REVIEW ARTICLE

Gender Differences in Nonalcoholic Fatty Liver Disease

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Abstract

Nonalcoholic fatty liver disease (NAFLD) has currently emerged as the most common liver disorder in both developed and developing countries. It has been observed that NAFLD exhibits sexual dimorphism, and there is limited understanding on the sex differences in adults with NAFLD. Nonalcoholic fatty liver disease shows marked differences in prevalence and severity with regards to gender. There are considerable biological disparities between males and females attributed to differences in the chromosomal makeup and sex hormone levels, distinct from the gender differences resulting from the sociocultural influences that lead to differences in lifestyle, which have a significant impact on the pathogenesis of this complex disorder. A multitude of factors contributes to the gender disparities seen and need to be researched in-depth to better understand the mechanisms behind them and the therapeutic measures that can be taken. In this article, we will review the gender disparities seen in NAFLD, as well as recent studies highlighting certain gender-specific factors contributing to its varying prevalence and severity.

Keywords: Fibrosis, Gender, Gender difference, Liver cancer, Menopause, Metabolic syndrome, Molecular pathogenesis, Nonalcoholic steatohepatitis, Prevalence, Sex hormones.

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Introduction

Nonalcoholic fatty liver disease is a chronic liver disease that includes a spectrum of liver dysfunction ranging from steatosis and steatohepatitis to fibrosis and liver cirrhosis in the absence of alcohol intake. It is mainly seen in association with metabolic syndrome and is strongly linked to insulin resistance, obesity, type 2 diabetes mellitus (T2DM), and dyslipidemia. In recent years, the prevalence of NAFLD is increasing at alarming rates in the Asia-Pacific region due to the increasing number of cases of obesity and T2DM. The NAFLD–nonalcoholic steatohepatitis (NASH) spectrum *per se* has reached epidemic prevalence and new insights will help in focusing on those cohorts of individuals exposed to the highest risk of NAFLD. Nonalcoholic fatty liver disease has been considered a multifaceted complex systemic condition[1] that exhibits sexual dimorphism and follows a variable hepatic and extrahepatic course.[2,3]

Many diseases express sexual dimorphism. "Sexual dimorphism" implies the differing characteristics of diseases including incidence, clinical manifestations, and outcomes between males and females. "Sex differences" are the biological disparities seen between males and females attributed to the chromosomal makeup without any influence by nature and culture, whereas "gender differences" define the sociocultural influences that lead to differences in the specific roles, behavior, and relations of men and women. The understanding of clinically relevant features characterizing sex differences in adults with NAFLD is still limited.[4–6]

Prevalence and Gender

The global prevalence of NAFLD was reported to be 25% of the general population based on imaging diagnosis.[7] The prevalence for Asia was reported to be 27% and for Europe was 24%.[7] The prevalence of NAFLD in the Asia-Pacific region has been increasing at a tremendous rate in the past years due to the diabetes-obesity epidemic and it is equaling the prevalence in developed countries.[8]

Nonalcoholic fatty liver disease and NASH are known to demonstrate gender differences concerning the age in prevalence and severity of progression. In a Japanese study conducted over 12 years, the average prevalence of fatty liver in men was 26%, which was double than that seen in women (13%). However, women showed a steady increase in prevalence with age, while men had a similar prevalence in all age-groups. The prevalence was higher in females than in males in the

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70–79 age-group.[9] In another study in South China, NAFLD prevalence was reported to be significantly more in men as compared to women under 50 years of age (22.4% vs 7.1%, p <0.001). This prevalence was reversed when compared among men and women over the age of 50 years. (20.6% vs 27.6%, p <0.05).[10] The gender-based prevalence of NAFLD in various regions is outlined in Table 1.

Causative Factors of Sex Differences seen in NAFLD

Sex Hormones

There is significant evidence to suggest the importance of sex hormones in the occurrence of NAFLD. A meta-analysis conducted showed that an increase in serum testosterone in women increases the risk of NAFLD [as seen in women with polycystic ovary syndrome (PCOS)], and decreased levels in males increase the risk. Sex hormone-binding globulin levels were noted to be lower in both males and females with NAFLD than in controls.[11] Testosterone deficiency in males as seen in hypogonadism is also associated with an increased risk of NAFLD.

Sex hormones are involved in the regulation of hepatic glucose and lipid metabolism through various mechanisms. The liver is known to exhibit a functional sexual dimorphism. The increased risk of NAFLD in postmenopausal women is due to decreased estrogen levels which alter the visceral distribution of fat and promote dyslipidemia milieu.[20]

Estrogen has a protective role against the development of hepatic steatosis in both men and women via estradiol signaling through ER-α, as seen in several rodent studies as well as clinical studies. Deletion of ER-α in female mice leads to increased hepatic steatosis via hepatic lipogenesis as well as the occurrence of insulin resistance.[21] Estrogen shows a beneficial effect due to its protective effect against the development of insulin resistance, decreasing triglyceride synthesis, and enhancing free fatty acid oxidation in the liver.[22] A combination of estrogen and androgen therapy in male orchidectomized rats was shown to decrease the steatosis induced by high-fat diets as compared to either agent alone. This highlighted the protective roles of estrogen and androgens in males against hepatic steatosis and NAFLD.[23] Although androgen deficiency promotes hepatic steatosis, this review also showed that with regards to the sequelae of NAFLD, specifically hepatic fibrosis and hepatocellular carcinoma (HCC), in both men and women, androgens are responsible for their progression. However, the mechanism behind this remains to be established. Estrogens decrease the risk of hepatic fibrosis and HCC development in men and women due to the antifibrogenic action of estrogen. Thus, it is seen that men have increased hepatic fibrosis severity, increased HCC incidence, and increased HCC-associated mortality. While in women, postmenopausal status or a longer duration of estradiol deficiency was reported to lead to increased hepatic steatosis.[21]

More recently, the loss of estrogen signaling was linked to oxidative damage in liver due to low levels of peroxisome

Table 1: Gender-based prevalence of NAFLD in the general population

Author Year	*Country*	*Population screened*	*Male prevalence**	*Female prevalence***	*Other findings*
Butt et al.[12] 2011	Pakistan	163 patients with T2DM and MS	51.3%	40.7%	Overall NAFLD prevalence–72.4%. Prevalence was higher in patients with metabolic risk factors.
Eguchi et al.[13] 2012	Japan	5,075 subjects from the general population (2,448 female/2,627 male)	41%	18%	Positive linear relationship seen between BMI, LDL cholesterol, TG levels, and NAFLD prevalence.
Kalra et al.[14] 2013	India	924 T2DM patients (355 female/569 male)	54.3%	60%	Highest prevalence in the 61–70-year age-group.
Alam et al.[15] 2018	Bangladesh	2,782 participants from general population	33.82%	33.91%	Highest prevalence among females was seen in rural participants of 45–54 years. Higher risk identified in people with higher BMI, middle-aged adults and diabetics.
Park et al.[16] 2006	Korea	6,648 subjects from the general population (3,118 females/3,530 males)	21.6%	11.2%	Metabolic risk factors were significantly associated in both genders. Estrogen use and postmenopausal status were risk factors in women only.
Wong et al.[17] 2012	China	922 subjects from the general population (533 females/389 males)	37%	23%	Overall NAFLD prevalence–27.3%. In women, the prevalence increased after menopause.
Li et al.[18] 2014	China	3,56,367 subjects from the general population (1,52,124 females/2,01,481 males)	25%	13%	The prevalence of NAFLD increased with age up to 60 years.
Caballería et al.[19] 2010	Spain	766 subjects from the general population (443 females/323 males)	33%	20%	The factors associated with NAFLD were male sex, age, insulin resistance, ALT levels, and MS.

*Among total males in study; **Among total females in study; ALT, alanine aminotransferase; LDL, low-density lipoprotein; MS, metabolic syndrome; T2DM, type 2 diabetes mellitus; TG, triglyceride

proliferator-activated receptor-γ (PPARG) coactivator 1α, leading to worsened steatohepatitis in mice associated with a high-fat diet.[24] In another recent study conducted on mice, Quinn et al. demonstrated a glucocorticoid receptor-mediated mechanism for the development of hepatic steatosis in estrogen-deficient mice.[25]

Sex Chromosomes

Apart from the well-known hormonal factors playing a role in the development of metabolic syndrome and its associated disorders, studies have suggested the sex chromosomes themselves may be responsible for the sexual dimorphism seen in these conditions. The sex chromosomes independent of gonadal status in the mouse model have been associated with plain steatosis and NAFLD.[26] A study by Chen et al. demonstrated that the sex chromosome complement influences adiposity and weight gain, as XX mice showed greater adiposity than XY mice, even after gonadectomy was performed to remove the influence of sex hormones. It purported that the increased adiposity was due to the presence of an extra X chromosome instead of the absence of a Y chromosome, as genetic studies with XO and XXY chromosome mice demonstrated. The mechanism was shown to be that certain genes escaping X chromosome inactivation displayed increased expression levels in adipose tissue and liver of XX mice than XY mice.[27] Similar deductions can be made in syndromes associated with an extra X chromosome, such as Klinefelter's syndrome, in which insulin resistance and metabolic syndrome occur at a high rate. Rodent studies have shown increased adiposity in XXY mice as compared to XY mice. There is an increased occurrence of metabolic syndrome even in prepubertal Klinefelter's boys compared to control group boys, suggesting chromosomal influences prior to any hormonal influences. The study reported that out of 89 boys with Klinefelter syndrome 37% had elevated low-density lipoprotein levels, 24% had insulin resistance, and 7% were diagnosed with metabolic syndrome.[28,29]

Gut Microbiota

Disruption of gut microbiota has been recently linked to NAFLD pathogenesis. The mechanisms behind the influence of the gut microbiome on NAFLD are due to the complex microbiome–host interactions. The possible factors involved in the association with NAFLD include the metabolism of choline, bile acids, and amino acids, as well as the production of short-chain fatty acids and ethanol by gut microorganisms and the altered gut permeability.[30] Sex differences are also seen in this aspect which could likely be due to sex hormone effects on the gut microbiome. Studies have shown the varying diversity of gut microorganisms based on age and sex.[31] A recent study reported that bile acids and farnesoid X receptor (FXR) with the gut microbiota are involved in the gender differences seen in metabolic disorders. The male western diet-fed FXR KO mice had the more severe steatosis, insulin resistance, and elevated hepatic and serum lipids compared to the female mice. The gender differences reported in western diet-induced steatosis, insulin sensitivity, and predicted microbiota functions in mice were all FXR dependent.[32]

Insulin Resistance

Insulin resistance forms the bedrock for the interplay of sex and genetic differences and executes a prominent role in the causation of NAFLD as well as the progression of fibrosis.[33] Estrogen is a known regulator of body metabolism, and the loss of circulating estrogen seen in postmenopausal women leads to changes in body adiposity as well as loss of insulin sensitivity causing increased insulin resistance.[34,35] E2 administration, i.e., estradiol, has been shown to improve insulin sensitivity in adipose tissue of postmenopausal women compared to placebo.[36]

Gender Disparities in NAFLD Patients Based on Severity and Complications

Hepatic Fibrosis

The crucial question is if hepatic fibrosis is sex-dependent. Hepatic fibrosis is mediated by the excessive deposition of the extracellular matrix (ECM), which causes thickening of the hepatic septae. Hepatic stellate cells play a key role in the pathogenesis of fibrosis. After an injury, hepatic stellate cells undergo a transformation from quiescent cells to a highly proliferative and fibrogenic myofibroblast cell type. Prolonged duration of injury leads to permanent remodeling with cytokine-induced deposition of large quantities of ECM and proliferation of contractile cells.[37] It has been shown that estrogen exhibits a protective effect against the development of fibrosis in women by activating estrogen receptor-β on the liver which in turn inhibits hepatic fibrosis via inhibition of hepatic stellate cells. Estrogen receptor-α and G-protein-coupled estrogen receptors were not noted to be involved in the antifibrogenic effects of estrogen.[38,39] Epidemiological studies suggest that women may be spared the processes that lead to enhanced fibrosis. In a study among 541 histologically confirmed NASH patients, the severity of fibrosis was noted to be higher in men and postmenopausal women compared to premenopausal women.[40] In a meta-analysis of 12 studies (conducted among a morbidly obese NAFLD population of 1,620 patients) by Machado et al., male sex was reported to be associated with the occurrence of NASH and hepatic fibrosis in these patients.[41] In a Japanese study among 762 NAFLD patients (404 being men), advanced fibrosis was seen much more common among severely obese men (60.9%) compared to severely obese women (33.7%). The prevalence of NASH was not reported to be significantly different among the sexes.[42] However, in a meta-analysis of 11 studies including 411 biopsy-proven NAFLD patients (NAFL-150 and NASH-261), gender was not detected as a significant risk factor when the progression of hepatic fibrosis was taken into account.[43] In a Japanese study with 193 biopsy-proven NASH patients (86 women, 107 men, stratified as less than 55 years and more than 55 years), fibrosis was associated with older age, and women more than 55 years predominated in the fibrosis group (67% older vs 28% younger). It did not reach statistical significance, therefore, the authors concluded that gender exclusively was not a risk factor for fibrosis progression.[44]

Malignancy

Nonalcoholic steatohepatitis predisposes patients to the development of cirrhosis as well as HCC. Hepatocellular carcinoma due to NASH can develop in the absence of cirrhosis. NAFLD has also been reported as the fastest-growing cause of HCC in the United States of America and parts of Europe. Risk factors for HCC in NAFLD are older age, male sex, Latino/Latina ethnicity, presence of cirrhosis, diabetes, and obesity.[45] A meta-analysis was conducted to identify the pooled risk of HCC in the non-cirrhotic population, and 168,571 participants from 19 studies were included. It was seen that the prevalence of HCC in non-cirrhotic NASH (38%) was significantly larger (p <0.001) than HCC from other non-cirrhotic etiologies (14.2%).[46]

A study by Tobari et al. compared NAFLD-related HCC patients with and without cirrhosis to demonstrate that in the non-cirrhotic group, males predominated. On comparing non-cirrhotic NAFLD

patients with or without HCC, it was seen that non-cirrhotic HCC patients had greater male predominance than non-cirrhotic NAFLD patients, with a significantly higher prevalence of light drinkers and a higher FIB4 index. The overall gender disparities are not strikingly clear as far as NAFLD with HCC is concerned.[47]

Nongastrointestinal malignancies are also commonly seen in NAFLD. It is the second most common cause of death in NAFLD patients and the most common cause of cancer-related deaths.[48] A recent study showed NAFLD to be significantly associated with colorectal adenomatous and hyperplastic polyps in males. However, a similar association was not significant in females.[49] In another study among women with breast cancer as compared to controls, NAFLD was seen to be significantly associated with breast cancer, excluding the influence of traditional risk factors. However, only the women in the non-obese group showed this association when compared to the obese group in the subgroup analysis.[50]

Sex Differences in NAFLD-associated Disorders

Type 2 Diabetes Mellitus (T2DM)

Type 2 diabetes mellitus commonly occurs in patients with metabolic syndrome. There is a bidirectional relationship proposed between the occurrence of NAFLD and T2DM. Nonalcoholic fatty liver disease is a risk factor for the development of T2DM, and T2DM has been shown to increase the rate of progression of NAFLD.[51]

Dai et al. reported a significant difference in the male and female prevalence of NAFLD in subgroup analyses of patients with T2DM. In a study by Yi et al., they reported an increased prevalence of NAFLD in males (48%) vs females (42.9%) with T2DM and increased BMI. Type 2 diabetes mellitus has also been reported as a secondary event to NAFLD. In a study of NAFLD patients in Japan, the rate of T2DM was 9.95 per 1000 person-years. Female gender was identified as a statistically significant factor influencing the progression to T2DM.[52–54]

Obesity

Sex hormones play an important role in the varying adiposity levels and distribution among men and women. Women have more subcutaneous fatty deposition and men have more visceral distribution.[55] Women are known to have decreased cardiovascular and metabolic risk as compared to men due to endogenous estrogens. A decrease in estrogen after menopause leads to redistribution of body fat with a more visceral distribution.[56] Sex differences are also noted in fatty acid, triglyceride, and cholesterol metabolism and its correlation with hepatic physiology.[57] In a study among age and BMI-matched obese men and women, women showed increased hepatic insulin sensitivity compared to men but similar adipose tissue and peripheral sensitivity.[58]

In morbidly obese NAFLD patients undergoing gastric bypass (365 total patients, with 58 men and 307 women), it was seen that NASH was much more common in males as compared to females, irrespective of weight (63.3% vs 30.9%).[59]

A study among 710 patients who underwent bariatric surgery showed a prevalence of 29% metabolically healthy obese (MHO–obese individuals without any metabolic derangements, i.e., diabetes and hypertension). In this MHO cohort, the prevalence of liver steatosis was 88%, and these patients were reported to be more likely to be females, with an odds ratio of 2.1.[60]

In a recent study by Li et al., the prevalence characteristics of Lean-NAFLD or non-obese NAFLD compared to obese NAFLD were explored in a cross-sectional study of 1,608 cases. It showed that the prevalence of NAFLD was higher in the obese group with no gender difference, while the non-obese group demonstrated a lower prevalence with a male predominance.[61]

Atherosclerosis and Cardiovascular (CV) Disease

The protective effect of estrogen against atherosclerotic cardiovascular disease risk in the female sex has been well established.[20] However, a recent study among 3,869 patients with NAFLD and 15,209 age- and sex-matched subjects with a 7-year follow-up period showed that ischemic CV events incidence was less in the general female population as compared to the male population.[62] However, this difference was not seen in women with NAFLD, indicating that the development of NAFLD in women leads to loss of the CV disease protection offered by their female sex.[62] In addition, it is important to note that among patients with NAFLD, the males had a lesser amount of excess CV events (18% vs 9%) and mortality rates (9% vs 6%) as compared to the female cohort.[62]

Polycystic Ovary Syndrome

There is a known association between PCOS and the occurrence of NAFLD. Traditionally, it was believed to be due to only shared risk factors leading to metabolic syndrome. However, in a study conducted on 88 premenopausal women with PCOS (median age of 31.4 years), fatty liver was identified in 55% of subjects with PCOS, nearly 40% of whom were lean women.[63] This suggests that NAFLD is associated with PCOS, irrespective of comorbid obesity. Other risk factors noted were increased BMI and insulin resistance. Women being treated with oral contraceptives showed a lower prevalence of steatosis (38% vs 64%).[63]

In a systematic review and meta-analyses conducted by Rocha et al., the prevalence of NAFLD was noted to be higher in women with PCOS who had high serum androgen concentrations compared to women with PCOS who did not have high androgen concentrations.[64] In women with PCOS who had NAFLD, the serum testosterone levels were noted to be higher than those who did not have NAFLD.[64] This suggests that the pathophysiology behind the association of NAFLD and PCOS is most likely linked to the increased androgen levels seen in PCOS.

Management of NAFLD

The mainstay of treatment for NAFLD includes lifestyle modifications including diet, exercise, and weight loss with add-on pharmacotherapy and surgical approaches for weight loss at higher BMIs. There are currently no differing guidelines on the management of NAFLD in men and women, however, certain predisposing conditions can be targeted to cause a decrease in the progression of NAFLD in women.

Weight management: Weight loss is the main modality of treatment in NAFLD patients. In a study conducted to assess gender differences in the sites of adipose tissue loss among obese patients, 17 obese men and 17 obese women were given daily fenfluramine as well as subjected to caloric restriction. Reduction of visceral adipose tissue (VAT) was reported to be significantly more in men as compared to women. In the same study, men were reported to have lost more VAT as compared to subcutaneous or thigh. However, on measuring initial levels of VAT in these cohorts, gender differences in the adipose tissue reduction during weight loss were no longer apparent.[65] In a systematic review conducted by Williams et al. on weight loss interventions' effectiveness among men and women, 11 studies (out of 21) reported that men lost significantly more weight

than women with diet only as well as diet plus exercise weight loss regimes. It reported that although men appear to lose more weight than women overall in most studies, women also lost a significant amount of weight. They reported little evidence to employ differing weight-loss strategies in men and women.[66]

A meta-analysis of 13 RCTs reported no significant difference in weight loss in men and women, including weight loss in kilograms ($p = 0.90$) or weight loss in percentage ($p = 0.78$).[67] However, men lost more weight with intensive low fat reducing diets, with or without meal replacements, and structured physical activity/exercise programs as compared to women. Orlistat was shown to be not as effective for weight maintenance in men as compared to the placebo group. However, in women, significant weight loss was reported with orlistat compared to the placebo group.[67]

In an analysis of 2,942 patients with NAFLD who underwent bariatric surgery compared to 5,884 NAFLD patients matched for age, sex, and comorbidities who did not undergo surgery, it was seen that patients who underwent bariatric surgery had a decreased risk of developing cirrhosis (hazard ratio 0.31).[68] Male gender was linked to an increased risk of developing cirrhosis among the same cohort (hazard ratio 2.07).[68]

In PCOS: Polycystic ovary syndrome has been demonstrated as a significant risk factor, leading to increased prevalence of NAFLD in women. Lifestyle interventions are the first line of management to target insulin resistance. Diet, weight loss, and exercise are the mainstay for PCOS patients with NAFLD. Metformin can be used to improve outcomes, and it has been shown to decrease the prevalence of metabolic syndrome and the hepatic parameters of NAFLD if treatment is continued long-term.[69]

In menopause: Considering the metabolic effects induced by estrogen deficiency after menopause and its link to the occurrence of NAFLD, the role of hormone replacement therapy (HRT) in the management of NAFLD in postmenopausal women has been in consideration for a long time.[70] In 50 women with T2DM, significantly decreased levels of liver enzymes were seen after 6 months of HRT containing low dose estradiol and norethisterone. This suggested a potential for HRT therapy in women with NAFLD.[71] In a study among 93 menopausal women with NAFLD, significantly lower levels of high waist circumference, insulin resistance, ferritin, and gamma-glutamyl transferase (GGT) were seen in women who completed ≥6 months of HRT ($N = 14$) compared to women not taking HRT ($N = 79$).[72] In another study, levels of GGT, alanine transaminase (ALT), and the insulin resistance index were reported to be significantly lower in postmenopausal women taking HRT compared to those who were not on HRT.[73] However, there was no significant association seen with NAFLD in comparison to the type of hormone used in HRT, its route of administration, and the duration of use.[73] The study also showed that postmenopausal women, both with and without NAFLD, had a higher prevalence of overweight, obesity, and insulin resistance compared to those who were on HRT.[73]

Liver transplant: Disparities have been noted in the context of patients with NAFLD listed for liver transplant but data are lacking to allow any conclusions to be drawn about post-transplant outcomes.

In a study of the UNOS–STAR database (2005–2012) that listed 76,149 patients for a liver transplant, 7.2% (5,492 cases) were NASH related.[74] The analysis showed NASH to be the more likely etiology in females than males throughout this period, however, NASH incidence in both increased in this duration. Overall, the rate of liver transplantation was less in women than in men (52.4% vs 64.3%), and women were more likely to experience death on the waitlist (17% vs 11%).[74] Although, in the past, BMI variations were identified as the cause for gender disparity in transplant, gender disparity in transplantation was noted to be larger for NASH compared to hepatitis C virus (HCV) suggesting reasons other than BMI differences. Women with NAFLD more frequently required dual liver and kidney transplantation, another dimension that was noted by the researchers and could explain this gender disparity for liver transplant in NASH.[74]

A study among 127,164 adult patients registered for a liver transplant on UNOS/OPTN database from 2004 to 2016, reported that NASH was found to be the leading cause for waitlist registration and liver transplantation in females surpassing alcoholic liver disease (ALD) (previously the highest in both genders) and HCV.[75] There was a 2383% increase reported in NASH with HCC in female patients among waitlist registrants ($p < 0.0001$), around twice the change in males (1172%) during this same period. Alcoholic liver disease remained the leading cause of waitlist registration in men, although the incidence of NASH as an etiology had increased.[75] The NASH Clinical Research Network reported that NASH is more likely to develop in women with NAFLD than men with NAFLD at a ratio of 2:1.[76] This could be the explanation for increased cases of a liver transplant due to NASH etiology in women as seen in the above transplant studies. As of yet, there have been no studies reporting significant gender differences in post-transplant recurrence of NAFLD.[77] The existence of varying risk of NAFLD recurrence based on gender is yet to be determined.[78]

Conclusion

Nonalcoholic fatty liver disease shows marked differences in prevalence and severity with regards to gender. A multitude of factors contributes to the gender disparities seen and need to be researched in-depth to better understand the mechanisms behind them. Obesity and menopausal status are major contributing factors to NAFLD occurrence and progression to NASH in women. Early recognition and screening are necessary for women in the high-risk group, with comorbid obesity, T2DM, and PCOS.

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