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Adherence to clinical evaluations in women with pre-existing diabetes during pregnancy: A call to action from an Italian real-life investigation

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ABSTRACT

Aims: Women with pre-existing diabetes should plan for optimal care of the disease before, during and after pregnancy. The aim of this study was to assess the quality of diabetes mellitus monitoring and care before, during and after pregnancy in a large cohort of women.
Methods: 1913 diabetic women resident in the Lombardy Region (Italy) who experienced at least a birth between 2011 and 2015 and exhibited signs of diabetes ≥2 years before delivery were identified using the healthcare utilization database. Antidiabetic care was defined via outpatient examinations (i.e., assessments of glycated haemoglobin, lipid profile, urine albumin excretion and serum creatinine, and dilated eye exams) and use of antidiabetic drugs. Differences in adherence to recommendations before, during and after pregnancy were assessed by the non-parametric McNemar's test among the whole cohort and among the subgroup with type 1 diabetes.
Results: Adherence to recommendations was very poor before pregnancy, ranging from 13% to 42% for dilated eye and serum creatinine exam, respectively. During pregnancy, a significant portion of women increased adherence to all recommendations (e.g., glycated haemoglobin from 20% to 47%, p-value < 0.001), with the exception of lipid profile control. After pregnancy, adherence dropped to pre-pregnancy levels. A similar trend was observed in the use of antidiabetic drugs. Although women with type 1 diabetes showed better adherence across all periods, the same patterns emerged.
Conclusions: Besides an improvement in the indicators of clinical adherence during pregnancy, the management of diabetes among pregnant women remains sub-optimal both before and after the birth.

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1. Introduction

Globally, the prevalence of hyperglycaemia in pregnancy in women aged 20–49 years is 17% [1]. In Italy, from 6% to 7% of women are affected by diabetes during pregnancy [2,3], making diabetes the most frequent gestational complication. Maternal diabetes is classified in pregestational diabetes mellitus (type 1 diabetes or type 2 diabetes already diagnosed before pregnancy), and gestational diabetes mellitus (high blood glucose level during pregnancy without signs of pre-existing diabetes) [4]. Although gestational diabetes mellitus is still the more common form of diabetes during pregnancy [5], both type 1 and type 2 diabetes are progressively increasing in women of childbearing age [6,7], and, consequently, among pregnant women.

Although evidence-based recommendations for managing diabetes during gestation are currently available [8–11] and several initiatives have been implemented for improving pregnancy preparation among women with type 1 and type 2 diabetes [12,13], pregnancies complicated by pre-existing diabetes still frequently generate adverse outcomes [14–18] such as spontaneous abortions, pregnancy complications, neonatal deaths and congenital malformations [19–22]. As such, improved care for women with pregestational diabetes mellitus presents a growing clinical challenge and priority during pregnancy [23,24]. Ideally, pregnancies should be carefully planned and optimal glycaemic control should be achieved prior to, during and after pregnancy among women with pregestational diabetes mellitus.

The purpose of this population-based study is to investigate the quality of diabetes mellitus monitoring and care before, during and after pregnancy in a large cohort of women with signs of diabetes who experienced childbirth in the Italian Region of Lombardy. To achieve this aim, we adopted a set of indicators developed and validated by a working group of the Italian Health Ministry to estimate the management of diabetes [25].

2. Methods

2.1. Data source

The data used for the present study were retrieved from the healthcare utilization databases of Lombardy, a Region of Italy that accounts for about 16% (~10,000,000) of its population. The Italian National Health System (NHS) provides universal healthcare, including inpatient (e.g., hospital admissions for delivery etc.) and outpatient (e.g., antidiabetic drugs, tests and examinations for diabetic monitoring, specialist visits etc.) services mainly covered by the NHS. Any co-payments are waived for individuals with chronic disease, including diabetes. In Lombardy, the NHS has been associated since 1997 with an automated system of databases to collect a variety of anonymized healthcare information. Details of healthcare utilization databases of the Lombardy Region and of their use in the field of diabetes and pregnancy are reported elsewhere [26–29].

2.2. Study cohort

As shown in Fig. 1, all 653,416 NHS beneficiaries in Lombardy from January 1st 2009 until December 31th 2012 with healthcare system utilization suggestive of diabetes were selected. In particular, beneficiaries who during this period (i) had at least two prescriptions of antidiabetic agents in two distinct dates over 365 days, and/or (ii) experienced at least one hospital admission with primary or secondary diagnosis of diabetes, and/or (iii) took advantage of co-payment exemption for diabetes, were considered suffering from diabetes [25]. Among the 50,053 diabetic women aged 18 to 55 years identified, 3299 women who experienced at least a birth from January 1st 2011 until December 31st 2015 were identified and the first birth occurred during this period was considered the index delivery. We began identifying eligible diabetic women with first pregnancies two years into the data collection period to allow assessment of their clinical history in the two years preceding the index pregnancy. We excluded women who in the period between 3 years before and 2 years after the date of the index delivery (i) were not NHS beneficiaries (to ensure the complete ascertainment of exposure along the entire period of interest, see below) (ii) experienced another pregnancy other than that index (to ensure complete ascertainment of exposure in the pre- and post-pregnancy time period and that exposure to antidiabetic care was not affected by other pregnancies, see below). The final study cohort, therefore, consisted of 1913 diabetic women.

2.3. Exposure to recommendations and care

Antidiabetic care was identified in two ways. First, outpatient examinations, including assessments of glycated haemoglobin, lipid profile (total and HDL cholesterol and triglycerides), urine albumin excretion, and serum creatinine and dilated eye exams were evaluated. A woman was considered adherent to recommendations if she had at least two glycated haemoglobin evaluations and at least one of the other assessments annually [25]. Second, dispensations of antidiabetic drugs, both insulin and oral hypoglycaemic agents, were assessed. Both adherence to recommendations and prescriptions for both types of antidiabetic drugs were independently assessed during three one-year timeframes: (i) during pregnancy (i.e. the year before the date of index delivery), (ii) before pregnancy (i.e. the year before the pregnancy period), and (iii) after pregnancy (i.e. the year after the date of index delivery).

2.4. Data analyses

The null hypothesis that adherence to recommendations and prescription of antidiabetic drugs did not change between each possible pair of time-windows (i.e., before and during pregnancy, during and after pregnancy, and before and after pregnancy) was tested by means of the non-parametric McNemar's test with Bonferroni correction, performing a within-woman (between-periods) comparison (Fig. S1, box

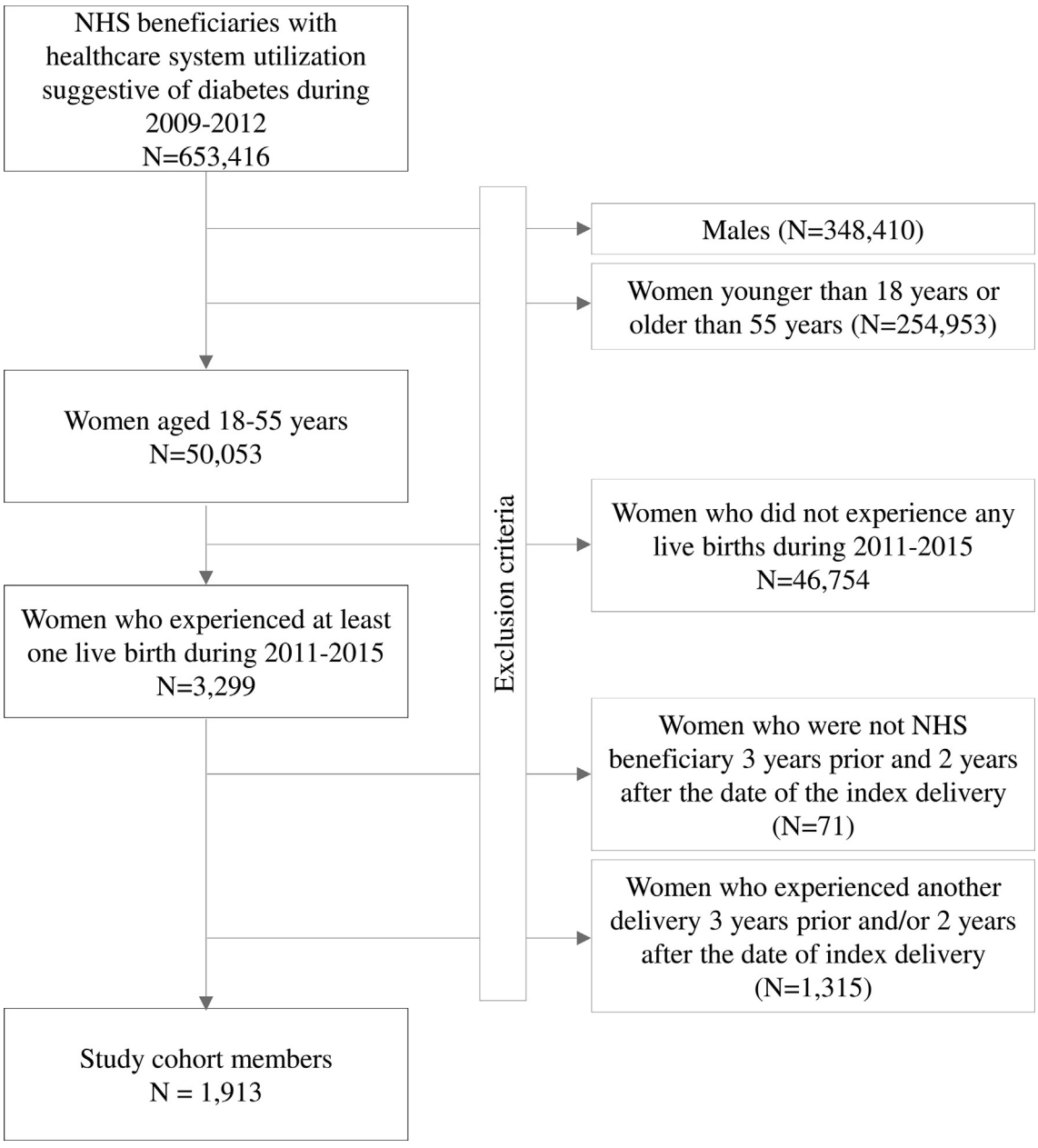

Fig. 1 – Flow-chart of inclusion and exclusion criteria.

A). The same analyses were restricted to women younger than 35 years who used insulin before the index pregnancy, namely to women likely suffering from type 1 diabetes.

2.5. *Sensitivity analysis*

To understand whether our results for pre-pregnancy period reflect real-world care of childbearing age women in general, a reference cohort of diabetic women who did not experience a live birth during the considered period was created. The 46,754 women who did not experience any birth during 2011–2015 were subjected to the same exclusion criteria as the 3299 women with births (Fig. 1) to form the eligible reference cohort. For each study cohort member, a reference woman was matched for age at the index delivery and date of first evidence of diabetes. Adherence to recommendations and antidiabetic drug prescriptions during the one-year pre-pregnancy period of the matched study cohort member were measured for each member of the reference cohort. Again, the null hypothesis that study and reference women did not differ in adherence to recommendations and antidiabetic drug prescriptions during the pre-pregnancy period was tested by means of the non-parametric McNemar's test with Bonferroni correction (Fig. S1, **box B**).

3. Results

The mean age of the diabetic women included in the study cohort was 35 years (interquartile range, 32–38). Four out of five women were identified by co-payment exemption (82%),

Table 1 – Adherence to recommendations and use of antidiabetic drugs of the 1913 study cohort mothers before, during and after pregnancy. Italy, Lombardy region, 2011–2015.

	Peri-pregnancy periods[a]						Between-period comparisons[b]	
	Before pregnancy (A)		During pregnancy (B)		After pregnancy (C)		A vs. B	B vs. C
Recommended examinations								
Glycated haemoglobin	390	(20.4%)	902	(47.2%)	375	(19.6%)	<0.001	<0.001
Lipid profile	673	(35.2%)	523	(27.3%)	524	(27.4%)	<0.001	0.962
Urine albumin excretion	365	(19.1%)	564	(29.5%)	363	(19%)	<0.001	<0.001
Serum creatinine	803	(42%)	1157	(60.5%)	665	(34.8%)	<0.001	<0.001
Dilated eye exam	251	(13.1%)	364	(19%)	219	(11.5%)	<0.001	<0.001
Antidiabetic drug therapy								
Insulin	382	(20.0%)	646	(33.8%)	442	(23.1%)	<0.001	<0.001
Oral hypoglycaemic agents	212	(11.1%)	173	(9.0%)	137	(7.2%)	<0.001	0.001

[a] Before pregnancy: within the year before the 3 months prior the expected date of conception. During pregnancy: within the year before the date of index delivery. After pregnancy: within the year after the date of index delivery.
[b] According to the non-parametric McNemar's test with Bonferroni correction for multiple comparisons.

with 40% identified by antidiabetic drug dispensations and 24% by hospital admission with diagnosis of diabetes.

Before pregnancy, study cohort members showed poor adherence to recommendations, with only a portion of them ranging from 13% to 42% undergoing dilated eye and serum creatinine exams respectively (Table 1). During or just before pregnancy a significant portion of women increased adherence to all recommendations, with the exception of lipid profile control, which was less controlled during pregnancy. Despite the gain, it should be noted that adherence continued to be low during or just before pregnancy, as during this period only a portion of women ranging from 19% to 61% underwent dilated eye and serum creatinine exams respectively. After pregnancy, the prevalence of women adhering to considered recommendations dropped to pre-pregnancy levels, or even lower for lipid profile and serum creatinine (**Supplementary Table S1**). Use of antidiabetic drugs roughly followed the same trends seen for recommended adherence. Less than one woman in three received drug therapy before pregnancy, with a significant increase of insulin during pregnancy and return to pre-pregnancy levels afterwards (Table 1). A significant reduction of oral hypoglycemic agents was seen across the periods during and post- pregnancy.

As shown in Table 2, study cohort members likely affected by type 1 diabetes showed better adherence to recommendations. With the exception of the dilated eye exam, more than half of women with type 1 diabetes adhered to treatment recommendations. Adherence further increased during pregnancy in this sub-group, reaching almost optimal levels for urine albumin excretion, serum creatinine and above all glycated haemoglobin testing, returning to pre-pregnancy levels afterwards (**Supplementary Table S2**).

Fig. 2 shows that in the one-year period coinciding with the pre-pregnancy period of study cohort members, referent women did not differ in adherence to recommendations and antidiabetic drug prescriptions, with the exception of the lipid profile exam.

Table 2 – Adherence to recommendations of the 253 study cohort mothers aged ≤35 years and in treatment with insulin (before pregnancy) before, during and after pregnancy. Italy, Lombardy region, 2011–2015.

	Peri-pregancy periods[a]						Between-period comparisons[b]	
	Before pregnancy (A)		During pregnancy (B)		After pregnancy (C)		A vs. B	B vs. C
Recommended examinations								
Glycated haemoglobin	190	(75.1%)	244	(96.4%)	165	(65.2%)	<0.001	<0.001
Lipid profile	174	(68.8%)	169	(66.8%)	166	(65.6%)	0.600	0.753
Urine albumin excretion	170	(67.2%)	222	(87.8%)	152	(60.1%)	<0.001	<0.001
Serum creatinine	191	(75.5%)	227	(89.7%)	169	(66.8%)	<0.001	<0.001
Dilated eye exam	106	(41.9%)	150	(59.3%)	72	(28.5%)	<0.001	<0.001

[a] Before pregnancy: within the year before the 3 months prior the expected date of conception. During pregnancy: within the year before the date of index delivery. After pregnancy: within the year after the date of index delivery.
[b] According to the non-parametric McNemar's test with Bonferroni correction for multiple comparisons.

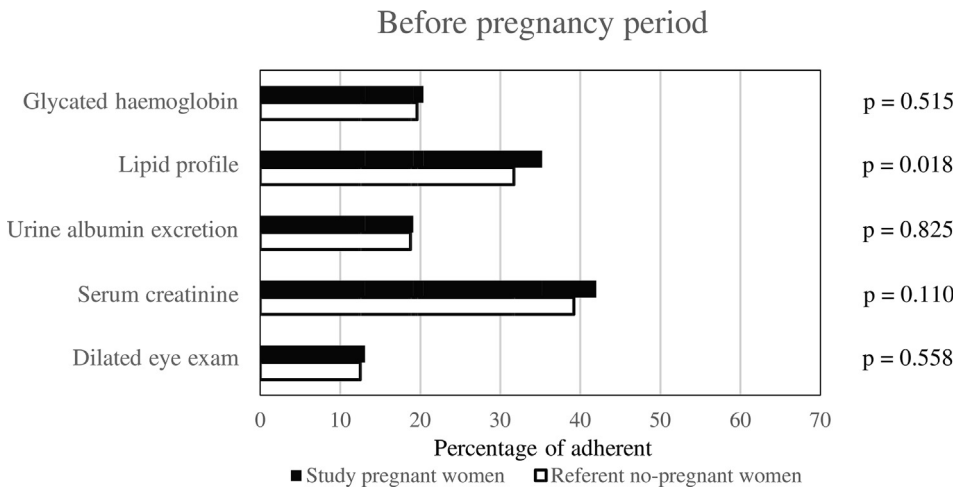

Fig. 2 – Adherence to recommendations of the 1913 study cohort mothers and the corresponding 1913 matched study cohort members during the one-year pre-pregnancy period.

4. Discussion

Planning for diabetes care during pregnancy and optimization of metabolic control in the preconception period and during pregnancy are recognized pillars of the health care of diabetic women and their children. Our study, which was focused on diabetic women with a birth during 2011–2015 in Lombardy (Italy), aimed to establish in a retrospective fashion the adherence to recommended clinical monitoring and prescription of antidiabetic drugs in these women in the preconception period, during pregnancy and after birth. Our results clearly demonstrate that, although the efforts of health care practitioners improved the indicators of clinical adherence and prescription of antidiabetic drugs during pregnancy, the pre-pregnancy period was characterized by lack of a proper preconception clinical monitoring and in a similar fashion the after-birth period demonstrated a returned to preconception poor adherence to treatment recommendations and low rates of antidiabetic drug prescription. However, much higher adherence to treatment recommendations was observed among women likely affected by type 1 diabetes (i.e., those aged less than 35 years and on treatment with insulin), probably because of the difficulty of management of this condition.

The Italian Society of Diabetes recommends careful monitoring during pregnancy including physical and laboratory evaluations at least once every two months for women with pre-existing diabetes [9]. Although we adopted looser criteria (i.e., those validated from a working group of the Italian Health Ministry for clinical examinations of diabetic patients [25]), our results are disconcerting for several reasons. First, adherence to recommendations was very low in all the considered periods, even if during pregnancy women appeared to be more adherent to the clinical monitoring, especially in the assessments of glycated haemoglobin and serum creatinine. Second, only a small proportion of women were on treatment with oral antidiabetic drugs or insulin, although the prevalence of insulin use increased during pregnancy. We cannot however exclude that in women with pregravidic type 2 diabetes, metabolic control could be achieved by diet and physical activity alone [30,31].

To the best of our knowledge, this is the first study that assesses the quality of diabetes care by means of these outpatient examinations in pregnant women with pregestational diabetes. Charlton et al. [32] evaluated antidiabetic medicine prescribing to women before, during and after pregnancy. Although the patterns were similar to ours (i.e., increase of insulin prescriptions during pregnancy and return to pre-pregnancy levels after pregnancy), the authors carried out the investigation among all pregnant women rather than those with pre-existing diabetes. Therefore, a comparison of drug use between studies cannot be performed. However, our results could be explained by the tendency to avoid drug therapies other than insulin during pregnancy. Lower adherence to oral hypoglycaemic agents during the post- pregnancy period could be interpreted as poor care but also as the desire for planning a second pregnancy relying on alternative monitoring care of diabetes rather than drug-based care.

Pregestational diabetes mellitus can represent a danger for the foetus. High blood sugar in the gestation period, particularly during the first trimester, is in fact an established risk factor for congenital anomalies, especially those of cardiovascular and nervous systems [33–36]. Nonetheless, a diabetic woman who receives careful diabetes care from the stage before conception may reduce the risk of congenital anomalies and neonatal events to the same risk levels of non-diabetic women [37]. For this reason, it is important that diabetic women plan their pregnancy with optimal care of diabetes for at least six months before conception [38,39]. Despite these recommendations, the results of our study indicate insufficient antidiabetic care in diabetic women before and after pregnancy and, most importantly, document a lack of sufficient improvement in diabetes care during pregnancy.

This study has several strengths. First, the investigation was based on data from a large unselected population, which was made possible by the fact that the publicly funded Italian

healthcare system involves virtually all citizens. Second, the drug prescription database provided highly accurate data because pharmacists are required to report prescriptions in detail to obtain reimbursement, and incorrect reports about the dispensed drugs have legal consequences [40]. Three, the results were not affected by the presence of a temporal trend in recommendation adherence among the periods of interest because the findings were replicated by matching the cohort members to non-pregnant women of the same age.

However, our study also had some limitations. First, the exclusion of miscarriages might have excluded less healthy women from our study cohort. Second, information about health service outpatient facilities supplied by private organizations are not available from our databases. Therefore, a portion of examinations might have been lost. However, an Italian investigation showed that administrative data and medical records had good concordance in detecting microalbuminuria, glycated haemoglobin, lipid profile and creatinine controls, while eye exams were often not captured [41]. Third, as mentioned above, not all diabetic patients need drug therapy since some of them achieve glycaemic control with diet and exercise alone. Nevertheless, these two limitations do not affect the main finding of our study, i.e., the increase of adherence during pregnancy and the drop afterwards. Finally, the lack of clinical information (above all, haemoglobin A1c and folic acid intake) recorded in our database did not allow complete ascertainment of the patients (i.e., determining the glycaemic control and the whole care quality of the women). In addition, the lack of socioeconomic and educational background of the mother did not allow to assess their impact on the adherence to medical recommendations and clinical evaluations, especially in the observed difference between the type 1 and type 2 diabetes patients. Future researches on this topic are needed.

In conclusion, the results of our study provide convincing evidence for the need to improve education of all health care professionals involved in diabetes care, and of diabetic women of childbearing age, to improve management of the disease and prevent the excess of spontaneous abortions, fetal congenital anomalies and pregnancy complications related to diabetes. These efforts would most likely also substantially reduce health care cost. Since this process takes time from the preconception period but it also must last after-birth, it is of paramount importance that a multidisciplinary team of health care professionals (general practitioner, nurses, diabetologist, obstetrician/gynecologist) develop specific community-based pre- and post-pregnancy programmes of prevention and care in all women within gestational age.

Acknowledgement

AC and FR conceived the idea for this manuscript. AC and GC designed the study and drafted the manuscript. AC, FR, and RL performed the data analysis. LM extracted the data and authorised their utilisation. AL and GP assisted in interpreting the results under the clinical perspective. All authors assisted the results interpretation and manuscript revision. All authors read and approved the final manuscript.

Declaration of Competing Interest

Giovanni Corrao received research support from the European Community (EC), the Italian Agency of Drug (AIFA), and the Italian Ministry of Education, University and Research (MIUR). He took part to a variety of projects that were funded by pharmaceutical companies (i.e., Novartis, GSK, Roche, AMGEN and BMS). He also received honoraria as member of Advisory Board from Roche.

Other authors declare that they have no conflict of interest to disclose.

Data availability

The data that support the findings of this study are available from Lombardy Region but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of Lombardy Region.

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Role of the funding source

The Italian Ministry of the Education, University and Research had no role in the design of the study, the collection, the analysis, the interpretation of the data, or the decision to approve publication of the finished manuscript.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2019.06.006.

REFERENCES

[1] Guariguata L, Linnenkamp U, Beagley J, et al. Global estimates of the prevalence of hyperglycaemia in pregnancy. Diabetes Res Clin Pract 2014;103:176–85. https://doi.org/10.1016/j.diabres.2013.11.003.

[2] Buckley BS, Harreiter J, Damm P, et al. DALI Core Investigator Group. Gestational diabetes mellitus in Europe: prevalence, current screening practice and barriers to screening. A review. Diabet Med 2012;29:844–54. https://doi.org/10.1111/j.1464-5491.2011.03541.x.

[3] Bianchi C, de Gennaro G, Romano M, et al. Italian national guidelines for the screening of gestational diabetes: Time for a critical appraisal? Nutr Metab Cardiovasc Dis 2017;27:717–22. https://doi.org/10.1016/j.numecd.2017.06.010.

[4] Xie GH, Zheng Z, Liu TC, et al. Health care and risk of adverse pregnancy outcomes among diabetic women: an updated meta-analysis. Arch Gynecol Obstet 2019;299:891–9. https://doi.org/10.1007/s00404-019-05042-x.

[5] Deputy NP, Kim SY, Conrey EJ, Bullard KM. Prevalence and changes in preexisting diabetes and gestational diabetes among women who had a live birth - United States, 2012–2016. MMWR Morb Mortal Wkly Rep 2018;67:1201–7. Available from: https://doi.org/10.15585/mmwr.mm6743a2.
[6] Bardenheier BH, Imperatore G, Devlin HM, et al. Trends in pre-pregnancy diabetes among deliveries in 19 U.S. states, 2000-2010. Am J Prev Med 2015;48:154–61. https://doi.org/10.1016/j.amepre.2014.08.031.
[7] Hruby A, Hu FB. The epidemiology of obesity: a big picture. Pharmacoeconomics 2015;33:673–89. https://doi.org/10.1007/s40273-014-0243-x.
[8] National Institute for Health and Care Excellence (NICE). Diabetes in pregnancy: management of diabetes and its complications from preconception to the postnatal period; 2015.
[9] Standard italiani per la cura del diabete mellito, SID-AMD 2018 http://aemmedi.it/wp-content/uploads/2009/06/AMD-Standard-unico1.pdf [Accessed on 28 April 2019]
[10] World Health Organization. Diagnostic criteria and classification of hyperglycaemia first detected in pregnancy; 2013.
[11] American Diabetes Association. 13. Management of Diabetes in Pregnancy: Standards of Medical Care in Diabetes-2018. Diabetes Care 2018;41(Suppl 1):S137–43. https://doi.org/10.2337/dc18-S013.
[12] Yamamoto JM, Hughes DJF, Evans ML, Karunakaran V, Clark JDA, Morrish NJ, et al. Community-based pre-pregnancy care programme improves pregnancy preparation in women with pregestational diabetes. Diabetologia 2018;61:1528–37. https://doi.org/10.1007/s00125-018-4613-3.
[13] Owens LA, Egan AM, Carmody L, Dunne F. Ten years of optimizing outcomes for women with Type 1 and Type 2 diabetes in pregnancy-the Atlantic DIP experience. J Clin Endocrinol Metab 2016;101:1598–605. https://doi.org/10.1210/jc.2015-3817.
[14] Mackin ST, Nelson SM, Kerssens JJ, Wood R, Wild S, Colhoun HM, et al. SDRN Epidemiology Group. Diabetes and pregnancy: national trends over a 15 year period. Diabetologia. 2018;61:1081–88. https://doi.org/10.1007/s00125-017-4529-3
[15] Bashir M, Naem E, Taha F, et al. Outcomes of type 1 diabetes mellitus in pregnancy; effect of excessive gestational weight gain and hyperglycaemia on fetal growth. Diabetes Metab Syndr 2019;13:84–8. https://doi.org/10.1016/j.dsx.2018.08.030.
[16] Bashir M, Dabbous Z, Baagar K, et al. Type 2 diabetes mellitus in pregnancy: The impact of maternal weight and early glycaemic control on outcomes. Eur J Obstet Gynecol Reprod Biol 2018;233:53–7. https://doi.org/10.1016/j.ejogrb.2018.12.008.
[17] McCarthy EA, Williamson R, Shub A. Pregnancy outcomes for women with pre-pregnancy diabetes mellitus in Australian populations, rural and metropolitan: a review. Aust N Z J Obstet Gynaecol 2019;59:183–94. https://doi.org/10.1111/ajo.12913.
[18] Beyerlein A, Lack N, von Kries R. No further improvement in pregnancy-related outcomes in the offspring of mothers with pre-gestational diabetes in Bavaria, Germany, between 2001 and 2016. Diabet Med 2018;35:1420–4. https://doi.org/10.1111/dme.13691.
[19] Lapolla A, Dalfrà MG, Spezia R, et al. Outcome of pregnancy in type 1 diabetic patients treated with insulin lispro or regular insulin: an Italian experience. Acta Diabetol 2008;45:61–6. https://doi.org/10.1007/s00592-008-0024-0.
[20] Wahabi HA, Alzeidan RA, Bawazeer GA, et al. Preconception care for diabetic women for improving maternal and fetal outcomes: a sistematic review and meta-analysis. BMC Pregnancy Childbirth 2010;10:63–77. https://doi.org/10.1186/1471-2393-10-63.
[21] Negrato CA. Adverse pregnancy outcomes in women with diabetes. Diabetol Metabol Syndr 2012;4:41. https://doi.org/10.1186/1758-5996-4-41.
[22] ACOG Committee on Practice Bulletins. ACOG Practice Bulletin. Clinical Management Guidelines For Obstetrician-Gynecologists. Obstet Gynecol 2005;105:675–85.
[23] Lewis H, Egerman R, Kazory A, Sattari M. Diabetes and pregnancy: risks and opportunities. Cleve Clin J Med 2018;85:619–28. https://doi.org/10.3949/ccjm.85a.16138.
[24] Tripathi A, Rankin J, Aarvold J, Chandler C, Bell R. Preconception counseling in women with diabetes: a population-based study in the north of England. Diabetes Care 2010;33:586–8. https://doi.org/10.2337/dc09-1585.
[25] Corrao G, Rea F, DI Martino M, et al.; working group 'Monitoring and assessing diagnostic-therapeutic paths' of the Italian Heath Ministry. effectiveness of adherence to recommended clinical examinations of diabetic patients in preventing diabetes-related hospitalizations. Int J Qual Health Care 2018 [Epub ahead of print] https://doi.org/10.1093/intqhc/mzy186.
[26] Santucci C, Franchi M, Staszewsky L, et al. Incretin-based drugs and hospitalization for heart failure in the clinical practice: a nested case-control study. Diabetes Res Clin Pract 2018;146:172–9. https://doi.org/10.1016/j.diabres.2018.10.006.
[27] Corrao G, Monzio Compagnoni M, Rea F, et al. Clinical significance of diabetes likely induced by statins: evidence from a large population-based cohort. Diabetes Res Clin Pract 2017;133:60–8. https://doi.org/10.1016/j.diabres.2017.08.008.
[28] Cantarutti A, Merlino L, Giaquinto C, Corrao G. Use of antidepressant medication in pregnancy and adverse neonatal outcomes: a population-based investigation. Pharmacoepidemiol Drug Saf 2017;26:1100–8. https://doi.org/10.1002/pds.4242.
[29] Cantarutti A, Merlino L, Monzani E, Giaquinto C, Corrao G. Is the risk of preterm birth and low birth weight affected by the use of antidepressant agents during pregnancy? A population-based investigation. PLoS One 2016;11. https://doi.org/10.1371/journal.pone.0168115 e0168115.
[30] Di Biase N, Balducci S, Lencioni C, Bertolotto A, Tumminia A, Dodesini AR, et al. Review of general suggestions on physical activity to prevent and treat gestational and pre-existing diabetes during pregnancy and in postpartum. Nutr Metab Cardiovasc Dis 2018;pii: S0939–4753(18):30312. https://doi.org/10.1016/j.numecd.2018.10.013.
[31] Abell SK, Nankervis A, Khan KS, Teede HJ. Type 1 and Type 2 diabetes preconception and in pregnancy: health impacts, influence of obesity and lifestyle, and principles of management. Semin Reprod Med 2016;34:110–20. https://doi.org/10.1055/s-0035-1571196.
[32] Charlton RA, Klungsøyr K, Neville AJ, et al. Prescribing of Antidiabetic Medicines before, during and after Pregnancy: a Study in Seven European Regions. PLoS One 2016;11. https://doi.org/10.1371/journal.pone.0155737 e0155737.
[33] Zhao E, Zhang Y, Zeng X, Liu B. Association between maternal diabetes mellitus and the risk of congenital malformations: a meta-analysis of cohort studies. Drug Discov Ther 2015;9:274–81. https://doi.org/10.5582/ddt.2015.01044.
[34] Øyen N, Diaz LJ, Leirgul E, et al. Prepregnancy diabetes and offspring risk of congenital heart disease: a nationwide cohort study. Circulation 2016;133:2243–53. https://doi.org/10.1161/CIRCULATIONAHA.115.017465.
[35] Gabbay-Benziv R, Reece EA, Wang F, Yang P. Birth defects in pregestational diabetes: Defect range, glycemic threshold and pathogenesis. World J Diabetes 2015;6:481–8. https://doi.org/10.4239/wjd.v6.i3.481.

[36] Kitzmiller JL, Gavin LA, Gin GD, et al. Preconception care of diabetes: glycemic control prevents congenital anomalies. JAMA 1991;265:731–6.
[37] American Diabetes Association – Preconception Care of woman with Diabetes in pregnancy. Diabetes Care 2004;27 (suppl 1):S76–8. https://doi.org/10.2337/diacare.27.2007.S76
[38] NICE guidelines. Diabetes in pregnancy: management of diabetes and its complications from preconception to the postnatal period NICE guideline; 2015. nice.org.uk/guidance/ng3
[39] Handelsman Y, Bloomgarden ZT, Grunberger G, et al. American association of clinical endocrinologists and American college of endocrinology - clinical practice guidelines for developing a diabetes mellitus comprehensive care plan. Endocr Pract 2015;21(Suppl 1):1–87. https://doi.org/10.4158/EP15672.GL.
[40] Strom BL. Overview of automated databases in pharmacoepidemiology. In: Strom BL, editor. Pharmacoepidemiology. Chichester, UK: Wiley; 2000. p. 219–22.
[41] Gini R, Schuemie MJ, Pasqua A, et al. Monitoring compliance with standards of care for chronic diseases using healthcare administrative databases in Italy: strengths and limitations. PLoS One 2017;12. https://doi.org/10.1371/journal.pone.0188377 e0188377.