Abstract

Polycystic ovary syndrome (PCOS) is a frequent endocrine disease affecting 10 to 15% of women. Menstrual disorders, hyperandrogenism and ultrasonographic aspect of ovaries are typical of the disease and are established diagnostic criteria. But PCOS has also long term complications frequently forgotten and underestimated. During pregnancy, gestational diabetes and gestational hypertensive disorders can occur. At an older age, metabolic disease such as glucose intolerance, type 2 diabetes or dyslipidemia are frequently described. Women with PCOS have increased classical cardiovascular risks and increased subclinical cardio-vascular disease without proven increase of cardiovascular morbidity and mortality. Finally, endometrial cancer seems to be more frequent in women with PCOS. Therefore, PCOS have numerous long-term health risks and a life-long follow-up is necessary for these women “at-risk” to detect and prevent complications as soon as possible.

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1. Medium term complications: pregnancy complications

Women with PCOS have a higher risk of pregnancy complications such as gestational diabetes (OR = 2.94) [1,2]...
and associated foetal macrosomia. A screening of gestational diabetes should be proposed to every woman with PCOS performing the usual tests: fasting glucose measurement during the first trimester of pregnancy and, if this first test is normal, Oral Glucose Tolerance Test (OGTT) (75 g, 0-, 1-hour and 2-hour values) between 24 and 28 weeks of gestation (WG). Gestational hypertensive disorders are also more frequent (preeclampsia OR = 3.67, gravid hypertension OR = 3.47) [1]. Even without official guidelines, a closer monitoring of blood pressure and measurement of uterine blood flow during second trimester of pregnancy should be considered (Table 1) [3]. Finally, the risks of preterm delivery (OR = 1.75) and perinatal mortality (OR = 3.07) are higher in women with PCOS [1]. Obesity, altered glucose metabolism and disturbances in uterine blood flow have been incriminated [4] and might be confounding factors [3]. Since no benefit was found with the use of metformin before conception or during pregnancy, its routine use is not recommended [4] but lifestyle management, especially during pregnancy, is essential.

2. Overweight, obesity and their consequences

The prevalence of overweight (Body Mass Index [BMI] 25 to 30 kg/m²) or obesity (BMI > 30 kg/m²) in PCOS women is quite

| Table 1 Major long-term complications of PCOS and method of screening. |
|---------------------------------|-------------------------------------------------|
| **Major complications**         | **Screening**                                   |
| Pregnancy complications         | (No official guidelines)                        |
| Gestational diabetes            | Fasting glucose measurement during the first trimester of pregnancy and OGTT during the second trimester |
| Hypertensive disorders          | Monitoring blood pressure and, maybe, measurement of uterine blood flow during second trimester of pregnancy |
| Glucose intolerance             | Amsterdam ESHRE consensus [3]                   |
|                                 | Oral Glucose Tolerance Test (75 g, 0- and 2-hour values) in PCOS women with BMI>30 kg/m² and/or |
|                                 | Waist circumference over 88 cm and/or           |
|                                 | Acanthosis nigricans and/or                     |
|                                 | Familial history of type 2 diabetes and/or      |
|                                 | Personal history of gestational diabetes and/or |
|                                 | Both menstrual disorders and hyperandrogenia present |
| Cardiovascular risk             | Amsterdam ESHRE consensus [3]                   |
|                                 | At any age, in women with PCOS, screening of    |
|                                 | Waist circumference                             |
|                                 | Blood pressure                                  |
|                                 | Lipide profile                                  |
|                                 | Physical activity                               |
|                                 | Nutrition                                       |
|                                 | Smoking                                         |
| Endometrial cancer              | Amsterdam ESHRE consensus [3]                   |
|                                 | Checking the endometrium by ultrasond or endometrial biopsy in women with a long amenorrhea period |
|                                 | To prevent endometrial hyperplasia, a minimum of 4 induced withdrawals bleeding per year is needed |
variable from one country to another one. For example, in the UK 90% of PCOS women have a BMI > 25 kg/m² whereas they are only 20% in China. The highest prevalence of obesity in women with PCOS is reported in USA (61%) and Australia (76%) [4]. Compared with weight-matched controls, women with PCOS are more likely to have abdominal obesity which is associated with metabolic diseases. Indeed, abdominal fat is directly correlated with insulin resistance. As the waist circumference is directly correlated to abdominal fat, it is a precious and easily measurable marker of metabolic disease. In Europe a waist circumference over 80 cm defines abdominal adiposity. In addition, as explained further, women with PCOS, even the lean ones, are more insulin-resistant and obesity magnifies this disease [5,6].

Abdominal obesity can be part of the so-called “metabolic syndrome”. It is defined by the association of three of the following: abdominal obesity, low HDL-cholesterol, high triglyceride level, high blood pressure, glucose intolerance. These additional cardiovascular risks must be screened, as explained further in the “cardiovascular risk” chapter. The prevalence of metabolic syndrome in PCOS patients seems to be higher than in control patients in several studies [7–12] but a bias exists. In fact, in these studies, women with PCOS were more obese than controls. In a recent study by Panidis et al. [13] the prevalence of metabolic syndrome is not different between women with PCOS and BMI-matched controls. Therefore, PCOS does not seem to increase the risk of metabolic syndrome independently from abdominal obesity.

As in control women, obesity in PCOS patients can be complicated by arterial hypertension, obstructive sleep apnea, dyslipidaemia, mood disorders, etc., which must be screened as explained further in the “cardiovascular risk” chapter, but these complications seem more severe and more frequent when associated to PCOS [14], presumably because insulin resistance is more prominent in PCOS.

Regarding mood disorders, a specific link may exist with PCOS [14], for example more depression and more anxiety. The high prevalence of psychological pathologies does not seem to be exclusively linked to obesity, infertility and/or hirsutism and should imply a psychological assessment in the initial evaluation and in the follow-up [14].

3. Insulin resistance, glucose intolerance and type 2 diabetes

Insulin resistance (IR) is a prominent feature of PCOS. Pathophysiology of IR remains controversial and could be due to a defect in signal transduction of insulin [15–18]. Except for clinical features such as acanthosis nigricans and abdominal adiposity, IR diagnosis is not easy. IR Index, such as Homeostasis Model Assessment (HOMA) or quantitative insulin sensitivity check (QUICKI), have been developed but in clinical practice the ratio fasting glycaemia (mg/dL) /insulinaemia (µU/mL) is the easiest criteria to evaluate IR [19].

Progressively, IR can lead to glucose intolerance, which occurs in 40% of women with PCOS after the age of 40 [20] and, in six years, half of these women become diabetic. Indeed, in the meta-analysis of Moran et al. [6], the risk of becoming glucose intolerant and type 2 diabetic is respectively 2.5 and 4.1 fold higher in women with PCOS than in BMI-matched controls. Thus, even with a normal weight, women with PCOS are exposed to the risk of glucose intolerance and type 2 diabetes and the risk is magnified by obesity. Insulin resistance is mostly prevalent and severe in women with the PCOS phenotype involving hyperandrogenism and anovulation. The Amsterdam ESHRE consensus [4] recommends a systematic screening of glucose intolerance in PCOS women with BMI > 30 kg/m² and/or waist circumference over 88 cm and/or acanthosis nigricans and/or familial history of type 2 diabetes and/or personal history of gestational diabetes (Table 1). The screening must be performed by Oral Glucose Tolerance Test (OGTT) (75 g, 0- and 2-hour values). They also recommended OGTT when both menstrual disorders and hyperandrogenia are present because some studies proved a direct correlation between the number of PCOS symptoms and the occurrence of glucose intolerance or type 2 diabetes [4]. If the patient can not or do not want to perform OGTT, HbA1C measurement can be considered [21].

The PCOS has recently been identified by the American Diabetes Association as a specific risk factor for type 2 diabetes. However, only cross sectional observational, retrospective and short term prospective studies were available [6] until a recent long term prospective Italian study by Gamberini et al. [22]. This study demonstrated that the risk of type 2 diabetes is elevated in middle-age women with PCOS (incidence rate of 1.05 per 100 person-years, 2.6 times higher than that of the general population). This risk increases with BMI, high fasting glucose and low sex hormone-binding globulin (SHBG) circulating levels. This study reinforce the need for routine screening for diabetes in PCOS patients over time [22].

The first-line treatment of glucose intolerance is the lifestyle management, especially with physical activity [21]. Counselling by non-medical professional groups seems to be efficient and may be recommended [23]. Metformin treatment can be indicated in case of proved glucose intolerance and when the lifestyle management is ineffective [4,24].

4. Cardiovascular diseases

4.1. Cardiovascular pathology

Numerous observational studies focused on cardiovascular disease in women with PCOS. Their conclusions are still contradictory. For example, in Rizzo et al. review [25], five studies concluded that PCOS women are at risk for cardiovascular diseases, which was not proved in three other studies. Definition of PCOS, cardiovascular endpoints and median age of patients were different in each study. Series were sometimes very small, some included patients too young to have time to develop cardiovascular disease and after menopause it is difficult to retrospectively diagnose PCOS. The meta-analysis of Groot et al. [26] based on five cohort studies, again with different definitions of PCOS, showed a higher risk of coronary heart disease or cerebrovascular disease in PCOS women compared to controls (effect size = 2.195 = 1.47–2.76). Recently, a large retrospective study by Mani et al. [27], conducted in more than 2000
women with PCOS over 11 years, has reported an increased age-specific prevalence for both myocardial infarction and angina in women with PCOS. However, in this population with 80% of the subjects under 45 years old, the overall rates of myocardial infarction and angina did not differ from the reference population. Finally, a very large dataset in UK (21,000 women with PCOS) reported no evidence of an increase in cardiovascular disease, but once again the population was young and the diagnosis of PCOS was questionable [28].

In contrast with cardiovascular heart disease, cerebrovascular disease is unanimously proved to be more frequent in women with PCOS (OR = 2.8), even when patients are compared to BMI-matched controls (OR = 3.4) [29].

In conclusion, a higher cardiovascular morbidity or mortality of women with PCOS is not obviously demonstrated. Nevertheless, in post-menopausal women, a personal history of clinical hyperandrogenism or menstrual disorders expose to an increased cardiovascular disease risk [30,31]. Large scale prospective studies are needed to clearly prove an increased prevalence of cardiovascular events in PCOS women compared to age- and BMI-matched controls.

4.2. Subclinical vascular disease

Even if a higher cardiovascular pathology in PCOS women is still controversial, the subclinical vascular disease is proved to be higher in PCOS women compared with age- and BMI-matched controls. Three markers are commonly used in clinical research to evaluate sub-clinical atherosclerosis: the carotid intima-media thickening, the arterial stiffness and the coronary artery calcification. They are all increased in women with PCOS compared to controls, independently from age and BMI [32–36].

4.3. Classical cardiovascular risk factors

As expected, since the subclinical cardiovascular disease is higher in PCOS women, the classical cardiovascular risks are more frequent.

Indeed, arterial hypertension, dyslipidaemia and especially low HDL-cholesterol (High Density Lipoprotein-cholesterol), insulin resistance or type 2 diabetes and obesity, especially abdominal obesity, are more frequent in PCOS women [4,37,38]. Dyslipidaemia is very frequent among women with PCOS. Almost 70% of women with PCOS suffer from dyslipidaemia, most often represented by hypertriglyceridemia and low HDL-cholesterol and sometimes by high LDL-cholesterol (low density lipoprotein cholesterol) [14]. The abdominal obesity, detected by the waist circumference over 88 cm (and over 80 cm in Europe population), and the decrease of HDL-cholesterol under 0.5 g/L are the first risk factors to appear; they must be screened as soon as possible.

The metabolic syndrome, as defined above, is not required for cardiovascular risk disease since even with one criteria the cardiovascular risk is increased [39].

In some studies, the risk of obstructive sleep apnea is five times higher in PCOS women compared to controls regardless the BMI [40]. But, normal weight women with PCOS do not seem to have an increased risk of sleep disorders compared to healthy BMI-matched women [14]. The presence of obstructive sleep apnea must be screened by questionnaires and patient should be referred to a center of sleep disorders for further evaluation [14].

Jovanovic and al. [41] proved that the more the PCOS phenotype is complete the more the cardiovascular risk markers are present.

The recommended cardio-vascular risk assessment by Amsterdam ESHRE consensus includes assessment of blood pressure, glucose and lipid profiles, waist circumference, physical activity, nutrition and smoking at any age [4] (Table 1). If the lipid profile and the OGTT are normal, they must be rechecked every two years [42].

In conclusion, classical cardiovascular risk markers are more prevalent in women with PCOS, even if they are not obese, and these risks are magnified by obesity. The long-term metabolic disease of women with PCOS affects the subclinical vascular pathology markers and, even if a higher cardiovascular morbidity or mortality is not definitively proved, caution is warranted. Indeed, a life-long metabolic dysfunction can exaggerate the risk for cardio-vascular disease, especially after menopause.

5. Gynaecological malignancies

5.1. Endometrial cancer

A meta-analysis in 2009 [43], proved that the risk to develop an endometrial cancer was higher in women with PCOS (OR = 2.7, IC95 = 1.00–7.29), which was confirmed in a recent systematic review with a 3 fold higher risk in women with PCOS compared to controls [44]. Another previous study concluded that the risk of endometrial cancer was 5.3 times higher in PCOS women and 6.1 times increased in obese PCOS women [29]. Nevertheless, most endometrial cancers are well differentiated and have good prognosis. Chronic anovulation and therefore the prolonged exposure to unopposed oestrogen can lead to endometrial hyperplasia and to endometrial cancer. But other factors could interact in cancer process, such as progesterone dependant gene dysregulation, hyperandrogenism, hyperinsulimism and/or LH hypersecretion [45]. Moreover, when adjusted with BMI, endometrial cancer risk in women with PCOS is half-reduced, demonstrating that obesity is a very important confounding factor [45].

The recent Amsterdam ESHRE consensus recommends checking the endometrium by ultrasound or endometrial biopsy in women with a long amenorhoea period. To prevent endometrial hyperplasia, a minimum of four induced withdrawals bleeding per year is needed [4] (Table 1).

5.2. Breast cancer

Data about breast cancer in PCOS women are limited. The meta-analysis of Chittenden et al. [43], based on three old studies with a few PCOS patients, showed no difference between women with and without PCOS for breast cancer risk.
Nowadays, there is no particular recommendation for the follow-up of women with PCOS about breast cancer.

5.3. Ovarian cancer

Limited data exists. Indeed, only one study tried to evaluate the association between PCOS and ovarian cancer. Even if it is usually said that the less is the ovulation number the less is the risk for ovarian cancer, this study showed that PCOS women have 2.5-fold more risk to develop ovarian cancer than non PCOS women [46]. However, the number of PCOS women in this study was very small. In the opposite, another study showed a lower mortality by ovarian cancer in PCOS patients than in non PCOS women [47]. Thus, these limited data do not allow concluding that women with PCOS are at increased risk for ovarian cancer.

However, it must be reminded that women with PCOS have other recognized risk factors such as nulliparity, infertility and its treatment, anovulation and obesity.

There is no current particular recommendation for screening ovarian cancer in PCOS women.

6. Conclusions

PCOS is a life-long disease and has long term complications frequently forgotten and underestimated. Obesity and altered glucose metabolism are the most common complications described in women with PCOS. Metabolic dysfunction leads to pregnancy complications and to metabolic disease with increased classical cardiovascular risks and increased subclinical cardio-vascular disease without proven increase of cardiovascular morbidity and mortality with aging. More data are needed to definitively prove a higher cardiovascular morbidity or mortality. Indeed, longitudinal studies are very scarce and without standardisation of diagnostic criteria of PCOS. Endometrial cancer seems to be more frequent in women with PCOS. Therefore, PCOS has numerous long-term health risks and a life-long follow-up is necessary. Indeed, for prevention of long-term complications of PCOS, information and education are crucial because all complications, metabolic disorders and endometrial cancer, can be prevented by an early care.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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