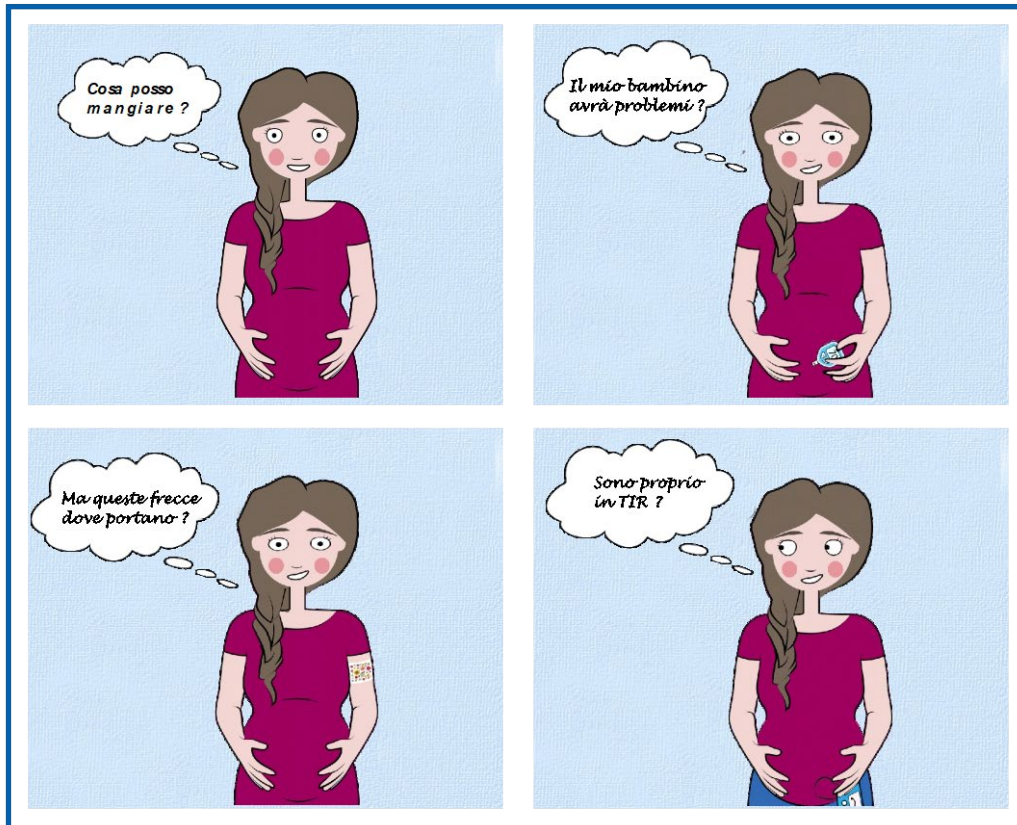


DIABETE IN GRAVIDANZA: ISTRUZIONE PER LA GESTIONE

Sabato 2 Marzo 2024 Unahotels Thotel, Cagliari



Le relazioni pericolose: Diabete, PMA e
comorbidità materne

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La Prof./ssa Elena Succurro dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

- Novo Nordisk, Abbott, Eli Lilly

Dichiara altresì il proprio impegno ad astenersi, nell'ambito dell'evento, dal nominare, in qualsivoglia modo o forma, aziende farmaceutiche e/o denominazione commerciale e di non fare pubblicità di qualsiasi tipo relativamente a specifici prodotti di interesse sanitario (farmaci, strumenti, dispositivi medico-chirurgici, ecc.).

Continua il calo delle nascite



Ancora un record negativo per la natalità: nel 2022 le nascite scendono a 393mila, registrando un calo dell'1,7% sull'anno precedente.

La denatalità prosegue anche nel 2023: secondo i primi dati provvisori a gennaio-giugno le nascite sono circa 3.500 in meno rispetto allo stesso periodo del 2022.

Il numero medio di figli per donna scende a **1,24**, evidenziando una lieve flessione sul 2021 (1,25); la stima provvisoria elaborata sui primi 6 mesi del 2023 evidenzia una fecondità pari a 1,22 figli per donna. Nel 2010 il numero medio di figli per donna aveva toccato il massimo relativo registrato nell'ultimo ventennio di 1,44.

1,18

Numero medio di figli
delle donne di
cittadinanza italiana

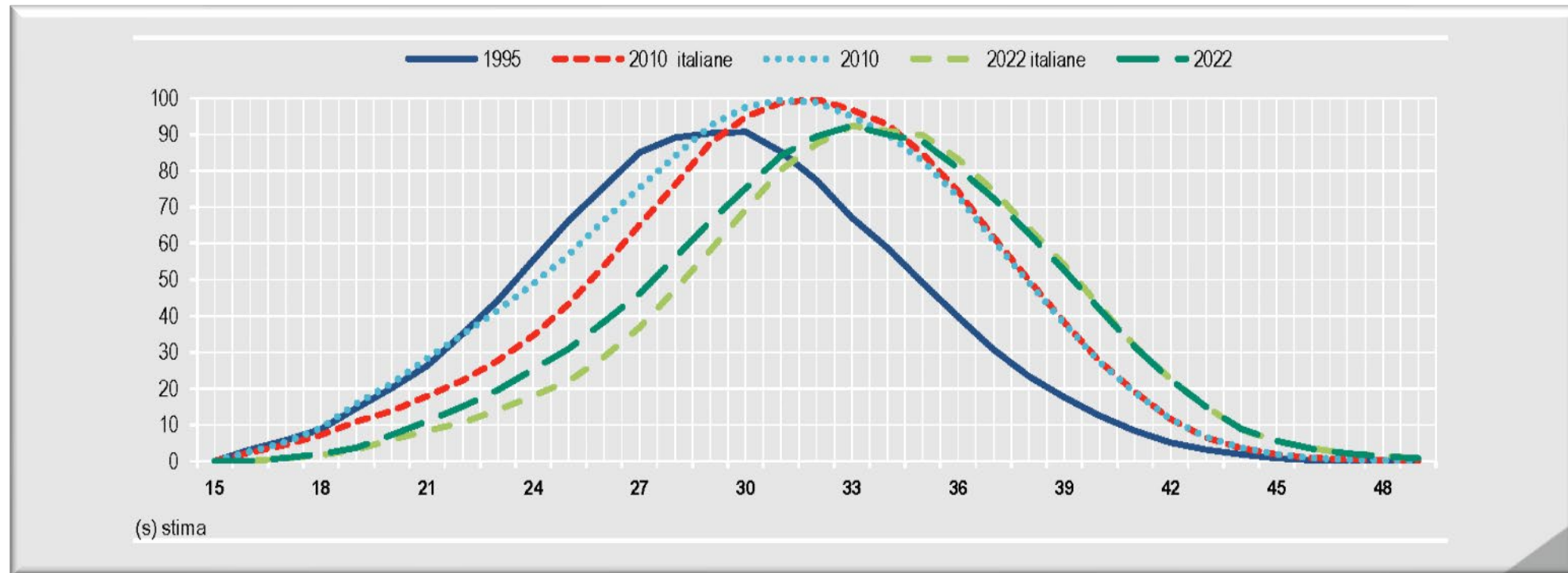
31,6

Età media alla nascita del
primo figlio (stabile
rispetto all'anno
precedente)

41,5%

Percentuale di nascite
fuori dal matrimonio

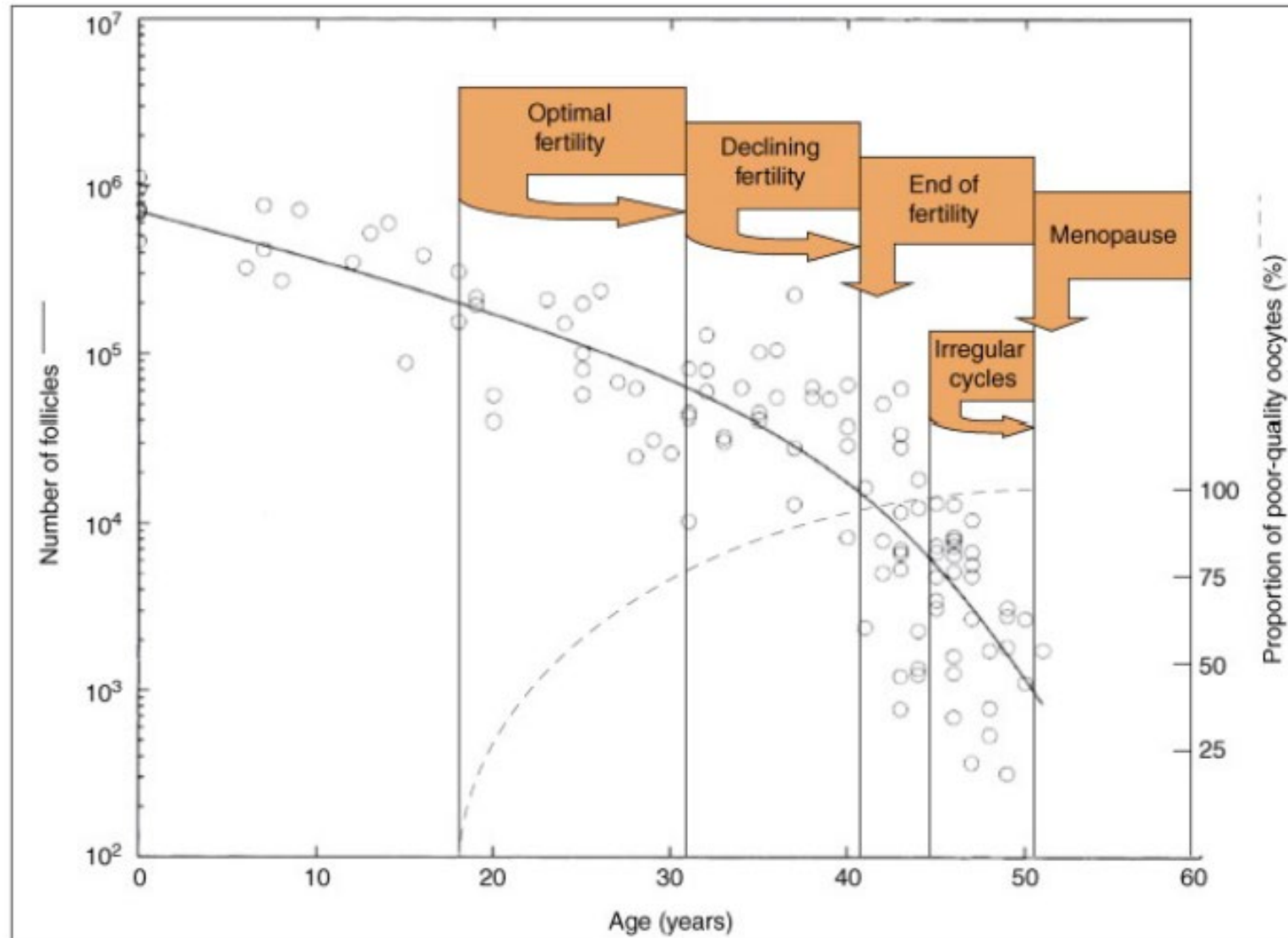
Tasso di fecondità nelle donne residenti in Italia



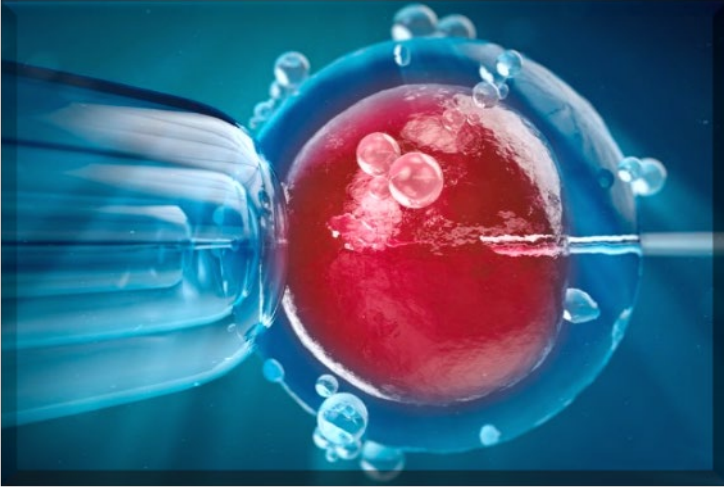
Nel 2022 le donne residenti in Italia tra 15 e 49 anni hanno in media 1,24 figli, in linea con il trend decrescente in atto dal 2010. Inoltre, la fecondità in Italia si sposta verso età sempre più mature. Nei primi anni Duemila si assisteva ad un recupero dopo il minimo storico registrato nel 1995, recupero attribuibile in larga misura al crescente contributo delle donne straniere.

Rispetto al 1995, i tassi di fecondità sono cresciuti nelle età superiori a 30 anni mentre sono diminuiti tra le donne più giovani, un fenomeno ancora più accentuato per le sole cittadine italiane.

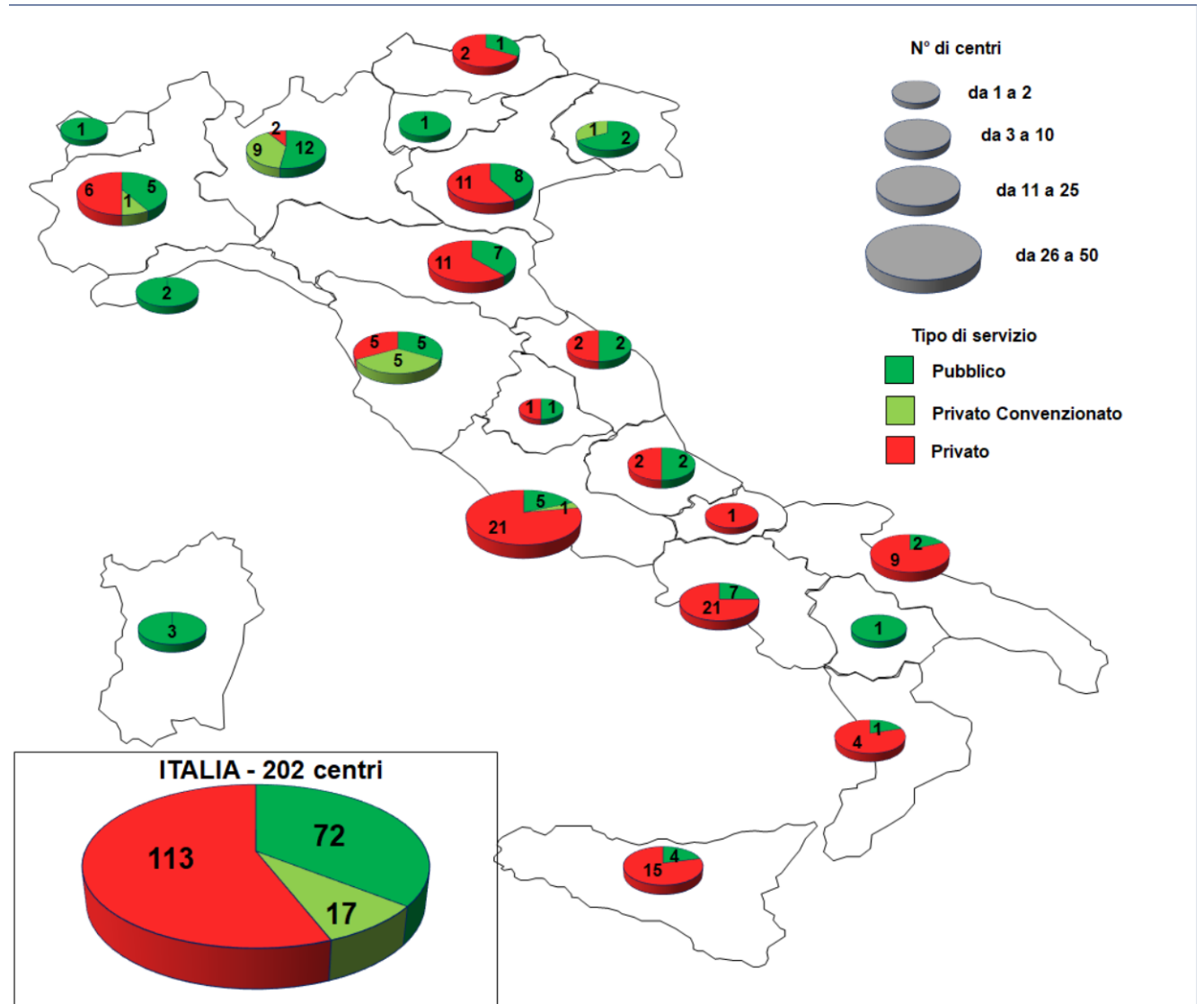
Età femminile e fertilità



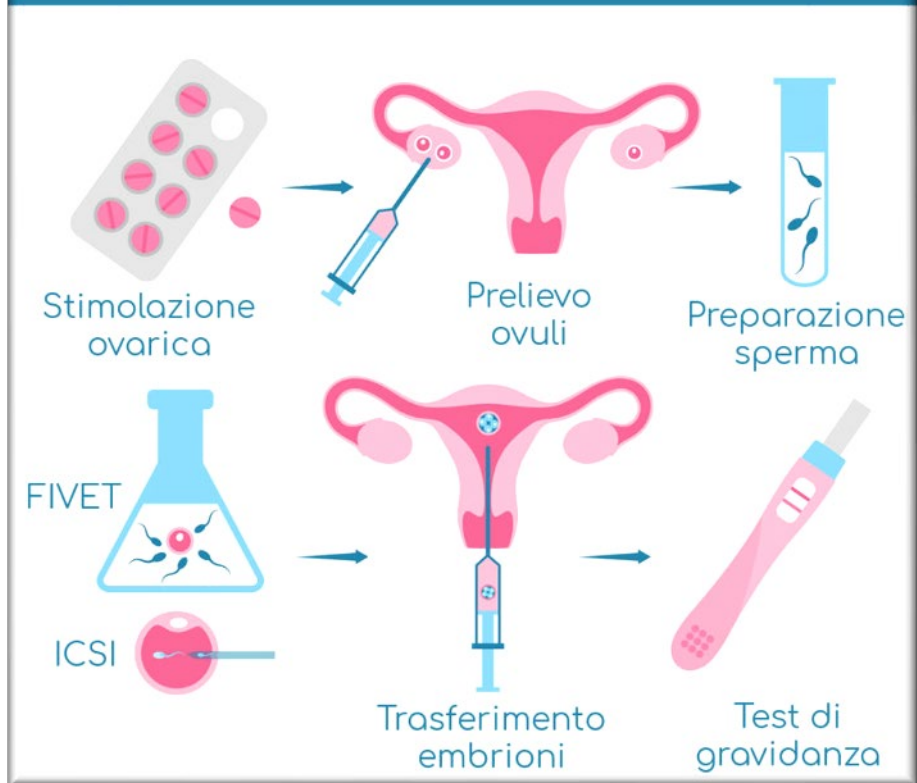
PMA e fertilità



- 86.090 coppie trattate
- 23.404 gravidanze ottenute
- **16.625** bambini nati vivi che rappresentano il **4.2%** del totale dei nati in Italia nel 2021



Fecondazione assistita



Aumentato rischio di outcome avversi in donne con PMA con gravidanze singole

Outcome	IVF/ICSI conceptions, n	Overall effect (RR, 95% CI), fixed effect	Heterogeneity (I^2) (%)	Subgroup analysis (Matched cohorts)	Sensitivity analysis, good-quality studies (CASP > 10)	Sensitivity analysis, studies with infertility in unexposed cohort removed	Risk difference	Overall effect (RR, 95% CI), random effect
APH	20 807	2.49 (2.30–2.69)	82	1.98 (1.61–2.43)	2.70 (2.48–2.93)	2.53 (2.34–2.74)	0.02 (0.02–0.03)	2.44 (1.85–3.20)
Congenital anomalies	4382	1.67 (1.33–2.09)	0	1.82 (1.36–2.45)	na	na	0.02 (0.01–0.02)	Na
Hypertensive disorders of pregnancy	16 923	1.49 (1.39–1.59)	63	1.33 (1.12,1.58)	1.49 (1.39–1.60)	1.52 (1.42–1.63)	0.02 (0.01–0.02)	1.28 (1.06–1.54)
PPROM	14 141	1.16 (1.07–1.26)	86	1.52 (1.35–1.71)	1.16 (1.07–1.26)	1.16 (1.07–1.26)	0.01 (0.00–0.01)	1.17 (0.79–1.73)
Caesarean Section	12 950	1.56 (1.51–1.60)	80	1.47 (1.38–1.56)	1.54 (1.50–1.59)	1.57 (1.53–1.62)	0.09 (0.09–0.10)	1.50 (1.34–1.68)
Birthweight < 2500 g	28 352	1.65 (1.56–1.75)	45	1.72 (1.54–1.92)	1.65 (1.55–1.75)	1.66 (1.56–1.77)	0.02 (0.02–0.03)	na
Birthweight < 1500 g	27 105	1.93 (1.72–2.17)	46	1.72 (1.45–2.05)	1.96 (1.74–2.20)	1.85 (1.64–2.09)	0.01 (0.01–0.01)	na
Perinatal mortality	14 054	1.87 (1.48–2.37)	73	2.46 (1.35–4.46)	1.44 (1.06–1.95)	1.89 (1.49–2.39)	0.00 (0.00–0.00)	1.82 (0.98–3.35)
Delivery at <37 weeks	27 819	1.54 (1.47–1.62)	75	1.58 (1.43–1.75)	1.51 (1.44–1.59)	1.55 (1.48–1.64)	0.03 (0.02–0.03)	1.62 (1.40–1.86)
Delivery at <32 weeks	24 170	1.68 (1.48–1.91)	45	1.22 (0.88,1.70)	1.68 (1.47–1.90)	1.65 (1.44–1.90)	0.01 (0.00–0.01)	na
Transfer to NICU	3530	1.58 (1.42–1.77)	0	1.58 (1.42–1.77)	na	na	0.07 (0.05–0.09)	na
Gestational diabetes	13 399	1.48 (1.33–1.66)	43	1.53 (1.36–1.72)	1.51 (1.35–1.69)	1.52 (1.35–1.70)	0.01 (0.01–0.01)	na
Induction of labour	3557	1.18 (1.10–1.28)	0	1.19 (1.10–1.28)	na	na	0.05 (0.03–0.07)	na
Small for gestation age	13 207	1.39 (1.27–1.53)	0	1.49 (1.10–2.01)	1.39 (1.26–1.53)	1.39 (1.27–1.53)	0.01 (0.01–0.01)	na

Aumentato rischio di GDM in donne con PMA

Studio retrospettivo di popolazione australiana su 3732 donne sottoposte ad ART e 386.660 donne non ART

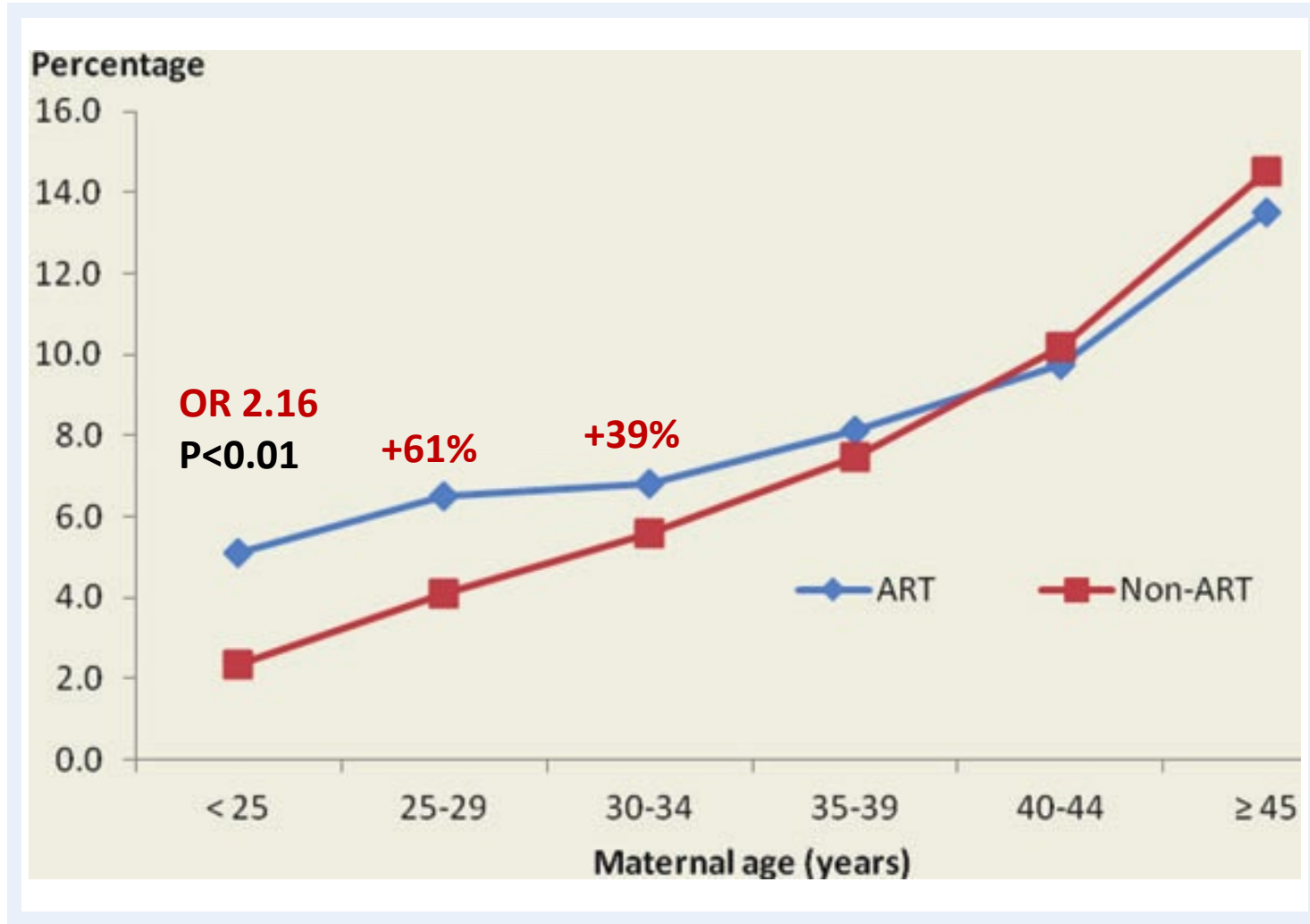
	Non-ART		ART			
	Total	GDM rate (%)	Total	GDM (%)	OR (95%) CI	AOR ^a (95%) CI
All mothers	(n = 386 660)		(n = 13 732)			
Singleton	381 402	5.0	12 105	7.5	1.53 (1.43–1.64)	1.26 (1.18–1.36)
Twin	5208	7.3	1571	8.8	1.22 (0.99–1.49)	1.18 (0.94–1.48)
All ^b	386 660	5.0	13 732	7.6	1.55 (1.45–1.65)	1.28 (1.20–1.37)
Mothers with BMI stated	(n = 113 105)		(n = 4733)			
Singleton	111 685	5.1	4191	7.5	1.52 (1.35–1.71)	1.36 (1.20–1.54)
Twin	1407	7.1	521	8.4	1.21 (0.83–1.75)	1.29 (0.83–2.02)
All ^b	113 105	5.1	4733	7.6	1.53 (1.37–1.71)	1.37 (1.22–1.54)

+28%

+37%

Adjusted for age, parity, BMI, health insurance, smoking during pregnancy and essential hypertension.

Aumentato rischio di GDM in donne con PMA

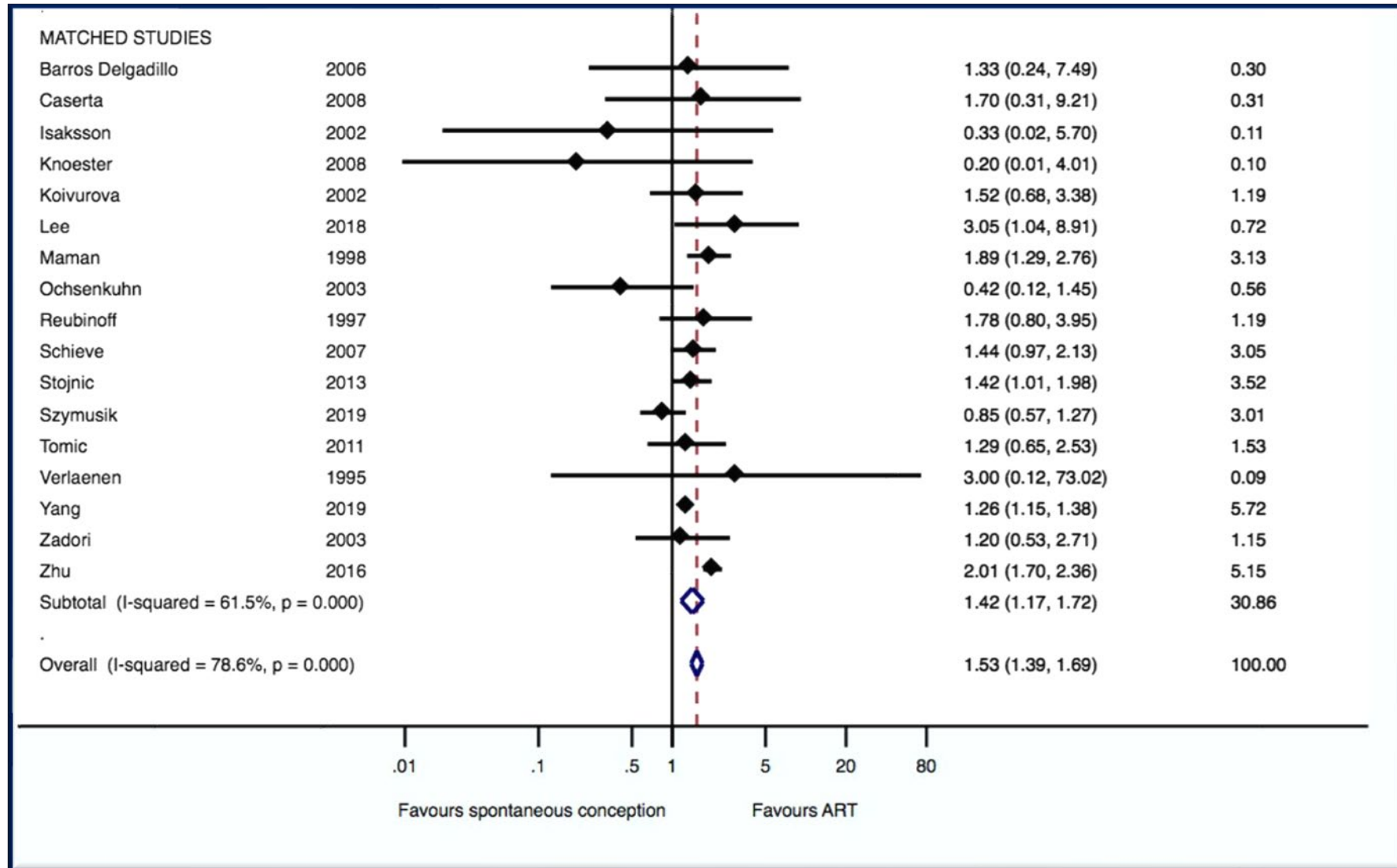


Aumentato rischio di GDM in donne con PMA con gravidanze singole

Groups	Studies	Risk		Model	Z	Heterogeneity		
		Risk % (95% CI)	<i>p</i> Value			Chi square	<i>p</i> Value	<i>I</i> square (%)
Total studies	59	9.0 (7.9–10.20)	<.001	Random	15.72	3072.34	<.001	98.1
Subgroup analyses								
Time period								
1987–2010	16	6.1 (4.6–7.6)	<.001	Random	7.85	118.55	<.001	87.3
2011–2017	43	9.8 (8.5–11.2)	<.001	Random	14.15	2936.90	<.001	98.6
Region								
Asia	21	12.1 (19.0–14.2)	<.001	Random	11.52	633.50	<.001	97.0
Europe	21	7.3 (5.6–9.1)	<.001	Random	8.20	284.34	<.001	93.0
America	17	6.8 (5.2–8.3)	<.001	Random	8.67	883.64	<.001	98.2

Aumentato rischio di GDM in donne con PMA

Metanalisi su 63 760 con ART e 1 870 734 di donne con gravidanza naturale



+53%



- **Rischio indipendente?**
- **Presenza di fattori di rischio sottostanti**

Aumentato rischio di GDM in donne con problemi di infertilità

40.773 gravidanze dal Nurses' Health Study II

Prepregnancy History of Infertility	No. of Cases	No. of Pregnancies	Age-Adjusted Model			Multivariable Model 1 ^a			Multivariable Model 2 ^b		
			RR	95% CI	P Value	RR	95% CI	P Value	RR	95% CI	P Value
No	1,024	33,057	1.00	Referent		1.00	Referent		1.00	Referent	
Yes	381	7,716	1.50	1.34, 1.69	<0.0001	1.38	1.23, 1.55	<0.0001	1.39	1.24, 1.57	<0.0001

+39% Rischio di GDM

Aumentato rischio di GDM in donne con problemi di infertilità

Nationwide population-based cohort study

Adjusted odds ratios for GDM in 372,677 singleton pregnancies in Denmark (2004–2010) associated with fertility problems overall and according to years since first infertility evaluation and type of infertility.

Fertility problems	GDM cases/noncases (n)	Age-adjusted model ^a		Multivariate model ^{a,b}	
		OR	95% CI	OR	95% CI
No	5,785/317,276	1.00	Reference	1.00	Reference
Yes	1,648/47,968	1.58	1.49–1.67	1.41	1.33–1.50
Years since first infertility evaluation ^c					
<1	237/7,519	1.58	1.40–1.78	1.46	1.28–1.67
1–2	368/12,198	1.48	1.34–1.64	1.36	1.22–1.52
2–4	348/12,552	1.33	1.20–1.47	1.22	1.10–1.36
≥4	695/15,699	1.80	1.66–1.96	1.55	1.42–1.69
Type of infertility ^d					
Primary	1,304/39,460	1.55	1.45–1.66	1.40	1.30–1.49
Secondary	344/8,328	1.73	1.54–1.94	1.46	1.30–1.65

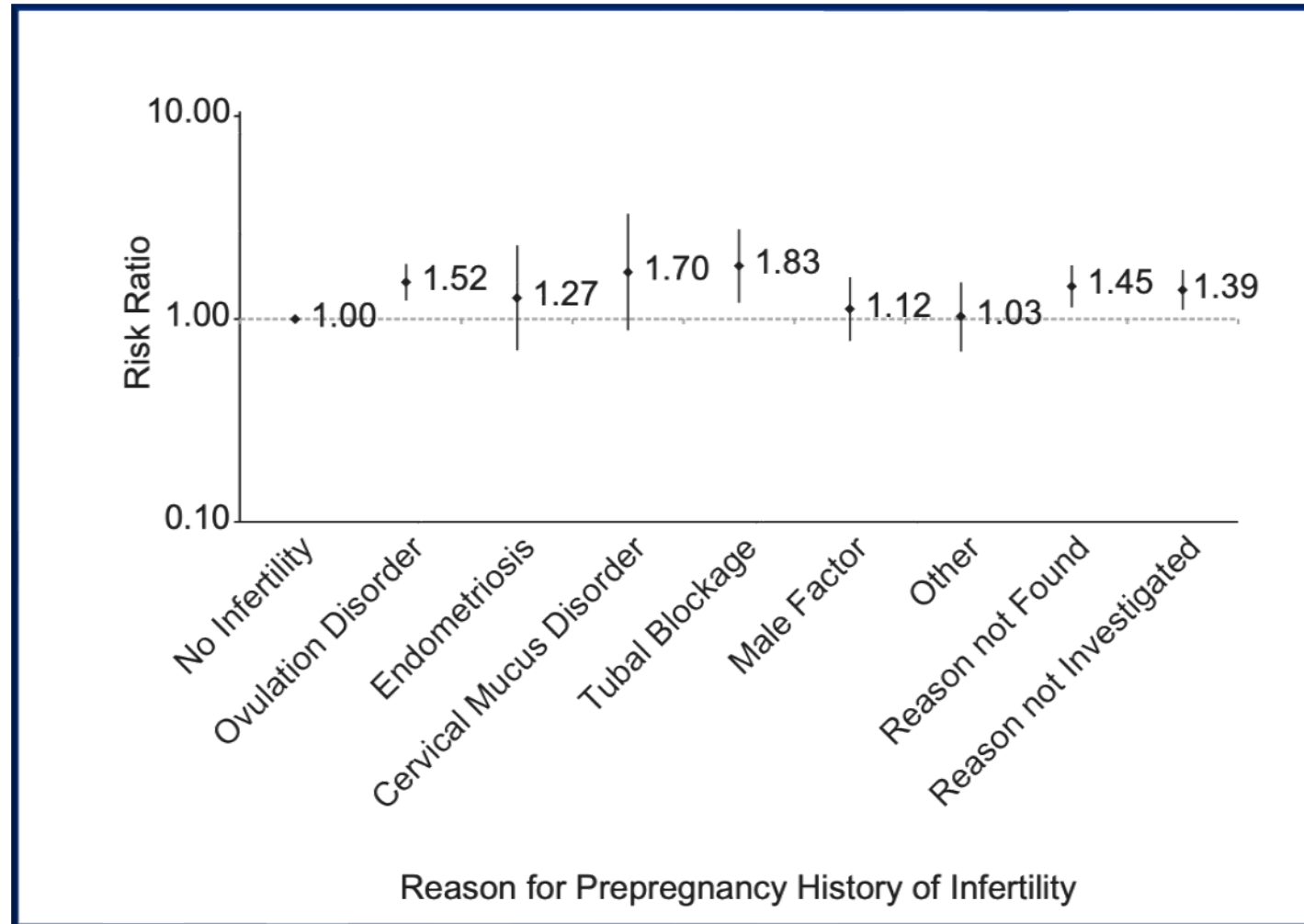
Aumentato rischio di GDM in donne con problemi di infertilità

Adjusted ORs for GDM in 372,677 singleton pregnancies in Denmark (2004–2010) associated with fertility problems, according to maternal age, pre-pregnancy BMI, PCOS, parity, parental history of diabetes, education level, and smoking status.

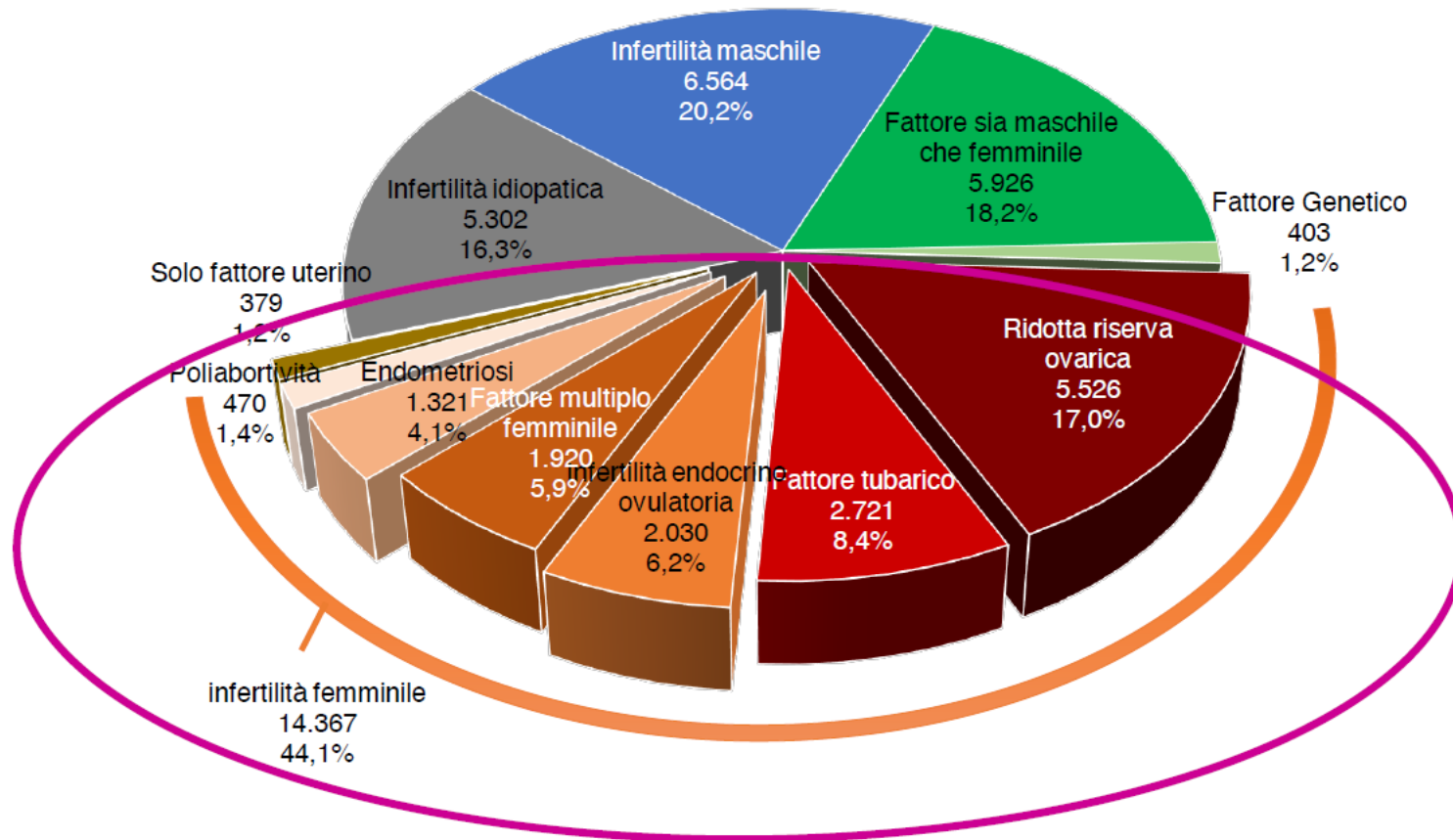
Characteristic	Fertility problems		OR	95% CI	Effect modification P value ^c
	Yes	No (ref.)			
	GDM cases/ noncases (n)	GDM cases/ noncases (n)			
Age at time of pregnancy (y)					
<25	71/1,936	632/52,202	2.39	1.85–3.10	<.01
25–29	332/12,461	1,740/117,362	1.54	1.36–1.74	
30–34	649/20,331	2,096/107,200	1.43	1.31–1.57	
≥35	596/13,240	1,317/40,512	1.31	1.19–1.46	
Prepregnancy BMI (kg/m ²)					
<18.5	19/1,707	87/13,250	1.36	0.80–2.30	.67
18.5–24.9	386/29,559	1,562/202,892	1.34	1.19–1.50	
25–29.9	500/10,593	1,765/66,602	1.45	1.30–1.61	
≥30	743/6,109	2,371/34,532	1.45	1.32–1.59	
PCOS					
No	1,465/45,832	5,754/316,526	1.33	1.25–1.42	.02
Yes	183/2,136	31/750	2.09	1.38–3.15	
Parity ^d					
Primiparous	778/22,079	2,275/140,570	1.51	1.39–1.65	.03
Multiparous	870/25,889	3,510/176,706	1.33	1.23–1.44	
Parental history of diabetes					
No	1,230/42,286	4,403/285,124	1.43	1.33–1.53	.39
Yes	418/5,682	1,382/32,152	1.35	1.19–1.53	
Education					
Short	334/5,696	1,403/60,740	1.54	1.35–1.76	.26
Medium	722/19,024	2,542/131,153	1.41	1.29–1.55	
Higher	592/23,248	1,840/125,383	1.34	1.21–1.48	
Smoking during pregnancy					
Nonsmoker	1,422/42,701	4,770/267,255	1.41	1.32–1.50	.97
Smoker	226/5,267	1,015/50,021	1.43	1.23–1.66	

Cause di infertilità e rischio di GDM in NHS

40.773 gravidanze dal Nurses' Health Study II

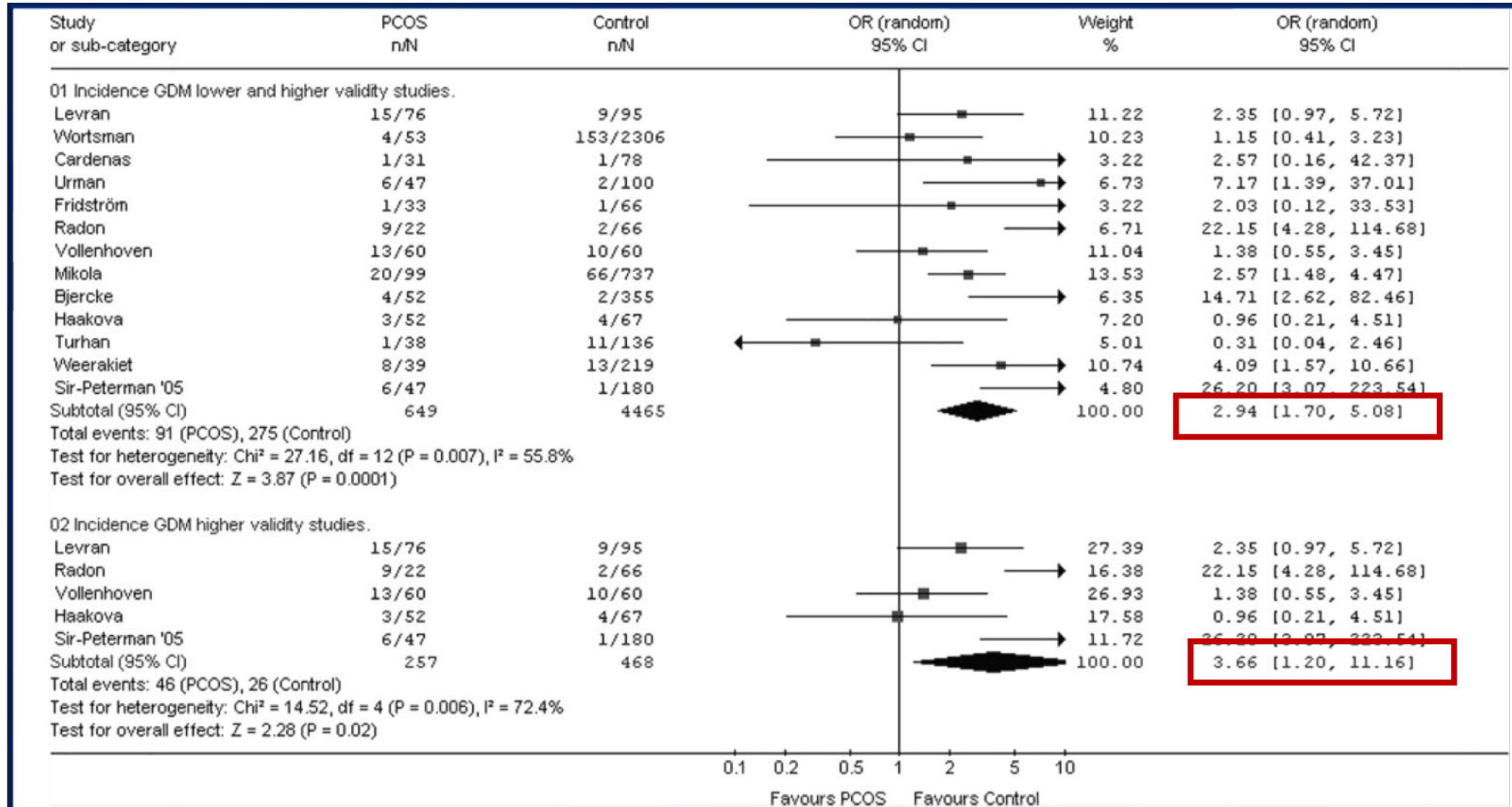


Cause di infertilità e PMA

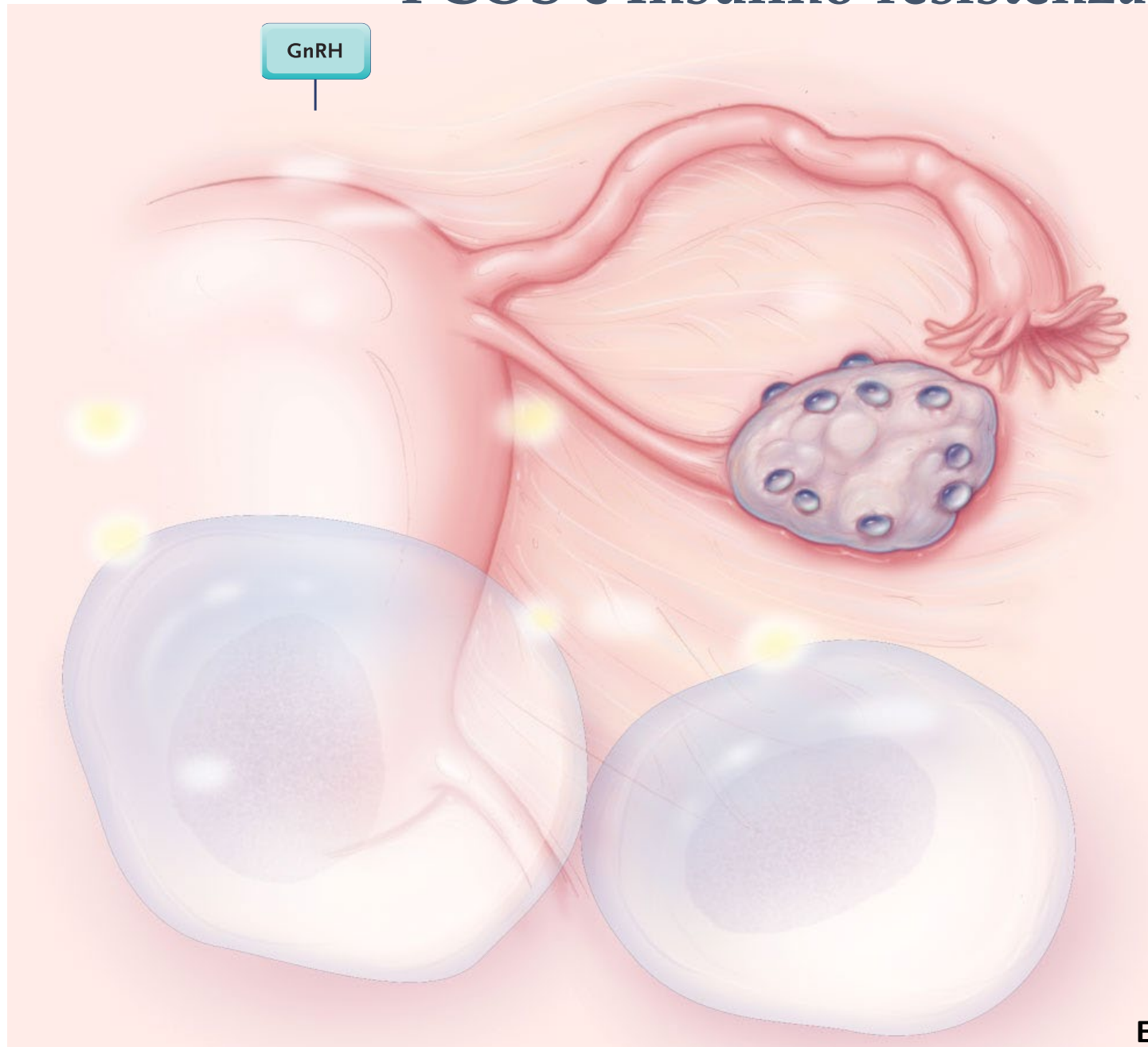


PCOS fattore di rischio indipendente del GDM

Metanalisi su 720 donne con PCOS e 4505 donne controllo



PCOS e Insulino-resistenza



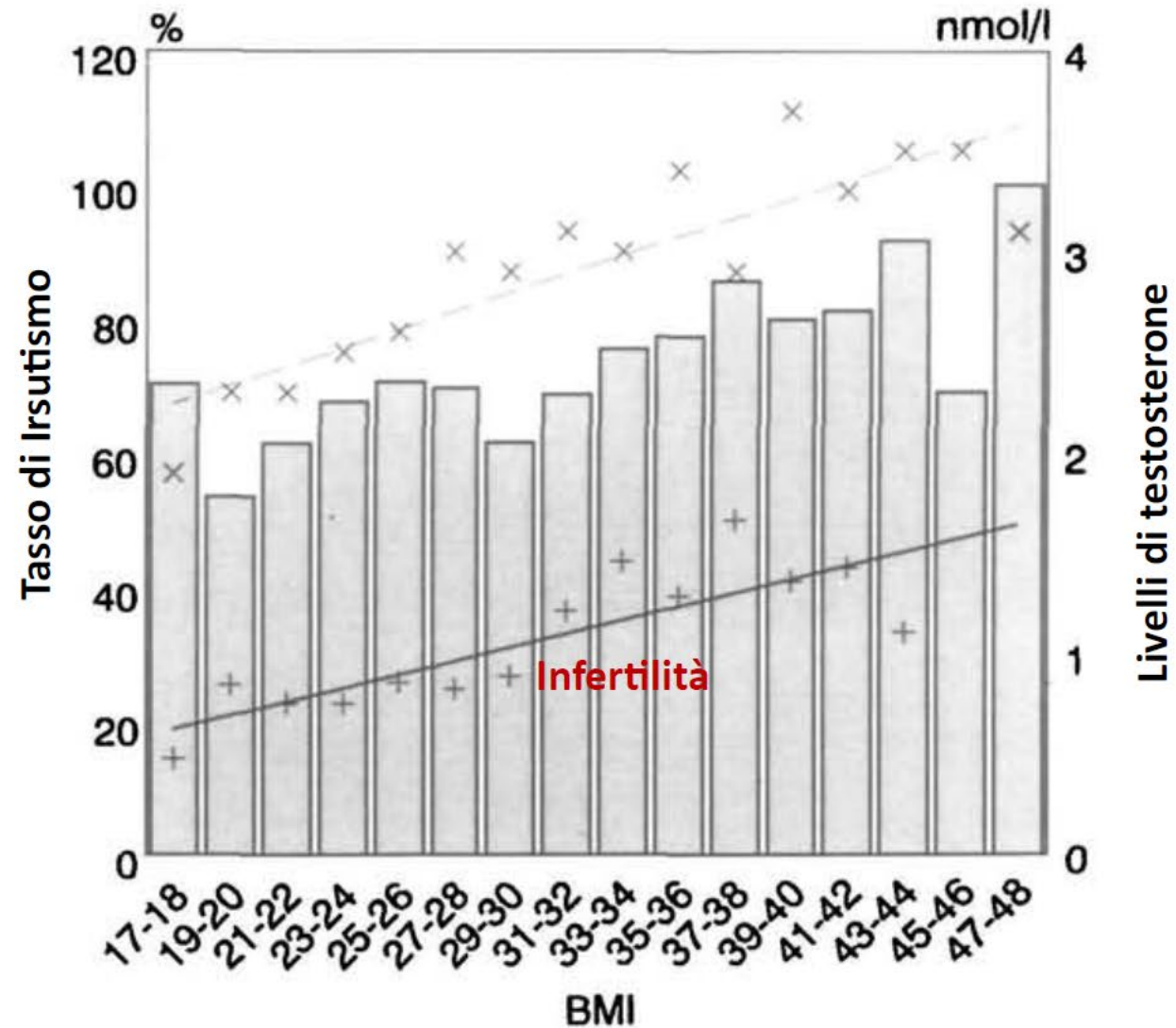
- Direct stimulation of ovarian androgen secretion.
- Augmentation of luteinizing hormone (LH)-stimulated androgen secretion by induction of steroidogenic enzymes.
- Enhancement of the amplitude and frequency of gonadotropin-releasing hormone (GnRH)-stimulated LH pulses, leading to ovarian dysfunction.
- Decreased hepatic production of sex hormone-binding globulin.
- Decreased ovarian insulin-like growth factor-binding protein 1 α gives rise to increased free insulin-like growth factor 1, which in turn stimulates androgen production.
- Hyperinsulinemia may contribute to midantral follicular arrest by enhancing anti-Müllerian hormone (AMH).

Obesità e PCOS

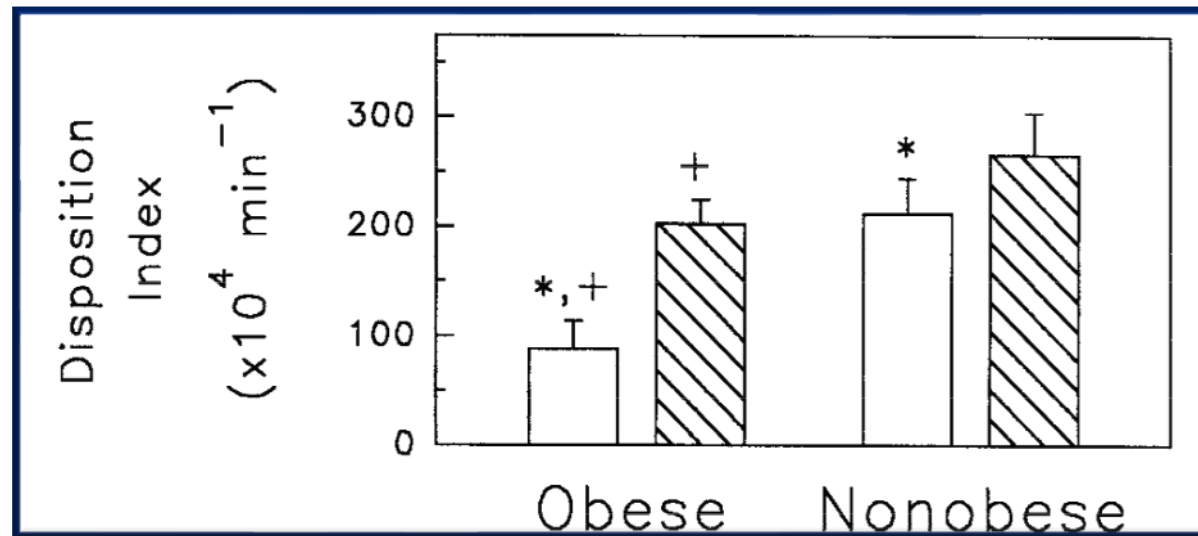
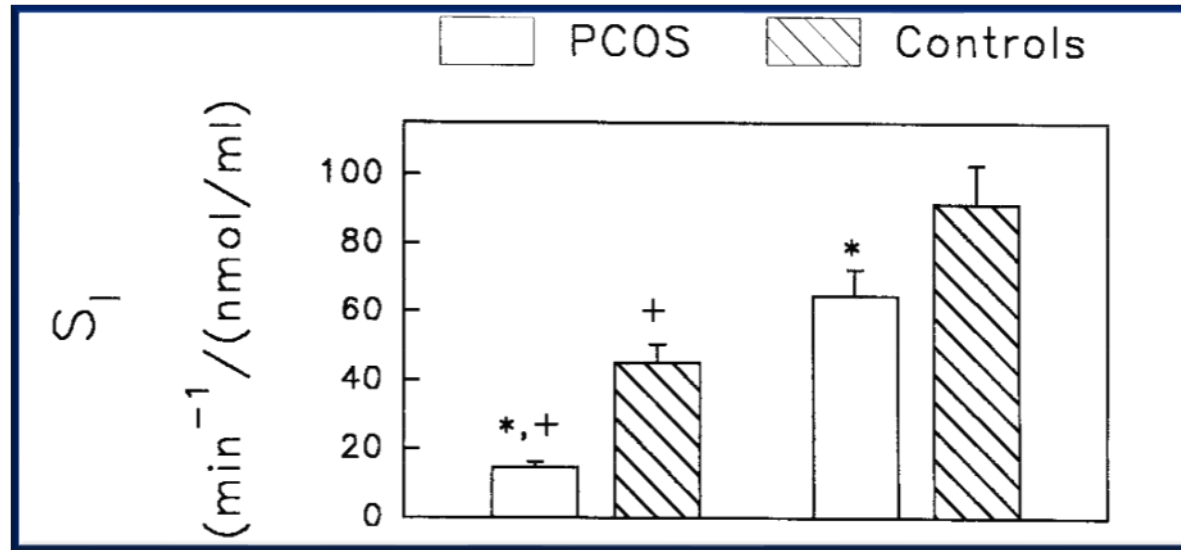
Tra il 40 e 50% dei casi la PCOS è associata ad obesità

Features	Obese PCOS	Lean PCOS
Hirsutism ⁶⁰	++	+
Total testosterone/androstenedione ratio ⁶⁰	1	1
Sex hormone-binding globulin ⁶⁰	2	Normal
Free testosterone ⁶⁰	—	1
Androsterone glucuronide ⁶⁰	—	1
Oligomenorrhea/anovulation ⁹⁴	++	+
Infertility ¹⁷⁵	++	+
Acanthosis nigricans ^{169,178}	++	+
Insulin resistance ¹⁷¹	++	+
IGT/diabetes mellitus ^{169,179}	++	+
Hyperlipidemia ¹⁸⁰	+	—
Hypertension ^{169,181}	+ (?)	—
Cardiovascular risk ¹⁸²	++ (?)	+ (?)
Endometrial carcinoma risk ⁹	++	+

Relazione diretta tra obesità e infertilità in PCOS



Ridotta secrezione insulinica in PCOS



BMI-pregravidico predittore indipendente di GDM

Variables	Coefficient	Chi-square (χ^2)	<i>P</i> -value
Age	0.094	78.833	< 0.0001
Previous pregnancies	14.39	1.126	0.89
Family history of DM	0.46	17.24	0.0017
Height	− 2.596	7.63	0.02
Pre-pregnancy BMI	0.110	72.28	< 0.0001
Weight gain	0.048	21.818	< 0.0001

Aumento del BMI-pregravidico si associa ad aumento del rischio di GDM in gravidanze ottenute con PMA

	Normal weight (<i>n</i> = 5,897)	Overweight (<i>n</i> = 1,613)	Obesity (<i>n</i> = 308)	χ^2/F -value	<i>P</i> -value
PTB					
Spontaneous PTB, <i>n</i> (%)	115 (1.95)	31 (1.92)	8 (2.30)	0.659	0.719
Medically indicated PTB, <i>n</i> (%)	292 (4.95)	128 (7.94)	24 (7.79)	23.724	<0.001
Pre-eclampsia, <i>n</i> (%)	220 (3.73)	96 (5.95)	21 (6.82)	20.034	<0.001
Gestational diabetes mellitus, <i>n</i> (%)	1,188 (20.14)	530 (32.86)	129 (41.88)	172.672	<0.001
Post-partum hemorrhage, <i>n</i> (%)	148 (2.51)	46 (2.85)	9 (2.92)	0.720	0.698
Cesarean delivery, <i>n</i> (%)	2,071 (35.12)	384 (23.81)	65 (21.10)	92.391	<0.001
Neonatal RDS, <i>n</i> (%)	197 (3.34)	51 (3.16)	10 (3.25)	0.130	0.937
NICU recovery, <i>n</i> (%)	115 (1.95)	32 (1.98)	7 (1.94)	0.160	0.923

PTB, preterm birth; RDS, respiratory distress syndrome; NICU, neonatal intensive care unit.

Aumento del BMI-pregravidico si associa ad aumento del rischio di GDM in gravidanze ottenute con PMA

	<18.5 (kg/m ²)	18.5-<23 (kg/m ²)	23-<27.5 (kg/m ²)	≥27.5 (kg/m ²)
^a Caesarean section Crude OR	0.676 (0.522-0.877)	1 (Reference)	1.345 (1.138-1.589)	1.578 (1.145-2.174)
Adjusted OR	0.699 (0.519-0.943)	1 (Reference)	1.463 (1.195-1.792)	2.233 (1.465-3.405)
^b Gestational hypertension and preeclampsia Crude OR	0.809 (0.465-1.405)	1 (Reference)	2.373 (1.820-3.094)	3.840 (2.573-5.731)
Adjusted OR	0.728 (0.390-1.360)	1 (Reference)	2.289 (1.709-3.066)	4.365 (2.775-6.866)
^b Gestational diabetes mellitus Crude OR	0.732 (0.498-1.077)	1 (Reference)	1.895 (1.553-2.313)	2.800 (2.005-3.909)
Adjusted OR	0.882 (0.570-1.365)	1 (Reference)	1.633 (1.295-2.059)	2.004 (1.336-3.006)
^c Low birth weight Crude OR	0.940 (0.478-1.847)	1 (Reference)	1.085 (0.723-1.627)	1.989 (1.075-3.680)
Adjusted OR	0.798 (0.374-1.704)	1 (Reference)	0.951 (0.612-1.476)	1.338 (0.633-2.826)
^c Fetal macrosomia Crude OR	0.304 (0.111-0.837)	1 (Reference)	1.429 (1.011-2.020)	2.681 (1.597-4.500)
Adjusted OR	0.312 (0.112-0.872)	1 (Reference)	1.403 (0.964-2.043)	3.004 (1.693-5.330)

^aAdjusted for maternal age, parity (nulliparous, multiparous), and rate of GWG.

^bAdjusted for maternal age, parity (nulliparous, multiparous), mode of delivery (vaginal delivery, caesarean section) and rate of GWG.

^cAdjusted for maternal age, parity (nulliparous, multiparous), mode of delivery (vaginal delivery, caesarean section), sex of newborn and rate of GWG.

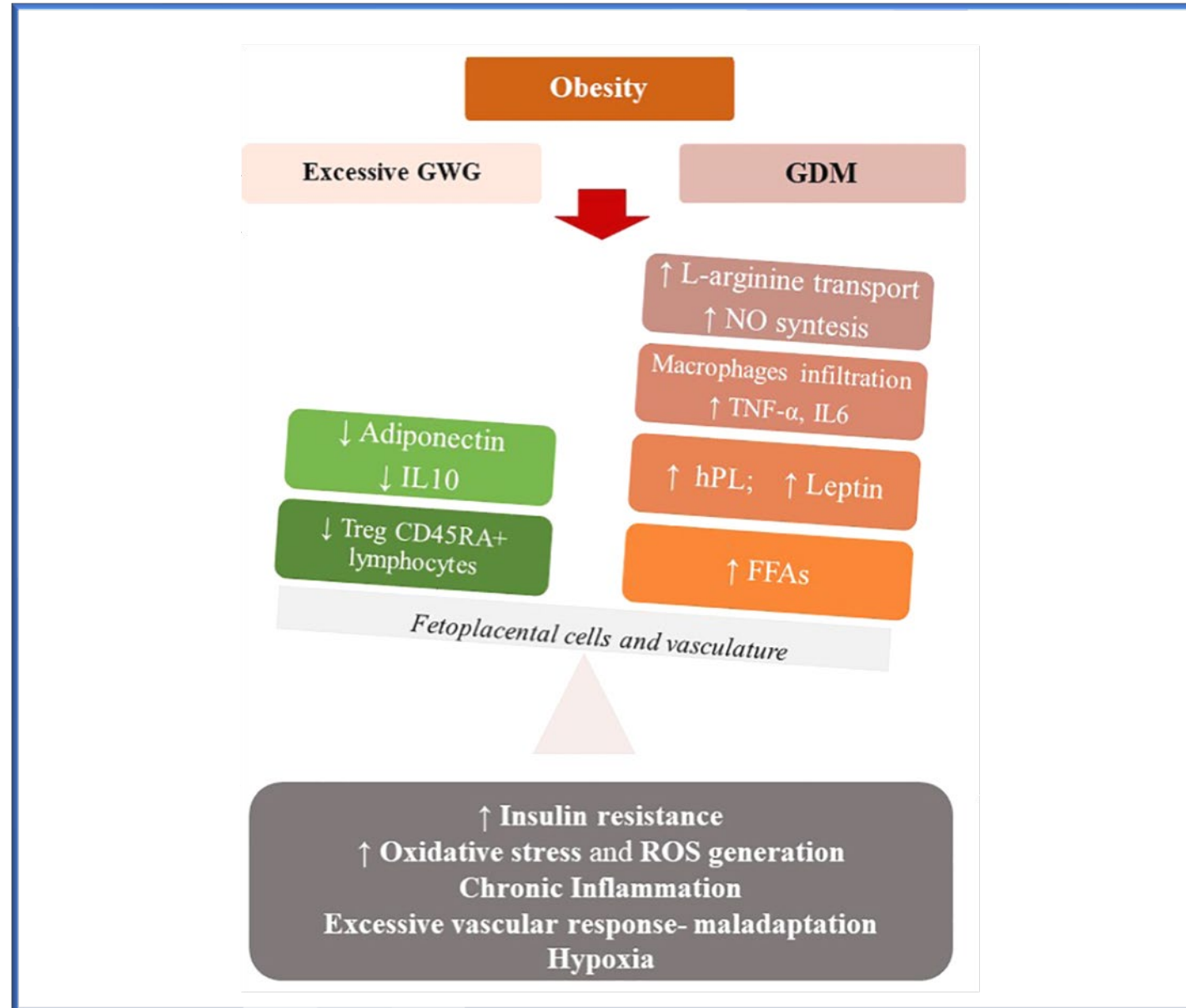
Aumento del BMI-pregravidico si associa ad aumento degli outcome avversi neonatali in gravidanze ottenute con PMA

	<18.5 (kg/m ²)	18.5-<23 (kg/m ²)	23-<27.5 (kg/m ²)	≥27.5 (kg/m ²)
Fetal distress	12 (4.49)	100 (5.67)	41 (4.92)	12 (6.78)
Gender of newborn	125 (46.82)	965 (54.67)	422 (50.60)	105 (59.32)
^a Low birth weight	10 (4.29)	73 (4.55)	37 (4.92)	13 (8.67)*
^a Fetal macrosomia	4 (1.72)*	87 (5.43)	57 (7.58)*	20 (13.33)*
^a Apgar score at one minute ≤ 7	1 (0.43)	22 (1.37)	7 (0.93)	3 (3.33)

**P* < 0.05.

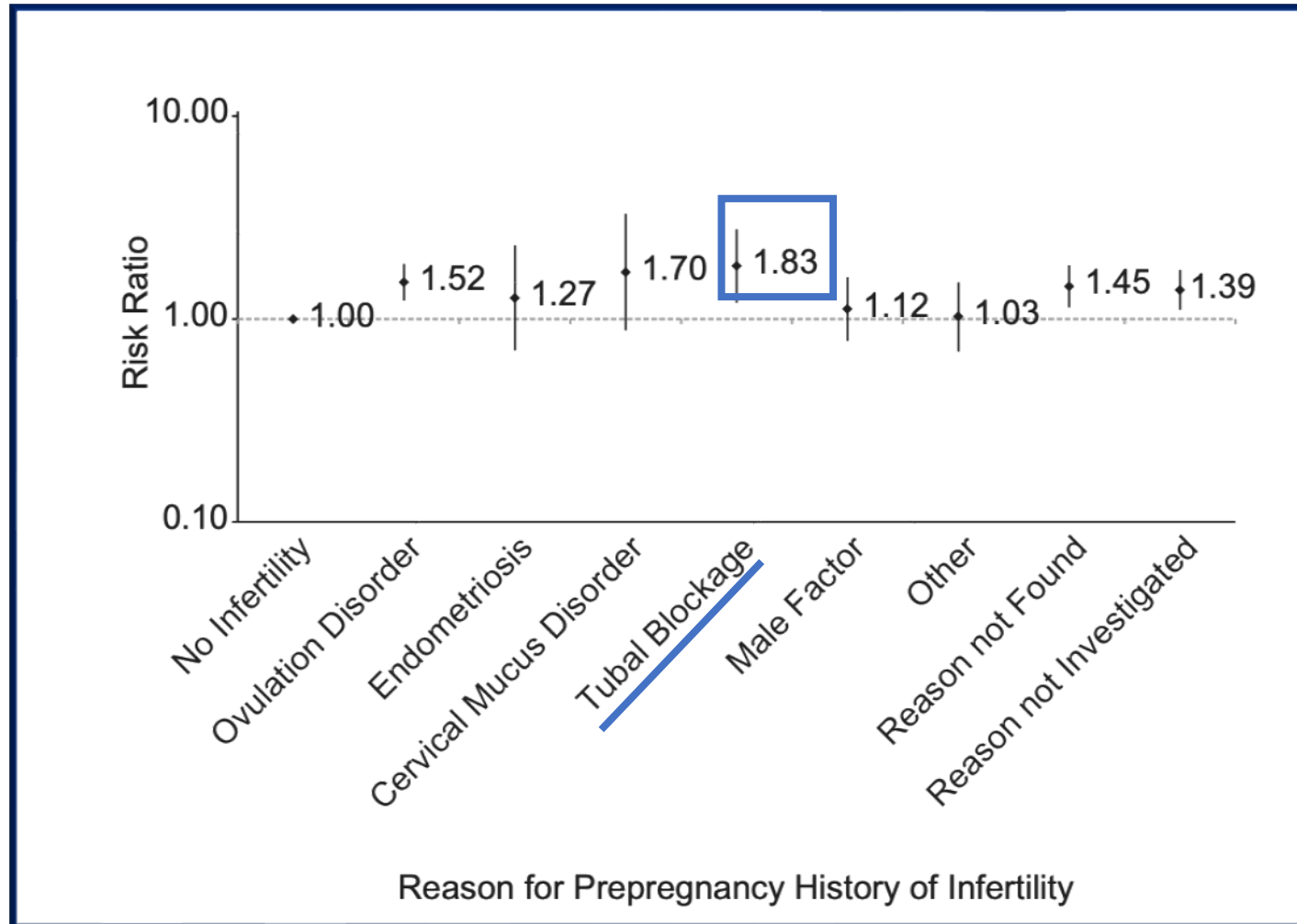
^a*Due to the partial missing data on neonatal outcomes, 2738 newborns were finally included in the study.*

Obesità, infiammazione, GDM e sindrome metabolica della gravidanza



Cause di infertilità e rischio di GDM in NHS

40.773 gravidanze dal Nurses' Health Study II



Nel 50% la causa è l'infezione da *Chlamydia trachmydia* che evolve in Malattia infiammatoria pelvica

Infiammazione sistemica è associata ad aumentato rischio di GDM

	Tertile of maternal serum CRP concentrations (mg/L)			<i>P</i> -value for trend
	1 (Low)	2 (Intermediate)	3 (High)	
Interval	≤2.1	2.2–5.2	≥5.3	
Tertile median	1.2	3.5	8.8	
GDM Cases, <i>n</i>	5	7	26	
Total population, <i>N</i>	284	284	283	
RR [95% CI]	1.0 (Reference)	1.4 [0.4, 4.4]	5.2 [2.0, 13.6]	<0.001
ARR ^a [95% CI]	1.0 (Reference)	1.3 [0.4, 4.2]	4.6 [1.8, 12.1]	<0.001
ARR ^b [95% CI]	1.0 (Reference)	1.2 [0.4, 3.7]	3.5 [1.2, 9.8]	0.007

	Tertile of maternal serum CRP concentrations (mg/L)	
	Lower two tertiles	Highest tertile
Interval	≤5.2	≥5.3
Strata 1 – lean women (BMI < 25 kg/m ²)		
GDM cases, <i>n</i>	10	11
Total population, <i>N</i>	486	146
RR [95% CI]	1.0 (Reference)	3.7 [1.6, 8.6]
ARR ^a [95% CI]	1.0 (Reference)	3.7 [1.6, 8.7]
Strata 2 – overweight women (BMI ≥ 25 kg/m ²)		
GDM cases, <i>n</i>	2	15
Total population, <i>N</i>	76	130
RR [95% CI]	1.0 (Reference)	4.4 [1.0, 19.2]
ARR ^a [95% CI]	1.0 (referent)	3.6 [0.8, 15.7]

PMA predittore indipendente di GDM



PMA predittore indipendente di GDM

Logistic regression backward analysis for determining risk factors of gestational diabetes mellitus in the study population.

	Adjusted OR	95% CI	<i>p</i> -Value
Age	1.07	1.0–1.1	0.02
Body mass index	2.9	1.2–6.9	<0.001
ART conception mode	2.0	2.1–4.5	0.05
Progesterone use during pregnancy	35.5	10.2–52.7	0.01

Aumentata incidenza di GDM in PMA indipendentemente dai noti fattori di rischio

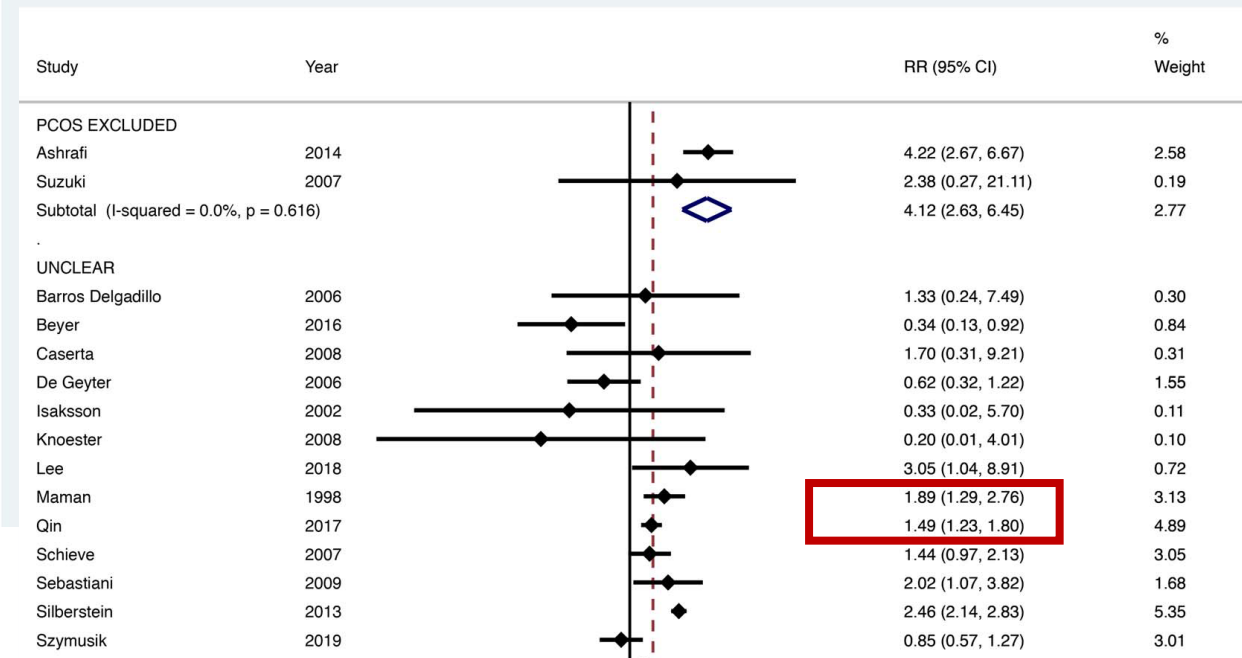
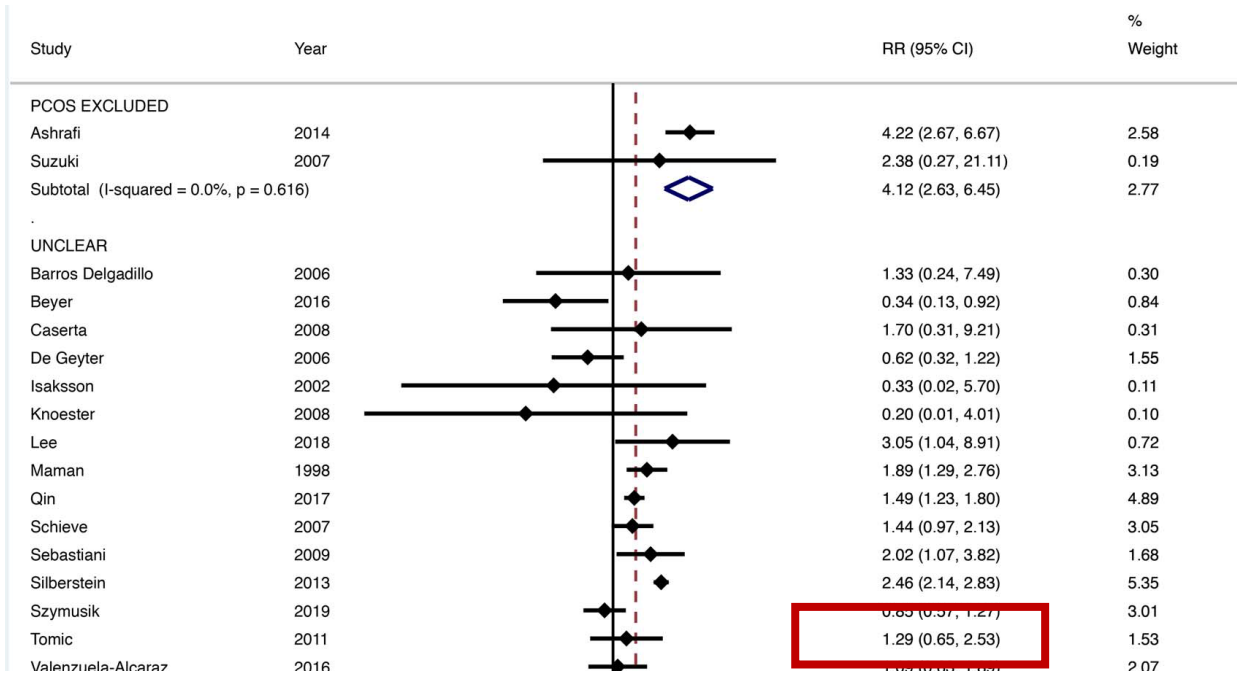
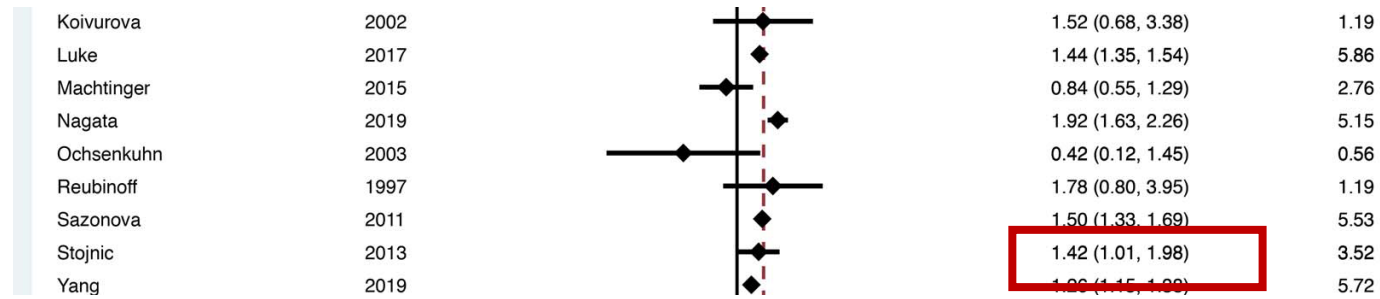
Studio Cross-sectional: Criteri di esclusione: PCOS, pregresso GDM, età>40, macrosomia, familiarità per DM

Characteristics of women in the spontaneous pregnancy, in-vitro fertilization/intracytoplasmic sperm injection (IVF/ICSI) and intra-uterine injection (IUI) groups.				
Variables	Spontaneous pregnancy group (n = 215)	IVF/ICSI group (n = 95)	IUI group (n = 50)	p-Value
Age (years)	26.6 ± 5.8	31.3 ± 4.9	29.4 ± 5.8	<0.001 ^a
Age at menarche (years)	12.6 ± 1.4	13.3 ± 1.5	13.5 ± 2.3	0.001 ^b
Regular menses, n (%)	205 (95.3)	86 (90.5)	41 (82)	0.005
Pre-pregnancy body mass index (kg/m ²)	27.0 ± 3.9	25.4 ± 4.6	26.0 ± 3.3	0.004 ^c
Weight gain in pregnancy (kg)	10.7 ± 2.5	11.5 ± 2.6	11.9 ± 2.0	0.004 ^d
Nulliparous, n (%)	84 (39.1)	66 (69.5)	30 (60)	<0.001
Incidence of pregnancy-induced hypertension, n (%)	14 (7.2)	20 (21.0)	7 (14)	0.01
Incidence of gestational diabetes mellitus, n (%)	22 (10.2)	41 (43.1)	13 (26)	<0.001

Characteristics associated with gestational diabetes mellitus in the women in the spontaneous pregnancy, in-vitro fertilization/intracytoplasmic sperm injection (IVF/ICSI) and intra-uterine injection (IUI) groups.

Variables	Spontaneous pregnancy group (n = 20)	IVF/ICSI group (n = 41)	IUI group (n = 13)	p-Value
Age (years)	30.7 ± 4.9	32.2 ± 5.0	29.4 ± 4.4	0.17
Age at menarche (years)	12.8 ± 1.5	13.1 ± 1.7	13.3 ± 2.0	0.68
Regular menses, n (%)	18 (90)	36 (87.8)	10 (76.9)	0.52
Pre-pregnancy body mass index (kg/m ²)	29.0 ± 3.9	26.6 ± 4.4	27.0 ± 3.4	0.1
Weight gain in pregnancy (kg)	10.9 ± 2.3	11.2 ± 2.6	11.2 ± 2.9	0.89
Nulliparous, n (%)	5 (25)	30 (73.2)	8 (61.5)	0.002
Progesterone use for luteal phase support, n (%)	0 (0)	41 (100)	7 (53.8)	<0.001
Progesterone use after 12 weeks of pregnancy, n (%)	2 (10)	29 (70.7)	6 (46.2)	<0.001
Insulin therapy for gestational diabetes mellitus, n (%)	4 (20)	10 (24.4)	3 (23.1)	0.8

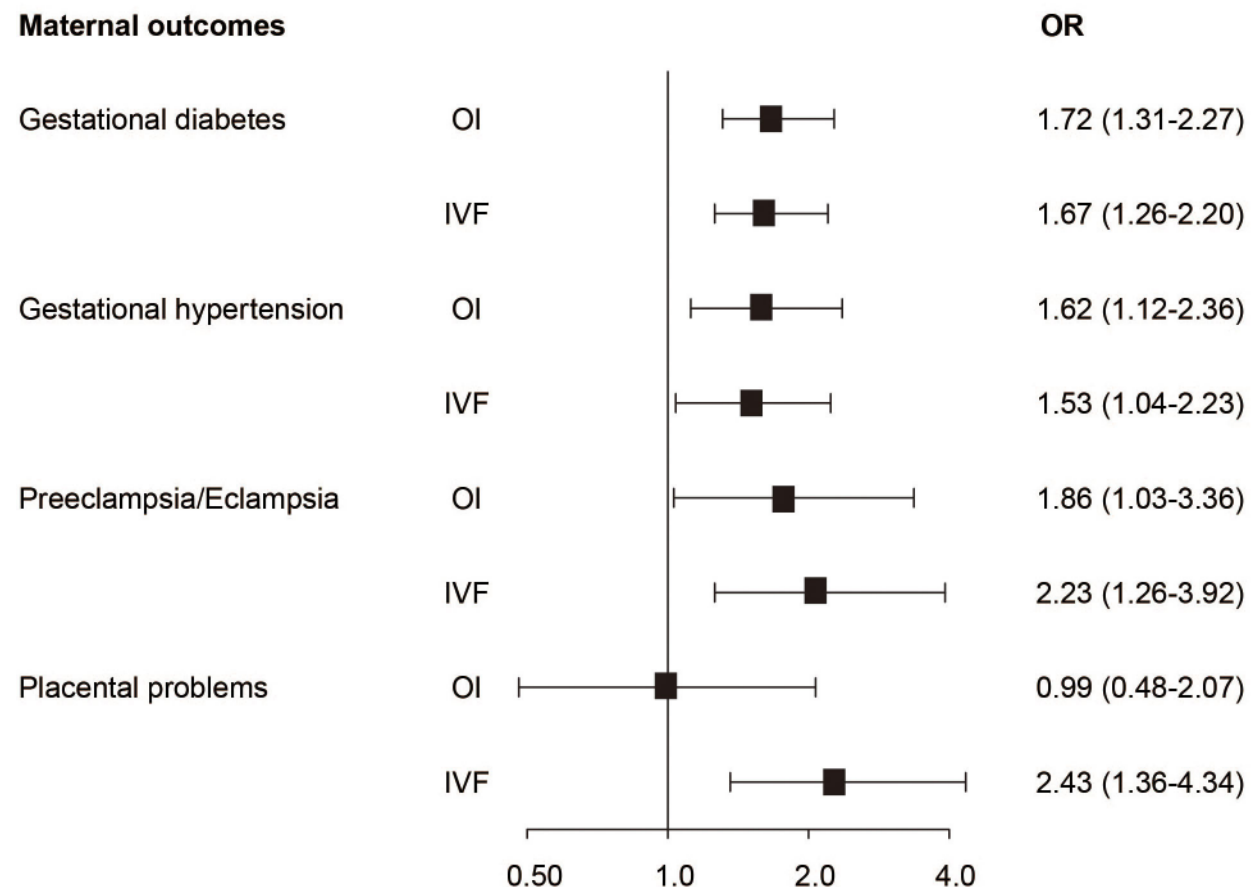
Aumentata incidenza di GDM in PMA indipendentemente dalla PCOS



Aumentata incidenza di GDM in PMA indipendentemente dalla tecnica

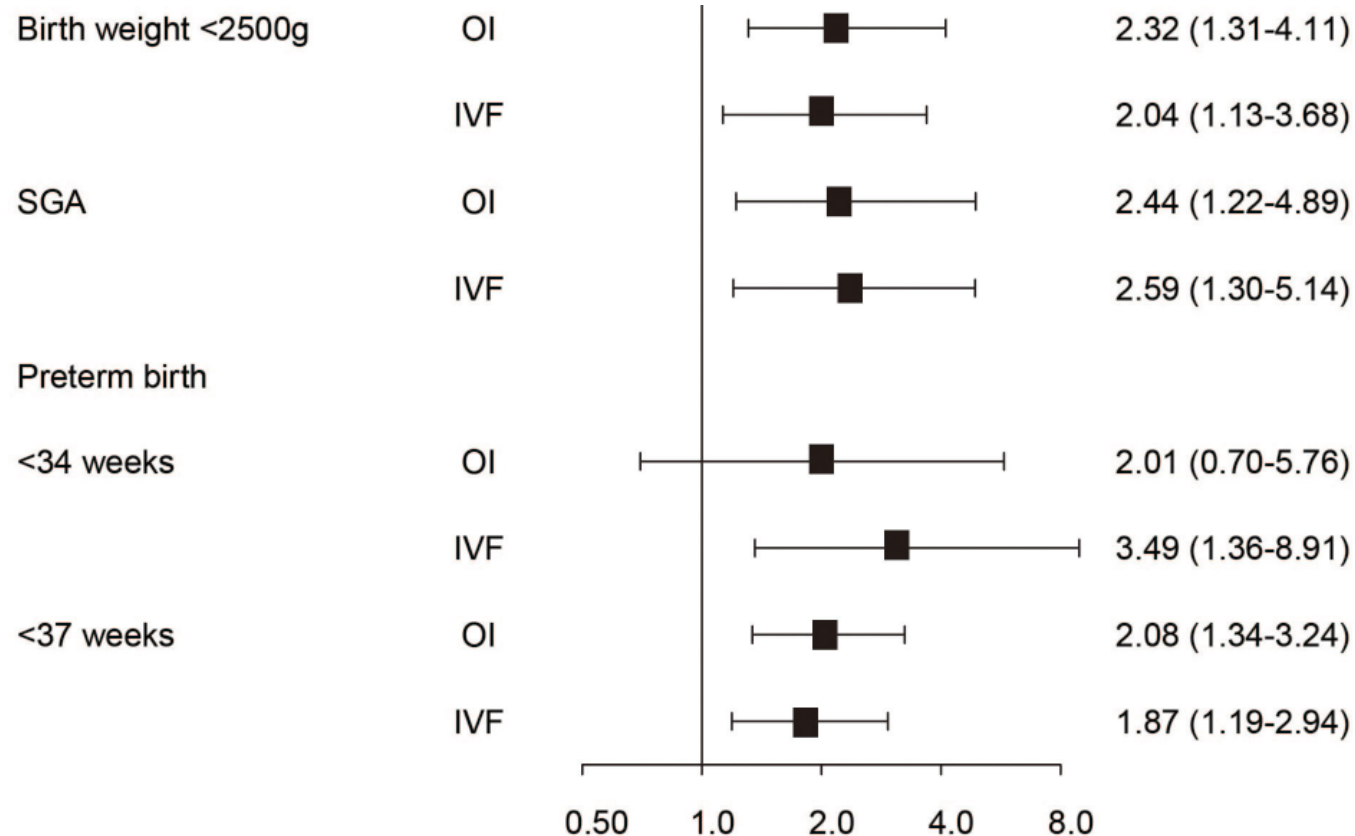
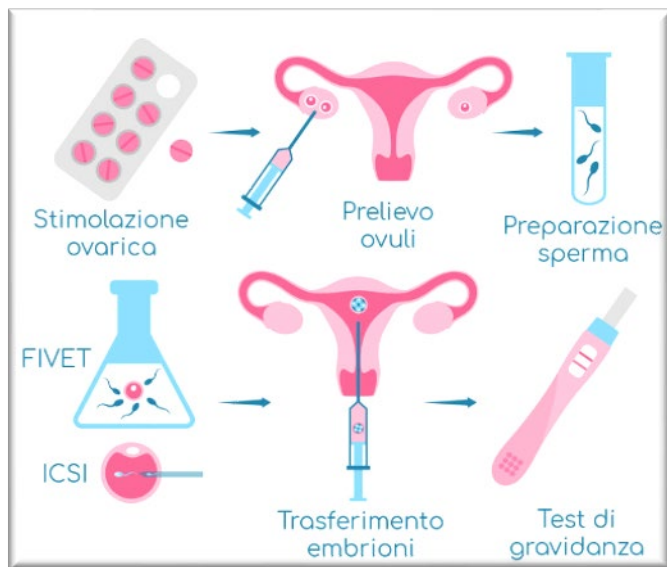
51.172 gravidanze singole, di cui 3.285 ottenute con IVF, 539 ottenute con induzione dell'ovulazione e 47.348 naturali

Induzione dell'Ovulazione
Fertilizzazione in vitro



Aumentata incidenza di outcome fetal in PMA indipendentemente dalla tecnica

51.172 gravidanze singole, di cui 3.285 ottenute con IVF, 539 ottenute con induzione dell'ovulazione e 47.348 naturali



Aumentata incidenza di GDM in PMA indipendentemente dai noti fattori di rischio

Studio Cross-sectional: Criteri di esclusione: PCOS, pregresso GDM, età>40, macrosomia, familiarità per DM

Characteristics associated with gestational diabetes mellitus in the women in the spontaneous pregnancy, in-vitro fertilization/intracytoplasmic sperm injection (IVF/ICSI) and intra-uterine injection (IUI) groups.

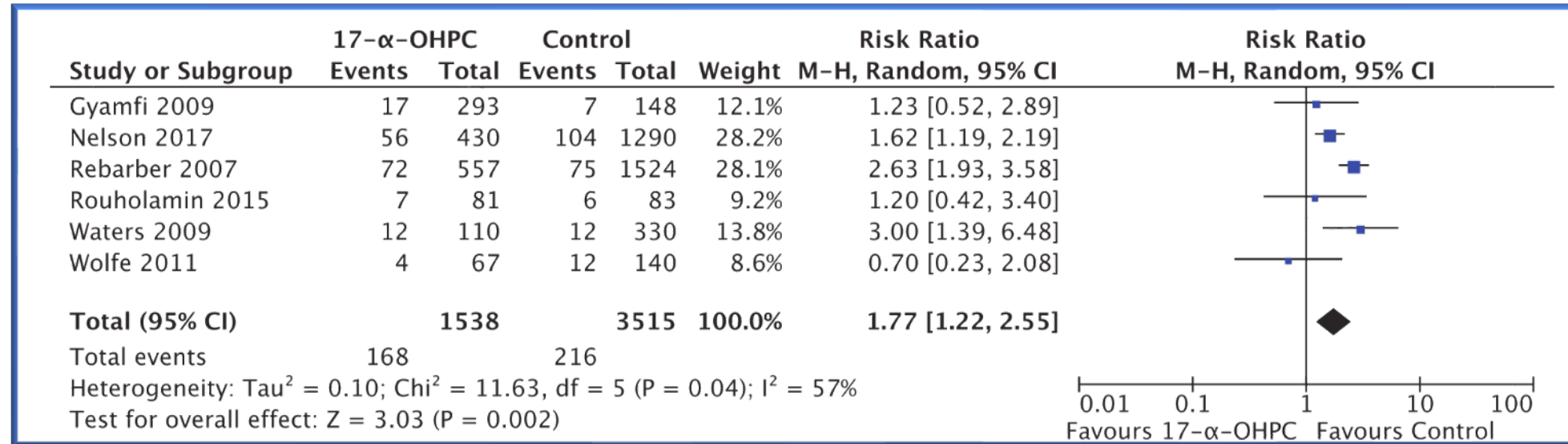
Variables	Spontaneous pregnancy group (n = 20)	IVF/ICSI group (n = 41)	IUI group (n = 13)	p-Value
Age (years)	30.7 ± 4.9	32.2 ± 5.0	29.4 ± 4.4	0.17
Age at menarche (years)	12.8 ± 1.5	13.1 ± 1.7	13.3 ± 2.0	0.68
Regular menses, n (%)	18 (90)	36 (87.8)	10 (76.9)	0.52
Pre-pregnancy body mass index (kg/m ²)	29.0 ± 3.9	26.6 ± 4.4	27.0 ± 3.4	0.1
Weight gain in pregnancy (kg)	10.9 ± 2.3	11.2 ± 2.6	11.2 ± 2.9	0.89
Nulliparous, n (%)	5 (25)	30 (73.2)	8 (61.5)	0.002
Progesterone use for luteal phase support, n (%)	0 (0)	41 (100)	7 (53.8)	<0.001
Progesterone use after 12 weeks of pregnancy, n (%)	2 (10)	29 (70.7)	6 (46.2)	<0.001
Insulin therapy for gestational diabetes mellitus, n (%)	4 (20)	10 (24.4)	3 (23.1)	0.8

Terapia con progesterone predittore indipendente di GDM

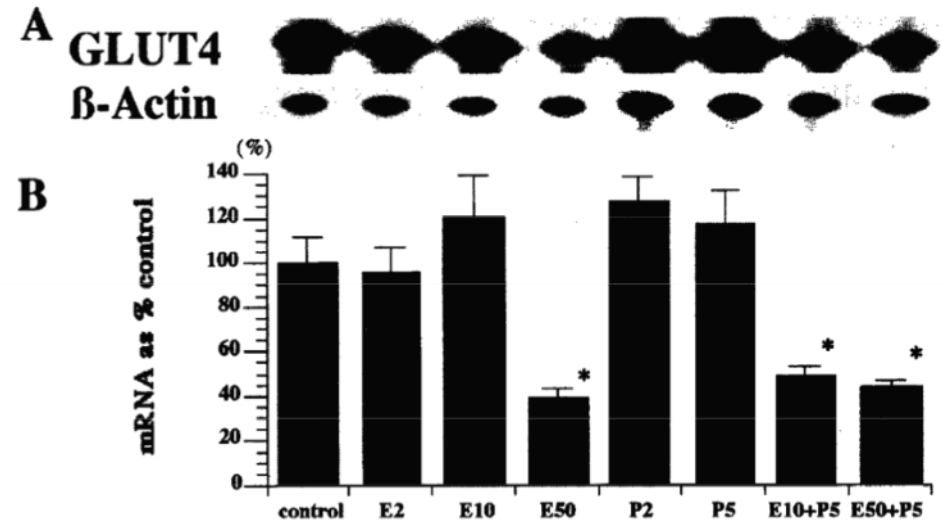
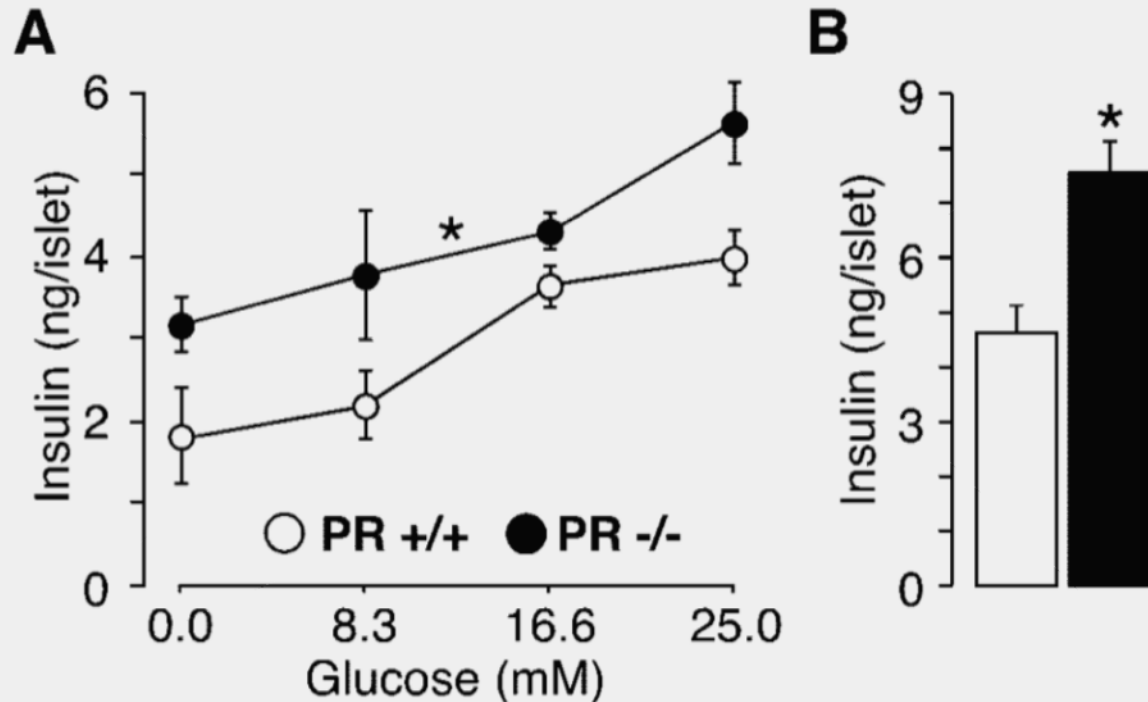
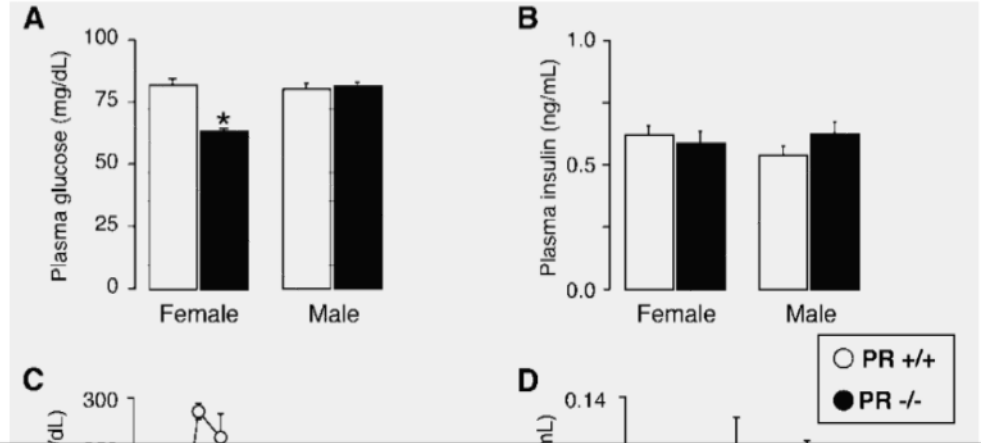
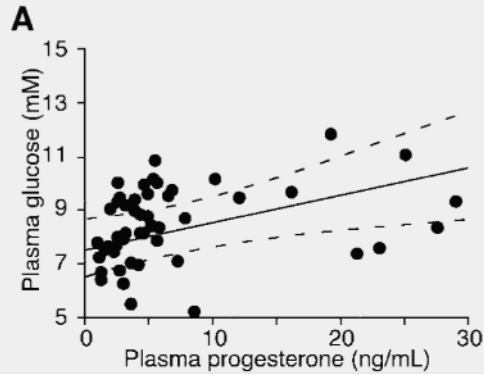
	Variable	OR (95% CI)	P	OR (95% CI)
	Abnormal 1-h 50-g glucose screen			
Obese BMI	17OHPC exposure	2.6 (1.4–5.1)	0.004	.91 (2.93–16.28)
Overweight	Maternal age (y)	1.3 (0.1–16.9)	0.84	.70 (1.53–8.92)
17P proph	BMI (kg/m ²)	3.0 (0.8–11.3)	0.10	.09 (2.17–4.40)
Normal BMI	African-American race	0.23 (0.01–0.57)	0.001	.80 (0.74–4.38)
Betamimetic	Previous delivery	1.6 (0.6–4.6)	0.35	.04 (0.67–1.64)
Gestational	Gestational diabetes			.97 (0.933–1.000)
Tobacco use	17OHPC exposure	3.3 (1.3–8.1)	0.01	.57 (0.24–1.33)
	Maternal age (y)	0.3 (0.02–3.7)	0.33	
	BMI	0.8 (0.2–3.0)	0.76	
	African-American race	0.7 (0.2–2.4)	0.57	
	Previous delivery	1.1 (0.2–5.8)	0.89	

Terapia con progesterone aumenta il rischio di GDM

Metanalisi su 5053 donne con gravidanza singola e pregresso parto pretermine



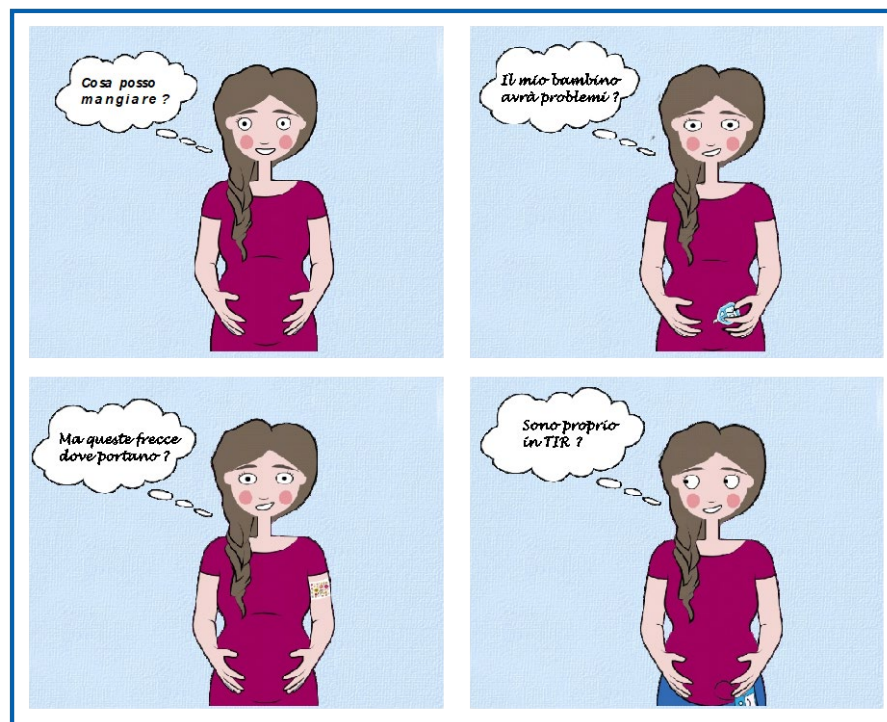
Il progesterone aumenta la glicemia, riduce la sensibilità insulinica e la secrezione insulinica



Picard F et al, Proc Natl Acad Sci USA 2002; 99, 15644–15648

Sugaya A et al Life Sci 2000 66: 641-648

PMA predittore indipendente di terapia insulinica in GDM



PMA predittore indipendente di terapia insulinica in GDM

Model	OR (CI 95%) ^a	
Age ≥ 35 yr. (Yes/No)	2.91 (1.28–6.62) [†]	
Prior history of GDM (Yes/No)	3.22 (0.83–12.51)	

Variable	Odds Ratio	95% CI
Altered FPG at OGTT	1.6176	1.3371–1.9568
Pre pregnancy BMI >30	1.8630	1.4159–2.4513
Age >35	1.2259	1.0176–1.4768
Family history DM	1.1433	1.0138–1.2894
ART pregnancy	1.8060	1.1940–2.7318
Previous GDM	1.8141	1.3558–2.4272
Hypothyroidism	1.5197	1.0728–2.1527

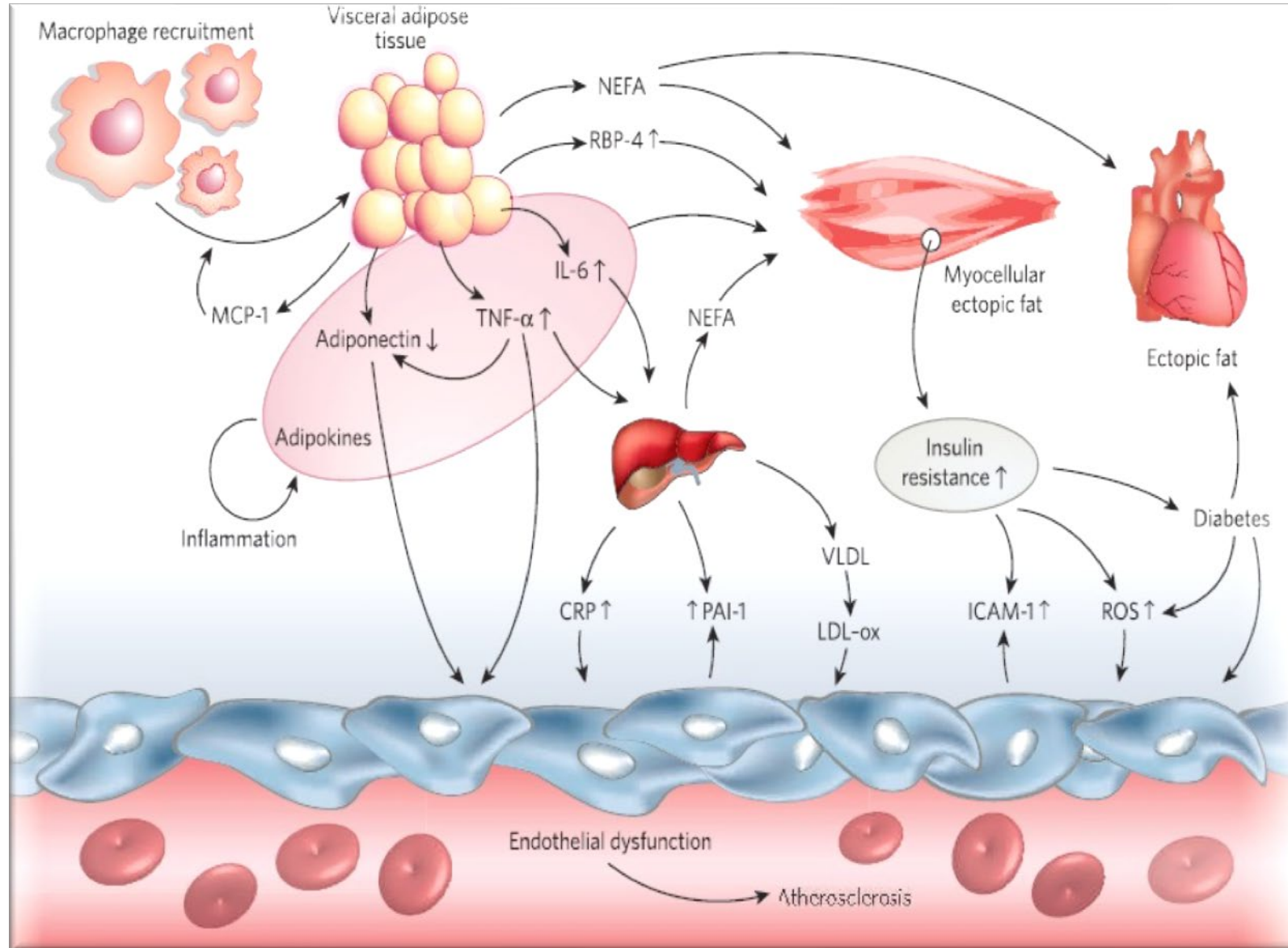
PMA predittore di terapia insulinica in GDM indipendentemente da infertilità e tecniche

Variables	MNT (<i>n</i> = 60)	MNT-IT (<i>n</i> = 40)	<i>P</i> -value
Menarche age, years (Mean ± SE)	13.1 ± 0.2	13.6 ± 0.3	0.532
Infertility duration, years, (Mean ± SE)	6.2 ± 0.5	7.5 ± 0.8	0.117
Irregular menstrual cycle, <i>n</i> (%)	7 (11.7)	3 (7.5)	0.496
Infertility type (Secondary), <i>n</i> (%)	25 (41.7)	17 (42.5)	0.934
Prior OHSS risk, <i>n</i> (%)	23 (38.3)	17 (42.5)	0.677
COH protocol			
Standard long GnRH agonist, <i>n</i> (%)	44 (77.2)	35 (87.5)	0.199
ART mode			
Fresh ET, <i>n</i> (%)	28 (51.9)	23 (57.5)	0.587

Maggiore infiammazione in donne con PMA e terapia insulinica in GDM

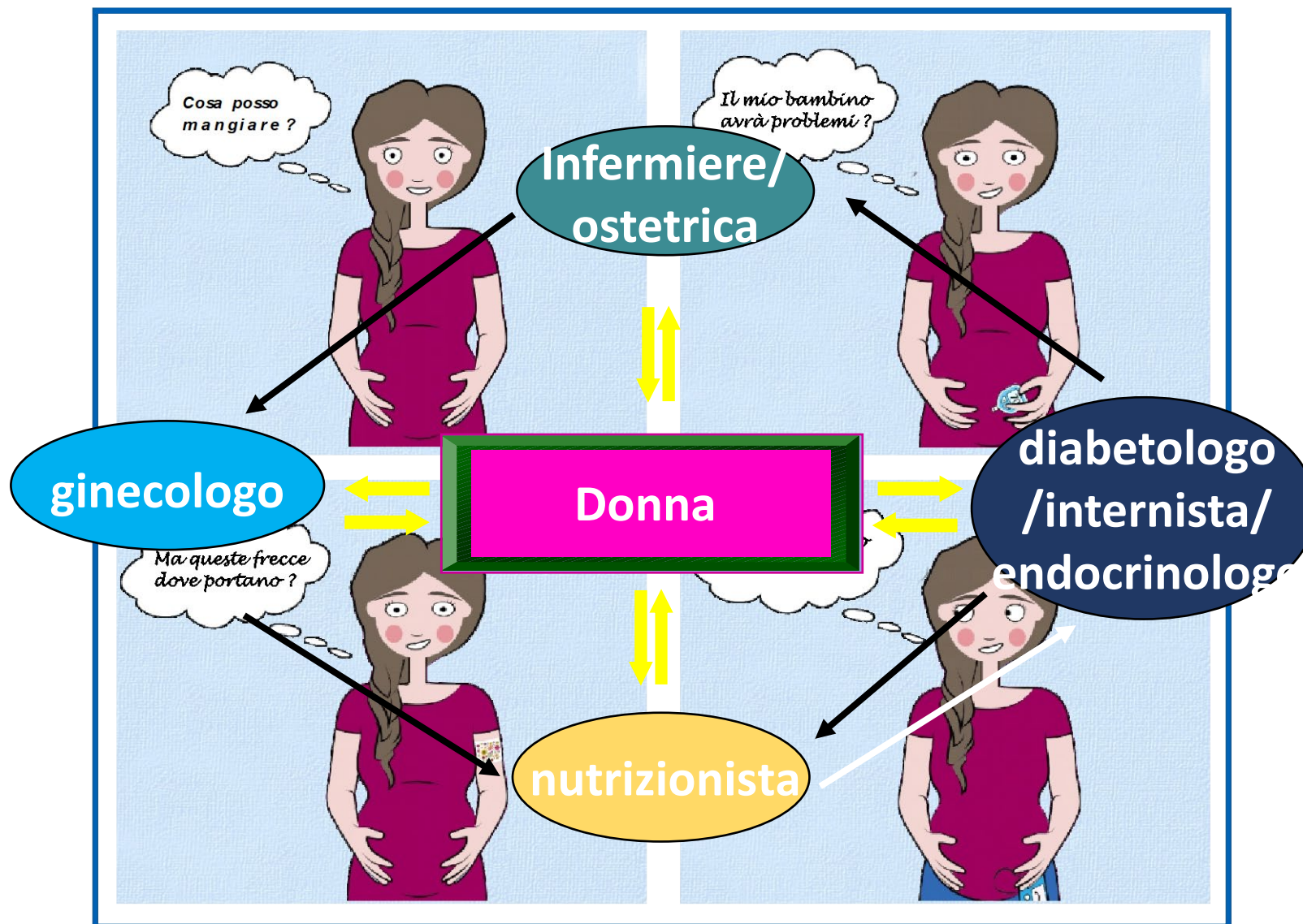
Variables	SC (n = 136)			ART (n = 100)			P-value ^c
	MNT (n = 102)	MNI-IT (n = 34)	P-value ^a	MNT (n = 60)	MNT-IT (n = 40)	P-value ^b	
GTT-FBS (mg/dl)(Mean ± SE)	91.69 ± 0.95	98.18 ± 1.66	0.001*	90.67 ± 1.20	96.92 ± 1.42	0.001*	0.002*
GTT-1 h (mg/dl)(Mean ± SE)	156.10 ± 4.46	183.90 ± 8.66	0.003*	159.14 ± 5.98	156.82 ± 7.98	0.813	0.014*
GTT-2 h (mg/dl)(Mean ± SE)	129.38 ± 4.19	147.40 ± 7.34	0.003*	131.0 ± 4.50	136.58 ± 6.39	0.464	0.046*
FBS (mg/dl) (Mean ± SE)	82.89 ± 1.21	88.03 ± 1.77	0.032*	85.98 ± 0.99	91.44 ± 1.77	0.004*	0.030*
HbA1c (%) (Mean ± SE)	4.92 ± 0.07	5.40 ± 0.12	0.005*	4.85 ± 0.10	5.16 ± 0.08	0.022*	0.004*
TG (mg/dl) (Mean ± SE)	201.12 ± 6.83	199.11 ± 13.71	0.887	175.31 ± 8.16	204.97 ± 9.69	0.026*	0.065
Cholesterol (mg/dl) (Mean ± SE)	221.33 ± 4.20	215.71 ± 6.36	0.491	202.09 ± 4.58	223.13 ± 7.97	0.019*	0.066
HDL (mg/dl) (Mean ± SE)	64.61 ± 1.56	62.85 ± 2.60	0.573	65.20 ± 1.74	60.81 ± 1.65	0.097	0.083
LDL (mg/dl) (Mean ± SE)	117.30 ± 3.89	112.52 ± 6.54	0.496	101.83 ± 4.35	121.42 ± 6.93	0.014*	0.105
VLDL (mg/dl) (Mean ± SE)	40.19 ± 1.36	39.59 ± 2.84	0.836	35.06 ± 1.66	40.90 ± 1.92	0.029*	0.089
hs-CRP (mg/l) (Mean ± SE)	4.60 ± 0.41	5.06 ± 1.16	0.651	6.45 ± 0.75	8.69 ± 1.95	0.049*	0.010*
IL-17(pg/mL) (Mean ± SE)	1.21 ± 0.27	0.70 ± 0.60	0.660	0.91 ± 0.19	5.52 ± 2.35	0.017 ^b	0.061
Insulin (mU/L) (Mean ± SE)	12.90 ± 1.64	15.87 ± 2.58	0.375	13.26 ± 1.36	14.92 ± 1.29	0.411	0.191
HOMA-IR	2.76 ± 0.42	3.39 ± 0.49	0.443	2.86 ± 0.33	3.40 ± 0.31	0.255	0.202

Adiposità, insulino-resistenza, GDM e sindrome metabolica della gravidanza



Take home messages

- Evidenze crescenti dimostrano come la PMA sia un emergente fattore di rischio per il GDM
- E' plausibile che fattori legati all'infertilità così come la terapia utilizzata per l'infertilità possano incrementare il rischio di GDM
- Evidenze suggeriscono che la PMA è predittore di terapia insulinica in donne con GDM
- E' necessario ridurre i fattori di rischio sottostanti al fine di ridurre il rischio di diabete gestazionale



Grazie per l'attenzione!

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