Recommendations and management of hyperglycaemia in pregnancy during COVID-19 pandemic in Italy

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ABSTRACT

Many specialists use the remote management of people with chronic disease as diabetes, but structured management protocols have not been developed yet. The COVID-19 pandemic has given a big boost to the use of telemedicine, as it allows to maintain the physical distance, essential to the containment of contagion having regular health contact. Encouraging results related to the use of telemedicine in women with hyperglycaemia in pregnancy, have been recently published. It is well known that hyperglycaemia alters the immune response to infections, that inflammation, in turn, worsens glycaemic control and that any form of hyperglycaemia in pregnancy (HIP) has effects not only on the mother but also on development of the foetus. Therefore, the Italian Diabetes and Pregnancy Study Group, together with a group of experts, developed these recommendations in order to guide physicians in the management of HIP, providing specific diagnostic, therapeutic
1. Introduction

In recent weeks, some studies have been published on COVID-19 infection in pregnancy, evaluating maternal and foetal outcomes, and the vertical mother-foetus transmission of infections even in pregnancies complicated by pregestational diabetes [1–6]. The data are discordant, especially with regard to vertical transmission, but undoubtedly the high risk of developing hypertensive and respiratory complications (based on the evidence available in the non-pregnant diabetic population) allows to assume that the risk of unfavourable outcomes and mortality, are higher in pregnant women with diabetes [7,8]. In fact, during pregnancy, even modest glycaemic alterations are more frequently associated with gestational hypertension and preterm birth.

Usually, hyperglycaemia affects one in seven pregnancies, and hypertension affects one in ten. This means that we need a standardized protocol for managing all pregnancies complicated by both gestational (GDM) and pre-gestational diabetes, in order to prevent and reduce the risk of adverse maternal and neonatal outcomes. This is in agreement with current ministerial measures aiming at protecting public health, such as physical distancing and self-isolation, for controlling the risk of exposure to SARS-CoV-2 [9,10].

The Italian Prime Ministry Decree -dated March 11, 2020- detailed such measures for the containment of Coronavirus infection, including travel restrictions throughout the Country, closure of non-essential businesses and public places, etc. Listed among the exceptions is the possibility for patients to travel for “outpatient visits during pregnancy”. The decree confirmed the current setting of networks for outpatient maternal-neonatal care, as well as the access to hospitals and clinics. Diagnostic imaging, laboratory testing and other procedures specific for gestational age are also guaranteed, if all recommended safety measures are in place.

The use of telemedicine in women with GDM has been assessed in a recent meta-analysis of 32 studies [11]; the results showed that pregnant women followed through telemedicine have better glyco- metabolic parameters than the control population and a lower incidence of adverse maternal and foetal outcomes, including caesarean section (C-section), neonatal hypoglycaemia, macrosomia, preeclampsia, preterm birth, neonatal asphyxia and polydramnios.

Therefore, in light of the current emergency and given the potential of telemedicine in the management of diabetes in pregnancy, rapid implementation of remote access to prenatal care is needed to ensure a high quality of care, minimise the travel of pregnant women to reach specialised centres and ensure direct contact with health staff.

In this scenario, the number of outpatient visits for pregnant diabetic women with good metabolic control could be reduced; a portion of the visits should be conducted by telemedical contacts (telephone, telemedicine and/or PC), after the patient has sent the clinical data, laboratory results and home glucose monitoring records needed for medical evaluation.

2. Aim

The purpose of these Diagnostic, Therapeutic and Assistance Pathways (PDTAs) is to offer specific recommendations to clinicians on the management of hyperglycaemia in pregnancy (HIP) during COVID-19 pandemic.

The recommendations provided in this document should be intended as suggestions, which should be adjusted according to the needs, resources and limitations of individual centres and on the basis of the risk-to-benefit contingent ratio as assessed by the CARE TEAM in each specific situation.

The goal of this document is not to replace previous guidelines on the management of diabetes in pregnancy [SID/AMD Care Standard 2018 [12] or any subsequent updates], but it should instead be considered as a tool for the emergency period for the COVID-19 pandemic, for the following period and could be supportive in the future reorganization of the specialist services too. Scientific evidence clearly indicates that hyperglycaemia alters the immune response to infections while the inflammatory state, in turn, worsens glycaemic control; for these reasons it is mandatory to seek optimal glycaemic control in all pregnant women, with any level of hyperglycaemia even and especially during COVID-19 pandemic [13].

2.1. Rational

Although pregnancy involves changes in the immune system that may increase the risk of contracting viral respiratory infections, there are still no reliable data on the transmission of COVID-19 infection to the foetus [5–7,14], as in the previous SARS-CoV and MERS [2] outbreaks. For this reason, it is essential that pregnant women take preventive actions to reduce the risk of infection and avoid contact with sick people. Consequently, the access to healthcare facilities should be reduced, and procedures of shared management through communication, recording and monitoring of clinical data need to be defined and standardized. In Italy, most diabetology outpatient clinics use the same informatic folder tool and remote registration processes of glycaemic self-monitoring data are being developed through specific Apps.

The drafting of PDTAs, provides support to the clinical practice and is aimed at standardizing visits. In the coming months, visits should be carried out mainly by telematics, aiming to protect pregnant women from possible infections and, at the same time, in order to continue to provide women with an effective and efficient service for the management of diabetes in pregnancy.
2.2 Preconception counselling in women with diabetes

We reiterate the importance of pregnancy planning for the woman with pregestational diabetes. It is necessary to evaluate the degree of metabolic control and thyroid function and the presence of chronic complications of diabetes. If the parameters are off target, it will be necessary to achieve stabilization-optimization before conception.

The choice of a specific hypoglycaemic and/or antihypertensive treatment must be appropriate and indicated for pregnancy. Any oral antidiabetic drugs and any non-insulin injection therapy should be discontinued and, when appropriate, insulin therapy should be started. Folic acid is recommended before conception, whereas treatment with statins, ACE inhibitors and angiotensin receptor blockers should be discontinued.

2.3 Glycaemic targets

We confirm the glycaemic targets for pregnancy indicated in the current guidelines and shown below: Fasting glucose < 90 mg/dl (<5 mmol/L).

One-hour postprandial glucose < 130 mg/dl (<7.22 mmol/L).

Two-hour postprandial glucose < 120 mg/dl (<6.66 mmol/L).

We reiterate the need for intensive self-monitoring of blood glucose and for the optimization of insulin doses to be balanced against the risk of hypoglycaemia. The frequency of self-monitoring blood glucose (SMBG) or flash glucose monitoring (FGM) should be adjusted.

Keeping in mind these premises, below we propose type, frequency and mode of diabetes care visits during pregnancy, in accordance with the restrictions needed for COVID-19 emergency.

3.0 Type 1 diabetes

At the recognition of pregnancy in progress, the haematological test listed below should be prescribed, and diabetes care visit should be scheduled within the first trimester (Fig. 1):

**Haematological tests:** Complete blood count, HbA1c, Urine exam, TSH (TPO-Ab if not available during pregnancy programming), total cholesterol, triglycerides, HDL cholesterol, creatinine, azotaemia, microalbuminuria.

Screening for Chronic Complications:

a. **Ophthalmologic exam:** recommended before delivery in pregnant women with good glycaemic control and without Diabetic Retinopathy (DR) 12 months prior conception; a new control should be scheduled shortly if DR is already present or if a rapid reduction of glycaemic values is required; any further follow-up should be evaluated according to the ophthalmologist opinion.

b. **ECG:** recommended before delivery if already performed within the 12 months prior to conception and in the absence of significant abnormalities. Otherwise, ECG should be scheduled in the first trimester. In case of significant abnormalities at the ECG, a cardiac ultrasound examination should be performed, according to the cardiologist opinion.

The reports of the exams may be sent electronically to the diabetologist, who will assess the need for an outpatient visit, or digitally provide the necessary indications.

At the first visit during pregnancy the patient will be provided with:

- Educational therapy by nursing staff for the management of Self-Monitoring Blood Glucose (SMBG) controls; patient’s skills for the prevention and management of hypoglycaemia and ketones will also be evaluated.

- All materials necessary for SMBG.

- Instructions for telematic contacts and for the APPs useful for clinical Data Sharing.

- Dietary plans for the first and second trimester.

- Up-dated Insulin to Carbohydrates ratio (I:CHO) and Insulin Sensitivity Factor (ISF).

- Advice for physical-activity (indoor or outdoor if possible) in accordance with the obstetric team.

- A final report and informative brochures.

If insulin pump therapy and/or continuous glucose monitoring is ongoing, specific instructions regarding the management of these instruments will be provided, with particular attention to the electronic transmission of recorded data to the diabetes care team.

It is strictly needed to provide all the required instructions if they have not been already provided during the phase of pregnancy planning.

During scheduled controls, pump setting and/or continuous glucose monitoring profiles on dedicated platforms will be verified. Alternatively, the patient should be asked to send the relevant reports electronically before the telematic contacts.

Periodic visits should include:

1. 6-8 times/day blood glucose determinations (depending on metabolic control) in case of SMBG.

2. HbA1c; urine exam concurrently with haematological tests required for pregnancy (generally 1/month).
Fig. 1 – Management of pregestational diabetes during COVID-19 pandemic. In the event of unscheduled pregnancy in T2DM, suspend, if in progress, lipid-lowering therapy with statins or antihypertensive drugs contraindicated during pregnancy. In the case of T2DM diagnosed at the beginning of pregnancy, consider as valid the indications reported in the pregestational diabetes section; Chronic complications should also be assessed in these patients. § Instructions for Apps to monitor and share capillary blood glucose data, continuous glucose monitoring and sensor/insulin pump therapy reports (SAP). MySweetGestation and MyGDMoving are free APPs designed by GDS Diabetes and Pregnancy AMD-SID able to supply GDM information. Telemedicine establishes a remote contact with the patient for collecting information related to her health status, the ability to follow the nutritional indications provided and to perform physical activity. The patient must necessarily send the results of weight, PA, glycaemia and ketonemia measurement together with the results of haematological tests, instrumental investigations and obstetrical examinations performed using specific APPs or by sending written documentation to the e-mail address of the centre or to the diabetologist of reference. In case of cough, fever, flu symptoms or in case of positivity to coronavirus infection or quarantine status, the examination must necessarily be performed by telemedicine visit. In the case of coronavirus infection and/or presence of other infective pathologies, it is reiterated the.
3. Microalbuminuria: should be evaluated every 3 months if albumin excretion is normal at the first control and in patients with normal BP values; in case of abnormal albumin excretion, increase the frequency of monitoring according to guidelines [12].

4. Fasting ketonemia (before breakfast) 2–3 times a week and if glycaemic values are persistently >180 mg/dl. Ketones should also be monitored during intercurrent diseases or persistent nausea and vomiting, even with normal glucose values.

5. Registration of obstetrics examination records.

6. Weight gain and blood pressure weekly.

The results of the above examinations/monitoring should be sent electronically to the diabetologist every two weeks. It will be appropriate to increase the frequency of measurements in case of significant changes in BP values. The diabetologist will evaluate the need for an outpatient visit, or will provide the patient with the necessary information electronically.

The frequency of contacts may be increased in case of glycaemic values out of targets for 3 consecutive days, excessive weight gain, or if any complications occur.

An outpatient visit, in person, at the diabetes care clinic should be scheduled when the obstetric evaluation is planned.

During the last visit, at the end of the third trimester, provide the final report containing instructions for the management of insulin therapy during labour and post-partum, as indicated in the guidelines. A scheduling of subsequent outpatient controls should be also provided.
3.1. Type 2 diabetes

Diabetes evaluation must be scheduled at recognition of pregnancy: this is strictly needed in case of unplanned pregnancy. Type 2 diabetic patients are often overweight/obese and frequently present the features of metabolic syndrome, thus it is necessary to carry out specific nutritional counselling and set up a specific nutritional plan with a dietitian (when available). In these patients it is important to consider the increased risk of hypercholesterolemia and/or hypertriglyceridemia during pregnancy, moreover statin therapy, if ongoing, should be discontinued. Antihypertensive therapy should be appropriate for pregnancy (e.g. calcium antagonists or alpha methylldopa). Regarding diabetes therapy, insulin is recommended during pregnancy, whereas other hypoglycaemic agents (both oral and injectable), should be discontinued. During the first evaluation, educational therapy will be provided for: (a) SMBG, (b) ketone monitoring, (c) insulin therapy management, and (d) prevention and correction of hypoglycaemic episodes (Fig. 1). Regarding haematological tests and screening of complications, please refer to what suggested for type 1 diabetes.

In case of type 2 diabetes diagnosed at the beginning of pregnancy, the aforementioned recommendations and the frequency of controls remain valid. In these patients it is necessary to set the screening for complications, in particular microalbuminuria and retinal scan, since the duration of hyperglycaemic state is unknown.

3.2. Rational

Given the current health emergency, in order to minimize the risk of contagion, we hereby propose to limit outpatient access and instrumental investigation of complications in T1DM and T2DM pregnant women without diabetes complications at previous checks. Nonetheless, the screening of complications should be necessarily performed if not recently done or if significant alterations emerged in previous controls, because a new onset or a worsening of retinal and renal microangiopathy is often observed during pregnancy, and also determined by the need to achieve a good glycaemic control shortly.

In order to limit hospital access, it is recommended to match diabetes visits with obstetrics check. This will allow the diabetologist to maintain a direct contact with pregnant patients during a very delicate period. At the same time this will allow to respect the limitations imposed by COVID-19 emergency. In this context, it is appropriate to provide since the first visit all the necessary indications/information in order to reduce woman’s outpatient accesses, limiting them only to the necessary situations (worsening of glycaemic control, obstetric complications, excessive weight gain).

4. Gestational diabetes

For diagnosis please refer to the document regarding GDM screening during COVID-19 pandemic [15]. Once obtained a
Fig. 3 – Management of gestational diabetes treated with insulin therapy during COVID-19 pandemic. Monitoring of plasma ketones must be carried out in the morning before breakfast, particular attention is needed in obese women (BMI > 30 kg/m² before pregnancy) and in case of poor adherence to nutritional therapy during pregnancy with insufficient intake of carbohydrates at the evening meal or in case of prolonged night fasting. In the pre-delivery period, the control of ketones is useful to avoid the onset of metabolic acidosis induced by ketosis due to the metabolic stress of active birth or secondary to prolonged fasting even in case of euglycemia. Fasting blood glucose target < 90 mg/dl and 1 h after meals < 130 mg/dl. In case of greatly altered glycaemic values and in case of doubts on the patient’s actual ability to follow the therapeutic indications provided, it may be useful to plan a further visit to the centre in order to check the patient's skills and the ability in management of the therapy. MySweetGestation and MyGDMoving are free APPs designed by GDS Diabetes and Pregnancy AMD-SID able to supply GDM information. Telemedicine establishes a remote contact with the patient for collecting information related to her health status, the ability to follow the nutritional indications provided and to perform physical activity. The patient must necessarily send the results of weight, PA, glycaemia and ketonemia measurement together with the results of haematological tests, instrumental investigations and obstetrical examinations performed, using specific APAs or by sending written documentation to the e-mail address of the centre or to the diabetologist of reference. In case of cough, fever, flu symptoms or in case of positivity to coronavirus infection or quarantine status, the examination must necessarily be performed by telemedicine visit. In the case of coronavirus infection and/or presence of other infective pathologies, it is reiterated the need for strict glycaemic monitoring and ketonemia, if appropriate, in order to reach an adequate metabolic control.
GDM diagnosis, the following tests are required if not available:

- HbA1c, Urine exam and lipid profile. TSH should be required only in high risk women or if not previously assessed. ATPO should be required if TSH > 2. 5 mU/L [16].

- The results of the above examinations will be sent electronically to the diabetologist who will assess the need for an outpatient visit. The necessary information will be sent to patients electronically and a contact will be arranged via web or phone (Fig. 2).

### 4.1 First visit during pregnancy

- Nutritional evaluation: a nutritional plan appropriate for gestational age will be provided by the dietitian (if available)

- Advice will be provided for physical-activity (indoor or outdoor if possible) in accordance with the obstetric team.

- Educational therapy for SMBG and ketonemia assessment; if the OGTT values suggest the need of insulin therapy, it may be useful to provide an educational session for the management of insulin therapy and hypoglycaemic episodes.

- Instructions for telemedicine, teleconsulting and for the APPs useful for clinical data sharing.

The first diabetes evaluation should be scheduled after 1 week, and then every 2–3 weeks. The patient should electronically send the report of:

1. SMBG (as indicated by the guidelines from the Italian National Diabetes Societies, SID-AMD, 2018 or any subsequent updates) [12]; SMBG frequencies will be re-evaluated according to metabolic control.
2. HbA1c, only at first visit; urine exams concurrently with laboratory tests required for pregnancy (usually 1/month).
3. Daily fasting ketonemia for the first week. If negative, the frequency will be reduced to 1–3 times a week. Ketonemia should be checked in case of intercurrent diseases.
4. Weight gain and blood pressure weekly.
5. Registration of obstetric examination reports.

The result of the aforementioned examinations/monitoring will be sent by the patient electronically. If the glycaemic target is not reached with nutritional therapy, insulin should be initiated according to blood glucose values (Fig. 3). If increased BP values are observed, an increment of the frequency of testing is needed. The diabetologist will evaluate the need for an outpatient visit, or will provide the patient with the necessary information electronically. An outpatient diabetes care visit should be scheduled in occasion of the obstetric checks. The frequency of visits may be increased in case of poor metabolic control, excessive weight gain, intercurrent diseases.

During the last visit, at the end of the third trimester, the diabetologist should provide the final report containing instructions for the management of insulin therapy during labour and post-partum, as indicated in the guidelines. A scheduling for subsequent outpatient controls should be also provided.

### 4.2 Rational

The care team will evaluate the best program for the patient considering the cost/benefit ratio (risk of contagion for outpatient access and care of maternal/foetal well-being) and the local health care system setting. GDM increases the risk of negative foetal/maternal pregnancy outcomes, thus an appropriate management of this condition is required with more frequent haematological and instrumental controls then a physiological pregnancy (e.g. parameters of foetal growth monitoring) in order to avoid the associated pregnancy, foetal and/or neonatal complications.

In case of cough, fever, flu symptoms or in case of positivity to coronavirus infection or quarantine status, the examination must necessarily be carried out by telemmedicine visit. In the case of coronavirus infection and/or presence of other infective pathologies, it is reiterated the need for strict glycaemic monitoring and ketonemia, if appropriate, in order to reach an adequate metabolic control.

### 5 Conclusions

The COVID 19 pandemic, in addition its terrifying effects, has given a significant boost to the use of telemedicine in people with chronic diseases such as diabetes. It is known that hyperglycaemia in pregnancy needs careful and constant monitoring and, in this perspective, telemmedicine can be a valuable aid. With this aim the Italian Diabetes and Pregnancy Study Group, together with a group of experts, developed these recommendations in order to guide physicians in the management of HIP, providing specific diagnostic, therapeutic and assistance pathways (PDTAs) for this emergency period. We hope that this document will be of help to telemmedicine implementation in the management of hyperglycaemia in pregnancy.

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