Imperial College Healthcare NHS Trust

Imperial College London

CAPRE-DM

Contraception and Pregnancy in Diabetes Mellitus

V1.1

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Protocol authorised by:

Name & Role	Date	Signature

Study Management Group

Chief Investigator:	Dr Rochan Agha-Jaffar (ICHT)
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Statistician:	Dr Ian Godsland (ICL)
Study Management:	Ms Maria Thomas (ICL)

Study Coordination Centre

For general queries, supply of study documentation, and collection of data, please contact:

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Clinical Queries

Clinical queries should be directed to Dr Rochan Agha-Jaffar who will direct the query to the appropriate person.

Sponsor

Imperial College London is the main research Sponsor for this study. For further information regarding the sponsorship conditions, please contact the Head of Regulatory Compliance at:

Joint Research Compliance Office
Imperial College London and Imperial College Healthcare NHS Trust
Room 215, Level 2, Medical School Building
Norfolk Place
London, W2 1PG
Tel: **0207 594 9459/ 0207 594 1862**
http://www3.imperial.ac.uk/clinicalresearchgovernanceoffice

This protocol describes the CAPRE-DM study and provides information about procedures for entering participants. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study. Problems relating to this study should be referred, in the first instance, to the Chief Investigator.

This study will adhere to the principles outlined in the UK Policy Frame Work for Health and Social Care Research. It will be conducted in compliance with the protocol, the Data Protection Act and other regulatory requirements as appropriate.

Table of Contents

GLOSSARY OF ABBREVIATIONS

T1DM	Type 1 Diabetes Mellitus
T2DM	Type 2 Diabetes Mellitus
DM	Diabetes Mellitus

KEYWORDS

Diabetes Mellitus, Pregnancy, Women, Knowledge

STUDY SUMMARY

TITLE	Contraception and pregnancy in diabetes mellitus
DESIGN	Non-interventional, Cross-sectional study
AIMS	To examine the knowledge base women of reproductive age with diabetes have regarding contraception and pregnancy
OUTCOME MEASURES	Quantitative and qualitative questionnaires
POPULATION	n=100
ELIGIBILITY	Women of reproductive age (18-52) with diabetes
DURATION	1 hour per participant, 5 months total

1. INTRODUCTION

1.1 Background

Worldwide, 44% of pregnancies are unplanned (Bearak et al. 2018); in the UK 45% of pregnancies and one third of births are unplanned (Public Health England). If a woman wants 2 children, she will spend, on average, 5 years trying to conceive or being pregnant, and 30 years trying to prevent pregnancy (Gnoth *et al*. 2003; Jensen *et al*. 2001).

Women with diabetes are known to have 'high-risk' pregnancies. Complications for the mother include worsening diabetic control, particularly with increased hypoglycaemia in the 1st trimester; deterioration in retinopathy and nephropathy; pre-eclampsia; birth trauma due to fetal macrosomia (Weissgerber & Mudd 2015; Temple et al 2001; Alexopoulos et al 2019). For the fetus, there are increased risks of congenital abnormalities; macrosomia with resultant birth trauma including shoulder dystocia; intrauterine growth restriction; miscarriage; still birth; neonatal unit admission and neonatal death (Ludvigsson et al, 2018; Jensen et al 2009; Jensen et al 2004).

NICE guidance (NG3) contains a number of recommendations to prepare women with diabetes for a healthy pregnancy, and recommendations to avoid a pregnancy in poorly controlled diabetes; it also has recommendations about contraception. However, the National Diabetes in Pregnancy Audit 2019 shows that seven out of eight women are not adequately prepared pre-pregnancy, and there are still increased numbers of neonatal deaths, stillbirths, congenital anomalies, large and small for gestational age babies and neonatal unit admissions, compared to pregnancies in women without diabetes.
The cause for these poor outcomes, despite the NICE guidance, needs to be understood to enable pregnancy outcomes to improve. One likely factor is poor patient knowledge about the complications associated with pregnancy. One study, undertaken in 2009, showed that only 35% of women with diabetes of reproductive age recalled having any discussion about pregnancy, and only 25% were aware of any of the risks associated with pregnancy (Cartwright et al; 2009). Another study in women with diabetes seen in an antenatal clinic showed that even if a woman was aware of the risks associated with diabetes in pregnancy, she often did not attend for pre-conception counselling and preparation (Murphy et al; 2010). The reasons for this were multifactorial, including falling pregnant faster than expected, and pervious poor interactions with healthcare professionals.

1.2 Rationale for current study

This study seeks to expand upon and update this body of work. It will explore the knowledge and understanding women with diabetes have around pregnancy and conception, as well as establish how well prepared these women are for a pregnancy. Using this data, we will develop better services to inform women with diabetes about the contraception and pregnancy, as well inform the development of pre-conception counselling services for women with diabetes. If successful, we would anticipate seeing an improvement in performance in future National Diabetes in Pregnancy audits.

2. STUDY OBJECTIVES

Primary Objective

- To establish what knowledge women of childbearing age with diabetes have of
    - The risks and management of diabetes in pregnancy
    - The effect of diabetes on fertility
    - What forms of contraception women with diabetes use

Secondary Objective

- To describe the typical diabetes treatment regimes in women with diabetes of reproductive age.
- To determine the overall diabetes control in women with diabetes of reproductive age.
- To examine the number of women of reproductive age who have diabetes-related complications.

3. STUDY DESIGN

Non-interventional, cross-sectional questionnaire study in women of child-bearing age
1 hours per participant, 6 months total
n=100 participants total

3.1 Study Outcome Measures

1. Quantitative data:

- Number of women planning a pregnancy within the next year
- Invitation to and attendance at pre-conception counselling
- Current contraceptive choices
- Knowledge of effect of diabetes on fertility
- Number of women who have had the importance of a planned pregnancy explained to them

2. Descriptive data

- Women's knowledge of the risks to the mother during pregnancy if the mother has diabetes
- Women's knowledge of the risks to the fetus during pregnancy if the mother has diabetes

Additional baseline participant data:

- Age
- Ethnicity
- Number of previous pregnancies
- Type of diabetes
- Length of diabetes
- Current diabetes treatment
- Diabetes complications: nephropathy, neuropathy, retinopathy, cardiovascular disease
- Recent HbA1C
- Other medical conditions
- Other medications

4. PARTICIPANT ENTRY

4.1 Pre-registration evaluations

Potential participants will be identified by the clinical diabetes team from the list of people who attend the diabetes clinics at Imperial College Healthcare NHS Trust.

4.2 Inclusion Criteria

- Women aged 18-52 years (reproductive age) who are not currently pregnant
- Previous diagnosis of Diabetes Mellitus

4.2 Exclusion Criteria

- Inability to understand and write in the English language
- Unable to participate due to other factors, as assessed by the Chief Investigators
- A history of gestational diabetes but not diabetes mellitus.
- Pregnant women

4.3 Withdrawal criteria

- Loss of capacity to give informed consent
- Investigator initiated discontinuation of study due to participation concerns

Withdrawal will be immediate, and participants will be followed up in the appropriate out-patient diabetes clinic at their usual appointments.

If a participant, who has given informed consent, loses capacity to consent during the study the participant will be withdrawn from the study. Identifiable data already collected with consent will be retained and used in the study. No further data would be collected or any other research procedures carried out on or in relation to the participant.

5. ADVERSE EVENTS

5.1 Definitions

Adverse Event (AE): any untoward medical occurrence in a patient or clinical study subject.

Serious Adverse Event (SAE): any untoward and unexpected medical occurrence or effect that:

- **Results in death**
- **Is life-threatening** – *refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe*
- **Requires hospitalisation, or prolongation of existing inpatients' hospitalisation**
- **Results in persistent or significant disability or incapacity**
- **Is a congenital anomaly or birth defect**

Medical judgement should be exercised in deciding whether an AE is serious in other situations. Important AEs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

5.2 Reporting Procedures

All adverse events should be reported. Depending on the nature of the event the reporting procedures below should be followed. Any questions concerning adverse event reporting should be directed to the Chief Investigator in the first instance.

5.2.1 Non serious AEs

All such events, whether expected or not, should be recorded.

5.2.2 Serious AEs

An SAE form should be completed and faxed to the Chief Investigator within 24 hours. However, relapse and death due to diabetes mellitus, and hospitalisations for elective treatment of a pre-existing condition do not need reporting as SAEs.

All SAEs should be reported to the <name of REC> where in the opinion of the Chief Investigator, the event was:

- 'related', i.e. resulted from the administration of any of the research procedures; and
- 'unexpected', i.e. an event that is not listed in the protocol as an expected occurrence

Reports of related and unexpected SAEs should be submitted within 15 days of the Chief Investigator becoming aware of the event, using the NRES SAE form for non-IMP studies. The Chief Investigator must also notify the Sponsor of all SAEs.

Local investigators should report any SAEs as required by their Local Research Ethics Committee, Sponsor and/or Research & Development Office.

Contact details for reporting SAEs
jrco@imperial.ac.uk
CI email (and contact details below)
Fax: 0202 312 1563 for attention Dr Rochan Agha-Jaffar
Please send SAE forms to: Department of Diabetes and Endocrinology, St Mary's Hospital, Praed Street, London W2 1NY
Tel: 0203 312 1253 (Mon to Fri 09.00 – 17.00)

6. ASSESSMENT AND FOLLOW-UP

This study will consist of completing a questionnaire. This should take no more than 1 hour to complete by the participant at a time and location convenient to them.

All eligible participants will be identified by the clinical care team. A list of potential participants will be identified from the database of all people who attend the diabetes clinics at Imperial College Healthcare NHS Trust (subsequently known as the participant database).

Potential participants will be contacted in one of 3 ways by the clinical team:

a) Participants whose emails are available on Cerner will be contacted by email by a member of their direct care team (who is also part of the research team). The email will include the PIS and a link to Qualtrics (an online data collection platform which is supported by the college). Informed consent will be taken via this platform with questionnaires to follow (only accessible if participant has consented to all clauses and signed electronically). Participants will be able to arrange a phone call with the research team to discuss any issues or concerns before signing the consent if they wish. Participants will be provided with a unique code to enable researchers to link their questionnaire data with their medical records. This will be different to the study code and which will be assigned to participants after consent in order of enrolment.
b) For potential participants whose emails are not available or who prefer a hard copy approach, study packs, including the patient information sheet, consent form and questionnaire will be sent by post for completion at home, and returned in a pre-paid addressed envelope to the research team.
c) Patients who are seen in clinic by either the diabetes team will be approached by their clinical team about participating in the study. Those who are interested will then be provided with a consent form and study questionnaire which can either be completed and returned to the research team whilst in the clinic or taken home and returned in a stamped addressed envelope at the participant's convenience.

In all cases, the research team will make blank study packs (including the consent form, patient information sheet and questionnaire) which can be addressed to the individual woman by the clinical team. All women will be asked to return the questionnaire by the end of the study for inclusion in the study analysis.

Within the patient information sheet there will be contact details for the research team, should the participant wish to discuss the study and obtain any further details.

Once returned, the pseudonymised questionnaire data will be recorded in a password encrypted database on an Imperial College Healthcare NHS Trust computer (subsequently known as the results database). Informed consent will be filed in the trial master file. . Data from Qualtrics will be downloaded in a PDF format on either an ICL or ICHT computer and printed for hard copy records. Questionnaire scoring data will be pulled from Qualtrics in a

pseudonymised format and saved on either an ICL or ICHT computer within an encrypted, password protected document.

Once informed consent has been provided, The research team will then review the electronic health records of those participants who have consented to record biochemical data, medical history and baseline demographics. This data will be recorded in pseudonymised form in the results database.

In all cases, no samples are taken and all data will be pseudonymised. No follow up outside of usual care will be provided.

End of study will be defined as last subject last visit (LSLV).

7. STATISTICS AND DATA ANALYSIS

Approximately 100 potential participants will be identified from the list of persons who attend the Imperial College Healthcare NHS Trust diabetes clinics. This is based on the known total number of people who attend these clinics (approximately 2000), assuming that 50% will be women and 50% of these will be of reproductive age. All potential participants will be sent the study pack. A response rate of 10-20% is assumed following previous questionnaire studies undertaken at Imperial College of patient populations.

This study contains both descriptive and quantifiable data. The quantitative outcomes may be either ordinal or categorical, and proportions tests, including Chi squared tests, t-tests and ANOVAs will be used to determine differences between these outcomes.

The descriptive data will be tabulated and presented as such without statistical analysis.

All personal details will be sent via encrypted email (nhs.net).
Record linking participant information to study ID will be stored securely on an Imperial College NHS trust Computer. All study data will be stored in a pseudonymised format in an encrypted database on an Imperial College NHS trust computer.
Direct quotations may be published in anonymous fashion. Care will be taken to ensure no other incidental details (such as ethnicity or age) will be associated with the quotation, in order to ensure anonymity. The NHS Code of Confidentiality will be followed at all times. All data is to be stored in a pseudonymised form by using study codes for de-identification of participants. Examples of such a code includes: CAPRE-DM 0001 (assigned in order of enrolment). Identifiable Personal data will be kept in files in a locked office within Imperial College Healthcare NHS Trust, accessible only by the research/clinical team.
Pseudonymised data will be stored in a password encrypted spreadsheet on ICHT computers, accessible only by the research team.

Data and all appropriate documentation will be pseudonymised and stored for a minimum of 10 years after the completion of the study in line with Imperial College policy.

8. REGULATORY ISSUES

8.1 Ethics approval

The Study Coordination Centre has obtained approval from the xxx Research Ethics Committee (REC) and Health Regulator Authority (HRA). The study must also receive confirmation of capacity and capability from each participating NHS Trust before accepting participants into the study or any research activity is carried out. The study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.

8.2 Consent

Consent to enter the study must be sought from each participant only after a full explanation has been given, an information leaflet offered and time allowed for consideration. Signed participant consent should be obtained. The right of the participant to refuse to participate without giving reasons must be respected. After the participant has entered the study the clinician remains free to give alternative treatment to that specified in the protocol at any stage if he/she feels it is in the participant's best interest, but the reasons for doing so should be recorded. In these cases the participants remain within the study for the purposes of follow-up and data analysis. All participants are free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing further treatment.

8.3 Confidentiality

Anonymised quotes may be used in publications if the participant has given written informed consent. The Chief Investigator will preserve the confidentiality of participants taking part in the study and is registered under the Data Protection Act.

8.4 Indemnity

Imperial College London holds negligent harm and non-negligent harm insurance policies which apply to this study.

8.5 Sponsor

Imperial College London will act as the main Sponsor for this study. Delegated responsibilities will be assigned to the NHS trusts taking part in this study.

8.6 Funding

The study is funded by the Imperial College Diabetes team. No payments will be made to participants or investigators in this study.

8.7 Audits

The study may be subject to inspection and audit by Imperial College London under their remit as sponsor and other regulatory bodies to ensure adherence to GCP and the UK Policy Frame Work for Health and Social Care Research.

9. STUDY MANAGEMENT

The day-to-day management of the study will be co-ordinated through Dr Rochan Agha-Jaffar.

10. PUBLICATION POLICY

The study will be registered on the clinicaltrials.gov system and results will be disseminated by peer reviewed scientific journals, internal report, conference presentation and publication on websites. No identifiable personal data will be published. Anonymised quotes may be included in publications if the participant has given informed written consent. All anthropometry and personal clinical data will be expressed as mean/ median and spread of the population in the study. All participants will be informed of the results by letter at the conclusion of the study and details of any publications that arise from the study will be disseminated to participants.

11. REFERENCES

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12. APPENDICES

Appendix 1. Study Questionnaires (attached separately)

Appendix 2. Data Flow Mapping