Strategies to Improve Iodine Status in Early Pregnancy

IRAS Number: 285499

Sponsor number: EAT/5578/19

Study Title	Strategies to improve iodine status in early pregnancy
Internal ref. no. (or short title)	Strategies to improve iodine status in early pregnancy
Study Design	Quantitative randomized control trial (RCT) with dietary intervention Qualitative semi-structured interview
Study Participants	Women currently 6-16 weeks pregnant Women currently pregnant or with a child under 3 years old.
Planned Size of Sample (if applicable)	160 for RCT 20 for semi-structured interview
Follow up duration (if applicable)	Until approximately 6 weeks post-natal – total of approximately 40 weeks involvement.
Planned Study Period	36 months
Research Question/Aim(s)	Does increasing daily cows' milk consumption significantly improve iodine nutrition status in the first trimester of pregnancy to reach sufficiency?

FUNDER(S) (Names and contact details of ALL organizations providing funding and/or support in kind for this study)	**FINANCIAL AND NON FINANCIALSUPPORT GIVEN**
Public Health Agency, R&D Division	**Doctoral Fellowship**
Queen's University Belfast	**Supervision**
Belfast Trust and Social Care Trust	**Supervision**

Role of Study Sponsor and Funder

This research project is being undertaken at Queen's University Belfast as part of a PhD.

Funding is from the Public Health Agency (PHA), Research and Development (R&D) Office in the form of a doctoral fellowship. Regular updates on progress are required, however the PHA do not directly influence study design or results dissemination.

Contents

1.0 Background

Iodine is an essential component of thyroid hormones. Iodine requirements increase during pregnancy and iodine deficiency in-utero and early life is accepted as the leading cause of preventable mental impairment worldwide. Two billion people are thought be iodine deficient worldwide. While the effects of severe iodine deficiency are well described (cretinism and goitre), the effects of mild iodine deficiency are not well understood, particularly in pregnancy. However, a recent observational study in the United Kingdom (UK) has reported a dose-dependent relationship between the degree of mild iodine deficiency of the mother in first trimester and subsequent offspring cognition scores(Bath, 2019).

In the UK, mild-moderate iodine deficiency was endemic in the past but from the 1930s onwards, "an accidental public health triumph" (Phillips, 1997) occurred with the use of iodine-containing cattle feed and cleaning agents in milking parlours. The richest source of iodine in the UK is cows' milk and other dairy products. Salt fortification programmes exist in many parts of the world, endorsed as the optimal protection by the World Health Organisation (WHO). Historically food fortification has been a politically challenging issue in the UK and iodised salt availability is very low. A study of iodine fortified salt availability across stores on the island of Ireland showed that of 89 stores, only 11 sold iodine-fortified salt, and 10 of these were in ethnic stores with a low market share(O'Kane et al., 2018; Shaw et al., 2019; Vanderpump et al., 2011; WHO, 2013).

Our group in Northern Ireland (NI) surveyed one of the largest cohorts of teenage girls in the UK and demonstrated borderline sufficiency with geographical variations. There was also a positive correlation between iodine status and milk consumption. Our group has recently reported low levels of iodine awareness among pregnant women, with only 5% of pregnant women having any knowledge of iodine-containing foods and their importance. Iodine deficiency in a large cohort of pregnant women in NI has been documented, which persisted across the trimesters, despite 50% of women taking a supplement containing iodine(Bath et al., 2016; McMullan, Hamill, et al., 2019; McMullan, Hunter, et al., 2019).

Neonatal thyroid stimulating hormone (nTSH) levels from babies in Northern Ireland over 15 years were analysed and our group reported a rise in nTSH, indicative of a possible re-emergence of iodine deficiency. Seasonality was also demonstrated, which suggests that seasonal feeding patterns among milking cows may be relevant to the iodine in the food chain. Our group has also published on selenium levels in pregnancy, air circulation of iodine on the island of Ireland and mapping of iodine status throughout Europe(Ittermann et al., 2020; Mullan et al., 2018; Smyth et al., 2011).

The Scientific Advisory Committee for Nutrition UK has called for further research on improving iodine nutrition. To our knowledge, this milk-based intervention study is the first of its kind and may offer an urgently required evidence base for options outside of fortification in the UK(Nutrition, 2014).

2.0 Research Aims

We will conduct an RCT testing the hypothesis: increased intake of cows' milk early in pregnancy will improve iodine nutrition. We aim:

1. To determine if 12-week free milk provision, along with education around iodine nutrition, compared with education alone increases the proportion of women who achieve adequate iodine status in pregnancy and the puerperium.
2. To determine if 12-week free milk provision, along with education around iodine nutrition, compared with education alone, leads to a change in dietary behaviour throughout the rest of pregnancy and puerperium, once the intervention period has completed.
3. To understand the possible barriers to increased iodine intake in pregnancy

3.0 Plan of Investigation

3.1 Milk Intervention RCT

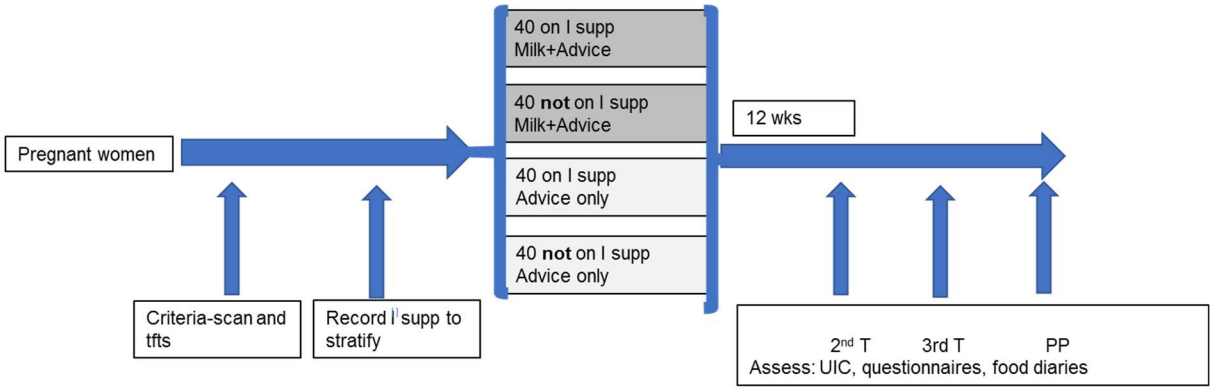


Figure One: Flow chart showing the original plan for the RCT.

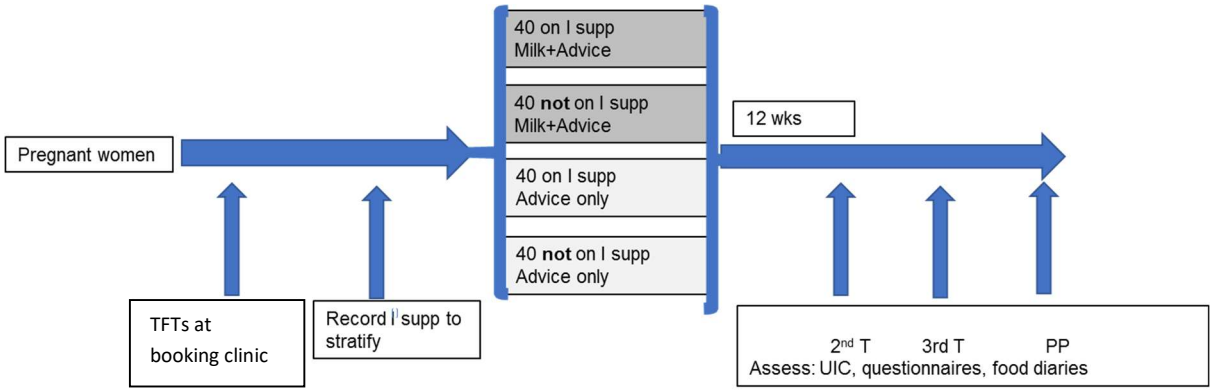


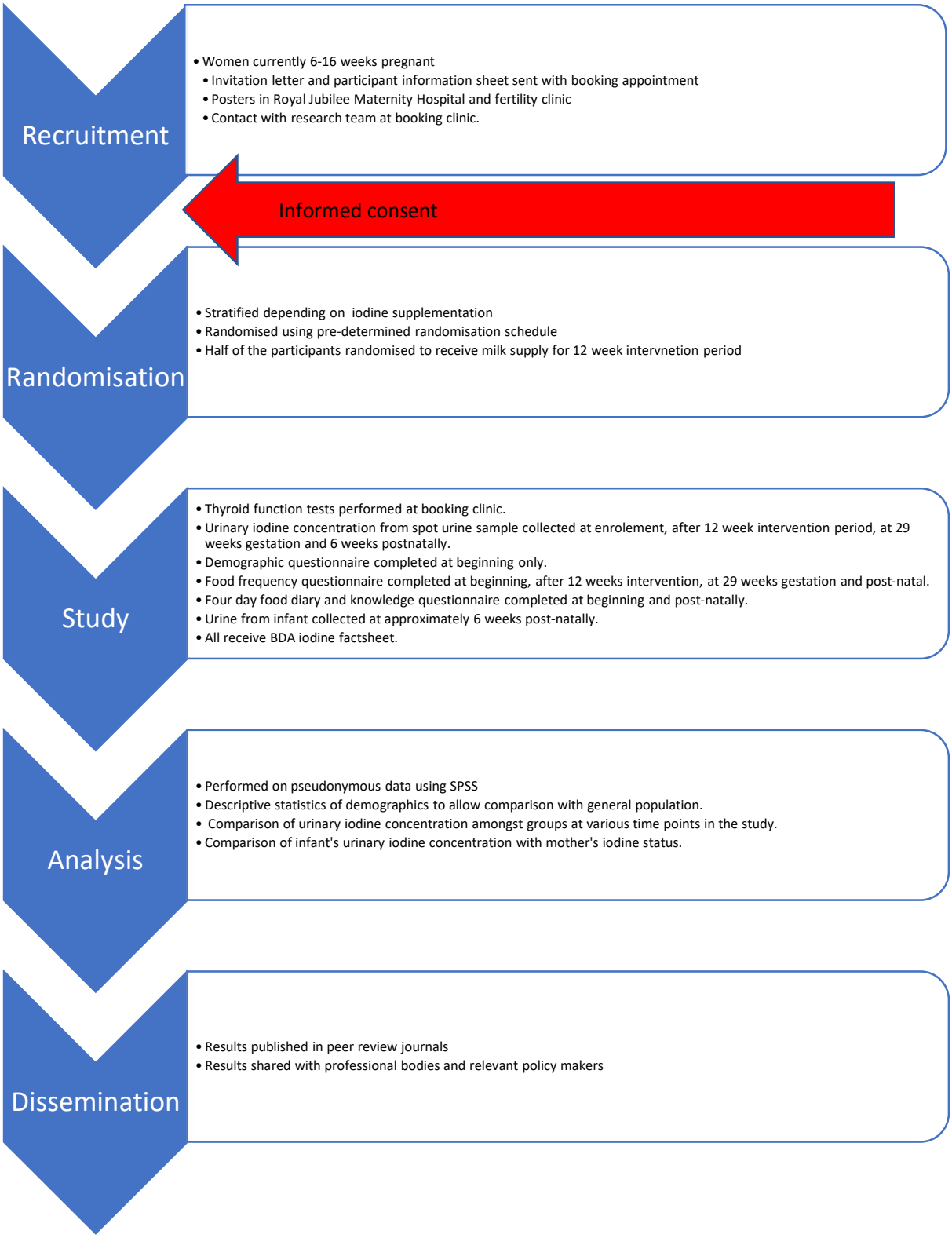
Figure Two: Flow chart showing the changes made due to the ongoing COVID-19 pandemic.

The ongoing COVID-19 pandemic has meant that we have had to review our original research plan taking mitigating actions to ensure participant safety. This has meant removing all visits to clinical areas, other than those required for usual clinical care. In summary, these changes are as follows:

- Last menstrual period will be used to estimate gestational age. This will avoid attending a clinical area for an ultrasound scan.
- In addition to remote recruitment, women will be recruited at their booking appointment. There are no additional visits to clinical areas and contact with the research team at the booking appointment would be socially distanced and with appropriate personal protective equipment worn.
- Participants will complete consent forms and questionnaires (demographics, iodine knowledge and iodine specific food frequency questionnaire) online using Qualtrics software. Women recruited during their booking appointment will complete the consent form in the clinic prior to the collection of blood samples and the first urine sample.
- Four-day food diaries will be given (in person or by post) to participants, once consent form has been completed, along pre-paid envelope for returning food diaries.
- Thyroid function tests will be carried out at the participant's booking appointment when routine bloods in prenatal care are being taken. Participants will be asked to bring a specimen form to their appointment for the attention of the phlebotomist. This will ensure blood samples taken for the purposes of this research are processed under the appropriate research code.

- All urine samples, except the first, collected at the booking appointment, will be collected by post, or by contactless, doorstep, collection to avoid visits to clinical areas for research purposes.
- If randomised to receive free milk supply, contactless delivery will be provided.

3.1.1 Study flow chart



3.1.2 Recruitment

Recruitment will be via several routes. Women will receive an invitation letter and participant information sheet along with their booking appointment letter, if attending a booking clinic where a member of the research team will be in attendance. Women will be asked to indicate to a receptionist if they are agreeable to being approached by the research team while attending booking clinic. Women in NI commonly self-refer to maternity services resulting in early presentation to the maternity hospital and less GP input.
Women will also be recruited within NI using posters around the Royal Jubilee Maternity Hospital (RJMH) and the Fertility Clinic. All participants will be receiving antenatal care within the Belfast Trust.
Women will be able to contact the research team via the contact details provided on the invitation letter prior to their booking appointment. When attending the booking clinic women will be approached by a member of the research team and any questions they may have will be answered. If agreeable, the consent form will be completed, and research bloods taken as well as the first urine sample collected.

3.1.3 Study design

This will be a randomised controlled trial of cows' milk provision, along with education around iodine nutrition, compared with education alone, on iodine nutrition in pregnancy and the puerperium. A total of 160 women will be recruited in early pregnancy. The randomisation will be stratified based on current use of iodine-containing supplements and performed using a predetermined randomisation schedule.

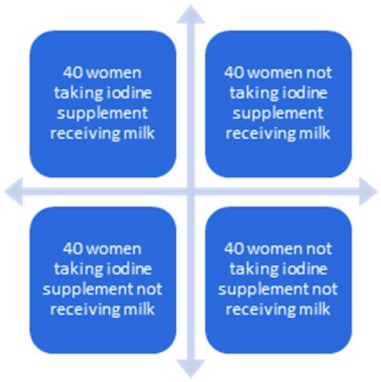


Figure three: Figure indicating intervention groups

Women will be recruited at 6-16 weeks gestation based on dates of last menstrual period (LMP) and confirmed on scan at booking clinic. They will be provided with a participant information sheet (PIS) along with the invitation letter included with their booking clinic appointment. A researcher will be available in person at the booking clinic, via telephone or by email to answer questions throughout. During the booking clinic, women who are willing to participate will complete a consent form. They will then have research bloods taken, along with their routine antenatal bloods, and provide the first urine sample. Once the consent form has been completed the participant has been enrolled in the study and will be assigned an identification number. Following attendance at the booking clinic, they will then be sent an email containing a pseudonymous link to the Qualtrics platform to complete the initial questionnaires: demographic questionnaire (including information about current use of iodine containing supplements), iodine specific food frequency questionnaire (FFQ) and iodine knowledge questionnaire. The participant will also be asked to complete a four-day food diary. This will be returned by post; a pre-paid envelope will be provided.

All participants will receive the British Dietetic Association (BDA) iodine factsheet by post and email. If the participant is randomised to receive milk supply contactless delivery will be arranged. Milk will be supplied for a total of 12 weeks ('the intervention period') at a volume of a pint/day (4 L/week) for the participant along with 2 L/week for their family if appropriate. On receipt of the first urine sample and all questionnaires women will be provided with £20 shopping voucher.

Women attend for their booking appointment at around 12 weeks gestation as part of routine antenatal care. At this time routine bloods for clinical care are obtained. We will use this opportunity to take 10ml of blood from participants for thyroid function tests (TFTs) and for storage. If TFTs are found to be abnormal, using local

trimester specific values, the participant will be excluded from the study and data collected to that point removed. Access to specialised endocrine input will be available if required for management of thyroid function. The participant's general practitioner will be informed, along with the team providing antenatal care. Results will be accessed using Labcentre and the research code used to label all blood samples taken for this study.

After the intervention period of 12 weeks participants will be asked to complete an online FFQ and return a second urine sample by post or by contactless, doorstep, collection. Depending on gestation at recruitment this will be between 18-28 weeks gestation. Approximately six weeks (+/- one week) after the intervention period a further urine sample will be collected by post, or by contactless, doorstep, collection along with an online FFQ.

Finally, between 6-12 weeks post-partum women will be asked to provide a final urine sample, again by post or by contactless, doorstep, collection. They will also be provided with a 'nappy pad' to collect a sample of urine from their child. A final online FFQ will be complete along with an iodine knowledge questionnaire. A four-day food dairy will be completed and returned by post.

When all data collection has been completed women will receive another £40 shopping voucher. Women who have been involved in the milk intervention will also be invited to participate in the semi-structured interviews.

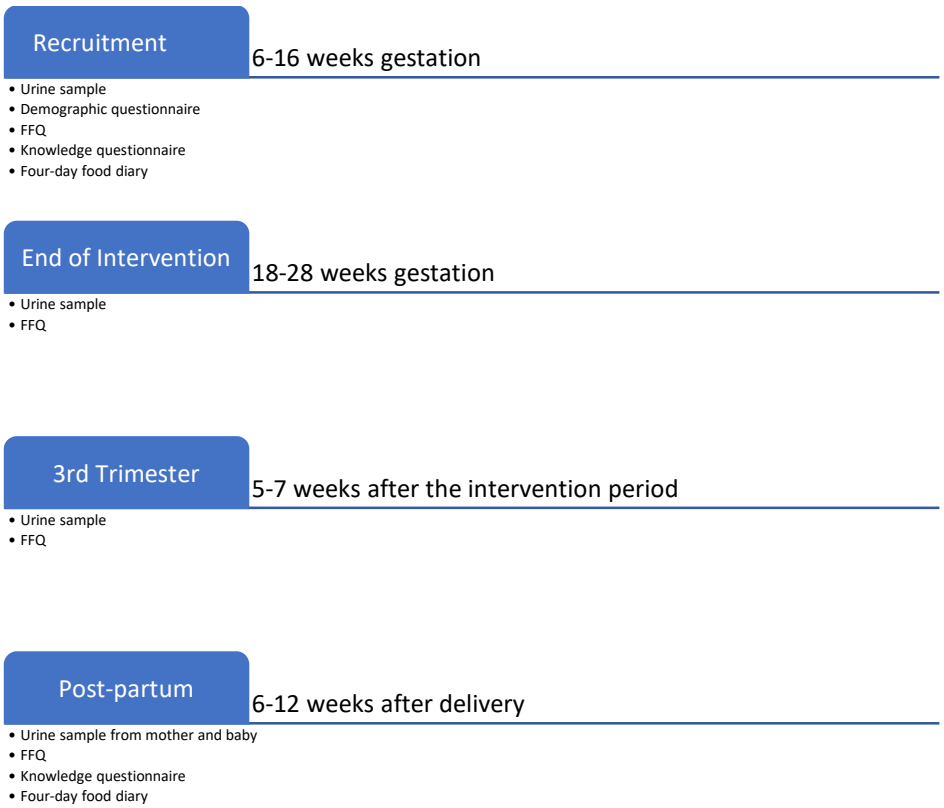


Figure four: Summary of data collection throughout the study.

3.1.4 Eligibility criteria

3.1.4.1 Inclusion criteria

- Women at 6-16 weeks pregnant estimated by LMP.
- Women receiving antenatal care within Belfast Health and Social Care Trust.

3.1.4.2 Exclusion criteria

- Women with known thyroid disease currently taking thyroid medication
- Women with type one diabetes (as this may alter urinary iodine secretion)
- Women under the age of 18 years
- Those unable to provide informed consent
- Women with abnormal thyroid function test at booking appointment.

3.1.5 Laboratory methods

All biological samples will be processed and stored within the Centre for Public Health, QUB. Samples will be stored in temperature-monitored -80°C freezers. The risk of contamination with urinary dipsticks will be eliminated as samples are being sent directly to the laboratory rather than being collected from a clinical setting. Infant samples will be collected using nappy pads which can also be returned by post.
Urinary iodine concentration (UIC) will be measured alongside creatinine to correct for dilution.
UIC will be measured using a multiplate persulphate digestion method followed by Sandel-Kolthoff colorimetry and expressed as µg/L. Samples will be analysed in triplicate with the limit of detection at 10µg/L. The laboratory is registered and participated with the Ensuring the Quality of Urinary Iodine Procedures (EQUIP) quality assurance programme in the UC Centers for Disease Control and Prevention. Urinary creatinine concentration will be measured using an ILAB 600 chemistry analyser (Werfen, UK) using the Jaffe rate method.

Blood samples taken at the participant's booking appointment will be used to measure TFTs (free thyroxine and thyroid stimulation hormone) at the laboratory within the Belfast Health and Social Care Trust (BHSCT). Abnormal results, according to local trimester specific reference ranges, will exclude the participant from the study and she will be referred for appropriate clinical treatment. Blood will also be drawn for storage to explore other markers of thyroid function in the event of a positive study (thyroglobulin, selenium and thyroid antibodies). This is in-keeping with other iodine studies of this kind and will help generate future research hypotheses.

3.1.6 Outcome measures

- Proportion of the maternal cohort who achieve WHO urinary iodine concentration (UIC) of $\geq$ 150µg/L on early morning spot urinary sampling at 12 weeks post intervention i.e. at 18-22 weeks gestation.
- Knowledge regarding iodine intake in the diet in pregnancy and into postpartum
- Intake of iodine rich foods at 29 weeks and postpartum in those who breastfeed
- Proportion of offspring with adequate UIC levels at 6-12 weeks old

3.1.7 Statistics

3.1.7.1 Power calculation

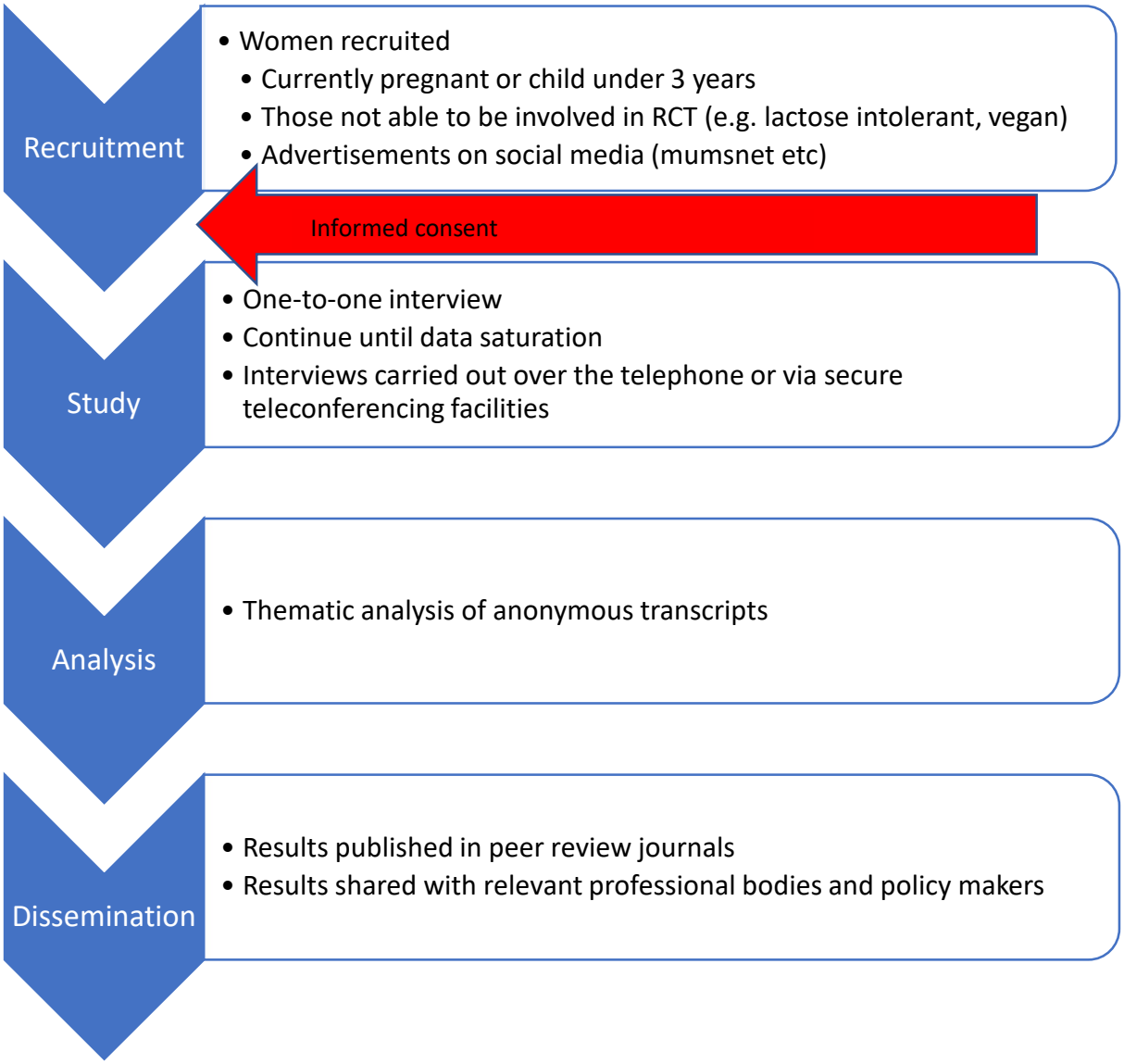
Sample size has been determined to give power of 80% to detect a 25% difference in UIC. We have allowed for non-completers based on drop out rate from previous dietary intervention studies.

3.1.7.2 Statistical analysis

In keeping with our other published data estimates of the proportion of iodine deficient samples will be obtained, and 95% confidence intervals calculated. The proportion of women achieving iodine sufficiency (defined by UIC ≥150µg/L after 12-week intervention period) in each group will be compared, with more complex analyses adjusting for baseline data should this be indicated by balance of groups at baseline. SPSS for windows, version 27 will be used for all analyses, and analyses will be directed by a medical statistician within the Centre for Public Health at QUB.

3.2 Semi-structured interviews

3.2.1 Study flow chart



3.2.2 Recruitment

We plan to recruit from:

- The 160 participants from the main study to seek their views both before and after the intervention.
- Women who have shown an interest in the study but who are ineligible because of barriers to iodine intake e.g. veganism, lactose intolerance, strongly held views on health and nutrition and unpalatability of dairy products.
- Women who have approached our team because of our advertisement of the study and who, on reflection, do not wish to participate in the main study because of the inconvenience but consent to be interviewed as a one-off participation.
- Women will be recruited from the general population through posters in the RJMH and Fertility Clinic at RVH
- Women self-referring to RJMH will be sent an invitation letter with the confirmation of their booking appointment. This method of recruitment has previously been used successfully.

3.2.3 Eligibility criteria

3.2.3.1 Inclusion criteria

- Pregnant women
- Women with child under 3 years old

3.2.3.2 Exclusion criteria

- Women under the age of 18 years
- Those unable to provide informed consent.

3.2.4 Study design

A total of ten women participating in the trial, and ten further pregnant women, including some who are non-milk consumers, will be recruited, although numbers may be smaller if data saturation has been achieved. Women will be asked to participate in a one-to-one semi-structured interview. The interview will be conducted based on a topic guide, which will explore current knowledge, attitudes and perceived barriers to iodine intake during pregnancy and into the postpartum period, and preferred education communication methods.

3.2.5 Data collection

Interviews will be carried out via the telephone or using secure teleconference applications. Interviews will be audio recorded and transcribed verbatim. Transcripts will be anonymous, and the audio recording destroyed. Thematic analysis will be used to identify and synthesise participant views. Contact details and consent forms will be kept in a locked filing cabinet. Anonymous transcripts used for thematic analysis will be stored in a password-protected folder on an encrypted laptop.

Data saturation will be confirmed by two members of the research team reviewing the anonymous transcripts and agreeing that no new themes are emerging.

3.2.6 Outcome measures

To reach data saturation allowing for meaningful conclusions to be drawn from the semi-structured interviews, with 20 women recruited initially exploring:

- barriers to increased iodine intake in pregnancy,
- for those participating in the trial, changes in these barriers over the course of the trial,
- preferred methods of education around nutrition during pregnancy.

4.0 Data Management

4.1 RCT

Consent forms completed via Qualtrics will be downloaded and stored in a dedicated, password protected folder. Qualtrics software allows for data to be collected using personalised links while using the participant ID to pseudonymise the data. Data collected in the questionnaires on Qualtrics will then be exported to Microsoft Excel. Qualtrics is GDPR compliant and is password protected.

Completed four-day food diaries will be stored in a fire-proof filing cabinet in a secure office. The relevant information will be transferred to an anonymous spreadsheet for analysis.

4.2 Semi-structured interviews

Consent forms completed and returned by email will be moved to a dedicated research folder and deleted from the inbox where they would be associated with contact details.

Audio recordings of the interviews will be kept in a locked office and transcribed at the earliest opportunity. Transcripts will be anonymous. These will be stored on an encrypted laptop in a password protected folder.

Data will only be accessed by the necessary members of the research team. Data will be stored for 5 years in line with the policy of Queen's University Belfast.

5.0 Ethical and Regulatory Considerations

The study is low risk.

- The dietary intervention will not result in iodine excess, even in the group of women already taking an iodine containing supplement.
    - The WHO recommends an intake of 250 µg iodine in pregnancy.
    - One pint of cows' milk (568 ml) equates to approximately 140-224 µg of iodine.
    - Iodine in most supplements in 150 µg.
    - Maximum daily iodine intake 550-1100 µg(Supplements, 2020; WHO, 2007).
    - A NI pregnant cohort demonstrated iodine deficiency throughout all trimesters, despite 53% of women taking a pregnancy-related supplement containing iodine.
    - The SACN, has taken the position in its 2014 paper that "at a population level in the UK there are no concerns about excessive dietary iodine intakes"(Nutrition, 2014).
- The only blood sample required will be taken with routine blood tests during prenatal care.
- Given the ongoing COVID-19 pandemic we have removed all visits to clinical areas, instead collecting the urine samples and questionnaires by post or electronically.
- The topics discussed during interview are unlikely to lead to the disclosure of sensitive information that would have to be discussed with members of the healthcare team or emergency services.
- Interviews will be performed remotely via telephone with recording on university Dictaphones or secure teleconferencing application (Microsoft Teams or Skype) using application recording.

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