Impact of Physiological Fluctuations of Sex Hormones During the Menstrual Cycle on Glucose Metabolism and the Gut Microbiota

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ABSTRACT

Diabetes mellitus is one of the most prevalent chronic diseases. Previous studies have shown differences in glucose metabolism between males and females. Moreover, difficulties in medication adherence have been reported in females with type 2 diabetes. These observations are believed to be caused by fluctuations in sex hormone concentrations during the menstrual cycle. Furthermore, gut microbiota is linked to female host metabolism and sex hormone production. Understanding the interactions between fluctuating hormone concentrations during the menstrual cycle, gut microbiota, and glucose metabolism in humans is significant because of the increasing prevalence of diabetes and the consequent need to expand preventive efforts. A literature search was performed to determine and summarize the existing evidence, deduce future research needs to maintain female health, and investigate the relationship between the physiological menstrual cycle and glucose metabolism. Studies from 1967 to 2020 have already examined the relationship between variations during the menstrual cycle and glucose metabolism in healthy female subjects using an oral-glucose tolerance test or intravenous glucose tolerance test. However, the overall number of studies is rather small and the results are contradictory, as some studies detected differences in glucose concentrations depending on the different cycle phases, whereas others did not. Some studies reported lower glucose levels in the follicular phase than in the luteal phase, whereas another study detected the opposite. Data on gut microbiota in relation to the menstrual cycle are limited. Conflicting results exist when examining the effect of hormonal contraceptives on the gut microbiota and changes in the course of the menstrual cycle. The results indicate that the menstrual cycle, especially fluctuating sex hormones, might impact the gut microbiota composition.
The menstrual cycle may affect the gut microbiota composition and glucose metabolism. These results indicate that glucose tolerance may be the greatest in the follicular phase; however, further well-conducted studies are needed to support this assumption.

Introduction

Cardiovascular diseases, cancer, chronic respiratory diseases, and diabetes mellitus are the most common non-communicable chronic diseases worldwide, causing 41 million deaths annually [1]. In 2021, diabetes affected approximately 10.5 % (536.6 million) of the global population aged 20–79 years. Its prevalence is expected to increase to 12.2 % by 2045, indicating its high relevance in the prevention and treatment of diabetes [2].

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Early studies have shown that men and women respond differently to oral-glucose tolerance test (OGTT) [3, 4], which is used to assess glucose tolerance. Moreover, OGTT is used as a reference method for diagnosing type 2 diabetes in unclear cases, according to the current German guidelines [5]. Similar results were observed for insulin sensitivity; however, these findings are contradictory [6]. On the one hand, reduced insulin sensitivity in young normal-weight women as compared to men [7]; subsequent differences in postprandial glucose metabolism have been reported [8]. In contrast, in another study, normal-weight women (< 40 years) had higher insulin sensitivity than men of the same age [9]; no differences in plasma insulin concentrations between normal-weight men and women were found in other studies [10, 11].

Additional studies detected an interaction between diabetes and the female menstrual cycle, including a higher prevalence of oligomenorrhea, increased cycle duration, and glycemic variations along the cycle phases [12, 13]. Furthermore, difficulties in medication management in women with diabetes during different menstrual cycle phases have been reported, [14, 15] with a higher risk of hypoglycemia in the follicular phase (FP) and hyperglycemia in the luteal phase (LP) [16]. In addition, Ezenwaka et al. detected higher insulin resistance in the LP than in the FP [17]. These observations may be due to the fluctuating sex hormone concentrations during the menstrual cycle, which may be associated with glucose tolerance [18].

Similar to glucose tolerance, the gut microbiota shows sex-dependent differences in animal and human studies [19] and has been associated with the metabolism of female sex hormones [20, 21]. In addition, alterations in the microbiota can play a role in the pathogenesis of type 2 diabetes by dysregulating host-microbiota interactions via various pathways, such as intestinal hormones or inflammatory reactions. A low-grade inflammatory state, which has been associated with insulin resistance and type 2 diabetes [22], can be affected by certain gut microbes or their metabolites, which can increase the levels pro- or anti-inflammatory cytokines, inhibit inflammatory cytokines and chemokines, or modulate the intestinal barrier function as well as the secretion of gut hormones. For example, the levels of anti-inflammatory cytokines IL-10 and IL-22, can be increased by certain microbes and have been shown to protect against insulin resistance in muscles and improve insulin sensitivity. Moreover, short-chain fatty acids, butyrate, and propionate produced by bacteria can regulate gut permeability [23, 24] and enhance gut hormone release of glucagon-like peptide 1 (GLP-1), glucagon-like peptide 2 (GLP-2), and peptide YY (PYY), thereby affecting insulin secretion and glucose homeostasis [25–27].

Therefore, this review aims to reveal the nature of the mutual relationship of glucose metabolism and gut microbiota with the menstrual cycle, particularly for better prevention and management of diabetes in women.

Relationship between the menstrual cycle and glucose metabolism

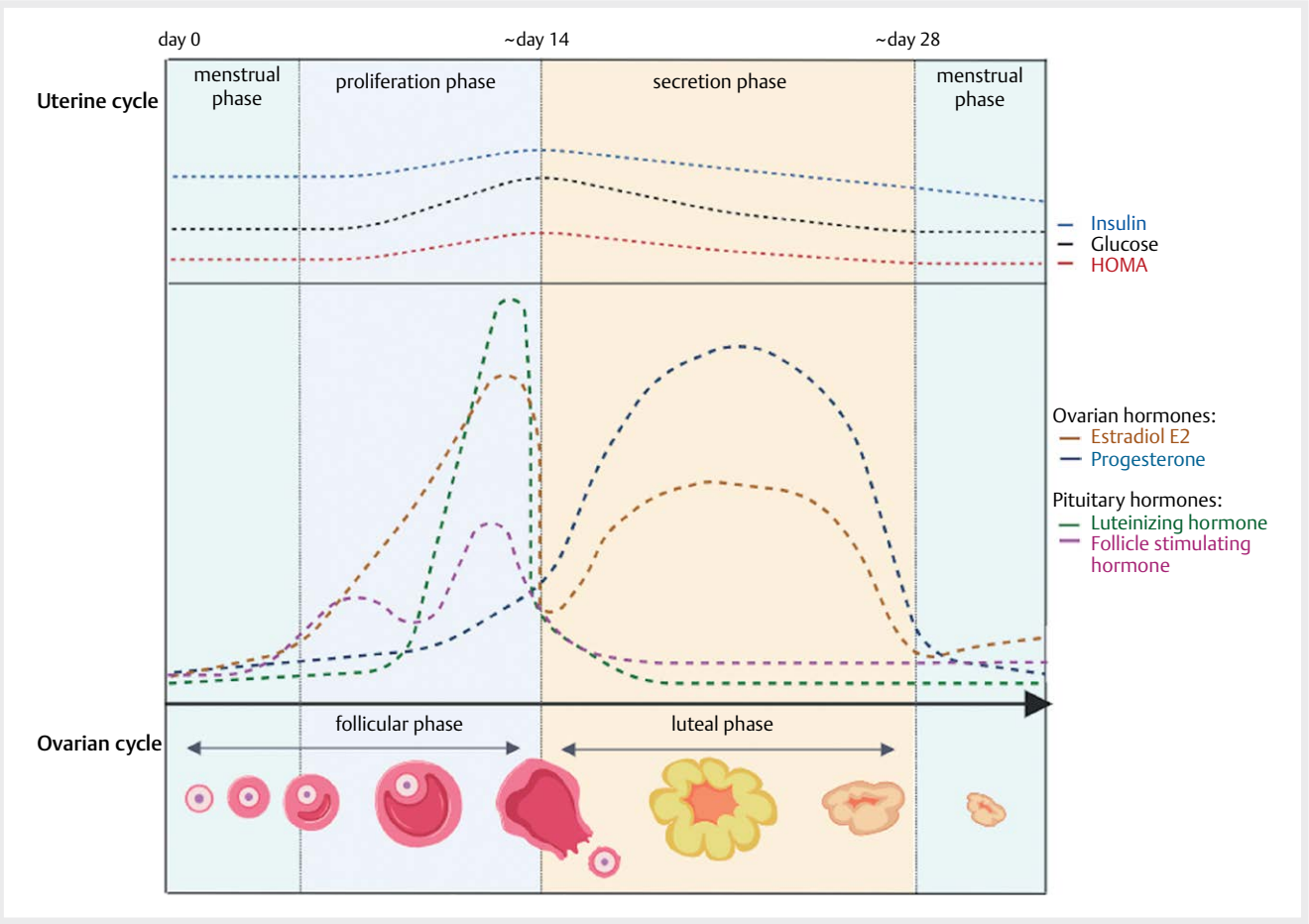
The menstrual cycle is characterized by cyclic changes in reproductive hormones and structural changes in the ovaries and endometrium. Under normal physiologic conditions, oocyte maturation occurs in a cyclical pattern over approximately 28 days and results from the interaction of various organs and hormones: ovaries, uterus, pituitary gland, luteinizing hormone (LH), follicle-stimulating hormone (FSH), estrogen, and progesterone. A regular menstrual cycle length is between 25 and 35 days [28]; recent studies have shed light on the high variability within the population that is dependent on ethnicity, age, and body mass index (BMI) and reported that the average menstrual cycle extends over 29.3 days [29]. The same study reported that menstrual bleeding, which marks the beginning of the menstrual cycle [28], has an average duration of 4 days [29]. The menstrual cycle can be divided according to the changes in the ovaries or uterus, referred to as the ovarian or uterine cycle, respectively. The FP and LP phases of the ovarian cycle occur alongside the menstrual (MP), proliferative (PP), and secretory (SP) phases of the uterine cycle. The individual phases, corresponding hormone fluctuations, and hypothetical curves of glucose, insulin, and HOMA are shown in ▶ **Fig. 1** and are discussed in the following paragraphs. A healthy woman goes through the menstrual cycle monthly, from the beginning of her first menstrual bleeding (menarche) to menopause, defined as 12 months without menses [28].

Epidemiological studies showing a higher prevalence of diabetes in men than in women have sparked interest in investigating the role of sex hormones in diabetes susceptibility and the underlying metabolic changes [30]. This was further supported by data showing an increased risk of type 2 diabetes in women with early menopause or premature ovarian insufficiency [31] and a reduced incidence in postmenopausal women receiving hormonal therapy [32, 33], thereby indicating a protective effect of estrogens. Variations in hormones during the menstrual cycle influence glucose tolerance in women differently, as abnormal levels of female sex hormones may play a role in the pathogenesis of impaired fasting glucose and glucose tolerance [18].

Impact of the menstrual cycle on glucose tolerance

To date, studies examining the influence of menstrual cycle phases on glucose metabolism via OGTTs [34–42] in humans are scarce and have provided contradictory results. Five of nine observational studies showed no significant differences in glucose levels during OGTT between different cycle phases [36, 38–40, 42], whereas four studies showed significant differences [34, 36, 37, 41]. In three of these four studies, glucose levels were significantly lower in the FP than in the LP [34, 37, 41]; Walsh and O'Sullivan reported the opposite result [36]. All studies examined healthy women with regular menstrual cycles. The women included were between 19 and 39 years of age and had a normal BMI or body weight. None of the studies included male controls. Most studies examined the same participants at two to four different time points of their menstrual cycle, whereas two studies [38, 40], and Peppler et al. in a subgroup [37] assessed participants at only one time-point. Details on the age and BMI of the participants, methodology, and results of the studies are presented in ▶ **Table 1.**

The results of Jarrett and Graver using an OGTT indicated variations in glucose tolerance between different menstrual cycle phases. The cycle phases in which the OGTTs were performed were not precisely defined; therefore, the results should be interpreted with caution. However, the examination times could be roughly assigned to the FP and LP. Accordingly, blood glucose levels were low during



▶ **Fig. 1** Schematic curves of ovarian and pituitary hormone concentrations as well as hypothetical curves for glucose and insulin levels and HOMA along the course of the menstrual cycle phases (figure adapted from ▶ **fig. 2** by Welt et al. [103]). Created with BioRender.com [rerif]

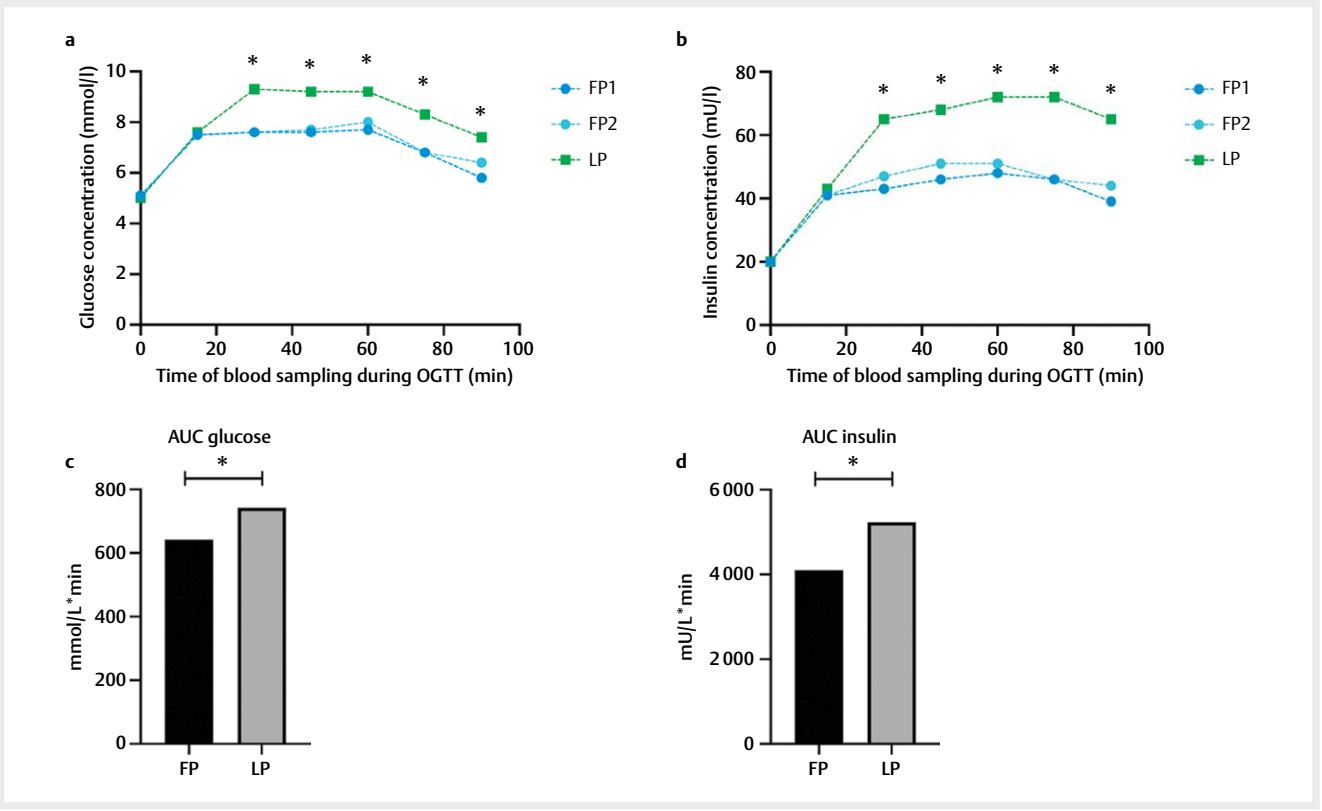
the FP and elevated during ovulation [34]. Peppler et al. and Brennan et al. reported congruent results [37, 41], indicating that glucose tolerance was greatest at the beginning of the cycle and decreased after ovulation **(▶ Fig. 2)**. Walsh and O'Sullivan showed minor but statistically significant differences in glucose values between different menstrual cycle phases when adjusted for the time point in the cycle when the tests were performed [36]. However, contrary to the findings of the three other studies by Jarrett and Graver, Peppler et al., and Brennan et al., they found higher glucose levels at the beginning of the cycle (FP) as compared to the end of the cycle (LP). Thus, studies by Jarrett and Graver, Walsh and O'Sullivan, Peppler et al., and Brennan et al. indicated that the time point of the menstrual cycle at which an OGTT is performed in women is relevant and should be considered when investigating glucose metabolism.

Contrary to these results, Cudworth and Veevers, Bonora et al., Toth et al., and Busby et al. found no differences in glucose levels during an OGTT between the examined menstrual cycle time points. Williams et al., who compared early and late FP, did not detect any differences in glucose tolerance. Interestingly, in the studies showing differences in glucose levels, lower amounts of glucose (50 g) were used for the OGTT [34, 36, 37, 41] as compared to the studies that detected no differences (67–100 g glucose) [35, 38–40, 42]. This might be due to the strong amplification of the physiological processes of glucose metabolism during an OGTT with a higher glucose load, which may potentially mask more subtle phase-specific effects on glucose metabolism. It would be interesting to address this hypothesis in future studies by comparing the effects of different glucose-loading levels.

Impact of sex hormones on insulin secretion

The mechanisms underlying the influence of sex hormones on insulin secretion are not yet fully understood, as they appear to be tissue-specific and exert their effects via various metabolic, genomic, endocrine, and immunological pathways [43]. Possible mechanisms include direct effects on the pancreas by estrogen- or progesterone-binding receptors [44], hormonal influences on glucose uptake via glucose transporters, hormone-sensitive lipase expression in adipose tissue, and general changes in gene expression and cell function (e. g., in the liver) [45].

Data from human studies on insulin secretion in relation to the menstrual cycle phases are contradictory. Insulin levels were not measured in all studies that performed an OGTT to assess glucose tolerance; however, the results were consistent with those observed for glucose levels. While Cudworth and Veevers, Bonora et al., Toth et al., and Williams et al. found no significant differences



▶ **Fig. 2** Blood glucose (**a**) and insulin (**b**) concentrations and AUC values of glucose (**c**) and insulin (**d**) after an OGTT during FP and LP phases of the menstrual cycle (data are mean values based on Brennan et al., 2009). *p < 0,05. AUC, area under the curve; OGTT, oral glucose tolerance test; FP, follicular phase; LP, luteal phase.

in insulin secretion [35, 38, 39, 42], Walsh and O'Sullivan, and Brennan et al. detected differences that were in agreement with the described changes in glucose levels [36, 41]. Spellacy et al. performed two intravenous glucose tolerance tests (IVGTTs; 25 g of glucose infused as a 50 % glucose solution over a period of 2 minutes) in 19 women, once in the PP and once in the SP. Blood insulin (and glucose) levels measured at different time points over the course of two hours did not differ significantly between the two menstrual cycle phases [46].

Impact of sex hormones on insulin sensitivity

The effects of progesterone and the main estrogen, estradiol (E2), on insulin sensitivity have been investigated in female rats. The results showed that progesterone contributes to a decrease in insulin sensitivity, whereas E2 maintained insulin sensitivity. This indicates that female sex steroid hormones are important for regulating glucose homeostasis, insulin sensitivity, and insulin response in rats [47]. The protective effect of estrogen on insulin sensitivity, for example, via the estrogen receptor α (ERα), has also been demonstrated in mouse models [30]. As E2 levels rise and drop before and after ovulation, then rise to a lower level in the LP, while progesterone levels are increased in the LP, the associations observed in rats would align with the results from human studies showing decreased glucose tolerance in the LP. However, current results from human studies on the effects of fluctuating sex hormones on insulin sensitivity in the course of the menstrual cycle are inconsistent [6–11, 48–50]. A decrease in insulin sensitivity has been observed in some studies in the LP [49, 51–53]. Hummel et al. showed that brain insulin action may also be important in this context; nasal application of insulin improved peripheral insulin sensitivity in women only in the FP, whereas this effect was absent in the LP. Moreover, they observed a significant interaction between a high estradiol: progesterone ratio (present in the FP) and this effect [54]. Concurrently, other studies reported no relationship between menstrual cycle phases and insulin sensitivity [39, 48, 55] or only when adjusting for confounding factors such as BMI, physical activity, or cardiorespiratory fitness [50]. Likewise, Bingley et al. detected no differences in insulin sensitivity between FP and LP when performing an IVGTT (0.3 g glucose/kg body weight infused as a 50 % glucose solution over a period of one minute) with a bolus insulin infusion (0.03 U/kg body weight) 20 minutes after glucose infusion [55].

Impact of age and body mass index on the menstrual cycle and glucose metabolism

Age and BMI are known to affect glucose metabolism [56, 57]. Accordingly, an increase in blood glucose levels has been observed with increasing age [40]. In addition, markers of insulin resistance are associated with older age and abnormal BMI [57]. The menstrual cycle is also influenced by age [58] and BMI [59]. Between the

▶ **Table 1** Study characteristics and significant results of the included observational studies investigating glucose metabolism in relation to the menstrual cycle.

Authors Country	Number of patients	Age (years)	BMI (kg/m²)	Sampling method	Sampling time points	Determination of cycle phases	Significant results
(Jarrett und Graver 1968) [34]	10	19–39	N/A	3–4 × 2-h **OGTT** (50 g Glc (Lucozade))	3–4 visits at weekly interval**,** 3 of 10 ♀: measurements repeated over several cycles	Days calculated from the first day of bleeding; **2** ♀ ovulation determined by oral BBT	AUC glc values lowest at the beginning of MC, higher before ovulation, and maximum after ovulation
n.s.				Capillary blood samples (earlobe) Blood glucose			
(Cudworth und Veevers 1975) [35]	20	Ø 19	BW: Ø 56.8	3 × 2-h **OGTT** (100 g Glc in 400 mL water, over 4 min)	PP (day 9), SP (day 18), before MP (day 27)	Days calculated from the first day of bleeding; ovulation not determined	No significant differences
UK				Venous blood samples Blood glucose, serum insulin	7 of 20 ♀: repeated examinations in one more cycle		
(Walsh and O'Sullivan, 1975) [36]	33	Ø 23	N/A	4 × 2-h **OGTT** (50 g Glc in 200–500 mL flavored water, over 5 min[a]	Four visits at weekly intervals	Days calculated from the first day of bleeding; ovulation not determined	Glc and insulin values [b] highest at the beginning of MC;$p < 0.05$ between all MC quarters for 0 (glc) and 30 min (glc and insulin)
Ireland				Venous blood samples Plasma glucose, serum insulin			
(Peppler et al. 1978) [37]	213 (109 without HC)	20–54	N/A	1 or 2 × 2-h-**OGTT** (50 g Glc in 200 mL water)	MP, FP, LP	Classification by questionnaires; ovulation not determined	Glc values lowest at the beginning of MC**;** continued phase-specific glc behavior after stratification for HC intake
Germany				Capillary blood samples (earlobe) Blood glucose			
(Bonora et al. 1987) [38]	FP: 55 LP: 55	Ø 36–37	Ø 23	1 × 2-h **OGTT** (75 g Glc)	FP (day 5–10), LP (day 20–25)	No information	No significant differences
Italy				Blood samples Plasma glucose and insulin			
(Toth et al., 1987) [39]	6	Ø 25	Ø 22.5	3 × 3-h **OGTT** (75 g Glc (Trutol))	MP (day 1–6), FP (day 9–14), LP (day 20–28)	Measurement of progesterone levels confirmed FP and LP	No significant differences
Canada				Blood samples Plasma glucose and insulin			
(Busby et al. 1992) [40]	Early FP: 29	Ø 35.5–36.5	Ø 22.2–22.7	1 × 2-h **OGTT** (40 g Glc/m² body surface (Ø 67 g Glc))	Early FP, late FP, LP	Measurement of E2 and progesterone levels confirmed early and late FP and LP, Ovulation not determined	No significant differences
USA	Late FP: 21			Venous blood samples Plasma glucose			
	LP: 40						
(Brennan et al. 2009) [41]	9	Ø 31	Ø 21	3 × 1.5-h-OGTT (50 g Glc in 300 mL water, over 2 min)	FP in 2 MC (FP1 and FP2: day 6–12), LP (day 18–24)	E2 and progesterone measured	Glc and insulin values and AUC lowest at the beginning of MC; $p < 0.01$ for all (FP1/2 vs. LP) No differences between FP1 and FP2
Norway				Venous blood samples Blood glucose, plasma insulin			
(Williams et al. 2019) [42]	17	Ø 21	Ø 22.2	2 × 0.5-h **OGTT** (75 g Glc in 300 mL water, over 3 min)	Early FP (day 2–6), late FP (3 ± 2 days before ovulation)	Days calculated from the first day of bleeding; ovulation determined by ovulation kit	No significant differences
Canada				Venous blood samples Blood glucose and insulin			

All studies included healthy women with a regular menstrual cycle. Only significant results shown ($p < 0.05$); OGTTs were performed in sitting position, unless otherwise indicated; ♀, women; Ø, mean; [a] design according to "British Diabetic Association"; [b] values adjusted for the study time point; AUC, area under the curve; BBT, basal body temperature; BW, body weight; E2, estradiol; FP, follicular phase; Glc, glucose; HC, hormonal contraceptives; N/A, not available; n.s., not specified; LP, luteal phase; min, minutes; MP, menstrual phase; MC, menstrual cycle; OGTT, oral glucose tolerance test; PP, proliferation phase; SP, secretion phase; UK, United Kingdom; USA, United States of America.

ages of 40 and 55 years, changes in follicle recruitment occur [58], and menopause sets in [28]. Menstruation and LP may last longer in women with obesity (defined by a BMI > 30 kg/m^2) and they are less likely to experience an increase in LH levels, possibly resulting from an absence of ovulation [59]. In addition, severe weight loss, such as in anorexia nervosa, can result in amenorrhea [60]. Energy intake and expenditure, which may be affected by the menstrual cycle, are important in regulating glucose metabolism and affect the BMI. Using an ad libitum buffet meal, Brennan et al. reported that study participants consumed a significantly lower amount of food (measured in grams and kilojoules) in the FP than in the LP [41]. These observations are consistent with those of previous studies on energy expenditure [61] and the basal metabolic rate [62] during the menstrual cycle. Webb et al. reported an increase in energy expenditure during the LP [61]. In agreement with this is the decrease in the basal metabolic rate during the menstrual phase (MP), the minimum basal metabolic rate one week before ovulation, and the increasing basal metabolic rate after ovulation [62]. MacGregor et al. found that the rhythmicity of insulin sensitivity during the menstrual cycle was modified by BMI [50].

Therefore, age, BMI (as an indicator of the nutritional status of the participants), and diet plus basal metabolic rate should be considered when evaluating the results of studies examining the menstrual cycle **(▶ Fig. 3)**. However, in some OGTT studies, clear information on the age and BMI of the study participants was missing.

Impact of health status and medication on the menstrual cycle and glucose metabolism

In addition to age and BMI, markers of insulin resistance and sensitivity are associated with factors that indicate health status, such as physical activity and cardiorespiratory fitness [50, 57]. Peppler et al. and Jarrett and Graver provided no information on the medication or health status of their participants, both of which can influence glucose metabolism [63]. Although discussing the effects of hormonal contraceptives on glucose metabolism is beyond the scope of this review, it is important to note that physiological fluctuations in female sex hormones are affected by hormonal contraceptive intake. Synthetic steroid analogs used in contraceptives induce metabolic effects, affecting liver metabolism and protein synthesis; however [64], the influence of hormonal contraceptives on glucose metabolism is sparse and shows contradictory results. Some studies have shown that oral steroid contraceptives may affect insulin sensitivity. Peppler et al. detected 10–20 mg/dl higher glucose levels in women who used hormonal contraceptives than in those who did not [37]. In addition, in another study, hormonal contraceptives were associated with an increased insulin reaction, depending on the type and dose of progestogen [65]. Perseghin et al. recorded a decrease in insulin sensitivity of 40 % compared to women not using contraceptives [11]. On the other hand, in another examination, various hormonal contraceptives did not reveal any impairment of glucose metabolism [66].

Impact of pregnancy on glucose tolerance

Although a detailed assessment of the effects of hormonal changes on glucose metabolism during pregnancy is beyond the scope of this review, it is important to note that pregnancy can affect glucose metabolism in women of normal weight by reducing insulin sensitivity [67]. Furthermore, there are various risk factors for the development of gestational diabetes during pregnancy (e. g., maternal BMI > 27 kg/m^2 before pregnancy, advanced age, and family history of diabetes). Due to gestational diabetes, the risk of developing type 2 diabetes within 10 years of gestation is 8- to 10-times higher [68]. Owing to the lack of information on the subjects in most studies, it is unclear whether they belong to the risk group for type 2 diabetes.

Methodological aspects and their interaction with data on glucose tolerance along the menstrual cycle

The methodological and technical characteristics of the studies, such as the OGTT procedure, blood sampling methods, time points of glucose measurement, and examined time points (phases of the menstrual cycle), have an impact on the results. Therefore, well-designed studies focusing on these aspects with proper documentation should be conducted.

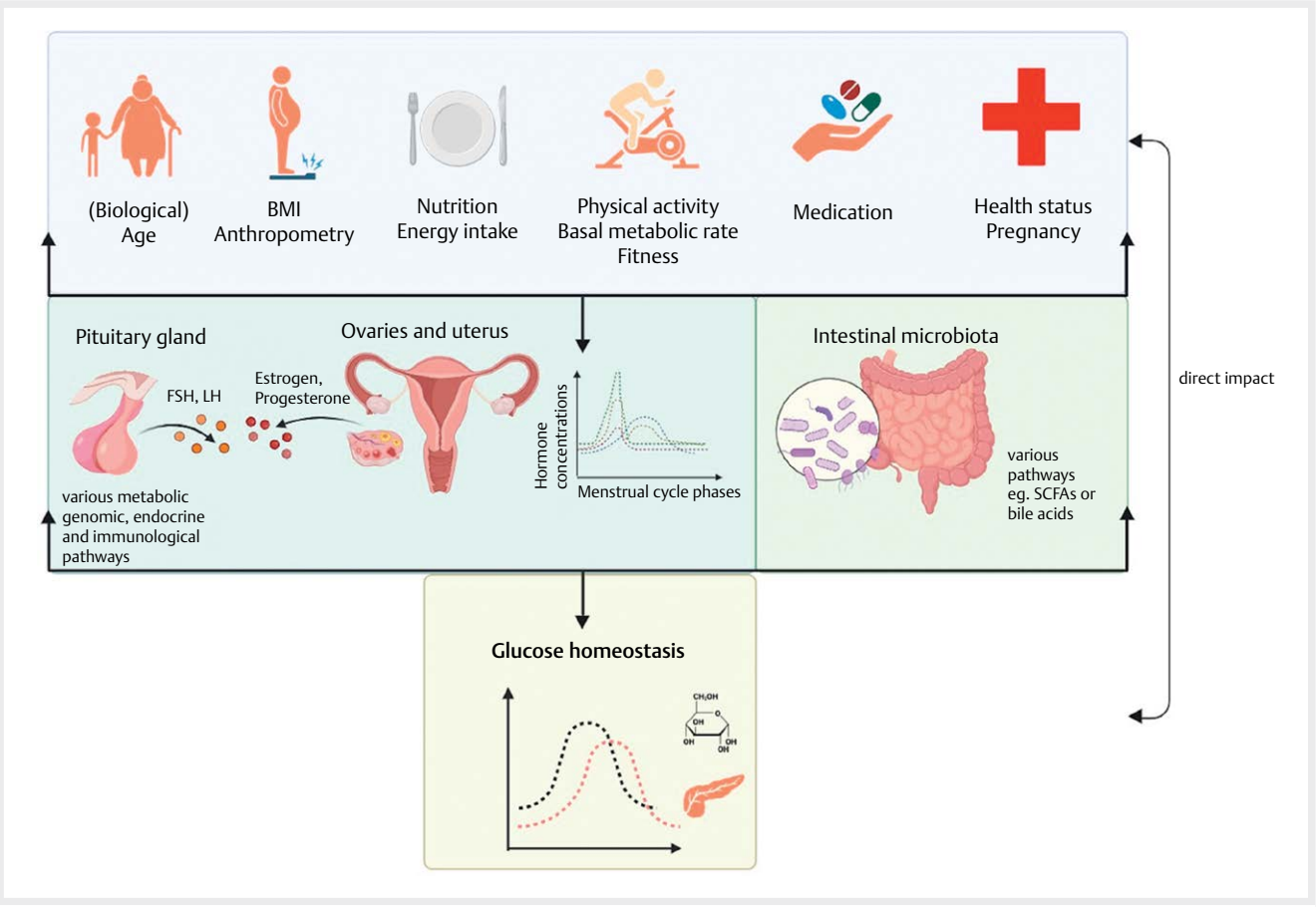
Impact of test procedure on glucose values

According to World Health Organization (WHO) guidelines, an amount of 75 g of glucose (or 82.5 g of glucose monohydrate) is recommended for the standard OGTT [69]. Unfortunately, the studies in which OGTTs were performed differed in the amounts of glucose and water, making a comparison of blood glucose values between different studies difficult.

Oral glucose administration affects gastric emptying. The release of GLP-1 induced by oral glucose administration was greater in the LP than in the FP. In this context, faster gastric emptying also occurs in the LP [41]. Moreover, glucose concentrations 15 and 30 minutes after glucose administration are directly related to the rate of gastric emptying [70]. Thus, gastric emptying affects the glucose levels after oral glucose loading and appears to be influenced by the cycle phase.

Other factors that may be related to gastric emptying and may affect glucose absorption are food restrictions and physical activity on the day prior to administering OGTT. According to the WHO guidelines, the performance of an OGTT should follow a three-day diet with at least 150 g of carbohydrate per day [69]. Therefore, in future studies, this should be the standard procedure before performing an OGTT by means of standardized meals or the provision of appropriate recipes. Accordingly, limiting physical activity the day before the OGTT is also relevant to avoid influencing the results [71]. Adherence to the WHO guidelines may help compare data and shed light on the expected slight differences in glucose metabolism depending on the menstrual cycle phases.

Neither of the two studies that performed the IVGTT showed any differences between the menstrual cycle phases [46, 55]. Since the IVGTT is a very accurate and sensitive method for measuring first-phase insulin secretion of the pancreas, as the gastrointestinal tract and thus the incretin effect is bypassed [72, 73], the strong effects induced by the intravenous glucose injection might have concealed the effects of the menstrual cycle on glucose homeostasis. This is in line with the results of the OGTTs with a higher glucose load and might indicate that test methods that induce higher blood glucose levels, and thus higher insulin secretion and glucose uptake, might overshadow the phase-specific effects on glucose metabolism, which are expected to be more subtle. In addition, the



▶ **Fig. 3** Various factors such as age, BMI, diet, physical activity as well as medication, health status, and pregnancy play a role in the mutual relationship of fluctuating sex hormones in the course of the menstrual cycle with glucose metabolism and the gut microbiota. BMI, body mass index; SCFAs, short-chain fatty acids. Created with BioRender.com [rerif]

impact of the menstrual cycle on glucose metabolism seems to be multifactorial and systemic, since effects in different tissues have been observed (as outlined previously). Therefore, the association between sex hormones and glucose metabolism may be better reflected by more physiological conditions during OGTT involving the gastrointestinal tract.

Impact of blood sampling method on glucose values

Another factor that can influence the measured glucose values is the blood collection method. Glucose values obtained by venous blood sampling were significantly lower than those obtained by capillary blood sampling, especially during the OGTT [74]. Most studies, except those by Jarrett and Graver and Peppler et al., performed venous blood sampling. Consequently, the direct comparison of glucose values between studies was limited. However, the differences between the cycle phases within these studies should not have been affected by this.

In addition, the duration of the OGTT and the time points at which the blood samples were collected could have affected the results. This might explain the lack of statistically significant results reported by Williams et al. Here, blood samples were collected only in a fasting state and after 30 minutes [42]. Thus, there is a possibility that phase-specific differences in glucose levels may have been overlooked. This approach was motivated by reports showing that glucose and insulin levels were the highest during oral glucose loading at this point [42]. However, Brennan et al. showed that fluctuations could still occur after the first 30 minutes of the OGTT [41]. Similarly, Busby et al. only measured fasting and 120-minute glucose values [40]. Blood glucose levels 120 minutes after glucose administration were similar to those in the fasting state. Therefore, mild fluctuations might have remained undiscovered. Lin et al. addressed the issue of limited blood sampling time points by analyzing glucose variance in the course of the menstrual cycle using continuous glucose measurement. While not performing an OGTT, their results support the findings of Jarrett and Graver, Peppler et al., and Brennan et al., as they found that glucose values were the lowest during late FP, increased during ovulation, and peaked in the LP phase [75].

Impact of measurement time points during the menstrual cycle on the assessment of glucose metabolism

There is high variability among the studies in the time points (i. e., cycle days) chosen across the menstrual cycle to represent the different cycle phases, which leads to inconsistent assignment of measurements to the cycle phases. In the study by Walsh and

O'Sullivan, the time points examined were initially divided into menstrual cycle quarters, which could be assigned to the MP, FP, and LP by specifying the days on which the blood samples were collected. However, because Walsh and O'Sullivan did not determine the timing of their subjects' ovulation, days 17 and 18 (the third quarter of the menstrual cycle) could represent late FP, ovulation, or early LP, respectively [36]. This depends on the individual variation in menstrual cycle length and the time of ovulation, with both showing high variability in the general population [29]. A similar approach was adopted by Jarrett and Graver with weekly examinations. Similarly, the key ovulation time point, which defines the transition from FP to LP, was determined only in a small subgroup of two participants [34]. To be able to distinguish the values of the FP from those of the LP more clearly, it would have been useful to clearly determine the time point of ovulation. Another suboptimal method for classifying the menstrual cycle phases was performed by Peppler et al. [37] using self-administered questionnaires to classify the menstrual cycle phase, which is prone to error (misclassification bias [76]). In contrast, Brennan et al. measured the hormone concentrations [41]. In conclusion, future studies should accurately classify menstrual cycle phases and determine ovulation by recording LH, estrogen, and progesterone concentrations, or by using another accurate method [77].

Considering inter-cycle variability to enhance reproducibility

Inter-cycle variability within a single participant raises the issue of reproducibility. Duplicate tests conducted in the FP by Brennan et al. did not show significant differences [41]. The glucose values collected in the FP were reproducible over two cycles, indicating that intra-individual variations were not the driving factor of variance during the menstrual cycles **(▶ Fig. 2)**. Similar results were reported by Jarrett and Graver, in which a small subcohort of three women underwent repeated examinations in subsequent cycles. The patterns of the glucose values appeared similar, although no statistical tests were performed [34]. Cudworth et al. also did not detect significant differences in blood sugar-time areas between two cycles in a sub-cohort of seven women [35]. Peppler et al. investigated the reproducibility of glucose values in the LP in addition to the MP/FP. For this purpose, a double examination of 192 female participants was performed. The results showed that glucose values in the MP/FP were reproducible by 60 %, whereas those in the LP were only by 25 %. This indicates that a greater variation in glucose levels may be present during the second half of the menstrual cycle [37]. Ideally, studies should be performed over more than two menstrual cycles in the same participants to provide greater confidence in the reproducibility of glucose values and capture intra- and inter-individual differences.

Interactions between the gut microbiota, glucose homeostasis, and sex hormones

The gut microbiota significantly impacts host metabolism and the etiology of metabolic diseases. Type 2 and gestational diabetes have been linked to changes in the gut microbiota (dysbiosis), indicating a key role of the microbiota in host glucose metabolism [25]. In a recent scoping review, 40 bacterial taxa were associated with glucose-related parameters and 17 with insulin-related outcomes. Five of these bacterial taxa (*Akkermansia muciniphila. Bifidobacterium longum, Clostridium leptum* group, *Faecalibacterium prausnitzii, Faecalibacterium*) were the taxa most frequently and inversely associated with glucose levels [78]. The various pathways along the microbiota-gut-brain axis and microbiota-gut-liver axis by which the gut microbiota affects glucose homeostasis have been reviewed in detail elsewhere [79–81]. For instance, microbial metabolites such as short-chain fatty acids butyrate, acetate, and propionate can modulate glucose metabolism by reducing the glycemic response by affecting glucose uptake. In addition, short-chain fatty acids, as well as nutrient intake, stimulate the secretion of the gut hormones GLP-1, GLP-2, and PYY from intestinal endocrine cells, affecting glucose and insulin metabolism, gastrointestinal motility, appetite, and microbiome composition [25, 78].

Another mechanism linking the gut microbiota, glucose metabolism, and menstrual cycle might be the gut transit time, which is regulated by gut hormones as well as the enteric nervous system [80]. While the upper intestinal transit time (gastric emptying and small intestinal motility) affects the glycemic responses to a meal, the lower intestinal transit time (colonic transit time) has a more pronounced effect on the gut microbiota. Colonic transit time has been associated with microbiome composition and the relative abundance of certain species, as well as with postprandial glucose metabolism [82], recently also in a study with more than 800 participants [83]. Moreover, the intestinal transit time has been shown to vary between cycle phases in some early studies [84, 85], whereas others have detected no differences [86]. The underlying mechanisms remain to be elucidated, but progesterone levels have been hypothesized to be relevant, potentially influencing gut motility via intestinal muscle contraction and alterations in gastrointestinal hormones (e. g., motilin). The effect of progesterone on gut motility is dose-dependent [87, 88]. Low progesterone doses, in comparison to pregnancy, increase the gastric emptying rate with higher postprandial glucose, insulin, and GLP-1 levels and can also disturb the microbiota diversity through frequent bowel movement [41, 82]. On the other hand, higher progesterone levels, as present in the second and third trimester of pregnancy, can decrease intestinal motility and prolong gastrointestinal transit time [88–90] but can impair glucose tolerance by affecting glucose transporters in skeletal muscles and enhancing hepatic gluconeogenesis, especially in susceptible patients with limited insulin secretion or suffering from sub-clinical insulin resistance [91, 92]. In addition, changes in food intake (e. g., fibers) and physical activity that can occur depending on the cycle (as described previously) can also affect the transit time [82, 93]. Hence, a variation in transit time in relation to sex hormones might affect the gut microbiome composition as well as glucose metabolism and should be assessed, along with the underlying mechanisms, in future studies.

Another pathway affecting glucose homeostasis and sex steroid hormone synthesis is the metabolism of bile acids, which is largely influenced by microbiota. By metabolizing primary bile acids to secondary bile acids and activating bile acid receptors in the intestine, the gut microbiota can affect the secretion of GLP-1, insulin sensitivity, and glucose tolerance by activating the transcription factor FXR or G protein-coupled bile acid receptor 1 (TGR5) [79, 81]. Sex hormones are metabolized via an enterohepatic cycle that depends on biologically active gut microbiota. They pass through a

cycle that includes biliary excretion (approximately 60 % [94]), bacterial deconjugation, and intestinal reabsorption. Deconjugation is necessary for the absorption of circulating estrogens, in which the gut microbiota plays an important role [95]. In addition to bile acids, microbial enzyme activity, and microbially activated phytoestrogens can also affect sex hormone metabolism [21].

Furthermore, changes in the gut microbiota are associated with diseases related to the menstrual cycle, such as polycystic ovarian syndrome (PCOS) and irregular (anovulatory) menstrual cycle [96, 97]. However, the influence of pathophysiological impairments on the menstrual cycle and microbiome should be the subject of a separate review. Here, the interaction between sex hormones and gut microbiota is reviewed, considering studies that have examined the influence of hormonal contraceptives on fecal microbiota. Studies in rodents have shown an influence of sex hormones on the gut microbiota [95], which might impact the state of health [95, 98], while results of human observational studies indicate that the β-diversity of the gut microbiota is not affected by hormonal contraceptives [99, 100]. With regard to α-diversity, the results of a study by Krog et al. indicate that there are no differences [100] while Mihajlovic et al. found a slightly higher α-diversity in the control group compared to the group using hormonal contraceptives. Three genera–*Eubacterium*, *Haemophilus*, and *unclassified Firmicutes*–were enriched in the control group, whereas two genera, *Akkermansia* and *Barnesiella*, were enriched in the contraceptive group. These differences may be due to the decreased estrogen and progesterone concentrations caused by the use of hormonal contraceptives [99]. Furthermore, they hypothesized that lower concentrations are also the cause of *Akkermansia* accumulation, as animal studies indicate that mice treated with conjugated estrogens [101] have lower concentrations of *Akkermansia*. Hence, Mihajlovic et al. assumed a negative correlation between *Akkermansia* and estrogens.

Associations between menstrual cycle phases and the gut microbiota

Data on the possible associations between gut microbiota and the physiological menstrual cycle are limited. In a study by Mihajlovic et al., stool samples were collected continuously over the course of a 28-day menstrual cycle. While there was no significant difference in α or β-diversity between LP and FP, taxonomic analysis detected *Akkermansia* and *Lactococcus* in higher abundances (4-fold and 2-fold) in the LP compared to the FP. Based on the suspected negative correlation between *Akkermansia* and estrogens, the authors expected that *Akkermansia* would be reduced during the LP (high estrogen concentrations) compared to the FP, which was not the case. Thus, Mihajlovic et al. concluded that the estrogen concentration exerts a complex function in *Akkermansia* growth. In this regard, there might be a sensitive response by *Akkermansia* to circulating estrogen and progesterone levels, whereas the increase in *Lactococcus* in the LP is assumed to be influenced by rising estrogen concentrations [99]. However, these results need to be interpreted with caution, as they are derived from one study with a small cohort of 16 women, nine of whom were in the group with a physiological menstrual cycle. *Akkermansia* has been negatively associated with type 2 diabetes and obesity in humans and has shown beneficial effects on glucose metabolism in animal studies [25, 81]. Strains of *Akkermansia muciniphila* are commonly present in the human gut and positively impact host health by strengthening intestinal barrier integrity and promoting anti-inflammatory actions. Bacterial species of the *Lactococcus* genus are lactic acid producers frequently used in the production of fermented foods and probiotics. As the methods applied in the study by Mihajlovic et al. did not allow taxa differentiation below the genus level, it is difficult to draw concise conclusions about the health implications of the enrichment of *Akkermansia* and *Lactococcus* detected in the LP, as the effects are often species- or strain-specific.

Krog et al. investigated changes in the microbial composition of different body sites (saliva, vagina, feces, and rectum) during menstruation, FP, and LP in a cohort of 160 participants (54 of these had a physiological cycle). While vaginal microbial diversity differed significantly between cycle phases, no differences were detected in other body sites, including feces. In general, shifts in microbiome composition were subtle in fecal samples and the highest in vaginal samples. Estradiol and progesterone levels were not correlated with fecal microbiome composition [100].

One observational study focusing on the temporal variability in gut microbiome profiles by continuous stool sample analysis over six weeks in 20 women found high day-to-day inter-individual variations. However, these variations were not significantly influenced by the menstrual cycle parameters [102]. This highlights the difficulty in interpreting studies examining the relationship between the gut microbiota and sex hormones, as estrogen and progesterone levels fluctuate throughout the menstrual cycle with similar times for rising and falling concentrations. Hence, the effects of individual sex hormones may only be clearly differentiable [99] if both sex hormones and the composition of the gut microbiota are examined using continuous sample collection during the menstrual cycle.

Conclusion

To date, data on the changes in glucose metabolism and gut microbiota during the course of the menstrual cycle are limited. The results of previous studies on the respective topic suggest that there may be phase-specific variations induced by fluctuations in sex hormone concentrations. Therefore, when assessing glucose tolerance in women, the phase of the menstrual cycle at which the OGTT is performed may be relevant, as the greatest glucose tolerance appears to occur during the onset of the menstrual cycle (FP).

Several factors, such as age, BMI, diet, physical activity, health status, and medication, can influence the mutual relationship of glucose metabolism and gut microbiota with the menstrual cycle **(▶ Fig. 3)**. In addition, the methodological issues of the studies have been outlined, which might explain the inhomogeneity of the study results. Therefore, future studies should carefully consider these confounding factors. For example, standardized implementation of the OGTT (glucose load, carbohydrate intake, and physical activity) is relevant for obtaining reliable and comparable results. Moreover, continuous glucose measurements may be preferable to examine the differences in glucose levels more precisely and over the course of the entire menstrual cycle. To determine systematic cycle-dependent fluctuations, the reproducibility of glucose values in the respective cycle phases must be recorded by collecting data from multiple cycles. In addition, recording hor-

mone concentrations may be essential for the precise classification of the menstrual cycle phases (FP and LP) and ovulation time. Recording the habitual diet and composition of the gut microbiota is also relevant for the transferability and comparability of the results.

The extent to which variations in glucose metabolism during the different menstrual cycle phases, shown in some studies, are associated with changes in the gut microbiota is not fully understood. Accordingly, there is a need for future research to investigate the interplay between glucose metabolism and the gut microbiota in relation to sex hormones in a healthy group of participants with a regular menstrual cycle.

Phase-specific variations in glucose tolerance may have implications for diabetes management, as the required doses of diabetes medication may also be dependent on the cycle, possibly requiring adjustment of the medication (e. g., insulin dose). A personalized diet adapted to glucose tolerance in correspondence with the menstrual cycle may prospectively improve female health or prevent diabetes in women at high risk.

Authors' contributions

SK and AS conducted the research and prepared the first draft of the manuscript, which was subsequently finalized in close collaboration with MCS and TP. All authors provided substantial content contributions and edited the manuscript. MCS provided the initial ideas for this manuscript. SK and AS created and edited the table. AS and MCS created and edited the figures. All the authors have read and approved the final manuscript.

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Conflict of interest

The authors declare that they have no conflict of interest.

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