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Review of nonalcoholic fatty liver disease in women with polycystic ovary syndrome

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Abstract

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in reproductive-aged women. Women with PCOS frequently have metabolic complications including insulin resistance (IR), early diabetes, hypertension and dyslipidemia. Recent studies have demonstrated an association between PCOS and another metabolic complication: nonalcoholic fatty liver disease (NAFLD). NAFLD occurs as a result of abnormal lipid handling by the liver, which sensitizes the liver to injury and inflammation. It can progress to nonalcoholic steatohepatitis (NASH), which is characterized by hepatocyte injury and apoptosis. With time and further inflammation, NASH can progress to cirrhosis. Thus, given the young age at which NAFLD may occur in PCOS, these women may be at significant risk for progressive hepatic injury over the course of their lives. Many potential links between PCOS and NAFLD have been proposed, most notably IR and hyperandrogenemia. Further studies are needed to clarify the association between PCOS and NAFLD. In the interim, clinicians should be aware of this connection and consider screening for NAFLD in

PCOS patients who have other metabolic risk factors. The optimal method of screening is unknown. However, measuring alanine aminotransferase and/or obtaining ultrasound on high-risk patients can be considered. First line treatment consists of lifestyle interventions and weight loss, with possible pharmacologic interventions in some cases.

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Key words: Polycystic ovary syndrome; Fatty liver; Non-alcoholic fatty liver disease; Nonalcoholic steatohepatitis

Core tip: Nonalcoholic fatty liver disease (NAFLD) is a relatively common condition that can progress to non-alcoholic steatohepatitis (NASH) and even cirrhosis. Polycystic ovary syndrome (PCOS) has recently been recognized as a potential risk factor for NAFLD/NASH. Although screening for NAFLD is problematic, clinicians need to be aware that some patients with PCOS may develop significant liver disease, and at a much younger age than is typical. Identifying PCOS patients at risk for NAFLD, and early intervention in these patients, is needed to help prevent long term and serious complications of fatty liver.

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INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is the most common form of liver disease in the western world and is now recognized as the leading cause of cryptogenic cirrhosis^[1,2]. NAFLD encompasses a spectrum of

Table 1 Summary of polycystic ovary syndrome diagnostic criteria

	Recommended tests	¹ NIH diagnosis ^[17]	¹ Rotterdam diagnosis ^[18]	Androgen excess polycystic ovary syndrome society ^[19]
Hyperandrogenism	Clinical: hirsutism, acne, androgenic alopecia Biochemical: elevated total, bioavailable, or free testosterone level	x	x	xx
Oligo- or anovulation	Assessment of frequent bleeding intervals < 21 d or infrequent bleeding intervals > 35 d	x	x	x
PCO morphology	Presence of 12 or more follicles 2-9 mm in diameter and/or an increased ovarian volume > 10 mL in either ovary		x	x
Exclusion of other diagnoses ²	Thyroid disease (thyroid stimulating hormone) Prolactin excess (prolactin) Nonclassical congenital adrenal hyperplasia (17-hydroxy progesterone)	xx	xx	xx

¹All criteria require exclusion of other diagnoses. Rotterdam additionally requires 2 of the remaining 3 criteria; NIH criteria do not include PCO morphology for diagnosis; the Androgen Excess Society requires hyperandrogenism with 1 of 2 remaining criteria; ²In select women, may also consider pregnancy, hypothalamic amenorrhea, primary ovarian insufficiency, androgen-secreting tumor, Cushing's syndrome, acromegaly^[103]. NIH: National Institutes of Health; PCO: Polycystic ovary.

diseases ranging from simple steatosis to nonalcoholic steatohepatitis (NASH) to cirrhosis^[3,4]. Diagnosis of NAFLD depends on evidence of hepatic steatosis, either by imaging or histology, in the absence of other possible causes for hepatic fat accumulation, such as significant alcohol consumption, use of teratogenic medication, hepatitis C virus infection, nutritional disorders, or hereditary disorders^[5,6]. Hepatic steatosis occurs as a result of abnormal lipid handling by the liver, which sensitizes the liver to injury and inflammation while NASH is characterized by increased hepatocyte injury and apoptosis^[7]. Simple hepatic steatosis is often benign and reversible, rarely progresses to NASH, and carries a 1%-2% risk of developing cirrhosis^[8]. On the other hand, NASH carries a 30% risk of progressive fibrosis, which may develop further into cirrhosis, or hepatocellular carcinoma^[9,10]. Data from two registry-based cohorts^[11,12] indicated that patients with NAFLD had a 2.6-fold increased mortality compared to the general population; these data were confirmed by Adams *et al*^[10] who showed an excess mortality risk in NAFLD patients with longer follow-up^[13].

The estimated worldwide prevalence of NAFLD is 6.3%-33% with a median of 20% in the general population^[5,14]. However, in the presence of obesity or type 2 diabetes, the prevalence of NAFLD increases to about 75%^[6]. Additional risk factors for the development of NAFLD are dyslipidemia, older age, male gender, ethnicity, hypothyroidism, hypopituitarism, hypogonadism, and sleep apnea^[5]. Most important to this review, polycystic ovary syndrome (PCOS) has emerged as a significant risk factor for the development of NAFLD in young women.

PCOS is a complex endocrine disorder of uncertain etiology^[15]. Clinical features consist of anovulatory infertility, hirsutism, menstrual dysfunction, acne, and alopecia. Metabolic aberrations include insulin resistance, with compensatory hyperinsulinemia, type 2 diabetes, endometrial carcinoma and possibly cardiovascular disease. Endocrine evaluation may reveal elevated androgens and luteinizing hormone (LH) levels. The ovarian follicles develop poorly, giving rise to the multiple cysts commonly seen in this disorder^[16]. After exclusion of related disor-

ders, the diagnosis of PCOS is made using the National Institutes of Health (NIH) 1990 definition^[17], Rotterdam 2003 criteria^[18], or Androgen Excess Society criteria^[19]. (Table 1) The reported prevalence of PCOS is anywhere from 5%-18% in the general population, depending on the diagnostic criteria used^[15,20].

In this review, we will discuss the association between NAFLD and PCOS and risk factors for development of NAFLD in women with PCOS. We will then discuss the pathophysiology, screening, and finally management of NAFLD in this select group of women.

INCREASED PREVALENCE OF NAFLD IN WOMEN WITH PCOS

The first connection between NAFLD and PCOS was reported in 2005 and subsequent retrospective studies have confirmed this association^[21]. The prevalence of NAFLD within the PCOS population is now estimated to be anywhere between 15% and 55%, depending on the diagnostic index used for both NAFLD and PCOS, since NIH criteria identify a more metabolic PCOS phenotype^[22-25]. In 2005, Schwimmer *et al*^[22] found a 30% risk of alanine aminotransferase (ALT) elevation (> 35 U/L) amongst a cohort of PCOS patients attending a fertility clinic. We found elevated aminotransferases in 15% of our PCOS population using a higher cut-off value for abnormal ALT (> 60 U/L)^[23]. However, applying the same ALT elevation criteria as Schwimmer *et al*^[22], 28% of our cohort had an ALT > 35 U/L. Further, using ultrasound to diagnose hepatic steatosis, Gambarin-Gelwan *et al*^[24] demonstrated hepatic steatosis in 55% of the 88 PCOS women in their retrospective study. The first study to include a control group was a prospective study of Chilean women with PCOS by Cerda *et al*^[25]. In this study, the prevalence of hepatic steatosis diagnosed by ultrasound was 41.5% amongst PCOS women compared to 19.4% in controls while ALT was elevated (> 25 U/L) in 39% of PCOS women *vs* 3.2% of controls.

Of note, the presence of PCOS is also common in

patients with NAFLD. Brzozowska *et al*^[26] found a 71% prevalence of PCOS amongst reproductive aged women with NAFLD attending a liver clinic. Interestingly, all PCOS women in this study had biopsy-proven NASH. Similarly, we included a subset of women with liver biopsies; all six liver biopsies demonstrated steatohepatitis with fibrosis despite the young mean age of 29 in our cohort to suggest that PCOS women may have an increased risk for more advanced disease at diagnosis^[23]. Hossain *et al*^[27] supported this finding, when they compared PCOS patients and controls with similar clinical and laboratory profiles: 44% of patients with PCOS and 20.8% of controls had histologic NASH.

Prevalence of NAFLD in adolescents with PCOS

NAFLD is prevalent in adolescent females with PCOS. A retrospective chart review by Barfield *et al*^[28] found a 15.4% prevalence rate of elevated aminotransferases within an adolescent PCOS population. Michaliszyn *et al*^[29] demonstrated that in obese adolescent girls with PCOS, liver fat is associated with increasing age, even in the narrow adolescent age range, increasing abdominal adiposity, worsening insulin sensitivity, and dyslipoproteinemia; age and total testosterone made the greatest contribution to liver fat in this study.

Prevalence of NAFLD in lean women with PCOS

The data are less clear on whether or not NAFLD is also more prevalent in lean PCOS patients. Importantly, PCOS has been noted to affect 28% of obese women, but only 5% of lean women^[20,30]. Of the previous studies discussed thus far, Gambarin-Gelwan *et al*^[24] was the only one to include both lean and obese patients. They found a prevalence of NAFLD in 39% of lean PCOS women to suggest that PCOS may confer a risk for NAFLD that is independent of obesity. However, these findings have not been confirmed in other studies including a small study of 17 young women with PCOS as well as an additional study that included a subgroup of 34 lean PCOS women compared to lean controls^[31,32].

CARDIOVASCULAR RISK ASSOCIATED WITH NAFLD IN WOMEN WITH PCOS

NAFLD is considered to be the hepatic manifestation of the metabolic syndrome while PCOS may be the ovarian manifestation of the metabolic syndrome^[33]. The prevalence of the metabolic syndrome in PCOS is 50%, which is about seven times the prevalence in the female population of a similar age. Both PCOS and NAFLD are thus associated with cardiovascular risk factors, which embody the metabolic syndrome: insulin resistance (IR), obesity, dyslipidemia, type 2 diabetes, endothelial dysfunction, and carotid atherosclerosis^[33-35]. Convincing epidemiological data now exist linking NAFLD with long-term risk of adverse cardiovascular outcomes^[36], but the data on long-term cardiovascular outcomes in PCOS are less clear. A recent study looked at cardiovascular risk in women with

PCOS and NAFLD compared to PCOS alone^[37]. Mean weight and body mass index (BMI) were higher in the NAFLD group but there was no difference in other cardiovascular risk factors, such as fasting lipids, blood pressure, and endothelial function. Therefore, these authors suggested that the presence of NAFLD does not amplify the cardiovascular risk profile in women with PCOS.

PATHOPHYSIOLOGY OF NAFLD IN PCOS

Role of insulin resistance in the pathogenesis of NAFLD in PCOS

Insulin resistance is detected in up to 80% of cases of NAFLD and there is a near universal association between NAFLD and IR irrespective of obesity^[33,38]. While the exact pathogenesis of NAFLD is still unclear, evidence supports IR as a primary factor in its development^[39]. The “two-hit theory” that was initially suggested about 15 years ago suggested that IR is the first “hit” to cause hepatic steatosis, when insulin resistant visceral adipocytes release free fatty acids that flow to the liver and accumulate; cytokine stresses and apoptosis are the second “hit”, which mediate the progression to NASH^[7,40,41].

More recently, two additional concepts, “multiple-hit” and “distinct hit” theories, are being considered to explain the pathogenesis of NAFLD/NASH, and both still include IR as an integral component^[41,42]. The “multiple-hit” theory conceptualizes NAFLD/NASH pathogenesis in the same way as the “two-hit” theory, where NASH is generally a condition preceded histologically by simple steatosis and pathophysiologically by IR and its associated metabolic disturbances^[41]. However, fatty infiltration of the liver then leads to a series of parallel multiple hits, such as cytokines, adipokines, and oxidative stresses, which mediate the progression to NASH and fibrosis. The “distinct hit” hypothesis was generated by evidence that NASH and pure fatty liver could arise as two independent conditions, since inflammation occasionally precedes steatosis and patients with NASH may present with very little steatosis^[41,42]. Therefore, according to this model, distinct pathways are activated (potentially by IR) which lead to either simple steatosis or NASH, rather than an accumulation of multiple parallel hepatotoxic injuries^[41].

Similarly, IR is thought to play a central pathophysiological role in PCOS that is not explained alone by its frequent association with obesity^[43]. The landmark 1989 study by Dunaif *et al*^[44] first showed that IR is present in both obese and non-obese women with PCOS and this was confirmed in later studies^[45,46]. There are several proposed reasons why PCOS women may have a decreased sensitivity to insulin, which include both insulin receptor defects and insulin signaling defects at the level of glucose transport into skeletal muscle^[47].

A systematic review determined that IR is present in 50%-80% of women with both PCOS and NAFLD^[47] and multiple studies have shown that PCOS women with hepatic steatosis have elevated levels of IR compared to

PCOS women without steatosis^[24,25,48-50]. Those with steatosis showed higher BMI, waist-hip ratio, fasting insulin, and homeostasis model assessment-estimated insulin resistance (HOMA-IR) scores than PCOS women without steatosis^[25]. Further, Targher *et al.*^[51] found that insulin sensitivity by euglycemic hyperinsulinemic clamp measures markedly decreased in PCOS women with abnormal ALT levels (defined as ALT over 19 U/L) whereas it was similar between PCOS women with normal ALT levels and matched healthy controls.

Role of androgens and their connection to insulin resistance

Insulin resistance in the ovaries may be central to the pathogenesis of PCOS^[52]. The ovaries are abundant with insulin receptors and the dysregulation of insulin signaling may augment the production of androgens in theca cells, the primary source of excessive androgen biosynthesis in women with PCOS^[47]. IR leads to compensatory hyperinsulinemia, which stimulates theca cells in LH-sensitized ovaries to secrete testosterone and androstenedione^[53]. Interestingly, if a patient with PCOS and hyperandrogenism has chemical or surgical ablation of the ovaries, the hyperandrogenism is reversed but elevated insulin levels persist^[22,54-56].

This combination of hyperandrogenism and IR may contribute to the pathogenesis of NAFLD in PCOS, but there is still speculation as to their independent effects and relationship to each other. A case report of a woman with hyperthecosis and biopsy-proven NAFLD documented the reversal of abnormal liver tests and hirsutism after bilateral oophorectomy^[57]. Because an oophorectomy should not improve IR, this report suggests an independent contribution of hyperandrogenism to fatty liver in these women^[22,57].

One theory for how hyperandrogenism puts PCOS women at risk for NAFLD regards its effects on the low-density lipoprotein receptor (LDLR), which is down-regulated 0.51 fold in PCOS women^[33]. Androgens may suppress LDLR gene transcription to prolong the half-life of very low-density lipoprotein (VLDL) and LDL and thus induce lipid accumulation in the liver. The LDLR gene is a subject of estrogen control that is maintained through the estrogen-responsive region adjacent to the sterol response element within the LDLR promoter; androgen receptor agonists have been shown to attenuate the estrogen-induced up-regulation of LDLR in hepatocytes^[33,58]. It is possible that hyperandrogenemia may have a direct suppressive influence on LDLR levels in both adipocytes and the liver, thus making PCOS women more prone to liver disease^[33].

Observational findings from multiple studies suggest that to better understand and control NAFLD in women with PCOS, not only metabolic variables, but also hyperandrogenism should be taken into consideration. For instance, hirsutism may be a risk factor for elevated ALT^[22]. In addition, hyperandrogenemia has been associated with elevation of ALT levels in PCOS women independent

of obesity^[49,58]. Further, Jones *et al.*^[45] showed that after statistical adjustment for BMI, HOMA-IR, and visceral adipose tissue, 19 hyperandrogenic PCOS women had a significantly higher quantity of liver fat, as measured by proton magnetic resonance spectroscopy (H-MRS) compared with 10 non-hyperandrogenic PCOS or 22 controls (3.7% and 2.1% respectively; $P < 0.05$).

Further evidence that androgens may exert harmful effects to the liver was noted by Chen *et al.*^[59]: (1) men have been shown to have higher serum levels of ALT and a higher risk of NAFLD than women, after adjusting for obesity^[60-64]; (2) long-term administration of androgens for female-to-male transsexuals has been noted to be associated with borderline elevated ALT levels^[65]; (3) androgens and androgen receptors are known to be involved in the carcinogenesis of hepatocellular carcinoma (HCC) both in men and women^[66,67]; and (4) androgen ablation therapy is one of the potential therapeutic treatment options for HCC^[68,69].

Role of obstructive sleep apnea and its connection to insulin resistance

Obstructive sleep apnea (OSA), while common in women with PCOS, may contribute to NAFLD development and accelerate its progression to NASH^[70-74]. A recent meta-analysis found that NAFLD is 2.6 times more frequent in OSA patients and these patients have a 2.6-fold higher risk of progressing to liver fibrosis^[74]. The presence of OSA has been shown to increase the chance of NAFLD by 7.6 times in women with PCOS^[70]. The mechanism through which this occurs is likely related to IR. Chronic intermittent hypoxia increases production of inflammatory cytokines, increases oxidative stress, and decreases adiponectin, all of which contribute to IR and to fat accumulation in the liver. This process may be androgen-driven, since generally men are at a higher risk for OSA^[75]. Therefore, the high free testosterone levels in women with PCOS may be one of the predisposing factors leading to OSA in this group^[70].

Role of apoptosis in the progression of NAFLD

There is evidence for a pro-apoptotic environment contributing to the progression from NAFLD to NASH^[7]. Hepatic apoptosis triggers regenerative mechanisms to replace dead hepatocytes; however, aberrant responses may occur in some individuals, resulting in the activation of hepatic stellate cells to myofibroblasts and the hepatic recruitment of pro-inflammatory, pro-fibrogenic immune cells. Induction of apoptosis occurs through the activation of effector caspases that cleave a host of intracellular substrates including cytokeratin 18 (CK18), a member of the intermediate filament family of cytoskeletal proteins^[76,77]. It has been shown that the plasma-borne caspase-generated CK18 fragment levels correlate with the magnitude of hepatocyte apoptosis and independently predict NASH in multivariate analysis^[78].

Two studies examined CK18 fragment levels (measured as "M30") as both a marker of apoptotic cell

death and a qualifier for NAFLD/NASH in women with PCOS^[33,76]. M30 levels were significantly elevated in PCOS patients compared to non-PCOS age-matched controls after correction for BMI^[76]. Tan *et al*^[76] found that 27.6% of PCOS patients compared to only 1.4% of the non-PCOS controls showed M30 levels considered high enough to qualify for NASH though no confirmatory biopsies were done. A separate study of biopsy-proven NAFLD patients undergoing bariatric surgery found higher M30 levels in the PCOS-NAFLD group compared to the non-PCOS-NAFLD group^[33]. These data by Baranova *et al*^[33] are interesting, because patients with histologically confirmed NASH were excluded, thus indicating that an increase in apoptosis is an early feature of NAFLD observed in PCOS subjects.

Some have hypothesized that the pro-apoptotic environment is exacerbated by androgens^[33]. Androgens are known as pro-apoptotic agents and have been shown to act upon many types of peripheral cells, including hepatocytes^[33,79]. The hyperandrogenism of PCOS may therefore contribute to an increased risk of NAFLD progression through its effects on apoptosis.

Dysfunctional adipose tissue in the pathogenesis of NAFLD in women with PCOS

Visceral fat accumulation and adipose tissue dysfunction have been implicated in the pathogenesis of NAFLD in PCOS women. Central obesity has been shown to be associated with both hepatic steatosis and hepatic IR in women with PCOS^[80,81]. Women with PCOS have higher global adiposity and increased amounts of visceral adipose tissue, especially in the intraperitoneal and mesenteric depots^[80,82]. Furthermore, on multivariate logistic regression, fasting insulin and mesenteric fat thickness were identified as independent predictors of fatty liver among subjects with PCOS^[80].

Villa *et al*^[83] suggests that the distribution of fat to abdominal/visceral sites is not the only explanation for the metabolic abnormalities in women with PCOS. These women also exhibit clear abnormalities in their adipose tissue, compared to similarly obese women without PCOS. PCOS women have an adipocyte diameter that is generally increased by 25% relative to that in comparably obese control women who do not have PCOS^[83,84]. Their obesity is therefore characterized by an increase in fat cell size, termed “hypertrophic obesity”, rather than an increase in number, or “hyperplastic obesity.” Hypertrophic obesity is associated with IR, because the hypertrophic adipocyte cells themselves are insulin resistant^[83,85]. Androgens again may play an extrinsic role, since they have been shown to induce IR in subcutaneous adipose cells *in vitro*^[83,86].

Adipokines and inflammatory mediators in the pathogenesis of NAFLD in women with PCOS

A number of adipokines have been implicated in the pathogenesis of PCOS: leptin, adiponectin, vaspin, visfatin, chimerin, and acute-phase amyloid A^[87]. Adiponectin may have anti-inflammatory and insulin-sensitizing

effects. Secreted by adipocytes, it is the only adipokine downregulated by obesity^[47]. PCOS women have been shown to have lower levels of adiponectin when compared to weight-matched controls and low levels of adiponectin were correlated with IR^[88]. In cases where lean women with PCOS maintain normal sensitivity to insulin, adiponectin biosynthesis deficiency or chronic low level inflammation is often present^[47]. However, Baranova *et al*^[47] found no difference in levels of adiponectin between PCOS and non-PCOS obese women undergoing bariatric surgery with biopsy-proven NAFLD.

A number of inflammatory and macrophage-derived factors have also been studied in the pathogenesis of PCOS: resistin, tumor necrosis factor-alpha (TNF α), interleukins, and C-reactive protein (CRP)^[87]. TNF α impairs insulin action and individuals with IR show higher serum levels of TNF α ^[7]. Its expression is up regulated in both PCOS and NASH, independent of obesity^[87]. The effects of TNF α may actually lie in part with its biological relationship to adiponectin. Higher TNF α may activate downstream kinases that induce cytokine production, while attenuating the expression and activity of adiponectin^[7].

Protective role of estrogen

One study looked at the role of estrogens in NAFLD and PCOS^[89]. Gutierrez-Grobe *et al*^[89] found that women without NAFLD had significantly higher levels of serum estradiol (100 +/- 95.4) compared to women with NAFLD (55.5 +/- 66.6). The estradiol level specifically in PCOS women with NAFLD was 64.9 compared to 101.36 in PCOS women without NAFLD. The prevalence of NAFLD in premenopausal, postmenopausal, and PCOS women was 32.2%, 57.9%, and 62% respectively. These results suggest that NAFLD is more prevalent in postmenopausal and PCOS women than premenopausal women and estrogens may have a protective effect. Furthermore, it has been shown that NAFLD severity worsens after menopause and this is believed to be due to the loss of estrogens^[90,91].

Harmful role of bisphenol A

One study suggested a potential role for bisphenol A (BPA)^[92]. BPA at very low doses alters several metabolic functions, including oxidative stress, a key component of inflammatory reactions. Studies have implicated BPA in the global rise of obesity, type 2 diabetes, cardiovascular disease, and most recently, PCOS^[93-95]. Tarantino *et al*^[92] showed that in premenopausal women with PCOS, there was an association of serum BPA levels with hepatic steatosis and markers of low-grade inflammation, particularly spleen size. Increased spleen volume has been proposed as an index of chronic inflammation associated with fatty infiltration of the liver^[92,96]. It is possible that BPA acts as a pro-inflammatory primer, *via* macrophage activation and pro-inflammatory cytokine hypersecretion; within this context, the spleen enlargement could represent a marker of this inflammatory process, and the

inflammation may contribute to NASH^[92]. Further studies are needed to investigate this hypothesis.

Role of genetics

A number of genes have been implicated in both PCOS and NAFLD and some of them are linked to the pathogenetic mechanisms already discussed above. Some examples of these genes are the following: LDLR, genes involved in steroidogenesis, 5-alpha reductase, sex hormone binding globulin, fat mass gene, inflammatory mediators (such as hsCRP, which is increased by interleukin 6 produced by macrophages and adipocytes), and adiponectin^[47].

ISSUES REGARDING SCREENING FOR NAFLD AND IMPLICATIONS FOR WOMEN WITH PCOS

Early detection of NAFLD in PCOS patients is important, because these women develop NAFLD at a relatively young age. Furthermore, intervention at an early stage may decrease or even eliminate the possibility of disease progression^[49]. The progression to NASH should be an important concern in patients with PCOS, because PCOS patients seem to have more histologic NASH than women with similar clinical and laboratory profiles^[27]. The young age of this population puts them at increased risk to develop metabolic and hepatic complications over their lifetime^[97]. The mean age of women with NASH in our study^[23] was 29, though NASH is not typically diagnosed until age 41–60 years^[98].

The 2012 guidelines by the American Association for the Study of Liver Diseases (AASLD), American College of Gastroenterology, and the American Gastroenterological Association^[5] argue that there should be systematic screening for NAFLD, at least among higher-risk individuals; however, routine screening is not advised at this time, because of significant gaps in our knowledge. The gold standard for NAFLD diagnosis is liver biopsy. However, liver biopsy is limited by cost, sampling error, and procedure-related morbidity and mortality. Liver biopsy is therefore a limited tool. It should be considered in patients with NAFLD who are at an increased risk to have steatohepatitis and advanced fibrosis or for those with metabolic syndrome. It should also be used in patients with suspected NAFLD in whom competing etiologies for hepatic steatosis and co-existing chronic liver diseases can't be excluded without a liver biopsy.

Because liver biopsy in all cases would not be feasible or cost effective, there is a need for optimization of noninvasive testing^[48]. Serum aminotransferase levels and imaging tests such as ultrasound, computed tomography (CT) scan, and magnetic resonance (MR) are the noninvasive tests that are more frequently used^[5]. A number of other noninvasive tests have been researched, but are still under investigation: transient elastography, scoring systems, and serum markers of cell death^[5,99].

None of the imaging modalities have sufficient sensitivity and specificity for staging NAFLD and they cannot distinguish between simple steatosis and NASH with or without fibrosis^[100]. Ultrasound is often combined with aminotransferase levels for detection of NAFLD. Aminotransferase levels alone are not sufficiently sensitive for screening, because they may actually be within the normal range for patients with NAFLD and NASH^[5]. Gambarin-Gelwan *et al*^[24] found that only 15% of the PCOS subjects with ultrasound evidence of fatty liver had concurrent abnormal aminotransferases, which is concerning, because significant liver pathology could potentially go unrecognized for long periods of time in a group of women who are at risk of progressive and severe hepatic disease^[23].

An additional area of contention to recognize is the disagreement over the upper limit of aminotransferase value to consider abnormal. Prati *et al*^[101] suggested a cut-off value of 19 U/L for ALT, which has a 76% sensitivity and 88% specificity compared to a lower 55% sensitivity and higher 97% specificity using a cut-off ALT value of 30 U/L.

Targeted approach to screening for NAFLD in PCOS women

Early recognition of NAFLD in PCOS patients is warranted, but as discussed above, routine screening is not currently recommended and our screening tests are limited. Therefore, screening in this population of women should potentially target those more likely to develop NASH, such as those with metabolic syndrome^[5,87]. The presence of metabolic syndrome is a strong predictor for the presence of steatohepatitis in patients with NAFLD, so guidelines by AASLD recommend using the presence of metabolic syndrome to target patients for liver biopsy^[5].

Gangale *et al*^[97] studied a group of 140 hyperinsulinemic overweight women with PCOS and showed that all cases of the metabolic syndrome in their cohort were detected in women with NAFLD. Furthermore, NAFLD affected up to nearly half of their overweight hyperinsulinemic patients, so they suggested NAFLD screening in all PCOS women who are overweight and hyperinsulinemic. On the other hand, Ciotta *et al*^[102] found a NAFLD incidence rate of 40% in lean PCOS women and therefore felt that it would be prudent to screen all PCOS women, regardless of BMI. Some suggest screening PCOS women with both liver biochemistries and ultrasound, while others feel that an ultrasound is warranted regardless of the serological evaluation of the liver^[32,97,102,103]. Although the Endocrine Society clinical practice guidelines^[104] for PCOS recommend against routine screening for NAFLD, they suggest obtaining serum markers of liver dysfunction in women with metabolic risk factors and/or IR. If serum markers are elevated, ultrasound and liver biopsy can then be considered.

The fatty liver index (FLI) might serve as a simple and accurate tool to help physicians select subjects for liver ultrasonography and intensified lifestyle counseling, be-

cause it has been shown to correlate well with hepatic steatosis on ultrasound^[105,106]. The FLI is an algorithm based on BMI, waist circumference, triglycerides, and GGT. PCOS women had an odds ratio of 2.52 for elevated FLI compared to non-PCOS BMI matched controls. The FLI may therefore identify PCOS patients at high risk for hepatic disturbances, though future confirmatory studies are needed.

Finally, a hepatology referral should be considered if there is concern that the patient has steatohepatitis, her ALT is double the upper limit of the reference range, or there is evidence of cirrhosis^[37]. On the contrary, an endocrinology referral should be considered and the existence of PCOS should be investigated in a young woman with NAFLD^[26].

MANAGEMENT OF NAFLD IN WOMEN WITH PCOS

There is currently no medication licensed to treat NAFLD, so the current advice to patients is to lose weight, screen for cardiovascular risk factors, and appropriately treat those risk factors^[5,87]. Weight loss of 5%-10% of initial body weight should be implemented as first-line therapy in all patients with NAFLD/NASH and is usually enough to reduce steatosis and improve liver function tests^[5]. However, weight loss alone is not enough to reverse fibrosis, so more advanced cases may be treated with medications that correct IR and metabolic disorders or specific hepatoprotectors, such as antioxidants and anti-inflammatory agents. The decision about which specific therapy to use should include a consideration of both the efficacy and the adverse effects of therapy as compared to other available therapies^[107].

A personalized, or pathogenesis-based, approach should be taken to treating PCOS women with NAFLD/NASH^[108]. Younossi *et al.*^[108] suggests that patients may share risk factors for the first insult to the liver, the accumulation of hepatic fat. However, patient cohorts may then have distinctly different second or subsequent insults (as per the “two-hit” or “multiple hit” theories^[41,42]). In other words, different pathogenic pathways may be involved in the development of NASH, so one single treatment for all of NASH is unlikely to be successful^[108]. The following section will highlight the various treatments options for NAFLD to date, focusing only on those that have been studied in women with PCOS.

Lifestyle intervention

Weight loss is a key treatment for both PCOS and NAFLD. A systematic review of 23 studies supports the link between weight reduction and/or increased physical activity and reduced liver fat and improved glucose control/insulin sensitivity in patients with NAFLD^[109]. We reported a young woman with PCOS and NASH who showed histopathologic improvement on liver biopsy after lifestyle modification^[21]. However, no large studies to date have examined the effects of lifestyle

interventions on NAFLD specifically in women with PCOS. A Cochrane review found that lifestyle therapy gave modest benefits in women with PCOS compared with minimal treatment for a variety of other surrogate outcomes, including lower total testosterone, improved hirsutism, weight, lower waist circumference, and fasting serum insulin; however, markers of liver disease were not reviewed^[110]. No specific diet has been shown to improve PCOS and generally the recommendation from experts has been for a hypo-caloric diet with a 500 kcal/d deficit and a composition likely to increase adherence^[52,111]. Similarly, no specific diet has been proven superior for treatment of NAFLD; in fact, studies published to date do not allow a clear differentiation of the effects of diet composition or of diet relative to physical activity^[109].

A systematic review and meta-analysis^[112], which examined 78 randomized trials for the treatment of NAFLD found that although weight loss of greater than or equal to 7% improved histological disease activity, this was only achieved in less than 50% of patients. Hurdles to implementation of lifestyle changes specifically in the PCOS population may include the following: (1) high dropout rates; (2) difficulty in morbidly obese women to adapt to significant lifestyle changes; and (3) the overall lack of clinical infrastructure to implement lifestyle therapy in many settings throughout the United States and the world^[52,113,114].

Pharmacotherapy: treating insulin resistance

Metformin is a widely utilized diabetes drug that works by suppressing hepatic gluconeogenesis and improving insulin-sensitizing ability^[52]. Metformin is generally not recommended as a specific treatment for liver disease in adults with NASH, because studies have shown mixed results^[5]. In women with PCOS, metformin has been shown to improve markers related to liver disease and the metabolic syndrome^[97]. In this study by Gangale *et al.*^[97], long-term treatment with metformin in 70 overweight women with PCOS and NAFLD demonstrated a significant reduction in AST levels and AST/ALT ratio at 6 mo despite no significant change in BMI; however, no change in hepatic steatosis was detected by ultrasound at 12 mo. Another study showed significantly reduced levels of ALT and GGT in 66 obese women with PCOS after 8 mo of treatment with metformin^[115]. Data are limited on metformin treatment in lean PCOS patients with NAFLD. Gastrointestinal discomfort is a common side effect, but metformin otherwise has a low risk of severe adverse effects and has been studied fairly extensively in women of reproductive age^[52,116].

Thiazolidinediones (TZDs) are known to enhance insulin sensitivity by acting on peroxisome proliferator-activated receptor gamma and increasing circulating adiponectin^[117]. They also reduce fat accumulation in the liver through stimulation of free fatty acid storage in adipose tissue. TZDs have shown promising effects on treating NAFLD/NASH in the general population. A multicenter study of troglitazone for PCOS provided important

proof of concept for the use of TZDs in the treatment of these women, due to the resultant improvements in ovulatory function, hirsutism, hyperandrogenism, and insulin resistance^[52,117-119]. However, this class of medication has not been specifically studied with regards to its effects on NAFLD in PCOS.

There are a number of limitations in using TZDs in patients with NAFLD and PCOS, particularly the associated weight gain^[52,107,108]. Patients are likely to relapse after the drug's discontinuation, so it would have to be taken indefinitely^[108]; however, the significant weight gain detracts from its long-term usefulness. Additionally, the safety concerns regarding this class of medication have restricted their availability or removed them from the market: toxicity from troglitazone, increased cardiovascular events with rosiglitazone, and bladder cancer with pioglitazone. The risk-benefit ratio is inadequate for women with PCOS when taking all these factors into account on top of concerns for teratogenicity^[52].

Liraglutide is the first glucagon-like peptide-1 analogue shown to improve liver fibrosis markers in obese women with PCOS and NAFLD^[120]. This medication may be an attractive option for obese women with PCOS, because it causes glucose dependent insulin secretion, promotes weight loss, and may subsequently improve IR. In a case control study of young obese PCOS women with age and weight matched controls, 6 mo of liraglutide treatment resulted in a mild reduction in weight and significant improvement of IR, inflammation, and liver fibrosis markers. However, liraglutide is not FDA approved for NAFLD treatment and further studies are needed to confirm these findings before use of this medication is recommended in this setting.

Pharmacotherapy: antioxidants and anti-inflammatory medications

Antioxidant supplements may potentially protect cellular structures against damage from oxygen-free radicals and reactive products of lipid peroxidation^[121]. Vitamin E is thought to be the "last antioxidant defense" in lipid metabolism, thus justifying its use in preventing the progression of NAFLD to NASH. A 2007 Cochrane review^[121] found insufficient data to either support or refute the use of antioxidant supplements for treatment of NAFLD and data from subsequent clinical trials have shown mixed results^[107,122]. However, no studies have examined the effects of Vitamin E on NAFLD in women with PCOS.

Omega-3 fatty acids may treat NAFLD through a number of mechanisms. In addition to their anti-inflammatory and antioxidant properties, they inhibit triglyceride synthesis, alter hepatic genes involved in lipid and glucose metabolism, decrease postprandial lipemia, and increase lipoprotein lipase activity^[123]. It is therefore not surprising that omega-3 fatty acid supplementation has been shown to significantly reduce liver fat, triglycerides, fasting insulin, and HOMA-IR scores in PCOS women with hepatic steatosis. A recent systematic review and meta-

analysis further supports the role of omega-3 fatty acids in reducing liver fat, but suggests that the optimal dose is not currently known^[124]. Omega-3 fatty acids are an attractive option for women with PCOS and NAFLD, but they are not recommended as first line treatment for NAFLD unless the patient has concurrent hypertriglyceridemia^[5].

Other pharmacotherapies

Other pharmacotherapies include ursodeoxycholic acid, probiotics therapies^[125], pentoxifylline^[126], traditional chinese herbal medicine^[127], and most recently the farnesoid X receptor ligand Obeticholic Acid^[128]. None of these therapies have been studied specifically in women with PCOS.

Treatment with statins

Controversy surrounds the use of statins in both PCOS and NAFLD. Although some open-label trials have suggested improvement in liver enzymes with statins, there is no convincing histological data supporting their use for treating NAFLD^[5]. The AASLD guidelines^[5] state that there is a lack of evidence to show that patients with NAFLD and NASH are at an increased risk for serious drug-induced liver injury from statins and suggest that they can be used to treat dyslipidemia in patients with NAFLD and NASH. Statins may have intrinsic antioxidant properties that justify treatment for PCOS and many of these women have dyslipidemia that will benefit from treatment with statins. However, these benefits must be weighed with the possibility that statin therapy will worsen insulin sensitivity in this group of women who are at a higher risk of developing type 2 diabetes^[129]. The teratogenicity of statins must also be kept in mind when treating women of reproductive age.

Treatment with bariatric surgery

Finally, bariatric surgery may improve steatosis, steatohepatitis, and fibrosis; some cases of NAFLD/NASH may even resolve^[108,130]. The AASLD guidelines suggest that it is premature to consider this surgery as an established option to specifically treat NASH, but it is important to note that foregut bariatric surgery is not contraindicated in otherwise eligible obese individuals with NAFLD or NASH (but without established cirrhosis)^[5]. A study of 389 PCOS women who underwent Roux-en-Y gastric bypass surgery resulted in a significant decrease in liver aminotransferases for Hispanic women only^[131]. It is possible that cardio-metabolic disease risk improvements vary by ethnicity. Thus, obesity may impact liver function changes more in Hispanic vs non-Hispanic women with PCOS.

CONCLUSION

NAFLD encompasses a wide spectrum of liver disease, ranging from simple steatosis to NASH and even cirrhosis. The prevalence of NAFLD is greater in women with PCOS compared to the general population. Data are conflicting on whether PCOS represents an indepen-

dent risk factor for NAFLD or whether the increased risk in this population is due to obesity, insulin resistance, metabolic syndrome, or hyperandrogenemia. Early recognition of NAFLD in women with PCOS is important, because they develop a more progressive, severe form of liver disease at a younger age. Although routine screening is not recommended, it should be considered for some high-risk PCOS women, especially those with insulin resistance and/or the metabolic syndrome. There are no proven treatments for NAFLD to date, but a personalized pathogenesis-based approach to treatment should be considered for this multifactorial disease. More research is needed to determine the best approach to management of NAFLD in women with PCOS.

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