SPECIAL REPORT

The challenge of multidisciplinary research: improving diabetic pregnancy together

D.N. Voormolen*, J.H. de Vries, A. Franx, B.W. Mol, I.M. Evers

Department of Gynaecology, University Medical Centre Utrecht, the Netherlands, *corresponding author: tel. 088-7554913, fax 088-7555320, e-mail: d.p.vanmunster-2@umcutrecht.nl

ABSTRACT

Improving diabetic pregnancy outcome is a goal shared by many involved specialists. Despite proper glucose control, the incidence of maternal and perinatal complications is very high, including a high risk for pre-eclampsia, congenital malformations, perinatal mortality and macrosomia. To improve outcome, not only collaborating in the doctor's office is required but also participation in critical evaluation of our treatment strategies by means of randomised clinical trials.

KEYWORDS

Diabetes, pregnancy, multidisciplinary research

PROBLEM

Modern health care is at a turning point. Over the last decades increasing insights into physiology and pathophysiology of disease, as well as a raising number of technical and pharmaceutical tools to interfere with the natural course of disease, have enriched diagnostic and therapeutic opportunities. Until recently, these new opportunities were welcomed and introduced with limited concerns on costs and effectiveness.

However, recent social and economic developments have changed the context. Budget pressure forces politicians to make choices between the reimbursement of different medical interventions. The Minister of Health recently asked doctors and patients to advise in these difficult choices. Such choices can only be made in view of knowledge of the effectiveness of these interventions. Possibly, the reimbursement status of Continuous Glucose Monitoring (CGM) during pregnancy will be reconsidered since solid scientific support is lacking.

DIABETES AND PREGNANCY

A decade ago, a nationwide prospective cohort study was performed on pregnancy outcome of women with DM type 1 (n=323). During pregnancy, the mean HbA_{1c} value was reassuring, namely 6.2% (44 mmol/mol). However, the incidence of maternal and perinatal complications was remarkable. Most outstanding were the relative risks for pre-eclampsia (12.1), congenital malformation (3.4), perinatal mortality (3.5) and macrosomia (4.5).[1] Two important conclusions were made. First, women with diabetes still have high-risk pregnancies and second, near-normal HbA_{1c} values do not automatically translate into good pregnancy outcome.

Consequently, the question arose whether or not we have reached the maximum effect on pregnancy outcome that strict glycaemic control can accomplish. Can pregnancy outcome be further improved by additional interventions focusing on glycaemic control or do we need to target other features?

CGM provides detailed information on daily glycaemic profiles and may provide an opportunity to further improve pregnancy outcome of women with diabetes. 'Does the additional use of CGM improve pregnancy outcome?' Gynaecologists and endocrinologists together wrote a research proposal to address this matter in the GlucoMOMS trial.[2] After ZonMW funding was obtained, indicating the relevance, preparations for a national randomised clinical trial (RCT) started.

Meanwhile, the Health Care Insurance Board (CVZ) discussed reimbursement of this promising new tool. An invited review of literature was written in which it was clearly stated that evaluation of CGMS during pregnancy was lacking.[3] Furthermore, the Endocrine Society Task Force formulated practice guidelines to identify patient groups that are most likely to benefit from CGM, in which pregnancy was not mentioned.[4,5] Nevertheless, CGM came to be reimbursed for use during diabetic pregnancy. It

should be noted that reimbursement facilitates evaluation, but does not imply that doctors have to prescribe CGMS to their patients. In contrast, an often heard critique is that insurance companies take over control from doctors on the content of care. The fact that CGM is currently reimbursed allows its evaluation. Without such evaluation, it might very well be that the reimbursement status will be reconsidered in the coming years.

REAL TIME VERSUS OFFLINE

CGM can be applied in two fundamentally different ways. First, as a retrospective instrument that stores a large number of glucose measurements per day. The patient is blinded for the measurements, and data from the CGM together with a detailed diary can be analysed retrospectively. Patients can be educated on the basis of the daily graphs and insulin treatment can be adjusted. The real time (RT) CGM is a more extensive strategy. Glucose measurements are directly communicated to the patient by displaying the real time glucose values. Furthermore, trends in glucose levels are shown and alarms can be set for upper and lower limits. Patients can upload their data onto their computer and detailed reports are provided in graphs, charts and tables. Adjustments in insulin dose can be made directly. Both techniques require blood glucose meter readings (fingersticks) at least 3-4 times a day to recalibrate and verify the glucose sensor.

The complex strategy of RT-CGM requires a highly motivated patient. Due to a major role of this 'human factor', RT-CGM is not appropriate for every patient. The correct prerequisites for pregnant women to be eligible for RT-CGM use have yet to be clarified. It remains unclear which group of patients would benefit from the use of CGM during pregnancy, either retrospective or real time. Doctors will continue to be confronted with the question of which type of monitor to use, if any, for which patient, at least until research provides clarity. Initiatives such as the GlucoMOMS trial are of great importance for an evidence-based foundation of CGM use in the future.

CONSORTIUM

The Dutch Obstetric Consortium is a national research network that has been conducting multicentre RCTs since 2003. Over 80 hospitals contribute to multicentre RCTs facilitated by the consortium.[6] The consortium on women's health research is not a formal structure, but rather an informal agreement between different researchers who all want to execute multicentre studies on comparative effectiveness and health care efficiency research. Each project contributes financially to a common infrastructure. The central office of the consortium is located at the AMC in Amsterdam, and is responsible for central and local approval of the trials by the medical ethics commissions. Once the financial and administrative issues are covered, a trial is initiated throughout the country. Each hospital is part of a cluster, associated around a perinatal centre (mostly academic hospitals). The logistics of the trials are covered by the practical task forces: the research nurses, guided by cluster coordinators (gynaecologists). They manage daily local logistics, inform the hospitals on the ongoing trials, handle patient counselling, and perform data entry. This streamlined collaboration of the majority of hospitals in the Netherlands guarantees high-quality research while minimising the workload for clinicians.

Many RCTs have been completed and resulted in interesting insights, not seldom against general expectations. Some simple interventions turn out to be surprisingly effective. For example, when women are immobilised for 15 minutes after intra-uterine insemination, they have a 50% increased chance of pregnancy from 20% to 30% after four cycles.[7] On the other hand, sometimes, well intended and reasonable interventions are proven to be ineffective. Prolonged tocolysis in case of threatened preterm labour, for example, does not improve perinatal complications,[8] and conservative surgery that aims to maintain the fallopian tube in case of tubal pregnancy does not result in higher pregnancy rates as compared with radical surgery. Recently, the ProTwin trial showed a massive 50% reduction of preterm birth and perinatal morbidity and mortality in short cervix twin pregnancies by the use of a simple pessary. These concrete contributions to world-wide medical care resulted from mutual effort.

Potentially, millions if not billions of Euros are spent on ineffective and therefore by definition useless treatments. This generates a burden to patients or even complications and a worsened health outcome. In order to decide which treatments are worth spending our limited health care budget on and which are not, scientific evaluation is a prerequisite.

MULTIDISCIPLINARY RESEARCH

Until recently, trials conducted by the consortium were limited to obstetrical or gynaecological issues. However one of the most challenging features of the obstetric patient population is that it involves many pre-existing diseases requiring a multidisciplinary approach. Such is the case for pregnant women with diabetes. The consortium extended its playing field by initiating a multidisciplinary multicentre RCT on this specific patient group. Although the road for obstetric RCTs is paved,

side roads connecting other disciplines are still a bit bumpy. With the introduction of the GlucoMOMS trial, which evaluates the effect of additional use of Continuous Glucose Monitoring on pregnancy outcome, several challenges came across.

The way the national consortium structured research and integrated it in daily practice is unique to obstetrics/gynaecology. Every specialist knows how the organisation operates and how to optimally receive assistance from it. Naturally, the organisation is new to endocrinologists and may appear unduly assertive. Fortunately, in the project group of the trial both disciplines are represented and we should be able to overcome such challenges.

GLUCOMOMS

Despite the above-mentioned challenges, the project group of the GlucoMOMS trial still strongly feels implementation of an expensive tool as CGM in the routine care of patients during a specific, temporarily condition (pregnancy) should be supported by scientific proof on (cost-) effectiveness. Providing an intervention during the course of pregnancy must have an evident positive effect on pregnancy outcome.

Meanwhile, two RCTs have been published on effectiveness of CGM use on pregnancy outcome. Murphy *et al*. evaluated the additional use of intermittent retrospective CGM in 71 women with type 1 or 2 diabetes mellitus (DM). The incidence of macrosomia (birth weight >90th percentile) was significantly lower in the CGM group, 35% as opposed to 60% in the control group. Other pregnancy outcome measures did not differ.[9] Secher *et al*. randomised 154 women with type 1 or 2 DM for either additional intermittent use of RT-CGM or standard care. No difference was found in the prevalence of macrosomia or other pregnancy outcome measures, as well as in HbA_{1C}.[10] Hence, a definite conclusion cannot yet been drawn. The GlucoMOMS trial may further clarify these opposing results.

Although initiated by the Dutch obstetric consortium, it must be stressed that it is not intended to invade the professional autonomy of diabetes specialists. Endocrinologists and gynaecologists together bear responsibility for this particular patient group.

When contacting different endocrinology departments throughout the country to discuss participation in the GlucoMOMS trial, some interesting points of view were shared. Some examples underline the problems which currently exists:

'It's a dilemma: do we dare to subject a treatment strategy, which we find ourselves strongly believing in, to scientific evaluation?'

'In principal, we gladly participate in national trials, however this trial is in conflict with our daily practice, since all of our pregnant patients with DM type 1 are offered CGM'.

'Personally, I regret not participating in the national trial, scientific evaluation is important, but I fear practice has sailed passed science. Unfortunately this happens more often without evidence on cost-effectiveness'.

'Due to high morbidity and mortality in diabetic pregnancies, it is essential to pursue normoglycaemia during these pregnancies. Before the introduction of CGM, this was nearly impossible. CGM is now reimbursed for diabetic pregnancy and therefore I feel it is unethical not to offer my patients CGM'.

'This is very complicated. The reality is that evidence-based medicine is passed by the health care insurer (most of the time it is the other way around, as it should be), however, medical tools deal with other playing fields when it comes to reimbursement than does medication'.

'We can hardly get away with it, since many articles on CGM can be found on the internet to which patients refer'.

'Our hospital will not participate in the national trial because we already provide CGM for all pregnant patients with DM type 1'.

Current medical practice is filled with treatments based on faith rather than exact scientific proof. Doctors prefer offering their patient (un-evaluated) treatment options to offering nothing or even worse: the unpopular truth of 'we don't know what's the best thing to do'. Although intentions are evidently sincere, doctors should be critical. Doctors decide the appropriate treatment option and this should be done independently from the reimbursement status (instead of offering it for the mere fact that it is there to offer). Furthermore, a doctor should contribute to scientific evaluation in order to improve the quality of our profession and health care in general.

POTENTIAL IMPROVEMENTS

By reflecting on the current events regarding the GlucoMOMS trial we hope to motivate our colleagues to accept the fact that current evidence on CGM use in pregnancy is limited and to comprehend that by collaborating, indispensable evidence is within reach.

Regular multidisciplinary meetings to discuss diabetic pregnant patients should be held in every hospital treating such patients, in order to improve insight into each other's professional considerations. This may also facilitate the participation in national or international trials.

Furthermore, providing insight into treatment strategies and clinical outcomes may also help to map out current practice and evaluate national discrepancies.

CONCLUSION

Improving diabetic pregnancy outcome is a goal shared by endocrinologists and obstetricians. The best result will come from collaborating not only in the doctor's office but also in critical evaluation of our treatment strategies by means of randomised clinical trials. By providing a scientific basis for medical interventions we justify our current practice and enable rational future reimbursement policies.

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