

Diabetes detection in women with gestational diabetes and polycystic ovarian syndrome

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ABSTRACT

Gestational diabetes mellitus (GDM) and polycystic ovarian syndrome (PCOS) represent two of the highest risk factors for development of type 2 diabetes mellitus in young women. As these increasingly common conditions generally affect younger women, early detection of dysglycemia is key if preventative measures are to be effective. While international guidance recommends screening for type 2 diabetes, current screening strategies suffer from significant challenges. First, guidance lacks consensus in defining which tests to use and frequency of monitoring, thereby sending mixed messages to healthcare professionals. Second, conformity to guidance is poor, with only a minority of women having tests at the recommended frequency (where specified). Approaches to improve conformity have focused on healthcare related factors (largely technology driven reminder systems), but patient factors such as convenience and clear messaging around risk have been neglected. Third, and most critically, current screening strategies are too generic and rely on tests that become abnormal far too late in the trajectory towards dysglycemia to offer opportunities for effective preventative measures. Risk factors show wide interindividual variation, and insulin sensitivity and β cell function are often abnormal during pre-diabetes stage, well before frank diabetes. New, consistent, targeted screening strategies are required that incorporate early, prevention focused testing and personalised risk stratification.

Introduction

Gestational diabetes mellitus (GDM) and polycystic ovary syndrome (PCOS) are two of the most common metabolic conditions affecting women of reproductive age.^{1 2} Both conditions are risk factors for future metabolic and cardiovascular abnormalities,^{3 4} especially type 2 diabetes. This prevalence highlights the importance of sustained dysglycemia monitoring and early intervention in young, generally healthy women.

This review summarizes available screening guidance, highlights the challenges to implementing existing screening programs, and offers suggestions on how adherence to guidance could be improved. We examine the underlying pathophysiology of these two conditions, highlighting their similarities and illustrating how an understanding of insulin resistance and β cell function provides insight into alternative approaches to monitoring. We illustrate how this knowledge of pathophysiology exposes the limitations in current screening strategies and propose a new approach to earlier detection of glycemic irregularities, where intervention can

have a more meaningful impact on type 2 diabetes prevention.

The review is aimed at hospital specialists and community based generalists working in diabetes screening and management (diabetologists, endocrinologists, general practitioners, and community based and hospital based diabetes nurse specialists), as well as those providing obstetrics and gynecology services.

Sources and selection criteria

We searched PubMed and Medline databases for studies published between January 2002 and July 2022 using the terms (along with their associated derivatives) “gestational diabetes” and “polycystic ovary syndrome” separately with: (i) “epidemiology”, “prevalence”, “incidence”, and “type 2 diabetes” for the background section, (ii) “type 2 diabetes” with “risk factors”, “screening”, and “postnatal” or “postpartum” for the risk factors and screening section, (iii) “guidelines” or “guidance” for the guidelines section, (iv) “insulin resistance” and “ β cell function” for the pathophysiology section.

Earlier references were included where we saw a strong case for their inclusion. Priority was given on the basis of quality (systematic reviews and meta-analyses, randomized controlled trials, size of study) and direct relevance to the topic. References cited by, or themselves citing, key publications were explored where relevant. We also examined relevant international professional guidelines.

Epidemiology

The incidence of gestational diabetes mellitus and PCOS, as well as diabetes mellitus itself, is rising globally, and together represents a major public health challenge. Gestational diabetes mellitus and PCOS, which collectively affect up to 20% of generally young women, are two of the most significant risk factors for the future development of type 2 diabetes.^{5,6}

Diabetes mellitus

Globally, about 537 million adults are living with diabetes,⁷ with 86% affected by type 2 diabetes.⁸ Diabetes is a cause of premature death both directly and through its associated complications.^{3,9-12} About £15bn (€17.4bn; \$18.6bn) are spent on diabetes annually in the UK (roughly 10% of the National Health Service budget), 80% of which are spent on treating complications.¹³

Gestational diabetes mellitus

Gestational diabetes mellitus affects 4-10% of pregnancies worldwide.⁵ Its prevalence is reported to have increased by 10-100% in several ethnic groups

in the last 20 years,¹⁴ reaching 12.9% in North Africa followed by South East Asia, Western Pacific, and South and Central America (11.7%, 11.7%, and 11.2%, respectively).¹⁵

PCOS

PCOS is one of the most common endocrine disorders in women of reproductive age with a global prevalence between 7-12%,⁶ depending on the diagnostic criteria used. It has been suggested that up to 70% of women with PCOS remain undiagnosed.¹⁶ Prevalence is higher in women with type 1 diabetes (24%)¹⁷ and in girls with pediatric type 2 diabetes (20%),¹⁸ compared with the general population. PCOS has increased in the last decade in China, rising to 7.8% in women aged 20-49, with 24 million women of reproductive age affected in China alone.¹⁹

Risk factors for type 2 diabetes

Of the risk factors for type 2 diabetes used in the Q-Diabetes 2018 risk prediction algorithm, gestational diabetes mellitus and PCOS represent two of the largest in terms of adjusted hazard ratio.²⁰ The fact that they both affect otherwise generally healthy young women suggests that strategies for early detection and treatment could be particularly important in these groups.

Adherence to screening recommendations for type 2 diabetes is poor. Furthermore, screening strategies recommended in international guidance generally focus on detecting overt diabetes or pre-diabetes, and could, therefore, be too late to allow instigation of preventative interventions. Therefore,

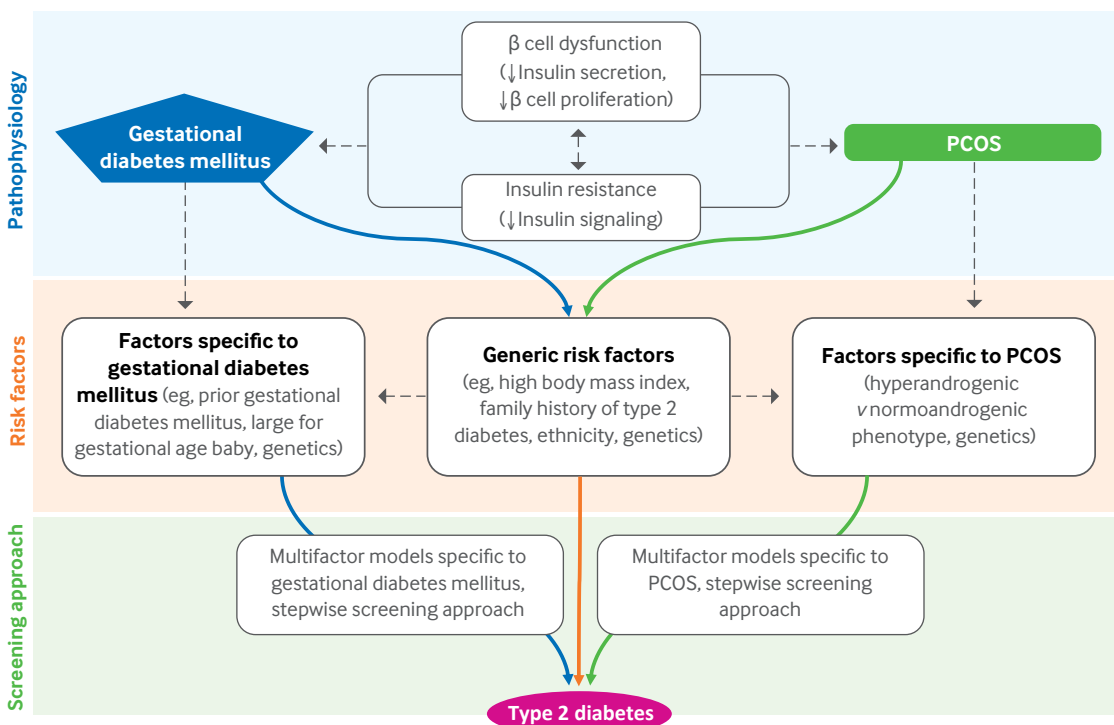


Fig 1 | Overlap in pathophysiology, risk factors, and type 2 diabetes screening approach in gestational diabetes mellitus and PCOS. PCOS=polycystic ovary syndrome

opportunities for early detection and delay of onset of diabetes or its complications are potentially being missed at a significant cost to healthcare systems and society.

Gestational diabetes mellitus and diabetes risk

Women with gestational diabetes mellitus have a 20-70% risk of developing type 2 diabetes within the first decade following delivery.¹ A recent meta-analysis suggested a 9.5-fold increase in overall relative risk for type 2 diabetes compared with women without gestational diabetes mellitus.²¹ A large prospective cohort study showed gestational diabetes mellitus was associated with a 3.9-fold risk of type 2 diabetes within 6-15 years after an affected pregnancy.²²

Risk factors for progression from gestational diabetes mellitus to type 2 diabetes include pregnancy specific (hypertensive disorders of pregnancy, preterm delivery, early gestational age at onset of gestational diabetes mellitus (though the latter could reflect early detection of pre-existing dysglycemia)) and generic risk factors for diabetes (raised body mass index, non-white ethnicity, family history of diabetes) (fig 1).²³

PCOS and diabetes risk

Studies have suggested that PCOS is a risk factor for the development of gestational diabetes mellitus.²⁴ Two meta-analyses have shown that PCOS imparts a twofold to threefold greater risk of developing gestational diabetes mellitus (odds ratio 2.89, 95% confidence interval 1.68 to 4.98)²⁴ and (with a random effects model) (odds ratio 2.02, 95% confidence interval 1.74 to 2.34).^{25 26} PCOS imparted higher risk for type 2 diabetes (odds ratio 2.87, 95% confidence interval 1.44 to 5.72).² A recent longitudinal study showed that 19% of women with PCOS developed type 2 diabetes, compared with 1% of women without PCOS over 24 years of follow-up.²⁷ However, this risk could be partly dependent on the PCOS phenotype.²⁸ Most studies on gestational diabetes mellitus risk in women with PCOS have been conducted in cohorts comprising largely obese populations of women with PCOS or in high risk groups (eg, after fertility treatment). However, some smaller studies have shown no significant differences between PCOS and non-PCOS groups in terms of gestational diabetes mellitus risk after long term follow-up,^{29 30} while a larger prospective cohort study has shown that PCOS might not be an independent risk factor for gestational diabetes mellitus (rather, PCOS shares risk factors with gestational diabetes mellitus).³¹

It appears that risk factors for progression to type 2 diabetes in PCOS mirror those generic factors seen in gestational diabetes mellitus (eg, high body mass index, family history of type 2 diabetes, non-white ethnicity) but might also include factors specific to PCOS such as hyperandrogenism (fig 1).³² These risk factors could form the basis of prediction models for type 2 diabetes in women with PCOS.³²⁻³⁴

Pathophysiology

The high risk of developing type 2 diabetes in both gestational diabetes mellitus and PCOS is secondary to the interplay between insulin resistance and β cell function (fig 1). Changes in these aspects over time predate the development of frank diabetes, and can be reversed, or at least delayed, by appropriate intervention.

Insulin secretion and resistance in gestational diabetes mellitus

During normal gestation, increased metabolic demand, secondary to reduced insulin sensitivity, is counterbalanced by β cell hypertrophy and hyperplasia. The increased insulin secretion ensures that the glucose levels do not increase excessively (fig 2a). After delivery, with the return of insulin sensitivity to normal, β cell function returns to baseline.

The hyperglycemia seen in gestational diabetes mellitus, however, results from β cell dysfunction on a background of chronic insulin resistance (fig 2b). The underlying mechanisms behind these are described below.

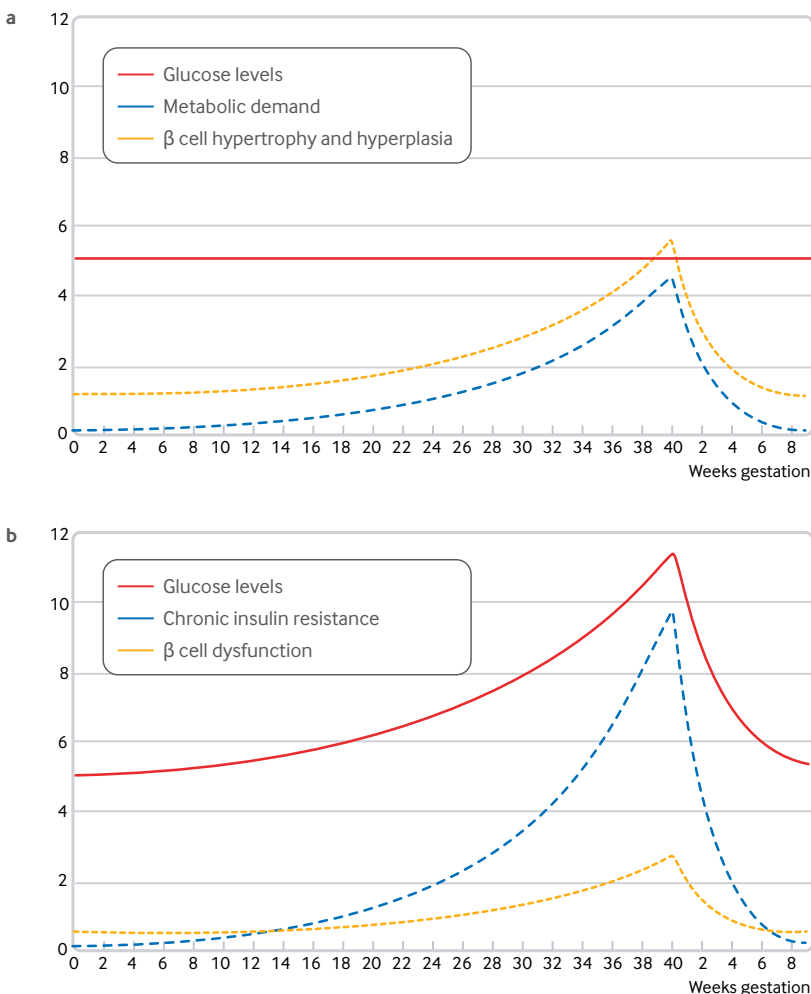


Fig 2 | Changes in insulin resistance and β cell function during pregnancy, and impact of blood glucose levels in (a) normal pregnancy and (b) gestational diabetes mellitus. PCOS=polycystic ovary syndrome

β cell dysfunction in gestational diabetes mellitus

Genome-wide association studies have shown that many susceptibility genes identified for gestational diabetes mellitus are related to β cell function, primarily via effects on insulin secretion and islet cell proliferation.^{35 36} A recent meta-analysis suggested that gestational diabetes mellitus and type 2 diabetes have a common underlying pathophysiology, with relatively few loci specific to glucose regulation in pregnancy.³⁷

The insulin resistance of gestation overburdens the β cells to produce more insulin, eventually failing to maintain the secretion to keep the glucose levels from rising. If untreated, systemic hyperglycemia directly contributes to β cell failure (termed glucotoxicity), causing a vicious cycle of hyperglycemia in the setting of insulin resistance, resulting in further aggravation of β cell dysfunction with eventual decompensation.³⁸ Glucotoxicity is thought to lead to β cell apoptosis, with patients with type 2 diabetes showing 40-60% reduction in β cells.³⁸

Chronic insulin resistance in gestational diabetes mellitus

While several additional susceptibility genes are known for gestational diabetes mellitus associated with insulin resistance,³⁶ a key component of the cellular mechanism of insulin resistance is failure of insulin signaling, resulting in suboptimal plasma

membrane translocation of glucose transporter 4 (GLUT4). Compared with normal pregnancy, the rate of insulin stimulated glucose uptake in gestational diabetes mellitus is reduced by 54%.³⁹ Reduced GLUT4 translocation did not appear to be secondary to insulin receptor abundance, but in gestational diabetes mellitus it was found to be a result of other molecular mechanisms. These mechanisms include altered expression or phosphorylation of downstream insulin signaling regulators (including phosphatidylinositol 3-kinase (PI3K) and insulin receptor substrate (IRS)-1), and a reduced tyrosine or enhanced serine/threonine phosphorylation of the insulin receptor, dampening insulin downstream signaling.^{39 40} Unlike normal gestation, these molecular changes persist after pregnancy,⁴¹ perpetuating the future risk for type 2 diabetes.

Insulin resistance and secretion in PCOS

While the underpinning factors giving rise to gestational diabetes mellitus and PCOS are different, insulin resistance and β cell function overlap significantly. This overlap is illustrated by the increased risk of gestational diabetes mellitus in women with PCOS, and vice versa.^{42 43} Insulin resistance and β cell function might show differences in their origin in women with PCOS, but their end result is similar.

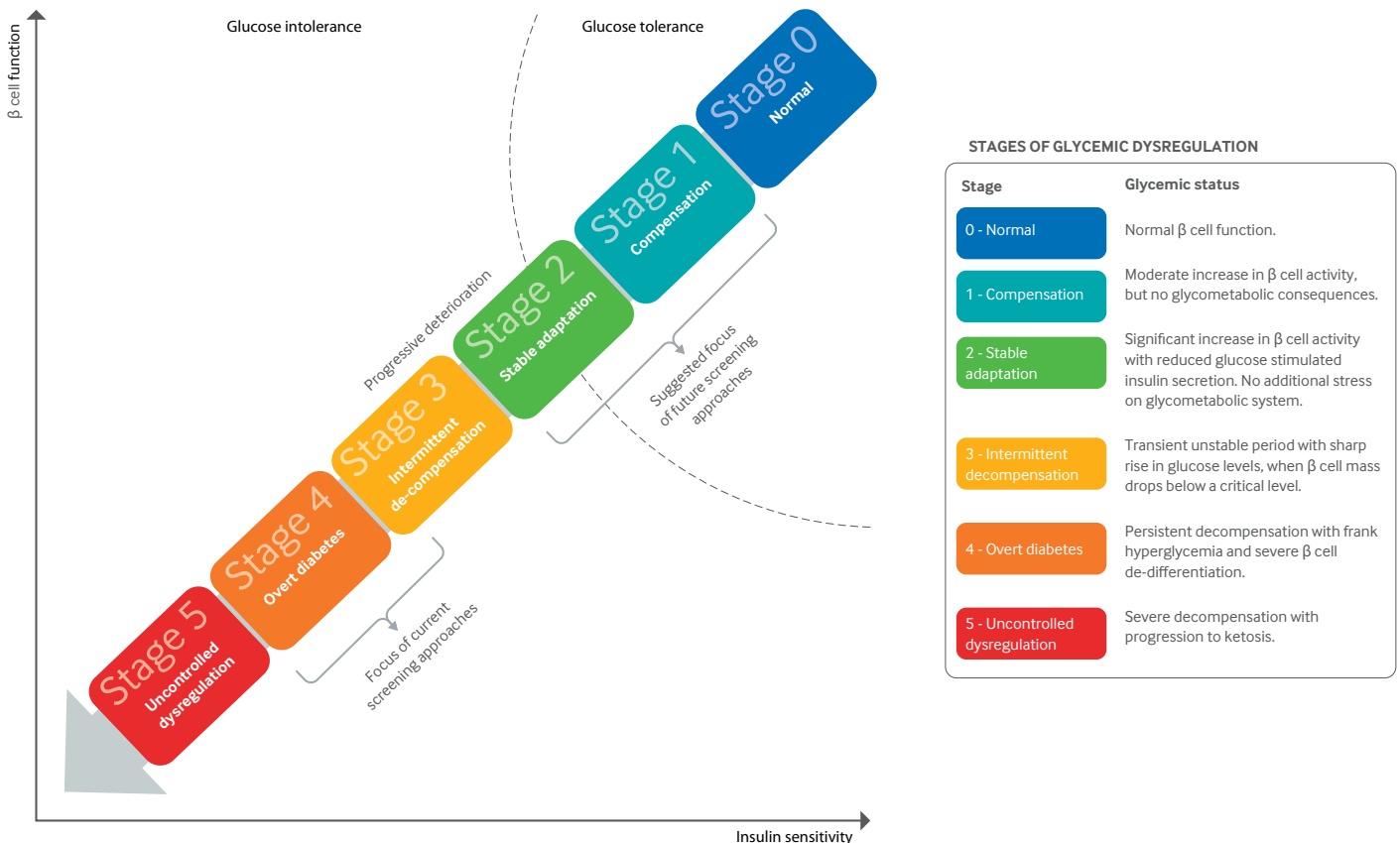


Fig 3 | Phases of progressive deterioration in glycemic status in women with gestational diabetes mellitus and PCOS (or both) in relation to insulin resistance and β cell function. PCOS=polycystic ovary syndrome

Chronic insulin resistance in PCOS

Insulin resistance was initially shown in both lean and obese women with PCOS, though this finding was based on PCOS defined as oligomenorrhea or anovulation.^{44 45} Subsequently, it has been observed that women who had polycystic ovaries also had insulin resistance.⁴⁶

The major defect in insulin action in PCOS is a post-binding defect, where increased inhibitory serine phosphorylation of the insulin receptor affects insulin mediated glucose uptake in both skeletal muscles⁴⁷ and adipose tissue.⁴⁴ Furthermore, selective insulin resistance, restricted to the metabolic effects of insulin, has also been noted in ovarian granulosa lutein cells⁴⁵ and skin fibroblasts.⁴⁸

Fewer genome-wide association studies to identify susceptibility genes for diabetes in PCOS have been done, though studies have highlighted genes associated with diabetes among those associated with susceptibility for PCOS itself.⁴⁹ Whatever the molecular causes, the cellular effect on phosphorylation pathways shows overlap with gestational diabetes mellitus. While pancreatic β cells are able to increase insulin production in response to underlying insulin resistance, individuals with PCOS remain euglycemic. However, when the β cells fail to maintain adequate insulin secretion, dysglycemia develops.⁵⁰

 β cell dysfunction in PCOS

The post-meal insulin secretory response is reduced in women with PCOS, particularly in those with first degree relatives with type 2 diabetes, indicating that they are at higher risk of deteriorating glucose tolerance.^{51 52} The importance of insulin resistance and β cell function is further supported by studies showing that the disposition index, a marker of both insulin resistance and secretion, is reduced in PCOS women (both lean and obese) compared with weight matched controls.⁵³ Importantly, this defect has been shown in adolescent girls with PCOS, illustrating that changes are apparent at a very early stage.⁵⁴ Collectively, these findings indicate defective glucose stimulated insulin secretion in PCOS, independent of body mass index, with potential inherited components.

The high prevalence of dysglycemia in women with PCOS argues for the coexistence of defective insulin secretion in addition to the insulin resistance, both of which need to be considered to capture the accurate glycometabolic status.⁵⁵ The current strategy for diabetes screening in PCOS using traditional markers of dysglycemia appears to be too little, too late.

The interaction between insulin resistance and β cell function in PCOS and gestational diabetes mellitus

Insulin secretion (β cell function) interacts with insulin sensitivity throughout all stages from normality to the development of type 2 diabetes. This interaction is not linear and has been described as hyperbolic (fig 3),⁵⁶ resulting in a more rapid

deterioration in glucose regulation once a critical threshold is reached. Acknowledging this association is critical to understanding and hence detecting the progression of glycemic dysregulation. To date, we have been limited by tests that become measurably abnormal too late in the progression (stage 2 in fig 3). We therefore need new tools that link insulin sensitivity with insulin reserve.

Disposition index and alternate measures of insulin reserve and sensitivity

Use of the minimal model intravenous glucose tolerance test (IVGTT) allows the simultaneous calculation of the acute insulin response together with the insulin sensitivity index; the first as a surrogate of early insulin secretion and the second as a reflection of systemic insulin sensitivity. The disposition index is the product of the acute insulin response and the insulin sensitivity index.

The disposition index was noted to be constant for individuals with the same degree of glucose tolerance.^{57 58} It enables accurate evaluation of the β cell function, taking into account the insulin sensitivity, as opposed to considering only insulin secretion. In response to insulin resistance, so long as the compensation is adequate (ie, normal disposition index), glucose tolerance remains normal.⁵⁹ However, once the disposition index drops, glucose intolerance develops, followed by frank diabetes. This intolerance has been shown in obesity⁶⁰ and in people treated with glucocorticoids.⁶¹

Further work attempted to use the disposition index concept with oral glucose tolerance test instead of the more complex IVGTT, enabling its more widespread use as a tool for investigating the balance between insulin sensitivity and β cell function. This work led to the creation of the insulin secretion sensitivity index 2 (ISSI2), which was developed with the oral glucose tolerance test (OGTT), replicating the principles of, and significantly correlating with, the disposition index.⁵⁸ If dysglycemia is to be identified at an early stage, assessment of both insulin secretion and sensitivity should therefore be key components of the type 2 diabetes screening strategy in both gestational diabetes mellitus and PCOS.

Guidelines for screening for type 2 diabetes in gestational diabetes mellitus and PCOS

Given the incidence of type 2 diabetes in these generally young women, early detection of dysglycemia provides the opportunity for effective intervention that can significantly improve the quality of life and clinical outcomes over a prolonged period. Hence, national and international guidelines are right to suggest long term screening for type 2 diabetes in both gestational diabetes mellitus⁶²⁻⁷³ and PCOS.⁷⁴⁻⁸⁰ Table 1 highlights the type 2 diabetes monitoring recommendations from some of the key international guidelines for both gestational diabetes mellitus and PCOS.

For gestational diabetes mellitus, a systematic review of these guidelines recommended an OGTT

Table 1 | Summary of international guidelines for the screening for type 2 diabetes in women with gestational diabetes mellitus and PCOS

Country	Publishing body	Title	Year	Postpartum screening recommendations Tests	Frequency	Long term screening recommendations Tests	Frequency	Reference
Gestational diabetes								
US	American College of Obstetricians and Gynecologists (ACOG)/American Diabetes Association (ADA)	ACOG Practice Bulletin No. 190: Gestational Diabetes Mellitus	2017	Fasting plasma glucose or ideally 75 g OGTT	4-12 weeks	Fasting plasma glucose or ideally 75 g OGTT	Every 1-3 years	64
International	The International Federation of Gynecology and Obstetrics (FIGO)	Initiative on Gestational Diabetes Mellitus: A Pragmatic Guide for Diagnosis, Management, and Care	2015	75 g OGTT	6-12 weeks	Ongoing surveillance for diabetes and cardiovascular problems using local protocol	Not defined	65
Europe	European Board and College of Obstetrics and Gynaecology (EBCOG)	A proposal for the use of uniform diagnostic criteria for gestational diabetes in Europe	2015	75 g OGTT	6-12 weeks	HbA _{1c} fasting plasma glucose, or 2 hour 75 g OGTT	At least every three years	66
Canada	Diabetes Canada Clinical Practice Guidelines Expert Committee	Diabetes and Pregnancy	2018	75 g OGTT	6 weeks to 6 months	Unclear. Guidance refers to fasting plasma glucose or ideally 75 g OGTT, but not explicit in recommendations	No specific recommendation, though guidance does refer to annual testing	67
France	Haute Autorité de Santé (HAS)	Screening and diagnosis of gestational diabetes mellitus	2005	No specific recommendations	No specific recommendations	No specific recommendations	No specific recommendations	68
US	Kaiser Permanente	Gestational Diabetes Screening and Treatment Guideline	2021	HbA _{1c}	3 months	HbA _{1c} fasting plasma glucose, or 2 hour 75 g OGTT	Annually	69
UK	National Institute for Health and Care Excellence (NICE)	Diabetes in pregnancy: management from preconception to the postnatal period (NG3)	2015	Fasting plasma glucose or HbA _{1c}	6-13 weeks	HbA _{1c}	Annually	62
Australia	Queensland Clinical Guidelines	Gestational diabetes mellitus (GDM)	2021	OGTT	6-12 weeks	HbA _{1c} or OGTT	At least every three years (annually if contemplating another pregnancy)	70
Scotland	Scottish Intercollegiate Guidelines Network (SIGN)	Management of diabetes (116)	2017	Fasting plasma glucose (75 g OGTT if clinically indicated)	At least 6 weeks	HbA _{1c} or fasting plasma glucose	Annually	71
International	World Health Organization (WHO)	Diagnostic Criteria and Classification of Hyperglycaemia First Detected in Pregnancy	2013	75 g OGTT	6 weeks	No specific recommendations	No specific recommendations	63
UK	The Endocrine Society	Diabetes and Pregnancy: An Endocrine Society Clinical Practice Guideline	2013	75 g OGTT	6-12 weeks	HbA _{1c} fasting plasma glucose, or 2 hour 75 g OGTT	Not defined (periodically)	72
International PCOS	International Diabetes Federation	Pregnancy and Diabetes	2009	"check for diabetes"	0-6 weeks	"check for diabetes"	1-3 years	73
Country Publishing body Title Year Baseline screening recommendations Tests Frequency Long term screening recommendations Tests Frequency								
US	American College of Obstetricians and Gynecologists (ACOG)	ACOG Practice Bulletin No. 194: Polycystic Ovary Syndrome	2018	75 g OGTT	At diagnosis	No explicit recommendations	No explicit recommendations	74
International	The International Federation of Gynecology and Obstetrics (FIGO)	International evidence based guideline for the assessment and management of polycystic ovary syndrome	2018	OGTT, fasting plasma glucose, or HbA _{1c}	At diagnosis	OGTT, fasting plasma glucose, or HbA _{1c}	A minimum of three yearly, informed by additional risk factors.	75
UK	The Endocrine Society	Diagnosis and treatment of polycystic ovary syndrome: an Endocrine Society clinical practice guideline	2013	75 g OGTT, or HbA _{1c} if patient unwilling	At diagnosis	75 g OGTT, or HbA _{1c} if patient unwilling	Every 3-5 years	76
UK	Royal College of Obstetrics and Gynaecologists	Long term Consequences of Polycystic Ovary Syndrome (Green-top Guideline No 33)	2014	75 g OGTT	At diagnosis	75 g OGTT in those with impaired glucose tolerance or impaired fasting glucose on baseline OGTT	Annual	77
UK	National Institute for Health and Care Excellence (NICE)	Clinical Knowledge Summaries	2022	75 g OGTT	At diagnosis	75 g OGTT in those with impaired glucose tolerance or impaired fasting glucose on baseline OGTT	Annual	78
International	International PCOS Network	Recommendations from the international evidence based guideline for the assessment and management of polycystic ovary syndrome	2018	OGTT, fasting plasma glucose, or HbA _{1c}	At diagnosis	75 g OGTT, fasting plasma glucose, or HbA _{1c}	1-3 years	79,80

GDM=gestational diabetes mellitus; PCOS=polycystic ovarian syndrome; T2DM=type 2 diabetes mellitus; OGTT=oral glucose tolerance test; HbA_{1c}=glycated hemoglobin.

six weeks to three months post partum,⁸¹ though there appears to be a move in the UK and Europe to replace it with fasting plasma glucose or glycated hemoglobin (HbA_{1c}), using the OGTT only where clinically indicated (table 1). No clear consensus prevails for longer term surveillance.

While fewer guidelines exist on screening for type 2 diabetes in women with PCOS,⁷⁴⁻⁸⁰ the consensus regarding screening for pre-existing diabetes at diagnosis is to use an OGTT, with HbA_{1c} being used if OGTT is either unfeasible or undesirable. As with gestational diabetes mellitus, consensus on longer term surveillance is less clear.⁸² However, the International PCOS Network, which brings together experts from a number of professional bodies, recommends that an OGTT is performed in high risk women with PCOS (including those with a body mass index >25 (or >23 in Asians), history of impaired fasting plasma glucose, impaired glucose tolerance or gestational diabetes, family history of type 2 diabetes, hypertension, or in ethnic groups with a high risk), at a frequency of every 1-3 years depending on the presence of other type 2 diabetes risk factors.^{79 80} Some UK guidance suggests that all women with impaired glucose tolerance or impaired fasting glucose at baseline should be screened for type 2 diabetes annually using the OGTT.^{77 78}

Current approaches to screening for type 2 diabetes in women with gestational diabetes mellitus and PCOS

Traditionally, screening approaches for dysglycemia generally focus on one or more biochemical markers, though the common signs and symptoms associated with type 2 diabetes should not be ignored, particularly in high risk subgroups.⁸³

The OGTT is the accepted gold standard for diabetes diagnosis. While the OGTT is still widely recommended for postpartum screening for pre-existing type 2 diabetes in women with gestational diabetes mellitus,⁶² HbA_{1c} or fasting plasma glucose are increasingly superseding it as the test of choice, at least for gestational diabetes mellitus in the UK.

Like fasting plasma glucose, HbA_{1c} levels represent a continuum, and the commonly accepted thresholds in the UK and Europe of 42 nmol/mol for pre-diabetes and 48 nmol/mol for diabetes (39 and 47 mmol/mol in the US) should be treated with some caution.^{62 64 74 77} Particularly so given that all biochemical tests show both biological and analytical variation, meaning that a significant number of cases would be classified differently on repeat testing. According to an analysis of the impact of analytical and biological variation, 29.7% of pre-diabetes cases identified using HbA_{1c} (42-47 mmol/mol) would be reclassified into other groups (6.3% as diabetes and 23.4% as normal) on repeat testing.⁸⁴ Similarly, for fasting plasma glucose, 37.0% of cases classified as "impaired" (6.1-6.9 mmol/L) would be reclassified into other groups (9.8% as diabetes and 27.2% as normal) on repeat testing.

The choice of whether to use HbA_{1c} or fasting plasma glucose is largely based on convenience, as

the performance of the two is relatively comparable,⁸⁴ though each have their limitations. For example, HbA_{1c} is affected by factors affecting red blood cell turnover⁸⁵ and differs from fasting plasma glucose in the effect of population demographics (eg, age and ethnicity distribution).⁸⁴ Fasting plasma glucose has a marginally poorer performance overall owing to higher biological variation, but can perform better (based on the assay variation and width of the diagnostic interval) around the diagnostic cut-offs because of the distribution of values at these levels.⁸⁴

These data emphasize the importance of repeat testing, as recommended in most guidance⁶²⁻⁷³ and other studies.⁸⁴ Hence, diagnosing young women with type 2 diabetes, which carries implications for their insurance and wellbeing, warrants careful consideration of serial results if biochemical markers alone are used.

In addition to assay performance, the relative costs and clinical deliverability of laboratory tests should be considered. Typically, in terms of laboratory costs, an HbA_{1c} test will cost about 10 times the cost of a plasma glucose test (~£3.00 v <£0.30). However, assessment of cost effectiveness will need to consider the other associated costs (both to the patient and healthcare system), as well as the performance of the tests in detecting diabetes. A health technology assessment suggested that, regarding the latter, HbA_{1c} and fasting plasma glucose differed only slightly.⁸⁶ OGTT is more inconvenient and unpleasant for patients, and more time consuming for healthcare staff, thereby limiting its practicability for large scale screening.

Challenges with current guidelines

Despite the guidance outlined above, effective monitoring of type 2 diabetes risk is not without challenges. The challenges are exacerbated by the current lack of international consensus on screening and diagnostic criteria for both gestational diabetes mellitus and PCOS. This lack of consensus causes confusion regarding diagnosis and treatment of gestational diabetes mellitus and PCOS, and thus, a loss of emphasis on their long term sequelae, including type 2 diabetes.⁸⁷⁻⁸⁹

Consistency

One reason for the lack of an effective screening strategy is the absence of a consensus on which tests to use and when. Indeed, for gestational diabetes mellitus, the International Federation of Gynecology and Obstetrics state that "There is no clear guidance about the type of tests...or the frequency and duration for ongoing surveillance."⁹⁰ Some of this uncertainty is derived from the balance between convenience (as offered by HbA_{1c}) versus sensitivity/specificity (as offered by OGTT, also not without its weaknesses). Consequently, as the European Board and College of Obstetrics and Gynaecology suggests, "Currently, there is insufficient evidence to recommend one test over another and therefore HbA_{1c}, FPG or 2 h 75 g OGTT are suitable to test for diabetes and prediabetes."⁹¹

Box 1: Tips for improving adherence to monitoring recommendations

1. Assess the scale of the problem
 - Are there ways in which existing IT systems could be used to assess which women require monitoring tests?
 - Could you work with the local clinical laboratory to audit whether patients are tested in line with guidance?
2. Maximize the potential of existing practice IT systems
 - Review if existing IT reminder systems could be used to track which patients require monitoring. Could these systems be used to automate reminders?
3. Be aware of logistical considerations
 - Review how updating of the reminder system links into current clinical practice. Is it possible, and logistically more straightforward, to link monitoring test ordering to existing regular appointments, even if it results in some overtesting?
 - For women with gestational diabetes mellitus, could this linked reminder system be aligned with existing postnatal appointments?
4. Consider the patient perspective
 - Could testing be provided at a time that is more convenient to patients?
 - For women with gestational diabetes mellitus, could testing be adapted to ensure women with babies or small children are catered for?
 - Are patients aware of the importance of the tests; could a simple leaflet be developed to explain?
 - How do patients prefer to be reminded of tests?
5. Communicate
 - How can communication between general practice and specialist services be improved to prevent missing or duplicating patient appointments? Local practice guidelines and shared care agreements can vary across regions and clinicians needs to be familiar with local arrangements.
6. Implement
 - Could healthcare professionals work with the existing healthcare IT system supplier to help implement any changes to reminder systems?
7. Embed evaluation as part of a continuous improvement cycle
 - Re-audit to see what impact the change has made. How might re-audit be done simply? Think about evaluation as part of the change so that data are collected automatically and reviewed regularly.

For PCOS, the situation appears even more confusing as some guidance suggests that tests should be performed “periodically” but without specific recommendation on what periodically means, or which tests to use.⁷⁴

Adherence, its implications, and how to improve it

Poor adherence to screening guidelines is common
Adherence to monitoring recommendations in guidance is inconsistent. For gestational diabetes mellitus, we and others have highlighted the poor adherence to both postpartum and longer term diabetes monitoring.⁹²⁻⁹⁷ With respect to immediate postpartum screening, the TRIAD cohort study of 14 448 pregnancies showed that the age adjusted and race/ethnicity adjusted proportion of women screened rose from 20.7% in 1995 to 53.8% in 2006.⁹³ Two systematic reviews showed that postpartum glucose screening rates varied between 34-73% and 30-60%.^{94 98} The reviews also noted that the tests used varied significantly between studies.

Fewer studies have been undertaken on longer term screening rates in gestational diabetes mellitus, though we showed that the proportion of women tested in any given year averaged only 34.2% over 17 years, and that the proportion of women tested over time from the index pregnancy progressively declined.⁹² A retrospective cohort study over five years in England showed that about 20% of women were screened in any given year, but only 0.4% had a test in each of the five years of the study.⁹⁷

Screening for type 2 diabetes in women with PCOS is less well studied, but monitoring appears similarly poor. A US cross sectional study in

adolescents showed that about 62% of women aged 11-21 years had an HbA_{1c}, insulin, glucose, or OGTT performed under three secondary care pediatric specialties during the 12 month study period.⁹⁹ In a UK study of requests from general practitioners, we demonstrated that fasting plasma glucose, random plasma glucose, and HbA_{1c} were checked in 7.9%, 6.0%, and 3.4% of women in the 24 months after diagnosis, respectively.¹⁰⁰

These findings of poor adherence to guidance on laboratory test monitoring are common to many other conditions.¹⁰¹⁻¹⁰⁵ We have previously shown that over half of HbA_{1c} tests for patients with frank diabetes are outside the recommended frequency (~20% too soon, ~30% too late).¹⁰³ We also identified similar patterns in thyroid test monitoring in people with hypothyroidism on thyroxine replacement therapy,¹⁰⁴ and in people with bipolar disorder on lithium therapy.¹⁰⁵

Reasons for poor adherence

The reasons for poor adherence to guidance on laboratory test monitoring are complex and multifactorial. They include factors associated with healthcare systems (both people and infrastructure) and those linked to patient factors.¹⁰⁶ For example, studies have highlighted problems such as communication (lack of clear, tailored messaging around importance of screening and risk of not attending for tests, importance of reminders), responsibility (who was responsible for follow-up), time (competing demands for both patients and healthcare staff, distance to travel to appointments), and access (such as for phlebotomy appointments).¹⁰⁷⁻¹⁰⁹

For PCOS, few studies examine the reasons for poor adherence to guidelines. This dearth could be linked to the lack of consensus on what tests to use, in whom, and how frequently.⁷⁵ This lack of consensus is reflected in an online survey of secondary care obstetricians and gynecologists, which showed that 22.3% of respondents would perform a diabetes screening test at diagnosis for at least half of their patients with PCOS.¹¹⁰ This study called for a renewed emphasis on training healthcare professionals on the importance of metabolic screening in these women.

Interventions to improve adherence

To combat the poor adherence to long term monitoring recommendations, a range of interventions have been proposed. In gestational diabetes mellitus, these interventions have generally focused on technology driven reminder systems (text messages, smartphone apps, telephone reminders),¹¹¹⁻¹¹³ with mixed success.¹¹⁴ For PCOS, again, fewer studies have explored this area. One survey based study suggested the development of reminder systems, such as those used in gestational diabetes mellitus,¹¹⁰ but these have yet to be tested. It appears that PCOS is some years behind gestational diabetes mellitus in instigating appropriate systems for metabolic follow-up.

Most interventions fail to accommodate patient centered requirements that deal with the time commitments and access problems raised by women.¹⁰⁷⁻¹⁰⁹ While from a healthcare perspective, developing technology based solutions is easier (and somewhat cheaper), future approaches to improving adherence need to be more holistic and co-produced.

Considering the above, box 1 provides some suggestions for how adherence might be improved based on our own experience and suggestions from the literature.^{107-109 115 116}

The real problem: are we missing the boat?

This lack of screening has, at least in women with gestational diabetes mellitus, been described as a “lost opportunity to prevent early onset of type 2 diabetes.”¹¹⁷ This lost opportunity is almost certainly also true for PCOS; while guidelines fail to achieve complete consensus, experts agree that metabolic risk is significant and warrants long term follow-up.⁷⁴⁻⁸⁰ The challenge is whether the tests recommended in current guidelines maximize the opportunity to “prevent early onset” of type 2 diabetes. Even current guidelines admit the existing shortcoming in current practice; regarding gestational diabetes mellitus, the International Federation of Gynecology and Obstetrics notes that “When guidance exists it is often glucose centric, missing out other important parameters but most importantly it is poorly implemented.”⁹⁰

Traditional tests reflect glycemic irregularities relatively late in the progression to frank diabetes, and might be too late to instigate effective prevention strategies.¹¹⁸ We suggest that the current approach to screening is shutting the door after the horse has

bolted and, therefore, a new strategy is needed. If we are to genuinely seek to prevent early onset, we need to examine the underlying pathophysiology to identify changes much earlier in the pathway, and create a new paradigm for diabetes screening and prevention.

Emerging approaches to detection and management Screening strategies

Given the pitfalls inherent in use of biochemical markers in isolation, strategies which integrate multiple parameters as part of stepwise risk stratification approaches have been proposed.¹¹⁸

Despite the overlap in underlying pathophysiology for both gestational diabetes mellitus and PCOS, a unified screening strategy might not be the best option, given the differences in risk factor profile for each group (fig 1). Furthermore, such strategies, which are likely to differ in the composition and weighting of the biochemical, anthropometric, personal, and other factors, would also need to take into account phenotypical subtypes (eg, in women with PCOS, lean v obese, and hyperandrogenic v normoandrogenic). The aim of such strategies would be to identify the preferred biochemical markers used and the frequency of screening, which itself could vary over time. The use of dynamic modeling approaches would allow the ongoing assessment of risk over time as parameters change.

Several models have been developed for predicting risk of gestational diabetes mellitus.¹¹⁹ However, most are based on studies with questionable methodological quality, and few have subsequently been independently validated. A systematic review and meta-analysis identified several risk factors for type 2 diabetes in women with gestational diabetes mellitus.¹²⁰ These included maternal age, body mass index, ethnicity, and family history of diabetes.¹²¹ More recently, models developed using the machine learning approaches highlight the importance of factors linked to key metabolic process (insulin sensitivity, β cell function, and insulin clearance).^{122 123} We are not aware of any equivalent models for PCOS, though several studies identified candidate predictors.³²⁻³⁴

In general practice, some models have been incorporated into risk prediction tools for type 2 diabetes (eg, QDiabetes-2018 diabetes risk calculator), though these are not specific to gestational diabetes mellitus or PCOS.^{124 125} While gestational diabetes mellitus itself is a strong predictor of type 2 diabetes risk in QDiabetes-2018, revised dynamic models specific to gestational diabetes mellitus and PCOS are needed, which incorporate condition specific factors such as those associated with pregnancy (for gestational diabetes mellitus) or hyperandrogenism (for PCOS), as well as common diabetes associated factors (fig 1).

Furthermore, current strategies for screening for type 2 diabetes in gestational diabetes mellitus and PCOS lack the ability to account for (a) differences in risk factors for development of type 2 diabetes and

its precursors (both composition and weight), (b) the nuances of the effect of subphenotypes, and (c) the need to consider different and novel biomarkers of dysglycemia, particularly those that allow earlier detection of dysglycemia. We propose that studies are needed to adapt models such as QDiabetes-2018¹²⁴ specifically for gestational diabetes mellitus and PCOS populations, to underpin new screening strategies. These would need to be clinically deliverable, integrated into existing systems, and then fed into revised guidelines.

Early detection

Little is known about the interaction between β cell function and insulin resistance before and leading up to type 2 diabetes. However, prospective data from the Whitehall II study attempted to characterize the glycometabolic 13 year trajectories, comparing those developing type 2 diabetes with those not developing it.¹²⁶ Multilevel models, adjusted for age, gender, and ethnic origin, showed that in the non-diabetes group, all metabolic measures followed linear trends (except for insulin secretion which remained unchanged). In the diabetes group, however, fasting glucose initially increased in a linear manner, followed by a steep quadratic increase (from 5.79 to 7.40 mmol/L) starting three years before diabetes diagnosis. The two hour post-glucose load rapidly rose (from 7.60 to 11.90 mmol/L) starting three years before diagnosis. Homeostatic model assessment (HOMA) insulin sensitivity decreased steeply during the five years before diagnosis. HOMA β cell function increased between years 4 and 3 pre-diagnosis, and then decreased until diagnosis.

These changes support the hypothesis of multistage evolution of diabetes (fig 3).¹²⁷ Therefore, our aim should be to identify women with gestational diabetes mellitus or PCOS at stage 1 or 2, rather than at stage 4 (or late stage 3).

Clearly measuring glycemic surrogates (including fasting plasma glucose and HbA_{1c}) are insufficiently sensitive for early detection. So, what alternatives could be considered that detect the early changes in both insulin resistance and β cell function?

Various surrogates exist for insulin resistance and β cell function, though most are currently not widely used in clinical practice. One prospective study suggested that the insulin-like growth factor system represents a potential area to explore in relation to markers for insulin resistance and risk of future type 2 diabetes.¹²⁸ Insulin sensitivity can be measured relatively easily by measuring HOMA (which uses the product of fasting glucose and insulin concentrations).¹²⁹ Estimation of insulin sensitivity (HOMA-S) had been proposed to have a role in epidemiological studies identifying women with PCOS with insulin resistance with a view to targeting them with insulin sensitizing agents.¹³⁰

β cell function is often evaluated using basal insulin. However, for this evaluation to be combined with assessment of insulin sensitivity, the measurements for insulin sensitivity should be as independent as

possible from the measurement for β cell function; otherwise, the measure risks erroneous results.¹²⁰ Out of the available options, the disposition index, which evaluates both components (see section above on disposition index and alternative measures of insulin reserve and sensitivity) was found to independently predict the conversion to diabetes irrespective of degree of glucose tolerance, risk of diabetes associated with family history, body mass index, race, and ethnicity.^{59 131} The disposition index, while it might seem to have the potential to become a gold standard, is not practical for clinical settings.

A promising tool for measuring the disposition index in epidemiological work has been established from the 75 g OGTT, termed OGIS (oral glucose insulin sensitivity). OGIS requires three samples for measurement of plasma glucose and insulin: fasting, 90 minutes, and 120 minutes. These samples provide adequate information for estimation of disposition index in large scale studies as a potentially cost effective tool for research purposes.^{132 133}

The challenge arises when the number of women who might require regular (possibly annual) monitoring is considered. Use of complex tests such as disposition index or HOMA-S are not cost effective or logistically practical for estimation of disposition index in a clinical setting for such large numbers if all cases are included. Hence, a stratified, model driven approach might be required; for example, use of risk stratification tools for future development of type 2 diabetes specific to gestational diabetes mellitus and PCOS. Such tools would allow testing modality and monitoring frequency to be tailored based on risk, with perhaps only those at highest risk warranting the three point OGTT and disposition index calculation described above. For those in the lower risk categories, monitoring using conventional tools might be appropriate, but with closer scrutiny of trajectories over time.

Ultimately, these studies will inform development of risk stratification models using anthropometric and laboratory measures suitable for wider community implementation.

Early intervention

Clearly, early detection is of little value without effective timely interventions. On the positive side, progressive deterioration in insulin resistance and β cell function is not irreversible. Studies on the effect of bariatric surgery and lifestyle interventions show that insulin production decreases in response to interventions that enhance insulin sensitivity.^{126 134} Furthermore, clinical trials and observational studies using metformin and other antidiabetic agents have shown promise in reducing insulin resistance and have been proposed as part of a primary prevention strategy.^{134 135} These results should encourage clinicians and researchers to evaluate the disposition index status in women with PCOS and gestational diabetes mellitus, by seeking to prevent, or at least delay, the onset of type 2 diabetes, rather than

merely screening for it. The current challenge is how to implement such interventions at a national level in the face of the increasing demands on global health systems. Exploring the process of implementation of a national diabetes prevention program and the availability of pharmacological weight interventions provide hope in this regard, and are reviewed elsewhere.^{136 137}

Conclusion

Both gestational diabetes mellitus and PCOS represent major and increasingly common risk factors for future development of type 2 diabetes, affecting up to 20% of women (most of whom are young). However, despite the importance of these factors, we are not aware of any clear public health strategy to deal with them, even in countries with mature healthcare systems. Adherence to guidance on monitoring, when present, is poor, and, in terms of PCOS, the lack of clear and consistent international guidance is hampering progress by sending mixed messages to healthcare professionals on the importance of ongoing monitoring. Tools used to deal with this lack of adherence are variable in their effectiveness and are overly reliant on technology based reminder systems. We advocate a more holistic approach to ensure women have adequate information regarding risk and sufficient access to services that meet their needs.

Furthermore, existing strategies for detecting dysglycemia in these women generally come too late to allow effective early intervention to prevent

GLOSSARY OF ABBREVIATIONS

- PCOS: polycystic ovarian syndrome
- PI3K: phosphatidylinositol 3-kinase
- IRS-1: insulin receptor substrate
- OGTT: oral glucose tolerance test
- OGIS: oral glucose insulin sensitivity
- IVGTT: intravenous glucose tolerance test
- ISSI2: insulin secretion sensitivity index 2
- HbA1c: glycated hemoglobin
- HOMA: homeostatic model assessment
- HOMA-S: estimation of insulin sensitivity

or delay the development of type 2 diabetes. Risk stratification modeling and glycemic trajectory tracking studies to facilitate effective, early, and targeted type 2 diabetes detection strategies are lacking. The development of more effective tools to identify early glycemic deterioration in young women is urgently required.

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Patient involvement: This work has been informed by our longstanding link with the local branch of Diabetes UK and ongoing discussion with many patients with gestational diabetes mellitus and PCOS in relation to their risk of type 2 diabetes.

In structured telephone interviews with seven patients with gestational diabetes mellitus on the topic, their appreciation of future type 2 diabetes risk based on earlier consultations varied widely from 10-50%. However, they all expressed concern about their future risk and would welcome a personalized screening approach that balances the need for both reassurance and early intervention where necessary without imposing on their busy lives. This feedback informed the structure of this review and the importance of consistent information on risk, early detection, and personalized approaches to monitoring.

The importance of (frequently neglected) discussions around future diabetes risk and the need for screening is also exemplified by the experience of one woman with PCOS as described in the patient perspective box.

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QUESTIONS FOR FUTURE RESEARCH

- How should international guidelines for long term screening for type 2 diabetes in gestational diabetes mellitus and PCOS be clarified to provide a clear message to patients and healthcare professionals on the risk of type 2 diabetes and importance of regular monitoring?
- How can patients be more included in the development of effective approaches to improve adherence to diabetes monitoring?
- What simple tests could be developed to facilitate earlier detection of dysglycemia in large numbers of women?
- What studies need to be designed to identify and validate these tests? How could their cost effectiveness be evaluated?

A PATIENT PERSPECTIVE

My experience with PCOS started with a visit to gynecology where I reported increased facial hair growth, a history of acne, and irregular menstrual cycles. While a resulting ultrasound scan did not detect cysts on the ovaries, I was diagnosed with PCOS swiftly and discharged with the order to “lose weight.”

Unfortunately, I wasn't made aware of any implications of the condition at this point, including the need to screen for diabetes. While it seems obvious in hindsight, a discussion on diabetes could have helped motivate me to be even more proactive with my efforts to lower my body mass index.

It was not until I raised the topic of fertility and hormonal imbalance at a gynecology appointment around two years later, that I felt appropriate attention was given to my diagnosis. Indeed, one of the greatest challenges has been dealing with the stigma of being overweight and finding a professional who can sensitively discuss this while acknowledging the difficulties compared with someone without PCOS.

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