1 RATIONALE FOR THE SCREENING OF GESTATIONAL DIABETES MELLITUS (GDM) IN HONG KONG

1.1 It has been shown by a study in a multiethnic population that there is increasing prevalence of GDM across all ethnic groups when the same Oral Glucose Tolerance Test (OGTT) and diagnostic approach was applied 1.

1.2 Studies conducted in multiethnic societies in North America, England, and Australia have all indicated that irrespective of the type of OGTT, Asians and Chinese have the highest prevalence of GDM 16.

1.3 Recent international recommendations on the screening of GDM have emphasized the need for screening in Asians irrespective of other additional risk factors 7-9.

1.4 There is now clear evidence in the literature for an association between GDM and increased obstetrical and perinatal complications. While the incidences of different complications may vary among different studies, increased risk of certain complications has been consistently reported in the literature. These complications include pre-eclampsia / pregnancy-induced hypertension, preterm birth, urinary tract infection, antepartum haemorrhage, caesarean delivery, neonatal polycythaemia and hyperbilirubinaemia, perinatal infection, birth asphyxia, birth trauma and increased fetal size 1,10-15. Furthermore, treatment can improve perinatal outcome and reduce mortality rates 1,5,13. The effect of treatment on the reduction of serious perinatal morbidity has been confirmed in the most recent study by Crowther et al 16.

1.5 There has been limited data from Hong Kong to allow an adequate assessment of the effect of GDM on pregnancy. In the annual statistics of the Department of Obstetrics and Gynaecology, The University of Hong Kong, there has been a progressive increase in the prevalence of GDM. Using the original World Health Organization (WHO) criteria 17, the prevalence of GDM increased progressively from 5.9% in 1988 to 10.8% in 2002. A study performed in the Prince of Wales Hospital, also using the WHO criteria, had found that the prevalence of GDM was 14.2% 18. Thus there can be little dispute that GDM has become one of the most common, if not the commonest, medical complication during pregnancy in Hong Kong.

1.6 A number of local studies that focused on diet-treated GDM have recently been published. The findings indicated that the impact of mild GDM in Chinese women is similar to that reported in the literature, and included increased incidence of preterm birth,
pre-eclampsia, urinary tract infection, large-for-gestational age infants, neonatal jaundice requiring treatment, and admission into the neonatal unit.\(^{19-21}\) Moreover, GDM remains to be one of the leading causes of stillbirth.\(^{22}\) These effects were found despite the instigation of treatment. These findings implied that if treatment was to be withheld, or that the diagnosis were not made, the pregnancy outcome would have been much worse. Such a concept is consistent with the finding that treatment reduces serious perinatal morbidity\(^{16}\) and stricter control of GDM has improved perinatal outcome.\(^{13}\) Thus the diagnosis and treatment of GDM is one of the effective means of maintaining a high standard of obstetric care in Hong Kong.

## 2 SCREENING OF GDM

### 2.1 Rationale for screening

The majority of the women with GDM remains asymptomatic, and only a small percentage display complications or features suggestive of GDM. Furthermore, these features tend to be late signs of the effect of GDM, and subsequent treatment may not be effective in time to prevent or reduce the occurrence of complications. In view of the high prevalence of GDM, screening is the only effective way of identifying those who are affected in time for treatment.

### 2.2 Screening by risk factors

It is already an established practice that women at high-risk of GDM are tested for glucose intolerance during pregnancy. Hence the identification of risk factors constitutes a form of screening. Among the risk factors identified in the literature, ethnicity appears to be the most significant, and various recommendations all stated that Asians constituted such a high risk category that they should undergo screening irrespective of the other risk factors such as maternal age.\(^{7-9}\) This would imply that the almost the entire obstetric population in Hong Kong should be tested, following the primary screening by ethnicity, with the OGTT. Indeed, in the Department of Obstetrics & Gynaecology, The University of Hong Kong, universal screening for GDM with the oral glucose tolerance test (OGTT) has become the protocol since 2003. However, a very high risk group can be further targeted using a combination of classical risk factors such as advanced age and obesity, together with other newly reported risk factors, to enable an early diagnosis of GDM to be made. Since women with these risk factors can be considered as having positive screening, they should proceed directly to the diagnostic OGTT. The risk factors for GDM\(^{3, 5, 9, 14, 19-21, 23-29}\) are listed in Appendix 1.

### 2.3 Screening by maternal blood glucose measurement

For the majority of the local obstetric population, there may not be any risk factor other than ethnicity. In this case, some form of biochemical test is necessary. The testing of glycosuria is not acceptable as a screening test. An acceptable screening test must involve the estimation of blood glucose in one of the following forms: (Appendix 2).

#### 2.3.1 Random glucose screening

This is used in several obstetric units in Hong Kong (Appendix 2). The postprandial glucose level is not influenced by gestation at testing.\(^{30,31}\) In the
recent recommendation of the WHO consultation \(^8\) a random capillary plasma glucose (RCPG) of \(\geq 12.2\) mmol/L is classified as “diabetes likely”, and RCPG of \(< 5.5\) mmol/L is “diabetes unlikely”. In a study on a non-pregnant Asian population, 4.7% of subjects with RCPG \(< 6.1\) mmol/L and 19.7% of subjects with RCPG between 6.1 and \(< 13.3\) mmol/L had diabetes. \(^32\) Nevertheless, while women with GDM had significantly higher random glucose level than the women with positive screening but normal OGTT, who in turn had higher random glucose level than the women with negative screening \(^31\), the validity of a random glucose measurement for screening has not been thoroughly tested in prospectively studies. Using the RCC curve, a local study has shown that the random glucose is inferior to both the glucose challenge test and the fasting glucose with the optimal cutoff value set at 4.7 mmol/L as guided by the Youden index. \(^33\) The advantage of the random glucose test is that it is convenient for both the patients and doctors, and a high enough random glucose value alone can be diagnostic of GDM. \(^3\)

2.3.2 The 50g Glucose Challenge Test (GCT)

The GCT has been a popular test and is used in many centres especially in the U.S.A, and it is administered without regard to the time of day or the time elapsed from the last meal. In Singapore, a study on 146 patients with no risk factors suggested that using a threshold plasma glucose level of 7.1 mmol/L, 36% of them needed to undergo the 75g OGTT and the diagnostic yield was 22.6% (12/53). \(^34\) Using 7.8 mmol/L as the threshold value, 20% needed the OGTT and the diagnostic yield was 28.6%. The study concluded that the GCT is useful for Singaporean women and the threshold of 7.8 mmol/L is appropriate. However, when the actual data was scrutinised, the threshold of 7.8 mmol/L allowed the identification of only 67% (8 out of 12) of the women with GDM, and the merit of this approach is debatable. It has been known for some time that the glucose response is lower if the GCT is performed 1 hour after a test meal \(^35\). This observation was subsequently confirmed in another study that demonstrated a significantly higher glucose response when the 50g glucose load was administered in the fasting state \(^36\). The study concluded that the prandial state (i.e. fasting or postprandial) exerts an effect sufficient enough to alter the sensitivity and specificity of the GCT. Recently, it has been shown that the percentage of women with a positive screening test result was significantly higher when the GCT was done in the afternoon (31.1%) compared to the morning (17.0%). \(^37\) On the other hand, women with a positive screening test result in the afternoon was less likely to be diagnosed with GDM by the 75g OGTT (31.5% versus 40.0%), but a greater percentage of the total number screened in the afternoon had GDM (9.8%)
versus 6.8%). It has been pointed out that since the screened positive women need to undergo an OGTT for confirmation, the diagnosis will be delayed, that the GCT is non-specific, and that some of the GCT-positive women who do have GDM will not return for the definitive GTT. Women who found the glucose load for the OGTT intolerable will have difficulty with the GCT as well. The logistical problem, the possible delay in making a diagnosis, and the effects of factors like meals and timing of the test all render the test less preferable than the OGTT for the high-risk population. In Hong Kong, it has been shown that the optimal cutoff value is 7.0 mmol/L for the local population, but that there was no significant difference with either the fasting or the 2-hour postbreakfast glucose, and this non-physiological test was recommended against. The recommended cutoff value for the GCT is shown in Appendix 2.

2.3.3 Fasting plasma glucose (FPG)

Fasting plasma glucose (FPG) has recently been recommended to be a more cost effective means of screening for GDM, and studies conducted in various centres with different ethnic group suggested that the OGTT can be eliminated in a significant proportion of the subjects with much cost saving. However, there is no consensus on the cutoff value, which varied from 5.17–5.39 mmol/L, 4.5–4.9 mmol/L, to 4.8 mmol/L, and which is related to the specific value in and the type of the OGTT. One of the studies also used a FPG value of <4.4 mmol/L to run out GDM and ≥ 5.3 mmol/L to rule in GDM. In the Hong Kong Chinese, the optimal value was suggested to be 4.1 mmol/L. However, another study in the same centre suggested that the FPG corresponding to a 2-hour plasma glucose value of 11.1 mmol/L was 5.6–5.8 mmol/L, and that 71.4% of women with the WHO category of diabetes mellitus will be missed if the 2-hour glucose level was not used for diagnosis. While the FPG has also been recommended to replace the GCT for the screening of GDM in Hong Kong, the optimal cutoff value may need to be further determined. Indeed, the sensitivity of using the FPG for screening has been challenged. Certainly, in an area with a high prevalence of GDM, there may not be any advantage to use the FPG for the screening of GDM.

2.3.4 2-hour postbreakfast glucose

This has been examined in the Prince of Wales Hospital and the result is comparable to that of the GCT as well as the FPG, with an optimal cutoff value set at 5.0 mmol/L. However, the major problem is the accurate timing of blood sampling for outpatients, and the exercise involved in commuting to the clinic for blood sampling after breakfast could have affect the glucose level and hence its sensitivity. There is not yet
enough evidence for its application as a standard screening test.

2.4 Time of screening

2.4.1 Screening by risk factors can be done at the very first antenatal visit. The later appearance of risk factors before any biochemical screening has taken place can also be considered as positive screening, an example of which is the appearance of polyhydramnios or excessive fetal growth. Under such circumstances, we should proceed directly to the OGTT.

2.4.2 For the low-risk population, the recommended gestation for universal screening is around 24-28 weeks \(^7,8\). This is because the majority of women with GDM develop this condition in the last trimester. In the public hospitals of Hong Kong, the current arrangement of shared-care with the Maternal and Child Health Centres for low-risk women means that they only return to the obstetric clinics at or after 28 weeks. Performing the screening at 28-30 weeks, together with a repeat blood count to screen for the development of anaemia, will be a more efficient approach. As well, this will reduce the chance of missing the development of GDM in the last trimester.

3.2 The diagnosis can also be made on the basis of a random glucose as recommended by the World Health Organization (WHO) (Appendix 3). This may happen in the situation where GDM is strongly suspected on clinical grounds, or where an incidental finding of a high glucose level was made during investigation and monitoring for other conditions, or when the women cannot tolerate the glucose drink for the OGTT.

3.3 A number of different OGTTs are used internationally, with the oral glucose load varying from 50g to 100g. A woman should be considered to have GDM if her OGTT result has satisfied the standard diagnostic criteria published in the literature for that form of OGTT. This scenario may occur especially if the woman has the OGTT arranged by doctors other than her obstetrician. In such cases, the documentation in the medical records should include the reference cutoff values.

3.4 For women tested for the first time in pregnancy, the standard test performed should be the WHO 75g OGTT. The 75g OGTT is being increasing adopted worldwide, and the data generated in Hong Kong can be compared with those from other centres as well as with the WHO figures. In the WHO criteria \(^8,17\), there are two categories i.e. impaired glucose tolerance (IGT) and diabetes mellitus (DM). In the WHO recommendation, both IGT and DM are included in the diagnostic spectrum of GDM. Studies outside Hong Kong have shown that the WHO 75g OGTT can identify more abnormal outcomes and missed fewer perinatal complications compared
with the 100g OGTT using the National Diabetes Data Group criterion \(^{24, 44}\). Local studies have confirmed that GDM, as diagnosed with the 75g OGTT, was similarly associated with increased maternal and perinatal morbidity \(^{19-21}\) as well as preterm birth \(^{45}\), despite the fact that the majority of the women belonged to the milder category of IGT. The impact of IGT on the fetus was also confirmed by another local study in which a significant biochemical effect can be found in the newborn of IGT pregnancies, with raised cord C-peptide and insulin concentrations \(^{46}\). Thus the WHO 75g OGTT is the preferred diagnostic test for GDM in Hong Kong.

3.5 In apparently “normal” women with or without a prior OGTT, the OGTT should be repeated or performed when unexpected outcomes or complications are encountered, such as unexplained fetal macrosomia (in the absence of risk factors such as postterm pregnancy, maternal obesity etc) or intrauterine death. There have been occasions when the diagnosis has been missed, or that GDM has developed very recently. The confirmation of otherwise of GDM will help the counseling of the woman and provide information for the subsequent management of the index or future pregnancy.

3.6 The use of glycosylated haemoglobin (HbA1c) in the diagnosis of GDM is not helpful because the glucose intolerance is of recent onset and cannot be reflected in the level of HbA1c, which serves as an indicator of the degree of glycaemia around 4-6 weeks before blood sampling. The measurement of HbA1c is useful when there is a need to distinguish genuine GDM from undiagnosed pre-existing diabetes, when glycaemic control is unsatisfactory; and when previously undiagnosed diabetes is thought to be the cause of stillbirth, infant macrosomia, and congenital anomalies, in the index pregnancy.

### 4 RECOMMENDATION

4.1 All low-risk pregnant women of Asian origin attending the antenatal clinics of Hong Kong should ideally be screened for gestational diabetes mellitus at between 24-30 weeks gestation, i.e. universal screening should be considered in Hong Kong.

4.2 For Asian/Chinese women without the aforementioned risk factors, the method of screening should be standardized and in the form of either a 50g GCT or a FPG. In an urgent situation, such as the late presentation of obstetric complications that could be related to GDM, a random glucose screening may also be helpful. An abnormal screening result should be followed by the 75g OGTT in order to establish or rule out the diagnosis of GDM.

4.3 Women with risk factor(s) should proceed directly to the 75g OGTT after booking for antenatal care. This will avoid missing women with asymptomatic pregestational diabetes which is associated with increased risk of fetal anomalies and loss. If the initial result was normal, a repeat test should be done at 28-30 weeks gestation to exclude GDM developing in the third trimester.

4.4 75 g OGTT can be adopted as a diagnostic test.

4.5 All pregnant women diagnosed to have IGT or DM by the WHO criteria should be managed as GDM. The treatment and monitoring of GDM is given in Part 2 of the guidelines.
Appendix 1  Risk Factors for the GDM in Asian /Chinese Women

- Maternal age ≥ 35
- Body Mass Index ≥ 25kg/m² before pregnancy or at booking in the first trimester
- Family history of diabetes mellitus, especially in parents
- Carrier of the α-thalassaemia trait
- Carrier of HBsAg

- Past Obstetric History
  - GDM
    - Macrosomic infant
    - Unexplained stillbirth
    - Congenital malformations that could be compatible with diabetic embryopathy
    - Pre-eclampsia/eclampsia

- Current Pregnancy
  - Conceived after ART/IVF, especially for conditions such as PCOS
    - Multiple pregnancy
    - Haemoglobin >13 g/dl in the first trimester
    - Polyhydramnios
    - Fetal size > date (AC > HC before 34 weeks, AC > 95th centile or EFW > 95th centile)
    - Recurrent and significant glycosuria (≥ 2 plus)
    - Currently on medications such as steroid or other immunosuppressants
    - Unexplained fetal demise
    - Unexplained macrosomic infant
Appendix 2 | Screening for GDM

A. Random glucose (local population):
   1. Plasma: venous ≥ 5.8 mmol/L if ≤ 2h postprandial\textsuperscript{21}
   Plasma: venous ≥ 5.0 mmol/L if > 2h postprandial\textsuperscript{21}
   or
   2. Plasma: venous > 4.7 mmol/L\textsuperscript{32}

B. 50g Glucose Challenge Test:
   1. International\textsuperscript{34}
      - Plasma: venous: > 7.8 mmol/l
   2. Local population\textsuperscript{33}
      - 7.0 mmol/L

C. Fasting glucose:
   1. International\textsuperscript{38-40}
      - Plasma: 4.5 – 5.39 mmol/L
   2. Local population\textsuperscript{33}
      - 4.1 mmol/L
Appendix 3  Diagnosis of GDM

- By 75g OGTT –

*Diabetes mellitus*:

Fasting - Whole Blood : venous ≥ 6.1 mmol/l

                  capillary ≥ 6.1 mmol/l

                                Plasma : venous ≥ 7.0 mmol/l

&/or 2 h postglucose load - Whole blood : venous ≥ 10.0 mmol/l

                  capillary ≥ 11.1 mmol/l

                                Plasma : venous ≥ 11.1 mmol/l

*Impaired glucose tolerance*:

Fasting - Whole Blood : venous < 6.1 mmol/l

                  capillary < 6.1 mmol/l

& 2h postglucose load - Whole blood : venous ≥ 6.7 and < 10.0 mmol/l

                  capillary ≥ 7.8 and <11.1 mmol/l

                                Plasma : venous ≥ 7.8 and <11.1 mmol/l

- By random glucose –

Whole Blood : venous ≥ 10.0 mmol/l

                  capillary ≥ 11.1 mmol/l

                                Plasma : venous ≥ 11.1 mmol/l

                  capillary ≥ 12.2 mmol/l

Note: GDM includes both the categories of DM and IGT.
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This guideline was produced by the Hong Kong College of Obstetricians and Gynaecologists as an educational aid and reference for obstetricians and gynaecologists practicing in Hong Kong. The guideline does not define a standard of care, nor is it intended to dictate an exclusive course of management. It presents recognized clinical methods and techniques for consideration by practitioners for incorporation into their practice. It is acknowledged that clinical management may vary and must always be responsive to the need of individual patients, resources, and limitations unique to the institution or type of practice. Particular attention is drawn to areas of clinical uncertainty where further research may be indicated.