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Clémence Delcour, Geoffroy Robin, Jacques Young, Didier Dewailly

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Clémence Delcour, MD[1,2], Geoffroy Robin, MD[3,4], Jacques Young, MD[5] and Didier Dewailly, MD[6]

[1]Department of Obstetrics and Gynecology, Robert-Debré hospital, AP-HP, Paris, France. [2]INSERM, U1141, Paris Diderot university, Sorbonne Paris Cité, Paris, France. [3]CHU Lille, Department of Reproductive Medicine & Lille University, Lille, France. [4]EA 4308, Lille University, Lille, France. [5]Department of Endocrinology and Reproductive Medicine, CHU Kremlin Bicetre, Paris, France. [6]INSERM U1172 Team 2, JPARC, Université de Lille, 59000 Lille, France.

ABSTRACT: Polycystic ovary syndrome (PCOS) and hyperprolactinemia (HPRL) are the two most common etiologies of anovulation in women.

Since the 1950s, some authors think that there is a pathophysiological link between PCOS and HPRL. Since then, many authors have speculated about the link between these two endocrine entities, but no hypothesis proposed so far could ever be confirmed. Furthermore, PCOS and HPRL are frequent endocrine diseases and a fortuitous association cannot be excluded.

The evolution of knowledge about PCOS and HPRL shows that studies conducted before the 2000s are obsolete given current knowledge. Indeed, most of the studies were conducted before consensual diagnosis criteria of PCOS and included small numbers of patients. In addition, the investigation of HPRL in these studies relied on obsolete methods and did not look for the presence of macroprolactinemia. It is therefore possible that HPRL that has been attributed to PCOS corresponded in fact to macroprolactinemia or to pituitary microadenomas of small sizes that could not be detected with the imaging methods of the time.

Recent studies that have conducted a rigorous etiological investigation show that HPRL found in PCOS correspond either to non-permanent increase of prolactin levels, to macroprolactinemia or to other etiologies. None of this recent study found HPRL related to PCOS in these patients.

Thus, the link between PCOS and HPRL seems to be more of a myth than a well-established medical reality and we believe that the discovery of an HPRL in a PCOS patient needs a standard etiological investigation of HPRL.

KEYWORDS: PCOS, Hyperprolactinemia, macroprolactinemia, hyperandrogenism, prolactinoma

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CORRESPONDING AUTHOR: Didier Dewailly, INSERM U1172 Team 2, JPARC, Université de Lille, 52 rue Paul Duez, Lille, 59000, France. Email: didier.dewailly@orange.fr

Introduction

Polycystic Ovarian Syndrome (PCOS) and hyperprolactinemia (HPRL) are the two most common endocrine disorders in women of reproductive age. Indeed, the prevalence of PCOS is estimated at about 4 to 21% when the PCOS is diagnosed according to the Rotterdam criteria[1] and the prevalence of HPRL was estimated at 4% in a cohort of female blood donors[2], and with an estimated incidence rate of 49 per 100 000 persons-years[3].

So, the concomitant discovery of hyperprolactinemia (HPRL) and polycystic ovarian syndrome (PCOS) is not a rare situation in women being investigated for menstrual disorders. The association between HPRL and PCOS has been described since the 1950s and has suggested the existence of a pathophysiological link between these two entities but data from the literature on this subject are unclear. Therefore, the question persists as to whether a moderate hyperprolactinemia can be attributed to PCOS or, given the high prevalence of both diseases, whether it is merely a fortuitous association.

The aim of this review was to clarify the hypothetical epidemiological and physiopathological links between PCOS and HPRL. To answer this question, we first recalled the complex history of the PCOS diagnosis as well as the management of the HPRL. Then, in a second part of this study, we performed a critical and updated review of the available literature on the subject.

A short history of PCOS: from the discovery of the disease to recent guidelines

Polycystic ovarian syndrome (PCOS) was first described in 1935 by Irving Stein and Michael Leventhal who reported 7 cases of patients presented with amenorrhea, infertility and enlarged multicystic ovaries[4].

That same year, Laquer and Butenandt discovered the testosterone and the world of biochemistry was upset down with the development of the first androgens assay and the better understanding of their physiological and pathological origins[5,6]. Subsequently, it was discovered that androgens were synthesized by the adrenal gland but also by the ovaries, and that excess of androgens was responsible for hyperandrogenism in women[7–11]. This knowledge has provided a better understanding of PCOS and these symptoms.

Subsequently, other authors described other patients with PCOS, which confirms the reality of this syndrome and allows to complete the phenotypic spectrum of the disease[12–17]. Thus, the presence of clinical and/or biological hyperandrogenism or obesity was added to the PCOS entity.

It also became clear that many other endocrine disorders could mimic the PCOS phenotype and that it was necessary to eliminate these diseases before the diagnosis of PCOS: non classic congenital adrenal hyperplasia, hypercorticism, ovarian or adrenal virilizing tumors, hypothyroidism, iatrogenic androgen excess and especially hyperprolactinemia[18,19].

Thus, the definition of the PCOS remained rather confused until 1990 when the first international diagnostic criteria of the PCOS were established by the National Health Institute (NIH), nearly 50 years after the first description of the syndrome[20]. These first diagnostic criteria defined PCOS by the presence of chronic oligoanovulation associated with clinical and/or biological hyperandrogenism. Morphological descriptions of the ovaries were excluded from these early guidelines[20].

The development of ultrasound technologies in the 1970s and 1980s gave notable changes in the diagnosis of PCOS[21,22]. Ultrasound technologies were rapidly improved and ultrasonography was soon validated for ovarian exploration of PCOS[23–27]. The use of ultrasound has become common in clinical practice since the 80s and old imaging techniques to assess the size of the ovaries (pneumography, culdoscopy, etc.) have quickly become obsolete.

With the improvement of hormonal assays and ultrasound techniques, it has become necessary to modify the PCOS diagnostic criteria.

The Rotterdam conference in 2003 integrated the ultrasound criteria for the diagnosis of PCOS[28,29]. These ultrasound criteria, although imperfect and subject to recurring revisions[30,31], have at least clarified the definition of PCOS up to the latest recent European Society of Human Reproduction and Embryology (ESHRE) recommendations[32,33] (Table 1).

Moreover, it has also become clear that there are different types of PCOS depending on whether the patient had all the symptoms of PCOS (phenotype A) or only 2 out of 3 criteria (phenotype B, C and D). This is why the Androgen Excess and PCOS Society (AE-PCOS) in 2009 and the NIH in 2012 proposed separating PCOS into different phenotypes, in order to clarify the phenotypic heterogeneity of PCOS[34,35] (Table 1).

To conclude this first part of our work, PCOS has experienced a complex history punctuated by a constant improvement of its understanding and accompanied by an evolution of diagnostic criteria (table I)[20,29,33,35–37]. Most studies conducted prior to 1990 (NIH guidelines) include patients labeled PCOS, according to non-consensual diagnostic criteria. In addition, the evolution of ultrasound techniques as well as hormonal assays makes it difficult to compare PCOS in the 1980s with current PCOS women. Then, this historical retrospective highlight that old studies are not applicable to our current practice.

Table I. Evolution of PCOS diagnosis criteria according to different guidelines.

NIH 1990 (THE 2 CRITERIAS ARE REQUIRED)*
1. Chronic anovulation
2. Clinical and/or biological hyperandrogenism
Rotterdam 2003 (2 out of 3 criteria are required)*
1. Oligo-anovulation
2. Clinical and/or biological hyperandrogenism
3. Ultrasound criteria: ovarian volume>10cm3, AFC>12
Androgen excess (AE) Society 2006 and AE-PCOS Society 2009 (the 2 criterias are required)*
1. Clinical and/or biological hyperandrogenism
2. Oligo-anovulation or ultrasound criteria
NIH 2012 (2 out of 3 criteria are required)*
1. Clinical and/or biological hyperandrogenism
2. Oligo-anovulation
3. Ultrasound criteria: ovarian volume>10cm3, AFC>12
Phenotypes: A 1+2+3, B 1+2, C 1+3, D 2+3
ESHRE 2018 (2 out of 3 criteria are required)*
1. Clinical and/or biological hyperandrogenism
2. Oligo-anovulation
3. Ultrasound criteria: ovarian volume>10cm3 (AFC>20 only with endovaginal ultrasound transducers with a frequency bandwidth that includes 8MHz)

*After exclusion of non classic congenital adrenal hyperplasia, hypercorticism, ovarian or adrenal virilizing tumors, hypothyroidism and hyperprolactinemia.
Abreviations: AE, Androgen Excess; AFC, antral follicular count; ESHRE, European Society of Human Reproduction and Embryology; NIH, National Health Institute; PCOS, Polycystic ovary syndrome.

Management of the hyperprolactinemia through the decades

Human prolactin was first assayed in New York in 1970 by Andrew Frantz and David Kleinberg, who successfully developed an assay which was able to separate prolactin and growth hormone (GH)[38].

This discovery helped to improve the knowledge on this hormone and the pulsatile secretion of prolactin was quickly described in the following years. It was then admitted that high serum prolactin level must be systematically controlled to ensure that it is a permanent hyperprolactinemia.

The first case of macroprolactinemia was published in 1981 by Whittaker[39] and the existence of macroprolactin was subsequently confirmed by other authors who published

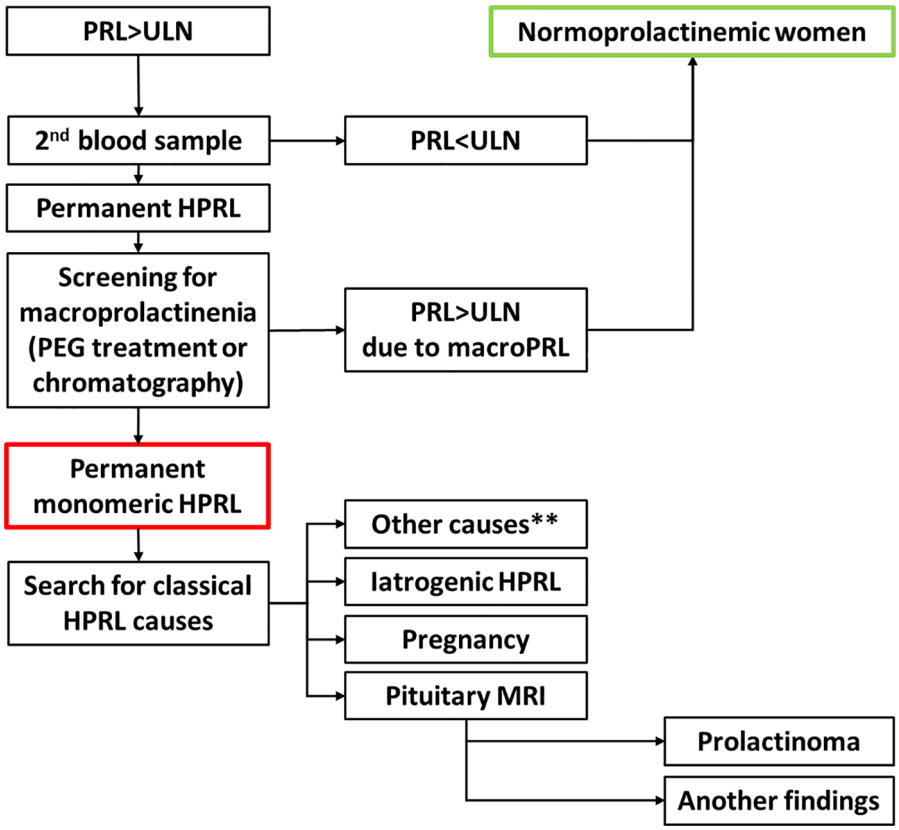

Fig 1. Diagnostic algorithm for the management of hyperprolactinemia.
Abbreviations: PRL, prolactin; HPRL, hyperprolactinemia; ULN, Upper limit of normal; MRI, magnetic resonance imaging.
** Others causes: hypothyroidism, chronic renal failure, cirrhosis, chest wall lesions, breast stimulation, etc.

similar observations and developed methods for its detection[40–42]. Briefly, the majority of prolactin in the bloodstream is monomeric but dimeric and polymeric (bind to immunoglobulin G) forms may also coexist. These forms of prolactin is unable to bind to prolactin receptors and exhibits no systemic response. Macroprolactinemia can cause artificially elevated serum prolactin value associated with a lack of symptoms of hyperprolactinemia and each kit of prolactin assays has a different sensitivity for the detection of macroprolactin[43,44].

To differentiate these different forms of circulating prolactin, the reference method is gel filtration chromatography. However, this exam is expensive and time consuming. It has thus been demonstrated that the detection of these inactive forms of prolactin is possible by carrying out a precipitation of the serum with polyethylene glycol (PEG)[45].

However, although macroprolactin has been known for a long time, its involvement in the misdiagnosis of hyperprolactinemia has not been seriously emphasized in different studies until the 2000s[46–49]. Currently, guidelines do not yet recommend a systematic screening of macroprolactinemia.

In 2005, the international guidelines for the management of HPRL clearly recommended that moderate hyperprolactinemia should be systematically monitored on a second assay and investigated for macroprolactin, especially in the absence of symptoms of hyperprolactinemia[50,51] (Fig. 1).

Obviously, studies conducted until the 2000s did not screen macroprolactinemia, which leads to an interpretation bias. Indeed, macroprolactinemia is a common cause of elevated prolactin and is present in approximately 4% to 40% of hyperprolactinemic patients depending on the referral population[52,53]. It is therefore possible that some idiopathic HPRL patient that have been described in older studies are elevated prolactin levels related to the presence of macroprolactin.

The other breakthrough in the management of HPRL was the development of MRI. Lanteburg and Mansfield received the Nobel Prize in 2003 for their work that led to the development of the first MRIs in the 1970s[54]. The first pituitary MRIs were described in the 1980s[55,56] and this modern and powerful imaging method has quickly replaced the radiographs of sella turcica, by improving the detection of pituitary adenomas. The gradual improvement of MRI techniques has allowed the detection of smaller adenoma, up to the current MRI allowing the detection of adenoma of about 3 mm[57].

Once again, this historical retrospective highlights the rapid progression of knowledge concerning the management of hyperprolactinemia over the past 30 years. Most studies conducted prior to the 2000s did not performed pituitary MRI but radiographs of sella turcica or did not search for macroprolactin and so it is likely that many cases of HPRL were misdiagnosed as idiopathic. Then, this historical retrospective highlight again that old studies are not applicable to our current practice.

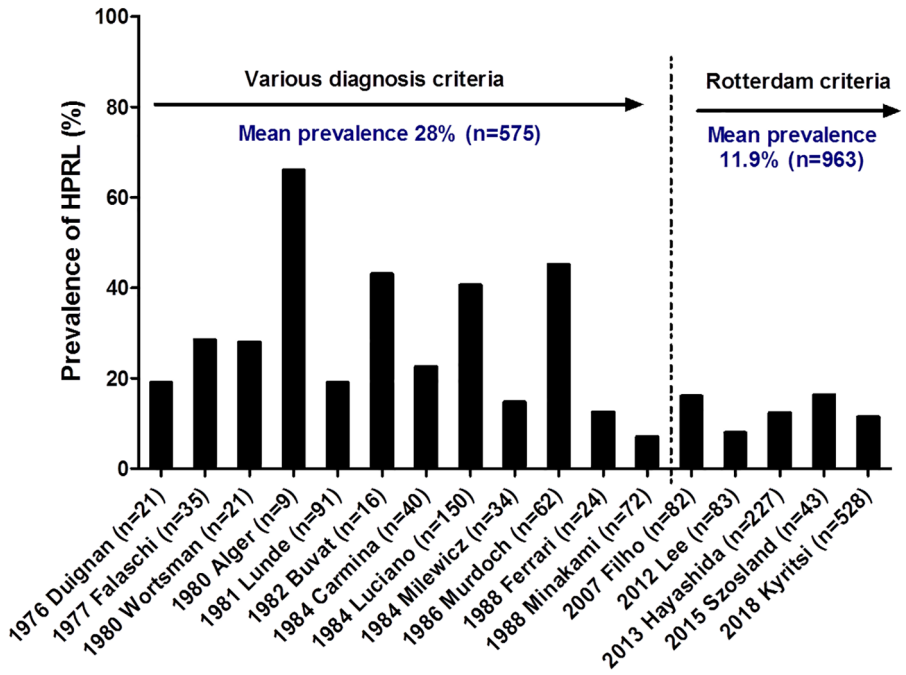

Fig 2. Prevalence of hyperprolactinemia in PCOS women in the literature over time.
The names of the first authors and the date of publication are given for each study as well as the number of PCOS women studied (indicated in parenthesis).

Link between HPRL and PCOS: what the literature analysis reveals?

In 1954, Forbes described 6 patients with prolactin adenoma associated with clinical hyperandrogenism[58]. Subsequently, other authors have published cases of patients with PCOS and hyperprolactinemia[59–62]. These observations have suggested the possibility of a common pathophysiological link between hyperprolactinemia and PCOS and many hypotheses were proposed to explain this association.

Prevalence and Causes of HPRL in PCOS Women

The prevalence of hyperprolactinemia in PCOS women is very variable in the literature, ranging from 3% to 67% (Fig. 2). The majority of this studies was conducted before the first diagnostic criteria of PCOS published in 1990 by the NIH[59,60,63–72]. When analyzing all of these studies according to their years of publication, we note that the prevalence of hyperprolactinemia is more homogeneous since the PCOS was diagnosed with consensus criteria[73–77] (Fig. 2).

In addition, these studies were conducted before the consensus for the management of HPRL and were methodologically very unequal. The existence of permanent and monomeric hyperprolactinemia (i.e., confirmed on a second independent sample and not explained by the presence of macroprolactin) has not been confirmed in the vast majority of these studies. Finally, these studies have focused on a small number of PCOS patients, except Kyritsi& al in 2018 [75]. Thus, the prevalence of hyperprolactinemia in women with PCOS is still unclear.

Concerning the causes of hyperprolactinemia found in PCOS women, the data in the recent literature are concordant and seem to invalidate the hypothesis that hyperprolactinemia is part of the PCOS. Indeed, Filho et al. analyzed a population of 82 women with PCOS and found that 16% (n = 13) had a pathological elevation of circulating prolactin levels. A rigorous etiological approach found a classical cause of hyperprolactinemia for each of these 13 women (prolactin adenomas (n = 9), hyperprolactinemic drugs (n = 3), macroprolactin (n = 1))[73].

Hayashida et al. in 2014 studied a larger population of 227 PCOS women. 6% of PCOS women had elevated prolactin (n = 16), which was consistently explained by the presence of macroprolactin[74].

These two studies are in contradiction with the results of Kyritsi et al. in 2018 that indicate a prevalence of idiopathic HPRL of 23% in 76 PCOS women with HPRL[75]. However, in this study, the exploration of HPRL was incomplete because the search for macroprolactin was not performed in most patients and pituitary MRI was not performed in all patients.

More recently, there have been reported cases of twin sisters presenting with features of PCOS associated with idiopathic hyperprolactinemia. In both of these sisters, normalization of prolactin with cabergoline treatment led to the normalization of menstrual cycles and plasma androgen measurements[78]. This cases convey a message that any prolactin elevation in patients presenting with features suggestive of PCOS should be rigorously evaluated, especially once the prolactin is normalized in order to confirm the reality of the PCOS .

Thus, data from recent literature do not seem to confirm the presence of hyperprolactinemia in women with PCOS when a

rigorous etiological investigation was conducted. However, data from the literature is still insufficient to be conclusive on the subject, and a rigorous study on a larger cohort of PCOS women is needed to confirm these findings.

Hypotheses to explain a physiopathological link between HPRL and PCOS

The most common hypothesis to explain the link between HPRL and PCOS is a possibly common hypothalamic-pituitary abnormality that can explain both PCOS and hyperprolactinemia.

Indeed, studies have shown a synchronization between the prolactin and LH secretion peaks in women with PCOS[71,79,80]. In addition, some studies have suggested that dopamine can also slow down the secretion of LH[81–83]. It has thus been hypothesized that the high levels of LH found in PCOS women would be secondary to a decrease in dopaminergic tone that would also be responsible for an increase in prolactin[82,84]. However, there is conflicting results regarding the effect of dopamine inhibitor or agonist therapy on LH levels in PCOS women[85–88].

Another hypothesis suggests that PCOS causes hyperprolactinemia because it induces relative hyperestrogenemia[89,90]. Indeed, various experimental studies have shown an increase in the secretion of prolactin under the action of estrogen[91,92]. However, different arguments oppose this hypothesis. First, various studies have shown that combined oral contraceptive (containing estrogens) does not result in an increase in prolactinoma size[93,94]. In addition, the few older studies that have studied the effect of wedge ovarian resection or ovarian drilling on prolactin values are conflicting[95,96]. Unfortunately, no recent study has evaluated the impact of combined oral contraceptive pills on prolactin levels.

It also has been suggested the possibility of an acceleration of GnRH pulsatility in PCOS women. This phenomena would be involved in the increase of LH and in the decrease of dopaminergic tone (which induce hyperprolactinemia)[90]. However, there was no evidence of decreased prolactin levels in PCOS women who benefit from pituitary desensitization with GnRH-agonists[97].

Thus, studies on the subject are rare and none has convincingly demonstrated a real physiopathological link between PCOS and hyperprolactinemia.

Conclusion

To conclude, we have shown here that the link between hyperprolactinemia and PCOS comes from old studies in which PCOS were diagnosed according to non-consensual criteria and in which hyperprolactinemia was insufficiently explored in the light of recent knowledge. In addition, data from the literature suggest that there is no hyperprolactinemia related to PCOS once HPRL was rigorously explored in these women.

The recent study of Hayashida& al. demonstrates that the elevation of prolactin linked to the presence of a macroprolactin is not uncommon in PCOS women and that it is therefore essential to screen it[74]. This first step is essential to limit the misdiagnosis and thus avoid the unnecessary prescription of a pituitary MRI or even dopaminergic agonist treatment, as already pointed out by Escobar-Morreale years ago[98].

In case of excessive prolactin level, it is recommended to confirm the reality of hyperprolactinemia by performing a second independent sample and eliminating an excess related to the presence of macroprolactin[51] (Fig. 1).

Finally, in case of confirmation of hyperprolactinemia, it is necessary to carry out a thorough etiological investigation in search of classical etiologies of HPRL before concluding that HPRL is secondary to PCOS (prolactinoma, drug induced HRPL, pregnancy, hypothyroidism, chronic renal failure, cirrhosis, chest wall lesions, breast stimulation, etc..).

Filho in 2007 and already Luciano in 1984 clearly demonstrated that when the etiological investigation of hyperprolactinemia was rigorous, there was no hyperprolactinemia related to PCOS[67,73] (Fig. 1).

Author Contribution

CD and GR performed the literature review and co-wrote the first draft, JY and DD took care of draft revision.

ORCID iD

Didier Dewailly https://orcid.org/0000-0001-8521-5163

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