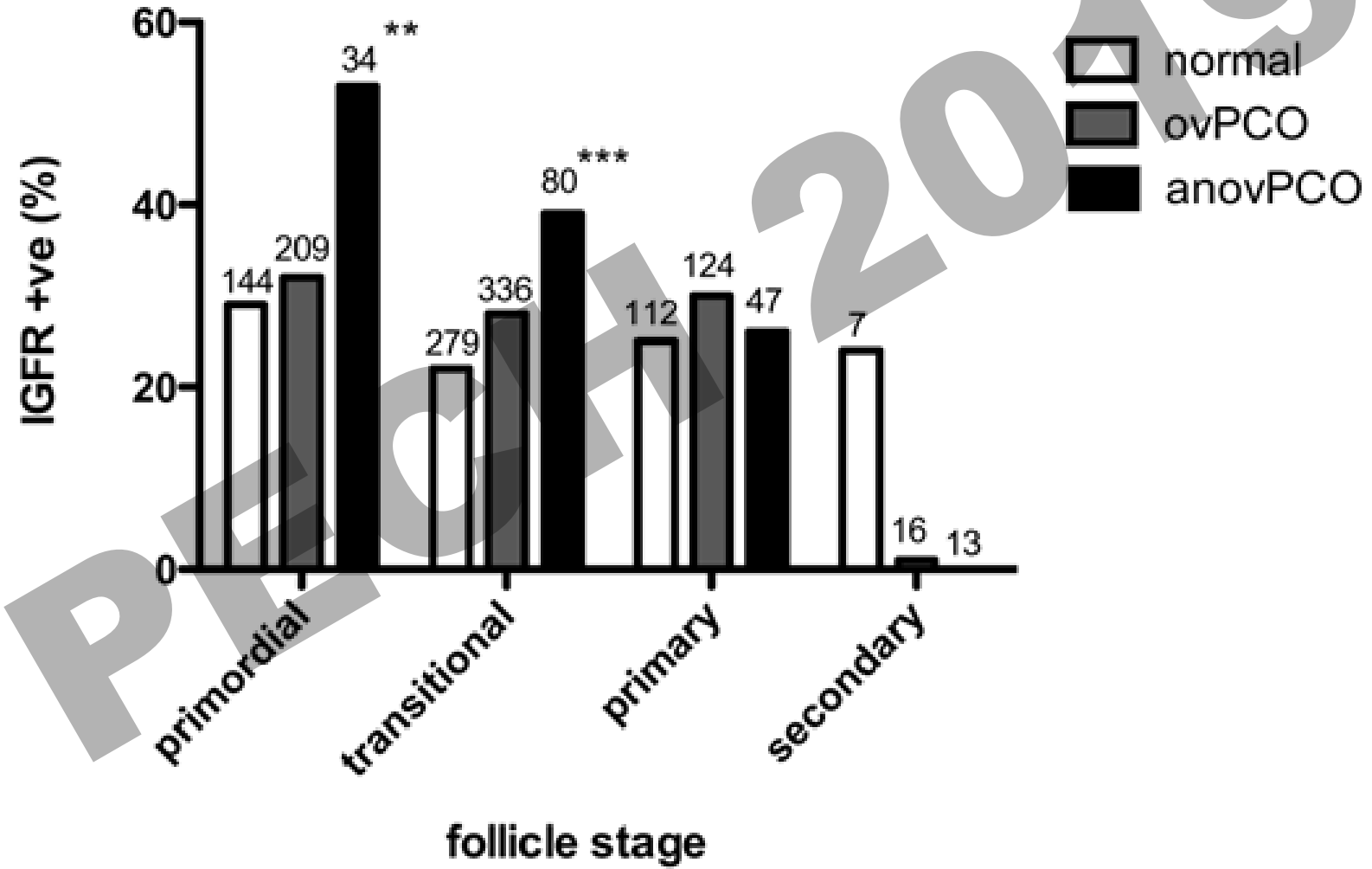


Glucose transport in adipocytes isolated from control (cont) and PCOS subjects. A, Absolute rates of 3-OMG transport in the absence (*open bars*) and presence (*solid bars*) of a maximally stimulating (8.5 nM) concentration of insulin. B, Insulin sensitivity. Results are presented as percentage of the maximal insulin effect attained in each individual's cells at a submaximal (0.17 nM) insulin level. Results are average + SEM; n = 8 for control, n = 10 for NGT, and n = 16 for IGT. *, $P < 0.05$ *vs*. paired basal; †, $P < 0.05$ *vs*. control.

Maximally insulin-stimulated whole body glucose disposal in normal cycling control (cont) and PCOS (NGT and IGT) subjects as determined from the hyperinsulinemic/euglycemic clamp procedure.

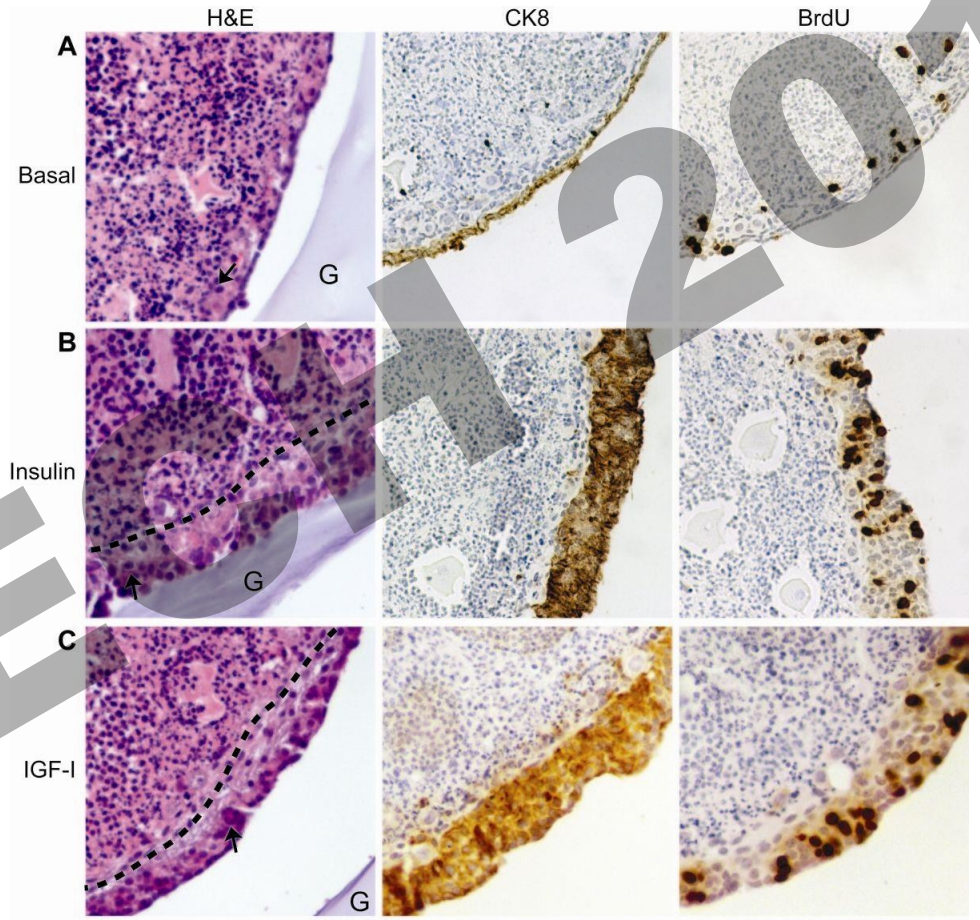


Proportion of follicles in which >50% of GCs were positive for IGFR-1 protein by immunohistochemistry. Expression of IGF was greater in follicles from women with anovPCO than in either ovPCO or controls at both primordial and transitional stages. **, $P < .01$; ***, $P < .001$

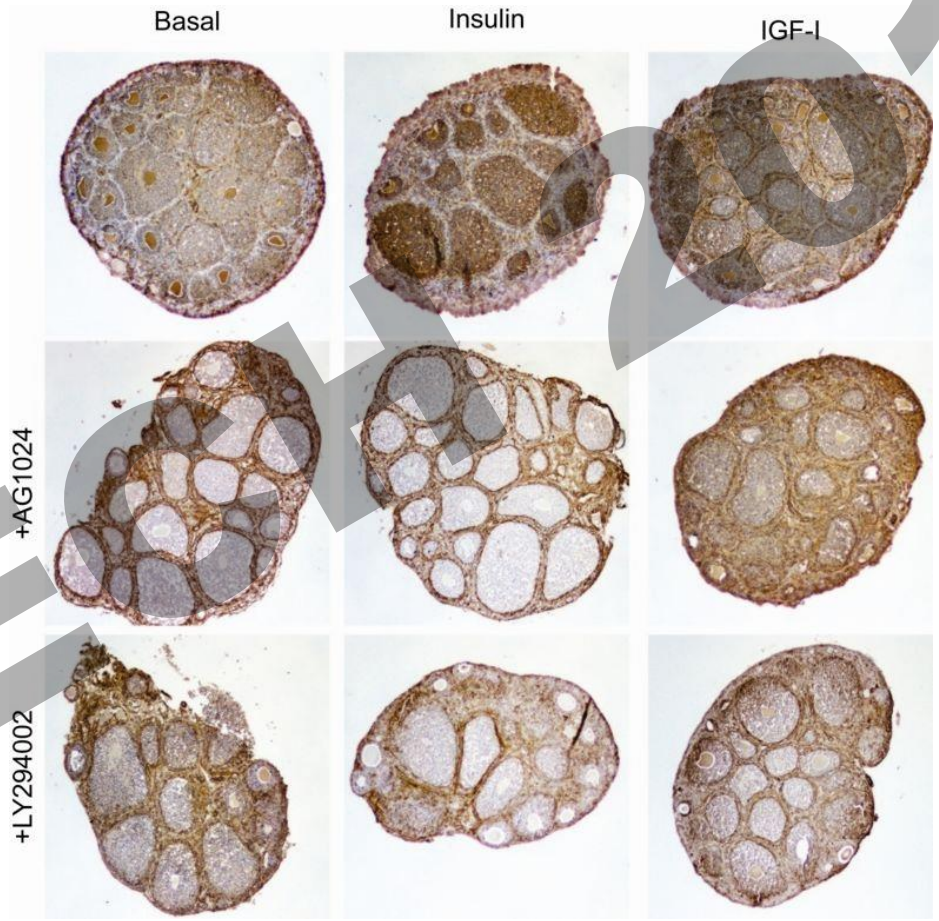


Role of Insulin-like Growth Factors in Initiation of Follicle Growth in Normal and Polycystic Human Ovaries Sharron A. Stubbs, Lisa J. Webber, Jaroslav Stark, Suman Rice, Raul Margara, Stuart Lavery, Geoffrey H. Trew, Kate Hardy, and Stephen Franks ; J Clin Endocrinol Metab, August 2013, 98(8):3298 –3305

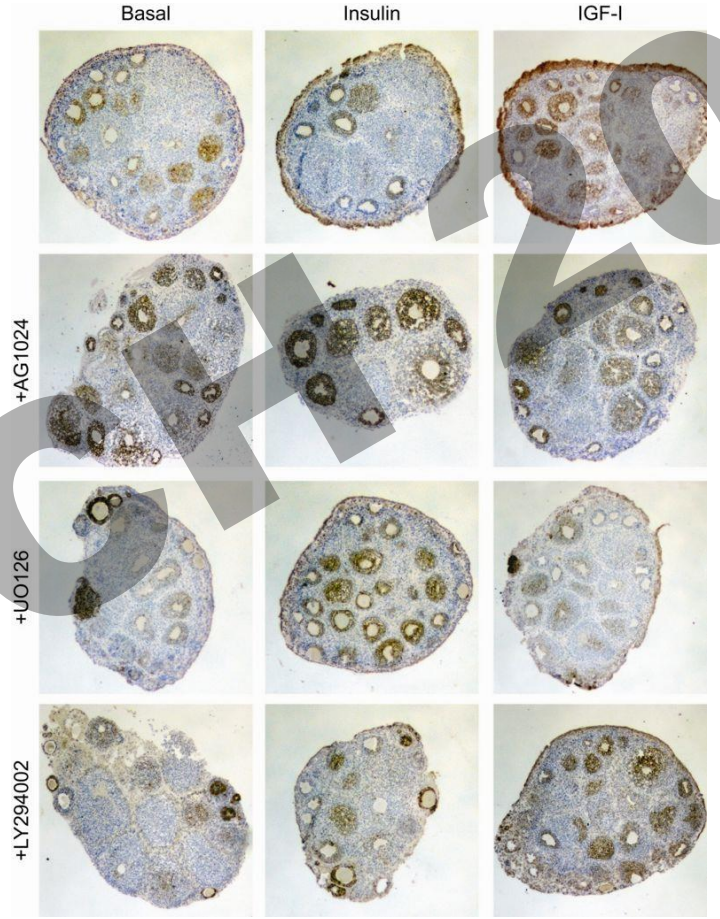
Insulin and IGF-I induce ovarian surface epithelium hyperplasia and proliferation



Culture of ovaries with insulin or IGF-I disorders collagen-IV organization.



High levels of insulin and IGF-I decrease secondary follicle AMH expression



Ovaries from CD1 mice were cultured in alginate hydrogels in the presence or absence of 5 µg/ml insulin or IGF-I, as well as small molecule inhibitors of IR/IGF1R, PI 3-kinase signaling, or MAPK signaling. Tissues were analyzed by immunohistochemistry for expression of cytokeratin 8 to mark the ovarian surface epithelium, Müllerian inhibiting substance (AMH) to mark secondary follicles, and BrdU incorporation to assess proliferation. Changes in gene expression in the ovarian surface epithelium in response to insulin or IGF-I were analyzed by transcription array. Extracellular matrix organization was evaluated by expression and localization of collagen IV.

Elevated Insulin Exposure of Follicles During Oocyte Growth Increases Oocyte GSK3 Phosphorylation and Meiotic Chromatin Remodeling Errors

Table 2

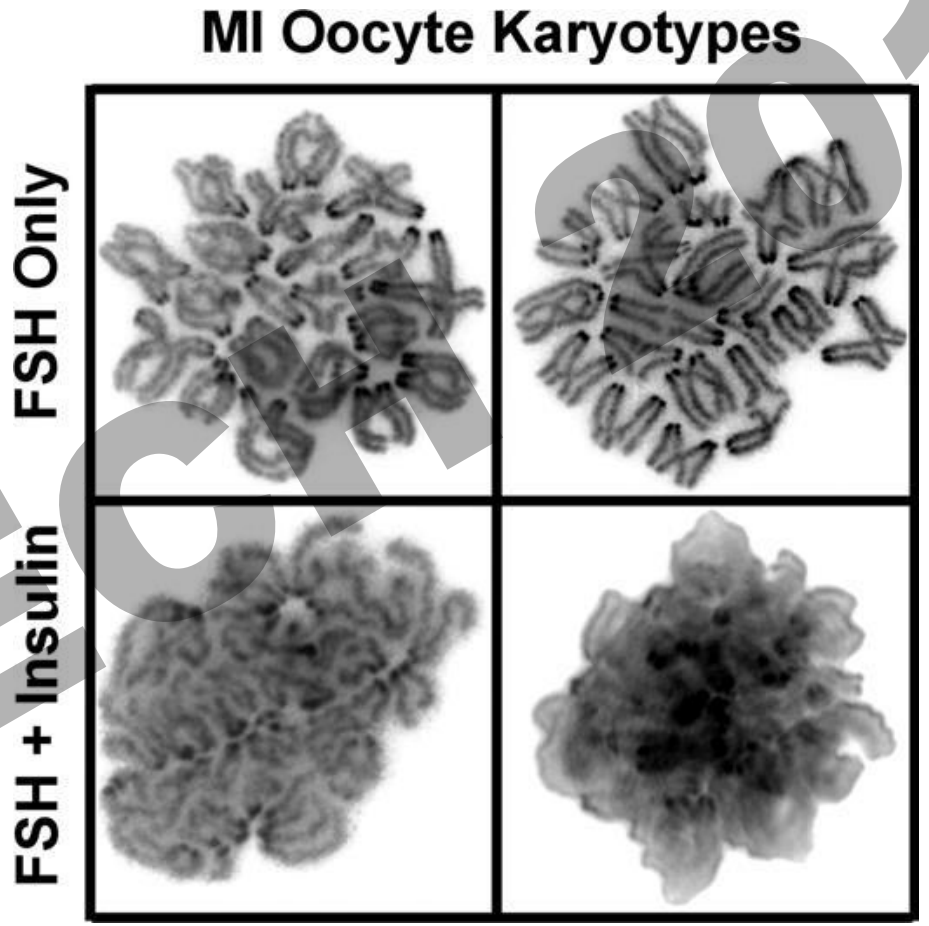
Chromatin analysis of oocytes matured in vitro (7 h) following follicle culture in the presence or absence of insulin.

Treatment	N [a]	MI development (%)	Normal condensation of MI oocytes (%)
FSH only (10 ng/ml)	134	49	96
FSH (10 ng/ml) + insulin (5 µg/ml)	116	47	13 [b]

[a] N = number of oocytes assessed in each treatment group.

[b] Value is significantly different from FSH only ($P < 0.01$).

Elevated Insulin Exposure of Follicles During Oocyte Growth Increases Oocyte GSK3 Phosphorylation and Meiotic Chromatin Remodeling Errors



Insulin binding to its receptor initiates a signal transduction cascade through phosphorylation of insulin receptor substrates, IRS1 and/or IRS2, and subsequent activation of phosphatidylinositol pathways [21]. Specifically, activated phosphoinositide-3 kinase signals through second messenger molecules to phosphorylate 3-phosphoinositide-dependent protein kinase-1 (PDPK1), which, in turn, phosphorylates its substrate thymoma viral proto-oncogene 1 (AKT1) [22, 23]. Activated AKT1 is the primary regulator of the terminal enzyme in insulin signaling, glycogen synthase kinase 3A/B (GSK3A/B), and AKT1-mediated phosphorylation of GSK3A at serine 21 or GSK3B at serine 9 results in GSK3 inactivation

High Insulin-Like Growth Factor 1 (IGF-1) and Insulin Concentrations Trigger Apoptosis in the Mouse Blastocyst via Down-Regulation of the IGF-1 Receptor

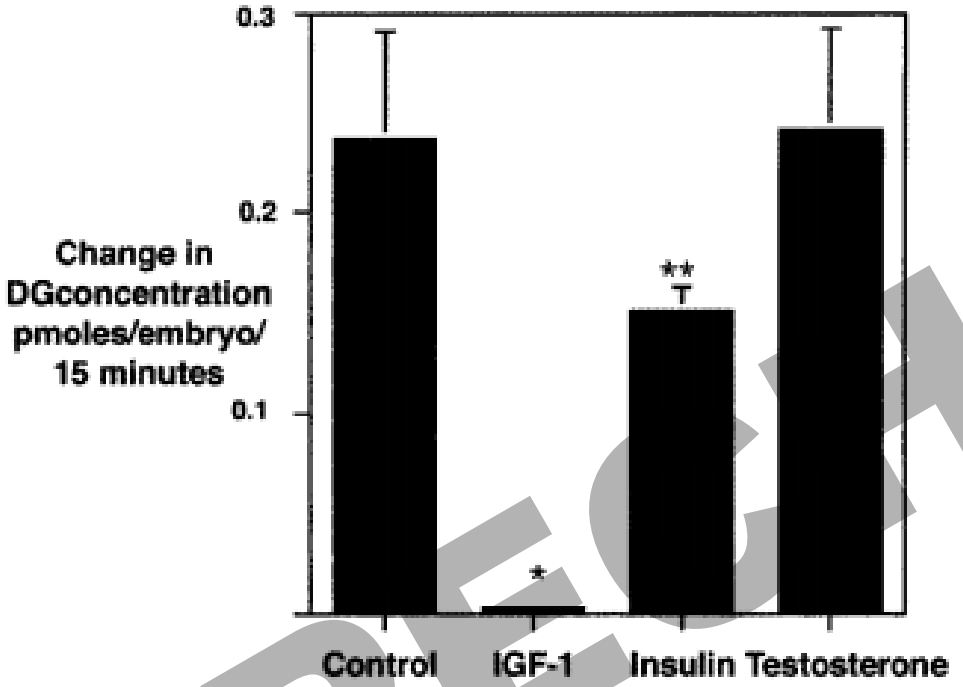


FIG. 5. High concentrations of IGF-1 decrease insulin-stimulated glucose transport into the blastocyst. 2-Deoxyglucose uptake in blastocysts exposed to the control conditions of 1.3 nM IGF-1, 130 nM IGF-1, 700 nM insulin and 400 nM testosterone. High concentrations of IGF-1 or insulin result in a significant decrease in insulin-stimulated glucose uptake as measured by 2-deoxyglucose uptake. Significance between control and IGF-1, $*P < 0.001$, between control and insulin, $**P < 0.01$.

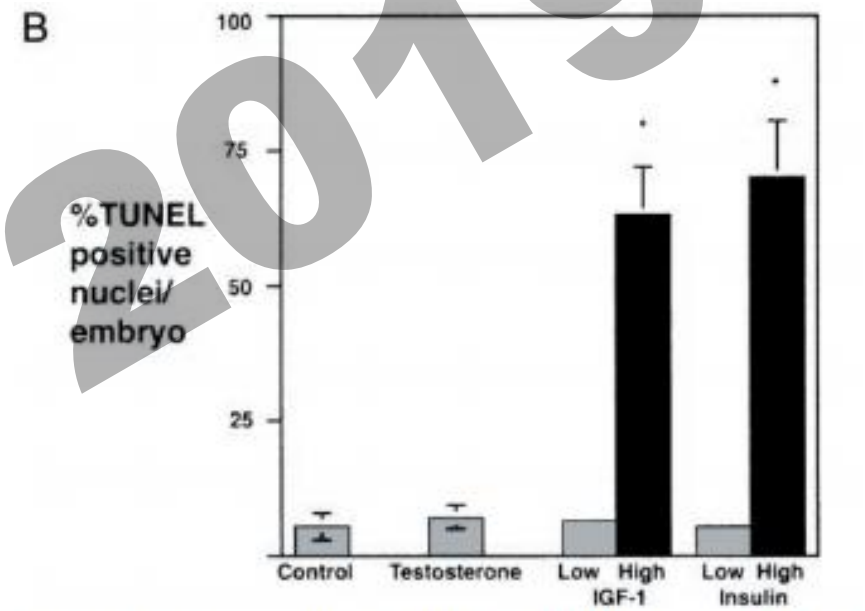


FIG. 1. High concentrations of IGF-1 or insulin increase TUNEL-staining nuclei. A, Embryos cultured in control HTF, HTF with 1.3 nM IGF-1 or 130 nM IGF-1, HTF with 6 nM insulin or 700 nM insulin, or 400 nM testosterone, were examined for TUNEL-positive staining. The *red channel* represents propidium iodide staining; the *green channel* represents FITC-labeled 3′ fragmented DNA. The figure shows one of a Z-series representative of the results. Note the predominance of the TUNEL-positive nuclei in what appears to be the ICM. B, Percent TUNEL-positive nuclei demonstrating DNA fragmentation per total embryonic nuclei. Embryos cultured in the higher concentrations of IGF-1 or insulin demonstrated in a significantly higher percentage of apoptotic nuclei (*, $P < 0.001$).

The endometrium in polycystic ovary syndrome

Lathi, Ruth B. MD*; Swiersz, Lillian MD*; Basina, Marina MD†; Giudice, Linda C. MD, PhD*

Current Opinion in Endocrinology & Diabetes: December 2002 - Volume 9 - Issue 6 - p 480-485

- Polycystic ovary syndrome (PCOS) is a common endocrinopathy and cause of anovulation, with abnormally elevated circulating androgens and insulin levels being common components of PCOS. The potential effects of the metabolic and endocrinologic changes seen in PCOS on the human endometrium are likely to be complex and comprise an important area of research.

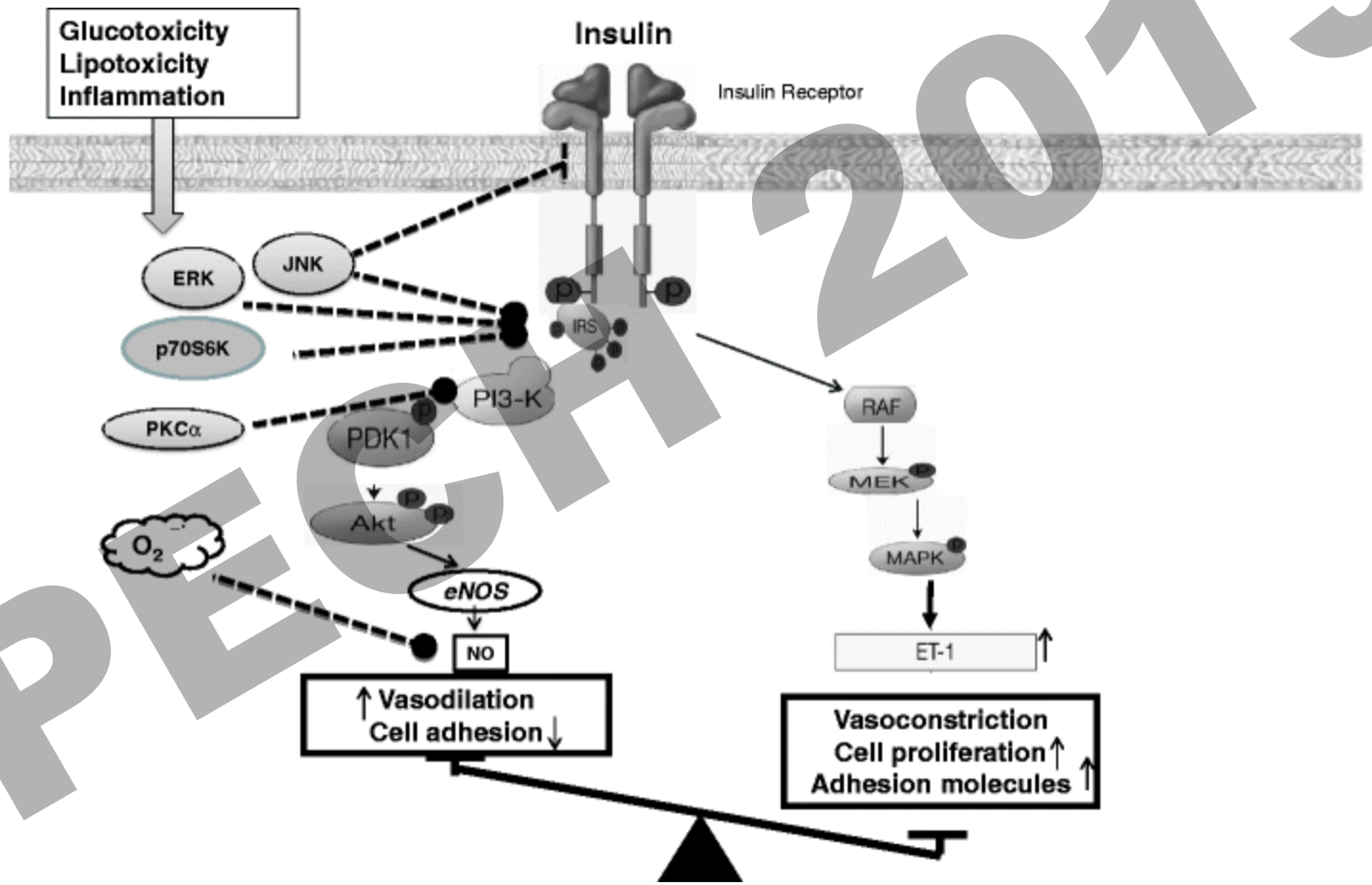
- Androgen receptors and steroid receptor co-activators are overexpressed in the endometrium of women with PCOS. In addition, molecular markers of endometrial receptivity including αvβ3 integrin and glycodelin are decreased in endometrial biopsy specimens from patients with PCOS. Clinically, reproductive performance of women with PCOS is improved by insulin-lowering agents such as metformin, primarily by restoring ovulation; however, the effects of insulin-lowering agents on endometrium are unknown. In vitro studies on the effects of insulin on endometrial stromal cells demonstrate that insulin inhibits the normal process of decidualization. Insulin-like growth factors (IGFs) and their binding proteins (IGFBPs) are important in the maternal–fetal interface and in the circulation. Hyperinsulinemia results in decreased circulating IGFBP-1 and increased free IGF-1. Thus, a combination of elevated unopposed estrogen, hyperinsulinemia, elevated free IGF-1, elevated androgens, and obesity likely contribute to the endometrial dysfunction, infertility, increased miscarriage rate and endometrial hyperplasia seen in PCOS.

Biomarkers of PCOS endometrium

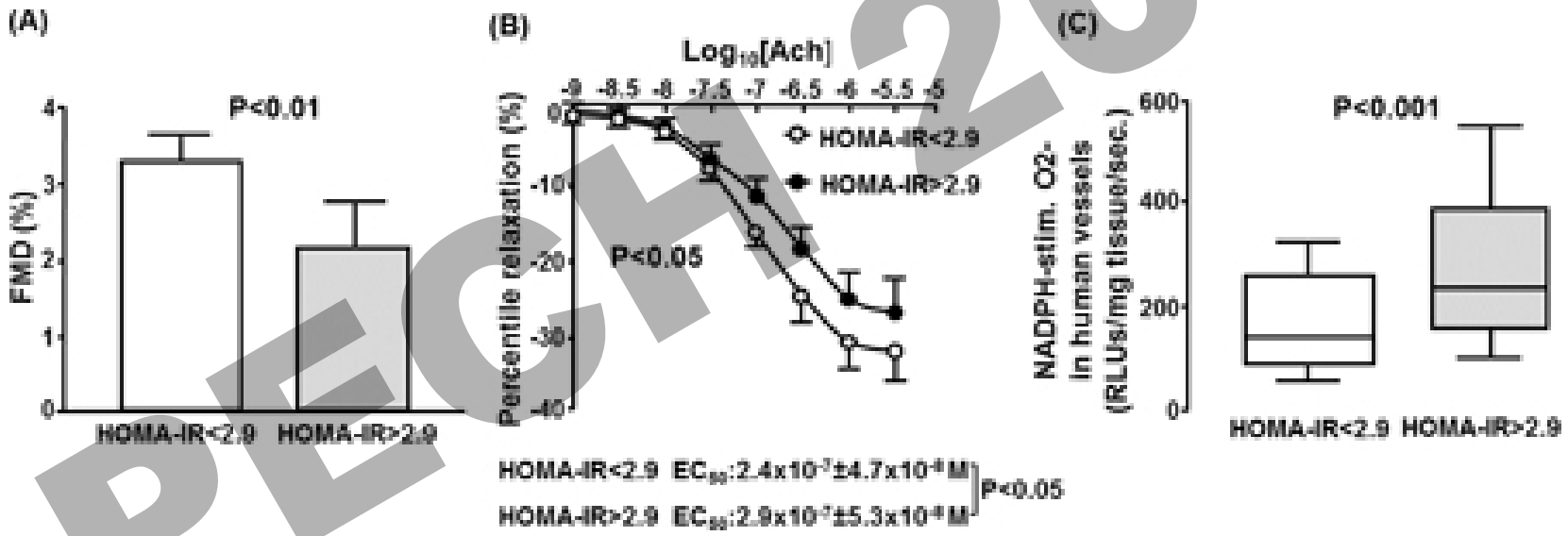
Marker	PE	SE	
Glucose metabolism			
IGFBP-1		▼	SE (in vitro)▼ (Piltonen 2015)
GLUT 4	▼		PE▼, HP▼ (Li 2015); PE▼ (Fornes 2010); Zhai PE▼ (Zhai 2012*); PE▼ (Ujvari 2014*)
IRS-1	▼		PE▼ (Fornes 2010); PE▼ (Ujvari 2014*)
Glucose action	▼		PE▼ (Kim 2010*); PE▼ (Piltonen 2013*)
Inflammation			
TNFR1/TNFR2		△	△(Orostica 2016)
NfKb		△	△(Orostica 2016)
IL-6	△	△	PE△ (Piltonen 2013*); SE (in vitro)△ (Piltonen 2015)
CCL2 (MCP-1)	△		PE △(Piltonen 2013*)
IL-8	△	△	PE△ (Piltonen 2013*); SE (in vitro)△ (Piltonen 2015)
RANTES		△	SE (in vitro)△ (Piltonen 2015)
uNK-cells		▼	SE▼(Matteo 2010*)
Macrophages		△	△(Orostica 2016)
MMPs			
MMP2		△	SE (in vitro)△ (Piltonen 2015)
MMP3		△	SE (in vitro)△ (Piltonen 2015)
Steroid hormone action			
HOXA10		▼	SE▼(Taylor JCEM), downregulated in EC (ref)
AR	△	△	PE(-) (Piltonen 2013*); SE △ (Quezada 2006 FS*); PE△, HP△ (Li 2015); HP△(Villavicencio 2006)
PR		△	SE △(Margarit 2010*)
Era	△(-)	△	PE(-) (Piltonen 2013*); PE(-) (Kim 2010*); SE△(Gregory 2002)
			PE?△ and HP△(Villavicencio 2006); SE△(Quezada 2006 FS*); SE△(Margarit 2010*)
Erb	△	(-)	SE (-) (Quezada 2006 FS*); PE?△ and HP△(Villavicencio 2006)
(avb3) integrin	▼	▼	PE▼ (Kim 2010*); SE▼(Quezada 2006 FS*); ▼progestin treatment (Lopez 2014)
MUC1		△▼	SE△ovulatory PCOS, ▼anovulatory PCOS (Margarit 2010*)
Steroid horomone co activators			
AIBI	△	△	PE?△(Villavicencio 2006); SE△(Gregory 2002)
TIF2		△	SE△(Gregory 2002)
NCoR	(-)		PE?(-)(Villavicencio 2006)

Is the Endometrium in Women with PCOS Compromised?
Terhi T. Piltonen ; Cambridge University Press
DOI: https://doi.org/10.1017/9781108236263.022

Az inzulin vaszkuláris hatásai egészséges anyagcsere és inzulin rezisztencia esetén

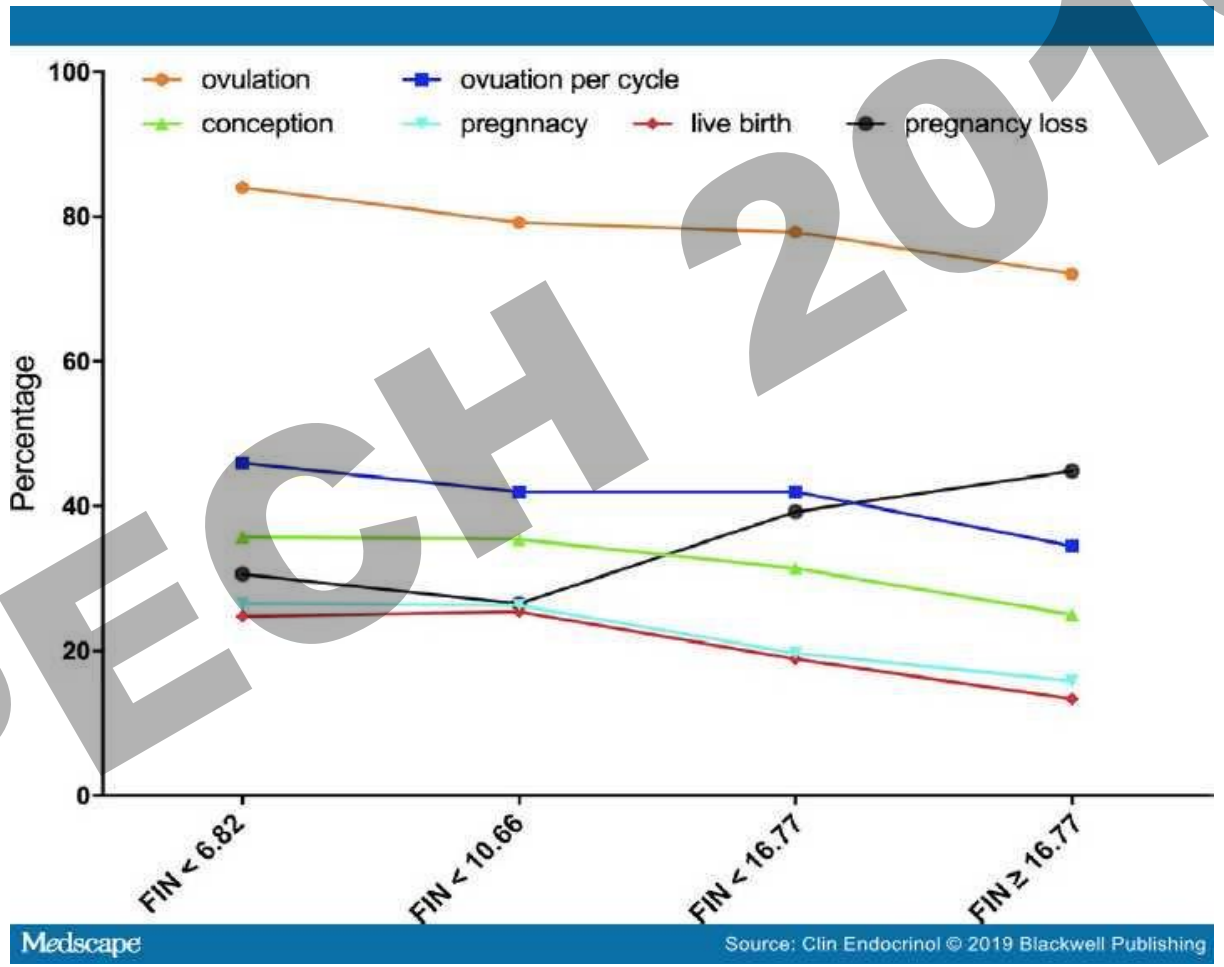


Acetilkolin dependens arteria relaxáció a HOMA index függvényében



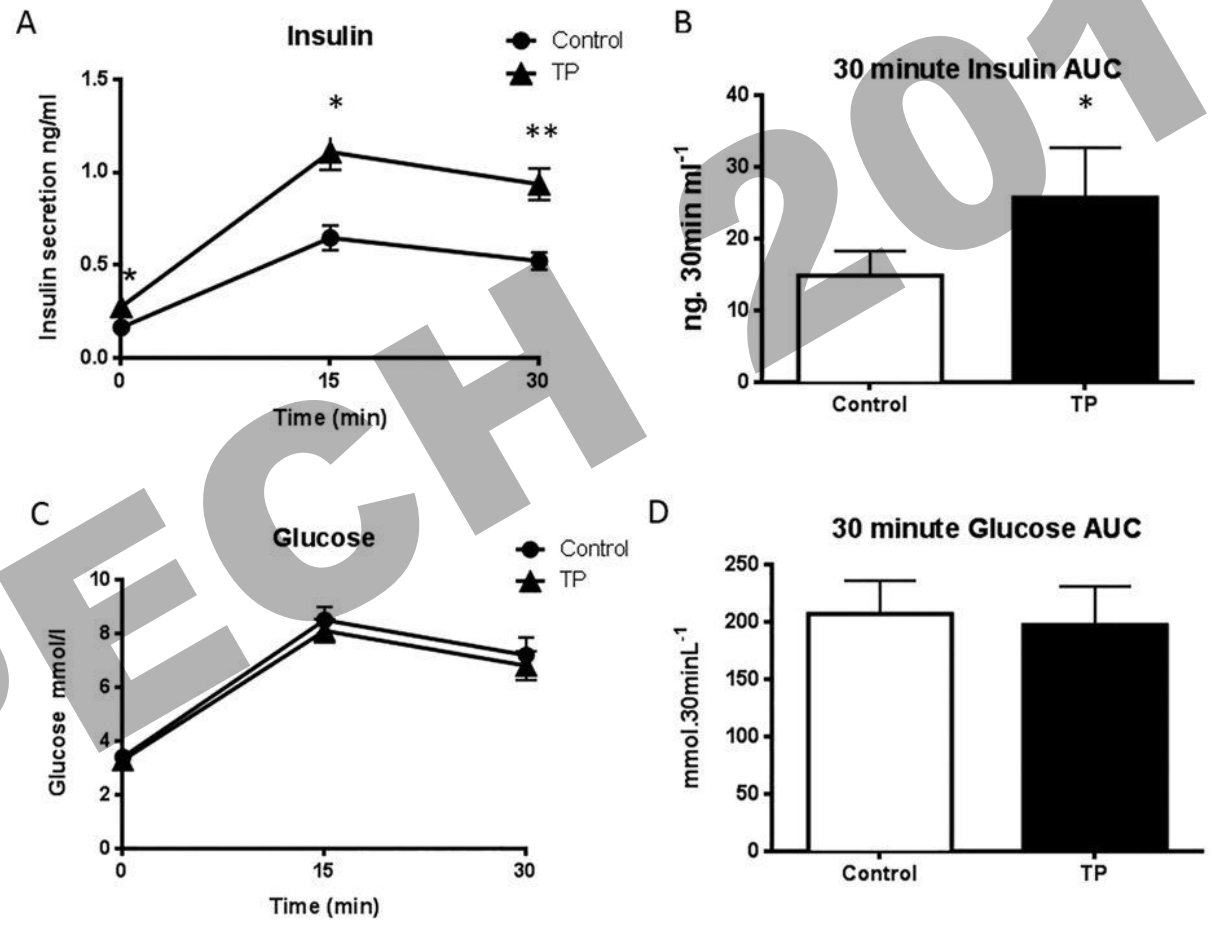
The presence of IR (HOMA-IR>2.9) was associated with impaired FMD (A), reduced vasorelaxations of human vessels in response to acetylcholine (B) and elevated vascular O2- generation (C).

Az éhgyomri inzulin és a fertilitás kapcsolata PCO syndromában



Effect of Hyperinsulinaemia and Insulin Resistance on Endocrine, Metabolic and Fertility Outcomes in Women With Polycystic Ovary Syndrome Undergoing Ovulation Induction
Duojia Zhang; Xinming Yang; Jian Li; Jiarui Yu; Xiaoke Wu
Clin Endocrinol. 2019;91(3):440-448.

A prenatális androgén expozíció hatása az utód inzulin érzékenységére



Köszönöm megtisztelő figyelmüket

endocare
ENDOKRINOLÓGIAI KÖZPONT