Prescribing of oral antihyperglycaemic agents in gestational diabetes by the antenatal diabetes team within the UK: an observational survey

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Introduction
Approximately 700 000 women give birth each year in England and Wales. Between 2–5% of pregnancies are complicated by diabetes with approximately 90% of these due to gestational diabetes (GDM). Diabetes in pregnancy confers risk to mother and fetus as well as having implications for the long-term health for both mother and child. At the time of undertaking this survey, there was a variety of sources of evidence and guidelines from governing bodies with differing advice regarding the use of oral antihyperglycaemic agents (OAHAs) in GDM. In consequence, this may lead to confusion for health care professionals (HCPs) involved in GDM management with OAHAs.

Aim
The aim of the study was to obtain a cross-sectional perspective of current practice in the prescribing of OAHAs for GDM in specialist care. This was undertaken by conducting an anonymous online multi-question survey which was open to all prescribing members of the diabetes pregnancy multidisciplinary team (MDT) across centres in England, Scotland, Wales and Northern Ireland. It was conducted over a five-month period.

Abstract
The incidence of gestational diabetes (GDM) continues to rise and requires management by a multidisciplinary diabetes antenatal team. Multiple national and international guidelines exist on the management of hyperglycaemia in pregnancy which are not concordant and may lead to confusion in clinical practice. Limited studies have been conducted examining prescribing habits for hyperglycaemia in GDM.

Our survey examined the prescribing practices relating to oral antihyperglycaemic agents (OAHAs, unlicensed for use in pregnancy but widely prescribed) by health care professionals within the UK caring for women with GDM. Although metformin is widely used, our survey highlights heterogeneity in the use of OAHAs with respect to drug choice, timing of introduction, dosage and escalation of glucose lowering therapy. The cause of this heterogeneity appears multi-factorial. Copyright © 2016 John Wiley & Sons.

Key words
diabetes; gestational; antihyperglycaemics; metformin; survey; prescribing

Participants and methods
An online questionnaire was devised which allowed either single or combination answers to examine the prescription of OAHAs in GDM by members of the diabetes pregnancy MDT. These questions sought answers on a range of topics including: the grade of HCP completing the survey; details of the provision of antenatal clinics within their service; the type, dose and prescription of OAHAs for GDM; trimesters in which OAHAs were prescribed; reasons for OAHAs withdrawal; whether written patient consent for OAHAs was obtained; and examined concerns regarding OAHAs use. (See https://www.surveymonkey.com/s/FV6HJNH to view the complete questionnaire.)

The questionnaire was emailed out as a link to diabetes HCPs involved in GDM management within the UK and was also available to HCPs who visited the Young Diabetologists and Endocrinologists’ Forum website. The survey was open for five months from May to September (inclusive) 2014, at which time 140 questionnaires had been submitted. Simple descriptive statistical analysis was undertaken.

Results
In all, 140 questionnaires were submitted online. Of the respondents,
86/140 (61.43%) were consultants, 2/140 (1.43%) were staff grades, 29/140 (20.71%) were specialist registrars, 16/140 (11.43%) were diabetes specialist nurses, 3/140 (2.14%) were associate specialists and 2/140 (1.43%) were dietitians. The vast majority of respondents (129/140, 92.14%) confirmed that they worked in a specialist setting that offered a joint diabetes antenatal MDT clinic and were able to provide 1–2 weekly appointments if needed. The majority of HCPs used metformin exclusively as an OAHA in pregnancy; no respondents used glibenclamide exclusively, and a few HCPs used both OAHAs. The minority avoided the use of OAHAs in GDM (Figure 1).

Figure 2 demonstrates the considerable variation in time allowed to assess the efficacy of the OAHA once introduced and, if sub-optimal glucose control, the second-line therapeutic option for unresolved hyperglycaemia. There was a noticeable split in opinion between choosing to titrate upwards the dose of the OAHA versus the addition of insulin. Furthermore, there was an even split across the trimesters with regard to the timing of when HCPs would prescribe metformin: 100/128 (78.13%) in the first trimester, 107/128 (83.59%) in the second and 109/128 (85.16%) in the third trimester. The majority of HCPs (95/128, 74.22%) prescribed metformin up to 2g as a maximum total daily dose. Very few HCPs prescribed glibenclamide and, of those who did, there was a broadly even distribution of initiation across the trimesters: 3/110 (2.73%) respondents prescribed it in the first trimester, 5/110 (4.55%) in the second and 6/110 (5.45%) in the third trimester. Figure 3 demonstrates the heterogeneous timing as regards the latest week of gestation that clinicians would consider initiating an OAHA in GDM.

While NICE guidelines2 recommended consent for the use of OAHAs in GDM given they are unlicensed, the majority of respondents did not ask their patients to sign a consent form when prescribing OAHAs (118/127, 92.91%).

Figure 4 shows the survey results relating to HCPs’ reasons for withdrawing OAHAs during pregnancy. The most common reasons were due to gastrointestinal side effects, lack of efficacy and patient preferences. Finally, HCPs not prescribing OAHAs expressed a number of reasons for avoiding oral therapy. These included: the above reasons; lack of clarity about the use of OAHAs in GDM (conflicting guidelines); concerns regarding metformin crossing the placenta and affecting cell division and fetal exposure (metformin is unlicensed for use in children under the age of 12 years); and OAHAs adversely affecting adiposity in infancy.

Discussion
This survey provides unique information on the OAHA prescribing habits of HCPs involved in the management of GDM. It highlights that metformin, a drug unlicensed for use in GDM, is widely used. However, the practical implications
Prescribing of oral antihyperglycaemic agents for women with GDM

Gestational diabetes is characterised by insulin resistance, and utilising therapeutics with a mechanism of action involving increasing insulin sensitivity (or relative insulin availability) may in part address this. Metformin reduces hepatic glucose output as well as increasing insulin sensitivity without causing hypoglycaemia or significant weight gain. Glibenclamide, a second generation sulphonylurea, potentiates the secretion of insulin by beta cells. Although effective glucose lowering therapies have been used in the treatment of GDM for years, concerns regarding the impact of OAHA use in GDM upon maternal as well as fetal outcomes have been raised previously. Historically, studies showed a possible link between OAHAs and teratogenicity, neonatal hypoglycaemia, macrosomia, jaundice and intra-uterine growth retardation. However, recent trials have been more reassuring in demonstrating better safety for the mother and fetus in GDM. Although metformin has been used in the treatment of GDM since the 1970s, the largest randomised controlled trial (RCT) of metformin in GDM—the MiG trial—was reported in 2008 with 751 women randomised to metformin or insulin. This showed no significant difference in the primary fetal outcomes between the two groups although the risk of pre-term birth was slightly increased in the metformin group.

The landmark RCT for the use of glibenclamide in GDM was reported by Langer et al. in 2000 and randomised 404 women to either glibenclamide or insulin. Results showed similar perinatal outcomes and no significant difference in maternal glucose levels, and no detection of glibenclamide in the cord serum of infants (as opposed to metformin which is known to cross the placenta).

In 2015, a systematic review and meta-analysis of metformin versus glibenclamide (and insulin) for hyperglycaemia management in GDM examined 14 primary outcomes (six maternal and eight fetal) and 16 secondary outcomes (five maternal and 11 fetal). It showed that, comparing glibenclamide with insulin, babies whose mothers were treated with glibenclamide were significantly more at risk of increased birth weight, macrosomia and neonatal hypoglycaemia. Comparing metformin with insulin, there was significantly less maternal weight gain and neonatal hypoglycaemia with metformin, but decreased age at delivery and increased pre-term birth with this group too. When metformin was compared directly with glibenclamide, those treated with metformin had significantly less maternal weight gain, less macrosomia and fewer large for gestational age babies, but with reduced birth weight. Consequently, the study authors concluded that glibenclamide was inferior to both insulin and metformin, with metformin performing slightly better than insulin, and that glibenclamide should not be used for hyperglycaemia in GDM if metformin or insulin was available.

NICE guidelines and the American College of Obstetrics and Gynecology both recommend that metformin and glibenclamide could be used off-licence in GDM, but did not state how or when they should be used. NICE guidelines also specified that ‘informed consent should be obtained and documented’ and that their recommendations were not currently reflected in the summary of product characteristics (SPCs). In contrast, the Recent Standards of Care in
Diabetes published in 2015 from the American Diabetes Association recommended insulin as first-line glucose lowering therapy in GDM.\textsuperscript{14} Given the lack of clarity on prescribing OAHAs, as well as conflicting recommendations within these different guidelines, this may explain the variability in the practical use of OAHAs observed in our study.

The MiG study demonstrated that 46% of women randomised to metformin needed supplemental insulin to obtain optimal glycaemic control and that these women tended to be more obese and more hyperglycaemic at presentation.\textsuperscript{15} With the adverse effects of hyperglycaemia in pregnancy well known, the addition of insulin so soon after the introduction of an oral agent may demonstrate the HCP’s desire to obtain euglycaemia as quickly as possible. However, it is also possible that this reflects the clinician’s doubt regarding the efficacy of OAHAs to resolve hyperglycaemia. In addition, other complications such as macrosomia or polyhydramnios, even in the context of reasonable glycaemic control, may prompt the HCP to switch to insulin in the belief that this may attenuate risk from these complications.\textsuperscript{15}

Our study identifies considerable variation in the latest week of initiation of OAHAs (see Figure 3). This heterogeneity probably reflects the lack of evidence examining the benefits associated with OAHAs according to the gestational week introduced. The major studies looking at the efficacy of glucose lowering therapies (including insulin) in GDM only initiated them up to 33 weeks gestation with very limited evidence for their initiation beyond this point.\textsuperscript{5,6} However, intuitively and based upon clinical experience, the degree of hyperglycaemia and time left in pregnancy may still prompt some HCPs to initiate OAHAs at a much later gestational age.

The reasons for withdrawal of OAHAs (Figure 4) were predictable since they were related to the well known side effects of metformin. Apart from lack of efficacy, respondents were also concerned about the impact of OAHAs upon fetal growth, liver function tests and metformin’s effects on cell division (commenting on its use as an adjunct in cancer treatments). However, a more recent systematic review on the use of metformin in pregnancy has not substantiated these concerns.\textsuperscript{16}

There are limitations related to our survey. The sample size of 140 may be considered relatively small and our survey did not address the geographic spread of responders. However, the sample size may be in part explained by the specialist nature of diabetes antenatal services and the limited number of HCPs involved in managing GDM.

Furthermore, the management of individual patients should be based upon their particular characteristics with individually tailored treatment plans. We would not recommend that treatment decisions are made based upon these data, as this is an observational study and beyond the remit of this article.

We recognise there are many other drugs that are prescribed ‘off-label’ for use in pregnancy, where initiating specialists do not routinely request consent; however, as diabetologists and members of the antenatal teams, we feel that, when initiating treatment with metformin, obtaining consent as per NICE guidance would be considered best practice.

In summary, the majority of HCPs involved in managing GDM prescribed metformin despite it being unlicensed, while, in contrast, few HCPs prescribed glibenclamide. There were heterogeneous responses regarding how metformin was employed, the dosing regimen and the latest point at which OAHAs were initiated, highlighting the lack of research evidence available to address optimal practice. Further study evidence would be helpful for HCPs in addressing these practical aspects when considering the use of OAHAs in pregnancy.

We feel this survey offers important data that highlight the need for local, detailed protocols in the use of metformin in GDM in conjunction with a robust audit of practice and associated pregnancy outcomes.

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Declaration of interests

There are no conflicts of interest declared.

References