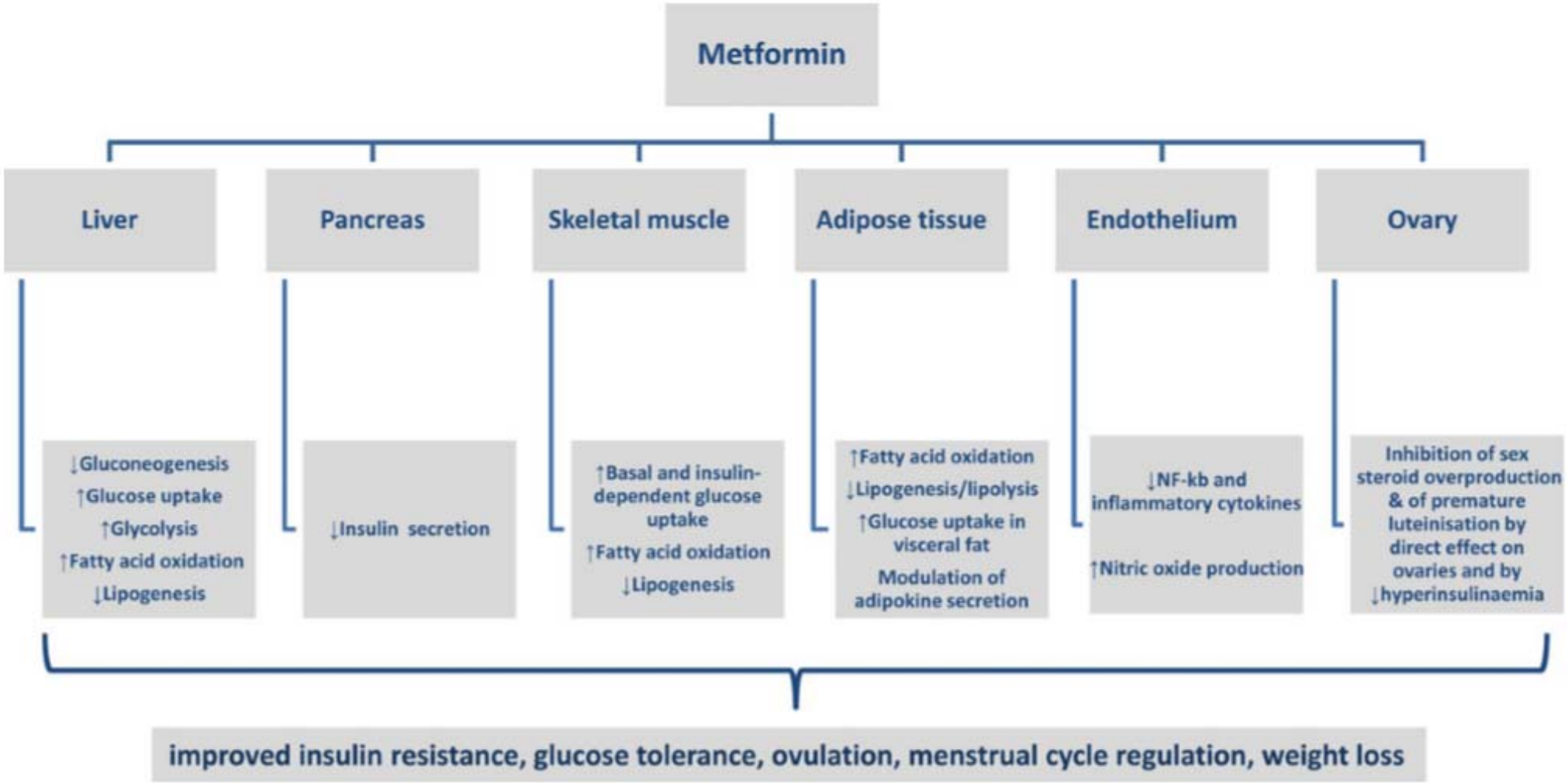
Metformin and Lifestyle Modifications in Polycystic Ovary Syndrome

DRAMS 15/12/15 – CAITLIN

Background

- Polycystic Ovary Syndrome (PCOS) is an imbalance of hormones in women
  - Affects 6-21% of females at reproductive age
  - T2DM and obesity association
  - Reproductive and metabolic features

- Lifestyle management is current first line treatment
- Small studies show metformin to improve hyperinsulinaemia, ovulation and regularity of the menstrual cycle


Metformin
Liver
Pancreas
Skeletal muscle
Adipose tissue
Endothelium
Ovary
↓Gluconeogenesis
↑Glucose uptake
↑Glycolysis
↑Fatty acid oxidation
↓Lipogenesis
↓Insulin secretion
↑Basal and insulin-dependent glucose uptake
↑Fatty acid oxidation
↓Lipogenesis
↑Fatty acid oxidation
↓Lipogenesis/lipolysis
↑Glucose uptake in visceral fat
Modulation of adipokine secretion
↓NF-kb and inflammatory cytokines
↑Nitric oxide production
Inhibition of sex steroid overproduction & of premature luteinisation by direct effect on ovaries and by ↓hyperinsulinaemia
improved insulin resistance, glucose tolerance, ovulation, menstrual cycle regulation, weight loss

Problem

Does the use of metformin alongside lifestyle modifications have better overall outcomes than just using metformin or lifestyle modifications alone?

Measured outcomes:

1. Anthropometric (BMI/body fat), metabolic (surrogate insulin markers measured)
2. Reproductive capability (menstruation, pregnancy rate) and psychological impact (QOL)

Best outcome: greater reduction in BMI with metformin + lifestyle

Design

- Systemic review and meta-analysis of previous research papers
- Intervention ranged from 3-12months
- All papers followed participants for at least 6 months
- Some papers followed up again at 12 months but as this was not consistent for all, this data was not included
- Scientific quality assessed by 2 experienced reviewers (discussed if doubt)
- No explanation for the first exclusions?
  - 98.7%

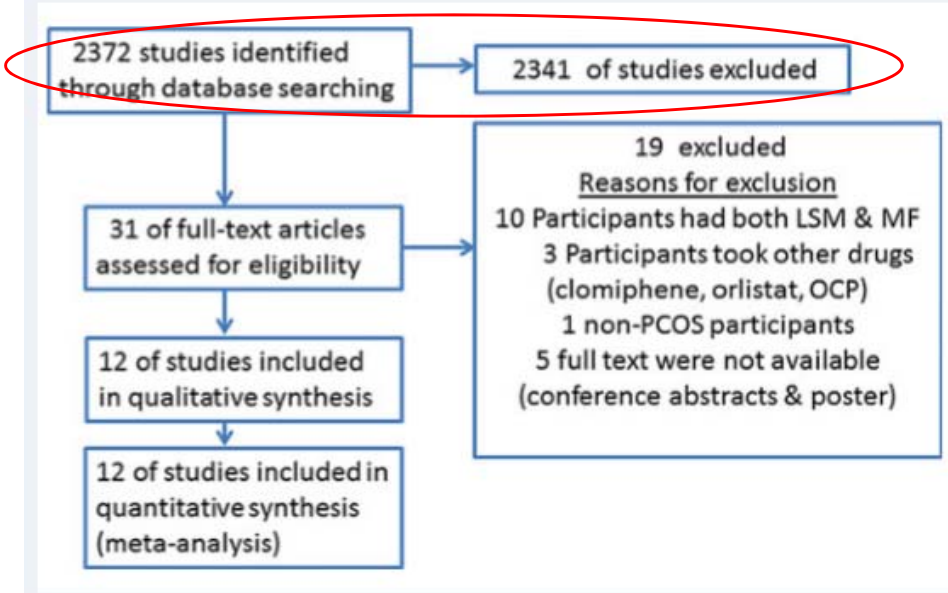


Figure 2 The flow of study selection. LSM, lifestyle modification; MF, metformin; OCP, oral contraceptive pill; PCOS, polycystic ovary syndrome.

Population

- Each study had their own selection and exclusion criteria
- Studies conducted in obsgyn clinics, endocrine and infertility outpatient clinics or research centres
  - All in USA
- Search Criteria: Diagnosis of PCOS at any age and any BMI, with no other aetiologies or medications for hyperandrogenism or infertility. Pregnancy included.
- Ages 12-39
  - Why not older age groups? Age of fertility problems? Studies included up to 45?
- Pregnant women with PCOS in one study not included
- Mean BMI>30kg/m^2 in all but one study

Population Variation

- Dropout rate varied across groups. Not reported why in one study.
  - Thought to be due to non-compliance or side effects of metformin
- Different inputs of lifestyle modifications
  - 3/12 used dietary advice ONLY (rest included exercise too)
  - Behavioral education and support in 2/12
  - Access to a fitness facility provided in another 2/12
  - 500kcal reduction in 8/12
  - Diets individualized in 10/12
- One study found to have a high risk of bias score

Number

- Data from all studies collated – 608 participants total
  - Low considering starting availability of studies
- Don’t know how many came from each study
- No evidence of power calculation
- No limits on year if publication. Search up to August 2014. limited to English Language articles.

Intervention and Comparison

- Complied all studies and mixed all data of similar studies
- Nine papers compared lifestyle + metformin with lifestyle +/- placebo.
  Four papers compared lifestyle +/- placebo with metformin alone.
- Split into 3 categories, all compared against each other:
  - Lifestyle + metformin
  - Lifestyle +/- placebo
  - Metformin alone
- All given immediate release metformin hydrochloride, ranging from1.5-2g/day

Statistics (Lifestyle + Metformin vs Lifestyle Alone)

- Lifestyle + metformin had a 0.73kg/m^2 lower BMI at study completion (p=0.0005)
  - No effect on glucose tolerance
- No significant difference in insulin resistance (p=0.31)
- No difference in reproductive parameters. Menstrual cycle data only included from 3 papers due to irregularity of self reported data. From these 3, the lifestyle + metformin group had a greater number of menstrual cycles over 6 months (p=0.006)
- No difference in QOL
- Heterogenicity random effect model allowed for data to be collated

Statistics (Metformin Alone vs Lifestyle Alone)

- No difference in BMI after 6 months
- Lower testosterone in metformin group
- No report on other measureable factors
- Reliability and percentages not given
- Heterogenicity random effect model allowed for data to be collated

Outcomes

- Proposed study specifically monitoring patients in two groups: Lifestyle +/- placebo vs lifestyle + metformin, with lifestyle modifications standardized and done over a longer time with a bigger sample of patients
- Early intervention with metformin to prevent T2DM development
- Lifestyle management is still first line until further outcomes

Summary

Good points:

+Fairly long follow up period

+No conflicts of interest declared

+Multiple authors and literature databases

+Small p values

+608 individual participant's data used

Not so good points:

-Exclusion of 98.7% with no justification

-Not all the data was included (age groups)

-Variation in lifestyle interventions

-Different size groups

-No clear scientific quality appraisal

-Didn't measure all outcomes from all papers

- Limitation of studies reviewed

Questions?

Thank You!