Consensus of French Endocrine Society on female hyperandrogenism

Should physicians prescribe metformin to women with polycystic ovary syndrome PCOS?

Rôle de la metformine dans le SOPK

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Abstract

1. Metformin is not efficient enough in order to regulate menstrual cycles.
2. Metformin is not efficient enough in order to treat hyperandrogenism.
3. Metformin should not be used as a first-line treatment in order to treat infertility. Clomiphene citrate (CC) is the reference treatment.
4. Metformin in addition to CC is not recommended as a second line treatment, after the failure of CC alone.
5. Metformin should not be used during pregnancy in non diabetic women with PCOS, in order to prevent the risk of gestational diabetes.
6. Metformin should be prescribed to PCOS women when they are diabetic, in order to prevent their cardiovascular risk, after lifestyle modification.
7. Metformin should not be used in PCOS non diabetic women in order to lose weight. Metformin should not be used in order to treat dyslipidemia in women with PCOS.
8. In PCOS women, without diabetes, but with fasting hyperglycemia or carbohydrate intolerance, metformin should be prescribed if: BMI > 35.

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Keywords: Metformin; Polycystic ovary syndrome; French consensus

Metformin has been used in Europe since the seventies in order to treat type 2 diabetes. It has been prescribed in the United States since 1994. This molecule improves insulin resistance as it increases glucose capture in muscles and decreases neogluconeogenesis in the liver. Women with polycystic ovary syndrome (PCOS) present insulin resistance with hyperinsulinemia in 50 to 70% of cases [1]. Therefore, in theory, metformin represents a good candidate to treat PCOS.

The use of metformin has been studied in order to regulate cycle disturbances. It regulates menstrual frequency, using doses ranging from 1000 to 2500 mg per day. However, only few randomized studies have been performed and the duration of treatment reached a maximum of one year. Metformin’s efficacy remains lower than combined oral contraceptive pill [2].

Progestins alone remain the treatment of reference in order to regulate menstrual bleeding (Table 1).

Metformin has been used in order to reduce hyperandrogenism and hirsutism. According to different meta-analysis, its effect is not higher than placebo and lower than antiandrogen treatments [3] (Table 2).

In order to treat infertility, many hopes arrived in the late nineties, concerning metformin treatment. However, most recent randomized studies performed on large groups of patients have demonstrated that it induces a lower number of live births than clomiphene citrate (CC) [4]. Therefore, CC should remain the first line treatment in order to induce ovulation and pregnancy in women with PCOS, after lifestyle modifications (Table 3). In CC resistant women, metformin has been added to CC. This treatment has a low cost and induces few ovarian hyperstimulation and multiple pregnancies. However, its efficacy remains low and the phenotype of women responding to this regimen needs to be characterized. Studies have shown that metformin
Clomiphene citrate is not efficient enough in order to regulate menstrual cycles.

Metformin, in addition to clomiphene citrate (CC), is not recommended as a second line treatment, after the failure of CC alone.

PCOS: polycystic ovary syndrome.

Table 2
Metformin is not efficient enough in order to regulate menstrual cycles.

Table 3
Metformin should not be used as a first-line treatment in order to treat infertility

Table 4
Metformin should not be used during pregnancy in non diabetic women with PCOS, in order to prevent the risk of gestational diabetes (GD).

On a long term basis, metformin could potentially reduce the risk of type 2 diabetes. The Diabetes Prevention Trial has shown a beneficial effect of metformin, reducing the risk of type 2 diabetes by 31%, as compared to placebo. However, few studies have specifically focused on the population of women with PCOS. As recommended by the American Diabetes Association (ADA), metformin should be prescribed in patients with high risk of diabetes and obesity, below the age of 60 [7]. As PCOS represents a risk factor for diabetes, metformin should be prescribed to obese patients with PCOS. However, metformin does not have significant effects on reducing weight [8]. In women with glucose intolerance or diabetes, it represents the best molecule, in addition to lifestyle modifications (Table 6).

Metformin could potentially reduce the cardiovascular risk as women with PCOS present an increased risk [9]. However, new studies are necessary in order to detect “good responders to metformin”.

Table 5
Metformin and gestational diabetes. Recommendation no. 5.

Table 6

PCOS: polycystic ovary syndrome.
Table 7
Metformin in cardiovascular prevention. Recommendation no. 7.
Rôle dans la prévention cardiovasculaire. Recommandation no 7.

<table>
<thead>
<tr>
<th>Commentaries</th>
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<tbody>
<tr>
<td>Metformin should not be used in PCOS non diabetic women in order to lose weight</td>
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<tr>
<td>Metformin has no impact on weight nor on the waist/hip ratio, according to Lord’s meta-analysis</td>
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<tr>
<td>Metformin should not be used in order to treat dyslipidemia in women with PCOS</td>
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<td>Metformin has a low impact on LDL cholesterol</td>
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PCOS: polycystic ovary syndrome; LDL: low density lipoproteins.

Table 8
Rôle dans la prévention cardiovasculaire. Recommandation no 8.

<table>
<thead>
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<tr>
<td>In PCOS women, without diabetes, but with fasting hyperglycemia or carbohydrate intolerance, metformin should be prescribed if BMI &gt; 35 = ADA Recommendations</td>
</tr>
<tr>
<td>Metformin actions demonstrated on clinical and biological markers of cardiovascular risks</td>
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<tr>
<td>Diabetes Prevention Program (DPP) has shown a reduction in the risk of developing a diabetes if intensive coaching, diet and/or metformin with a beneficial cost effect</td>
</tr>
<tr>
<td>But: No study of mortality in PCOS Data are extrapolated from UKPDS No authority approval in France for using metformin apart from diabetic women</td>
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PCOS: polycystic ovary syndrome; BMI: body mass index; UKPDS: United Kingdom Prospective Diabetes Study; ADA: American Diabetes Association; DPP: Diabetes Prevention Program.

In summary, metformin is not the best treatment in order to regularise menstrual cycle, nor to treat hyperandrogenism. It is not as effective as CC as first-line therapy for women with PCOS, for ovulation induction. It does not reduce the risk of pregnancy loss. However, it may be beneficial in order to reduce the risk of diabetes in overweight women with PCOS and to reduce the cardiovascular risk in those women with glucose intolerance or type 2 diabetes.

1. French version

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References