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No further improvement in pregnancy-related outcomes in the offspring of mothers with pre-gestational diabetes in Bavaria, Germany, between 2001 and 2016

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Dear Dr. Balkau,

thank you again for considering our paper for publication in *Diabetic Medicine.* We have answered the remaining comments as follows:

Reviewer: 3, statistical reviewer
Comments to the Author

Thank you for your careful and expansive replies to my queries.

Perhaps you should make a comment in the methods section about not being able to identify women who have had more than one pregnancy?

Thank you. We followed your advice.

The figure is a useful addition.

Perhaps add a sentence or two about the possible impact on GDM rates and on pregnancy outcomes of the increasing proportion of babies born to women over 35?

Thank you. We added the following: "We observed a higher number of women with advanced maternal age at delivery in 2008-2016 compared to 2001-2007, a factor which has been found to be associated with increased rates of both GDM and adverse perinatal outcomes [12]. However, advanced maternal age was a stronger predictor of perinatal mortality and malformations in non-diabetic than in diabetic women in our data, so that it appears unlikely that we missed effects of potential improvements in the management of diabetic pregnancies only due to temporal trends related to maternal age at delivery."

Yours sincerely,

Andreas Beyerlein (for all authors)

No further improvement in pregnancy-related outcomes in the offspring of mothers with pre-gestational diabetes in Bavaria, Germany, between 2001 and 2016

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Novelty statements:

- Our data cover all deliveries in obstetric units in Bavaria, Germany, between 1987 and 2016 (about 100,000 per year).
- The data have been recorded and quality-checked in a uniform manner over time for the purpose of benchmarking health-care provision.

- Other than in previous periods, there was no further improvement with respect to a number of adverse perinatal outcomes such as stillbirths in women with pre-gestational diabetes between 2001-2007 compared to 2008-2016.
- These risks were still significantly higher than in non-diabetic pregnancies, indicating that the goals of the St Vincent declaration have not yet been achieved.

Abstract

Aims: We had previously shown that the risk of adverse outcomes in diabetic pregnancies dropped considerably between 1987 and 2007 in Bavaria, Germany. Here, we investigated whether there was further improvement until 2016.

Methods: We analyzed cross-sectional data on all n=1,716,170 deliveries in Bavarian hospitals between 2001 and 2016. We assessed the risks of stillbirth, early neonatal death, preterm delivery, large for gestational age, malformations, low Apgar score and low umbilical cord pH by maternal diabetes group (gestational, pre-gestational, or none) separately for 2001-2007 and 2008-2016. We also investigated the associations of specific risk factors such as maternal smoking with respect to early mortality and malformations in each diabetes group in 2008-2016.

Results: We observed no further reduction in the risk for any adverse outcome in mothers with pre-gestational diabetes and their offspring in 2008-2016. Maternal smoking, multiple delivery and sub-standard use of antenatal care were the strongest additional predictors of both early perinatal mortality and malformations for mothers with pre-gestational diabetes. The respective risks were lower and also decreased over time for mothers with gestational diabetes.

Conclusions: No considerable improvement has been achieved in the management of pregnancies affected by pre-gestational diabetes during the last decade. The apparent risk reductions in women with gestational diabetes may partly be due to a change in diagnostic criteria over time. Women with pre-gestational diabetes who smoke, carry more than one child or are not regularly seen during pregnancy may need particular attention.

Introduction

According to the St Vincent declaration of 1989 the rates of adverse perinatal outcomes in diabetic pregnant women should be reduced to numbers comparable to those in pregnancies not affected by diabetes. We had previously shown that this goal was not achieved in women with pre-gestational diabetes mellitus (pre-DM) in Bavaria, Germany, by 2007 although considerable improvements were observed since 1987 [1]. Also in later studies, diabetes in pregnancy was still reported to be associated with increased risk for adverse perinatal outcomes [2-6]. However, there seems to be a lack of data on recent cohorts in this context as most of these studies were based on data recorded up until 2012 or earlier. Here we present an update of our previous analysis including data from deliveries between 2008 and 2016 in order to assess whether further improvement has been achieved in the management of diabetic pregnancies. We compared perinatal outcomes in women with pre-DM as well as gestational diabetes mellitus (GDM) with reference to non-diabetic pregnancies.

Patients and methods

As in our previous publication [1] we used routinely collected maternal and neonatal data on all deliveries in obstetric units from Bavaria, Germany, since 1987. We analyzed the data of all 1,716,170 deliveries recorded from 2001 to 2016 to compare perinatal outcomes between the periods of 2001-2007 (in line with our previous analysis) and 2008-2016. The data did not contain an identifier variable for the pregnant women so that we were not able to identify repeated pregnancies in the same mother. We assessed associations of pre-DM and DM with respect to the following adverse pregnancy outcomes: preterm delivery (<37 completed weeks of gestation), stillbirth, early neonatal death (within first seven days of life), malformations and large for gestational age neonate as defined by the upper 10% of German

birth weight percentiles [7]. Additionally, associations with low five-minute Apgar score (<7) and low umbilical cord pH (<7.1) as measures of the new-born's condition [8] were explored. We calculated the rates of these adverse pregnancy outcomes in GDM and pre-DM pregnancies in 2001-2007 and 2008-2016, respectively, derived odds ratios (ORs) with 95% confidence intervals (CIs) of each outcome for both diabetes groups compared to no diabetes as a reference, and calculated ratios of these ORs for the comparison of the later to the earlier period. We performed stepwise adjustment to explore potential confounding by maternal overweight (body mass index > 25 kg/m²) and substandard use of antenatal care (defined as less than one antenatal visit per four weeks of gestation [9]). As perinatal mortality and malformations are the most important severe and irreversible adverse pregnancy outcomes in diabetic mothers, we assessed a number of potential risk factors in each maternal diabetes group in order to identify potential high-risk subgroups. Specifically, we calculated multiple logistic regression models for the outcomes perinatal mortality (stillbirths and early neonatal deaths) according to the World Health Organization (WHO) definition and malformations with foreign country of origin, maternal smoking during pregnancy, high maternal age at delivery (≥ 35 years), maternal overweight, multiple delivery, hypertension and substandard use of antenatal care as predictors for all three groups (no diabetes, GDM, pre-DM) in 2008-2016. All calculations were performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

In 2001-2007, 0.45 % of all pregnant women were reported to have pre-DM, and 1.55 % GDM. These rates increased to 0.73 % and 3.80 % in 2008-2016, respectively (for yearly rates from 1987 to 2016 see supplementary figure 1). In 2001-2007, pre-DM was associated with increased risks for all adverse perinatal outcomes except early neonatal deaths (e.g. OR [95% CI] for stillbirths: 1.88 [1.24, 2.87], table 1). In 2008-2016, no significant

improvements compared to the previous period were observed for any adverse outcome in pregnancies with pre-DM (OR [95% CI] for stillbirths: 1.83 [1.33, 2.51]). The ORs for all adverse perinatal outcomes in pregnancies with GDM were somewhat lower than for pregnancies with pre-DM, and GDM was not significantly associated with either stillbirths or early neonatal deaths. In the latter group, significant risk reductions in the second compared to the first observation period were observed with respect to preterm deliveries (OR ratio [95% CI] for 2008-2016 compared to 2001-2007: 0.92 [0.86, 0.98]), malformations (OR ratio [95% CI]: 0.83 [0.72, 0.96]), large for gestational age births (OR ratio [95% CI]: 0.78 [0.73, 0.82]) and low Apgar scores (OR ratio [95% CI]: 0.80 [0.67, 0.96]). None of the observed associations changed considerably after adjustment for maternal overweight and substandard use of antenatal care (data not shown).

In pre-DM mothers maternal smoking was the strongest predictor of both early mortality (OR [95% CI]: 3.82 [1.95, 7.51]) and malformations (OR [95% CI]: 2.90 [1.76, 4.78]). Multiple delivery and substandard utilization of antenatal care were also found to be significantly associated with increased risks of early mortality in this subgroup, and non-German descent with malformations (table 2). In the GDM or no diabetes subgroups, multiple delivery and substandard use of antenatal care were observed to be the most important risk factors for early mortality, the same as foreign country of origin for malformations. There were decreasing prevalences over time with respect to maternal smoking during pregnancy (2001-2007: 7.77 %; 2008-2016: 5.11 %) and substandard use of antenatal care (29.90 %; 26.07 %) and an increasing rate of a maternal age ≥ 35 years at delivery (17.80 %; 26.78 %), while relatively stable rates were observed for all other potential risk factors (e. multiple delivery: 3.55 %; 3.68 %). All these temporal trends were similar across women with pre-DM, GDM or no diabetes (data not shown).

Discussion

No considerable improvement seems to have happened in the management of women with pre-DM during the last decade while the rates of several adverse perinatal outcomes were markedly reduced in GDM women. Interestingly, mothers with GDM had much more favorable perinatal outcomes than those with pre-DM in accordance with findings from another study [2]. There it had been suggested that this may be due to the fact that GDM women are more often seen by their obstetricians than pre-DM women. Indeed, we observed that sub-standard antenatal care was less common in GDM compared to pre-DM pregnancies (e.g. 19.79 % compared to 25.86 % in 2008-2016) and was associated with perinatal mortality risk in all groups of pregnant women, just as in previous time intervals [1]. Additionally, the risk of perinatal mortality remained particularly increased in smoking pre-DM mothers, while in contrast hypertension appeared to be not such a relevant predictor any more. At least, the rates of maternal smoking during pregnancy and sub-standard antenatal care decreased from 2001-2007 to 2008-2016, indicating an overall improvement in the awareness of pregnant women irrespectively of their diabetes status. Most women with type 1 diabetes in Germany are treated by diabetologists. Education on pregnancy is part of the diabetes training. Even after training, however, a substantial part of women with type 1 diabetes conceive unplanned [10]. Additionally there is an increasing number of women in child bearing age – with a substantial proportion of migrants – for whom treatment intensity may vary [11]. We observed a higher number of women with advanced maternal age at delivery in 2008-2016 compared to 2001-2007, a factor which has been found to be associated with increased rates of both GDM and adverse perinatal outcomes [12]. However, advanced maternal age was a stronger predictor of perinatal mortality and malformations in non-diabetic than in diabetic women in our data, so that it appears unlikely that we missed

effects of potential improvements in the management of diabetic pregnancies only due to temporal trends related to maternal age at delivery.

These analyses are based on a very large dataset and together with our previous results [1] now cover a time span of just under three decades. Data quality is high as completeness of the data is monitored annually across obstetric units as an integral part of benchmarking health-care provision. Our observation that the proportion of pregnancies affected by diabetes has further increased over time is consistent with the general trend of a growing diabetes prevalence in the German population [13]. A limitation is that we were not able to differentiate between type 1 and type 2 diabetes in pre-DM pregnancies. With respect to GDM it should also be noted that adaptation of the new WHO diagnostic criteria in Germany in 2011 and the offer of a charge-free GDM screening in 2012 may have contributed to the observed rise in GDM diagnoses [14]. Therefore the apparent improvement in adverse perinatal outcomes in GDM women may partly be due to a broader inclusion of less severe GDM cases which may have attenuated the associated outcomes [15]. Unfortunately, we were not able to investigate this assumption in more detail because our data do not contain any laboratory measurements related to diabetes diagnosis such as HbA1c or glucose values during an oral glucose tolerance test. As another limitation, we were not able to differentiate between repeated pregnancies in the same mother.

In summary there still seems to be much room for improvement in the management of diabetic pregnant women, in particular if diabetes already exists before onset of pregnancy and if these women smoke, carry more than one child or do not attend their gynecologists regularly during pregnancy.

Acknowledgements

The authors' responsibilities were as follows: AB (guarantor) developed the study hypothesis, performed the statistical analyses and wrote the first and final draft of the manuscript. NL was responsible for provision and interpretation of the raw data and contributed to the final draft of the manuscript. RvK contributed to the first and final draft of the manuscript. AB had full access to all the data in the study and had final responsibility for the decision to submit for publication. The authors thank Anitha Pitchika (Institute of Diabetes Research, Helmholtz Zentrum München) for statistical assistance.

Disclosure

None of the authors had a personal or financial conflict of interest.

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Table 1. Prevalences and crude odds ratios (OR) with 95% confidence intervals (CI) of adverse pregnancy outcome in deliveries of mothers with pre-gestational / gestational diabetes mellitus (pre-DM / GDM) vs. no diabetes (reference) in Bavarian hospitals, 2001-2007 and 2008-2016.

	No diabetes		Pre-DM		GDM		OR pre-GM [95% CI]		OR GDM [95% CI]	
Outcome	**2001-2007 (n=725,767)**	**2008-2016 (n=931,388)**	**2001-2007 (n=3,348)**	**2008-2016 (n=7,130)**	**2001-2007 (n=11,472)**	**2008-2016 (n=37,065)**	**2001-2007**	**2008-2016**	**2001-2007**	**2008-2016**
Stillbirths	0.35 % (n=2,541)	0.30 % (n=2,790)	0.66 % (n=22)	0.55 % (n=39)	0.34 % (n=39)	0.26 % (n=98)	1.88 [1.24, 2.87]	1.83 [1.33, 2.51]	0.97 [0.71, 1.33]	0.88 [0.72, 1.08]
Early neonatal deaths	0.16 % (n=1,176)	0.13 % (n=1,224)	0.15 % (n=5)	0.24 % (n=17)	0.13 % (n=15)	0.08 % (n=29)	0.92 [0.38, 2.22]	1.82 [1.12, 2.93]	0.81 [0.49, 1.34]	0.60 [0.41, 0.86]
Preterm delivery (<37 weeks)	8.68 % (n=62,999)	8.62 % (n=80,305)	17.59 % (n=589)	16.10 % (n=1,148)	12.06 % (n=1,384)	11.04 % (n=4,092)	2.25 [2.05, 2.46]	2.03 [1.91, 2.17]	1.44 [1.36, 1.53]	1.32 [1.27, 1.36]
Malformations	1.54 % (n=11,173)	1.29 % (n=12,046)	2.60 % (n=87)	1.91 % (n=136)	2.34 % (n=268)	1.64 % (n=607)	1.71 [1.38, 2.11]	1.48 [1.25, 1.76]	1.53 [1.35, 1.73]	1.27 [1.17, 1.38]
Large for gestational age	8.69 % (n=63,047)	8.38 % (n=78,022)	24.25 % (n=812)	23.42 % (n=1,670)	16.99 % (n=1,949)	13.26 % (n=4,916)	3.37 [3.11, 3.65]	3.35 [3.17, 3.54]	2.15 [2.05, 2.26]	1.67 [1.62, 1.73]
Low Apgar score at 5 minutes (<7)	1.04 % (n=7,513)	1.18 % (n=11,011)	1.97 % (n=66)	2.24 % (n=160)	1.50 % (n=172)	1.38 % (n=510)	1.92 [1.51, 2.46]	1.92 [1.64, 2.25]	1.46 [1.25, 1.70]	1.17 [1.07, 1.28]
Low umbilical cord pH (<7.1)	1.79 % (n=13,006)	1.72 % (n=16,047)	3.17 % (n=106)	2.96 % (n=211)	2.05 % (n=235)	1.91 % (n=707)	1.79 [1.48, 2.18]	1.69 [1.34, 2.13]	1.15 [1.01, 1.31]	1.11 [1.03, 1.20]

Table 2. Mutually adjusted odds ratios [95% confidence intervals] of risk factors for perinatal mortality (stillbirths and deaths within 7 days) and malformations in pregnancies with or without pre-gestational / gestational diabetes mellitus (pre-DM / GDM) in Bavaria, 2008-2016.

	Perinatal mortality			**Malformations**		
Risk factor	**No Diabetes**	**Pre-DM**	**GDM**	**No Diabetes**	**Pre-DM**	**GDM**
Non-German descent	1.20 [1.12, 1.30]	0.81 [0.40, 1.61]	1.02 [0.69, 1.50]	1.53 [1.47, 1.60]	1.48 [1.01, 2.18]	1.66 [1.40, 1.96]
Smoking during pregnancy	1.34 [1.19, 1.52]	3.82 [1.95, 7.51]	1.74 [0.98, 3.11]	1.12 [1.03, 1.21]	2.90 [1.76, 4.78]	0.97 [0.67, 1.40]
Maternal age at delivery ≥ 35 years	1.26 [1.18, 1.35]	1.05 [0.60, 1.82]	1.20 [0.84, 1.71]	1.45 [1.40, 1.51]	1.15 [0.81, 1.64]	1.19 [1.01, 1.40]
Maternal overweight (BMI>25 kg/m²)	1.33 [1.24, 1.42]	1.32 [0.76, 2.29]	1.45 [1.001, 2.09]	0.87 [0.84, 0.91]	0.76 [0.54, 1.07]	0.73 [0.62, 0.86]
Multiple delivery	4.55 [4.16, 4.98]	2.41 [1.02, 5.70]	2.91 [1.74, 4.87]	1.28 [1.17, 1.39]	0.71 [0.29, 1.75]	1.41 [1.03, 1.94]
Hypertension	1.17 [0.93, 1.48]	0.69 [0.17, 2.90]	1.78 [0.92, 3.44]	1.52 [1.33, 1.73]	1.77 [0.88, 3.54]	1.17 [0.78, 1.77]
Substandard utilization of antenatal care	3.98 [3.74, 4.24]	2.03 [1.17, 3.50]	2.54 [1.77, 3.64]	0.96 [0.92, 1.003]	1.08 [0.74, 1.58]	0.73 [0.58, 0.90]

Supplementary figure 1. Yearly rates of pre-gestational / gestational diabetes mellitus (pre-DM / GDM) as recorded in routinely collected maternal and neonatal data on all deliveries in obstetric units from Bavaria, Germany, 1987-2016. The dashed vertical line corresponds to the year 2011 when new criteria for GDM diagnosis were introduced in Germany. Based on the new criteria GDM was diagnosed if at least one of the values for fasting, 1-hour, and 2-hour plasma glucose concentration as measured in a 75-g oral glucose tolerance test exceeded diagnostic thresholds, while at least two elevated values were required for GDM diagnosis before 2011.