

PMD	First Author	Title	Year	Study Type	CVD	RF by CQ	Country	Setting	Blinding	Int Length	Total Study Duration	Main Study Objective	Total N	Target Population	Eligibility Criteria	Patient Characteristics	Int. n at Baseline (n at Follow-up)	Int. Type	Specific Intervention	Control n at Baseline (n at Follow-up)	Specific Control	Outcomes Measured	Results/CI	Significance	Safety and Adverse Events	Additional Findings	Summary	Main Reported Findings by Critical Question	
14557446	Ibanez L	Flutamide-metformin therapy to reduce fat mass in hyperinsulinemic ovarian hyperandrogenism: effects in adolescents and in women on their generation oral contraception	2003	RCT	None	Q10 (RF5, RF12, RF14) Q13 (RF8)	Spain	Clinical	None/NR	3 mo	3 mo	Determine whether a combination of flutamide and metformin reverses the abnormalities in body composition in women with PCOS, especially if the flutamide dose is further reduced, the combination is given at a young age, and an oral contraceptive is added	45	Pediatric/Young Adults	Adolescent girls or young women Hyperinsulinemic ovarian hyperandrogenism Exclusions: BMI > 25 kg/m <sup>2</sup> Glucose intolerance Family or personal history of diabetes mellitus	Mean age (SD): No oral contraceptive provided: 15 yr (0.3) Oral contraceptive provided: 18 yr (0.3)	Arm 1: 11 (NR) Arm 2: 11 (NR) Arm 3: 13 (NR)	Pharmacologic	Arm 1: Flutamide 62.5 mg/d + metformin 1,275 mg/d (NT) Arm 2: Flutamide 62.5 mg/d + metformin 1,275 mg/d + oral contraceptive-women only Arm 3: Oral contraceptive alone - women only Oral contraceptive was monophasic, low-dose estrogen (ethinyl-estradiol 20 µg + gestodene 75 µg, 21 dmo)	10 (NR)	Control Arm: No treatment	<b>Primary:</b> Mean BMI change [kg/m <sup>2</sup> ] (SEM) Mean fat mass change [kg] (SEM) Mean abdominal fat mass change [kg] (SEM) Mean lean mass change [kg] (SEM) Mean fasting glucose/insulin ratio change [mg/dL.mU/L] (SEM) Mean LDL-C change [mg/dL] (SEM) Mean HDL-C change [mg/dL] (SEM) Mean TG change [mg/dL] (SEM) Mean change in sex hormone binding globulin [µg/dL] (SEM) Mean testosterone change [ng/dL] (SEM) Mean change in androstenedione [ng/dL] (SEM) IGFBP-1 change [ng/mL] (SD)	<b>Primary:</b> Adolescents: INT: 0.0(0.0) vs CON: 0.2(0.1) INT: -1.7(0.7) vs CON: 1.1(0.4) INT: -0.7(0.2) vs CON: 4.8(0.07) INT: 1.2(0.5) vs CON: -0.5(0.2) INT: 2.4(0.6) vs CON: 0.14(0.06) INT: -14(4) vs CON: 3(4) INT: 10(3) vs CON: -3(1) INT: -89(7) vs CON: 68(4) INT: 0.30(0.074) vs CON: 0.14(0.06) INT: -50(12) vs CON: 3(7) INT: -47(23) vs CON: 7(9) INT: 9(2) vs CON: -1(2)	NS;NS S*,S** S*,S* S*,NS S**,NS S**,NS S**,NS S**,NS S*,NS S**,NS	Not reported	All outcomes of interest significant and in the desired direction.  In young women, there was no change with OC alone; addition of flutamide-metformin improved lean body mass & total fat but not abdominal fat.	In non-obese adolescents with PCOS with high insulin and androgen, metformin with flutamide increased LBM, reduced total & abdominal fat mass and improved all endocrine and lipid measures.	Q10: Risk factors (RF5 dyslipidemia, RF12 PCOS, RF 14 insulin resistance) can be decreased in non-obese adolescents with hyperandrogenism and hyperinsulinemia with drug treatment.  Q13: The acquisition of risk factors (RF8 obesity) may be prevented in children in children with hyperandrogenism and hyperinsulinemia with drug treatment.	
15356029	Ibanez L	Insulin sensitization for girls with precocious pubarche and with risk for polycystic ovary syndrome: effects of prepubertal initiation and postpubertal discontinuation of metformin treatment	2004	RCT (partial crossover)	None	Q13 (RF5, RF8, RF12, RF14)	Spain	Clinical	None/NR	Study 1 (prepubertal): 6 mo Study 2 (postpubertal): Arm 1: 12 mo Arm 2: 6 mo	18 mo This follow-up study includes 12 mo of treatment in post-pubertal girls during original study	Examine the efficacy of insulin sensitization with metformin to disrupt progression from precocious pubarche to PCOS	Study 1: 33 Study 2: 24	Pediatric/Young Adults	Girls LBW Study 1: BMI < 21 kg/m <sup>2</sup> Study 2: BMI < 26 kg/m <sup>2</sup> Hyperinsulinemia Subclinical ovarian hyperandrogenism	Mean age (SEM): Study 1: 8.0 yr (0.1) Study 2: 12.4 yr (0.2)	Study 1: Arm 1: 16 Study 2: Arm 1: 12 Arm 2: 12	Pharmacologic	Study 1: Arm 1: Metformin 425 mg/d Study 2: Arm 1: Metformin 850 mg/d for 12 mo, followed by no treatment for 6 mo Arm 2: No treatment for 12 mo, followed by metformin 850 mg/d for 6 mo	Study 1: Control Arm: 17 Study 2: N/A	Study 1: Control Arm: No treatment Study 2: N/A	<b>Primary:</b> Mean LDL-C change [mg/dL] (SEM) Mean HDL-C change [mg/dL] (SEM) Mean TG change [mg/dL] (SEM) Mean fat mass change [kg] (SEM) Mean abdominal fat mass change [kg] (SEM) Mean lean mass change [kg] (SEM) SHBG change [µg/dL] (SEM) Androstenedione change [ng/dL] (SEM) DHEAS change [µg/dL] (SEM) IL6 change [pg/mL] (SEM) Adiponectin change [µg/mL] (SEM)	<b>Primary RESULTS:</b> ON vs OFF Metformin ON: -15(5) vs OFF: -2(5) ON: 7(3) vs OFF: -1(3) ON: -16(5) vs OFF: 12(5) ON: -0.1(0.1) vs OFF: 1.0(0.3) ON: -0.3(0.1) vs OFF: 0.3(0.1) ON: 1.2(0.1) vs OFF: 0.7(0.2) ON: 0.2(0.1) vs OFF: -0.2(0.1) ON: -16(4) vs OFF: 9(7) ON: -6(5) vs OFF: 19(7) ON: -218(49) vs OFF: 32(54) ON: 0.7(0.6) vs OFF: -1.3(0.3)	S* between groups S* between groups S** between groups S between groups S* between groups S between groups S between groups S between groups S between groups S between groups	Minimal discussion: Prepubertal group had 1 subject with GI discomfort & 1 with rash, none mentioned for post-pubertal group.	In postpubertal girls, discontinuation of metformin resulted in reversal of all the advantageous changes seen on treatment.	Treatment with metformin in LBW girls with precocious pubarche reverses abnormal endocrine/metabolic state (lipids, hormone, adiponectin) and improves body composition. The benefit is lost after 6 months off treatment.	Q13: The acquisition of adverse risk factors (RF5 dyslipidemia, RF8 obesity, RF12 predisposing condition of PCOS) can be prevented in children at risk to develop PCOS because of precocious pubarche. Effect on insulin resistance (RF14) is less clear.	
15356029	Ibanez L	Insulin sensitization for girls with precocious pubarche and with risk for polycystic ovary syndrome: effects of prepubertal initiation and postpubertal discontinuation of metformin treatment	2004																										
16520442	Bridger T	Randomized placebo-controlled trial of metformin for adolescents with polycystic ovary syndrome	2006	RCT	None	Q10 (RF8, RF12, RF14) Q13 (RF5)	Canada	Clinical	Double	12 wk	12 wk	Determine whether metformin or placebo could, in conjunction with healthy lifestyle counseling, decrease serum testosterone levels and related aberrations in adolescents with hyperandrogenism, hyperinsulinemia, and PCOS	22	Pediatric/Young Adults	> 12 yr Hyperinsulinemia PCOS Exclusions: Diabetes mellitus Renal or hepatic disease	Mean age (SD): Arm 1: 16.07 yr (0.97) Control Arm: 16.08 yr (1.39)  White, non-Hispanic: Arm 1: 7 Control Arm: 10  Black, non-Hispanic: Arm 1: 2 Control Arm: 0  Hispanic: Arm 1: 1 Control Arm: 0  Asian: Arm 1: 1 Control Arm: 1  Overweight or obese: 100%	11 (11)	Multiple Interventions	Arm 1: Metformin 750 mg bid + counseling (MET)  All subjects were given healthy eating and physical activity counseling according to the Health Canada and Fitness Vitality healthy lifestyle program	11 (10)	Control Arm: Placebo (CON)	<b>Primary:</b> Mean difference in BMI [kg/m <sup>2</sup> ] (95% CI) Mean insulin AUC [µU/m <sup>2</sup> min] (95% CI) Mean fasting glucose [mg/dL] (95% CI) Mean HOMA (95% CI) Mean QUICKI (95% CI) Mean TC [mg/dL] (95% CI) Mean LDL-C [mg/dL] (95% CI) Mean HDL-C [mg/dL] (95% CI) Mean TG [mg/dL] (95% CI) Mean change in total testosterone level [ng/dL] Girls with restored menses [number] RR=2.50  <b>Secondary:</b> Mean change in Ferriman and Gallwey score	<b>Primary:</b> INT: -0.16 vs CON: -0.19 (-1.01 to 0.32) INT: -3662 vs CON: 2093 (-17,531 to 6024) INT: 0.31 vs CON: 0.36 (-3.42 to 5.22) INT: -1.06 vs CON: 0.86 (-9.26 to 5.42) INT: 0.00 vs CON: -0.01 (-0.03 to 0.05) INT: -0.78 vs CON: -8.15 (-17.07 to 31.82) INT: -3.10 vs CON: -7.76 (-12.80 to 20.56) INT: 6.98 vs CON: -2.33(0.78 to 18.23) INT: -13.13 vs CON: 7.00 (-70.00 to 29.75) INT: -38.3 vs CON: -0.86(-inf to -0.29) INT: 10/11 vs con: 4/11(1.12 to 5.58) RR=2.50  <b>Secondary:</b> No change in either group	NS NS NS NS NS NS NS NS NS NS NS NS	Not adequately studied although reported GI disturbance in 5 of 11 in treatment group and 1 of 10 placebo patients	Additional entrance criteria is obesity; diet/exercise is not an intervention; useless for ethnicity (sample size too small); limited relevance, incomplete compliance with treatment, underpowered	A trial of metformin + lifestyle change vs lifestyle change alone resulted in a decrease in testosterone levels, a higher rate of restored menses and slightly higher HDL in the metformin group but no other significant changes. The predisposition to PCOS (RF12) was improved but obesity (RF8) and insulin resistance (RF14) were not decreased in this trial.	Q10,13 A trial of metformin + lifestyle change vs lifestyle change alone resulted in a decrease in testosterone levels, a higher rate of restored menses and slightly higher HDL in the metformin group but no other significant changes. The predisposition to PCOS (RF12) was improved but obesity (RF8) and insulin resistance (RF14) were not decreased in this trial.	