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Review

Reproductive risk factors across the female lifecourse and later metabolic health

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SUMMARY

Metabolic health is characterized by optimal blood glucose, lipids, cholesterol, blood pressure, and adiposity. Alterations in these characteristics may lead to the development of type 2 diabetes mellitus or dyslipidemia. Recent evidence suggests that female reproductive characteristics may be overlooked as risk factors that contribute to later metabolic dysfunction. These reproductive traits include the age at menarche, menstrual irregularity, the development of polycystic ovary syndrome, gestational weight change, gestational dysglycemia and dyslipidemia, and the severity and timing of menopausal symptoms. These risk factors may themselves be markers of future dysfunction or may be explained by shared underlying etiologies that promote long-term disease development. Disentangling underlying relationships and identifying potentially modifiable characteristics have an important bearing on therapeutic lifestyle modifications that could ease long-term metabolic burden. Further research that better characterizes associations between reproductive characteristics and metabolic health, clarifies underlying etiologies, and identifies indicators for clinical application is warranted in the prevention and management of metabolic dysfunction.

INTRODUCTION

Metabolic health generally encompasses optimal levels of blood glucose, triglycerides, high-density lipoprotein (HDL) cholesterol, blood pressure, and waist circumference without medication therapy, although consensus on a definition of metabolic health does not exist.[1] Generally, metabolic health is the absence of metabolic dysfunction characteristic of diseases that include cardiovascular diseases (CVDs), type 2 diabetes mellitus (T2DM), and metabolic syndrome. Poor metabolic health is responsible for a substantial population burden of disability, disease, and death. Two of the leading causes of death in the United States are related to poor metabolic health, namely CVD and T2DM,[2] the latter recently labeled "a defining disease of the 21st century."[3] In North America and the Caribbean, one in seven adults has diabetes, and this region has the highest worldwide diabetes expenditure and average cost per individual.[4] To date, treatment efforts have not alleviated the burden of metabolic diseases: associated deaths have increased since 1990.[5]

Multiple biologic, social, behavioral, and demographic risk factors for metabolic diseases have been identified.[1,6,7] Further, evidence suggests that sex-specific risk factors exist,[8,9] including reproductive characteristics, especially among females.[8] It is increasingly recognized that different traits related to reproduction are associated with metabolic diseases across the lifecourse. This subject of inquiry is nested within the framework of lifecourse epidemiology, which posits that biological, behavioral, and social factors during sensitive life stages—i.e., those characterized by rapid growth or development, and/or hormonal fluctuation—act independently, cumulatively, and interactively to influence later health and disease risk.[10,11]

In this review, we will examine evidence linking female reproductive traits to chronic metabolic health and disease. We begin with a brief review of major milestones in the female reproductive lifespan, then we will highlight characteristics with evidence linking them to metabolic disease, characterize biological parallels of the metabolic spectrum of these reproductive characteristics, and highlight shared risk factors (e.g., hormonal fluctuations, adiposity, genetics) as well as potentially modifiable risk factors and opportunities for prevention or therapeutic management. We will focus particularly on the outcome of T2DM and related metabolic conditions of hyperglycemia, glucose intolerance, and dyslipidemia. Further, hypertensive disorders during reproductive milestones constitute important risk factors for cardiometabolic dysfunction, but we have excluded this topic given that reviews published elsewhere have addressed pregnancy and reproductive risk factors for CVD.[8] Finally, we recognize that sex and gender are not discrete concepts and that definitions continue to evolve. Reviewed studies may have used different definitions of these constructs, and many did not report how research subjects identified. Hence, throughout this review, we use the descriptor female to refer to individuals assigned female at birth and/or who have the ability to become pregnant.

Human investigations delineating relationships between reproductive characteristics and metabolic health are primarily observational studies, as it is not possible to assign or randomize

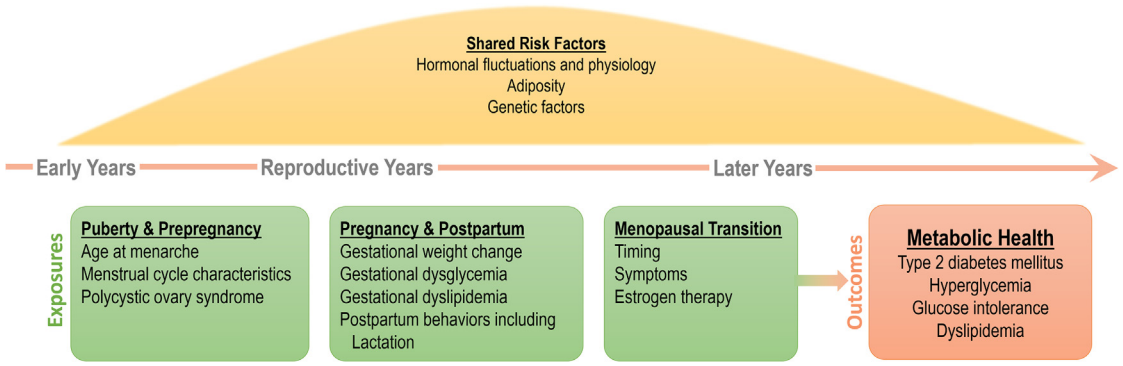

Figure 1. Female reproductive life stages and later life metabolic health

many reproductive traits, such as timing of puberty or presence of gestational diabetes mellitus (GDM). In some cases, it is possible to derive some causal conclusions even from observational data, for example, using study designs taking advantage of natural experiments or applying advanced causal influence analytic approaches.[12–14] Also, for some exposures it is possible to assign therapeutic interventions that may provide insights into mechanisms or causality. The majority of therapeutic intervention studies focused on lifestyle changes (diet, activity) or specific medications (e.g., metformin). This review will primarily focus on describing relationships between reproductive risk factors and metabolic health or disease. Our goal is not to explicate the mechanisms by which these reproductive traits "cause" metabolic disease, particularly because many of these risk factors may be due to shared upstream causes and are thus not truly causal exposures but, rather, markers of underlying metabolic health. We will touch on potential interventions and treatments throughout.

Milestones in the female reproductive lifespan

The female reproductive lifespan begins during puberty, for many includes one or more pregnancies, and ends at menopause (Figure 1). Within each phase, physiological and pathological differences may occur. As an example, menstrual cycle characteristics throughout the reproductive lifetime can serve as a vital sign[15] for reproductive potential as well as for overall health. Reproductive traits that manifest earlier in the reproductive lifespan include age at menarche, menstrual cycle characteristics, and the potential development of polycystic ovary syndrome (PCOS). Extensive evidence now links experiences specific to pregnancy and the postpartum period to later metabolic disease risk, including gestational glycemia, gestational weight change, lipidemia, and adipokine profiles. Finally, menopause may be differentially experienced, with variations in timing of onset and severity of symptoms that may have implications for later health.

Potential underlying relationships explaining associations of reproductive traits with metabolic dysfunction

Many systems and mechanisms are involved in the complex and somatically extensive etiology of T2DM, including adipokines, which are both strong predictors of metabolic disease[16] and associated with reproductive risk factors linked to T2DM pathogenesis (e.g., onset of menses, PCOS, GDM, menopausal vasomotor symptoms [VMSs]). The underlying etiology of metabolic disease typically begins many years before symptoms or diagnosis and may be related to shared risk factors, including hormonal fluctuations or physiology, adiposity, and genetic factors. Reproductive hallmarks may be related to later metabolic health through shared upstream risk factors, they may set in motion mechanisms that result in disease outcomes, or they may dampen or amplify other risk factors that result in diverging metabolic trajectories: in other words, reproductive hallmarks may simply be markers of future risk, causal risk factors, or effect modifiers (example: PCOS; Figure 2). Shared upstream risk factors may manifest in higher metabolic risk even before the reproductive years, resulting in an even greater upward slope of risk thereafter. The trajectory may be further impacted by a "second hit," either an additional risk factor, such as a pregnancy complicated by GDM, or a mitigating factor, such as adoption of healthful lifestyle behaviors.

REPRODUCTIVE TRAITS AND THEIR RELATIONSHIPS WITH METABOLIC FUNCTION AND HEALTH

Puberty

The pubertal transition to sexual maturity defines initiation of the female reproductive lifecycle that continues until menopause. Typically, puberty begins between 8 and 13 years of age in females,[17,18] when major hormonal shifts alter primary (e.g., menstrual cycle) and secondary (e.g., breast development) sex characteristics. The first process, adrenarche, causes maturation of the adrenal glands and androgen secretion that results in secondary sex characteristics. Subsequent activation of the hypothalamic-pituitary-ovarian (HPO) axis results in pulsatile hypothalamic secretion of gonadotropin-releasing hormone (GnRH) and subsequent release of pituitary luteinizing hormone (LH) and follicle-stimulating hormone (FSH). These gonadotropins stimulate the ovaries to secrete estrogen, resulting in follicular maturation, ovulation, and the first menses (menarche).[18–20]

Thelarche, the initiation of breast development, and menarche, are the two distinctive events primarily used to stage pubertal development in clinical practice.[21] Thelarche is typically the first physical sign of puberty at mean age 10.2 years.[22]

However, due to the potential for oversight of thelarche in some adolescent females with excess adiposity,[21,22] and because menarche involves the entirety of the HPO axis, including production of estrogen and progesterone,[21] menarche may be a superior marker for pubertal timing. Age at menarche is highly heritable (>60%),[23] but a relatively late marker of pubertal development.[24] Median age at menarche is 12–13 years, occurring approximately 2–3 years after thelarche.[15,22]

Puberty is characterized by a dramatic rate of growth and development in which lean mass doubles[25] and is accompanied by dynamic hormonal and metabolic changes.[26] This rapid growth requires an increase in insulin that peaks in mid to late puberty.[25] The pubertal transition is associated with a marked decrease in peripheral, vs. hepatic, insulin sensitivity that allows for higher concentrations of circulating glucose.[25,27] However, growth hormone (GH) and insulin-like growth factor 1 (IGF-1) concentrations are elevated during the pubertal transition, and it is well documented that GHs cause insulin resistance.[28–31] Insulin resistance increases across puberty, decreasing insulin sensitivity by as much as 30% at mid-puberty compared with prepubertal or adult periods.[25] Diagnosis of prediabetes, an antecedent to T2DM,[32] has increased in adolescents aged 12–19 years from 11.5% in 1999–2002 to 28.2% in 2015–2018.[33] Despite dramatic changes in insulin resistance during adolescence, diagnostic criteria for prediabetes is identical among youth and adults: fasting plasma glucose 100–125 mg/dL, 2 h plasma glucose 140–199 mg/dL during oral glucose tolerance test, hemoglobin A1c 5.7%–6.4%, or random plasma glucose >200 mg/dL with hyperglycemic symptoms.[34] Whether use of adult criteria is optimal for diagnosis during these dynamic metabolic and hormonal changes of adolescence is not known, although screening may lead to earlier detection and intervention.[35]

During puberty, increasing insulin resistance in both sexes aligns with the pubertal growth spurt beginning at puberty onset, increases across puberty, and wanes toward cessation of puberty.[36] Insulin resistance plays an important role in somatic growth during puberty, regardless of adiposity; however, excess adiposity may exacerbate insulin resistance or prevent recovery of insulin sensitivity in later puberty.[37] Although evidence is limited, pubertal insulin resistance is greater in females, particularly with excess adiposity, which may predispose some adolescents to higher risk for later metabolic dysfunction.[36,38] Studies have reported strong associations of pubertal insulin resistance with adiposity, skinfold thicknesses, and waist circumference. However, the absence of excess adiposity has not completely explained insulin resistance identified in gold standard hyperinsulinemic euglycemic clamp studies, suggesting adiposity is not the sole determinant of insulin resistance.[26,36,39] Further, limited evidence suggests that adolescents with obesity may have difficulty resolving pubertal insulin resistance, increasing risk for T2DM development.[26] Sex differences in insulin resistance during puberty have been partially attributed to sex differences in adiposity[36]: both sexes gain lean mass during puberty, but females also gain fat mass.[40,41] Changes in other metabolic risk factors, namely lipids, blood pressure, and adipokines, coincide with pubertal insulin resistance.[26] Thus, the implications for later life metabolic outcomes are unclear, although suggestive of increased risk from insulin resistance in pubertal youth with obesity,[38] which is potentially more pronounced in females.[36]

The following sections will discuss three characteristics of early reproductive traits for which variation may have bearing on long-term metabolic health: age at menarche, menstrual regularity/irregularity, and development of PCOS. We will primarily focus on pertinent physiology and evidence of associations with long-term metabolic outcomes, then briefly discuss potential opportunities for prevention or management.

Earlier age at menarche

Age at menarche signals the inception of the female reproductive cycle and may be an important marker of future metabolic health.[42] Earlier menarche, menstruation before age 12,[15] is linked to later life metabolic conditions, including abnormal glycemia,[43] hypercholesterolemia,[44] metabolic syndrome,[45–47] PCOS, insulin resistance,[45] and T2DM.[44,48] Later menarche may also be associated with adverse outcomes.[8,45,48] Likely due, at least in part, to environmental and social factors,[45] a secular trend of declining age at puberty onset[18] and menarche[45,49] has been observed over the last century globally[50] and in the US,[51,52] although this trend appears to be stabilizing.[45] However, one longitudinal study found that higher plasma concentrations of several per- and polyfluoroalkyl substances (perfluorooctanoic acid, PFOA; perfluorooctanesulfonic acid, PFOS; perfluorodecamoic acid, PFDA)—chemicals associated with higher adiposity and diabetes risks—in female mid-childhood were associated with later puberty onset, suggesting environmental exposures have complex and perhaps unpredictable relationships with pubertal timing.[53]

Age at menarche is inversely associated with later risk for T2DM, metabolic syndrome, and obesity in both childhood and adulthood.[43] In a small systematic review and meta-analysis of age at menarche and risk for T2DM, Janghorbani et al. examined 10 studies and found 22% increased risk (relative risk [RR] = 1.22, 95% confidence interval [CI] 1.17–1.28) for T2DM in those with early age at menarche (<12 years).[54] Additionally, an examination of the Mexican National Health Survey found that risk for diabetes decreased 5% for each year of later menarcheal onset, even after adjustment for body mass index (BMI).[44]

To date, the true mechanisms explaining the relationship between early pubertal timing and subsequent metabolic risk remain unclear. Early life obesity is clearly an important factor,[24,55] because childhood adiposity may influence both the timing of menarche[55,56] and the risk for adult obesity,[55–57] itself a risk factor for T2DM.[58] Elks et al. found that higher adult BMI partially mediated the relationship between early menarche and T2DM.[59] In a meta-analysis, Prentice and Viner reported that early menarche <12 years (vs. ≥12 years) was associated with 0.34 kg/m^2 higher adult BMI, as well as a 2-fold increased risk for obesity, greatest in females <40 years of age. Late menarche ≥15 years (vs. <15 years) was associated with a 0.24 kg/m^2 lower adult BMI.[43] Interestingly, although earlier age at menarche predicted higher adult BMI, this signal was partially independent of childhood BMI. Eight studies included childhood BMI as a possible confounder, with large variation in attenuation of association between early menarche and later risk for obesity, from no effect[60] to a 28-fold reduction in β-coefficient.[61] A body composition study using air displacement plethysmography with adolescent (~age 18) and adult (~age 30) body composition measures demonstrated that associations of early

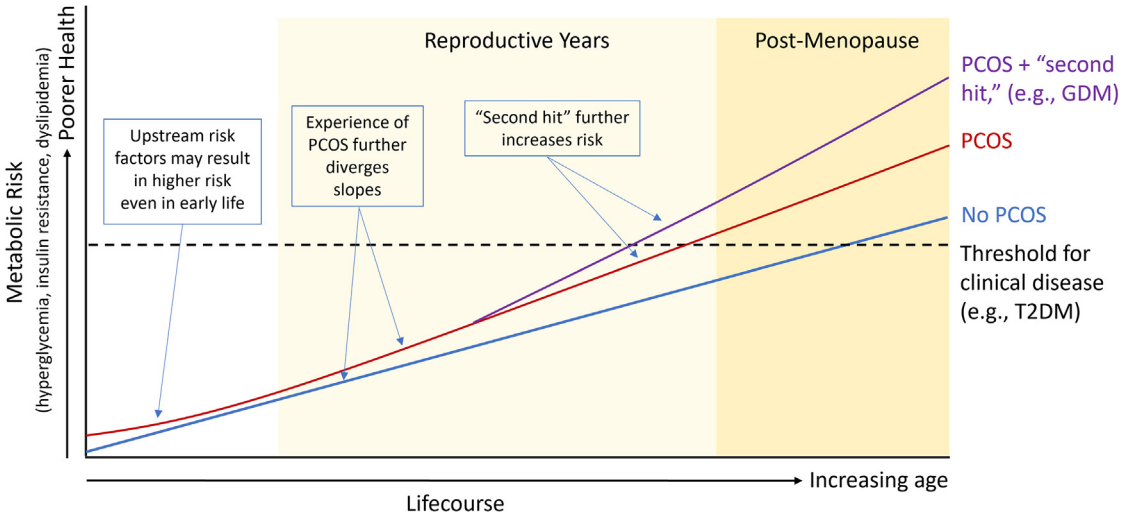

Figure 2. Representation of reproductive risk factors and impact on metabolic health trajectory using PCOS as an example

age at menarche ≤11 years (vs. late ≥14 years) with adult adiposity measures were strongly explained by prepubertal adiposity (e.g., fat mass index β = 2.33 kg, 95% CI 1.64–3.02).[57] In a Mendelian randomization study by Wang et al., genetically predicted lower birthweight and higher childhood BMI were associated with earlier puberty.[62] Specifically, each 1-standard deviation lower birthweight predicted earlier menarche by 0.1479 years (95% CI 0.0422–0.2535 years), whereas each 1-standard deviation higher child BMI predicted earlier menarche by 0.3966 years (95% CI −0.5294 to −0.2639). These findings are consistent with other Mendelian randomization studies that detected this relationship,[63,64] as well as some observational data linking low birthweight to childhood obesity and childhood obesity to earlier puberty in girls.[65–67] A strong relationship exists between birthweight, early life adiposity, menarcheal timing, adult adiposity, and T2DM but, based on current evidence, the function of early menarcheal timing within this schema is undetermined.

In combination and closely intertwined with adiposity are the effects of estrogen. Age at menarche is estrogen dependent, as is cycle regularity, which is discussed in more detail further below. Early menarche <12 years leads to earlier onset of ovulatory cycles characterized by an earlier, higher circulating concentration of estradiol and lower concentrations of sex-hormone-binding globulin (SHBG), testosterone, and dehydroepiandrosterone sulfate (DHEAS) compared with those with later menarche.[68,69] Estrogen also stimulates subcutaneous fat accumulation,[70] appetite, energy regulation, insulin secretion, and glucose regulation.[71,72] However, estrogens, through various actions, appear to protect against T2DM by improving glucose homeostasis, regulating body weight and adiposity, and modulating systemic inflammation associated with chronic morbidity.[72]

The interplay of sex hormones with promotion of fat accumulation may be an underlying mechanism explaining the relationship of earlier age at menarche with higher adiposity and metabolic dysfunction later in life. Although, in females, estrogens increase during puberty, circulating SHBG decreases 2-fold.[73] SHBG transports sex steroids, regulates their access to tissues,[73] and has an antagonistic effect on estrogen.[74] SHBG is inhibited by insulin and the insulin resistant state—especially in females.[75] Low circulating SHBG is widely considered a marker for development of insulin resistance and T2DM[76,77] and correlates with increased abdominal fat, hyperinsulinemia, glucose intolerance, insulin resistance, and increased risk for CVD and T2DM in females.[78] One study found that plasma SHBG may be a stronger predictor of T2DM compared with HbA1c and C-reactive protein.[77] Apter et al. showed that menarche <12 years leads to earlier onset of ovulatory cycles, characterized by an earlier, higher concentration of estradiol and lower SHBG compared with those with later menarche.[68,69] In premenopausal individuals, the relationship between low SHBG and increased metabolic disease risk is independent of visceral adipose tissue accumulation.[79]

Some evidence demonstrates that the mechanism associating SHBG with glucose homeostasis may be linked to insulin's direct inhibitory effect on secretion of SHBG in the liver.[80,81] Hepatic SHBG mRNA is directly correlated with circulating SHBG concentration; hence, SHBG decreases with increasing insulin resistance.[76] Additionally, two polymorphisms of SHBG—rs6257 and rs6259—have been directly associated with circulating SHBG and are strongly predictive of T2DM.[77] These effects may be due to SHBG's ability to modulate the effects of estrogen on peripheral tissues; SHBG is a cellular estrogen antagonist at the estrogen receptor (ER).[69,74,82] In two randomized trials, transdermal estradiol elevated plasma glucose whereas oral estrogen lowered glucose levels.[83,84] The reasoning behind the differing effects included that transdermal estradiol did not affect SHBG levels, whereas oral estrogen increased SHBG.[85–87] These associations among sex hormones, insulin secretion, and insulin resistance may partially explain why female adolescents have more pronounced insulin resistance during puberty,[36] which is associated with later risk for T2DM. Adding another layer of complexity to the potential for lifelong metabolic dysfunction, adolescents with excess adiposity may have more difficulty resolving insulin resistance

associated with puberty.[26] Despite the exaggerated increase in estrogen and decrease in SHBG with early vs. late menarche, the current evidence has yet to identify which factor—estrogen, SHBG, adiposity, or a combination—provides the strongest link between early age at menarche and later metabolic risk.

Another possible shared risk factor is genetics: age at menarche is highly heritable,[88] perhaps up to 66%.[89] One meta-analysis identified two specific genes that robustly influence age at menarche. The strongest signal was observed at 9q31.2 with variant rs2090409 associated with a 5-week reduction in age at menarche for each A allele.[90] The *LIN28B* gene (variant rs7759938), which also influences height in adulthood, demonstrates the second strongest signal, with a parallel 5-week reduction for each T allele.[90] A later meta-analysis identified 30 new loci associated with menarche in addition to *LIN28B* and 9q31.2, four previously associated with BMI, three associated with energy homeostasis, and three associated with hormonal regulation.[91] Interestingly, murine models with overexpressed genetic homologs to *LIN28B* (*Lin28*/*let-7* tumor suppressor RNAs) demonstrate later puberty and increased glucose uptake, as well as resistance to obesity and T2DM, with a high-fat diet.[92] Specifically, the regulation of glucose metabolism in these mouse models occurs through suppression at various points in the insulin-phosphatidylinositol-3-kinase and mammalian target of rapamycin (PI3K-mTOR) pathway at IGF-1 receptor (IGF-1R), insulin receptor (INSR), and insulin receptor substrate 2 (IRS2).[92] The strong association between earlier age at menarche and higher BMI has been established[93] but may be attributable, in part, to a common genetic profile.

Treatment for early puberty most commonly includes GnRH analogs, e.g., leuprolide acetate, to suppress pubertal development by overriding the intermittent pulses of GnRH and inhibit secretion of FSH, LH, and, ultimately, estrogen.[94] Few studies have examined the long-term metabolic outcomes associated with these analogs. One study reported higher adiposity without adverse metabolic changes at 3 years follow-up in females with early-onset puberty treated with analogs vs. not treated,[95] and another reported that BMI *Z* scores increased but returned to pre-treatment values after cessation of treatment.[96] Finally, one investigation found no differences in weight or BMI between the GnRH analog treated and untreated groups at ~9 years follow-up, but reported increased insulin resistance and DHEAS ($p < 0.001$), as well as higher LH/FSH ratio ($p = 0.002$) and lower SHBG ($p < 0.01$) in females treated vs. untreated.[97] Further, a higher prevalence of hirsutism (odds ratio [OR] = 5.53, $p = 0.005$), PCOS (OR = 3.11, $p < 0.04$), and oligomenorrhea (32.2% vs. 11.0%, $p = 0.01$) were observed in the treated vs. untreated groups. These associations may signal an effect of the medication, an effect of delaying pubertal onset, or reflect higher baseline risk among those for whom treatment was indicated (i.e., confounding by indication). No long-term studies have examined metabolic outcomes from treatment with GnRH analogs for early puberty.

The current evidence remains indeterminate as to whether earlier age at menarche or its treatment is a marker for underlying metabolic dysfunction or a factor that increases the slope of the metabolic risk trajectory. How much of the relationship between younger age at menarche and risk for later T2DM may be attributable specifically to adiposity, hormonal fluctuations, genetics, a combination of these characteristics, and/or other unknown factors remains unclear. Further, adiposity may be a shared, modifiable risk factor, and the evidence suggests that it may be important before and after menarche. Screening prepubertal individuals for excess adiposity, familial age at menarche before menarcheal onset, family history of T2DM, and patient age at menarche may be the clearest indicator(s) of risk.

Abnormal menstrual bleeding and menstrual irregularity

During the reproductive years before the menopausal transition begins (around 45–50 years), cycle regularity and frequency, both high and low, are associated with metabolic outcomes in later life,[98] including increased risk for GDM[99] and T2DM,[100–103] although the data are limited. Menstrual cycle regulation is a complex interplay between hypothalamic, pituitary, and gonadal axis hormones, and imbalance in this system may result in abnormalities in specific parameters: cycle frequency, regularity, duration, or volume of uterine bleeding.[104,105] In adults, menstrual irregularity is defined as high or low if cycles are <21 days or >35 days apart (or <8 cycles/year), respectively.[100] By 3 years post-menarche, up to 80% of menstrual cycles have stabilized into expected regularity of adult cycles that last between 21 and 34 days.[15] Menstrual regularity is considered a vital sign of female health because it reflects expected functioning of the HPO axis,[106] although potential for relative energy deficiency is an alternative explanation for menstrual irregularity that should be assessed in research studies.[107] However, irregular menstrual bleeding is common,[108] affecting 3%–30% of reproductive-aged females worldwide, with variability highest during adolescence and as age nears 50 years.[105] True population values may be higher because as many as half of those with abnormal uterine bleeding do not seek healthcare.[105]

Short cycles (occurring every 25 days or more frequently) before pregnancy have been associated with decreased odds for GDM,[99] as well as earlier age at menopause and more severe menopausal symptoms.[109] Conversely, long or irregular cycles (occurring every 35 days or less frequently) have been associated with increased BMI,[103,106] hyperandrogenemia in PCOS,[110] insulin resistance,[111] insulin resistance in PCOS,[112] increased risk for pregnancy complications (preterm birth,[99,113] low birthweight,[114] GDM[99,115]), T2DM,[101–103,116] and premature mortality.[106] In the Menstruation and Reproductive History Study, longer menstrual periods at ages 28–32 years were associated with increased diabetes risk (adjusted rate ratio: 1.4, 95% CI 1.0–1.8) over 56 years of follow-up (median age 73), although no association of age at menarche, cycle regularity, or long cycles (>42 days) with risk for diabetes was observed.[116]

Some of the most robust evidence for links between cycle irregularity and metabolic disease risk comes from the prospective Nurses' Health Study II cohort of over 100,000 female nurses. Individuals with long (>40 days) or highly irregular menstrual cycles at ages 18–22 years had twice the risk of developing T2DM over 6 years of follow-up compared with those with a cycle length of 26–31 days.[101] Additionally, risk for T2DM was three times higher in individuals with a short cycle <21 days plus a first-degree relative with a history of T2DM; risk for T2DM in individuals with a long or irregular cycle remained elevated regardless of family history.[101] For individuals with symptoms of hyperandrogenism (hirsutism, severe

acne), short cycles were associated with T2DM risk (RR = 3.85, 95% CI 1.34–11.11), whereas absence of hyperandrogenism with long/irregular cycles was associated with T2DM risk (RR = 2.11, 95% CI 1.59–2.80). These results suggest that symptoms of PCOS may confound the relationship between short cycle length and T2DM risk, although PCOS was not specifically examined in this study. In a subsequent Nurses' Health Study II investigation with over 20 years of follow-up, individuals reporting long >40 days and/or chronic irregular menstruation were at the highest risk for developing T2DM across the course of the study compared with age-matched individuals with very regular cycles.[103] However, associated risk was age-dependent, from 32% (95% CI 22%–44%) higher risk with irregularity at 14–17 years up to 66% (95% CI 49%–84%) higher risk with irregularity in the 29–46 years age range. Further, those with a long cycle length >40 days between ages 18–22 years and ages 29–46 years were 37% (95% CI 19%–57%) and 50% (95% CI 36%–65%) more likely to develop T2DM, respectively, compared with age-matched counterparts with a cycle length of 26–31 days. Risk for both irregular and long cycles appeared to be higher among individuals with overweight or obesity, physical inactivity, and low-quality diet.[103] Thus, short or long cycles are associated with increased risk for T2DM, particularly in those with short cycles plus a family history of T2DM.

Disruptions in the hormonal environment likely play a critical role in the link between menstrual cycle irregularity and metabolic risks. Long or irregular cycles strongly indicate hyperinsulinemia, alongside which pituitary gonadotropins may stimulate ovarian androgen production, exacerbating insulin resistance and increasing T2DM risk.[117] Further, hyperinsulinemia may inhibit SHBG secretion,[80] resulting in inhibited estrogen action, insulin resistance, and increased metabolic risk as previously discussed. Additionally, menstrual disorders are associated with dysregulated inflammatory processes and, potentially, T2DM development.[118] One specific disorder, PCOS (discussed below), is characterized by long or irregular cycles, insulin resistance, and is a strong risk factor for T2DM development.[111,119] From the current literature, it is unknown how many individuals with long or irregular menstrual cycles have undiagnosed PCOS. Guidelines such as the International Federation of Gynecology and Obstetrics abnormal uterine bleeding diagnostic matrix[105] may be a clinically useful tool when individuals present with abnormal uterine bleeding. This guide provides a structured decision tree to indicate when assessment may be warranted to discern potential for underlying endocrinopathy.[105]

PCOS

PCOS constitutes the most common endocrine system disorder during the female reproductive years.[120,121] Prevalence of this condition among reproductive-aged females is between 8% and 13%, depending on the diagnostic criteria used.[121] PCOS is associated with a constellation of metabolic and endocrine disruptions: uncontrolled ovarian steroidogenesis, aberrant insulin signaling and insulin resistance, excessive oxidative stress and inflammation, dyslipidemia, abdominal obesity, potential for infertility, CVD, and T2DM.[120,122] Updated diagnostic characteristics for PCOS use reproductive risk factors discussed above, including irregular cycles (<21 or >45 days in adolescence; <21 or >35 days premenopausal) plus clinical or biochemical hyperandrogenism (total or free testosterone, androstenedione, DHEAS; acne, alopecia, or hirsutism).[123] For those seeking care, oft cited reasons include irregular menstruation, symptoms of hyperandrogenism, or difficulty conceiving.[124] Among individuals diagnosed with PCOS, 30% will have normal menstrual cycles, whereas 85%–95% with oligomenorrhea and 30%–40% with amenorrhea will have PCOS.[124] Between 5% and 40% of pregnancies in individuals with PCOS will develop GDM,[125] and individuals with PCOS are seven times more likely to develop T2DM in their lifetimes compared with counterparts who do not have GDM.[126]

PCOS phenotype varies considerably, although excess adiposity is a known risk factor.[127] In most recent estimations, between 38% and 88% of individuals with PCOS have overweight or obesity.[127] It has been proposed that genetic susceptibility predisposes individuals to PCOS during adolescence, independent of obesity, but that obesity amplifies the characteristics of PCOS.[127] However, similar metabolic derangements exist in lean individuals with PCOS,[128] including insulin resistance, the defining feature of T2DM,[129] regardless of BMI.[128] Evidence of the true prevalence of insulin resistance in lean individuals with PCOS is mixed; for example, one study from Turkey found that 47% of PCOS cases in individuals without obesity had insulin resistance,[130] whereas a study in India found no difference in the prevalence of insulin resistance between PCOS phenotypes with or without obesity.[131] But, a meta-analysis (n = 35) found that individuals with PCOS were at higher risk (risk ratio = 2.77, 95% CI 1.88–4.10) for having obesity.[132] Overall, it appears that obesity is a risk factor for PCOS and that PCOS is a risk factor for obesity.[133]

Hyperandrogenemia is an established component of PCOS that also may indicate risk for early onset of metabolic dysfunction.[134] In a collection of non-human primate studies, induced hyperandrogenemia via testosterone infusion akin to elevated levels in PCOS resulted in increased fat mass and insulin resistance after 3 years.[134] Additional evidence demonstrated hypertrophy in omental white adipose tissue attributed to reduced basal lipolysis, β-adrenergic stimulated lipolysis, and blood vessel density alongside increased free fatty acid uptake and adipocyte hypertrophy.[135] Further, hyperandrogenemia impaired ovarian and uterine structure and function.[136] Animals in the fertility arm of these trials demonstrated impaired fertility and gestational metabolic function, potentially from diminished endometrial receptivity or reduced-quality oocytes.[137] In all of these studies, metabolic disturbances were observed with testosterone or western diet alone, but effects were exacerbated with hyperandrogenemia in conjunction with a high-fat, western diet. Further, after 5 years of follow-up, animals receiving testosterone and consuming a western diet had increased fasting insulin and insulin secretion.[138] Although modification of pubertal hyperandrogenism may not be plausible, consuming a lower-fat diet could improve long-term metabolic outcomes in peripubertal females at risk for PCOS.[134,139,140]

Many investigations support a strong relationship between PCOS and the development of T2DM, including several large studies. In a systematic review (n = 35 studies) and meta-analysis (n = 30), individuals with PCOS had nearly 4.5 higher odds

of developing T2DM (OR = 4.43, 95% CI 4.06–4.82) compared with individuals without PCOS.[141] In BMI-matched studies (n = 6, four of which also matched waist circumference or waist-to-hip ratio), individuals with PCOS had four times greater odds of developing T2DM (OR = 4.00, 95% CI 1.97–8.10) compared with those without PCOS but similar BMI, suggesting that PCOS confers elevated risk beyond the associated excess adiposity. Two large population-based studies provide similar, but slightly lower, results. In two European national health databases from the United Kingdom and Denmark, risk for T2DM among females with PCOS was 3–3.5 times higher than matched controls.[129,142] Notably, treatment of PCOS symptoms by use of oral contraceptives in the Danish health database attenuated this relationship (adjusted hazard ratio [HR] = 1.0, 95% CI 0.9–1.2).[129]

The link between PCOS and subsequent diabetes—GDM or T2DM—has been well established, but the specific etiology of PCOS is unknown. Hyperinsulinemia, insulin resistance, and overall or abdominal obesity are shared risk factors between PCOS and diabetes.[124,143] Notably, the most insulin resistant PCOS phenotype is hyperandrogenic and anovulatory, regardless of adiposity.[144] Further, oxidative stress may contribute to the pathophysiology of PCOS. In those diagnosed with PCOS characterized by ovarian dysfunction with long or irregular cycles, insulin resistance, and excess androgens had increased circulating markers of oxidative stress (e.g., homocysteine, malondialdehyde, asymmetric dimethylarginine) and activity of superoxide dismutase alongside decreased levels of glutathione and paraoxonase-1 activity. These results were irrespective of excess weight.[119] Thus, oxidative stress is likely a component of the pathophysiology of characteristics defined by PCOS, including menstrual irregularity. Similar oxidative stress activity and damage has been well characterized in the pathogenesis and progression of T2DM, including via irregularities in metabolic cell signaling pathways, β cell function, and induction of insulin resistance.[145]

Whether PCOS and T2DM share underlying etiology or whether PCOS is an antecedent to T2DM remains unknown. However, insulin resistance is a shared risk factor that may be independent of obesity.[122] Several contradictory recommendations for T2DM screening with PCOS exist. According to Rubin et al., who examined data from Danish females with and without PCOS, the strongest predictors of T2DM in patients with PCOS were higher BMI and fasting blood glucose; inclusion of advancing age in risk calculations was not recommended because median age for development of T2DM with PCOS was 31 years (interquartile range: 26, 37).[129] The European Society of Endocrinology recommended an oral glucose tolerance test in all PCOS patients with obesity, as well as patients without obesity over 40 years of age with a history of GDM or family history of T2DM; timing or frequency of screening was not defined.[146] The Endocrine Society and the Rotterdam European Society of Human Reproduction and Embryology/American Society for Reproductive Medicine PCOS consensus recommend an oral glucose tolerance test for anyone with PCOS[147,148]; there is no evidence-based consensus for timing or frequency of screening.[122] For secondary prevention, according to the American College of Obstetricians and Gynecologists, lifestyle modification that includes increased physical activity and dietary changes reduces risk for T2DM as well or better than medication in patients with PCOS, although insulin-sensitizing agents improve androgen concentrations, ovulation, and glucose tolerance.[149]

PREGNANCY AND THE POSTPARTUM PERIOD

Pregnancy results in multiple metabolic adaptations to support the growth and development of the fetus and prepare for postpartum lactation.[150,151] A significant increase in insulin resistance during the second half of gestation results in increased circulating glucose to facilitate glucose transfer to the fetus for growth and development and is accompanied by an increase in insulin secretion to support maternal euglycemia.[152,153] Gestational weight change typically comprises gains related to products of conception (fetal growth, placental tissue, and amniotic fluid) as well as maternal blood volume, uterine size, breast tissue, adipose tissue, and extracellular fluid.[154] Lipid profiles change, with a 2- to 4-fold increase in triglycerides and a 50% increase in total cholesterol.[152] Leptin increases from early pregnancy onward, whereas adiponectin remains stable or declines across pregnancy in relation to adipose accretion.[155] Ideally, these metabolic adaptations revert to non-pregnant states after delivery.

Maladaptive or exaggerated metabolic adaptations in pregnancy may lead to pregnancy complications, such as GDM or inadequate or excessive weight gain, which are independently associated with long-term differences in metabolic risk. However, even the experience of pregnancy itself may confer permanent metabolic alterations. For example, despite similar daily food intake, mice that completed a pregnancy/lactation cycle maintained higher subsequent body weight compared with age-matched controls.[156] Although both the reproductively experienced and control mice gained a similar amount of body weight on a high-fat diet, only the reproductively experienced mice had impaired glucose tolerance when consuming the high-fat diet, demonstrating an increased susceptibility to the adverse consequences of a high-fat diet after pregnancy and lactation.[156] In humans, pregnancy is characterized predominantly by a central pattern of adipose accrual that is usually associated with non-pregnant insulin resistance,[157] suggesting further potential for exacerbated metabolic risk in reproductively experienced individuals. Similarly, among female individuals aged 18–30 years enrolled in the longitudinal Coronary Artery Risk Development in Young Adults (CARDIA) study, primiparas gained 2–3 kg more weight over 5 years compared with nulliparas and had greater increases in waist-to-hip ratios independent of weight gain.[158] Among females parous at baseline, each additional birth was associated with a 2–4 cm gain in waist circumference.[159] Increasing parity was also associated with the development of metabolic syndrome over two decades of follow-up, even in the absence of a pregnancy complicated by GDM.[160]

The remainder of this section will discuss four key metabolic adaptations to pregnancy, namely changes in glycemia, weight, blood lipids, and adipokines. We will briefly review their physiology, discuss evidence for their associations with long-term metabolic health outcomes, and identify opportunities for intervention during pregnancy and postpartum that may interrupt these connections.

Gestational glycemia

GDM, hyperglycemia first diagnosed in pregnancy, is common and increasing.[161] Insulin sensitivity increases in early gestation to promote glucose uptake into adipose tissue and maternal fat storage in preparation for later gestation and lactation. As pregnancy progresses, maternal and placental hormones, including estrogen, progesterone, leptin, cortisol, placental lactogen, and placental GH, together promote insulin resistance.[162] This insulin resistance fosters increased blood glucose to support placental and fetal growth, as well as the breakdown of maternal fat stores, resulting in a further increase in blood glucose and free fatty acid concentrations. GDM results when the pancreas is unable to secrete sufficient insulin to overcome this insulin resistance.[163]

In most cases, hyperglycemia meeting diagnostic thresholds for GDM occurs on a background of chronic insulin resistance.[153,164] Major risk factors for GDM include higher weight and a family history of diabetes, as well as PCOS, as discussed above.[164] Pregnancy has been termed a "stress test," with the diagnosis of GDM unveiling a preexisting susceptibility for T2DM and also serving as a harbinger of future disease risk.[165] Most people revert to euglycemia following delivery; however, robust literature confirms that both GDM and milder gestational dysglycemia predispose to dysglycemia after delivery.[166] In a study by Ratnakaren et al., individuals who developed GDM experienced greater annual increases in HbA1c and fasting glucose before ($p = 0.01$, $p < 0.001$) and after (both $p < 0.001$) pregnancy.[167] Further, individuals who developed GDM had increased postpartum rates of 6.9-fold higher HbA1c and 3.3-fold higher fasting glucose compared with pre-pregnancy values. Within the first 5 years postpartum, 20%–30% of individuals with GDM will develop T2DM.[168] Further, overall, GDM is associated with an estimated 7-fold higher subsequent risk for T2DM,[169] although estimates and outcome prevalence vary somewhat with different diagnostic thresholds for both GDM and subsequent outcomes.[170] The Hyperglycemia and Pregnancy Outcomes (HAPO) observational study has published follow-up data through 11 years postpartum. Among mothers with GDM, 52.2% (n = 346/663) developed a disorder of glucose metabolism vs. 20.1% (n = 791/3,946) of mothers without GDM (OR = 3.44, 95% CI 2.85–4.14; risk difference [RD] = 25.7%, 95% CI 21.7%–29.7%).[171] GDM history also predicts subsequent hyperlipidemia[172] and a 2-fold increased risk of cardiovascular events in the first decade postpartum, with persistently higher risk even in the absence of T2DM.[173]

Investigations into GDM pathophysiology have characterized heterogeneous subtypes based on underlying glycemic physiology that may provide targets for future interventions.[174,175] In the Genetics of Glucose regulation in Gestation and Growth (Gen3G) cohort of 809 pregnant individuals, 8.3% (n = 67) developed GDM. These individuals with GDM were further categorized as having impaired insulin sensitivity (50.7%) with hyperinsulinemia, impaired insulin secretion (29.9%) without impaired insulin sensitivity, or a mixture of the two defects (17.9%). Those in the impaired insulin sensitivity subgroup had greater risk for GDM-associated adverse outcomes, whereas the impaired insulin secretion or mixture subgroups had outcomes similar to the normal glucose tolerance group, even after adjustment for BMI. The impaired insulin sensitivity subtype had the highest average pre-pregnancy BMI and gestational weight gain, fasting glucose, adiponectin, and leptin levels.[174] Further examination of these subtypes found a similarly increased risk for poor obstetric outcomes and improved prediction of adverse outcomes.[175]

History of GDM confers higher risk for T2DM compared with other risk factors for T2DM.[176] The Diabetes Prevention Program (DPP) trial enrolled individuals at high risk for T2DM and included several hundred individuals with a history of GDM. Participants were randomized into a masked placebo arm (n = 1,082), 850 metformin twice/day arm (n = 1,073), or an intensive lifestyle intervention arm (n = 1,079). Although all had impaired glucose tolerance at study entry, mean age was younger (43 years GDM history vs. 51 years no GDM history) and glucose levels were similar at enrollment (e.g., fasting glucose 106 vs. 105 mg/dL), rates of transition to T2DM were higher among individuals with vs. without a history of GDM.[176]

Lifestyle modification, beyond glucose monitoring alone, in pregnancies complicated by GDM can result in improved gestational glycemia.[177] Randomized trials during pregnancy have shown the clear benefit of lifestyle modification for improving birth outcomes, such as in infant growth and reduced macrosomia (birthweight $\geq$ 4,000g).[178] A meta-analysis (15 trials in 45 reports) found that while there was evidence that more females in lifestyle intervention groups had met postpartum weight goals 1 year after birth than in the control groups (risk ratio = 1.75, 95% CI 1.05–2.90; n = 156; one trial), there was no demonstrated benefit for postpartum development of T2DM up to a maximum of 10 years follow-up (risk ratio = 0.98, 95% CI 0.54–1.76; n = 486, two trials).[178]

Results from the DPP trial found that intensive lifestyle intervention with diet, physical activity, and weight loss was significantly more effective at preventing diabetes than treatment with metformin alone.[179] Lifestyle intervention decreased T2DM incidence by 58% (95% CI 48–66), whereas metformin reduced incidence by 31% (95% CI 17–43). However, metformin may be three times more effective at preventing T2DM in individuals with a history of GDM compared with individuals with no history of GDM.[176] At 3 years follow-up in the DPP, lifestyle intervention resulted in greater weight loss (mean loss 4.03 ± 0.40 kg) in individuals with a history of GDM compared with intervention in individuals with no history of GDM (mean loss 1.60 ± 0.80 kg), and metformin was more effective at reducing incident diabetes in individuals with a history of GDM.[176] After 10 years of follow-up, lifestyle changes in individuals with a history of GDM reduced progression to T2DM by 35% and metformin reduced progression by 40%; metformin did not have this effect in those with no history of GDM.[180] In the long-term follow-up study, the DPP Outcomes Study (2002–2013) reported after 15 years that lifestyle intervention continued to be more effective than metformin compared with a placebo group, reducing T2DM rates by 27% ($p < 0.0001$) vs. 18% ($p = 0.001$), respectively. Overall, intensive lifestyle intervention was more effective at preventing T2DM, although metformin also may strongly prevent or delay diabetes onset—particularly in individuals with a history of GDM.[181]

Gestational weight change

Weight gain typically occurs in a sigmoidal pattern, being greatest in mid-pregnancy.[154] However, there is wide variation in

observed total and patterns of weight gain, with some individuals losing weight across pregnancy.[182] Gestational weight gain above recommended amounts, usually defined according to the Institute of Medicine's (IOM) 2009 recommendations,[154] is associated primarily with excess accrual of maternal fat, but not lean mass.[183] Some of the adipose gain is stored as visceral fat that may further promote insulin resistance.[184]

Risk factors for excess weight gain are multifactorial, and include social, environmental, chemical, and nutritional influences. Genetics also likely plays a role; several studies have observed higher gestational weight gain with obesity-associated genes.[185,186] Excess gestational weight gain is of concern because it is associated with dysmetabolic adverse outcomes of the current pregnancy,[154] including large-for-gestational age birth ($\geq 90^{th}$ percentile for birthweight at a given gestational age). The relationship of gestational weight gain with GDM is complex; although higher weight gain is generally associated with higher risk for GDM,[182] most studies include weight gain across the entirety of pregnancy—part of which occurs following GDM screening and diagnosis. Studies that have disaggregated the timing of gain have generally shown that weight gain in early pregnancy, or the first trimester, predicts risk for GDM, whereas associations may be null or even inverse in mid-gestation.[187–189]

Greater gestational weight gain also promotes postpartum weight retention. A 2017 meta-analysis (n = 17 studies) showed a significant relationship between excessive gestational weight gain and higher risk for postpartum weight retention (OR = 2.08, 95% CI 1.60–2.70).[190] This relationship not only has implications for long-term metabolic health, as described below, but also may result in a cycle of compounding interpregnancy weight retention across multiple pregnancies.[191] In an analysis of linked birth records from Wisconsin in 2006 through 2013, each 5 kg incremental weight change in the first pregnancy, interpregnancy, and second pregnancy periods contributed to a 0.75–5 kg weight change in subsequent periods, 9%–25% change in risk for adverse maternal outcomes, and 8%–47% change in risk for adverse neonatal outcomes in the subsequent pregnancy.[192] In another study, weight retention between the first and second pregnancy was associated with a significantly increased risk for GDM (OR = 2.25, 95% CI 1.33–3.78 per ≥ 2 BMI units), pregnancy-induced hypertension (OR = 3.76, 95% CI 2.16–6.57 per ≥ 3 BMI units), and cesarean delivery during the second pregnancy (OR = 2.04, 95% CI 1.41–2.95 per ≥ 2 BMI units).[193]

Moreover, associations of high gestational weight gain with higher postpartum weight persist up to 15 years after pregnancy.[194] In a 2011 meta-analysis, compared to those with gestational weight gain within the recommendations, those with weight gain above the IOM recommendations retained an additional 3.06 kg (95% CI 1.50–4.63 kg) after 3 years and 4.72 kg (95% CI 2.94–6.50kg) on average after ≥ 15 years postpartum.[195] Weight retention may be higher following a first pregnancy.[196]

Higher pre-pregnancy BMI, higher gestational weight gain, and higher postpartum weight retention each predict a longer-term likelihood of developing overweight or obesity.[194,197] In a cohort study of 484 females from Wisconsin, individuals who had obesity before pregnancy gained more than the IOM recommendations, retained pregnancy weight at 6 months postpartum, breastfed for a short duration or not at all, did not participate in postpartum aerobic exercise, and had the highest BMI after 15 years.[197] Individuals who developed T2DM or prediabetes had significantly higher average BMI at all time points as well as a more dramatic weight increase over the 15 years following pregnancy.[197]

Greater weight gain early in pregnancy appears to have the strongest association with later maternal metabolism. In the Project Viva cohort, each 1-SD increment in first trimester weight gain was associated with greater weight change from pre-pregnancy to 3 years postpartum among individuals with normal weight (2.08 kg; 95% CI, 1.32, 2.84), overweight (2.28 kg; 95% CI, 0.95, 3.61), or obesity (2.47 kg; 95% CI, 0.98, 3.97) prior to pregnancy.[198] Greater first trimester gain was also related to later dysmetabolic traits such as greater waist circumference and blood pressure; however, second and third trimester gains were not associated with any postpartum metabolic outcomes.[198]

Gestational weight gain below IOM guidelines is associated with lower postpartum weight retention, including among individuals with obesity,[154,191,199] although these associations may not persist long-term.[195] Among females at higher risk for dysmetabolism, such as those with pre-pregnancy obesity or GDM, weight gain below current guidelines—and even weight loss—appear to be associated with better outcomes at birth, such as cesarean delivery rates and macrosomia (birthweight $\geq 4{,}000$ g), but concern exists regarding the potential for maternal ketosis that could result in harm to the fetus.[200] Weight loss during pregnancy is not routinely recommended, but may be associated with better birth outcomes for those with higher classes of obesity,[201] although recent evidence indicates that the pattern of gestational weight change is likely more important than the total amount.[202] Few longer-term data exist to suggest whether low weight gain or weight loss in gestation may have long-term benefits for maternal metabolism.

Blood lipids

Normal pregnancy is hyperlipidemic.[151,203] In the first trimester, physiologic increases in maternal progesterone, cortisol, and insulin lead to increased lipid synthesis, decreased lipolysis, and increased lipid availability for fetal development and growth.[204] Although total cholesterol levels are slightly decreased in early pregnancy as the mother accrues adipose tissue, all blood lipids subsequently rise, with the greatest rise in the triglyceride components.[151] Lipids decline following delivery, but the return to pre-pregnancy levels is prolonged.[204]

Gestational lipid levels may provide insights into female cardiometabolic risk in later life. In the Generation R cohort, an atherogenic lipid profile in early pregnancy was independently associated with preeclampsia, higher blood pressure throughout pregnancy, and sustained hypertension through 9 years postpartum.[205] Gestational lipid levels were also positively associated with corresponding lipid levels 6 years after pregnancy, independent of pregnancy complications; gestational triglycerides and remnant cholesterol in the highest quartile and HDL cholesterol in the lowest quartile were associated with the highest risk for future metabolic syndrome, independent of smoking and BMI.[206]

Statins are highly effective at lowering lipids and improving future cardiometabolic risks, but their use in pregnancy has historically been limited due to concerns about teratogenicity.[204] Emerging evidence suggests that even in pregnancy some statins may be safe and that statin use may be associated with lower risks of pregnancy complications, such as preeclampsia and small-for-gestational-age birth (birthweight $\leq 10^{th}$ percentile), which predict future maternal cardiometabolic health.[207] Whether prenatal statin therapy is effective for improving longer-term postpartum metabolic health remains to be determined.

Adipokines

Leptin is an adipose-derived hormone whose role is to regulate energy homeostasis, insulin resistance, and lipid metabolism. Circulating leptin increases across pregnancy and may be abnormally high in pregnancies complicated by metabolic conditions such as diabetes mellitus and preeclampsia.[208] Leptin is elevated in individuals who develop GDM even in early pregnancy.[209] Interestingly, the decline in leptin following delivery is large and precipitous, and thus not related to a substantial decrease in adiposity.[210] This drop in leptin has been suggested to serve as a signal promoting glucose conservation during the transition from late pregnancy to early lactation.[210] Although there has been active investigation related to the role of maternal prenatal environment or breast milk in programming offspring growth and metabolism, evidence is limited regarding gestational leptin and any longer-term maternal outcomes. Although some data suggest that higher gestational leptin is associated with higher postpartum weight retention, this relationship is likely explained by the higher BMI and gestational weight gain seen with higher prenatal leptin.[211–213]

Adiponectin, the most abundant adipose-released cytokine, has a key role in metabolism, primarily through reducing insulin resistance. Adiponectin levels have been reported to be higher in females and may serve as a link between adipose tissue and the reproductive system.[214] Various studies have reported that adiponectin remains constant[215] or tends to decrease across pregnancy.[213,216] Evidence is similarly contradictory regarding whether levels further decrease or increase in the early postpartum period, perhaps related to differences in gestational glycemia.[213,217,218] Given its primary role in relation to insulin resistance, much of the research on adiponectin in pregnancy has focused on GDM. As expected, adiponectin levels have been consistently found to be lower with GDM, even in early pregnancy prior to GDM diagnosis.[209,219] Studies examining gestational adiponectin and postpartum outcomes are generally limited.[220] One observational study found that adiponectin levels during pregnancy independently predicted both insulin sensitivity and β cell function at 3 months postpartum, even after adjustment for GDM.[221] Furthermore, adiponectin emerged as a significant negative independent determinant of postpartum fasting glucose.[221] Other studies have found that, among individuals with GDM, gestational adiponectin did not predict postpartum abnormal glycemia or T2DM.[222] Individuals who went on to develop T2DM had stable adiponectin levels after delivery, whereas those with normoglycemia had increasing adiponectin.[218]

In non-pregnant adults, higher circulating leptin predicts future weight gain, resistance to weight loss, and diabetes risk,[223,224] and lower adiponectin is associated with future incident T2DM.[225] Given these strong associations and generally limited information on longer-term outcomes, future study into relationships of variation in gestational adipokines with maternal metabolic health is warranted.

The importance of postpartum behaviors

Lactation has been projected to play an important role in helping to "reset" the maternal metabolism following gestation.[226] Lactation is associated with mobilization of both glucose and fat from storage for milk production.[210] Lactating females compared with nonlactating females display more favorable metabolic parameters, i.e., those closer to non-pregnant values, including less atherogenic blood lipids, lower fasting and postprandial blood glucose, and greater insulin sensitivity in the first 4 months postpartum.[227] Longer lactation has been associated with lower short, intermediate, and long-term weight.[226,228] In the Project Viva cohort, longer duration of lactation was associated with lower weight retention and higher levels of appetite-suppressing hormones peptide YY (PYY) and ghrelin at 3 years postpartum, although not with markers of glucose or lipid metabolism after adjustment for pre-pregnancy BMI.[228,229] In other observational studies, longer duration of lactation has been associated with lower risk of later metabolic syndrome and T2DM, even after BMI adjustment,[230] with evidence that benefits may be strongest among those with a history of GDM.[231]

Lactogenic hormones likely have an important role in this relationship. Prolactin is produced by lactotrophs in the anterior pituitary gland for release into the systemic circulation, as well as by other tissues, including adipose tissue. Release of prolactin is stimulated by estradiol and thus secretion increases during pregnancy. Prolactin affects the biology of adipose tissue and lipid metabolism and decreases insulin binding in adipocytes.[153]

Beyond lactation, postpartum lifestyle behaviors can modify the relationship between pregnancy complications and postpartum weight. In one analysis at 6 weeks postpartum, every sedentary hour/day was associated with a 0.1% higher fat percentage ($p = 0.01$) at 12 months postpartum, and a higher emotional eating score was associated with a 0.2% higher fat percentage ($p < 0.001$) and a 0.3 cm higher waist circumference ($p < 0.001$) at 12 months.[232] In another study in the Project Viva cohort, individuals who watched fewer than 2 h of television, walked at least 30 min, and consumed trans-fat below the median per day had an OR of 0.23 (95% CI 0.08–0.66) of retaining at least 5 kg at 12 months postpartum.[233]

Some experimental evidence suggests that postpartum interventions may interrupt the link between pregnancy dysmetabolism and later metabolic disease. The most substantial body of evidence exists for progression from GDM to T2DM. A 2016 meta-analysis identified 12 randomized controlled trials of postpartum diet and lifestyle interventions to prevent type 2 diabetes in individuals with prior GDM. The mean annual T2DM incidence was lower in the intervention groups compared with controls (6.0% vs. 9.3%).[234] The majority of interventions demonstrated short-term efficacy in preventing T2DM development, reducing insulin resistance, and decreasing weight in those with GDM history.[234] An additional systematic review and meta-analysis of randomized controlled trials found that lifestyle intervention during pregnancy did not reduce risk for postpartum diabetes

(RR = 0.91, 95% CI 0.66–1.25), but postpartum interventions beginning within 3 years postpartum were associated with a 43% reduced risk for diabetes (95% CI 0.42–0.78).[235]

These benefits may be conferred even when intervention commences years after pregnancy. Study enrollment into the DPP trial that randomized those with impaired glucose tolerance to intensive lifestyle, metformin, or placebo, occurred an average of 12 years following the occurrence of GDM. During the initial ~3-year duration of the trial, the lifestyle intervention resulted in less weight loss among those with GDM but had a similar impact on risk reduction (vs. placebo) compared with females who were at high risk but did not have a history of GDM (53.4% vs. 49.2%, interaction p = 0.74). On the other hand, metformin tended to be more effective in reducing the incidence of diabetes in those with a history of GDM (50.4% vs. 14.4%, interaction p = 0.06).[176] Over 10 years of follow-up in individuals with a history of GDM, intensive lifestyle modification reduced progression to diabetes by 35% and metformin by 40% compared with placebo, whereas among those without a history of GDM, the lifestyle intervention reduced the progression to diabetes by 30%, and metformin did not reduce the progression to diabetes.[180] Therefore, not only can medication or lifestyle successfully prevent progression from GDM to T2DM when initiated years after pregnancy but these benefits may also be sustained for years into the future.

REPRODUCTIVE RISK FACTORS ACROSS LATER YEARS

Perimenopause and the menopausal transition

The female reproductive life span ends after cessation of ovulation and the menstrual cycle, termed menopause, which is identified at 12 months after the final menstrual period. Natural menopause occurs at 50–51 years of age on average[236] but typically varies between 45 and 55 years.[45] However, in approximately 5% of females, early menopause occurs between 40 and 45 years and another 1% experience premature menopause before 40 years of age.[237] The menopausal transition usually lasts around 7 years, although duration may be as high as 14 years.[238] Menopause is often accompanied by well-documented biological, behavioral, and psychosocial changes, together defining the menopausal transition called perimenopause.[236,239] Significant and recognized physiological symptoms of the menopausal transition include vaginal and VMSs that may have deleterious effects on quality of life.[240]

Onset of menopause confers higher risk for dyslipidemia, impaired glucose tolerance, insulin resistance, T2DM,[241] and the leading cause of death, CVD.[242] Advancing age itself is a primary predictor of T2DM development,[243] and early menopause and premature ovarian insufficiency are associated with increased T2DM risk.[244] Other factors associated with aging may also contribute to the diabetogenic environment, including increased adiposity, decreased physical activity, poorer diet quality, excess alcohol consumption, impaired vitamin D_3 metabolism, calcium deficiency, and some medications associated with perimenopause or aging.[245] However, postmenopausal estrogen deficiency may be the fundamental step in diabetogenesis for females.[246]

Perimenopause and associated symptoms are primarily driven by ovarian atresia, resulting in declining estrogen and rising pituitary secretin of FSH that is normally suppressed by estrogen. Generally, estrogen secretion begins to decline 2 years before, and FSH begins to rise 7 years before, the final menstrual period; both stabilize approximately 2 years after the final menses.[239,247] Protective roles of higher circulating estrogen concentrations include regulating adipose deposition, improving insulin sensitivity and glucose tolerance, improving β cell activity and survival, controlling inflammation, and regulating hepatic gluconeogenesis and insulin sensitivity.[72] Additionally, FSH is inversely associated with insulin resistance, prediabetes, and T2DM[248–250]; further, this relationship may be independent of obesity.[248] Hence, postmenopausal individuals with higher circulating FSH may be at lower risk for T2DM, but it is unclear whether FSH is a protective biomarker[250] or whether this relationship is independent of adiposity or insulin resistance.

Epidemiological evidence shows a strong relationship between estrogen deficiency and metabolic dysfunction.[72,251] Estrogen protects against T2DM pathogenesis through engagement in the central and peripheral regulation of glucose homeostasis; deficiency or impaired signaling increases risk for insulin resistance and metabolic dysregulation.[252] Estrogen lowers circulating glucose concentration through activation of ERα,[253] which should enhance muscular glucose uptake through activation of protein kinase B (Akt) and glucose transporter type 4 (GLUT4) expression.[254] But, some evidence suggests that estrogen suppresses hepatic glucose production.[255] These mechanisms may be mediated by transcription factor Foxo1, which promotes transcription of glucose-6-phosphatase, the rate-limiting step in gluconeogenesis[252]: insulin suppresses Foxo1 through Akt activation.[252] In animal models, blocking estrogen signaling in ERα knockout mice increased hepatic insulin resistance and glucose production; however, this effect was blocked by deletion of hepatic transcription factor Foxo1.[256,257] Thus, the reduction in estrogen that accompanies the end of the reproductive life phase results in removal of the protective effects associated with estrogen. Indeed, estrogen therapy has been shown to reduce perimenopausal-related weight gain and incidence of T2DM.[72]

Diminishing estrogen also leads to menstrual irregularities and physical symptoms characteristic of perimenopause and the onset of menopause, but variability in personal experiences indicate the complex phenomenon of the menopausal transition. Two important traits that may indicate future metabolic health include the occurrence and/or severity of VMSs and timing or age at perimenopausal initiation. But whether experiencing variations during this reproductive phase is metabolically contributory or simply a symptom of estrogen deficiency is unclear. Understanding the underlying etiology and relationship with metabolic function may delineate and aid therapeutic management of symptoms and T2DM.

Perimenopausal symptoms and timing

Menstrual irregularities are characteristic of the onset of perimenopause. Other common symptoms include hot flashes/flushing, night sweats, increasing weight, body shape changes, mood swings or irritability, sleep disturbances, fatigue, memory issues, and mental health changes, including depression.[236] Of these, the VMSs—including hot flashes and nights sweats—are generally the most common[236] and considered the hallmark

symptoms of perimenopause.[258] VMSs occur in up to 74% of perimenopausal individuals,[259] with 28.5% reporting moderate to severe symptoms.[260] Some individuals experience hot flashes as early as 38 years, suggesting functional ovarian changes start earlier than the expected perimenopausal period and transition over time.[261] These symptoms generally peak in late perimenopause or concurrently with the final menstrual period in early menopause.[261] Further, early age at menopause is associated with more severe perimenopausal symptoms.[262,263]

Several studies have specifically examined perimenopausal symptoms and timing with metabolic outcomes,[239,263–267] providing many of the epidemiological insights related to perimenopause and metabolic risk. Matthews et al. first reported dyslipidemia, as well as body weight gain and redistribution despite no changes in diet or physical activity, across the transition and postmenopausal periods in the absence of hormone replacement therapy.[266] Perhaps the most prolific study, the longitudinal Study of Women's Health Across the Nation (SWAN), demonstrated that menopausal VMSs, and the accompanying biological, psychological, social, and behavioral changes, affect midlife and future health.[239] Indeed, the American Heart Association recognizes menopause as a specific CVD risk factor,[268] in part due to evidence from SWAN that menopause is associated with dyslipidemia, redistribution of fat mass, and increased risk for metabolic syndrome.[269–272] Further, VMSs were positively associated with CVD risk, independent of age or sex hormones,[239] including metabolic risk factors of dyslipidemia,[258] hypertension,[273] and insulin resistance.[274] Finally, the menopausal transition is associated with impaired fasting glucose, but it is unclear whether this is due to menopause itself or fat mass gain during the transition.[267]

Severity of menopausal symptoms,[275] presence of multiple menopausal symptoms,[276] and early menopause (<45 years)[244] are associated with T2DM. Waning estrogen has a role in VMS onset: estrogenic transition from predictable cyclic to unpredictable acyclic patterns before and after the final menstrual period is associated with VMS occurrence.[277] Although declining estrogen coincides with VMS initiation and may drive hot flash experiences,[72] this decline does not fully explain VMSs or the relationship with T2DM because circulating estrogen does not differ between those with and without VMSs.[278] One investigation from SWAN found that higher FSH and lower estradiol concentrations were associated with reported VMSs and higher FSH concentrations with frequency of symptoms.[279] Prevalence of symptoms decreased with higher estradiol levels; testosterone and DHEAS were not associated with VMSs.[279]

Additionally, premature or early menopause[280,281] may occur due to genetic, autoimmune, surgical, or iatrogenic factors.[262] Because dwindling estrogen reduces exposure to its protective attributes,[72] early menopausal onset would decrease the total duration of metabolic protection from estrogen. This relationship may be related to estrogen or lower anti-Müllerian hormone (AMH). AMH decreases with ovarian reserve, reflecting the number of remaining follicles; therefore, AMH is used as a marker of ovarian reserve.[282,283] Accordingly, AMH is highly predictive of age at menopause,[284] from 3 to 4 years before and up to 14–15 years before menopause.[285] Evidence demonstrates that AMH decreases earlier with diabetes, potentially due to oxidative stress or hyperglycemic perturbation of granulocytes.[286–288] With PCOS, AMH may be dramatically increased due to properties of ovarian granulosa cells that have yet to be determined,[282] and those with early PCOS may experience earlier menopause, which may impact the slope of metabolic risk for T2DM.

Obesity may also tie together menopausal characteristics and metabolic health. Excess adiposity has been associated with a later rather than an earlier age at menopause[289] but with more severe VMSs.[290] In the postmenopausal state with obesity, excess adipose tissue leads to aromatization of androgens into estrogens, which results in higher estrogen synthesis and further inhibition of FSH.[248] After the final menstrual period, the dramatic rise in FSH was attenuated in those with obesity, whereas estradiol concentration was negatively associated with severity of obesity.[247] The pathophysiology behind obesity and severity of symptoms is less clear. It has been proposed that excess adiposity acts as insulation and reduces dissipation of body heat, leading to exaggerated VMSs.[291] An additional factor associated with age at menopause is that individuals with short ($\leq$25 days) menstrual cycles during the reproductive years have been shown to have earlier onset of menopause and higher frequency of menopausal symptoms.[109] If short menstrual cycles, which are associated with higher metabolic risk, lead to earlier onset at menopause and greater severity of perimenopausal symptoms, both of which are also associated with higher metabolic risk, this combination may indicate the potential that early menopause and more severe symptoms may act as additional metabolic "hits" that compound risk for poorer metabolic outcomes, similar to the relationship for PCOS and later GDM as illustrated in Figure 2.[109]

Although evidence points to associations of greater VMSs or early age at menopause with metabolic dysfunction, there are limited studies examining long-term outcomes. To our knowledge, only two studies found increased risk for incident diabetes with greater VMSs. Risk was increased with the presence of symptoms, as well as the severity, duration, and types of symptoms, in the Women's Health Initiative.[292] Herber-Gast et al. also identified increased risk with severe VMSs, but only for individuals who reported symptoms that peaked during the menopausal transition. Longitudinal studies are needed to investigate outcomes well beyond the menopausal transition.

Treatment of early or symptomatic perimenopause

The North American Menopause Society recommends supplemental estrogen therapy as a first line of defense against moderate to severe VMSs for individuals <60 years[290] and recommends its use with early menopause until the natural timing of menopause would have occurred.[262] For early menopause, estrogen therapy has the potential to, at least temporarily, stave off risks associated with metabolic disease.[262]

Estrogen is known to improve insulin sensitivity; thus, those who experience early menopause have decreased duration of lifetime estrogen exposure leading to increased risk for T2DM.[293] Results from the Postmenopausal Estrogen/Progestin Interventions study (PEPI), a placebo-controlled trial, found a 2%–3% lower fasting glucose and 2%–7% higher glucose after 2-h oral glucose challenge in the hormone intervention group compared with the placebo group.[294] Following PEPI, the Heart Estrogen/Progestin Replacement Study (HERS) described a 35% lower diabetes risk among those randomized to postmenopausal estrogen therapy compared with individuals

assigned placebo (HR = 0.65, 95% CI 0.48–0.89).[84] This finding was attributed to estrogen preventing increased glucose concentration. In one clinical trial, postmenopausal estrogen or estrogen-progestogen therapy did not affect fasting insulin during postmenopause without diabetes,[295] whereas two studies reported decreased insulinemia with combined hormone therapy.[83,296] Overall, postmenopausal estrogen therapy may lessen risk for, but not prevent, T2DM due to the complexity of action, risks, and benefits.

There is robust evidence that hormone therapy effectively reduces VMSs associated with menopause.[297] Nevertheless, using estrogen therapy to treat VMSs remains controversial because of potential concerns about elevated risks for breast cancer, thromboembolic disease, and myocardial infarction.[298] An added benefit of therapeutic estrogen to treat menopausal symptoms may be that it alters the course of metabolic disease and risks for longer-term metabolic dysfunction following menopause.[45,262] Perhaps more importantly, large, randomized controlled trials suggest that estrogen therapy reduces incidence of T2DM[83,84,296,299,300] through mechanisms that reduce fasting plasma glucose, insulinemia, and insulin resistance.[83,296,301] In a meta-analysis of 107 randomized controlled trials, evidence demonstrated that in female individuals without diabetes, therapeutic estrogen reduced new-onset T2DM as well as abdominal fat, obesity, insulin resistance, and blood lipids.[300] In those with previously diagnosed diabetes, postmenopausal estrogen therapy reduced fasting glucose and insulin resistance; compared to those with placebo or no hormone treatment, estrogen reduced homeostatic model assessment for insulin resistance (HOMA-IR) by 35.8% (95% CI 19.8%–51.7%), fasting glucose by 11.5% (95% CI 5.1%–18.0%), and fasting insulin by 20.2% (95% CI 4.2%–36.3%).[300] The relationship between timing and symptoms of the menopausal transition should be considered during active screening or management of reproductive and metabolic risk factors.

SUMMARY OF FEMALE REPRODUCTIVE RISK FACTORS AND LONG-TERM RISK FOR METABOLIC DYSFUNCTION

Throughout this review, we have provided insights into the potential underlying etiologies and shared risk factors between variations in reproductive milestones and later metabolic dysfunction or disease. The majority of shared risk factors fall into one of three categories, genetics, hormonal fluctuations and resulting physiology, or adiposity. Furthermore, increased insulin resistance is an expected physiologic response relative to the primary reproductive phases of puberty and pregnancy, and in response to body composition changes during menopausal transition.[302,303] Variations in reproductive risk factors during these time periods, e.g., timing of puberty, glycemic response during pregnancy, or age at menopausal transition and manifestation of VMSs, may primarily serve as markers of higher insulin resistance and, thus, heightened risk for T2DM. However, traits during reproductive milestones across the female lifecourse may lie on the pathway to metabolic dysfunction independent of insulin resistance,[302] with each additional trait potentially acting as an additional "hit" to the slope of metabolic trajectory (Figure 2), compounding risk for later disease.

To what extent variations in risk factors and irregular metabolic experiences are preventable is unclear. Genetics sets the framework for the reproductive lifecourse and may predispose individuals to insulin resistance and T2DM. Family and twin studies have provided evidence for heritability of metabolic traits and increasing risk if both parents have T2DM.[304] Some evidence suggests that certain genetic or epigenetic variants may influence risk factors during reproductive milestones. For example, polymorphisms in rs6257 and rs6259 are directly associated with circulating SHBG and strongly predictive of T2DM.[282] However, genetic predisposition does not augur metabolic disease: genetics is not the only factor contributing to the lifecourse metabolic trajectory and does not account for sociocultural, environmental, chemical, or nutritional factors. Further, excessive adiposity in early life is associated with reproductive risk factors, such as pubertal timing and level of insulin resistance, as well as with higher BMI in adulthood—which is also associated with T2DM development. Adiposity likely plays multiple roles: it may cause, mediate, and confound reproductive-metabolic relationships. The inflammatory state of obesity may serve as a link between reproductive traits and later life metabolic risk. Whatever the specific role(s) it plays, adiposity is a shared, modifiable contributor to both the reproductive risk factors and metabolic diseases discussed.

Prevention and therapeutic lifestyle management

Beyond traditional risk factors, such as smoking, poor diet, and physical activity,[58] certain metabolically sensitive reproductive traits in a female's lifecourse might signal risk and allow opportunities for screening and early, enhanced intervention. Studies examining different female reproductive life stages and later T2DM are limited, mostly focusing on the prenatal period or diagnosed PCOS. However, robust evidence has identified specific stages of the female lifespan associated with transient and expected insulin resistance, including puberty, pregnancy, and menopause.[26,305,306] Throughout the lifecourse, reproductive characteristics may provide specific therapeutic targets to address before metabolic disease manifests. Etiological factors underlying the pathophysiology of metabolic dysfunction may begin before adolescence, with further risk factors compounding potential pathways and outcomes throughout the lifecourse.

Screening for reproductive risk factors across the lifecourse may be an initial step to aid prevention or treat long-term metabolic dysfunction. Although not currently standardized practice, establishing baseline values for risk factors or indicators of metabolic sequelae may provide detailed information, including patterns of change, particularly when started before or during puberty. In healthcare settings, it might be beneficial for screening to occur early and regularly, such as during annual physical examinations that provide opportunities for lifestyle counseling to minimize risks. The American College of Obstetricians and Gynecologists recommends healthcare practitioners complete a comprehensive reproductive history and engage in shared decisions related to preventive or treatment pathways along the reproductive continuum, but this care need not be entrusted only to obstetrician-gynecologists.[307] For reproductive-aged patients, discussing reproductive plans[307] may provide opportunities for discussions about

family history and potential reproductive risk factors. If not already in use, appointment questionnaires may be simple to implement. Important data collection includes questions related to family history of metabolic disease, age at menarche, menstrual cycle characteristics, attempts to conceive, prior history of conception or pregnancy and resulting metabolic changes, use of fertility treatment, and perimenopausal age and severity of VMSs. For individuals with a history of GDM, interventions should optimally commence within 3 years of the affected pregnancy,[235] although the DPP study showed evidence of benefit with intervention commencing more than a decade after diagnosis.[169,308] Further, because females may have a higher risk burden than males at the time of T2DM diagnosis,[309] screening for excess adiposity and a family history of T2DM may provide the earliest, clearest indicator of ongoing risk and need for intervention.

Conclusions

Specific traits during the female reproductive milestones of puberty, pregnancy, and menopause are associated with risks for later metabolic dysfunction. Early age at menarche, menstrual irregularity, development of PCOS, greater gestational glycemia and lipidemia, excess gestational weight gain, and severity and timing of perimenopausal symptoms all appear to have a link to later life metabolic disease. However, it is unclear to what extent these traits are on the causal pathway or whether they represent markers of upstream characteristics or shared underlying mechanisms, such as higher insulin resistance during key reproductive transitions. The current evidence suggests that shared underlying risk factors include adiposity, hormonal variation, and genetics. However, our understanding of these relationships is limited due to methodological hindrances: disentangling the true role of these characteristics in the pathophysiology of metabolic disease is challenging, given their complexity, the decades-long time horizons, and the impossibility of randomizing many exposures of interest. The majority of therapeutic interventions have focused on lifestyle changes or medication management of high-risk individuals or those already experiencing impaired glucose tolerance or hyperglycemia. Current preventive strategies rely primarily on medication prescription or therapeutic lifestyle changes—including diet, physical activity, and weight loss—or a combination of therapies. Clinical evidence gathered in the healthcare setting during these reproductive hallmarks may be critical for patient education, implementing prevention strategies, and staving off disease onset. Moreover, additional research is needed into potential upstream factors, mechanisms, and effective interventions.

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AUTHOR CONTRIBUTIONS

Conception, A.R.N., J.E.C., and E.O.; design, A.R.N., J.E.C., and E.O.; interpretation, A.R.N., J.E.C., and E.O.; composition of the manuscript, A.R.N. and E.O.; oversight of composition and provision of critical manuscript review, J.E.C. and E.O.; and obtained funding, J.E.C. and E.O.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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