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Gestational Diabetes – Major New Clinically Relevant Aspects

Gestationsdiabetes – die wichtigsten neuen klinisch relevanten Aspekte

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ABSTRACT

The implementation of screening for gestational diabetes (GDM) in the German Prenatal Care guidelines of 2012 and the publication of numerous new studies have led to clinically relevant changes in the care of pregnant women with GDM to whom consideration was given in the new S3 Guideline on the Diagnosis, Management and Follow-up of Gestational Diabetes (AWMF 057/008) published in March this year. Certain aspects are addressed and discussed on the basis of additional background information.

ZUSAMMENFASSUNG

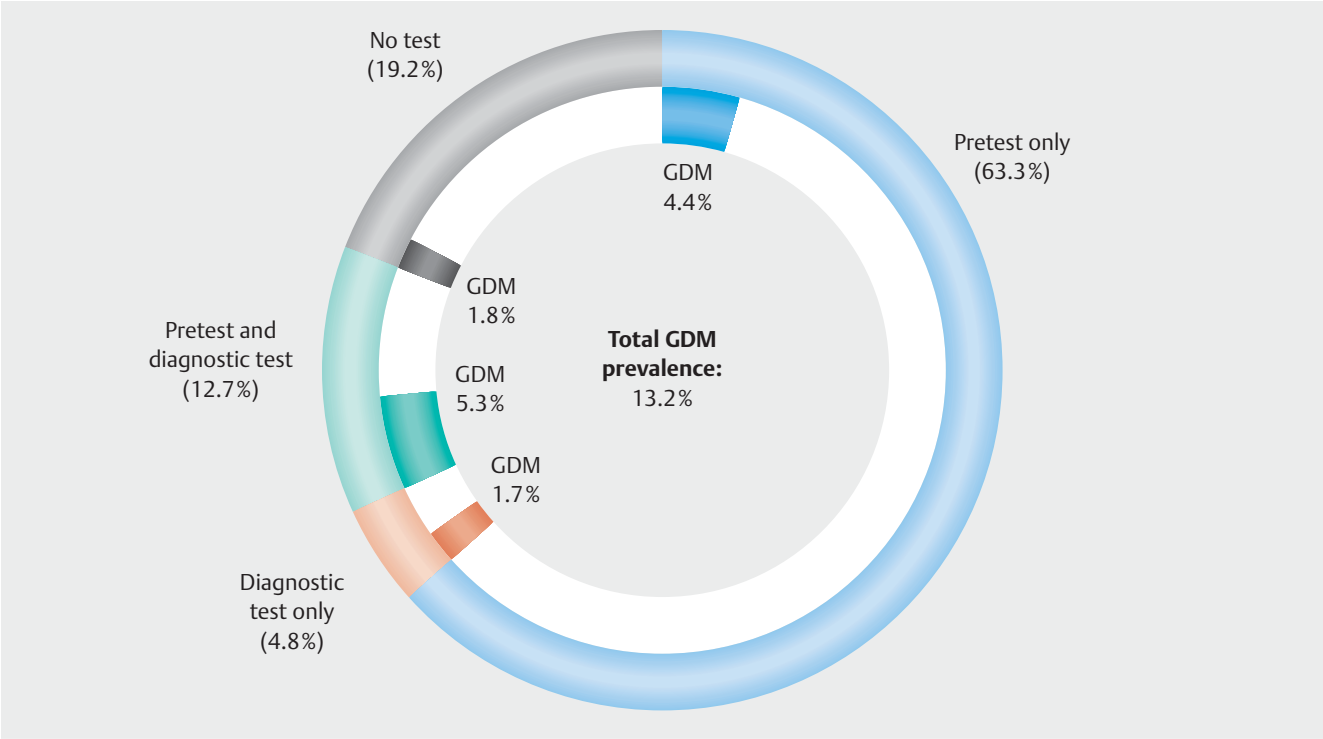
Die Aufnahme des Screenings auf Gestationsdiabetes (GDM) in die deutschen Mutterschafts-Richtlinien 2012 und die Publikation einer Vielzahl von neuen Studien führen zu klinikrelevanten Änderungen in der Versorgung der Schwangeren mit GDM, die in der im März dieses Jahres erschienenen neuen S3-Leitlinie zur Diagnostik, Therapie und Nachsorge bei Gestationsdiabetes (AWMF 057/008) berücksichtigt wurden. Einige Aspekte werden dargestellt und auf der Basis von weiteren Hintergrundinformationen diskutiert.

Introduction

The implementation of general screening for gestational diabetes (GDM) in the German prenatal guidelines of 2012 and the publication of numerous new studies have led to clinically relevant changes in the care of pregnant women with GDM to whom consideration was given in the new S3 Guideline on the Diagnosis, Management and Follow-up of Gestational Diabetes (AWMF 057/008) published in March this year. Certain aspects are addressed below and discussed on the basis of additional background information.

Conflicting Data on Prevalence

Gestational diabetes has now caught up with hypertensive disorders in the rankings of the most common complications of pregnancy. According to the German National Perinatal Database, GDM was documented in 5.9% (44907) of pregnant women in Germany in 2017, showing that the prevalence had again increased compared to 2016 by 10.5%. Despite the increase from 4.4 to 5.9% since introducing general screening, however, the figures for Germany are still low by European standards. The prevalence data from the perinatal Database do not confer with an analysis of performance data from all the statutory health mainte-



▶ **Fig. 1** Introduction of screening and GDM prevalence according to test method [1]. Outer ring: distribution of test methods or no test; inner ring: pregnant women diagnosed with GDM. GDM: gestational diabetes mellitus.

nance organisations (2014–2015) conducted by the National Association of Statutory Health Insurance Physicians (KBV) [1], which suggests that the prevalence is 13.2% higher. Looking at the figures in detail, several contradictions emerge which cast doubt over the validity of the data analysis by the KBV (▶ **Fig. 1**):

1. The stated GDM prevalence of 13.2% includes 1.3% of cases with pre-existing diabetes.
2. In 1.8% of cases, GDM was diagnosed without any form of glucose testing.
3. In 4.4% of the pregnant women, the diagnosis was made based on the 50 g screening test alone. Hence, 4.4% of all pregnant women in Germany must have had a blood glucose concentration of > 200 mg/dl at screening. This is not realistic.
4. A total of 12 300 cases of manifest diabetes were reported as opposed to 6500 cases in the analysis of the perinatal survey during the same period. It is conceivable that the coding of GDM may be forgotten in the stressful environment of a delivery room but debatable that two thirds of all women with gestational diabetes would be overlooked; it is more than unlikely that this would happen in 50% of the women with type 1 diabetes. Pregnancy in these women is considered high-risk. The "genuine" prevalence is likely to be 7–10%.

What Degree of Validity Does Screening for GDM Offer Based on the 50 g Test?

Based on their own data, the authors of the KBV survey rated the introduction and the method of screening as positive. However, the assessment relates only to the question whether blanket screening took place (80% of all pregnant women) and how many pregnant women could be spared the 75 g OGTT (63.3%). To determine the level of validity to be expected from the required two-step screening with the obligatory 50 g test as the primary method, the guideline group undertook a thorough literature search. The following critical points emerged from the available study data:

1. The validity of the 50 g test depends on the time of day when it is conducted and the time interval since food was last consumed.
2. The limits for the 50 g test were fixed arbitrarily in the 60s whereas the WHO limits (= IADPSG criteria) for the OGTT are evidence-based.
3. Depending on the applied limit, the sensitivity described in the literature fluctuates considerably: based on the value of 135 mg/dl used in the maternity guidelines, it ranges from 55–98% [2].
4. All studies into the validity of the 50 g test originate primarily in the 90s and are based on diagnostic criteria for GDM that today are no longer valid. This implies that, so far, no data on sensitivity have been generated in accordance with current GDM criteria.
5. According to the HAPO study 33% of the women with GDM were found to have only an increase in the fasting value; these are not identified by the 50 g GCT [3]. In the HAPO population, however, the fasting value was most closely correlated with an unfavourable gestational outcome.
6. In practice, there is sometimes a considerable time delay until treatment is commenced due to the long interval between the 50 g test and the 75 g OGTT.

▶ **Table 1** Sensitivity and specificity of the 50 g screening test for identifying pregnant women at risk of GDM using different limits; 1583 pregnant women underwent a 50 g test at GW 24–28 followed by a 75 g OGTT, irrespective of the outcome of the 50 g test [3].

50 g test limit	GDM prevalence (%)	Sensitivity (%) (n/N)	Specificity (%) (n/N)
≥ 140 mg/dl	7.5 (136)	59.6 (136/228)	81.0 (1282/1583)
≥ 135 mg/dl	8.3 (151)	66.2 (151/228)	76.1 (1204/1583)
≥ 130 mg/dl	9.1 (165)	72.4 (165/228)	70.2 (1111/1583)
≥ 125 mg/dl	9.8 (177)	77.6 (177/228)	64.2 (1016/1583)
≥ 120 mg/dl	10.3 (187)	82.0 (187/228)	56.0 (886/1583)

▶ **Table 2** Recommendations for GDM screening taken from AWMF 057/008 due to clinical relevance in original text.

Recommendations for GDM screening	Grade
Based on the available evidence, a 75 g OGTT should be performed in pregnant women between GW 24 + 0 and 27 + 6.	A
Based on the German maternity guidelines, screening should primarily entail a 50 g test. Given the questionable validity, this is not consistent with the recommendations of the professional associations.	B
If a 50 g GCT is performed between GW 24 + 0 and 27 + 6 as defined by the German maternity guidelines, fasting blood glucose should also be determined if the GCT proves negative.	B
If the GCT is negative, consideration should be given to the fact that current data on sensitivity of the GCT are lacking. Therefore, in the presence of clinical symptoms (asymmetric excessive growth in favour of the abdominal circumference, polyhydramnios, maternal glycosuria) an additional 75 g OGTT should be performed, irrespective of the previous result.	A

BEDIP Study Confirms Low Sensitivity of 50 g Test

In June this year, the analysis of the BEDIP study [4] was published, delivering recent data on the sensitivity of the 50 g screening test. Both a 50 g test and a 75 g OGTT were performed in 1583 pregnant women at GW 24–28 and evaluated in accordance with the current WHO criteria. The limit of 135 mg/dl (7.5 mmol/l) specified in the maternity guidelines offers a sensitivity (▶ **Table 1**) of only 66%, accordingly, for identifying pregnant women at risk of GDM. It can be assumed that primarily the 33% of pregnant women with an isolated increase in fasting blood glucose are not documented [3]. To achieve 77%, the limit would have to be reduced to 120 mg/dl, implying that 40.8% of pregnant women would have an abnormal value and thus would be tested twice by adding the 75 g OGTT. This is neither in the interests of the pregnant women nor economically effective. The full results will be presented by study coordinator Katrien Benhalima at the DGGG Congress in Berlin in November. The group also investigated whether a subset can be defined based on maternal characteristics where a risk of GDM cannot be identified with a limit of 130 mg/dl. The data have not yet been published.

The new GDM guideline was finalised before publication of the BEDIP study; hence, the results could not be included. However, the GDM guideline group had already considered the issue of sensitivity of the 50 g test. The recommendations in ▶ **Table 2** were formulated based on the available evidence and clinical experience in the last two years. The expert group is aware of the potential for conflict in these recommendations as far as implementation in the clinical routine is concerned, but according to the requirements when writing S3 guidelines there is an obligation to heed the evidence. Since completing the literature search for the guideline, a total of five Cochrane reviews from 2010, 2014 and 2015, and two from 2017, have been published [5, 6] which unanimously conclude that the available data are insufficient with respect to deciding which screening procedure will deliver a better maternal and neonatal outcome. The outcome parameter in the studies to date was primarily the prevalence of GDM, which as expected proves to be higher from general screening than when testing selectively for risk factors and performing one-sided screening with the 75 g OGTT compared to two-sided screening in the form of the 50 g test. So far there has been no RCT in which the outcome from screening with the 50 g test has been compared against the 75 g test.

It surely cannot be the objective of prenatal care to constantly increase the number of risk pregnancies by introducing screening tests. Unfortunately, there is a trend in this direction but the discussion must not overlook the fact that, given the change in population structure and the medical conditions, young pregnant women who do not present with pre-existing risks such as obesity, older age, sterility treatment, multiple pregnancies, are becoming increasingly rare. The prevalence of diabetes in the population is constantly growing, moreover. Perhaps there is a need to again discuss whether the WHO criteria for GDM are perhaps too low for certain populations, as recently addressed in a study from Denmark: Gestational Diabetes Mellitus: Does One Size Fit All? A Challenge to Uniform Worldwide Diagnostic Thresholds [7]. Fasting glucose values at 28 weeks of gestation were correlated with the outcome of pregnancy. If the fasting limit of the IADPSG criteria of 92 mg/dL (5.1 mmol/l) had been applied, 40.1% of the pregnant women in Denmark would have had GDM. The outcome

▶ **Table 3** Fasting blood glucose in the first trimester and GDM diagnosed in the third trimester with 75 g OGTT [8].

Fasting blood glucose (mmol/l)	n (%)	GDM n (% outcome)
> 4.1	1938 (11.3)	186 (9.6)
4.10–4.59	7055 (41.1)	872 (12.4)
4.6–5.09	6234 (36.3)	1165 (18.7)
5.10–5.59	1668 (9.7)	617 (37.0)
5.6–6.09	226 (1.3)	119 (52.7)
6.10–6.99	65 (0.4)	43 (66.2)
Total	17 186 (100.0)	3002 (17.5)

(LGA, pre-eclampsia, Caesarean section) did not differ, however, from those with a fasting value of < 100 mg/dl (5.6 mmol). It is difficult to justify vis-à-vis pregnant women in Germany that only one screening procedure is covered as a health insurance benefit and that based on the diagnostic criteria set out in the maternity guidelines only 66 % of women with a risk of GDM are identified. Based on the evidence of the HAPO study, the WHO criteria for GDM have been adopted in Germany. A logical consequence, therefore, would be to offer screening with an acceptable sensitivity based on these criteria.

Hence, based on the data from the BEDIP study, the Working Group for Obstetrics and Prenatal Medicine of the DGGG will file an application with the G-BA (Federal Joint Committee) for resumption of the consultation on GDM screening so that the procedure for clinical practice can be clarified.

OGTT After Bariatric Surgery Obsolete

After surgical procedures that influence absorption, an oral GDM diagnostic test based on oral glucose tolerance is not possible; false-negative results are obtained due to the dumping phenomenon. It is possible to take a venous fasting blood glucose measurement and diagnose GDM on this basis if the limit is exceeded. If the fasting value is unremarkable, investigation for treatment-dependent postprandial hyperglycaemia may be recommended in the form of monitoring the diurnal blood glucose profiles for two weeks from the one-hour postprandial blood glucose levels (two-hour values are not conclusive) under normal dietary conditions, e.g. at GW 12, 24 and 32, and appropriate diabetes care introduced if the target values are exceeded. So far, there have been no studies into this strategy. Working Group G has initiated an S3 guideline on "Obesity and Pregnancy" that will thoroughly address the specific features of prenatal care.

Blood Glucose Measurement Only Valid If Glycolysis Is Inhibited with Citrate Buffer

False-negative results due to inadequate inhibition of glycolysis on sample shipment are a significant problem in glucose determination. According to the latest guidelines, the vessel for collecting and shipping venous whole blood samples must contain not only an anticoagulant and sodium fluoride but also an immediate-acting glycolysis inhibitor in the form of citrate/citrate buffer. NaF takes effect only after approx. two hours and exerts its full effect after approx. four hours. Combined with citrate, however, NaF induces glycolysis immediately. The laboratory must provide those submitting samples with such collection systems. This does not happen across the board, however. At the beginning there were problems with submitted samples as valid measurement is only possible if the vessels are filled completely (dilution factor!).

Changes in Population Structure Necessitates Screening in Early Pregnancy

In Germany, 36 % of pregnant women are overweight or obese – a tendency that is increasing (IQTiG 2016). Also to be considered are women from ethnic groups with a high risk of diabetes, and the increase in age. Given the growing number of pregnant women not previously diagnosed with type 2 diabetes or corresponding precursors, screening during the first trimester would be desirable in this population. Early detection of type 2 diabetes is not an integral part of the maternity guidelines.

Fasting blood glucose and HbA_{1c} are the best indicators as far as estimating the risk in early pregnancy is concerned. The fasting value offers a good prediction of the emergence of GDM over the course of pregnancy (▶ **Table 3**). Above 92 mg/dl (5.1 mmol/l) in the first trimester the prevalence of GDM rises significantly [8]. A fasting value of 92 mg/dl (5.1 mmol/l) was therefore chosen as a cut-off for further diagnostic testing. A second measurement is taken if the blood glucose value in the venous plasma is ≥ 92 mg/dl (5.1 mmol/l). This measurement must be performed on a *different* day. The blood glucose measurements must fulfil laboratory standards. The result of the second measurement is decisive: *both* measurements must be above the limit, otherwise no diagnosis can be made.

The HbA_{1c} offers similarly good validity, which is why it has also been included as a screening method. As of conception, the HbA_{1c} concentration decreases and reaches a nadir early in the second trimester; throughout the pregnancy the HbA_{1c} levels remain lower overall than in non-pregnant women. A value of < 5.9 % is deemed unremarkable. If the HbA_{1c} concentration is 5.9–6.5 %, an OGTT should also be performed to rule out diabetes. This is consistent with the procedure in the latest practice recommendations of the DDG for diagnosing diabetes [9]. According to the WHO criteria for pregnancy, however, the OGTT is assessed.

It is not yet clear which test method and which limits are most sensitive and practicable during early pregnancy. The WHO recommends using the IADPSG criteria for the OGTT at any time during pregnancy (apps.who.int/iris/bitstream/10665/85975/1/WHO_NMH_MND_13.2_eng.pdf). However, the IADPSG criteria have been evaluated only in GW 24 + 0–28 + 0 but not during early pregnancy. In addition, there are no randomised studies so far into whether and which intervention in early pregnancy improves the maternal and neonatal outcome. Good data are available, however, which suggest that "early" GDM is associated with an unfavourable gestational outcome [10]. From a clinical per-

▶ **Table 4** Recommendations for treatment of GDM, summary of recommendations from AWMF 057/008.

Recommendations for treatment	Level of recommendation
When defining the frequency of BG monitoring, the priority should be to minimise the burden on the pregnant woman and limit self-monitoring to the decision-relevant minimum.	A
Pregnant women with GDM should be warned about the negative effects of excessive weight gain.	A
In obesity, weight gain can also be subjacent.	C
Insulin therapy should only be indicated if 50 % of the values exceed the limit within one week; this can also apply to singular diurnal measurements.	A
The indication should be checked carefully and rigorously as in addition to the strain on the pregnant woman insulin therapy can have significant obstetric consequences, such as inducing labour at term.	A
In pregnant women with GDM suspected to have pronounced insulin resistance with a very high insulin requirement, as well as when individually indicated, administration of metformin may be considered after therapeutic consultation concerning off-label use.	C

spective, however, early counselling and individual adjustment of the nature of the intervention can only be beneficial. The inclusion of structured advice in the maternity guidelines on nutrition and lifestyle during early pregnancy would be desirable.

Therapeutic Intervention – As Little As Possible, As Much As Necessary

It is often the case that too many blood glucose measurements are still taken due to uncertainty and concern. Hence, daily diurnal profiles with six measurements are frequently recommended even when stable, normal values are being registered. A recent development is the occasional prescription of continuous blood glucose measurement (CGM), a practice reserved for type 1 diabetics. In the case of GDM this places an unnecessary burden on the pregnant woman and increases the costs of care. The frequency of measurement specified in the guideline is based on interventional studies (▶ **Table 4**): four-point profile in the first one to two weeks – on an empty stomach in the morning and one or two hours after starting main meals. If all values are within the target range during the first two weeks, the frequency is then reduced to a rotating once-daily measurement or one four-point profile twice a week. The frequency and timing of self-monitoring can be continuously adapted individually depending on the results. First and foremost, however, the burden on the pregnant woman should be minimised and self-monitoring limited to the decision-relevant minimum. The treating gynaecologists can contribute here by involving themselves in diabetic logical care, asking to see the blood glucose diary is at follow-up appointments and even making a critical assessment of the insulin indication.

The indication for insulin therapy is also clearly defined in the guideline: within one week ≥ 50 % of self-measurements from the GDM four-point profiles above the target values. This also applies if only in isolated cases 50 % of the fasting glucose measurements (starting with basal insulin) or the postprandial values exceed the limit, which more often applies after breakfast (short-acting insulin). Even here, however, the indication is frequently applied too liberally. This is evident from the fact that a very low dose is selected, which during pregnancy tends to have a homeopathic effect due to the increased insulin resistance.

Metformin – Data in Favour of Metformin

The guideline provisionally recommends the use of metformin only in individual cases after therapeutic consultation concerning off-label use. This may entail an additional dose if the insulin requirement is very high (> 1.5 IU/kg BW) or be the last resort in the event of non-compliance, overload/risks from insulin therapy, among others. A daily dose of 2.0 g metformin should not be exceeded.

The version of 2011 stated that all oral antidiabetics were contraindicated. The collection of data is now very extensive, suggesting a good or even better maternal and neonatal outcome compared to insulin, with a mean failure rate of 31 % and dosage of 500–2500 mg/day (meta-analysis of 16 RCTs [11]):

- Lower maternal weight gain
- Less SIH
- Less LGA
- Same premature birth rate
- Less neonatal hypoglycaemia
- Fewer transferrals to neonatology

Long-term data for children were still lacking, however. Up to the age of two years, there were no differences in somatic [12], cognitive and motor [13] or neuromotor and psychomotor development [14]. In the children of the MiG trial (metformin in GDM) (REF.), the arm circumference was larger and more subcutaneous fatty tissue was found in the triceps and biceps, but the percentage of body fat was identical [12].

In February 2018 the Society of Maternal-Fetal Medicine [15] published a recommendation in which metformin was described "as a reasonable and safe first-line pharmacologic alternative to insulin". This is also consistent with the NICE guidelines and far exceeds the recommendation in the German guideline on GDM, which is aligned more with the second-line option of the ADA and AJOG.

Follow-up data on the children in the MiG trial in New Zealand at 7–9 years of age [16], which were published recently after the guideline was released, now give cause for concern: in contrast to the previous investigations in the very young children, long-term consequences of the intervention in the foetal metabolism have now become apparent. The follow-up data were analysed separately for the group in Adelaide (n = 109, 60% of the initial population) and the group in Auckland (n = 99, 25%). Whereas no difference was noted in the somatic development of the children in Adelaide at seven years, the children of the mothers in Auckland treated with metformin examined at nine years were significantly heavier and revealed signs of increased production of body fat. The authors speculate that there could be a variable long-term effect from metformin depending on birth weight and maternal blood glucose values – parameters that were significantly higher in the metformin group in Adelaide than in women treated only with insulin. Unlike in Auckland, moreover, no positive impact on weight gain was observed.

The recommendation of the SMFM and the current MiG data prompted leading American and European scientists to publish a corresponding statement in the AJOG which presents in hitherto unparalleled complexity the various levels of biochemical and physiological effects of metformin in vivo outside of pregnancy and in studies of pregnant animals. The potentially far-reaching intervention of metformin in foetal metabolism associated with the MiG data suggests to the authors that metformin can lead to a metabolic phenotype with childhood obesity. Based on the available data, they advise against metformin as first-line treatment, especially as an effective alternative that does not cross the placenta is available in the event of maternal hyperglycaemia (personal assessment so far). Metformin therefore should be used at present only if the overall situation and potential alternatives are considered very carefully.

Indication for Induction in GDM – Complex Interpretation of the Data

Numerous trials – mostly cohort studies with in some cases high sample sizes – have been published in recent years on the subject of induction in GDM and macrosomia [17–19]. In most of the available studies, however, no distinction is made with respect to whether GDM was treated dietetically only or insulin therapy was required.

One study in which the outcome from a watch-and-wait approach versus induction at GW 38 or 39 [17] in relation to GDM reveals that induction at < 39 + 0 GW increases neonatal morbidity and referral rates and thus should be avoided. Induction at 39 + 0–39 + 6 GW can be considered but is associated with a 50% increase in the induction rate and does not reduce neonatal morbidity. There was no differentiation between dietetic and insulin-dependent GDM.

Deliberation is especially difficult in the case of an estimated sonographic foetal weight > 95th percentile. An RCT published in the Lancet in 2016 involving 822 pregnant women with foetuses judged to be LGA both clinically and on ultrasound (> 95th percentile) received a lot of attention. In the group undergoing induction between 37 + 0 and 38 + 6 GW, shoulder dystocia (RR 0.32, 95% CI 0.15–0.71; p = 0.004) was significantly less frequent than in the expectant group whereas the incidence of fractured clavicle or humerus (RR 0.25; 95% CI 0.05–1.18), plexus palsy, death, and increased bleeding, was not. The rate of Caesarean section or operative vaginal delivery likewise did not differ. The need for phototherapy was significantly higher in the induction group, and the inpatient stay prior to parturition was 16.2 days in the induction group versus 7.6 days in the expectant group (p < 0.001). Hence, induction before the due date reduces the rate of shoulder dystocia albeit without influencing plexus palsy or fractures if there is an increased need for phototherapy and prolonged antepartum hospitalisation [19]. The number to treat for preventing shoulder dystocia is 67, combined with 523 additional days in hospital.

Conclusion

The numerous new studies in recent years into diagnosis, treatment and obstetric aspects are also reflected in the recommendations of the new guideline from the DGGG and DDG on the clinical management of GDM [20]. Some are hotly debated, especially the recommendation for screening in the third trimester, as they deviate from the procedures proposed in the maternity guidelines. Let us hope that the Obstetrics and Prenatal Medicine Working Group of the DGGG will be successful in urging the G-BA to resume the consultation concerning a valid screening procedure. Given the change in our population structure, screening for undetected type 2 diabetes during the first trimester is also urgently needed in those at risk of diabetes. Nevertheless, when caring for pregnant women the premise should remain: “as little intervention as possible, limited to a decision-relevant minimum”. This applies to the frequency of blood glucose monitoring, assessment of blood glucose in the overall context, and the strict indication for insulin therapy. An opening for supplementary use of metformin when the need for insulin is extremely high, or even instead of insulin in individual cases, now appears to be justified based on diverse studies and meta-analyses. There is still no generally valid answer to the question of when and in which indication induction is acceptable. The data suggest, however, that induction prior to 39 gestational weeks is associated with considerable neonatal problems and that even in the case of later induction, e.g. in the presence of macrosomia, the balance between the neonatal benefit on the one hand and the strain on the patient and our clinical resources, on the other, must be viewed more critically.

Conflict of Interest

The authors declare that they have no conflict of interest.

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