Pregnancy losses in women with type 1 or type 2 diabetes in the UK: an investigation using primary care records

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Novelty statement:

- Proportions of pregnancies resulting in deliveries and losses in women with type 2 diabetes were similar to those in women with type 1 diabetes. Using primary care records we found higher overall proportions of losses than have previously been reported (type 1 33.4%, type 2 35.4%) and higher proportions of spontaneous losses (type 1 19.6%, type 2 21.1%) than in the general population (13.2%).

- Oral treatment of type 2 diabetes in the three months before pregnancy start date or during the first trimester resulted in the highest proportion of spontaneous losses (25%).

Abstract

Aim: This study aims to investigate pregnancy losses in women with type 1 and type 2 diabetes and compare this with the general population.

Methods: Pregnancies ending between 1993 and 2006 in those with type 1 or type 2 diabetes were identified on the General Practice Research Database. Pregnancy losses were identified from medical records and the cohort described by their characteristics and prescribing for diabetes.

Results: Of 2001 pregnancies identified in women with type 1 diabetes, 678 ended in a pregnancy loss: 19.6% were spontaneous, 9.6% were induced and 4.3% were losses for unknown reasons. In women with type 2 diabetes there were 240 losses in 669 pregnancies: 21.1% were spontaneous, 10.3% induced and 4.0% were losses for unknown reasons. The proportion of spontaneous losses in women with diabetes was higher than in the general population (13.2%). Women with type 1 diabetes treated with human and analogue insulins were 60% more likely to have a delivery than a loss (OR=1.6 CI_{95} 1.18-2.18) compared with human insulin treatment alone although numbers were small.

Conclusion

We found that the proportions of spontaneous losses in women with type 1 and type 2 diabetes were similar at approximately 20% which is higher than in the general population and also higher than previous studies have reported. While much emphasis has been placed on pre-conception care for women with type 1 diabetes, the same is now needed for those with type 2 diabetes, given the similarity in outcomes and increasing prevalence of this condition.

Introduction

Women with pre-existing diabetes are known to have higher rates of spontaneous pregnancy loss which is thought to be due to poor glycaemic control. Pre-pregnancy counselling and planning of pregnancies is advised in order to achieve optimum control and thus give the greatest likelihood of a successful pregnancy.

Optimum glycaemic control in women with pre-exiting diabetes in preparation for and during pregnancy, especially in the organogenesis phase is the ideal. Previous work has indicated an increased rate of spontaneous losses and major congenital malformations in the offspring of women with type 1 diabetes (1-3) but until recently it was thought that the number of women with type 2 diabetes during pregnancy was low (4). Given the increasing age of women having pregnancies and the reducing age of diagnosis of type 2 diabetes, this is now not the case (5, 6). The aim of this study is to compare proportions of losses between women with type 1 and type 2 diabetes and the population who do not have diabetes. General practice records will be used to obtain data for the entire pregnancy rather than just from referral to secondary care. Other patient factors that may also be associated with pregnancy loss will be investigated including maternal age, BMI, smoking status and treatment of diabetes.

Patients and methods

Data source

Pregnancies that ended between 1993 and 2006 and that had prescribing for diabetes in the year before or during pregnancy were identified on the General Practice Research Database (GPRD). The GPRD contains anonymised primary health care records, prescriptions, diagnoses, test results and referrals for around 7% of the UK population that are recorded for the purposes of patient management. The database has been shown to be representative of the population of the UK in terms of the geographical location of contributing practices, age and sex of patients compared with the general population (7). The database is supplied by the Medicines and Healthcare products Regulatory Agency who provide indicators of data that is considered to be up to a standard suitable for research. Approval for this study was obtained from the GPRD Independent Scientific Advisory Committee.

Study population

Pregnancy losses were identified by an algorithm (8) that determined whether the loss was spontaneous or if it was induced for medical or non-medical reasons. Medical diagnoses, test and referral data were used to determine this classification. Where the algorithm was not able to classify the reason for the termination, extra information was requested in the form of 'free text' which included referral, hospital letters and notes made by the GP. This was requested for one month before and three months after the pregnancy end date. To be included in this study, each patient needed to have at least one medical code for diagnosis of type 1 or type 2 diabetes before the start of pregnancy and at least one prescription for diabetes medication in the year before the start of pregnancy or during pregnancy. This ensured that only those with pre-existing diabetes were included in the cohort. This excluded women with gestational diabetes and type 2 diabetes treated by diet alone.

Data collected

Prescriptions issued for diabetes medication were classified by type of insulin (animal, human, analogue) and type of oral treatment (biguanide, sulphonylurea, other oral) by three month period. All individuals included had to have at least one year of data up to research standard before pregnancy start date and at least three months of data after pregnancy end date and to be aged between 11 and 49 years at the end of their pregnancy. Pregnancy loss was reported by trimester and according to treatment regimen. Patient characteristics including age, BMI and smoking status at the start of pregnancy were identified.

Classification of diabetes

Type of pre-existing diabetes was determined using an algorithm based on previous work (9) that identified for each patient their age at first diagnosis of diabetes, the diagnosis received, the type of treatment received and use of glucose monitoring kits. Any individuals where the type of diabetes could not be reliably determined were reviewed manually using a medical records browser that we have developed in-house. The browser displays all of the individual's records in chronological order and this was also used to verify diabetes diagnoses for a random sample of women.

Analysis

Descriptive statistics were presented for type of diabetes, type of loss and prescribing in the three months before or during the first trimester of pregnancy.

This period of prescribing was chosen to avoid information bias because, especially for pregnancies in women with type 2 diabetes, prescribing is altered during the second or third trimester; for pregnancy loss, prescribing in the first trimester is the important consideration. Comparisons of proportions of losses were made with all pregnancies identified in the GPRD. This included all pregnancies with an end date between 1993 and 2006 occurring in females aged between 10 and 49 years at pregnancy start date whose GPRD data was of research standard; this excluded those already in the cohort of women with pre-existing diabetes. Patient characteristics at pregnancy start date were presented including BMI, age, smoking status, duration of diabetes, receipt of prescriptions for folic acid, medications for hypertension or dyslipidaemia, records indicating treatment in secondary care and HbA1c records. Confidence intervals for proportions were calculated using the score method with continuity correction (10). Multiple logistic regression was used to investigate loss; any missing data for BMI or smoking status was coded separately. Model fit was assessed using the Hosmer-Lemshow statistic, residuals were checked and leverage was determined with any outlying points investigated for their influence on the model fit.

Results

548 women with type 1 diabetes and 197 women with pharmacologically treated type 2 diabetes were identified as having had 909 pregnancy losses on the GPRD between 1993 and 2006. Characteristics for these women are given in table 1. The most striking differences between those with type 1 and type 2 diabetes were in age at pregnancy start date and BMI: 39.9% of those with type 1 diabetes compared with 79.6% of those with type 2 diabetes were older than 30 years at pregnancy start date; 10.3% of those with type 1 and 52.1% of those with type 2 diabetes had a BMI greater than 30. However, the proportion of non-smokers was higher in those with type 2 diabetes (63.8% versus 46.8%) compared with those with type 1 diabetes. Similar proportions of spontaneous losses (type 1: 58.59%, type 2: 59.58%; difference -0.99% [$CI_{95\%}$ -8.23%, 6.26%]), induced terminations (type 1: 28.70%, type 2: 29.17%; difference -0.47% [$CI_{95\%}$ -7.16, 6.23]]) and losses where the type was unknown (type 1: 12.71%, type 2: 11.25%; difference 1.46% [$CI_{95\%}$ -3.27, 6.18]) were found between those with type 1 and type 2 diabetes.

Table 2 also compares proportions of outcomes for all pregnancies identified in the GPRD and those in women with type 1 or type 2 diabetes. The main differences were the lower proportion of deliveries (type 1 66.6%; type 2 64.6%;

all GPRD 70.4%) and higher proportion of spontaneous losses in those with diabetes (type 1 19.6%; type 2 21.1%; all GPRD 13.2%). This was true in both trimesters with spontaneous losses in the second trimester twice the proportion of those recorded in all pregnancies in the GPRD (type 1 1.5%, type 2 2.1%, all GPRD 0.8%). Freetext reclassified 69 of the pregnancy losses in the type 'unknown' category with over half of these found to be induced terminations. This contributed to the reduced frequency of unknown losses in women with diabetes compared to all losses in the GPRD.

Fig. 1 shows changes in numbers of deliveries and pregnancy losses over time where spontaneous losses in women with type 1 diabetes decreased until 2003 but in recent years, numbers have increased which has coincided with an increase in spontaneous losses in women with type 2 diabetes. However the numbers of pregnancy losses each year were small and corresponded to changes in total numbers of losses in the database.

Table 3 gives further details about patient management for those with diabetes during pregnancy. Over half of women with type 1 diabetes had this diagnosed between five and nineteen years before their pregnancy start date whereas almost all those with type 2 diabetes were diagnosed fewer than nine years before pregnancy start date which also reflects the criteria used for determining type of diabetes. Those with the longest durations of type 2 diabetes and shortest durations of type 1 diabetes were checked to ensure the diagnosis was correct: the duration of diabetes may be incorrectly recorded for those who had moved to a contributing GP practice after their diabetes was diagnosed. 6.4% of women with type 1 diabetes and 11.9% of women with type 2 diabetes had an HbA1c measurement recorded in the three months before their pregnancy start date; in the first trimester these proportions were higher: 10.2% of women with type 1 diabetes and 13.3% of women with type 2 diabetes. Of these records, in the three months before pregnancy start date 35-42% indicated blood glucose levels <53 mmol/mol (<7.0%): proportions were similar irrespective of pregnancy outcome. In the first trimester, of those with recorded HbA1c values, 43.2% of women with type 1 diabetes and 54.5% for women with type 2 diabetes whose pregnancies resulted in a delivery had an HbA1c value <53mmol/mol (<7.0%). For pregnancies that resulted in a loss, these proportions were much lower (type 1: 26.3%, p=0.026; type 2: 25%, p=0.003) although numbers of records were small.

The GPRD data indicated that in the three months before and during the first trimester of pregnancy 183 women received prescriptions for medications for hypertension and 84 women received prescriptions for dyslipidaemia.

Utilisation

Type 1: Differences between type of pregnancy loss and prescribing can be seen in table 4. The lowest proportion of deliveries occurred in those only receiving prescriptions for analogue insulin (54.6% [$CI_{95\%}$ 47.6 – 61.5]) whereas the highest proportion of deliveries occurred in those receiving prescriptions for human and analogue insulins (76.5% [$CI_{95\%}$ 71.2 - 81.2]). Differences in proportions of pregnancy losses were also apparent with a greater proportion of induced terminations in those using analogue insulin (19.8% [$CI_{95\%}$ 14.7 – 26.0]) compared with those using human insulin (8.4 [$CI_{95\%}$ [6.9 – 10.1]); of these induced terminations, 33 (of 41; 80.5%) were for non-medical reasons for those using analogue insulin and 68 (of 107; 63.6%) for those using human insulin, however caution is required given the low numbers.

The results of the logistic regression model adjusting for age, BMI and smoking status are reported in the supplementary appendix. The model provided a good fit to the observed data (Hosmer-Lemeshow statistic p=0.69); removing observations found to have high leverage did not substantially alter the risk estimates presented. The results of the logistic regression indicated a moderately increased odds of delivery compared to loss [1.60 ($CI_{95\%}$1.18, 2.18)] in those using human and analogue insulin in the three months before or during the first trimester of pregnancy compared to human insulin. Age, BMI and smoking status also influenced odds of delivery with age over 35 years reducing odds of delivery compared to age 30-34 years, BMI ≥ 40 reducing odds of delivery compared to a BMI of 20-24 [0.23 ($CI_{95\%}$ 0.08-0.73)] and smokers having a reduced odds of delivery compared to non-smokers [0.57 ($CI_{95\%}$0.46-0.71)].

Type 2:

The main differences observed were in the higher proportions of losses in those receiving just oral treatment products: of all outcomes in those receiving prescriptions for biguanides alone, 27.5% ($CI_{95\%}$ 19.3 – 37.3) were spontaneous losses; of all outcomes in those receiving prescriptions for other oral products (mainly sulphonylureas), 24.6% ($CI_{95\%}$ 14.5 – 38.0) were spontaneous losses and 26.3% ($CI_{95\%}$ 15.9 – 39.9) were induced losses. However the numbers in these groups were small which limited further interpretation.

The results of the logistic regression given in the supplementary appendix were adjusted for age, BMI and smoking status. The fit of the model was good (Hosmer-Lemeshow statistic p=0.85) and adjusting for observations with high leverage did not affect the original estimates found. The model indicated that biguanide or other oral treatment alone gave a reduced odds of delivery compared to insulin treatment. Those who didn't receive any treatment in the three months before pregnancy or during the first trimester had an increased odds of delivery which may indicate milder cases of type 2 diabetes (2.43 [$CI_{95\%}$1.24, 4.77]). Increasing age contributed to a reduced odds of delivery for those aged 40 years and older (0.54 [$CI_{95\%}$ 0.31, 0.92]).

Discussion

In this study we have investigated pregnancy losses in women with pre-existing type 1 and type 2 diabetes using primary care records. This study has demonstrated the value of general practice records in studying this important subject. We found a similar proportion of spontaneous losses in those with type 1 (19.6%) and type 2 diabetes (21.1%) and as expected, this is higher than in the general population (13.2%). The St. Vincent declaration of 1989 aimed to improve pregnancy outcomes in women with insulin dependent diabetes to be of an equivalent level to outcomes in women who do not have diabetes (11). It is clear that while outcomes have improved, this aim has not been met.

While a higher rate of pregnancy loss in women with diabetes was expected, the rate of loss found in this work was higher than any other rate previously reported (3, 4, 6, 11-14). This can be explained by the study design: the majority of previous studies recruited women from their first antenatal appointment or from hospitals and found rates of spontaneous loss in those with type 1 diabetes to be between 13% and 18.6% (3, 4, 6, 11-14); these studies may have missed losses early in pregnancy whereas here, by using primary care records we have included all but the very earliest of losses.

There have been few studies of pregnancy outcomes in women with type 2 diabetes but since the prevalence of type 2 diabetes is increasing in younger women this needs to be rectified (15). It is striking that we found the proportions of losses were very similar for women with type 1 and type 2 diabetes since type 2 diabetes was previously thought to be a less serious condition than type 1

diabetes, both during and outside of pregnancy (15). It is possible that the rate of losses in those with type 2 diabetes has been overestimated by our study since we only included women who were being treated pharmacologically and therefore only those with a more severe condition. Other studies however suggest that this is unlikely: Murphy et al. (6) reported that 26.6% of women with type 2 diabetes were managed on diet alone at conception but 90% received fast acting insulin analogues during pregnancy; Dunne (16) reported that most women with type 2 diabetes received treatment during pregnancy.

Cundy *et al.* (17) indicated that pregnancy losses in women with type 1 diabetes were likely to be due to congenital malformations but in type 2 diabetes were more likely to be due to asphyxia, stillbirth and chorioamniotis. We found a higher proportion of induced terminations for medical reasons (mostly major congenital malformations) in women with type 1 diabetes. There was a slightly higher proportion of terminations for non-medical reasons in women with type 2 diabetes which may indicate more unplanned pregnancies.

Risk factors for type 2 diabetes include obesity, increasing age, having a non-Caucasian background and being of lower socio-economic status (17-19) therefore it was unsurprising that the distribution of these factors was different between those with type 1 and type 2 diabetes. Murphy *et al.* (6) and CEMACH (19) found similar proportions of women with type 2 diabetes were overweight or obese at enrolment (90% and 84% respectively): this corresponded to 87% found in our study. We found that increasing age and very high BMI reduced the odds of delivery in women with type 1 diabetes. This is in contrast with Temple et al. (14) who did not find an increased risk of spontaneous loss with age, weight or smoking in women with type 1 diabetes but did report an increase in risk with lack of pre-pregnancy care. While pre-pregnancy care has been highlighted by many as vital in the management of women with type 1 diabetes, those with type 2 diabetes may be less likely to receive this (15). Cundy found that women with type 2 diabetes presented for antenatal care on average 5 weeks later than those with type 1 diabetes but CEMACH reported no differences in antenatal care between those with type 1 and type 2 diabetes (19).

We found that only a small proportion of women had an HbA1c measurement recorded in their notes in the three months before pregnancy (type 1: 6.4%, type 2: 11.9%) or during the first trimester (type 1: 10.2%, type 2: 13.0%) but the higher proportion of women with type 2 diabetes with these records compared

with women with type 1 diabetes is surprising. Of these measurements, less than half indicated optimal glycaemic control which has implications for organogenesis and pregnancy loss. However, given the small numbers it is difficult to speculate whether this represents a wider trend. Numbers of women receiving prescriptions for statins and hypertension medication such as ACE inhibitors were low but are of concern given that these medications are contraindicated in pregnancy: this may indicate unplanned pregnancies. We found very few records indicating that women had their diabetes managed in secondary care (type 1: 61; type 2: 39) although these figures could be underreported in the database. Fewer than one third of women received prescriptions for folic acid during the first trimester of pregnancy however since low dose folic acid is available to buy over the counter this is unlikely to fully represent all those taking folic acid.

Very few studies have reported on the diabetes treatment received in conjunction with pregnancy outcomes. The NICE guidelines recommend the use of rapid-acting analogue insulins over soluble human insulin for type 1 diabetes and that use of glibenclamide and metformin should be assessed individually for each patient with type 2 diabetes. Lambert and Holt (20) have recently reviewed the evidence on the use of insulin analogues in pregnancy and recommend their use although information on foetal outcomes is still needed for some insulins. We found an increased odds of delivery in women with type 1 diabetes who used human and analogue insulin compared to human insulin alone while use of analogue insulin individually reduced the odds of having a delivery. Given that analogue insulin and evidence for its use has only become available in the later years of this study period, those who received prescriptions only for this may have different indications such as poor glycaemic control or hypoglycaemia. The small numbers of those receiving prescriptions for analogue insulin is a limitation of this study. Given the confounding factors relating to the choice of medication prescribed and the limited sample size of this study it is not possible to draw conclusions regarding potential benefits or risks of individual treatments prescribed for diabetes during pregnancy.

In type 2 diabetes those who did not receive treatment in the three months before pregnancy or during the first trimester of pregnancy had an increased odds of delivery compared to loss which may indicate a less severe condition. Whereas those who received only oral products had higher proportions of losses than those receiving insulin. This could indicate a lack of pre-pregnancy care or unplanned pregnancies, although the numbers found were small. Both studies (6,

17) that reported on outcomes of women with type 2 diabetes indicated that the majority used insulin during pregnancy.

While every effort has been made to correctly classify the type of diabetes diagnosed through the identification of GP's diagnoses, prescribing records, age of diagnosis and use of home monitoring equipment, there may be some misclassification. For example, where type 2 diabetes has occurred in those who are young or where treatment for type 2 diabetes has been solely with insulin. We expect that this would only occur very rarely and by using our in-house browser to review full medical records this will have minimised any associated errors. We have reviewed freetext entries for any outcomes that were reported to be terminations for unknown reasons, to identify whether more information existed about these outcomes. It was surprising to find women with type 1 diabetes who did not have prescribing in the three months before or after conception. A thorough check of all of these individuals' records indicated that they were diagnosed with type 1 diabetes and that all received prescriptions for insulin (mainly human insulin) during the year before pregnancy and also in later trimesters for those pregnancies that ended in a delivery. Prescribing records on the GPRD are known to be at least 95% complete (21) but there is the potential for women with diabetes to have their condition managed in secondary care. However, we found that the number of women who had a record for treatment in secondary care for diabetes was small. A limitation of this study is the low reporting of HbA1c or other measures of glycaemic control that were found in the GPRD. It is expected that these measurements are taken but not routinely recorded.

In summary, we have found that using primary care records to study pregnancy losses in women with pre-existing diabetes led to higher rates of pregnancy losses being found than have previously been reported. The proportions of losses in women with type 1 (33.4%) and type 2 diabetes (35.4%) were similar with a greater proportion of spontaneous losses (type 1 19.6%, type 2 21.1%) occurring compared with the general population (13.2%). These findings are very important when considering the increasing prevalence of type 2 diabetes in women of child-bearing age. While there have been improvements in pregnancy outcomes in women with diabetes following the St. Vincent declaration, emphasis on the evaluation of oral medication, given its widespread use in managing diabetes in pregnancy, is now needed.

Acknowledgements

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Duality of interest

None of the authors have any conflicts of interest that are relevant to the content of this paper.

Contribution statement

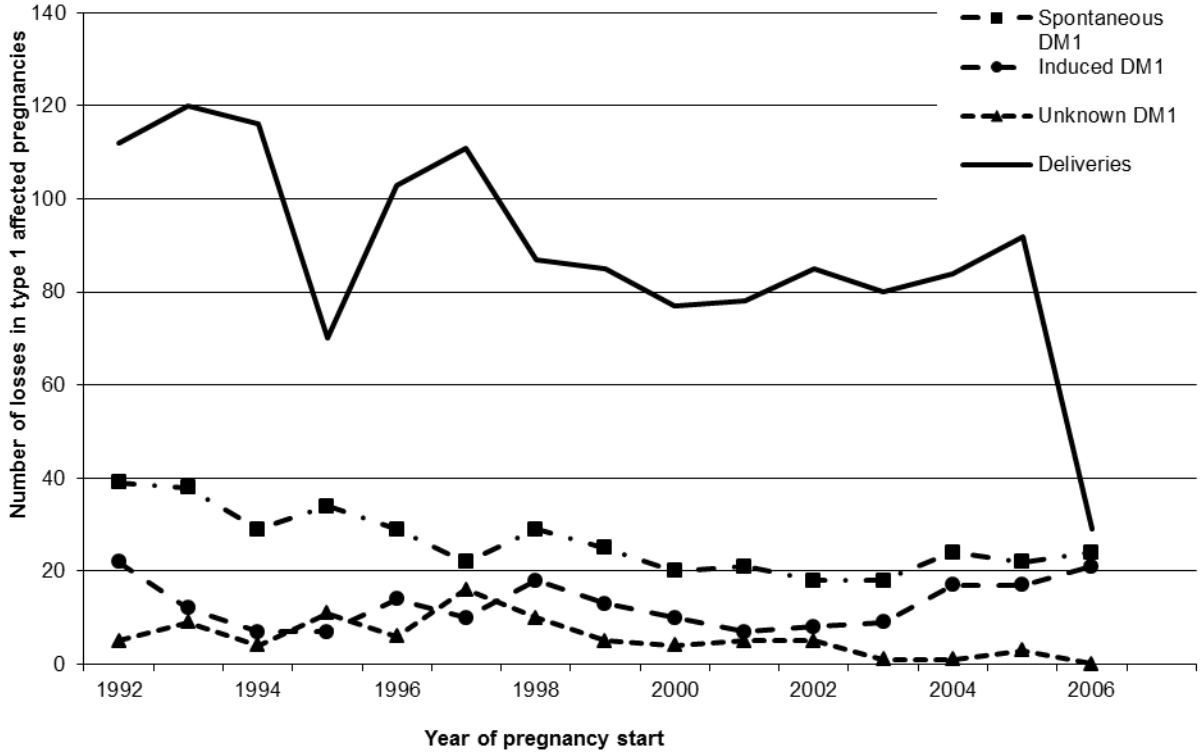
AMcG contributed to the design of the study, identified the cohort to be included, type of diabetes, treatment of diabetes by trimester, reviewed freetext to classify loss type, presented the results and wrote the paper. JS identified pregnancies on the GPRD, assisted with coding and processing of the data and contributed to the editing of the paper. CSdV designed the study, reviewed diagnosis of diabetes in women where this was complicated, discussed interpretation of results and contributed to the editing of the paper.

Table 1: Patient characteristics for women with type 1 or type 2 diabetes who had a pregnancy loss. Characteristics for all women with pregnancy losses recorded in the General Practice Research Database who were aged 10-49 years at pregnancy start date, whose pregnancies commenced between 1992 and 2006 and where data was of a standard suitable for research are also given; those in the population of women with pre-existing diabetes were excluded from the 'All GPRD' group.

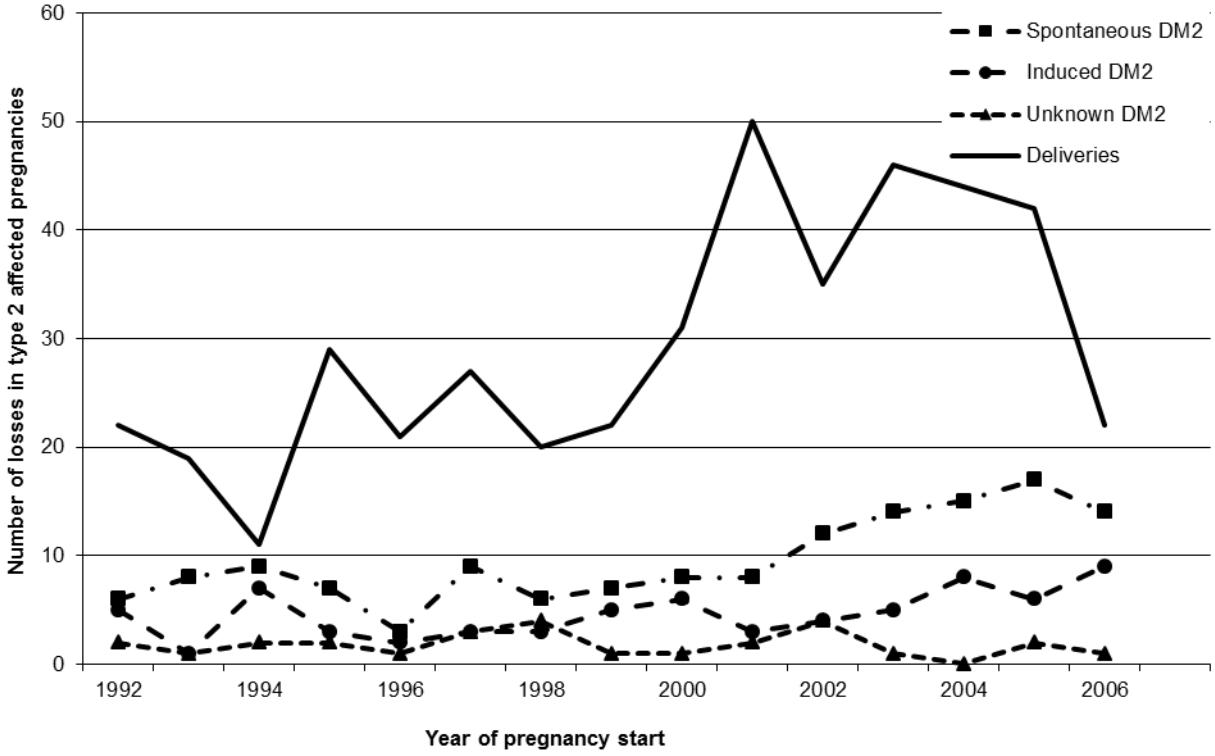
		Type 1		**Type 2**			**All GPRD**	
		N	**%**	**N**	**%**	**p**	N	%
Pregnancy losses		669		240			172927	
Age (years)	11-14	1		0			635	0.37
	15-19	81	12.1	4		<0.001	24728	14.30
	20-24	151	22.6	16	6.7	<0.001	36014	20.83
	25-29	166	24.8	29	12.1	<0.001	37730	21.82
	30-34	146	21.8	79	32.9	<0.001	37048	21.42
	35-39	94	14.1	59	24.6	<0.001	25197	14.57
	40-44	27	4	40	16.7	<0.001	10287	5.95
	45-49	3		13	5.4		1288	0.74
BMI (kgm^{-2})	<20	34	5.1	4	1.7		21571	12.47
	20-24	268	40.1	28	11.7	<0.001	64073	37.05
	25-29	153	22.9	57	23.8	0.782	25525	14.76
	30-34	48	7.2	61	25.4	<0.001	8638	5.00
	35-39	21	3.1	39	16.3	<0.001	2896	1.67
	≥40	9		25	10.4	<0.001	1325	0.77
	Unknown	136	20.3	26	10.8	0.001	48899	28.28
Smoking status	Smoker	251	37.5	65	27.1	<0.001	64544	37.32
	Non-smoker	313	46.8	153	63.8	<0.001	81803	47.30
	Ex-smoker	82	12.3	20	8.3	0.099	15724	9.09
	Unknown	23	3.4	2	0.8		10856	6.28

Table 2: Numbers and proportions of deliveries and pregnancy losses for women with type 1 and type 2 diabetes during pregnancy and for all pregnancies recorded in the General Practice Research Database (GPRD). All pregnancies included in the study were in women who were aged 10-49 years at pregnancy start date, whose pregnancies commenced between 1992 and 2006 and where data was of a standard suitable for research and excluded those identified in the population of women with pre-existing diabetes.

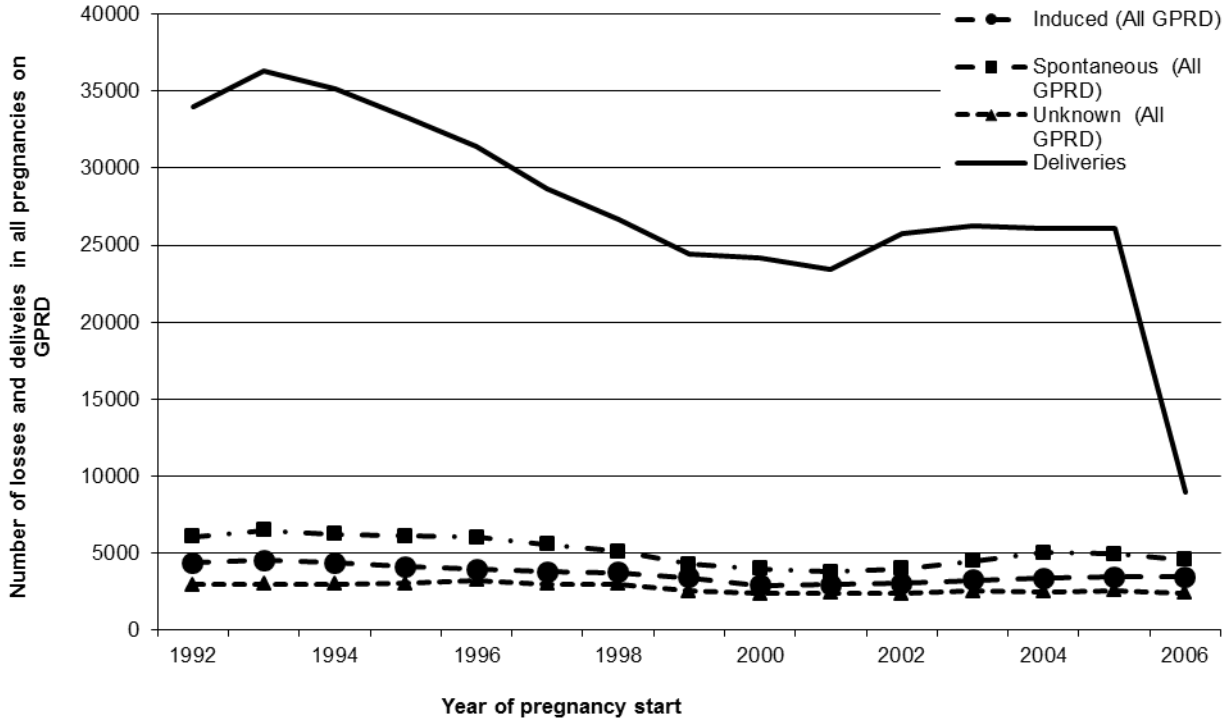
Outcome	**Trim**	**Type 1**		**Type 2**			**All in GPRD**	
		N	**% (CI 95%)**	**N**	**% (CI 95%)**	**Difference (CI 95%)**	**N**	**% (CI 95%)**
Spontaneous loss	1	362	18.1 (16.4-19.9)	129	19.0 (16.2-22.2)	-0.9% (-4.34%, 2.47%)	72019	12.33 (12.25 - 12.42)
	2	30	1.5 (1.0 -2.2)	14	2.1 (1.2 - 3.5)		4886	0.84 (0.81 - 0.86)
Induced loss	1	183	9.1 (7.9 - 10.5)	70	10.3 (8.2 - 12.9)	-1.2% (-3.79%, 1.44%)	53754	9.21 (9.14 - 9.28)
	2	9	0.4 (0.2 - 0.9)	0	0 (0 - 0.7)		1124	0.19 (0.18 - 0.20)
Unknown loss	1	82	4.1 (3.3 - 5.1)	25	3.7 (2.5 - 5.5)	0.4% (-1.25%, 2.07%)	39885	6.83 (6.77 - 6.90)
	2	3	0.1 (0.04 - 0.5)	2	0.3 (0.1 - 1.2)		1259	0.22 (0.20 - 0.23)
Total losses		669	33.3 (31.2 - 35.5)	240	35.4 (31.8 - 39.2)	-2.0% (-6.12%, 2.19%)	172927	29.63 (29.51 - 29.74)
Total deliveries		1332	66.6 (64.4 - 68.6)	438	64.6 (60.9 - 68.2)	2.2% (-2.19%, 6.12%)	410761	70.37 (70.26 - 70.49)
Total outcomes		2001		678			583688	


Number of losses in type 1 affected pregnancies
140
120
100
80
60
40
20
0
1992
1994
1996
1998
2000
2002
2004
2006
Year of pregnancy start
Spontaneous DM1
Induced DM1
Unknown DM1
Deliveries

(a)


Number of losses in type 2 affected pregnancies
60
50
40
30
20
10
0
1992
1994
1996
1998
2000
2002
2004
2006
Year of pregnancy start
Spontaneous DM2
Induced DM2
Unknown DM2
Deliveries

(b)



(c)

Figure 1: Numbers of deliveries and pregnancy losses including type of loss by year of start date for (a) type 1 diabetes (DM1), (b) type 2 (DM2) diabetes and (c) for all of the pregnancy losses on the General Practice Research Database (GPRD). (c) included all women who were aged 10-49 years at pregnancy start date, whose pregnancies commenced between 1992 and 2006 and where data was of a standard suitable for research and excluded those identified in the population of women with pre-existing diabetes..

Table 3: Details about duration of diabetes, treatment received in secondary care, HbA1c measurements, folic acid and medications for hypertension and dyslipidaemia recorded in the General Practice Research Database. p-values indicate the comparison of characteristics between women with type 1 and type 2 diabetes for pregnancies resulting in a delivery (p delivery) or a loss (p loss).

	Type 1		Type 2			
	Delivery	**Loss**	**Delivery**	**Loss**	**p delivery**	**p loss**
Duration of diabetes (years)						
<2	107 (8.03)	52 (7.77)	132 (30.14)	85 (35.42)	<0.001	<0.001
2-4	183 (13.74)	91 (13.6)	155 (35.39)	70 (29.17)	<0.001	<0.001
5-9	261 (19.59)	131 (19.58)	112 (25.57)	51 (21.25)	0.08	0.58
10-14	241 (18.09)	159 (23.77)	34 (7.76)	30 (12.5)	<0.001	<0.001
15-19	241 (18.09)	110 (16.44)	5 (1.14)	2 (0.83)	<0.001	<0.001
20-24	188 (14.11)	75 (11.21)	0	2 (0.83)	<0.001	<0.001
25-29	79 (5.93)	34 (5.08)	0	0	<0.001	<0.001
30-34	27 (2.03)	17 (2.54)	0	0	0.009	0.02
35-39	5 (0.38)	0	0	0	0.6	
Treatment in secondary care recorded						
3 months before LMP	9 (0.68)	4 (0.6)	5 (1.14)	2 (0.83)	0.42	>0.99
During pregnancy	37 (2.78)	8 (1.2)	19 (4.34)	9 (3.75)	0.11	0.03
Both	3 (0.23)	0	2 (0.46)	2 (0.83)	0.43	0.03
Folic acid prescriptions issued						
Year before LMP						
Low dose (350-500mcg)	81 (6.08)	35 (5.23)	32 (7.31)	33 (13.75)	0.36	<0.001
High dose (5mg)	105 (7.88)	29 (4.33)	19 (4.34)	9 (3.75)	0.01	0.7
Trimester 1						
Low dose (350-500mcg)	175 (13.14)	55 (8.22)	92 (21)	21 (8.75)	<0.001	0.8
High dose (5mg)	175 (13.14)	62 (9.27)	65 (14.84)	15 (6.25)	0.37	0.15
HbA1c measurements recorded						
3 months before LMP						
< 53mmol/mol (<7%)	30 (2.25)	17 (2.54)	22 (5.02)	11 (4.58)	0.005	0.12
53-86 mmol/mol (7-10%)	36 (2.7)	19 (2.84)	23 (5.25)	11 (4.58)	0.01	0.19
> 86 mmol/mol (>10%)	14 (1.05)	12 (1.79)	7 (1.6)	7 (2.92)	0.36	0.3
Trimester 1						
< 53mmol/mol (<7%)	64 (4.8)	15 (2.24)	36 (8.22)	6 (2.5)	0.007	0.59
53-86 mmol/mol (7-10%)	63 (4.73)	22 (3.29)	24 (5.48)	10 (4.17)	0.53	0.53
> 86 mmol/mol (>10%)	21 (1.58)	20 (2.99)	6 (1.37)	8 (3.33)	0.76	0.79
Trimester 2						
< 53mmol/mol (<7%)	101 (7.58)	3 (7.14)	38 (8.68)	2 (0.89)	0.46	0.85
53-86 mmol/mol (7-10%)	33 (2.48)	3 (7.14)	19 (4.34)	1 (0.45)	<0.001	>0.99
> 86 mmol/mol (>10%)	10 (0.75)	2 (4.76)	2 (0.46)	1 (0.45)	0.8	>0.99
Trimester 3						
< 53mmol/mol (<7%)	96 (7.25)	-	37 (8)	-	0.37	-
53-86 mmol/mol (7-10%)	24 (1.81)	-	14 (3.23)	-	0.08	-
> 86 mmol/mol (>10%)	5 (0.38)	-	1 (0.23)	-	0.99	-
Other medications prescribed in pregnancy						
ACE inhibitor						
3 months before LMP	22 (1.65)	12 (1.79)	6 (1.39)	5 (2.23)	0.68	0.78
Trimester 1	2 (0.15)	2 (0.3)	6 (1.39)	3 (1.34)	0.007	0.24

Both periods	11 (0.83)	12 (1.79)	23 (5.31)	10 (4.46)	<0.001	0.04
Angiotensin II receptor blocker						
3 months before LMP	1 (0.08)	1 (0.15)	3 (0.69)	2 (0.89)	0.1	0.34
Trimester 1	0	1 (0.15)	1 (0.23)	0	0.87	>0.99
Both periods	3 (0.23)	3 (0.45)	1 (0.23)	4 (1.79)	0.99	0.17
Beta blockers						
3 months before LMP	2 (0.15)	1 (0.15)	5 (1.15)	1 (0.45)	0.02	0.92
Trimester 1	3 (0.23)	3 (0.45)	4 (0.92)	3 (1.34)	0.14	0.38
Both periods	11 (0.83)	4 (0.6)	11 (2.54)	7 (3.13)	0.006	0.02
Calcium channel blockers						
3 months before LMP	4 (0.3)	2 (0.3)	3 (0.69)	0 (0)	0.48	0.79
Trimester 1	1 (0.08)	1 (0.15)	3 (0.69)	1 (0.45)	0.1	0.92
Both periods	9 (0.68)	3 (0.45)	9 (2.08)	6 (2.68)	0.04	0.03
Thiazide						
3 months before LMP	8 (0.6)	1 (0.15)	5 (1.15)	5 (2.23)	0.4	0.01
Trimester 1	0	1 (0.15)	2 (0.46)	0	0.31	>0.99
Both periods	2 (0.15)	1 (0.15)	8 (1.85)	5 (2.23)	<0.001	0.01
Statin						
3 months before LMP	4 (0.3)	6 (0.9)	7 (1.62)	5 (2.23)	0.01	0.27
Trimester 1	2 (0.15)	2 (0.3)	5 (1.15)	3 (1.34)	0.024	0.24
Both periods	12 (0.9)	9 (1.35)	12 (2.77)	11 (4.91)	0.004	0.003
Other lipid regulating medications						
3 months before LMP	0	0	0	0		
Trimester 1	0	0	0	0		
Both periods	1 (0.08)	2 (0.3)	5 (1.15)	1 (0.45)	0.009	>0.99

Note: LMP: last menstrual period

Table 4: Outcomes and prescribing in the three months before pregnancy and during the first trimester for women with type 1 and type 2 diabetes. Numbers (N) and proportions (%) with 95% confidence intervals are given for each outcome.

Outcome	Spontaneous loss		Induced loss		Loss for unknown reason		Delivery	
	N	% ($CI_{95\%}$)	N	% ($CI_{95\%}$)	N	% ($CI_{95\%}$)	N	% ($CI_{95\%}$)
Type 1								
Human	258	20.2 (18.0 - 22.5)	107	8.4 (6.9 - 10.1)	66	5.2 (4.0 - 6.6)	849	66.3 (63.7 - 68.9)
Analogue	48	23.2 (17.7 - 29.7)	41	19.8 (14.7 - 26.0)	5	2.4 (0.9 - 5.9)	113	54.6 (47.6 - 61.5)
Animal	17	16.8 (10.4 - 25.9)	14	13.9 (8.1 - 22.5)	3	3.0 (0.8 - 9.1)	67	66.3 (56.2 - 75.3)
Human and analogue	40	13.6 (10.0 - 18.2)	22	7.5 (4.9 - 11.3)	7	2.4 (1.0 - 5.1)	225	76.5 (71.2 - 81.2)
Other	15	31.3 (19.1 - 46.4)	1	2.1 (0.1 - 12.5)	1	2.1 (0.1 - 12.5)	31	64.6 (49.4 - 77.5)
Nothing	14	19.7 (11.6 - 31.2)	8	11.3 (5.3 - 21.5)	2	2.8 (0.5 - 10.7)	47	66.2 (53.9 - 76.7)
Type 2								
Insulin	50	20.8 (16.0 - 26.6)	19	7.9 (5.0 - 12.3)	9	3.8 (1.8 - 7.2)	162	67.5 (61.1 - 73.3)
Biguanide	28	27.5 (19.3 - 37.3)	15	14.7 (8.7 - 23.4)	7	6.8 (3.0 - 14.1)	52	51.0 (41.0 - 60.9)
Oral treatment[1]	14	24.6 (14.5 - 38.0)	15	26.3 (15.9 - 39.9)	6	10.5 (4.4 - 22.2)	22	38.6 (26.3 - 52.4)
Biguanide and oral treatment[1]	11	21.2 (11.5 - 35.1)	7	13.5 (6.0 - 26.4)	2	3.8 (0.7 - 14.3)	32	61.5 (47.0 - 74.4)
Insulin and biguanide	18	23.1 (14.6 - 34.3)	3	3.8 (1.0 - 11.6)	2	2.6 (0.4 - 9.8)	55	70.5 (59.0 - 80.0)
Insulin and oral treatment[1]	6	22.2 (9.4 - 42.7)	2	7.4 (1.3 - 25.8)	0	0 (0 - 15.5)	19	70.4 (49.7 - 85.5)
Insulin, biguanide and oral treatment[1]	9	20.9 (10.6 - 36.5)	5	11.6 (4.4 - 25.9)	0	0 (0 - 10.2)	29	67.4 (51.3 - 80.5)
Nothing	7	8.9 (3.9 - 18.0)	4	5.1 (1.6 - 13.2)	1	1.3 (0.07 - 7.8)	67	84.8 (74.6 - 91.6)

[1] Oral treatment included any other anti-diabetic treatment that is not a biguanide or insulin

Supplementary appendix: Odd ratios (OR) and 95% confidence intervals ($CI_{95\%}$) for delivery compared to pregnancy loss in type 1 and type 2 diabetes with prescribing in the three months before and first trimester of pregnancy. Model estimates were adjusted for age, BMI and smoking status.

	Type 1	**Type 2**
Age	**OR ($CI_{95\%}$)**	**OR ($CI_{95\%}$)**
15-19	0.26 (0.17, 0.39)	0.30 (0.06, 1.47)
20-24	0.54 (0.40, 0.72)	0.58 (0.27, 1.26)
25-29	0.90 (0.69, 1.17)	1.42 (0.84, 2.40)
30-34	Reference	Reference
35-39	0.58 (0.42, 0.80)	1.02 (0.67, 1.56)
40-44	0.39 (0.22, 0.69)	0.54 (0.31, 0.92)
45-49	0.36 (0.07, 1.90)	0.30 (0.11, 0.83)
BMI		
<20	0.89 (0.55, 1.43)	0.20 (0.04, 0.97)
20-24	Reference	Reference
25-29	1.11 (0.87, 1.42)	0.69 (0.39, 1.25)
30-34	1.17 (0.80, 1.71)	0.58 (0.32, 1.04)
35-39	0.67 (0.37, 1.21)	0.65 (0.34, 1.24)
≥40	0.23 (0.08, 0.73)	0.68 (0.33, 1.38)
Unknown	0.86 (0.65, 1.13)	0.85 (0.42, 1.71)
Smoking status		
Non-smoker	Reference	Reference
Smoker	0.57 (0.46, 0.71)	0.80 (0.54, 1.20)
Ex-smoker	0.87 (0.64, 1.18)	1.88 (1.04, 3.37)
Unknown	1.05 (0.60, 1.85)	0.84 (0.12, 5.80)
Treatment		
Human	Reference	
Analogue	0.64 (0.47, 0.88)	
Animal	0.83 (0.53, 1.30)	
Human and analogue	1.60 (1.18, 2.18)	
Other combination	0.97 (0.52, 1.81)	
No treatment		2.43 (1.24, 4.77)
Insulin alone		Reference
Biguanide alone		0.51 (0.31, 0.84)
Oral alone		0.33 (0.18, 0.63)
Biguanide and oral		0.80 (0.42, 1.53)
Insulin and biguanide		1.02 (0.57, 1.83)
Insulin and oral		0.92 (0.37, 2.24)
Insulin, oral, biguanide		1.19 (0.58, 2.45)

References

1. Dorman JS, Burke JP, McCarthy BJ, Norris JM, Steenkiste AR, Aarons JH, et al. Temporal trends in spontaneous abortion associated with Type 1 diabetes. Diabetes Res Clin Pract 1999; 43:41-7.
2. Lorenzen T, Pociot F, Johannesen J, Kristiansen OP, Nerup J. A population-based survey of frequencies of self-reported spontaneous and induced abortions in Danish women with Type 1 diabetes mellitus. Danish IDDM Epidemiology and Genetics Group. Diabet Med 1999; 16:472-6.
3. Penney GC, Mair G, Pearson DW. Outcomes of pregnancies in women with type 1 diabetes in Scotland: a national population-based study. BJOG 2003; 110:315-8.
4. Verheijen EC, Critchley JA, Whitelaw DC, Tuffnell DJ. Outcomes of pregnancies in women with pre-existing type 1 or type 2 diabetes, in an ethnically mixed population. BJOG 2005; 112:1500-3.
5. Langer O. Type 2 diabetes in pregnancy: exposing deceptive appearances. J Matern Fetal Neonatal Med 2008; 21:181-9.
6. Murphy HR, Steel SA, Roland JM, Morris D, Ball V, Campbell PJ, et al. Obstetric and perinatal outcomes in pregnancies complicated by Type 1 and Type 2 diabetes: influences of glycaemic control, obesity and social disadvantage. Diabetic Medicine 2011; 28:1060-7.
7. Lawson DH, Sherman V, Hollowell J. The General Practice Research Database Q J Med 1998 91:445-52.
8. Charlton RA, J S, Weil JG, Cunnington MC, De Vries CS. Recording of pregnancy losses on the General Practice Research Database. Pharmacoepidemiol Drug Saf 2010; 19:S122.
9. Soedamah-Muthu S, Fuller J, Mulnier H, Raleigh V, Lawrenson R, Colhoun H. All-cause mortality rates in patients with type 1 diabetes mellitus compared with a non-diabetic population from the UK general practice research database, 1992–1999. Diabetologia 2006; 49:660-6.
10. Tobi H, van den Berg PB, de Jong-van den Berg LTW. Small proportions: what to report for confidence intervals? Pharmacoepidemiol Drug Saf 2005; 14:239-47.
11. Higgins M, Galvin D, McAuliffe F, Coffey M, Firth R, Daly S, et al. Pregnancy in women with Type 1 and Type 2 diabetes in Dublin. Ir J Med Sci 2011; 180:469-73.
12. Casson IF, Clarke CA, Howard CV, McKendrick O, Pennycook S, Pharoah PO, et al. Outcomes of pregnancy in insulin dependent diabetic women: results of a five year population cohort study. BMJ 1997; 315:275-8.
13. Pearson DW, Kernaghan D, Lee R, Penney GC. The relationship between pre-pregnancy care and early pregnancy loss, major congenital anomaly or perinatal death in type I diabetes mellitus. BJOG 2006; 114:104-7.
14. Temple RC, Aldridge VJ, Murphy HR. Prepregnancy care and pregnancy outcomes in women with type 1 diabetes. Diabetes Care 2006; 29:1744-9.
15. Temple R, Murphy H. Type 2 diabetes in pregnancy - An increasing problem. Best Pract Res Clin Endocrinol Metab 2010; 24:591-603.
16. Dunne F. Type 2 diabetes and pregnancy. Semin Fetal Neonatal Med 2005; 10:333-9.
17. Cundy T, Gamble G, Neale L, Elder R, McPherson P, Henley P, et al. Differing causes of pregnancy loss in type 1 and type 2 diabetes. Diabetes Care 2007; 30:2603-7.
18. Dunne F, Brydon P, Smith K, Gee H. Pregnancy in women with Type 2 diabetes: 12 years outcome data 1990-2002. Diabet Med 2003; 20:734-8.

19. Confidential Enquiry into Maternal and Child Health. Diabetes in pregnancy: Are we providing the best care? Findings of a National Enquiry: England, Wales and Northern Ireland. London2007 [3/9/2012]; Available from: http://www.publichealth.hscni.net/sites/default/files/Diabetes%20in%20Pregnancy-%20are%20we%20providing%20the%20best%20care.pdf.
20. Lambert K, Holt RIG. The use of insulin analogues in pregnancy. Diabetes, Obesity and Metabolism 2013: doi: 10.1111/dom.12098.
21. Walley T, Mantgani A. The UK General Practice Research Database. Lancet 1997; 350:1097-9.