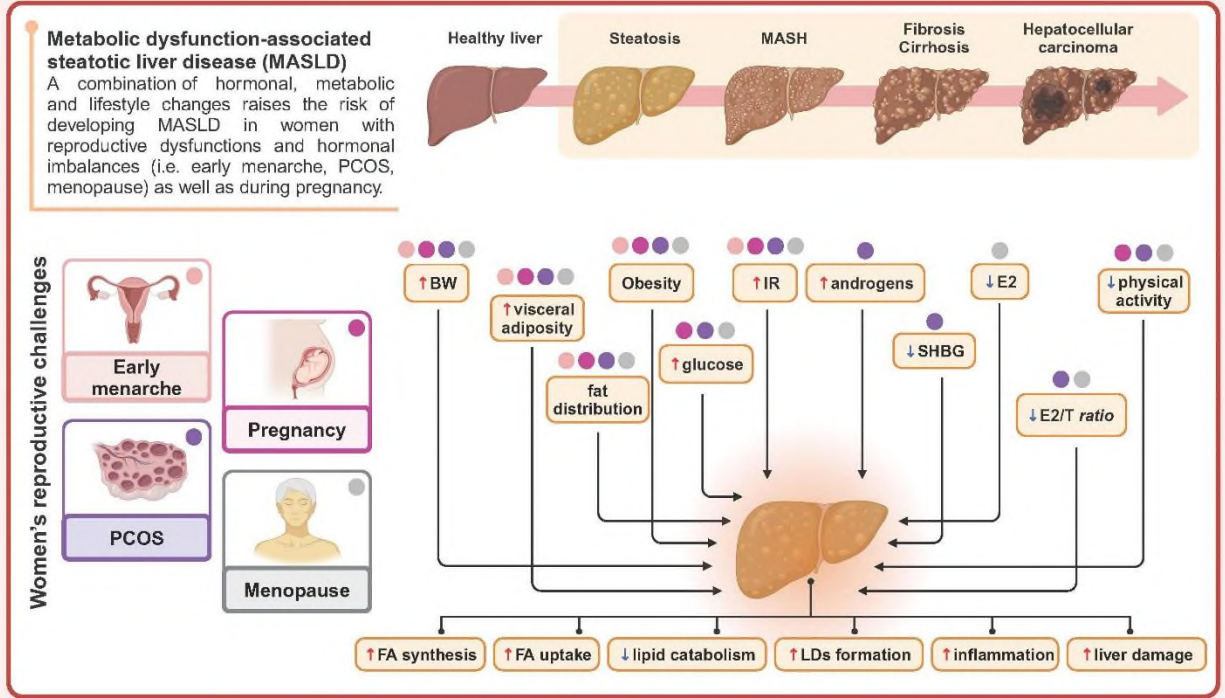
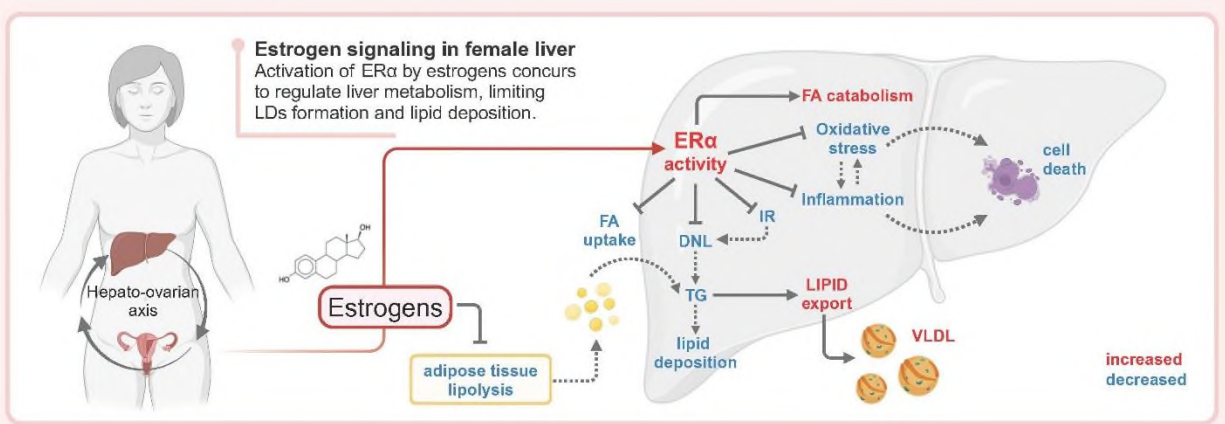


## MASLD across women' reproductive lifespan and issues

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## Introduction

Metabolic dysfunction-associated steatotic liver disease (MASLD) is the foremost cause of liver-related morbidity and mortality, affecting >30% of the global population <sup>1</sup>. MASLD ranges from reversible steatosis to severe conditions like steatohepatitis (MASH), cirrhosis, and hepatocellular carcinoma, and is frequently associated with other cardiometabolic disorders <sup>2</sup>.

With respect to men, women of fertile age show a lower susceptibility to develop MASLD <sup>3</sup>, pointing to the relevance of the hepato-ovarian axis and of estrogen signaling in female liver physiopathology. In the female liver, estrogen's effects are mainly mediated by the estrogen receptor alpha (ER $\alpha$ ), whose activation contributes to reduce lipid synthesis, uptake, and storage while promotes lipid catabolism and export <sup>3,4</sup>. Despite this general protection, women's risk of developing MASLD varies throughout their reproductive lifespan <sup>3,5-7</sup>. Hormonal, endocrine and metabolic changes, including body fat distribution and muscle quality and quantity, may influence the risk of developing MASLD throughout women reproductive lifespan <sup>6-10</sup>. Moreover, women with MASLD often exhibit different clinical and pathological features compared to men <sup>3,5-7</sup>.

With this Snapshot, we aim to point attention to reproductive-related stages (menarche, pregnancy, menopause) and issues (such as polycystic ovary syndrome, PCOS) that may account for MASLD susceptibility across a woman's lifespan. Increasing awareness of the impact of reproductive-related factors on female liver health can help to define personalized, sex-specific approaches for women with MASLD.

### **Age at menarche and MASLD**

Emerging evidence suggests a link between early menarche (before age 12) and an increased risk of developing MASLD later in life <sup>11-14</sup> (see also Table 1). This association is increasingly relevant due to the declining median age of menarche and rising childhood obesity rates <sup>6,15,16</sup>.

Early menarche may result in prolonged exposure to estrogen over a woman's lifetime, which can affect fat distribution and storage, insulin sensitivity, and metabolic processes critical to MASLD development <sup>11-14</sup>. Early menarche is also associated with increased insulin resistance, obesity, and hepatic fat accumulation <sup>11,13</sup>. Increased visceral adiposity and chronic low-grade inflammation further contribute to MASLD risk <sup>11,12</sup>.

Regular monitoring for metabolic conditions and liver health can help women who experienced early menarche to manage MASLD. Early intervention promoting healthy lifestyles, such as balanced diets and regular exercise, can limit MASLD risk factors <sup>6</sup>.

### **MASLD during pregnancy**

Pregnancy is a physiological status characterized by finely orchestrated metabolic shifts to ensure fetus growth and development <sup>17</sup>. During pregnancy, insulin resistance (IR) increases, lipid metabolism shifts, and levels of triglycerides and cholesterol rise <sup>17</sup>. There is also a physiological increase in weight, with greater fat deposition to support fetal growth and maternal energy reserves. These metabolic changes are influenced by hormones, especially estrogens, which play a key role in modulating insulin sensitivity, lipid metabolism, and energy balance <sup>17</sup>. Pregnancy-associated metabolic adaptations can impact maternal liver function and contribute to MASLD, especially in women with underlying risk factors such as obesity, metabolic syndrome, IR and gestational diabetes <sup>17,18</sup>. Over the past decade, the prevalence of MASLD during pregnancy has nearly tripled <sup>19</sup>, reaching nowadays a prevalence of approximately 14%–18% in studies using ultrasonography and/or the fatty liver index as diagnostic tools <sup>20,21</sup> (see also Table 1). Of note, the prevalence of MASLD among pregnant women may be underestimated due to diagnostic limitations and challenges <sup>21</sup>, as many standard diagnostic tools, such as liver biopsies, are typically avoided during pregnancy.

In pregnant women, MASLD is linked to serious maternal and fetal complications, including preterm birth, hypertensive complications, and postpartum hemorrhage <sup>18</sup>. MASLD during pregnancy also correlates with long-term health consequences, as it may contribute to the development of metabolic disorders including MASLD in children later in life <sup>18</sup>.

In this view, early intervention and appropriate management strategies, including nutritional and lifestyle interventions, can help mitigate the risks associated with MASLD in pregnancy<sup>22</sup>.

### **PCOS and MASLD: partners in crime**

PCOS is one of the most common endocrine and metabolic disorders, affecting ~10% of women of reproductive age. PCOS is defined by a combination of signs and symptoms of ovarian dysfunctions and androgen excess in the absence of other specific diagnoses<sup>23</sup>.

Recent studies found associations between MASLD and PCOS (see also Table 1), that share several risk factors, especially IR, obesity, unhealthy dietary choices and lifestyle, and hormonal imbalances<sup>24</sup>. However, recent evidence suggests that PCOS is a risk factor for MASLD, independent of obesity and other metabolic syndrome features, and *vice versa*<sup>25</sup>. PCOS is characterized by IR and is often linked to abdominal obesity, hyperandrogenism, and high levels of free androgens resulting from reduced sex hormone-binding globulin (SHBG)<sup>24</sup>. Alterations in gut microbiota and a sustained pro-inflammatory status may exacerbate MASLD progression in PCOS women, that develop more severe hepatic steatosis and advanced liver fibrosis compared to those without PCOS<sup>8</sup>. On the other hand, women with MASLD are more likely to develop PCOS, due to genetic factors and impaired synthesis and secretion of hepatokines<sup>24</sup>.

The co-occurrence of PCOS and MASLD requires a comprehensive and multifaceted approach that includes regular monitoring of relevant indicators (i.e. weight, serum glucose, HbA1c, blood lipid parameters, and glucose tolerance tests), lifestyle modifications as first-line treatment (weight loss through dietary interventions and exercise), and pharmacological treatments aimed to ameliorate insulin sensitivity (i.e. metformin), lower lipid (i.e. statins) and androgen levels (i.e. oral contraceptives; spironolactone)<sup>24,26,27</sup>. In patients with severe obesity, bariatric surgery can improve hepatic and endocrine dysfunctions in PCOS women suffering with MASLD and MASH<sup>24,26,27</sup>. Emerging therapies with glucagon-like peptide-1 (GLP-1) receptor agonists, dipeptidyl peptidase-4 (DPP-4) inhibitors, peroxisome proliferator-activated receptors (PPARs) agonists, and sodium-glucose cotransporter 2 (SGLT2) inhibitors, may represent additional options but require further investigation<sup>24,26,27</sup>.

### **Menopause-associated MASLD**

Menopause (typically occurring at the age of 50-51 years in high-income countries), early and premature menopause (happening at the age of 40-44 years or before age 40, respectively) raise

the risk of MASLD due to a combination of hormonal, metabolic, and lifestyle changes<sup>7</sup>. The drop in estrogens reduces fat breakdown and increases fat storage, contributing to liver lipid droplet accumulation, inflammation, and damage<sup>7,28</sup>. Post-menopausal women often experience increased IR, visceral fat redistribution, and reduced physical activity, all factors potentially triggering MASLD<sup>7,28,29</sup> (see also Table 1). Women who enter menopause at younger ages might also experience an increased likelihood of having more severe fibrosis, as a consequence of a longer duration of estrogen deficiency<sup>30</sup>.

For menopause-associated MASLD, effective management includes lifestyle modifications (especially dietary interventions and increased physical activity), hormone replacement therapy (HRT), and non-hormonal treatments<sup>7,28,31</sup>.

Estrogen-based HRT can lower the risk of menopause-associated MASLD, by promoting lipid breakdown and reducing lipid synthesis in the liver, improving insulin sensitivity, and limiting visceral fat<sup>28</sup>. HRT can decrease inflammation and oxidative stress, lowering the risk of more severe forms of MASLD<sup>28</sup>. Despite that, the clinical evidence remains limited and controversial, since the effects of estrogen-based HRT on menopause-associated MASLD may vary depending on the type of HRT, duration of use, and route of administration<sup>29,31,32</sup>.

Besides these benefits, HRT is associated with increased likelihood of certain cancers (i.e. breast and endometrial cancer), cardiovascular events, and thromboembolic disorders, particularly when therapy is started late in menopause or used for extended periods<sup>33</sup>. Conversely, HRT significantly reduces all-cause mortality and CVD risks when initiated in women younger than 60 years or within 10 years since menopause, known as the “window of opportunity”<sup>33,34</sup>. Therefore, HRT should be tailored to individual patient profile and should take advantage of regular monitoring and consultation with healthcare providers to manage and mitigate potential risks<sup>34,35</sup>.

A valuable alternative approach to estrogen-based HRT may be represented by a dietary formula enriched in essential amino acids. This approach has been shown able to restore the hepatic transcriptomic profile and prevent liver fat accumulation and body weight increase in a mouse model of menopause<sup>36</sup>.

## **Concluding remarks and future directions**

The strict interconnection between the regulation of liver metabolism and reproduction in females emphasizes the relevance of the hepato-ovarian axis and underscores the need to address potential liver metabolic complications in women according with their reproductive and hormonal status. Reproductive stages (menarche, pregnancy, menopause) and issues (such as PCOS), along with hormonal status, should be therefore considered key endpoints in studies involving female participants. Pre-clinical studies that incorporate female sex and reproductive stages as variables can deepen our understanding of the factors contributing to female-specific susceptibility and features of MASLD. Awareness of these factors throughout the reproductive lifespan can help to identify more personalized, sex-specific approaches to counteract MASLD in women.

## **Abbreviations**

BW, body weight; E2, estrogens; ER $\alpha$ , estrogen receptor alpha; FA, fatty acids; HRT, hormone replacement therapy; IR, insulin resistance; LDs, lipid droplets; MASH, metabolic dysfunction-associated steatohepatitis; MASLD, metabolic dysfunction-associated steatotic liver disease; PCOS, polycystic ovary syndrome; SHBG, sex hormone-binding globulin; T, testosterone.

## **Key figure**

During their fertile lifespan women are generally protected against MASLD, especially thanks to the regulatory activity of estrogens. Metabolic and endocrine changes associated with early menarche, pregnancy, PCOS and menopause may promote MASLD in women. Figure is adapted from images created with BioRender (<https://biorender.com/>).

## **Search strategy and selection criteria**

A literature search was performed to identify studies investigating MASLD (previously termed as NAFLD) in women, published up to July 2024. Original research and review articles were identified through the PubMed database, with the search especially focused on articles published in the last 3-5 years. We included basic science studies, randomized-controlled trials, reviews, original prospective studies, cross-sectional studies, retrospective studies and best practice guidelines using different combinations of the following search terms: “metabolic dysfunction-

associated steatotic liver disease”, “MASLD”, “non-alcoholic fatty liver disease”, “NAFLD”, “fatty liver”, “MASH”, “NASH”, and “women” or “female” or “fertility” or “reproduction” or “reproductive lifespan”. For effects of sex hormones, we used the search terms: “sex hormones”, “sexual dimorphism”, “sex differences”, “estrogens”, “androgens”, “testosterone”, “menopause”, “hormone replacement therapy”, “HRT”, and “MASLD” or “NAFLD” or “MASH” or “NASH”. For MASLD across women’ reproductive lifespan and issues, we used a combination of search terms including “MASLD and menarche”, “MASLD and pregnancy”, “MASLD and PCOS”, “MASLD and menopause”, “MASLD and post-menopause”, “MASLD and women aging”.

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Accepted article

Table 1. Prevalence of MASLD in women according to reproductive conditions.

<b>Women's reproductive condition</b>	<b>Mean MASLD prevalence</b>	<b>Main references</b>
<b>Early menarche</b>	19-51.5%	11,12,37,38
<b>Pregnancy</b>	14-18%	20,21,39
<b>PCOS</b>	34-70%	24,40-43
<b>Menopause</b>	~40%	6,28,29,44,45

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