Metformin in polycystic ovary syndrome
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Chapter 1

Introduction

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Introduction

In 1921 the first article of a severe case of - what we would now call- PCOS was published.\(^1\) The polycystic ovary syndrome (PCOS) affects 5% to 10% of women of reproductive age.\(^2\) PCOS is characterised by oligo-anovulation, clinical or biochemical hyperandrogenism and/or polycystic ovaries.\(^3\)-\(^5\) In 1935 the first treatment, involving ovarian wedge resection in women with amenorrhea and enlarged polycystic ovaries, was published: “The mechanical theory: The overproduction of cystic follicles which crowd the ovarian cortex but which do not rupture on the surface of the ovary, together with the presence of a thickened tunic, prevents the immature follicles from ripening and reaching the surface. We observed that by removing the cystic cortex which formed the barrier, physiologic function was restored.” Since then the syndrome was named the Stein Leventhal syndrome, after the two authors, doctors Stein and Leventhal.\(^6\)

Sixty years later, a connection was found between hyperandrogenism and hyperinsulinemia in PCOS patients,\(^7\) irrespective of weight.\(^8\) When these patients were treated with diazoxide, an insulin release inhibitor, insulin levels decreased and androgen parameters also decreased, whereas diazoxide in lean women without PCOS did not alter androgen parameters while insulin decreased.\(^9\)-\(^11\) It was concluded that hyperandrogenism is the consequence of hyperinsulinemia and not vice versa. Insulin resistance (IR) accompanied by compensatory hyperinsulinemia constitutes a major biochemical feature of PCOS, which leads to early luteinizing hormone-sensitivity of the follicle and to stimulation of both ovarian and adrenal androgen production.\(^12\)-\(^16\) Because of the link between IR and PCOS, metformin, an insulin sensitizer was put forward as a drug to improve the metabolic and endocrinological disturbances in women with PCOS.\(^17\)

In 1994, more than 70 years after the first description of a patient with insulin resistance and hyperandrogenism, the first study on metformin in women with PCOS was published.\(^18\) Originally, this trial was meant to study metabolic and endocrinological parameters, but the authors noticed that some of the women (12%) conceived naturally. Following this initial study, many small trials were set up to test insulin sensitizers (mainly metformin) for ovulation induction in women with PCOS.\(^19\);\(^20\) It was at this time that we initiated the studies described in this thesis.
Results from a systemic review showed that metformin alone gave higher ovulation rates in women with PCOS, but not higher live birth rates than placebo. Metformin in combination with clomifene also resulted in higher ovulation rates and higher pregnancy rates, but not in higher live birth rates than clomifene alone. Critical analysis of the data presented in this review however, showed the following: Almost all included patients were obese. Obese women in general have less spontaneous and less clomifene induced ovulations. Therefore, the difference in ovulation and therefore also in live birth rate between placebo and clomifene treated women, may not be representative for the general PCOS population (obese and non-obese). Almost all patients receiving clomifene were previously diagnosed as clomifene resistant. This biases the results, because these patients will most likely benefit more from combination therapy than a group of patients that were treatment naive. Furthermore, the primary endpoint was ovulation and not live birth. Nevertheless, risk ratios for live birth rate were calculated using data not powered for this endpoint and the pregnancy results from the individual trials should therefore be interpreted with some caution.

Besides impaired reproductive function, PCOS can also result in several metabolic abnormalities including impaired glucose tolerance, dyslipidemia and hypertension. As a result, women with PCOS seem to be at increased risk of having metabolic syndrome and thereby at risk for cardiovascular disease and diabetes. According to the ESHRE/ASRM PCOS consensus workshop group a woman with PCOS has the metabolic syndrome when she suffers from at least three of the five following criteria: abdominal obesity (waist circumference), high triglycerides, low HDL, high blood pressure and insulin resistance. The prevalence of metabolic syndrome in women with PCOS varies largely among various populations and has been reported to range between 16% and 46%. Since insulin resistance is one of the criteria for the metabolic syndrome, metformin has been suggested to reduce risk for metabolic syndrome in women with PCOS. In studies where metformin was used to treat patients with diabetes, insulin values as well as lipid profile and coagulation and fibrinolytic factors were reduced. In the UKPDS study a total of 1704 patients with diabetes mellitus type II were treated with either metformin or diet only. Follow up was ten years. For all macrovascular diseases combined (myocardial infarction, stroke, sudden death) there was a 30% risk reduction in the metformin group compared to the diet only group.
There are retrospective studies that claim to have data concerning cardiovascular disease in women with PCOS.\textsuperscript{38-41} None of these studies include patients with known or proven PCOS, let alone PCOS as defined following the Rotterdam criteria. Long term studies of women with well-defined PCOS are lacking. Therefore, it is not proven yet that women with PCOS suffer more from cardiovascular morbidity and mortality than women without PCOS.\textsuperscript{42} To improve the metabolic syndrome parameters seems worthwhile, but it is not clear if it will improve morbidity and mortality in the long term.

As PCOS is a heterogeneous condition,\textsuperscript{43} several authors have suggested that metformin would be most beneficial in specific subgroups of women with this condition. Increasing age and high waist hip ratio (WHR) are known risk factors in developing IR and, as such, these factors may also affect clinical response to metformin.\textsuperscript{44-47} One study showed that women with PCOS and with a high waist hip ratio (WHR) more often have insulin resistance and diabetes mellitus.\textsuperscript{45} In another study women with PCOS and a high WHR showed less insulin resistance and more weight loss as a reaction to metformin.\textsuperscript{47} At the time of our research it was not clear which specific subgroups of women with PCOS would benefit most from treatment with metformin.

In deciding to treat a patient with metformin or not, the burden of the treatment is important as well. Information on health related quality of life (HRQoL) of women with PCOS treated by different modalities for ovulation induction is limited. One study randomised between lifestyle adjustments combined with metformin or placebo.\textsuperscript{48} Women were advised to use barrier contraception and to avoid pregnancy. This study had a significant amount of drop-outs (60 vs 73%). No difference was found in HRQoL between the two groups during the study. A second study randomised between oral contraceptives (OC) combined with metformin or placebo in adolescents (12-18years).\textsuperscript{49} No difference in HRQoL was found between the two groups. In women with fertility problems lower psychological stress scores are found once an ongoing pregnancy is reached,\textsuperscript{50} and differences between treatment groups disappear. Women will choose the more effective treatment, even if it will give more discomfort.\textsuperscript{51}
**Background of the research of this thesis**

As clomifene is an effective treatment for ovulation induction in PCOS, the question arises what the added benefits of metformin would be. At the start of the studies described in this thesis, there was no randomised controlled trial comparing metformin combined with clomifene to placebo combined with clomifene for ovulation induction in women with PCOS.

At the time we started our studies the evidence on a beneficial effect of metformin in specific subgroups of patients was scarce. There was only one small study involving 32 patients with PCOS that had investigated the effect of metformin in specific subgroups. This study showed in a multivariable analysis that higher insulin, lower androstenedione and less severe cycle abnormalities appeared to be independent significant parameters for better response to metformin. We wanted to investigate if a treatment difference existed in the several subgroups of our population.

Data on prevalence and incidence of type 2 diabetes mellitus and cardiovascular disease in women with PCOS are poor. Studies that demonstrate a direct effect of lifestyle adjustments or metformin on the incidence of these diseases are lacking. Thus, the clinical value of treatment of the surrogate endpoints –the metabolic syndrome- is still unknown. Nevertheless, some authors suggest that treatment of the metabolic syndrome in women with PCOS is beneficial for preventing disease later in life. We wanted to investigate whether metformin has a positive effect on several parameters of the metabolic syndrome.

Although it is generally assumed that ovulation induction with metformin is more burdensome than ovulation induction with clomifene due to the higher amount of tablets which ought to be ingested (three or four tablets a day until pregnancy is achieved in contrast to 5 to 15 tablets a month) and the high incidence of side-effects, there are no data in adult women who receive ovulation induction with the purpose of conceiving.
**Outline of this thesis**

In **Chapter 2** we describe a randomized trial designed to evaluate whether a strategy of adding metformin to the standard treatment with clomifene, results in a higher ovulation rate, higher pregnancy rate and less clomifene resistance. The study was a randomised clinical trial among newly diagnosed women with PCOS.

**Chapter 3** offers an introduction to the whole spectrum of subfertility treatment in PCOS with metformin and gives a critical appraisal of all existing studies, which will be helpful to guide clinical practice.

**Chapter 4** reports whether co-treatment with metformin improves pregnancy rates compared to the standard treatment of clomifene alone in subgroups of women based on clinical and biochemical variables. For this purpose we reanalysed the data from the randomised trial described in chapter 2.

**Chapter 5** outlines whether metformin has a positive effect on a complete set of biomarkers that is associated with the metabolic syndrome.

**Chapter 6** examines the HRQoL of women treated with clomifene combined with metformin and clomifene combined with placebo by means of questionnaires.
References


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