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Journal

Cell Metabolism, 36(2)

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Publication Date

2024-02-06

DOI

10.1016/j.cmet.2024.01.002

Peer reviewed

HHS Public Access

Author manuscript

Cell Metab. Author manuscript; available in PMC 2025 February 06.

Published in final edited form as:

Cell Metab. 2024 February 06; 36(2): 240–262. doi:10.1016/j.cmet.2024.01.002.

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 development of type 2 diabetes mellitus or dyslipidemia. Recent evidence suggests female reproductive characteristics may be overlooked as risk factors that contribute to later metabolic dysfunction. These reproductive traits include age at menarche, menstrual irregularity, development of polycystic ovary syndrome, gestational weight change, gestational dysglycemia and dyslipidemia, and 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 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.

eTOC Blurb

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Contributions

ARN: conception, design, interpretation, and composition of the manuscript

JEC: conception, design, interpretation, oversaw composition and provided critical manuscript review, obtained funding

EO: conception, design, interpretation, composition of the manuscript, oversaw composition and provided critical manuscript review, obtained funding

Conflicts of interest

The authors declare no conflicts of interest.

Declaration of interests

The authors declare no competing interests.

Female reproductive characteristics may be overlooked as contributors to lifecourse metabolic dysfunction. Whether these characteristics are markers of future dysfunction or share underlying etiologies, disentangling these relationships may provide direction for therapeutic lifestyle modification that could improve long-term metabolic burden.

Keywords

Diabetes; Pregnancy; Risk Factors; PCOS; Metabolic dysfunction

Introduction

Metabolic health generally encompasses optimal levels of blood glucose, triglycerides, 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 (CVD), 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 labelled “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 that 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 type 2 diabetes mellitus 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 addressed pregnancy and reproductive risk factors

for cardiovascular disease.[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 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 since 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, that 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). 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 13y 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 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 12–13y, 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, versus hepatic, insulin sensitivity that allows for higher concentrations of circulating glucose.[25,27] However, growth hormone and insulin-like growth factor 1 (IGF-1) concentrations are elevated during the pubertal transition, and it is well documented that growth hormones cause insulin resistance.[28–31] Insulin resistance increases across puberty, decreasing insulin sensitivity by as much as 30% at mid-puberty compared to prepubertal or adult periods.[25] Diagnosis of prediabetes, an antecedent to T2DM,[32] has increased in adolescents aged 12 to 19y 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 100–125mg/dL, 2hr plasma glucose 140–199mg/dL during oral glucose tolerance test, hemoglobin A1c 5.7–6.4%, or random plasma glucose >200mg/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, that 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] that 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 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 (PFOA, PFOS, 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 (RR=1.22, 95%CI 1.17 to 1.28) for T2DM in those with early age at menarche (<12y).[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 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. ≥12y) was associated with 0.34kg/m^2 higher adult BMI, as well as a twofold increased risk for obesity greatest in females <40 years of age. Late menarche ≥15 years (vs. <15y) was associated with a 0.24kg/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 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=2.33kg, 95%CI 1.64 to 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 to 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 <12y 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 to 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. While in females estrogens increase during puberty, circulating SHBG decreases twofold.[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 to 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 to 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 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 strongly predictive of T2DM.[77] These effects may be due to SHBG's ability to modulate effects of estrogen on peripheral tissues; SHBG is a cellular estrogen antagonist at the estrogen receptor.[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] that 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 versus 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 five 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 five 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, regulation of glucose metabolism in these mouse models occurs through suppression at various points in the insulin-PI3K-mTOR pathway at IGF1R, INSR, and 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 gonadotropin-releasing hormone (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 analogues. One study reported higher adiposity without adverse metabolic changes at three years follow-up in females with early onset puberty treated with analogues versus 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 versus untreated.[97] Further, 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 versus 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 it may be important before and after menarche. Screening prepubertal individuals for excess adiposity, familial age at menarche before menarche 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 risks 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 three 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 since 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% to 30% of reproductive-aged females worldwide with variability highest during adolescence and as age nears 50 years.[105] True population values may be higher since as many as half 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 to 32y were associated with increased diabetes risk (Adjusted Rate Ratio: 1.4, 95%CI 1.0 to 1.8) over 56 years of follow-up (median age 73), although no association of age at menarche, cycle regularity, or long cycles (>42d) with risk for diabetes was observed.[116]

Some of the most robust evidence 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 (>40d) or highly irregular menstrual cycles at ages 18 to 22y had twice the risk of developing T2DM over six years of follow-up compared to those with a cycle length of 26–31d.[101] Additionally, risk for T2DM was three times higher in individuals with a short cycle <21d 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 to 1.11), whereas absence of hyperandrogenism with long/irregular cycles was associated with T2DM risk (RR=2.11, 95%CI 1.59 to 2.80). These results suggest 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 >40d and/or chronic irregular menstruation were at the highest risk for developing T2DM across the course of the study compared to age-matched individuals with very regular cycles.[103] However, associated risk was age-dependent, from 32% (95%CI 22 to 44%) higher risk with irregularity at 14 to 17y up to 66% (95%CI 49 to 84%) higher risk with irregularity in the 29 to 46y age range. Further, those with long cycle length >40d between ages 18 to 22y and ages 29 to 46y were 37% (95%CI 19 to 57%) and 50% (95%CI 36 to 65%) more likely to develop T2DM, respectively, compared to age-matched counterparts with cycle length 26 to 31d. 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 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]

Polycystic Ovary Syndrome (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 >45d in adolescence; <21 or >35d 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 to 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 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] However, the 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 prevalence of insulin resistance between PCOS phenotypes with or without obesity.[131] However, a meta-analysis (n=35) found that individuals with PCOS

were at higher risk (Risk Ratio=2.77, 95%CI 1.88 to 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 three 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 five 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 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 to 4.82) compared to 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 to 8.10) compared to those without PCOS but similar BMI, suggesting 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 to 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=1.0, 95%CI 0.9 to 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 if 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 age 40 years with a history of GDM or family history of T2DM; timing or frequency of screening were 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] 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 adaptions 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 two to fourfold increase in triglycerides and 50% increase in total cholesterol.[152] Leptin increases from early pregnancy onwards, 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, that 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 nonpregnant insulin resistance,[157] suggesting further potential for exacerbated metabolic risk in reproductively experienced individuals. Similarly, among female individuals aged 18 to 30 years enrolled in the longitudinal Coronary Artery Risk Development in Young Adults (CARDIA) study, primiparas gained 2 to 3kg more weight over five 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 2 to 4cm gain in waist circumference.[159] Increasing parity was also associated with 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 growth hormone, 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 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 to prepregnancy values. Within the first five years postpartum, 20% to 30% of individuals with GDM will develop T2DM.[168] Further, Overall, GDM is associated with an estimated sevenfold 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 versus 20.1% (n=791/3946) of mothers without GDM (OR=3.44, 95%CI 2.85 to 4.14]; risk difference, RD=25.7%, 95%CI 21.7 to 29.7%).[171] GDM history also predicts subsequent hyperlipidemia[172] and a two-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. who 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%). Individuals 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 prepregnancy BMI and gestational weight gain, fasting glucose, adiponectin, and leptin levels.[174] Further examination of these subtypes found 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=1082), 850 Metformin twice/d arm (n=1073), or an intensive lifestyle intervention arm (n=1079). Although all had impaired glucose tolerance at study entry, mean age was younger (43y GDM history vs. 51y no GDM history) and glucose levels were similar at enrollment (e.g., fasting glucose 106 vs. 105mg/dL), rates of transition to T2DM were higher among individuals with versus 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 clear benefit of lifestyle modification for improving birth outcomes, such as in infant growth and reduced macrosomia (birthweight ≥4000g).[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 one year after birth than in the control groups (Risk Ratio=1.75, 95%CI 1.05 to 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 to 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 to 66), whereas Metformin reduced incidence by 31% (95%CI 17 to 43). However, Metformin may be three times more effective at preventing T2DM in individuals with a history of GDM compared to individuals with no history of GDM.[180] At 3 years follow-up in the DPP, lifestyle intervention resulted in greater weight loss (mean loss 4.03 ± 0.40kg) in individuals with a history of GDM compared to intervention in individuals with no history of GDM (mean loss 1.60 ± 0.80kg), 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.[181] 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 to a placebo group, reducing T2DM rates by 27% ($p<0.0001$) versus 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.[182]

Gestational weight change

Weight gain typically occurs in a sigmoidal pattern, 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.[183] 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.[184] Some of the adipose gain is stored as visceral fat that may further promote insulin resistance.[185]

Risk factors for excess weight gain are multifactorial, and include social, environmental, chemical, and nutritional influences. Genetics also likely play a role; several studies have observed higher gestational weight gain with obesity-associated genes.[186,187] 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 (≥90th percentile for birthweight at a given gestational age). The relationship of gestational weight gain with GDM is complex; although generally, higher weight gain is associated with higher risk for GDM,[183] 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.[188–190]

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 to 2.70).[191] 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.[192] In an analysis of linked birth records from Wisconsin in 2006 through 2013, each 5kg incremental weight change in the first pregnancy, interpregnancy, and second pregnancy periods contributed to a 0.75 to 5kg weight change

in subsequent periods, 9% to 25% change in risk for adverse maternal outcomes, and 8% to 47% change in risk for adverse neonatal outcomes in the subsequent pregnancy.[193] 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 to 3.78 per ≥2 BMI units), pregnancy-induced hypertension (OR=3.76, 95%CI 2.16 to 6.57 per ≥3 BMI units), and cesarean delivery during the second pregnancy (OR=2.04, 95%CI 1.41 to 2.95 per ≥2 BMI units).[194]

Moreover, associations of high gestational weight gain with higher postpartum weight persist up to 15 years after pregnancy.[195] In a 2011 meta-analysis, compared with 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 to 4.63kg) after three years and 4.72kg (95%CI 2.94 to 6.50kg) on average after ≥15 years postpartum.[196] Weight retention may be higher following a first pregnancy.[197]

Higher pre-pregnancy BMI, higher gestational weight gain, and higher postpartum weight retention each predict longer-term likelihood of developing overweight or obesity.[195,198] 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.[198] Individuals who developed T2DM or prediabetes had significantly higher average BMI at all time points, as well as more dramatic weight increase over the 15 years following pregnancy.[198]

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 three years postpartum among individuals with normal weight (2.08kg, 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.[199] 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.[199]

Gestational weight gain below IOM guidelines is associated with lower postpartum weight retention, including among individuals with obesity,[154,192,200] although these associations may not persist long-term.[196] 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 ≥4000g) but concern exists regarding the potential for maternal ketosis that could result in harm to the fetus.[201] Weight loss during pregnancy is not routinely recommended, but may be associated with better birth outcomes for those with higher classes of obesity,[202] although recent evidence indicates that the pattern of gestational weight change is likely more important than the total amount.[203] 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.[151,204] 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.[205] 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 prepregnancy levels is prolonged..[205]

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 nine years postpartum.[206] Gestational lipid levels were also positively associated with corresponding lipid levels six 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.[207]

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.[205] 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 ≤10th percentile), that predict future maternal cardiometabolic health.[208] 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 pre-eclampsia.[209] Leptin is elevated in individuals who develop GDM even in early pregnancy.[210] Interestingly, the decline in leptin following delivery is large and precipitous, and thus, not related to a substantial decrease in adiposity.[211] This drop in leptin has been suggested to serve as a signal promoting glucose conservation during the transition from late pregnancy to early lactation.[211] While 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 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.[212–214]

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.[215] Various studies have reported that adiponectin remains constant[216] or tends to

decrease across pregnancy.[214,217] Evidence is similarly contradictory regarding whether levels further decrease or increase in the early postpartum period, perhaps related to differences in gestational glycemia.[214,218,219] 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.[210,220] Studies examining gestational adiponectin and postpartum outcomes are generally limited.[221] 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.[222] Furthermore, adiponectin emerged as a significant negative independent determinant of postpartum fasting glucose.[222] Other studies have found that, among individuals with GDM, gestational adiponectin did not predict postpartum abnormal glycemia or T2DM.[223] Individuals who went on to develop T2DM had stable adiponectin levels after delivery, whereas those with normoglycemia had increasing adiponectin.[219]

In non-pregnant adults, higher circulating leptin predicts future weight gain, resistance to weight loss, and diabetes risk,[224,225] and lower adiponectin is associated with future incident T2DM.[226] 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” maternal metabolism following gestation.[227] Lactation is associated with mobilization of both glucose and fat from storage for milk production.[211] Lactating 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.[228] Longer lactation has been associated with lower short, intermediate, and long-term weight.[227,229] In the Project Viva cohort, longer duration of lactation was associated with lower weight retention and higher levels of appetite-suppressing hormones PYY and ghrelin at three years postpartum, although not with markers of glucose or lipid metabolism after adjustment for prepregnancy BMI.[229,230] In other observational studies, longer duration of lactation has been associated with lower risk of later metabolic syndrome and T2DM, even after BMI adjustment,[231] with evidence that benefits may be strongest among those with a history of GDM.[232]

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, 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 six weeks postpartum, every sedentary hour/day was associated with 0.1% higher fat percentage ($p=0.01$) at 12 months postpartum, and a higher emotional eating score was associated with 0.2% higher

fat percentage (p <0.001) and 0.3cm higher waist circumference (p <0.001) at 12 months.[233] In another study in the Project Viva cohort, individuals who watched fewer than 2 hours of television, walked at least 30 minutes, and consumed trans-fat below the median per day had an odds ratio of 0.23 (95%CI 0.08 to 0.66) of retaining at least 5kg at 12 months postpartum.[234]

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%).[235] The majority of interventions demonstrated short-term efficacy in preventing T2DM development, reducing insulin resistance, and decreasing weight in those with GDM history.[235] 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 to 1.25), but postpartum interventions beginning within three years postpartum were associated with a 43% reduced risk for diabetes (95%CI 0.42 to 0.78).[236]

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 (versus 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.[181] Therefore, not only can medication or lifestyle successfully prevent progression from GDM to T2DM when initiated years after pregnancy, but these benefits may 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 to 51 years of age on average[237] but typically varies between 45 to 55 years.[45] However, in approximately 5% of females, early menopause occurs between 40 to 45 years, and another 1% experience premature menopause before age 40y.[238] The menopausal transition usually lasts around seven years, although duration may be as high as 14 years.[239] Menopause is often accompanied by well-documented biological, behavioral, and psychosocial changes, together defining the menopausal

transition called perimenopause.[237,240] Significant and recognized physiological symptoms of the menopausal transition include vaginal and vasomotor symptoms (VMS) that may have deleterious effects on quality of life.[241]

Onset of menopause confers higher risk for dyslipidemia, impaired glucose tolerance, insulin resistance, T2DM, [242] and the leading cause of death, CVD.[243] Advancing age itself is a primary predictor of T2DM development,[244] and early menopause and premature ovarian insufficiency are associated with increased T2DM risk.[245] 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.[246] However, postmenopausal estrogen deficiency may be the fundamental step in diabetogenesis for females.[247]

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 two years before, and FSH rises beginning seven years before, the final menstrual period; both stabilize approximately two years after the final menses.[240,248] 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;[249–251] further, this relationship may be independent of obesity.[249] Hence, postmenopausal individuals with higher circulating FSH may be at lower risk for T2DM, but it is unclear if FSH is a protective biomarker[251] or if this relationship is independent of adiposity or insulin resistance.

Epidemiological evidence shows a strong relationship between estrogen deficiency and metabolic dysfunction.[72,252] Estrogen protects against T2DM pathogenesis through engagement in central and peripheral regulation of glucose homeostasis; deficiency or impaired signaling increases risk for insulin resistance and metabolic dysregulation.[253] Estrogen lowers circulating glucose concentration through activation of estrogen receptor α (ERα),[254] which should enhance muscular glucose uptake through activation of Akt and GLUT4 expression.[255] But, some evidence suggests estrogen suppresses hepatic glucose production.[256] These mechanisms may be mediated by transcription factor Foxo1 that promotes transcription of glucose-6-phosphatase, the rate-limiting step in gluconeogenesis:[253] insulin suppresses Foxo1 through Akt activation.[253] 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.[257,258] 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 vasomotor symptoms 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.[237] Of these, the vasomotor symptoms (VMS) including hot flashes and nights sweats are generally the most common[237] and considered the hallmark symptoms of perimenopause.[259] VMS occur in up to 74% of perimenopausal individuals,[260] with 28.5% reporting moderate to severe symptoms.[261] 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.[262] These symptoms generally peak in late perimenopause or concurrently with the final menstrual period in early menopause.[262] Further, early age at menopause is associated with more severe perimenopausal symptoms.[263,264]

Several studies have specifically examined perimenopausal symptoms and timing with metabolic outcomes,[240,264–268] 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.[267] Perhaps the most prolific study, the longitudinal Study of Women's Health Across the Nation (SWAN), demonstrated that menopausal VMS, and the accompanying biological, psychological, social, and behavioral changes, affect midlife and future health.[240] Indeed, the American Heart Association recognizes menopause as a specific CVD risk factor,[269] in part due to evidence from SWAN that menopause is associated with dyslipidemia, redistribution of fat mass, and increased risk for metabolic syndrome.[270–273] Further, VMS were positively associated with CVD risk independent of age or sex hormones,[240] including metabolic risk factors of dyslipidemia,[259] hypertension,[274] and insulin resistance.[275] Finally, the menopausal transition is associated with impaired fasting glucose, but it is unclear if this was due to menopause itself or fat mass gain during the transition.[268]

Severity of menopausal symptoms,[276] presence of multiple menopausal symptoms,[277] and early menopause (<45y)[245] 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.[278] Although declining estrogen coincides with VMS initiation and may drive hot flash experiences,[72] this decline does not fully explain VMS or the relationship with T2DM because circulating estrogen does not differ between those with and without VMS.[279] One investigation from

SWAN found that higher FSH and lower estradiol concentrations were associated with reported VMS and higher FSH concentrations with frequency of symptoms.[280] Prevalence of symptoms decreased with higher estradiol levels; testosterone and DHEAS were not associated with VMS.[280]

Additionally, premature or early menopause[281,282] may occur due to genetic, autoimmune, surgical, or iatrogenic factors.[263] Since dwindling estrogen reduces exposure to its protective attributes,[72] early menopausal onset would decrease total duration of metabolic protection from estrogen. This relationship may be related to higher 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.[283,284] Accordingly, AMH is highly predictive of age at menopause,[285] from 3 to 4 years before and up to 14 to 15 years before menopause.[286] Evidence demonstrates that AMH decreases earlier with diabetes, potentially due to oxidative stress or hyperglycemic perturbation of granulocytes.[287–289] With PCOS, AMH may be dramatically increased due to properties of ovarian granulosa cells that have yet to be determined,[283] and those with early PCOS may experience earlier menopause that 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 later rather than earlier age at menopause,[290] but more severe vasomotor symptoms[291] In the postmenopausal state with obesity, excess adipose tissue leads to aromatization of androgens into estrogens that results in higher estrogen synthesis and further inhibition of FSH.[249] 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.[248] 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 vasomotor symptoms.[292] An additional factor associated with age at menopause is that individuals with short (≤25d) menstrual cycles during the reproductive years have been shown to have earlier onset of menopause and higher menopausal symptoms.[109] If short menstrual cycles, that 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 VMS 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 VMS. Risk was increased with presence of symptoms, as well as severity, duration, and type of symptoms, in the Women’s Health Initiative.[293] Herber-Gast et al. also identified increased risk with severe VMS, 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 VMS for individuals <60 years,[291] and recommends its use with early menopause until the natural timing of menopause would have occurred.[263] For early menopause, estrogen therapy has the potential to, at least temporarily, stave off risks associated with metabolic disease.[263]

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.[294] Results from the Postmenopausal Estrogen/Progestin Interventions study (PEPI), a placebo-controlled trial, found a 2% to 3% lower fasting glucose and 2% to 7% higher glucose after 2-hour oral glucose challenge in the hormone intervention group compared to the placebo group.[295] Following PEPI, the Heart Estrogen/progestin Replacement Study (HERS) described a 35% lower diabetes risk among those randomized to postmenopausal estrogen therapy compared to individuals assigned placebo (HR=0.65, 95%CI 0.48 to 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,[296] whereas two studies reported decreased insulinemia with combined hormone therapy.[297,298] Overall, postmenopausal estrogen therapy may lessen risk, but not prevent, T2DM due to the complexity of action, risks, and benefits.

There is robust evidence that hormone therapy effectively reduces VMS associated with menopause.[299] Nevertheless, using estrogen therapy to treat VMS remains controversial because of potential concerns about elevated risks for breast cancer, thromboembolic disease, and myocardial infarction.[300] 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.[45,263] Perhaps more importantly, large, randomized controlled trials suggest that estrogen therapy reduces incidence of T2DM[297,298,301–303] through mechanisms that reduce fasting plasma glucose, insulinemia, and insulin resistance.[297,298,304] 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.[303] 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 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%).[303] 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.[305,306] 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 VMS, 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[305] 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.[307] Some evidence suggests 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.[283] 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 – that 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.[26,308,309] 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.[310] For reproductive-aged patients, discussing reproductive plans[310] may provide opportunities for discussion 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 VMS. For individuals with a history of GDM, interventions should optimally commence within three years of the affected pregnancy,[236] although the DPP study showed evidence of benefit with intervention commencing more than a decade after diagnosis.[169,311] Further, since females may have a higher risk burden than males at the time of T2DM diagnosis,[312] screening for excess adiposity and a family history of T2DM may be the earliest, clearest indicators of ongoing risk and need for intervention.

Conclusion

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 if they represent markers of upstream characteristics or shared underlying mechanisms, such as higher insulin resistance during key reproductive transition. 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.

Acknowledgements

The authors thank Lauren D. Mangini, PhD, RD for her valuable review and insights during development of this manuscript. The authors also acknowledge the National Institute of Diabetes and Digestive and Kidney Diseases (T32DK007703), Eunice Kennedy Shriver National Institute of Child Health and Human Development (R01HD0960342), National Institute of Environmental Health Sciences (R24ES030894), and National Institute of Aging and Office of Research on Women's Health (U54AG062322) for financial support.

Acronyms

AMH	Anti-Müllerian hormone
BMI	Body mass index
CVD	Cardiovascular disease
DPP	Diabetes Prevention Program
ERα	Estrogen receptor α
FSH	Follicle-stimulating hormone
GDM	Gestational diabetes mellitus
GH	Growth hormone
GLUT	Glucose transporter
GnRH	Gonadotropin-releasing hormone
HDL	High-density lipoprotein
HPO	Hypothalamic-pituitary-ovarian
HR	Hazard ratio
IGF-1	Insulin-like growth factor 1
IOM	Institutes of Medicine
LH	Luteinizing hormone
OR	Odds ratio
PCOS	Polycystic ovary syndrome
PEPI	Postmenopausal Estrogen/Progestin Interventions study
RD	Risk difference
RR	Relative risk

SHBG	Sex hormone binding globulin
T2DM	Type 2 diabetes mellitus
VMS	Vasomotor symptoms

References

1. Araújo J, Cai J, and Stevens J (2019). Prevalence of Optimal Metabolic Health in American Adults: National Health and Nutrition Examination Survey 2009–2016. Metab. Syndr. Relat. Disord. 17, 46–52. 10.1089/met.2018.0105. [PubMed: 30484738]
2. Xu J, Murphy SL, Kochanek KD, and Arias E (2023). Deaths: Final Data 2019. Natl. Vital Stat. Rep. 70, 1–86.
3. Diabetes: a defining disease of the 21st century (2023). The Lancet 401, 2087. 10.1016/S0140-6736(23)01296-5.
4. International Diabetes Federation IDF Diabetes Atlas - Tenth Edition. https://diabetesatlas.org/.
5. Harris KM, Majmundar MK, and Becker T (2021). Cardiometabolic Diseases. In High and Rising Mortality Rates Among Working-Age Adults (National Academies Press (US)), pp. 311–362.
6. Cao H (2014). Adipocytokines in Obesity and Metabolic Disease. J. Endocrinol. 220, T47–T59. 10.1530/JOE-13-0339. [PubMed: 24403378]
7. Clark AM, Desmeules M, Luo W, Duncan AS, and Wielgosz A (2009). Socioeconomic status and cardiovascular disease: risks and implications for care. Nat. Rev. Cardiol. 6, 712–722. 10.1038/nrcardio.2009.163. [PubMed: 19770848]
8. O'Kelly AC, Michos ED, Shufelt CL, Vermunt JV, Minissian MB, Quesada O, Smith GN, Rich-Edwards JW, Garovic VD, El Khoudary SR, et al. (2022). Pregnancy and Reproductive Risk Factors for Cardiovascular Disease in Women. Circ. Res. 130, 652–672. 10.1161/CIRCRESAHA.121.319895. [PubMed: 35175837]
9. Gerdts E, and Regitz-Zagrosek V (2019). Sex differences in cardiometabolic disorders. Nat. Med. 25, 1657–1666. 10.1038/s41591-019-0643-8. [PubMed: 31700185]
10. Kuh D, Ben Shlomo Y, and Ezra S eds. (2004). A Life Course Approach to Chronic Disease Epidemiology (Oxford University Press) 10.1093/acprof:oso/9780198578154.001.0001.
11. Ben-Shlomo Y (2002). A life course approach to chronic disease epidemiology: conceptual models, empirical challenges and interdisciplinary perspectives. Int. J. Epidemiol. 31, 285–293. 10.1093/ije/31.2.285. [PubMed: 11980781]
12. Aris IM, Sarvet AL, Stensrud MJ, Neugebauer R, Li L-J, Hivert M-F, Oken E, and Young JG (2021). Separating Algorithms From Questions and Causal Inference With Unmeasured Exposures: An Application to Birth Cohort Studies of Early Body Mass Index Rebound. Am. J. Epidemiol. 190, 1414–1423. 10.1093/aje/kwab029. [PubMed: 33565574]
13. Kronborg H, Vaeth M, and Kristensen I (2012). The effect of early postpartum home visits by health visitors: a natural experiment. Public Health Nurs. Boston Mass 29, 289–301. 10.1111/j.1525-1446.2012.01019.x.
14. Hewitt B, Strazdins L, and Martin B (2017). The benefits of paid maternity leave for mothers' post-partum health and wellbeing: Evidence from an Australian evaluation. Soc. Sci. Med. 1982 182, 97–105. 10.1016/j.socscimed.2017.04.022.
15. American College of Obstetricians & Gynecologists (2015). ACOG Committee Opinion No. 651: Menstruation in Girls and Adolescents: Using the Menstrual Cycle as a Vital Sign. Obstet. Gynecol. 126, e143–e146. 10.1097/AOG.0000000000001215. [PubMed: 26595586]
16. Esteve E, Ricart W, and Fernández-Real JM (2009). Adipocytokines and Insulin Resistance. Diabetes Care 32, S362–S367. 10.2337/dc09-S340. [PubMed: 19875582]
17. Sopher AB, Oberfield SE, and Witchel SF (2022). Disorders of Puberty in Girls. Semin. Reprod. Med. 40, 003–015. 10.1055/s-0041-1735892.
18. Khan L (2019). Puberty: Onset and Progression. Pediatr. Ann. 48, 141–145. 10.3928/19382359-20190322-01.

19. Grumbach MM (2004). The Neuroendocrinology of Human Puberty Revisited. Horm. Res. 57, 2–14. 10.1159/000058094.
20. Ebling FJP (2005). The neuroendocrine timing of puberty. Reproduction 129, 675–683. 10.1530/rep.1.00367. [PubMed: 15923383]
21. Parent A-S, Teilmann G, Juul A, Skakkebaek NE, Toppari J, and Bourguignon J-P (2003). The Timing of Normal Puberty and the Age Limits of Sexual Precocity: Variations around the World, Secular Trends, and Changes after Migration. Endocr. Rev. 24, 668–693. 10.1210/er.2002-0019. [PubMed: 14570750]
22. Rosenfield RL, Cooke DW, and Radovick S (2021). Puberty in the Female and Its Disorders. In Sperling Pediatric Endocrinology (Elsevier), pp. 528–626. 10.1016/B978-0-323-62520-3.00016-6.
23. Kaprio J, Rimpelä A, Winter T, Viken RJ, Rimpelä M, and Rose RJ (1995). Common Genetic Influences on BMI and Age at Menarche. Hum. Biol. 67, 739–753. [PubMed: 8543288]
24. Widén E, Silventoinen K, Sovio U, Ripatti S, Cousminer DL, Hartikainen A-L, Laitinen J, Pouta A, Kaprio J, Järvelin M-R, et al. (2012). Pubertal Timing and Growth Influences Cardiometabolic Risk Factors in Adult Males and Females. Diabetes Care 35, 850–856. 10.2337/dc11-1365. [PubMed: 22338106]
25. Chowdhury S (2015). Puberty and type 1 diabetes. Indian J. Endocrinol. Metab. 19, S51–S54. 10.4103/2230-8210.155402. [PubMed: 25941652]
26. Kelsey MM, and Zeitler PS (2016). Insulin Resistance of Puberty. Curr. Diab. Rep. 16, 64. 10.1007/s11892-016-0751-5. [PubMed: 27179965]
27. Amiel SA, Sherwin RS, Simonson DC, Lauritano AA, and Tamborlane WV (1986). Impaired insulin action in puberty. A contributing factor to poor glycemic control in adolescents with diabetes. N. Engl. J. Med. 315, 215–219. 10.1056/NEJM198607243150402. [PubMed: 3523245]
28. Bratusch-Marrain PR, Smith D, and DeFronzo RA (1982). The effect of growth hormone on glucose metabolism and insulin secretion in man. J. Clin. Endocrinol. Metab. 55, 973–982. 10.1210/jcem-55-5-973. [PubMed: 6749883]
29. Caprio S, Boulware D, and Tamborlane V (1992). Growth hormone and insulin interactions. Horm. Res. 38 Suppl 2, 47–49. 10.1159/000182594. [PubMed: 1292982]
30. Vijayakumar A, Yakar S, and LeRoith D (2011). The Intricate Role of Growth Hormone in Metabolism. Front. Endocrinol. 2, 32. 10.3389/fendo.2011.00032.
31. Press M, Tamborlane WV, and Sherwin RS (1984). Importance of raised growth hormone levels in mediating the metabolic derangements of diabetes. N. Engl. J. Med. 310, 810–815. 10.1056/NEJM198403293101302. [PubMed: 6700669]
32. Perng W, Conway R, Mayer-Davis E, and Dabelea D (2023). Youth-Onset Type 2 Diabetes: The Epidemiology of an Awakening Epidemic. Diabetes Care 46, 490–499. 10.2337/dci22-0046. [PubMed: 36812420]
33. Liu J, Li Y, Zhang D, Yi SS, and Liu J (2022). Trends in Prediabetes Among Youths in the US From 1999 Through 2018. JAMA Pediatr. 176, 608–611. 10.1001/jamapediatrics.2022.0077. [PubMed: 35344013]
34. Arslanian S, Bacha F, Grey M, Marcus MD, White NH, and Zeitler P (2018). Evaluation and Management of Youth-Onset Type 2 Diabetes: A Position Statement by the American Diabetes Association. Diabetes Care 41, 2648–2668. 10.2337/dci18-0052. [PubMed: 30425094]
35. Jonas DE, Schaaf EBV, Riley S, Allison B, Middleton JC, Baker C, Ali R, Voisin CE, and LeBlanc E (2022). Introduction. In Screening for Prediabetes and Type 2 Diabetes Mellitus in Children and Adolescents: An Evidence Review for the U.S. Preventive Services Task Force [Internet] (Agency for Healthcare Research and Quality (US)).
36. Moran A, Jacobs DR, Steinberger J, Hong CP, Prineas R, Luepker R, and Sinaiko AR (1999). Insulin resistance during puberty: results from clamp studies in 357 children. Diabetes 48, 2039–2044. 10.2337/diabetes.48.10.2039. [PubMed: 10512371]
37. Goran MI, and Gower BA (2001). Longitudinal study on pubertal insulin resistance. Diabetes 50, 2444–2450. 10.2337/diabetes.50.11.2444. [PubMed: 11679420]
38. Reinehr T, Wolters B, Knop C, Lass N, and Holl RW (2015). Strong Effect of Pubertal Status on Metabolic Health in Obese Children: A Longitudinal Study. J. Clin. Endocrinol. Metab. 100, 301–308. 10.1210/jc.2014-2674. [PubMed: 25243573]

39. Tagi VM, Giannini C, and Chiarelli F (2019). Insulin Resistance in Children. Front. Endocrinol. 10, 342. 10.3389/fendo.2019.00342.
40. Dai S, Labarthe DR, Grunbaum JA, Harrist RB, and Mueller WH (2002). Longitudinal analysis of changes in indices of obesity from age 8 years to age 18 years. Project HeartBeat! Am. J. Epidemiol. 156, 720–729. 10.1093/aje/kwf109. [PubMed: 12370160]
41. Travers SH, Jeffers BW, Bloch CA, Hill JO, and Eckel RH (1995). Gender and Tanner stage differences in body composition and insulin sensitivity in early pubertal children. J. Clin. Endocrinol. Metab. 80, 172–178. 10.1210/jcem.80.1.7829608. [PubMed: 7829608]
42. Bleil ME, Booth-LaForce C, and Benner AD (2017). Race disparities in pubertal timing: Implications for cardiovascular disease risk among African American women. Popul. Res. Policy Rev. 36, 717–738. 10.1007/s11113-017-9441-5. [PubMed: 30127541]
43. Prentice P, and Viner RM (2013). Pubertal timing and adult obesity and cardiometabolic risk in women and men: a systematic review and meta-analysis. Int. J. Obes. 37, 1036–1043. 10.1038/ijo.2012.177.
44. Petersohn I, Zarate-Ortiz AG, Cepeda-Lopez AC, and Melse-Boonstra A (2019). Time Trends in Age at Menarche and Related Non-Communicable Disease Risk during the 20th Century in Mexico. Nutrients 11, 394. 10.3390/nu11020394. [PubMed: 30781889]
45. Forman MR, Mangini LD, Thelus-Jean R, and Hayward MD (2013). Life-course origins of the ages at menarche and menopause. Adolesc. Health Med. Ther. 4, 1–21. 10.2147/AHMT.S15946. [PubMed: 24600293]
46. Lakshman R, Forouhi NG, Sharp SJ, Luben R, Bingham SA, Khaw K-T, Wareham NJ, and Ong KK (2009). Early Age at Menarche Associated with Cardiovascular Disease and Mortality. J. Clin. Endocrinol. Metab. 94, 4953–4960. 10.1210/jc.2009-1789. [PubMed: 19880785]
47. Stöckl D, Meisinger C, Peters A, Thorand B, Huth C, Heier M, Rathmann W, Kowall B, Stöckl H, and Döring A (2011). Age at menarche and its association with the metabolic syndrome and its components: results from the KORA F4 study. PloS One 6, e26076. 10.1371/journal.pone.0026076. [PubMed: 22028807]
48. Day FR, Elks CE, Murray A, Ong KK, and Perry JRB (2015). Puberty timing associated with diabetes, cardiovascular disease and also diverse health outcomes in men and women: the UK Biobank study. Sci. Rep. 5, 11208. 10.1038/srep11208. [PubMed: 26084728]
49. Brix N, Ernst A, Lauridsen LLB, Parner E, Støvring H, Olsen J, Henriksen TB, and Ramlau-Hansen CH (2019). Timing of puberty in boys and girls: A population-based study. Paediatr. Perinat. Epidemiol. 33, 70–78. 10.1111/ppe.12507. [PubMed: 30307620]
50. Lee HS (2020). Why should we be concerned about early menarche? Clin. Exp. Pediatr. 64, 26–27. 10.3345/cep.2020.00521. [PubMed: 32683812]
51. Ong KK, Ahmed ML, and Dunger DB (2006). Lessons from large population studies on timing and tempo of puberty (secular trends and relation to body size): the European trend. Mol. Cell. Endocrinol. 254–255, 8–12. 10.1016/j.mce.2006.04.018.
52. Kaplowitz P (2006). Pubertal development in girls: secular trends. Curr. Opin. Obstet. Gynecol. 18, 487–491. 10.1097/01.gco.0000242949.02373.09. [PubMed: 16932041]
53. Carwile JL, Seshasayee SM, Aris IM, Rifas-Shiman SL, Claus Henn B, Calafat AM, Sagiv SK, Oken E, and Fleisch AF (2021). Prospective associations of mid-childhood plasma per- and polyfluoroalkyl substances and pubertal timing. Environ. Int. 156, 106729. 10.1016/j.envint.2021.106729. [PubMed: 34171588]
54. Janghorbani M, Mansourian M, and Hosseini E (2014). Systematic review and meta-analysis of age at menarche and risk of type 2 diabetes. Acta Diabetol. 51, 519–528. 10.1007/s00592-014-0579-x. [PubMed: 24671509]
55. Freedman DS, Khan LK, Serdula MK, Dietz WH, Srinivasan SR, and Berenson GS (2003). The relation of menarcheal age to obesity in childhood and adulthood: the Bogalusa heart study. BMC Pediatr. 3, 3. 10.1186/1471-2431-3-3. [PubMed: 12723990]
56. Werneck AO, Oyeyemi AL, Cyrino ES, Ronque ERV, Szwarcwald CL, Coelho-e-Silva MJ, and Silva DR (2018). Association between age at menarche and blood pressure in adulthood: is obesity an important mediator? Hypertens. Res. 41, 856–864. 10.1038/s41440-018-0079-4. [PubMed: 30087421]

57. Bubach S, Menezes AMB, Barros FC, Wehrmeister FC, Gonçalves H, Assunção MCF, and Horta BL (2016). Impact of the age at menarche on body composition in adulthood: results from two birth cohort studies. BMC Public Health 16, 1007. 10.1186/s12889-016-3649-x. [PubMed: 27660104]
58. Glovaci D, Fan W, and Wong ND (2019). Epidemiology of Diabetes Mellitus and Cardiovascular Disease. Curr. Cardiol. Rep. 21, 21. 10.1007/s11886-019-1107-y. [PubMed: 30828746]
59. Elks CE, Ong KK, Scott RA, van der Schouw YT, Brand JS, Wark PA, Amiano P, Balkau B, Barricarte A, Boeing H, et al. (2013). Age at menarche and type 2 diabetes risk: the EPIC-InterAct study. Diabetes Care 36, 3526–3534. 10.2337/dc13-0446. [PubMed: 24159179]
60. Pierce MB, and Leon DA (2005). Age at menarche and adult BMI in the Aberdeen children of the 1950s cohort study. Am. J. Clin. Nutr. 82, 733–739. 10.1093/ajcn/82.4.733. [PubMed: 16210700]
61. Laitinen J, Power C, and Järvelin MR (2001). Family social class, maternal body mass index, childhood body mass index, and age at menarche as predictors of adult obesity. Am. J. Clin. Nutr. 74, 287–294. 10.1093/ajcn/74.3.287. [PubMed: 11522550]
62. Wang L, Xu F, Zhang Q, Chen J, Zhou Q, and Sun C (2023). Causal relationships between birth weight, childhood obesity and age at menarche: A two-sample Mendelian randomization analysis. Clin. Endocrinol. (Oxf.) 98, 212–220. 10.1111/cen.14831. [PubMed: 36237121]
63. Fang J, Yuan J, Zhang D, Liu W, Su P, Wan Y, Zhang Z, Tao F, and Sun Y (2022). Casual Associations and Shape Between Prepuberty Body Mass Index and Early Onset of Puberty: A Mendelian Randomization and Dose-Response Relationship Analysis. Front. Endocrinol. 13, 853494. 10.3389/fendo.2022.853494.
64. Mumby HS, Elks CE, Li S, Sharp SJ, Khaw K-T, Luben RN, Wareham NJ, Loos RJF, and Ong KK (2011). Mendelian Randomisation Study of Childhood BMI and Early Menarche. J. Obes. 2011, 180729. 10.1155/2011/180729. [PubMed: 21773002]
65. Juul F, Chang VW, Brar P, and Parekh N (2017). Birth weight, early life weight gain and age at menarche: a systematic review of longitudinal studies. Obes. Rev. 18, 1272–1288. 10.1111/obr.12587. [PubMed: 28872224]
66. Hvidt JJ, Brix N, Ernst A, Lauridsen LLB, and Ramlau-Hansen CH (2019). Size at birth, infant growth, and age at pubertal development in boys and girls. Clin. Epidemiol. 11, 873–883. 10.2147/CLEP.S217388. [PubMed: 31572017]
67. Brix N, Ernst A, Lauridsen LLB, Parner ET, Arah OA, Olsen J, Henriksen TB, and Ramlau-Hansena CH (2020). Childhood overweight and obesity and timing of puberty in boys and girls: cohort and sibling-matched analyses. Int. J. Epidemiol. 49, 834–844. 10.1093/ije/dyaa056. [PubMed: 32372073]
68. Apter D, and Vihko R (1983). Early menarche, a risk factor for breast cancer, indicates early onset of ovulatory cycles. J. Clin. Endocrinol. Metab. 57, 82–86. 10.1210/jcem-57-1-82. [PubMed: 6222061]
69. Apter D, Reinilä M, and Vihko R (1989). Some endocrine characteristics of early menarche, a risk factor for breast cancer, are preserved into adulthood. Int. J. Cancer 44, 783–787. 10.1002/ijc.2910440506. [PubMed: 2511157]
70. Brown LM, and Clegg DJ (2010). Central effects of estradiol in the regulation of food intake, body weight, and adiposity. J. Steroid Biochem. Mol. Biol. 122, 65–73. 10.1016/j.jsbmb.2009.12.005. [PubMed: 20035866]
71. Godsland IF (2005). Oestrogens and insulin secretion. Diabetologia 48, 2213–2220. 10.1007/s00125-005-1930-0. [PubMed: 16193292]
72. Cignarella A, and Bolego C (2010). Mechanisms of estrogen protection in diabetes and metabolic disease. Horm. Mol. Biol. Clin. Investig. 4, 575–580. 10.1515/HMBCI.2010.084.
73. Hammond GL (2011). Diverse Roles for Sex Hormone-Binding Globulin in Reproduction. Biol. Reprod. 85, 431–441. 10.1095/biolreprod.111.092593. [PubMed: 21613632]
74. Fortunati N, Becchis M, Catalano MG, Comba A, Ferrera P, Raineri M, Berta L, and Frairia R (1999). Sex hormone-binding globulin, its membrane receptor, and breast cancer: a new approach to the modulation of estradiol action in neoplastic cells. J. Steroid Biochem. Mol. Biol. 69, 473–479. 10.1016/s0960-0760(99)00068-0. [PubMed: 10419027]

75. Pugeat M, Moulin P, Cousin P, Fimbel S, Nicolas MH, Crave JC, and Lejeune H (1995). Interrelations between sex hormone-binding globulin (SHBG), plasma lipoproteins and cardiovascular risk. J. Steroid Biochem. Mol. Biol. 53, 567–572. 10.1016/0960-0760(95)00102-6. [PubMed: 7626511]
76. Winters SJ, Gogineni J, Karegar M, Scoggins C, Wunderlich CA, Baumgartner R, and Ghooray DT (2014). Sex Hormone-Binding Globulin Gene Expression and Insulin Resistance. J. Clin. Endocrinol. Metab. 99, E2780–E2788. 10.1210/jc.2014-2640. [PubMed: 25226295]
77. Ding EL, Song Y, Manson JE, Hunter DJ, Lee CC, Rifai N, Buring JE, Gaziano JM, and Liu S (2009). Sex Hormone–Binding Globulin and Risk of Type 2 Diabetes in Women and Men. N. Engl. J. Med. 361, 1152–1163. 10.1056/NEJMoa0804381. [PubMed: 19657112]
78. Tchernof A, and Després J-P (2000). Sex Steroid Hormones, Sex Hormone-Binding Globulin, and Obesity in Men and Women. Horm. Metab. Res. 32, 526–536. 10.1055/s-2007-978681. [PubMed: 11246820]
79. Tchernof A, Toth MJ, and Poehlman ET (1999). Sex hormone-binding globulin levels in middle-aged premenopausal women. Associations with visceral obesity and metabolic profile. Diabetes Care 22, 1875–1881. 10.2337/diacare.22.11.1875. [PubMed: 10546023]
80. PLYMATE SR, MATEJ LA, JONES RE, and FRIEDL KE (1988). Inhibition of Sex Hormone-Binding Globulin Production in the Human Hepatoma (Hep G2) Cell Line by Insulin and Prolactin*. J. Clin. Endocrinol. Metab. 67, 460–464. 10.1210/jcem-67-3-460. [PubMed: 2842359]
81. NESTLER JE, POWERS LP, MATT DW, STEINGOLD KA, PLYMATE SR, RITTMASTER RS, CLORE JN, and BLACKARD WG (1991). A Direct Effect of Hyperinsulinemia on Serum Sex Hormone-Binding Globulin Levels in Obese Women with the Polycystic Ovary Syndrome*. J. Clin. Endocrinol. Metab. 72, 83–89. 10.1210/jcem-72-1-83. [PubMed: 1898744]
82. Catalano MG, Frairia R, Boccuzzi G, and Fortunati N (2005). Sex hormone-binding globulin antagonizes the anti-apoptotic effect of estradiol in breast cancer cells. Mol. Cell. Endocrinol. 230, 31–37. 10.1016/j.mce.2004.11.005. [PubMed: 15664449]
83. Margolis KL, Bonds DE, Rodabough RJ, Tinker L, Phillips LS, Allen C, Bassford T, Burke G, Torrens J, Howard BV, et al. (2004). Effect of oestrogen plus progestin on the incidence of diabetes in postmenopausal women: results from the Women's Health Initiative Hormone Trial. Diabetologia 47, 1175–1187. 10.1007/s00125-004-1448-x. [PubMed: 15252707]
84. Kanaya AM, Herrington D, Vittinghoff E, Lin F, Grady D, Bittner V, Cauley JA, and Barrett-Connor E (2003). Glycemic Effects of Postmenopausal Hormone Therapy: The Heart and Estrogen/progestin Replacement Study: A Randomized, Double-Blind, Placebo-Controlled Trial. Ann. Intern. Med. 138, 1–9. 10.7326/0003-4819-138-1-200301070-00005.
85. Vehkavaara S, Hakala-Ala-Pietilä T, Virkamäki A, Bergholm R, Ehnholm C, Hovatta O, Taskinen MR, and Yki-Järvinen H (2000). Differential effects of oral and transdermal estrogen replacement therapy on endothelial function in postmenopausal women. Circulation 102, 2687–2693. 10.1161/01.cir.102.22.2687. [PubMed: 11094033]
86. Taskinen MR, Puolakka J, Pyörälä T, Luotola H, Bjäörn M, Kääriänen J, Lahdenperä S, and Ehnholm C (1996). Hormone replacement therapy lowers plasma Lp(a) concentrations. Comparison of cyclic transdermal and continuous estrogen-progestin regimens. Arterioscler. Thromb. Vasc. Biol. 16, 1215–1221. 10.1161/01.atv.16.10.1215. [PubMed: 8857916]
87. Selby C (1990). Sex Hormone Binding Globulin: Origin, Function and Clinical Significance. Ann. Clin. Biochem. 27, 532–541. 10.1177/000456329002700603. [PubMed: 2080856]
88. Towne B, Czerwinski SA, Demerath EW, Blangero J, Roche AF, and Siervogel RM (2005). Heritability of age at menarche in girls from the Fels Longitudinal Study. Am. J. Phys. Anthropol. 128, 210–219. 10.1002/ajpa.20106. [PubMed: 15779076]
89. Jahanfar S, Lye M-S, and Krishnarajah IS (2013). Genetic and environmental effects on age at menarche, and its relationship with reproductive health in twins. Indian J. Hum. Genet. 19, 245–250. 10.4103/0971-6866.116127. [PubMed: 24019629]
90. Perry JRB, Stolk L, Franceschini N, Lunetta KL, Zhai G, McArdle PF, Smith AV, Aspelund T, Bandinelli S, Boerwinkle E, et al. (2009). Meta-analysis of genome-wide association data identifies two loci influencing age at menarche. Nat. Genet. 41, 648–650. 10.1038/ng.386. [PubMed: 19448620]

91. Elks CE, Perry JRB, Sulem P, Chasman DI, Franceschini N, He C, Lunetta KL, Visser JA, Byrne EM, Cousminer DL, et al. (2010). Thirty new loci for age at menarche identified by a meta-analysis of genome-wide association studies. Nat. Genet. 42, 1077–1085. 10.1038/ng.714. [PubMed: 21102462]
92. Zhu H, Shyh-Chang N, Segrè AV, Shinoda G, Shah SP, Einhorn WS, Takeuchi A, Engreitz JM, Hagan JP, Kharas MG, et al. (2011). The Lin28/let-7 Axis Regulates Glucose Metabolism. Cell 147, 81–94. 10.1016/j.cell.2011.08.033. [PubMed: 21962509]
93. Anderson SE, Dallal GE, and Must A (2003). Relative Weight and Race Influence Average Age at Menarche: Results From Two Nationally Representative Surveys of US Girls Studied 25 Years Apart. Pediatrics 111, 844–850. 10.1542/peds.111.4.844. [PubMed: 12671122]
94. Swayzer DV, and Gerriets V (2023). Leuprolide. In StatPearls (StatPearls Publishing).
95. Colmenares A, Gunczler P, and Lanes R (2014). Higher prevalence of obesity and overweight without an adverse metabolic profile in girls with central precocious puberty compared to girls with early puberty, regardless of GnRH analogue treatment. Int. J. Pediatr. Endocrinol. 2014, 5. 10.1186/1687-9856-2014-5. [PubMed: 24742263]
96. Lazar L, Kauli R, Pertzelan A, and Phillip M (2002). Gonadotropin-suppressive therapy in girls with early and fast puberty affects the pace of puberty but not total pubertal growth or final height. J. Clin. Endocrinol. Metab. 87, 2090–2094. 10.1210/jcem.87.5.8481. [PubMed: 11994346]
97. Faienza MF, Brunetti G, Acquafredda A, Delvecchio M, Lonero A, Gaeta A, Suavo Bulzis P, Corica D, Velletri MR, De Luca F, et al. (2017). Metabolic Outcomes, Bone Health, and Risk of Polycystic Ovary Syndrome in Girls with Idiopathic Central Precocious Puberty Treated with Gonadotropin-Releasing Hormone Analogues. Horm. Res. Paediatr. 87, 162–169. 10.1159/000456546. [PubMed: 28391271]
98. Okoth K, Smith WP, Thomas GN, Nirantharakumar K, and Adderley NJ (2023). The association between menstrual cycle characteristics and cardiometabolic outcomes in later life: a retrospective matched cohort study of 704,743 women from the UK. BMC Med. 21, 104. 10.1186/s12916-023-02794-x. [PubMed: 36941638]
99. Soria-Contreras DC, Perng W, Rifas-Shiman SL, Hivert M-F, Chavarro JE, and Oken E (2022). Menstrual cycle length and adverse pregnancy outcomes among women in Project Viva. Paediatr. Perinat. Epidemiol. 36, 347–355. 10.1111/ppe.12866. [PubMed: 35172020]
100. Kiconco S, Teede HJ, Earnest A, Loxton D, and Joham AE (2022). Menstrual cycle regularity as a predictor for heart disease and diabetes: Findings from a large population-based longitudinal cohort study. Clin. Endocrinol. (Oxf.) 96, 605–616. 10.1111/cen.14640. [PubMed: 34817084]
101. Solomon CG, Hu FB, Dunaif A, Rich-Edwards J, Willett WC, Hunter DJ, Colditz GA, Speizer FE, and Manson JE (2001). Long or Highly Irregular Menstrual Cycles as a Marker for Risk of Type 2 Diabetes Mellitus. JAMA 286, 2421–2426. 10.1001/jama.286.19.2421. [PubMed: 11712937]
102. Solomon CG, Hu FB, Dunaif A, Rich-Edwards JE, Stampfer MJ, Willett WC, Speizer FE, and Manson JE (2002). Menstrual Cycle Irregularity and Risk for Future Cardiovascular Disease. 87, 2013–2017.
103. Wang Y-X, Shan Z, Arvizu M, Pan A, Manson JE, Missmer SA, Sun Q, and Chavarro JE (2020). Associations of Menstrual Cycle Characteristics Across the Reproductive Life Span and Lifestyle Factors With Risk of Type 2 Diabetes. JAMA Netw. Open 3, e2027928. 10.1001/jamanetworkopen.2020.27928. [PubMed: 33346844]
104. American College of Obstetricians and Gynecologists (2013). ACOG committee opinion no. 557: Management of acute abnormal uterine bleeding in nonpregnant reproductive-aged women. Obstet. Gynecol. 121, 891–896. 10.1097/01.AOG.0000428646.67925.9a. [PubMed: 23635706]
105. Munro MG, Critchley HOD, Fraser IS, and Committee, the F.M.D. (2018). The two FIGO systems for normal and abnormal uterine bleeding symptoms and classification of causes of abnormal uterine bleeding in the reproductive years: 2018 revisions. Int. J. Gynecol. Obstet. 143, 393–408. 10.1002/ijgo.12666.
106. Wang Y-X, Arvizu M, Rich-Edwards JW, Stuart JJ, Manson JE, Missmer SA, Pan A, and Chavarro JE (2020). Menstrual cycle regularity and length across the reproductive lifespan and risk of premature mortality: prospective cohort study. The BMJ 371, m3464. 10.1136/bmj.m3464. [PubMed: 32998909]

107. Cabre H, Moore S, Smith-Ryan A, and Hackney A (2022). Relative Energy Deficiency in Sport (RED-S): Scientific, Clinical, and Practical Implications for the Female Athlete. Dtsch. Z. Sportmed. 73, 225–234. 10.5960/dzsm.2022.546. [PubMed: 36479178]
108. Kazemijaliseh H, Ramezani Tehrani F, Behboudi-Gandevani S, Khalili D, Hosseinpanah F, and Azizi F (2017). A Population-Based Study of the Prevalence of Abnormal Uterine Bleeding and its Related Factors among Iranian Reproductive-Age Women: An Updated Data. Arch. Iran. Med. 20, 558–563. [PubMed: 29048917]
109. Mínguez-Alarcón L, Rifas-Shiman SL, Soria-Contreras DC, Hivert M-F, Shifren J, Oken E, and Chavarro JE (2022). Self-reported menstrual cycle length during reproductive years in relation to menopausal symptoms at midlife in Project Viva. Menopause N. Y. N 29, 1130–1136. 10.1097/GME.0000000000002042.
110. West S, Lashen H, Bloigu A, Franks S, Puukka K, Ruokonen A, Järvelin M-R, Tapanainen JS, and Morin-Papunen L (2014). Irregular menstruation and hyperandrogenaemia in adolescence are associated with polycystic ovary syndrome and infertility in later life: Northern Finland Birth Cohort 1986 study. Hum. Reprod. Oxf. Engl. 29, 2339–2351. 10.1093/humrep/deu200.
111. Escobar-Morreale HF (2014). Menstrual dysfunction—a proxy for insulin resistance in PCOS? Nat. Rev. Endocrinol. 10, 10–11. 10.1038/nrendo.2013.232. [PubMed: 24275746]
112. Brower M, Brennan K, Pall M, and Azziz R (2013). The Severity of Menstrual Dysfunction as a Predictor of Insulin Resistance in PCOS. J. Clin. Endocrinol. Metab. 98, E1967–E1971. 10.1210/jc.2013-2815. [PubMed: 24092831]
113. Soltani M, Tabatabaee HR, Saeidinejat S, Eslahi M, Yaghoobi H, Mazloumi E, Rajabi A, Ghasemi A, Keyghobadi N, Enayatrad M, et al. (2019). Assessing the risk factors before pregnancy of preterm births in Iran: a population-based case-control study. BMC Pregnancy Childbirth 19, 57. 10.1186/s12884-019-2183-0. [PubMed: 30727983]
114. Bonnesen B, Oddgeirsdóttir HL, Naver KV, Jørgensen FS, and Nilas L (2016). Women with minor menstrual irregularities have increased risk of preeclampsia and low birthweight in spontaneous pregnancies. Acta Obstet. Gynecol. Scand. 95, 88–92. 10.1111/aogs.12792. [PubMed: 26453458]
115. Haver MC, Locksmith GJ, and Emmet E (2003). Irregular menses: an independent risk factor for gestational diabetes mellitus. Am. J. Obstet. Gynecol. 188, 1189–1191. 10.1067/mob.2003.311. [PubMed: 12748474]
116. Cooper GS, Ephross SA, and Sandler DP (2000). Menstrual patterns and risk of adult-onset diabetes mellitus☙. J. Clin. Epidemiol.
117. Dunaif A (1997). Insulin resistance and the polycystic ovary syndrome: mechanism and implications for pathogenesis. Endocr. Rev. 18, 774–800. 10.1210/edrv.18.6.0318. [PubMed: 9408743]
118. Alvergne A, and Tabor VH (2018). Is Female Health Cyclical? Evolutionary Perspectives on Menstruation. Trends Ecol. Evol. 33, 399–414. 10.1016/j.tree.2018.03.006. [PubMed: 29778270]
119. Murri M, Luque-Ramírez M, Insenser M, Ojeda-Ojeda M, and Escobar-Morreale HF (2013). Circulating markers of oxidative stress and polycystic ovary syndrome (PCOS): a systematic review and meta-analysis. Hum. Reprod. Update 19, 268–288. 10.1093/humupd/dms059. [PubMed: 23303572]
120. Singh S, Pal N, Shubham S, Sarma DK, Verma V, Marotta F, and Kumar M (2023). Polycystic Ovary Syndrome: Etiology, Current Management, and Future Therapeutics. J. Clin. Med. 12, 1454. 10.3390/jcm12041454. [PubMed: 36835989]
121. Teede HJ, Misso ML, Costello MF, Dokras A, Laven J, Moran L, Piltonen T, Norman RJ, and International PCOS Network (2018). Recommendations from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome. Fertil. Steril. 110, 364–379. 10.1016/j.fertnstert.2018.05.004. [PubMed: 30033227]
122. Anagnostis P, Tarlatzis BC, and Kauffman RP (2018). Polycystic ovarian syndrome (PCOS): Long-term metabolic consequences. Metabolism 86, 33–43. 10.1016/j.metabol.2017.09.016. [PubMed: 29024702]
123. Teede HJ, Tay CT, Laven JJE, Dokras A, Moran LJ, Piltonen TT, Costello MF, Boivin J, Redman LM, Boyle JA, et al. (2023). Recommendations From the 2023 International Evidence-

based Guideline for the Assessment and Management of Polycystic Ovary Syndrome. J. Clin. Endocrinol. 00.

124. Sirmans SM, and Pate KA (2013). Epidemiology, diagnosis, and management of polycystic ovary syndrome. Clin. Epidemiol. 6, 1–13. 10.2147/CLEP.S37559. [PubMed: 24379699]
125. Ghazeeri GS, Nassar AH, Younes Z, and Awwad JT (2012). Pregnancy outcomes and the effect of metformin treatment in women with polycystic ovary syndrome: an overview. Acta Obstet. Gynecol. Scand. 91, 658–678. 10.1111/j.1600-0412.2012.01385.x. [PubMed: 22375613]
126. Lo JC, Yang J, Gunderson EP, Hararah MK, Gonzalez JR, and Ferrara A (2017). Risk of Type 2 Diabetes Mellitus following Gestational Diabetes Pregnancy in Women with Polycystic Ovary Syndrome. J. Diabetes Res. 2017, 1–5. 10.1155/2017/5250162.
127. Barber TM, and Franks S (2021). Obesity and polycystic ovary syndrome. Clin. Endocrinol. (Oxf.) 95, 531–541. 10.1111/cen.14421. [PubMed: 33460482]
128. Toosy S, Sodi R, and Pappachan JM (2018). Lean polycystic ovary syndrome (PCOS): an evidence-based practical approach. J. Diabetes Metab. Disord. 17, 277–285. 10.1007/s40200-018-0371-5. [PubMed: 30918863]
129. Rubin KH, Glintborg D, Nybo M, Abrahamsen B, and Andersen M (2017). Development and Risk Factors of Type 2 Diabetes in a Nationwide Population of Women With Polycystic Ovary Syndrome. J. Clin. Endocrinol. Metab. 102, 3848–3857. 10.1210/jc.2017-01354. [PubMed: 28938447]
130. Yildizhan B, Anik Ilhan G, and Pekin T (2016). The impact of insulin resistance on clinical, hormonal and metabolic parameters in lean women with polycystic ovary syndrome. J. Obstet. Gynaecol. 36, 893–896. 10.3109/01443615.2016.1168376. [PubMed: 27140180]
131. Pande AR, Guleria AK, Singh SD, Shukla M, and Dabadghao P (2017). β cell function and insulin resistance in lean cases with polycystic ovary syndrome. Gynecol. Endocrinol. 33, 877–881. 10.1080/09513590.2017.1342165. [PubMed: 28704124]
132. Lim SS, Davies MJ, Norman RJ, and Moran LJ (2012). Overweight, obesity and central obesity in women with polycystic ovary syndrome: a systematic review and meta-analysis. Hum. Reprod. Update 18, 618–637. 10.1093/humupd/dms030. [PubMed: 22767467]
133. Barber TM, Hanson P, Weickert MO, and Franks S (2019). Obesity and Polycystic Ovary Syndrome: Implications for Pathogenesis and Novel Management Strategies. Clin. Med. Insights Reprod. Health 13, 1179558119874042. 10.1177/1179558119874042. [PubMed: 31523137]
134. True CA, Takahashi DL, Burns SE, Mishler EC, Bond KR, Wilcox MC, Calhoun AR, Bader LA, Dean TA, Ryan ND, et al. (2017). Chronic combined hyperandrogenemia and western-style diet in young female rhesus macaques causes greater metabolic impairments compared to either treatment alone. Hum. Reprod. Oxf. Engl. 32, 1880–1891. 10.1093/humrep/dex246.
135. Varlamov O, Bishop CV, Handu M, Takahashi D, Srinivasan S, White A, and Roberts CT (2017). Combined androgen excess and Western-style diet accelerates adipose tissue dysfunction in young adult, female nonhuman primates. Hum. Reprod. Oxf. Engl. 32, 1892–1902. 10.1093/humrep/dex244.
136. Bishop CV, Mishler EC, Takahashi DL, Reiter TE, Bond KR, True CA, Slayden OD, and Stouffer RL (2018). Chronic hyperandrogenemia in the presence and absence of a western-style diet impairs ovarian and uterine structure/function in young adult rhesus monkeys. Hum. Reprod. Oxf. Engl. 33, 128–139. 10.1093/humrep/dex338.
137. Bishop CV, Stouffer RL, Takahashi DL, Mishler EC, Wilcox MC, Slayden OD, and True CA (2018). Chronic hyperandrogenemia and western-style diet beginning at puberty reduces fertility and increases metabolic dysfunction during pregnancy in young adult, female macaques. Hum. Reprod. Oxf. Engl. 33, 694–705. 10.1093/humrep/dey013.
138. Bishop CV, Takahashi D, Mishler E, Slayden OD, Roberts CT, Hennebold J, and True C (2021). Individual and combined effects of 5-year exposure to hyperandrogenemia and Western-style diet on metabolism and reproduction in female rhesus macaques. Hum. Reprod. Oxf. Engl. 36, 444–454. 10.1093/humrep/deaa321.
139. Szczuko M, Kikut J, Szczuko U, Szydłowska I, Nawrocka-Rutkowska J, Ziętek M, Verbanac D, and Saso L (2021). Nutrition Strategy and Life Style in Polycystic Ovary Syndrome—Narrative Review. Nutrients 13, 2452. 10.3390/nu13072452. [PubMed: 34371961]

140. Zhang X, Zheng Y, Guo Y, and Lai Z (2019). The Effect of Low Carbohydrate Diet on Polycystic Ovary Syndrome: A Meta-Analysis of Randomized Controlled Trials. Int. J. Endocrinol. 2019, 4386401. 10.1155/2019/4386401. [PubMed: 31885557]

141. Moran LJ, Misso ML, Wild RA, and Norman RJ (2010). Impaired glucose tolerance, type 2 diabetes and metabolic syndrome in polycystic ovary syndrome: a systematic review and meta-analysis. Hum. Reprod. Update 16, 347–363. 10.1093/humupd/dmq001. [PubMed: 20159883]

142. Morgan CL, Jenkins-Jones S, Currie CJ, and Rees DA (2012). Evaluation of Adverse Outcome in Young Women with Polycystic Ovary Syndrome *Versus* Matched, Reference Controls: A Retrospective, Observational Study. J. Clin. Endocrinol. Metab. 97, 3251–3260. 10.1210/jc.2012-1690. [PubMed: 22767635]

143. Villa J, and Pratley RE (2011). Adipose tissue dysfunction in polycystic ovary syndrome. Curr. Diab. Rep. 11, 179–184. 10.1007/s11892-011-0189-8. [PubMed: 21424395]

144. Diamanti-Kandarakis E, Papalou O, and Kandaraki EA (2019). The Role of Androgen Excess on Insulin Sensitivity in Women. Hyperandrogenism Women 53, 50–64. 10.1159/000494902.

145. Bhatti JS, Sehrawat A, Mishra J, Sidhu IS, Navik U, Khullar N, Kumar S, Bhatti GK, and Reddy PH (2022). Oxidative stress in the pathophysiology of type 2 diabetes and related complications: Current therapeutics strategies and future perspectives. Free Radic. Biol. Med. 184, 114–134. 10.1016/j.freeradbiomed.2022.03.019. [PubMed: 35398495]

146. Conway G, Dewailly D, Diamanti-Kandarakis E, Escobar-Morreale HF, Franks S, Gambineri A, Kelestimur F, Macut D, Micic D, Pasquali R, et al. The polycystic ovary syndrome: a position statement from the European Society of Endocrinology. EJE Clin. Transl. Endocrinol. Globe 171.

147. Legro RS, Arslanian SA, Ehrmann DA, Hoeger KM, Murad MH, Pasquali R, and Welt CK (2013). Diagnosis and Treatment of Polycystic Ovary Syndrome: An Endocrine Society Clinical Practice Guideline. J. Clin. Endocrinol. Metab. 98, 4565–4592. 10.1210/jc.2013-2350. [PubMed: 24151290]

148. Rotterdam ESHRE/ASRM-Sponsored PCOS consensus workshop group (2004). Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). Hum. Reprod. Oxf. Engl. 19, 41–47. 10.1093/humrep/deh098.

149. American College of Obstetricians and Gynecologists (2018). Polycystic Ovary Syndrome: ACOG Practice Bulletin, Number 194. Obstet. Gynecol. 131, e157. 10.1097/AOG.0000000000002656. [PubMed: 29794677]

150. Zeng Z, Liu F, and Li S (2017). Metabolic Adaptations in Pregnancy: A Review. Ann. Nutr. Metab. 70, 59–65. 10.1159/000459633. [PubMed: 28297696]

151. Hadden DR, and McLaughlin C (2009). Normal and abnormal maternal metabolism during pregnancy. Semin. Fetal. Neonatal Med. 14, 66–71. 10.1016/j.siny.2008.09.004. [PubMed: 18986856]

152. Gabbe SG, Niebyl JR, Simpson JL, Landon MB, Galan HL, Jauniaux ERM, Drisoll DA, Berghella V, and Grobman WA (2016). Obstetrics: Normal and Problem Pregnancies 7th ed. (Elsevier).

153. Ramos-Román MA (2011). Prolactin and lactation as modifiers of diabetes risk in gestational diabetes. Horm. Metab. Res. Horm. Stoffwechselforschung Horm. Metab. 43, 593–600. 10.1055/s-0031-1284353.

154. National Research Council, and Institute of Medicine (2010). Weight Gain During Pregnancy: Reexamining the Guidelines (National Academies Press).

155. Catalano PM, Hoegh M, Minium J, Huston-Presley L, Bernard S, Kalhan S, and Hauguel-De Mouzon S (2006). Adiponectin in human pregnancy: implications for regulation of glucose and lipid metabolism. Diabetologia 49, 1677–1685. 10.1007/s00125-006-0264-x. [PubMed: 16752186]

156. Ladyman SR, Khant Aung Z, and Grattan DR (2018). Impact of Pregnancy and Lactation on the Long-Term Regulation of Energy Balance in Female Mice. Endocrinology 159, 2324–2336. 10.1210/en.2018-00057. [PubMed: 29659786]

157. Ehrenberg HM, Huston-Presley L, and Catalano PM (2003). The influence of obesity and gestational diabetes mellitus on accretion and the distribution of adipose tissue in pregnancy. Am. J. Obstet. Gynecol. 189, 944–948. 10.1067/S0002-9378(03)00761-0. [PubMed: 14586331]

158. Smith DE, Lewis CE, Caveny JL, Perkins LL, Burke GL, and Bild DE (1994). Longitudinal changes in adiposity associated with pregnancy. The CARDIA Study. Coronary Artery Risk Development in Young Adults Study. JAMA 271, 1747–1751. [PubMed: 8196117]

159. Gunderson EP, Murtaugh MA, Lewis CE, Quesenberry CP, West DS, and Sidney S (2004). Excess gains in weight and waist circumference associated with childbearing: The Coronary Artery Risk Development in Young Adults Study (CARDIA). Int. J. Obes. Relat. Metab. Disord. J. Int. Assoc. Study Obes. 28, 525–535. 10.1038/sj.ijo.0802551.

160. Gunderson EP, Jacobs DR, Chiang V, Lewis CE, Tsai A, Quesenberry CP, and Sidney S (2009). Childbearing is associated with higher incidence of the metabolic syndrome among women of reproductive age controlling for measurements before pregnancy: the CARDIA study. Am. J. Obstet. Gynecol. 201, 177.e1–9. 10.1016/j.ajog.2009.03.031.

161. Modzelewski R, Stefanowicz-Rutkowska MM, Matuszewski W, and Bandurska-Stankiewicz EM (2022). Gestational Diabetes Mellitus-Recent Literature Review. J. Clin. Med. 11, 5736. 10.3390/jcm11195736. [PubMed: 36233604]

162. RYAN EA, and ENNS L (1988). Role of Gestational Hormones in the Induction of Insulin Resistance*. J. Clin. Endocrinol. Metab. 67, 341–347. 10.1210/jcem-67-2-341. [PubMed: 3292560]

163. Brewster S, Zinman B, Retnakaran R, and Floras JS (2013). Cardiometabolic consequences of gestational dysglycemia. J. Am. Coll. Cardiol. 62, 677–684. 10.1016/j.jacc.2013.01.080. [PubMed: 23524050]

164. Plows JF, Stanley JL, Baker PN, Reynolds CM, and Vickers MH (2018). The Pathophysiology of Gestational Diabetes Mellitus. Int. J. Mol. Sci. 19, 3342. 10.3390/ijms19113342. [PubMed: 30373146]

165. Chasan-Taber L (2016). It Is Time to View Pregnancy as a Stress Test. J. Womens Health 2002 25, 2–3. 10.1089/jwh.2015.5653.

166. Retnakaran R, Qi Y, Sermer M, Connelly PW, Hanley AJG, and Zinman B (2008). Glucose intolerance in pregnancy and future risk of pre-diabetes or diabetes. Diabetes Care 31, 2026–2031. 10.2337/dc08-0972. [PubMed: 18628572]

167. Retnakaran R, and Shah BR (2021). Impact of pregnancy on the trajectories of cardiovascular risk factors in women with and without gestational diabetes. Diabetes Obes. Metab. 23, 2364–2373. 10.1111/dom.14479. [PubMed: 34189830]

168. Kim C, Newton KM, and Knopp RH (2002). Gestational diabetes and the incidence of type 2 diabetes: a systematic review. Diabetes Care 25, 1862–1868. 10.2337/diacare.25.10.1862. [PubMed: 12351492]

169. Bellamy L, Casas J-P, Hingorani AD, and Williams D (2009). Type 2 diabetes mellitus after gestational diabetes: a systematic review and meta-analysis. Lancet Lond. Engl. 373, 1773–1779. 10.1016/S0140-6736(09)60731-5.

170. Miao Z-R, Wu H-H, Zhang Y-Z, Sun W-J, Lu D-F, Yang H-X, Zhang J-Q, and Guo X-H (2020). Evaluation of the gestational diabetes mellitus diagnostic criteria recommended by the international association of diabetes and pregnancy study group for long-term maternal postpartum outcomes in mainland China. Medicine (Baltimore) 99, e19242. 10.1097/MD.0000000000019242. [PubMed: 32080127]

171. Lowe WL, Lowe LP, Kuang A, Catalano PM, Nodzenski M, Talbot O, Tam W-H, Sacks DA, McCance D, Linder B, et al. (2019). Maternal glucose levels during pregnancy and childhood adiposity in the Hyperglycemia and Adverse Pregnancy Outcome Follow-up Study. Diabetologia 62, 598–610. 10.1007/s00125-018-4809-6. [PubMed: 30648193]

172. Lowe LP, Perak AM, Kuang A, Lloyd-Jones DM, Sacks DA, Deerochanawong C, Maresh M, Ma RC, Lowe WL, Metzger BE, et al. (2022). Associations of glycemia and lipid levels in pregnancy with dyslipidemia 10–14 years later: The HAPO follow-up study. Diabetes Res. Clin. Pract. 185, 109790. 10.1016/j.diabres.2022.109790. [PubMed: 35192911]

173. Kramer CK, Campbell S, and Retnakaran R (2019). Gestational diabetes and the risk of cardiovascular disease in women: a systematic review and meta-analysis. Diabetologia 62, 905–914. 10.1007/s00125-019-4840-2. [PubMed: 30843102]

174. Powe CE, Allard C, Battista M-C, Doyon M, Bouchard L, Ecker JL, Perron P, Florez JC, Thadhani R, and Hivert M-F (2016). Heterogeneous Contribution of Insulin Sensitivity and Secretion Defects to Gestational Diabetes Mellitus. Diabetes Care 39, 1052–1055. 10.2337/dc15-2672. [PubMed: 27208340]

175. Madsen LR, Gibbons KS, Ma RCW, Tam WH, Catalano PM, Sacks DA, Lowe J, and McIntyre HD (2021). Do variations in insulin sensitivity and insulin secretion in pregnancy predict differences in obstetric and neonatal outcomes? Diabetologia 64, 304–312. 10.1007/s00125-020-05323-0. [PubMed: 33156358]

176. Ratner RE, Christophi CA, Metzger BE, Dabelea D, Bennett PH, Pi-Sunyer X, Fowler S, Kahn SE, and Diabetes Prevention Program Research Group (2008). Prevention of diabetes in women with a history of gestational diabetes: effects of metformin and lifestyle interventions. J. Clin. Endocrinol. Metab. 93, 4774–4779. 10.1210/jc.2008-0772. [PubMed: 18826999]

177. Yew TW, Chi C, Chan S-Y, van Dam RM, Whitton C, Lim CS, Foong PS, Fransisca W, Teoh CL, Chen J, et al. (2021). A Randomized Controlled Trial to Evaluate the Effects of a Smartphone Application-Based Lifestyle Coaching Program on Gestational Weight Gain, Glycemic Control, and Maternal and Neonatal Outcomes in Women With Gestational Diabetes Mellitus: The SMART-GDM Study. Diabetes Care 44, 456–463. 10.2337/dc20-1216. [PubMed: 33184151]

178. Brown J, Alwan NA, West J, Brown S, McKinlay CJ, Farrar D, and Crowther CA (2017). Lifestyle interventions for the treatment of women with gestational diabetes. Cochrane Database Syst. Rev. 5, CD011970. 10.1002/14651858.CD011970.pub2. [PubMed: 28472859]

179. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, Nathan DM, and Diabetes Prevention Program Research Group (2002). Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N. Engl. J. Med. 346, 393–403. 10.1056/NEJMoa012512. [PubMed: 11832527]

180. Ratner RE, Christophi CA, Metzger BE, Dabelea D, Bennett PH, Pi-Sunyer X, Fowler S, Kahn SE, and Diabetes Prevention Program Research Group (2008). Prevention of diabetes in women with a history of gestational diabetes: effects of metformin and lifestyle interventions. J. Clin. Endocrinol. Metab. 93, 4774–4779. 10.1210/jc.2008-0772. [PubMed: 18826999]

181. Aroda VR, Christophi CA, Edelstein SL, Zhang P, Herman WH, Barrett-Connor E, Delahanty LM, Montez MG, Ackermann RT, Zhuo X, et al. (2015). The effect of lifestyle intervention and metformin on preventing or delaying diabetes among women with and without gestational diabetes: the Diabetes Prevention Program outcomes study 10-year follow-up. J. Clin. Endocrinol. Metab. 100, 1646–1653. 10.1210/jc.2014-3761. [PubMed: 25706240]

182. Aroda VR, Knowler WC, Crandall JP, Perreault L, Edelstein SL, Jeffries SL, Molitch ME, Pi-Sunyer X, Darwin C, Heckman-Stoddard BM, et al. (2017). Metformin for diabetes prevention: insights gained from the Diabetes Prevention Program/Diabetes Prevention Program Outcomes Study. Diabetologia 60, 1601–1611. 10.1007/s00125-017-4361-9. [PubMed: 28770322]

183. Santos S, Voerman E, Amiano P, Barros H, Beilin LJ, Bergström A, Charles M-A, Chatzi L, Chevrier C, Chrousos GP, et al. (2019). Impact of maternal body mass index and gestational weight gain on pregnancy complications: an individual participant data meta-analysis of European, North American and Australian cohorts. BJOG Int. J. Obstet. Gynaecol. 126, 984–995. 10.1111/1471-0528.15661.

184. Berggren EK, Groh-Wargo S, Presley L, Hauguel-de Mouzon S, and Catalano PM (2016). Maternal fat, but not lean, mass is increased among overweight/obese women with excess gestational weight gain. Am. J. Obstet. Gynecol. 214, 745.e1–5. 10.1016/j.ajog.2015.12.026.

185. Einstein FH, Fishman S, Muzumdar RH, Yang XM, Atzmon G, and Barzilai N (2008). Accretion of visceral fat and hepatic insulin resistance in pregnant rats. Am. J. Physiol. Endocrinol. Metab. 294, E451–455. 10.1152/ajpendo.00570.2007. [PubMed: 18073320]

186. Groth SW, LaLonde A, Wu T, and Fernandez ID (2018). Obesity candidate genes, gestational weight gain, and body weight changes in pregnant women. Nutr. Burbank Los Angel. Cty. Calif 48, 61–66. 10.1016/j.nut.2017.11.008.

187. Santos KD, Rosado EL, da Fonseca ACP, Belfort GP, da Silva LBG, Ribeiro-Alves M, Zembrzuski VM, Martínez JA, and Saunders C (2022). FTO and ADRB2 Genetic Polymorphisms Are Risk Factors for Earlier Excessive Gestational Weight Gain in Pregnant

Women with Pregestational Diabetes Mellitus: Results of a Randomized Nutrigenetic Trial. Nutrients 14, 1050. 10.3390/nu14051050. [PubMed: 35268025]

188. MacDonald SC, Bodnar LM, Himes KP, and Hutcheon JA (2017). Patterns of Gestational Weight Gain in Early Pregnancy and Risk of Gestational Diabetes Mellitus. Epidemiol. Camb. Mass 28, 419–427. 10.1097/EDE.0000000000000629.
189. Yin A, Tian F, Wu X, Chen Y, Liu K, Tong J, Guan X, Zhang H, Wu L, and Niu J (2022). Excessive gestational weight gain in early pregnancy and insufficient gestational weight gain in middle pregnancy increased risk of gestational diabetes mellitus. Chin. Med. J. (Engl.) 135, 1057–1063. 10.1097/CM9.0000000000001972. [PubMed: 35184065]
190. Moore Simas TA, Waring ME, Callaghan K, Leung K, Ward Harvey M, Buabbud A, and Chasan-Taber L (2019). Weight gain in early pregnancy and risk of gestational diabetes mellitus among Latinas. Diabetes Metab. 45, 26–31. 10.1016/j.diabet.2017.10.006. [PubMed: 29129541]
191. Rong K, Yu K, Han X, Szeto IMY, Qin X, Wang J, Ning Y, Wang P, and Ma D (2015). Pre-pregnancy BMI, gestational weight gain and postpartum weight retention: a meta-analysis of observational studies. Public Health Nutr. 18, 2172–2182. 10.1017/S1368980014002523. [PubMed: 25411780]
192. Sawangkum P, and Louis JM (2020). Gestational Weight Gain: Achieving a Healthier Weight Between Pregnancies. Obstet. Gynecol. Clin. North Am. 47, 397–407. 10.1016/j.ogc.2020.04.003. [PubMed: 32762925]
193. Weiss M, Yakusheva O, and Kapinos K (2019). Effects of Women's Weight Changes on Adverse Outcomes in a Second Pregnancy. J. Obstet. Gynecol. Neonatal Nurs. JOGNN 48, 615–626. 10.1016/j.jogn.2019.08.006.
194. Bogaerts A, Van den Bergh BRH, Ameye L, Witters I, Martens E, Timmerman D, and Devlieger R (2013). Interpregnancy weight change and risk for adverse perinatal outcome. Obstet. Gynecol. 122, 999–1009. 10.1097/AOG.0b013e3182a7f63e. [PubMed: 24104777]
195. Linné Y, Dye L, Barkeling B, and Rössner S (2003). Weight development over time in parous women--the SPAWN study--15 years follow-up. Int. J. Obes. Relat. Metab. Disord. J. Int. Assoc. Study Obes. 27, 1516–1522. 10.1038/sj.ijo.0802441.
196. Nehring I, Schmoll S, Beyerlein A, Hauner H, and von Kries R (2011). Gestational weight gain and long-term postpartum weight retention: a meta-analysis. Am. J. Clin. Nutr. 94, 1225–1231. 10.3945/ajcn.111.015289. [PubMed: 21918221]
197. Hill B, McPhie S, and Skouteris H (2016). The Role of Parity in Gestational Weight Gain and Postpartum Weight Retention. Womens Health Issues Off. Publ. Jacobs Inst. Womens Health 26, 123–129. 10.1016/j.whi.2015.09.012.
198. Rooney BL, Schauberger CW, and Mathiason MA (2005). Impact of perinatal weight change on long-term obesity and obesity-related illnesses. Obstet. Gynecol. 106, 1349–1356. 10.1097/01.AOG.0000185480.09068.4a. [PubMed: 16319262]
199. Walter JR, Perng W, Kleinman KP, Rifas-Shiman SL, Rich-Edwards JW, and Oken E (2015). Associations of trimester-specific gestational weight gain with maternal adiposity and systolic blood pressure at 3 and 7 years postpartum. Am. J. Obstet. Gynecol. 212, 499.e1–12. 10.1016/j.ajog.2014.11.012.
200. Mustafa HJ, Seif K, Javinani A, Aghajani F, Orlinsky R, Alvarez MV, Ryan A, and Crimmins S (2022). Gestational weight gain below instead of within the guidelines per class of maternal obesity: a systematic review and meta-analysis of obstetrical and neonatal outcomes. Am. J. Obstet. Gynecol. MFM 4, 100682. 10.1016/j.ajogmf.2022.100682. [PubMed: 35728780]
201. Sussman D, Ellegood J, and Henkelman M (2013). A gestational ketogenic diet alters maternal metabolic status as well as offspring physiological growth and brain structure in the neonatal mouse. BMC Pregnancy Childbirth 13, 198. 10.1186/1471-2393-13-198. [PubMed: 24168053]
202. Voerman E, Santos S, Patro Golab B, Amiano P, Ballester F, Barros H, Bergström A, Charles M-A, Chatzi L, Chevrier C, et al. (2019). Maternal body mass index, gestational weight gain, and the risk of overweight and obesity across childhood: An individual participant data meta-analysis. PLoS Med. 16, e1002744. 10.1371/journal.pmed.1002744. [PubMed: 30742624]

203. Nichols AR, Burns N, Xu F, Foster SF, Rickman R, Hedderson MM, and Widen EM (2023). Novel approaches to examining weight changes in pregnancies affected by obesity. Am. J. Clin. Nutr. 10.1016/j.ajcnut.2023.03.001.

204. Zhu Y, Zhu H, Dang Q, Yang Q, Huang D, Zhang Y, Cai X, and Yu H (2021). Changes in serum TG levels during pregnancy and their association with postpartum hypertriglyceridemia: a population-based prospective cohort study. Lipids Health Dis. 20, 119. 10.1186/s12944-021-01549-y. [PubMed: 34587968]

205. Pham A, Polic A, Nguyen L, and Thompson JL (2022). Statins in Pregnancy: Can We Justify Early Treatment of Reproductive Aged Women? Curr. Atheroscler. Rep. 24, 663–670. 10.1007/s11883-022-01039-1. [PubMed: 35699821]

206. Adank MC, Benschop L, Peterbroers KR, Smak Gregoor AM, Kors AW, Mulder MT, Schalekamp-Timmermans S, Roeters Van Lennep JE, and Steegers EAP (2019). Is maternal lipid profile in early pregnancy associated with pregnancy complications and blood pressure in pregnancy and long term postpartum? Am. J. Obstet. Gynecol. 221, 150.e1–150.e13. 10.1016/j.ajog.2019.03.025.

207. Adank MC, Benschop L, van Streun SP, Smak Gregoor AM, Mulder MT, Steegers EAP, Schalekamp-Timmermans S, and Roeters van Lennep JE (2020). Gestational lipid profile as an early marker of metabolic syndrome in later life: a population-based prospective cohort study. BMC Med. 18, 394. 10.1186/s12916-020-01868-4. [PubMed: 33353543]

208. Eid J, Rood KM, and Costantine MM (2023). Aspirin and Pravastatin for Preeclampsia Prevention in High-Risk Pregnancy. Obstet. Gynecol. Clin. North Am. 50, 79–88. 10.1016/j.ogc.2022.10.005. [PubMed: 36822711]

209. Domali E, and Messinis IE (2002). Leptin in pregnancy. J. Matern.-Fetal Neonatal Med. Off. J. Eur. Assoc. Perinat. Med. Fed. Asia Ocean. Perinat. Soc. Int. Soc. Perinat. Obstet. 12, 222–230. 10.1080/jmf.12.4.222.230.

210. Bao W, Baecker A, Song Y, Kiely M, Liu S, and Zhang C (2015). Adipokine levels during the first or early second trimester of pregnancy and subsequent risk of gestational diabetes mellitus: A systematic review. Metabolism. 64, 756–764. 10.1016/j.metabol.2015.01.013. [PubMed: 25749468]

211. Fu L, Ramos-Roman MA, and Deng Y (2022). Metabolic Adaptation in Lactation: Insulin-dependent and - independent Glycemic Control. J. Transl. Intern. Med. 10, 191–196. 10.2478/jtim-2022-0036.

212. Sámano R, Martínez-Rojano H, Chico-Barba G, Godínez-Martínez E, Sánchez-Jiménez B, Montiel-Ojeda D, and Tolentino M (2017). Serum Concentration of Leptin in Pregnant Adolescents Correlated with Gestational Weight Gain, Postpartum Weight Retention and Newborn Weight/Length. Nutrients 9, 1067. 10.3390/nu9101067. [PubMed: 28953229]

213. Kim K-H, Kim YJ, Lee S, Oh SW, Lee K, Park Y, Kim HJ, and Kwak H (2008). Evaluation of plasma leptin levels & BMI as predictor of postpartum weight retention. Indian J. Med. Res. 128, 595–600. [PubMed: 19179678]

214. Jara A, Dreher M, Porter K, and Christian LM (2020). The association of maternal obesity and race with serum adipokines in pregnancy and postpartum: Implications for gestational weight gain and infant birth weight. Brain Behav. Immun. - Health 3, 100053. 10.1016/j.bbih.2020.100053. [PubMed: 34589839]

215. Angelidis G, Dafopoulos K, Messini CI, Valotassiou V, Tsikouras P, Vrachnis N, Psimadas D, Georgoulias P, and Messinis IE (2013). The emerging roles of adiponectin in female reproductive system-associated disorders and pregnancy. Reprod. Sci. Thousand Oaks Calif 20, 872–881. 10.1177/1933719112468954.

216. Mazaki-Tovi S, Kanety H, Pariente C, Hemi R, Wiser A, Schiff E, and Sivan E (2007). Maternal serum adiponectin levels during human pregnancy. J. Perinatol. Off. J. Calif. Perinat. Assoc. 27, 77–81. 10.1038/sj.jp.7211639.

217. Fried RL, Mayol NL, McDade TW, and Kuzawa CW (2017). Maternal metabolic adaptations to pregnancy among young women in Cebu, Philippines. Am. J. Hum. Biol. Off. J. Hum. Biol. Counc 29. 10.1002/ajhb.23011.

218. Mazaki-Tovi S, Kanety H, Pariente C, Hemi R, Yissachar E, Schiff E, Cohen O, and Sivan E (2011). Insulin sensitivity in late gestation and early postpartum period: the role of circulating

maternal adipokines. Gynecol. Endocrinol. Off. J. Int. Soc. Gynecol. Endocrinol. 27, 725–731. 10.3109/09513590.2010.500426.

219. Lee D-H, Lim JA, Kim JH, Kwak SH, Choi SH, and Jang HC (2021). Longitudinal Changes of High Molecular Weight Adiponectin are Associated with Postpartum Development of Type 2 Diabetes Mellitus in Patients with Gestational Diabetes Mellitus. Endocrinol. Metab. Seoul Korea 36, 114–122. 10.3803/EnM.2020.831.
220. Vitoratos N, Deliveliotou A, Vlahos NF, Mastorakos G, Papadias K, Botsis D, and Creatsas GK (2008). Serum adiponectin during pregnancy and postpartum in women with gestational diabetes and normal controls. Gynecol. Endocrinol. Off. J. Int. Soc. Gynecol. Endocrinol. 24, 614–619. 10.1080/09513590802342866.
221. Atarod Z, Ebrahemian M, Jafarpour H, Moraghebi M, and Sharafkhani E (2020). Association between serum adiponectin levels with gestational diabetes mellitus and postpartum metabolic syndrome:A case control study. Endocr. Regul. 54, 119–125. 10.2478/enr-2020-0014. [PubMed: 32597154]
222. Retnakaran A, and Retnakaran R (2012). Adiponectin in pregnancy: implications for health and disease. Curr. Med. Chem. 19, 5444–5450. 10.2174/092986712803833227. [PubMed: 22876921]
223. Durnwald CP, Downes K, Leite R, Elovitz M, and Parry S (2018). Predicting persistent impaired glucose tolerance in patients with gestational diabetes: The role of high sensitivity CRP and adiponectin. Diabetes Metab. Res. Rev 34. 10.1002/dmrr.2958.
224. Mendoza-Herrera K, Florio AA, Moore M, Marrero A, Tamez M, Bhupathiraju SN, and Mattei J (2021). The Leptin System and Diet: A Mini Review of the Current Evidence. Front. Endocrinol. 12, 749050. 10.3389/fendo.2021.749050.
225. Bidulescu A, Dinh PC, Sarwary S, Forsyth E, Luetke MC, King DB, Liu J, Davis SK, and Correa A (2020). Associations of leptin and adiponectin with incident type 2 diabetes and interactions among African Americans: the Jackson heart study. BMC Endocr. Disord. 20, 31. 10.1186/s12902-020-0511-z. [PubMed: 32131811]
226. Li S, Shin HJ, Ding EL, and van Dam RM (2009). Adiponectin levels and risk of type 2 diabetes: a systematic review and meta-analysis. JAMA 302, 179–188. 10.1001/jama.2009.976. [PubMed: 19584347]
227. Stuebe AM, and Rich-Edwards JW (2009). The reset hypothesis: lactation and maternal metabolism. Am. J. Perinatol. 26, 81–88. 10.1055/s-0028-1103034. [PubMed: 19031350]
228. Gunderson EP (2014). Impact of breastfeeding on maternal metabolism: implications for women with gestational diabetes. Curr. Diab. Rep. 14, 460. 10.1007/s11892-013-0460-2. [PubMed: 24402327]
229. Stuebe AM, Kleinman K, Gillman MW, Rifas-Shiman SL, Gunderson EP, and Rich-Edwards J (2010). Duration of lactation and maternal metabolism at 3 years postpartum. J. Womens Health 2002 19, 941–950. 10.1089/jwh.2009.1660.
230. Stuebe AM, Mantzoros C, Kleinman K, Gillman MW, Rifas-Shiman S, Gunderson EP, and Rich-Edwards J (2011). Duration of lactation and maternal adipokines at 3 years postpartum. Diabetes 60, 1277–1285. 10.2337/db10-0637. [PubMed: 21350085]
231. Stuebe AM, Rich-Edwards JW, Willett WC, Manson JE, and Michels KB (2005). Duration of lactation and incidence of type 2 diabetes. JAMA 294, 2601–2610. 10.1001/jama.294.20.2601. [PubMed: 16304074]
232. Gunderson EP, Jacobs DR, Chiang V, Lewis CE, Feng J, Quesenberry CP, and Sidney S (2010). Duration of lactation and incidence of the metabolic syndrome in women of reproductive age according to gestational diabetes mellitus status: a 20-Year prospective study in CARDIA (Coronary Artery Risk Development in Young Adults). Diabetes 59, 495–504. 10.2337/db09-1197. [PubMed: 19959762]
233. Bijlholt M, Ameye L, van Uytsel H, Devlieger R, and Bogaerts A (2021). Evolution of Postpartum Weight and Body Composition after Excessive Gestational Weight Gain: The Role of Lifestyle Behaviors-Data from the INTERACT Control Group. Int. J. Environ. Res. Public. Health 18, 6344. 10.3390/ijerph18126344. [PubMed: 34208162]

234. Oken E, Taveras EM, Popoola FA, Rich-Edwards JW, and Gillman MW (2007). Television, walking, and diet: associations with postpartum weight retention. Am. J. Prev. Med. 32, 305–311. 10.1016/j.amepre.2006.11.012. [PubMed: 17383561]

235. Guo J, Chen J-L, Whittemore R, and Whitaker E (2016). Postpartum Lifestyle Interventions to Prevent Type 2 Diabetes Among Women with History of Gestational Diabetes: A Systematic Review of Randomized Clinical Trials. J. Womens Health 2002 25, 38–49. 10.1089/jwh.2015.5262.

236. Li N, Yang Y, Cui D, Li C, Ma RCW, Li J, and Yang X (2021). Effects of lifestyle intervention on long-term risk of diabetes in women with prior gestational diabetes: A systematic review and meta-analysis of randomized controlled trials. Obes. Rev. Off. J. Int. Assoc. Study Obes. 22, e13122. 10.1111/obr.13122.

237. Hoga L, Rodolpho J, Gonçalves B, and Quirino B (2015). Women's experience of menopause: a systematic review of qualitative evidence. JBI Evid. Synth. 13, 250.

238. Okeke T, Anyaehie U, and Ezenyeaku C (2013). Premature Menopause. Ann. Med. Health Sci. Res. 3, 90–95. 10.4103/2141-9248.109458. [PubMed: 23634337]

239. National Institute on Aging. What Is Menopause? https://www.nia.nih.gov/health/what-menopause.

240. El Khoudary SR, Greendale G, Crawford SL, Avis NE, Brooks MM, Thurston RC, Karvonen-Gutierrez C, Waetjen LE, and Matthews K (2019). The menopause transition and women's health at midlife: a progress report from the Study of Women's Health Across the Nation (SWAN). Menopause N. Y. N 26, 1213–1227. 10.1097/GME.0000000000001424.

241. Rapkin AJ (2007). Vasomotor symptoms in menopause: physiologic condition and central nervous system approaches to treatment. Am. J. Obstet. Gynecol. 196, 97–106. 10.1016/j.ajog.2006.05.056. [PubMed: 17306645]

242. Stachowiak G, Pertyński T, and Pertyńska-Marczewska M (2015). Metabolic disorders in menopause. Przegląd Menopauzalny Menopause Rev. 14, 59–64. 10.5114/pm.2015.50000.

243. Bleil ME, Gregorich SE, McConnell D, Rosen MP, and Cedars MI (2013). Does accelerated reproductive aging underlie premenopausal risk for cardiovascular disease? Menopause N. Y. N 20, 1139–1146. 10.1097/GME.0b013e31828950fa.

244. Yan Z, Cai M, Han X, Chen Q, and Lu H (2023). The Interaction Between Age and Risk Factors for Diabetes and Prediabetes: A Community-Based Cross-Sectional Study. Diabetes Metab. Syndr. Obes. 16, 85–93. 10.2147/DMSO.S390857. [PubMed: 36760587]

245. Anagnostis P, Christou K, Artzouchaltzi A-M, Gkekas NK, Kosmidou N, Siolos P, Paschou SA, Potoupnis M, Kenanidis E, Tsiridis E, et al. (2019). Early menopause and premature ovarian insufficiency are associated with increased risk of type 2 diabetes: a systematic review and meta-analysis. Eur. J. Endocrinol. 180, 41–50. 10.1530/EJE-18-0602. [PubMed: 30400047]

246. Peterlik M, and Cross HS (2009). Vitamin D and calcium insufficiency-related chronic diseases: molecular and cellular pathophysiology. Eur. J. Clin. Nutr. 63, 1377–1386. 10.1038/ejcn.2009.105. [PubMed: 19724293]

247. Rossi R, Origliani G, and Modena MG (2004). Transdermal 17-β-Estradiol and Risk of Developing Type 2 Diabetes in a Population of Healthy, Nonobese Postmenopausal Women. Diabetes Care 27, 645–649. 10.2337/diacare.27.3.645. [PubMed: 14988279]

248. Randolph JF, Zheng H, Sowers MR, Crandall C, Crawford S, Gold EB, and Vuga M (2011). Change in Follicle-Stimulating Hormone and Estradiol Across the Menopausal Transition: Effect of Age at the Final Menstrual Period. J. Clin. Endocrinol. Metab. 96, 746–754. 10.1210/jc.2010-1746. [PubMed: 21159842]

249. Stefanska A, Cembrowska P, Kubacka J, Kuligowska –Prusinska M, and Sypniewska G (2019). Gonadotropins and Their Association with the Risk of Prediabetes and Type 2 Diabetes in Middle-Aged Postmenopausal Women. Dis. Markers 2019, e2384069. 10.1155/2019/2384069.

250. Bertone-Johnson ER, Virtanen JK, Niskanen L, Nurmi T, Ronkainen K, Voutilainen S, Mursu J, Kauhanen J, and Tuomainen T-P (2017). Association of follicle-stimulating hormone levels and risk of type 2 diabetes in older postmenopausal women. Menopause 24, 796. 10.1097/GME.0000000000000834. [PubMed: 28141661]

251. Wang N, Kuang L, Han B, Li Q, Chen Y, Zhu C, Chen Y, Xia F, Cang Z, Zhu C, et al. (2016). Follicle-stimulating hormone associates with prediabetes and diabetes in postmenopausal women. Acta Diabetol. 53, 227–236. 10.1007/s00592-015-0769-1. [PubMed: 25959422]
252. Danaei G, Finucane MM, Lu Y, Singh GM, Cowan MJ, Paciorek CJ, Lin JK, Farzadfar F, Khang Y-H, Stevens GA, et al. (2011). National, regional, and global trends in fasting plasma glucose and diabetes prevalence since 1980: systematic analysis of health examination surveys and epidemiological studies with 370 country-years and 2·7 million participants. The Lancet 378, 31–40. 10.1016/S0140-6736(11)60679-X.
253. Yan H, Yang W, Zhou F, Li X, Pan Q, Shen Z, Han G, Newell-Fugate A, Tian Y, Majeti R, et al. (2019). Estrogen Improves Insulin Sensitivity and Suppresses Gluconeogenesis via the Transcription Factor Foxo1. Diabetes 68, 291–304. 10.2337/db18-0638. [PubMed: 30487265]
254. Gorres BK, Bomhoff GL, Morris JK, and Geiger PC (2011). In vivo stimulation of oestrogen receptor α increases insulin-stimulated skeletal muscle glucose uptake. J. Physiol. 589, 2041–2054. 10.1113/jphysiol.2010.199018. [PubMed: 21486807]
255. Moreno M, Ordoñez P, Alonso A, Díaz F, Tolivia J, and González C (2010). Chronic 17beta-estradiol treatment improves skeletal muscle insulin signaling pathway components in insulin resistance associated with aging. Age Dordr. Neth. 32, 1–13. 10.1007/s11357-009-9095-2.
256. Matute ML, and Kalkhoff RK (1973). Sex steroid influence on hepatic gluconeogenesis and glucogen formation. Endocrinology 92, 762–768. 10.1210/endo-92-3-762. [PubMed: 4701480]
257. Bryzgalova G, Gao H, Ahren B, Zierath JR, Galuska D, Steiler TL, Dahlman-Wright K, Nilsson S, Gustafsson J-A, Efendic S, et al. (2006). Evidence that oestrogen receptor-alpha plays an important role in the regulation of glucose homeostasis in mice: insulin sensitivity in the liver. Diabetologia 49, 588–597. 10.1007/s00125-005-0105-3. [PubMed: 16463047]
258. Qiu S, Vazquez JT, Boulger E, Liu H, Xue P, Hussain MA, and Wolfe A (2017). Hepatic estrogen receptor α is critical for regulation of gluconeogenesis and lipid metabolism in males. Sci. Rep. 7, 1661. 10.1038/s41598-017-01937-4. [PubMed: 28490809]
259. Thurston RC, and Joffe H (2011). Vasomotor Symptoms and Menopause: Findings from the Study of Women's Health Across the Nation. Obstet. Gynecol. Clin. North Am. 38, 489–501. 10.1016/j.ogc.2011.05.006. [PubMed: 21961716]
260. Kritz-Silverstein D, Goldani Von Mühlen D, and Barrett-Connor E (2000). Prevalence and clustering of menopausal symptoms in older women by hysterectomy and oophorectomy status. J. Womens Health Gend. Based Med. 9, 747–755. 10.1089/15246090050147727. [PubMed: 11025867]
261. Gartoulla P, Islam MR, Bell RJ, and Davis SR (2014). Prevalence of menopausal symptoms in Australian women at midlife: a systematic review. Climacteric J. Int. Menopause Soc. 17, 529–539. 10.3109/13697137.2013.865721.
262. Rödström K, Bengtsson C, Lissner L, Milsom I, Sundh V, and Björkelund C (2002). A longitudinal study of the treatment of hot flushes: the population study of women in Gothenburg during a quarter of a century. Menopause N. Y. N 9, 156–161. 10.1097/00042192-200205000-00003.
263. Faubion SS, Kuhle CL, Shuster LT, and Rocca WA (2015). Long-term health consequences of premature or early menopause and considerations for management. Climacteric J. Int. Menopause Soc. 18, 483–491. 10.3109/13697137.2015.1020484.
264. Woods NF, and Mitchell ES (2016). The Seattle Midlife Women's Health Study: a longitudinal prospective study of women during the menopausal transition and early postmenopause. Womens Midlife Health 2, 6. 10.1186/s40695-016-0019-x. [PubMed: 30766702]
265. Kaufert PA (1984). Women and their health in the middle years: a Manitoba project. Soc. Sci. Med. 1982 18, 279–281. 10.1016/0277-9536(84)90091-1.
266. McKinlay JB, McKinlay SM, and Brambilla DJ (1987). Health status and utilization behavior associated with menopause. Am. J. Epidemiol. 125, 110–121. 10.1093/oxfordjournals.aje.a114492. [PubMed: 3788939]
267. Matthews KA, Meilahn E, Kuller LH, Kelsey SF, Caggiula AW, and Wing RR (1989). Menopause and risk factors for coronary heart disease. N. Engl. J. Med. 321, 641–646. 10.1056/NEJM198909073211004. [PubMed: 2488072]

268. Guthrie JR, Dennerstein L, Taffe JR, Lehert P, and Burger HG (2004). The menopausal transition: a 9-year prospective population-based study. The Melbourne Women's Midlife Health Project. Climacteric J. Int. Menopause Soc. 7, 375–389. 10.1080/13697130400012163.

269. Benjamin EJ, Muntner P, Alonso A, Bittencourt MS, Callaway CW, Carson AP, Chamberlain AM, Chang AR, Cheng S, Das SR, et al. (2019). Heart Disease and Stroke Statistics-2019 Update: A Report From the American Heart Association. Circulation 139, e56–e528. 10.1161/CIR.0000000000000659. [PubMed: 30700139]

270. Matthews KA, Crawford SL, Chae CU, Everson-Rose SA, Sowers MF, Sternfeld B, and Sutton-Tyrrell K (2009). Are changes in cardiovascular disease risk factors in midlife women due to chronological aging or to the menopausal transition? J. Am. Coll. Cardiol. 54, 2366–2373. 10.1016/j.jacc.2009.10.009. [PubMed: 20082925]

271. Janssen I, Powell LH, Crawford S, Lasley B, and Sutton-Tyrrell K (2008). Menopause and the metabolic syndrome: the Study of Women's Health Across the Nation. Arch. Intern. Med. 168, 1568–1575. 10.1001/archinte.168.14.1568. [PubMed: 18663170]

272. El Khoudary SR, Shields KJ, Janssen I, Hanley C, Budoff MJ, Barinas-Mitchell E, Everson-Rose SA, Powell LH, and Matthews KA (2015). Cardiovascular Fat, Menopause, and Sex Hormones in Women: The SWAN Cardiovascular Fat Ancillary Study. J. Clin. Endocrinol. Metab. 100, 3304–3312. 10.1210/JC.2015-2110. [PubMed: 26176800]

273. El Khoudary SR, Shields KJ, Janssen I, Budoff MJ, Everson-Rose SA, Powell LH, and Matthews KA (2017). Postmenopausal Women With Greater Paracardial Fat Have More Coronary Artery Calcification Than Premenopausal Women: The Study of Women's Health Across the Nation (SWAN) Cardiovascular Fat Ancillary Study. J. Am. Heart Assoc. 6, e004545. 10.1161/JAHA.116.004545. [PubMed: 28137715]

274. Jackson EA, El Khoudary SR, Crawford SL, Matthews K, Joffe H, Chae C, and Thurston RC (2016). Hot Flash Frequency and Blood Pressure: Data from the Study of Women's Health Across the Nation. J. Womens Health 2002 25, 1204–1209. 10.1089/jwh.2015.5670.

275. Thurston RC, El Khoudary SR, Sutton-Tyrrell K, Crandall CJ, Sternfeld B, Joffe H, Gold EB, Selzer F, and Matthews KA (2012). Vasomotor symptoms and insulin resistance in the study of women's health across the nation. J. Clin. Endocrinol. Metab. 97, 3487–3494. 10.1210/jc.2012-1410. [PubMed: 22851488]

276. Armeni E, Kopanos S, Verykouki E, Augoulea A, Paschou SA, Rizos D, Kaparos G, Eleftheriadis M, Haidich A-B, Goulis DG, et al. (2023). The severity of menopausal symptoms is associated with diabetes, and cardiometabolic risk factors in middle-aged women. Minerva Endocrinol. 10.23736/S2724-6507.23.03905-2.

277. Reeves AN, Elliott MR, Brooks MM, Karvonen-Gutierrez CA, Bondarenko I, Hood MM, and Harlow SD (2021). Symptom Clusters Predict Risk of Metabolic-Syndrome and Diabetes in Midlife: The Study of Women's Health Across the Nation. Ann. Epidemiol. 58, 48–55. 10.1016/j.annepidem.2021.02.011. [PubMed: 33631313]

278. Deecher DC, and Dorries K (2007). Understanding the pathophysiology of vasomotor symptoms (hot flushes and night sweats) that occur in perimenopause, menopause, and postmenopause life stages. Arch. Womens Ment. Health 10, 247–257. 10.1007/s00737-007-0209-5. [PubMed: 18074100]

279. Freedman RR (2005). Pathophysiology and treatment of menopausal hot flashes. Semin. Reprod. Med. 23, 117–125. 10.1055/s-2005-869479. [PubMed: 15852197]

280. Randolph JF Jr, Sowers M, Bondarenko I, Gold EB, Greendale GA, Bromberger JT, Brockwell SE, and Matthews KA (2005). The Relationship of Longitudinal Change in Reproductive Hormones and Vasomotor Symptoms during the Menopausal Transition. J. Clin. Endocrinol. Metab. 90, 6106–6112. 10.1210/jc.2005-1374. [PubMed: 16144949]

281. Wellons MF, Matthews JJ, and Kim C (2017). Ovarian aging in women with diabetes: An overview. Maturitas 96, 109–113. 10.1016/j.maturitas.2016.11.019. [PubMed: 28041589]

282. Guo C, Li Q, Tian G, Liu Y, Sun X, Yin Z, Li H, Chen X, Liu X, Zhang D, et al. (2019). Association of age at menopause and type 2 diabetes: A systematic review and dose-response meta-analysis of cohort studies. Prim. Care Diabetes 13, 301–309. 10.1016/j.pcd.2019.02.001. [PubMed: 30826290]

283. Dewailly D, Andersen CY, Balen A, Broekmans F, Dilaver N, Fanchin R, Griesinger G, Kelsey TW, La Marca A, Lambalk C, et al. (2014). The physiology and clinical utility of anti-Müllerian hormone in women. Hum. Reprod. Update 20, 370–385. 10.1093/humupd/dmt062. [PubMed: 24430863]

284. Verdiesen RMG, Onland-Moret NC, van Gils CH, Stellato RK, Spijkerman AMW, Picavet HSJ, Broekmans FJM, Verschuren WMM, and van der Schouw YT (2021). Anti-Müllerian hormone levels and risk of type 2 diabetes in women. Diabetologia 64, 375–384. 10.1007/s00125-020-05302-5. [PubMed: 33048171]

285. Broer SL, Eijkemans MJC, Scheffer GJ, van Rooij IAJ, de Vet A, Themmen APN, Laven JSE, de Jong FH, te Velde ER, Fauser BC, et al. (2011). Anti-Müllerian Hormone Predicts Menopause: A Long-Term Follow-Up Study in Normoovulatory Women. J. Clin. Endocrinol. Metab. 96, 2532–2539. 10.1210/jc.2010-2776. [PubMed: 21613357]

286. Nelson SM, Davis SR, Kalantaridou S, Lumsden MA, Panay N, and Anderson RA (2023). Anti-Müllerian hormone for the diagnosis and prediction of menopause: a systematic review. Hum. Reprod. Update 29, 327–346. 10.1093/humupd/dmac045. [PubMed: 36651193]

287. Soto N, Iñiguez G, López P, Larenas G, Mujica V, Rey RA, and Codner E (2009). Anti-Mullerian hormone and inhibin B levels as markers of premature ovarian aging and transition to menopause in type 1 diabetes mellitus. Hum. Reprod. Oxf. Engl. 24, 2838–2844. 10.1093/humrep/dep276.

288. Nayki U, Onk D, Balci G, Nayki C, Onk A, and Gunay M (2015). The Effects of Diabetes Mellitus on Ovarian Injury and Reserve: An Experimental Study. Gynecol. Obstet. Invest. 81, 424–429. 10.1159/000442287. [PubMed: 26682912]

289. Qin X, Du J, He R, Li Y, Zhu Q, Li Y, Li H, and Liang X (2023). Adverse effects of type 2 diabetes mellitus on ovarian reserve and pregnancy outcomes during the assisted reproductive technology process. Front. Endocrinol. 14.

290. Zhu D, Chung H-F, Pandeya N, Dobson AJ, Kuh D, Crawford SL, Gold EB, Avis NE, Giles GG, Bruinsma F, et al. (2018). Body mass index and age at natural menopause: an international pooled analysis of 11 prospective studies. Eur. J. Epidemiol. 33, 699–710. 10.1007/s10654-018-0367-y. [PubMed: 29460096]

291. Shifren JL, and Gass MLS (2014). The North American Menopause Society Recommendations for Clinical Care of Midlife Women. Menopause 21, 1038–1062. 10.1097/GME.0000000000000319. [PubMed: 25225714]

292. Koo S, Ahn Y, Lim J-Y, Cho J, and Park H-Y (2017). Obesity associates with vasomotor symptoms in postmenopause but with physical symptoms in perimenopause: a cross-sectional study. BMC Womens Health 17, 126. 10.1186/s12905-017-0487-7. [PubMed: 29216853]

293. Gray KE, Katon JG, LeBlanc ES, Woods NF, Bastian LA, Reiber GE, Weitlauf JC, Nelson KM, and LaCroix AZ (2018). Vasomotor symptom characteristics: are they risk factors for incident diabetes? Menopause 25, 520–530. 10.1097/GME.0000000000001033. [PubMed: 29206771]

294. Nanri A, Mizoue T, Noda M, Goto A, Sawada N, Tsugane S, and the Japan Public Health Center-based Prospective Study (JPHC Study) Group (2019). Menstrual and reproductive factors and type 2 diabetes risk: The Japan Public Health Center-based Prospective Study. J. Diabetes Investig. 10, 147–153. 10.1111/jdi.12853.

295. Effects of estrogen or estrogen/progestin regimens on heart disease risk factors in postmenopausal women. The Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial. The Writing Group for the PEPI Trial (1995). JAMA 273, 199–208. [PubMed: 7807658]

296. Seed M, Sands RH, McLaren M, Kirk G, and Darko D (2000). The effect of hormone replacement therapy and route of administration on selected cardiovascular risk factors in post-menopausal women. Fam. Pract. 17, 497–507. 10.1093/fampra/17.6.497. [PubMed: 11120722]

297. Espeland MA, Hogan PE, Fineberg SE, Howard G, Schrott H, Waclawiw MA, and Bush TL (1998). Effect of postmenopausal hormone therapy on glucose and insulin concentrations. PEPI Investigators. Postmenopausal Estrogen/Progestin Interventions. Diabetes Care 21, 1589–1595. 10.2337/diacare.21.10.1589. [PubMed: 9773716]

298. Margolis KL, Bonds DE, Rodabough RJ, Tinker L, Phillips LS, Allen C, Bassford T, Burke G, Torrens J, Howard BV, et al. (2004). Effect of oestrogen plus progestin on the incidence of diabetes in postmenopausal women: results from the Women's Health Initiative Hormone Trial. Diabetologia 47, 1175–1187. 10.1007/s00125-004-1448-x. [PubMed: 15252707]

299. Maclennan AH, Broadbent JL, Lester S, and Moore V (2004). Oral oestrogen and combined oestrogen/progestogen therapy versus placebo for hot flushes. Cochrane Database Syst. Rev. 2004, CD002978. 10.1002/14651858.CD002978.pub2. [PubMed: 15495039]

300. Langer RD, Hodis HN, Lobo RA, and Allison MA (2021). Hormone replacement therapy - where are we now? Climacteric J. Int. Menopause Soc. 24, 3–10. 10.1080/13697137.2020.1851183.

301. Kanaya AM, Herrington D, Vittinghoff E, Lin F, Grady D, Bittner V, Cauley JA, and Barrett-Connor E (2003). Glycemic Effects of Postmenopausal Hormone Therapy: The Heart and Estrogen/progestin Replacement Study: A Randomized, Double-Blind, Placebo-Controlled Trial. Ann. Intern. Med. 138, 1–9. 10.7326/0003-4819-138-1-200301070-00005.

302. Manson JE, Chlebowski RT, Stefanick ML, Aragaki AK, Rossouw JE, Prentice RL, Anderson G, Howard BV, Thomson CA, LaCroix AZ, et al. (2013). Menopausal hormone therapy and health outcomes during the intervention and extended poststopping phases of the Women's Health Initiative randomized trials. JAMA 310, 1353–1368. 10.1001/jama.2013.278040. [PubMed: 24084921]

303. Salpeter SR, Walsh JME, Ormiston TM, Greyber E, Buckley NS, and Salpeter EE (2006). Meta-analysis: effect of hormone-replacement therapy on components of the metabolic syndrome in postmenopausal women. Diabetes Obes. Metab. 8, 538–554. 10.1111/j.1463-1326.2005.00545.x. [PubMed: 16918589]

304. Bitoska I, Krstevska B, Milenkovic T, Subeska-Stratrova S, Petrovski G, Mishevska SJ, Ahmeti I, and Todorova B (2016). Effects of Hormone Replacement Therapy on Insulin Resistance in Postmenopausal Diabetic Women. Open Access Maced. J. Med. Sci. 4, 83–88. 10.3889/oamjms.2016.024. [PubMed: 27275336]

305. Hoyt LT, and Falconi A (2015). Puberty and Perimenopause: Reproductive Transitions and their Implications for Women's Health. Soc. Sci. Med. 1982 132, 103–112. 10.1016/j.socscimed.2015.03.031.

306. Bruns CM, and Kemnitz JW (2004). Sex Hormones, Insulin Sensitivity, and Diabetes Mellitus. ILAR J. 45, 160–169. 10.1093/ilar.45.2.160. [PubMed: 15111735]

307. Prasad RB, and Groop L (2015). Genetics of Type 2 Diabetes—Pitfalls and Possibilities. Genes 6, 87–123. 10.3390/genes6010087. [PubMed: 25774817]

308. Sonagra AD, Biradar SM, K. D, and Murthy DS, J. (2014). Normal Pregnancy- A State of Insulin Resistance. J. Clin. Diagn. Res. JCDR 8, CC01–CC03. 10.7860/JCDR/2014/10068.5081.

309. Kalyani RR, and Egan JM (2013). Diabetes and Altered Glucose Metabolism with Aging. Endocrinol. Metab. Clin. North Am. 42, 333–347. 10.1016/j.ecl.2013.02.010. [PubMed: 23702405]

310. American College of Obstetricians and Gynecologists (2018). ACOG Committee Opinion No. 755: Well-Woman Visit. Obstet. Gynecol. 132, e181–e186. 10.1097/AOG.0000000000002897. [PubMed: 30247364]

311. Song C, Lyu Y, Li C, Liu P, Li J, Ma RC, and Yang X (2018). Long-term risk of diabetes in women at varying durations after gestational diabetes: a systematic review and meta-analysis with more than 2 million women. Obes. Rev. 19, 421–429. 10.1111/obr.12645. [PubMed: 29266655]

312. Kautzky-Willer A, Leutner M, and Harreiter J (2023). Sex differences in type 2 diabetes. Diabetologia 66, 986–1002. 10.1007/s00125-023-05891-x. [PubMed: 36897358]

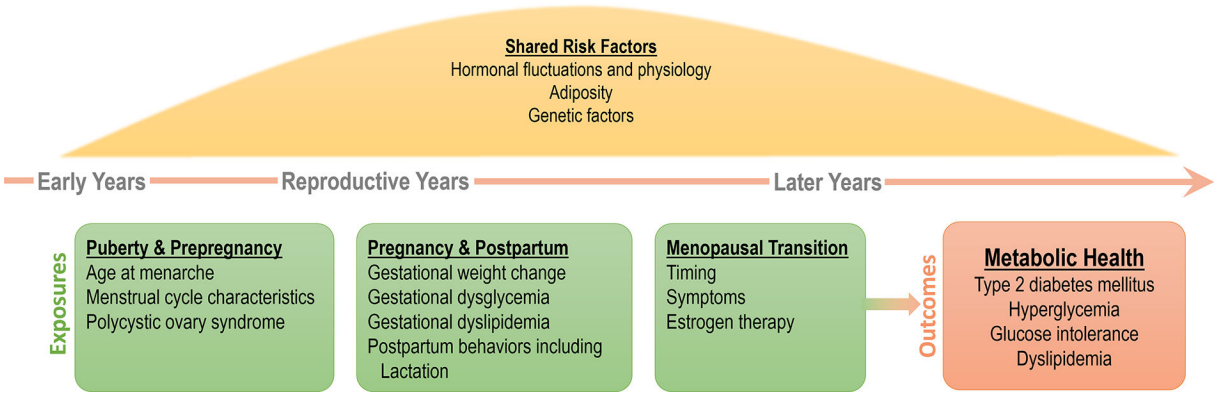

Figure 1.
Female reproductive life stages and later life metabolic health.

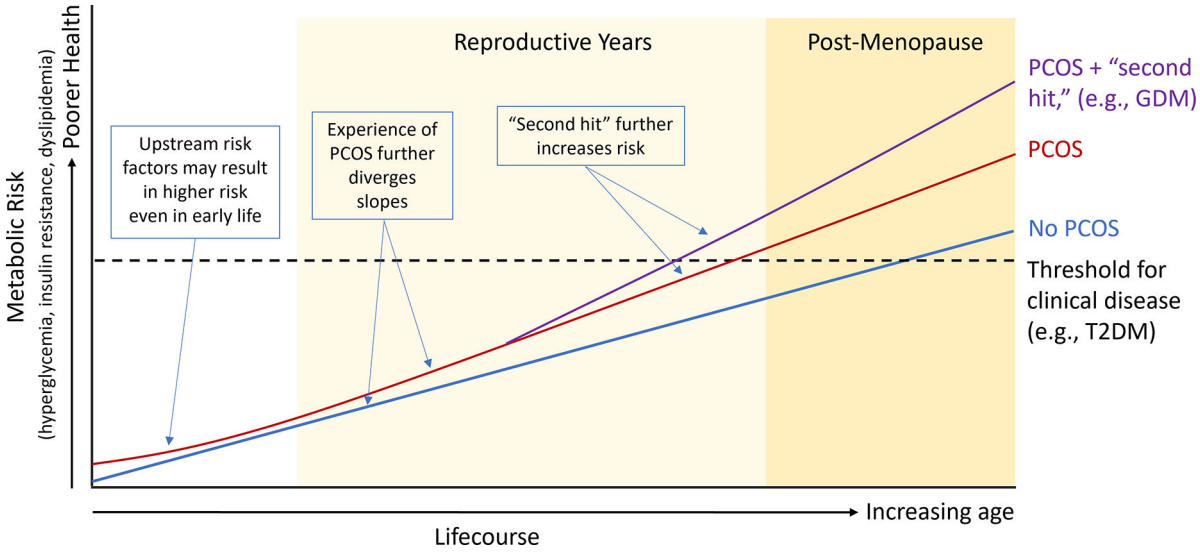

Figure 2.

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