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McMullan, P., Hamill, L., Doolan, K., Hunter, A., McCance, D., Patterson, C., Smyth, P., Woodside, J. V., & Mullan, K. (2019). Iodine deficiency among pregnant women living in Northern Ireland. *Clinical Endocrinology*. <https://doi.org/10.1111/cen.14065>

Published in:
Clinical Endocrinology

Document Version:
Peer reviewed version

Queen's University Belfast - Research Portal:
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Iodine deficiency among pregnant women living in Northern Ireland

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Key words: iodine, nutrition, pregnancy, deficiency

Declaration of interest, Funding, Acknowledgements and Data Sharing

We declare that there is no conflict of interest that could be perceived as prejudicing
the impartiality of the research reported.

This work was supported by the Metabolic Research Fund, Royal Victoria Hospital,
Belfast

We would like to acknowledge the help of Dr S Bath in allowing our use of the
iodine specific food frequency questionnaire that she developed.

The data that support the findings of this study are available from the corresponding
author upon reasonable request.

Abstract

Objective: Mild iodine deficiency has re-emerged among school girls in the UK. We wished to study a contemporaneous pregnant population because a relationship between maternal iodine deficiency and offspring cognitive scores has recently been reported. The WHO have set a median population urinary iodine concentration (UIC) of ≥ 100 and ≥ 150 $\mu\text{g/L}$ to define adequacy outside of and during pregnancy respectively. Iodine creatinine ratio (ICR) is also used to correct for dilution effects (sufficiency $\geq 150\mu\text{g/g}$ creatinine in pregnancy).

Design and methods: A total of 241 women were followed across trimesters (T) into the postpartum period (PPP) along with 80 offspring with spot urine sampling and food frequency questionnaires.

Results: Median UIC was $71.7\mu\text{g/L}$ in the 1st T (ICR $102\mu\text{g/g}$ creatinine) despite 55% taking iodine containing supplements. Median UICs were 94.2, 115.6 and $89.7\mu\text{g/L}$ in the 2nd T, 3rd T and PPP respectively. Corresponding ICRs were 120, 126 and $60\mu\text{g/g}$ creatinine. ICR was associated with volume of milk consumed throughout pregnancy. Median UIC among the offspring was $147.9\mu\text{g/L}$, with no difference between the breast or formula fed babies.

Conclusions: Pregnant women living in Northern Ireland are at risk of iodine deficiency across pregnancy and into the PPP while the offspring are iodine sufficient. This is the first study of its kind in the UK with data for pregnant women and their offspring. The UK does not provide an iodine fortification programme nor offer routine iodine dietary advice in pregnancy and this requires consideration by public health agencies.

44 **Background**

45 For many years, the population of the British Isles (UK and Republic of Ireland) was
46 thought to have adequate iodine nutrition. From the 1940s onwards, iodine was
47 added to cattle feeds as it was thought to enhance animal fertility and iodine
48 containing disinfectants were used to clean milking parlours. The resulting increase
49 in iodine in the food chain has been described as an “accidental public health
50 triumph”.¹ However a re-emergence of mild deficiency across the British Isles has
51 been reported by recent surveys using the gold standard population median urinary
52 iodine concentration (UIC).^{2,3} The UK survey of >700 UK teenage girls in 2009
53 found that 69% were mildly iodine deficient.² Causes for the re-emergence of iodine
54 deficiency include possible changing farming techniques and dietary habits.

55 There is an increase in iodine requirements during pregnancy because of an increase
56 in the production of maternal thyroid hormones; placental transfer of iodine for foetal
57 thyroid hormone production and increased urinary losses associated with the
58 increased glomerular filtration (GF) of later pregnancy. Early infancy is also thought
59 to be an important time for optimal iodine nutrition.⁶ Lactating breast tissue is known
60 to concentrate iodine through expression of the sodium/iodide symporter gene and
61 infant formula feeds available in the UK contain iodine, but it is not known whether
62 these meet requirements.⁷

63 During pregnancy moderate or severe iodine deficiency is associated with poor
64 cognitive outcomes in the offspring.⁴ The effect of mild iodine deficiency during
65 pregnancy is much less clear and iodine status is difficult to assess during pregnancy.
66 Difficulties include overly dilute urine samples provided in early pregnancy in
67 preparation for imaging and increased glomerular filtration in late gestation, which

may overestimate and underestimate iodine deficiency respectively. Corrections using urinary creatinine (iodine: creatinine ratio ICR) have been proposed with a cut off level of 150µg/g creatinine in pregnancy.⁵ The Avon Longitudinal Study of Parents and Children (ALSPAC) authors reported that lower ICR but not UIC in first trimester was associated with offspring IQ (age 8), reading ability (age 9) and Key Stage 2 scores (age 11) in a dose dependent fashion.

The WHO recommends an intake of 250mcg of iodine per day for mothers to meet these increasing demands while the European Food Safety Authority (EFSA) recommends 200 mcg/day. The American Thyroid Association (ATA) recommends that different regions develop strategies for ensuring adequate iodine intake during preconception, pregnancy and lactation according to dietary patterns and availability of iodized salt.^{8,9} With no formal iodine food fortification program in the UK or ROI, dietary sources are essential to help meet requirements. Iodine supplementation is also not specifically recommended during pregnancy in the UK with the Scientific Advisory Committee for Nutrition calling for further research.¹⁰ This position is at variance with other nations such as Australia and USA who recommend a supplement containing 150 µg iodine daily.^{9,11}

Epidemiological surveys assessing iodine nutrition status during pregnancy are limited in the UK and there is none in the geographical area of Northern Ireland (NI). The aim of this study is to assess iodine nutrition status among NI pregnant women in each trimester and the postpartum period and their offspring.

Methods

This survey was carried out in the Royal Jubilee Maternity Hospital Belfast. Participants were recruited at their booking visit and followed up at scheduled second and third trimester hospital clinic review appointments. Exclusion criteria included those participants under 18 years of age and those with known thyroid disease taking thyroid medications. One post-natal visit was undertaken for sampling of both maternal and infant urine from 6 weeks to 6 months post-partum. The study received ethical approval from the Office for Research Ethics Committees Northern Ireland (reference 14/NI/0047) and trust governance (13171KM-AS). Consent has been obtained from each patient or subject after full explanation of the purpose and nature of all procedures used.

~~A history~~ Women were asked to complete a short health and lifestyle questionnaire (Appendix 1). ~~and anthropometric measurements were taken.~~ Height was measured to the nearest 0.1cm using a wall-mounted stadiometer. Weight was measured using calibrated digital scales and recorded to the nearest 0.1kg. Body mass index was calculated by dividing weight by height squared and recorded to the nearest 0.1kg/m².

Occupation was graded according to the European Socio-economic Classification (ESeC).¹² Deprivation scores were assigned using postcode and national statistics information from the Northern Ireland Statistics and Research Agency.¹³

Iodine specific food frequency questionnaires (FFQ) developed by Bath et al were distributed at baseline; supplementation questions were included and data collected on an ordinal or nominal scale.¹⁴ A random non-fasting spot urine sample was collected from each participant at the booking visit and each subsequent visit when

possible. Care was taken to avoid contamination of samples with the use of urine dipsticks which contain iodine-based components. Infant urinary samples were collected using nappy pads inserted into nappies on the morning of the scheduled appointment. All urine samples were frozen at -80 degrees until analysis. Mothers were asked at the postnatal review if they were partially or exclusively breastfeeding. Urinary iodine concentration was measured using a multiplate persulphate digestion method followed by Sandel-Kolthoff colorimetry and expressed as $\mu\text{g/L}$ as previously described.^{2, 15} Samples were analysed in triplicate for iodine and the limit of detection was $10\mu\text{g/L}$. The laboratory participated in the Ensuring the Quality of Urinary Iodine Procedures (EQUIP) programme at the US Centers for Disease Control and Prevention (CDC Atlanta, Georgia, USA). The intra-assay coefficient of variation (CV) for urinary iodine was 15% for low QC (mean $30.5\mu\text{g/L}$) and 8% for high QC (mean $95.0\mu\text{g/L}$). Urinary creatinine concentration was measured singly using an ILAB 600 chemistry analyser (Werfen, UK) using the Jaffe rate method with CV <4%.

Statistical analysis

Statistical analyses were conducted using the statistical Package for the Social Sciences software (version 23.0; SPSS, Inc. USA) and significance set at $p < 0.05$. Median and interquartile range were used to present non-normally distributed data and to allow comparison with other studies. Log transformations were, however, carried out to allow for parametric testing and back transformed for presentation purposes. To compare means between groups an independent t-test and one-way ANOVA were used. Paired samples were compared using a paired samples t-test. eg breast and bottle fed babies, male and female babies and between breast and bottle feeding

mothers. ANOVA was used to compare differences between groups eg groups of mothers with differing milk consumption. Correlations between continuous variables was assessed using Pearson's correlation coefficients. In order to allow comparison with other papers we have presented the unadjusted data. For analyses the first trimester was defined as <14 weeks gestation, second trimester $\geq 18 \leq 22$ weeks gestation and third trimester as $\geq 28 \leq 32$ weeks gestation. Iodine: creatinine ratio (ICR) ($\mu\text{g/g creat}$) was calculated by dividing the UIC ($\mu\text{g/L}$) by the urinary creatinine (g/L). The 24-h excretion of iodine (UIE) was estimated by multiplying the ICR by the expected daily excretion of creatinine (1.23 g/day) in adult women as per Bath et al.¹⁹

Results

From July 2014 to March 2015 a total of 241 women were recruited to the study at booking. Twenty-four patients recruited at baseline were re-categorised as being in the 2nd trimester based on scans done for dates. Urine samples were collected from all participants. Two samples were contaminated by urine dip sticking and excluded from analysis. One hundred and thirty-four urine samples were collected at the 20-week scan visit and 153 in the early third. FFQ returns were 240, 130 and 150 at each visit respectively. Baseline characteristics are outlined in Table 1.

The mean gestational age at study baseline was 11 weeks (range 9-17). ~~Most women (71%) were recruited at 11-12 weeks gestation with 10% recruited before 11 weeks and the remainder at 13-14 weeks.~~ The mean age of participants was 30.3 ± 5.4 years with a range of 18-41 years. The mean BMI was in the overweight category ($26.2 \pm 4.9 \text{ kg/m}^2$) with a range of 18-34 kg/m^2 . Low deprivation scores (graded 4, 5) and low occupation scores were calculated in 42% and 35% women respectively.

Most reported a planned pregnancy (78%) and a normal diet with just over half reporting that they took a pregnancy supplement which contained iodine. About one quarter had persistent vomiting. Nearly two thirds of participants were recruited during the winter months.

Trimester specific and offspring median UIC (mUIC) are shown in Table 2 along with results corrected for urinary creatinine. The group at booking was iodine deficient (mUIC 72.6 $\mu\text{g/L}$) with 83% of participants having levels below the current recommendation from the WHO of 150 $\mu\text{g/L}$. The mUIC was also below the threshold even for outside of pregnancy (>100 $\mu\text{g/L}$). Median UIC at subsequent time points were also less than 150 $\mu\text{g/L}$ although ~~values~~ concentrations increased as pregnancy progressed. Figure 1 shows the proportion of participants above and below the WHO cut-off value of 150 $\mu\text{g/L}$ at each trimester. Postnatally maternal mUIC was also low.

The median estimated 24-hour urinary iodine excretion (UIE) in pregnancy has been suggested by Bath et al to be >225 $\mu\text{g/day}$ assuming the recommended 250 $\mu\text{g/day}$ intake of which 90% is excreted.¹⁹ Our cohort excreted 148 $\mu\text{g/day}$ (IQR 90-269), 181 $\mu\text{g/day}$ (IQR 115-311) and 184 $\mu\text{g/day}$ (IQR 117-293) across the three trimesters.

In the first trimester, ~~younger age and~~ pregnancy planning was associated with lower levels of mUIC ($r=0.16$, $p=0.05$). In contrast, several characteristics were associated with lower levels of ICR: younger age (<30 years) ($r=0.30$, $p=0.01$); persistent vomiting, a regular diet, and lack of family history of thyroid disease ($r=0.16$, 0.13, and 0.14 respectively, $p=0.05$). Reported iodine supplementation in first trimester was associated with higher ICRs than in those without supplementation (145 vs 96 $\mu\text{g/g creatinine}$ $p<0.001$) but this was still below the recommended 150 $\mu\text{g/g}$

187 creatinine for pregnancy. Supplementation invariably contained 140-150 µg/day
188 iodine.

189 Lower and intermediate occupations had ICR of 100 µg/g compared to 149 µg/g
190 creatinine for the higher occupations ($p<0.01$). Most of the ICR associations were
191 lost in later trimesters except first trimester vomiting ($r=0.18$ in 2nd trimester) and
192 lack of family history of thyroid disease ($r=0.18-0.24$) (all $p=0.05$). There were no
193 associations with parity, previous miscarriage, BMI, smoking, or season at booking
194 (results not shown). Only one set of twins were born in this cohort.

195 There were no significant associations between dietary habits and mUIC across the
196 trimesters. Associations between a selection of dietary habits and first trimester ICR
197 are shown in Table 3. ICR was positively associated with intake of milk ($<140\text{mls}$
198 daily vs $\geq 140\text{mls}$) and full fat yoghurt ($<1/\text{week}$ vs $\geq 1/\text{week}$) ($r=0.22, 0.19$
199 respectively, $p=0.01$); and white fish ($<1/\text{week}$ vs $\geq 1/\text{week}$) ($r=0.17, p=0.05$). ICR
200 levels increased in a dose dependent way with volume of milk consumed. Only milk
201 quantity continued to show significant associations with ICR in the second ($p<0.001$)
202 and third trimesters ($p<0.005$). There were too few participants who used milk other
203 than cow's milk to draw any meaningful conclusions about milk type. Increased egg
204 intake was trending to a higher ICR but did not reach significance. There was an
205 increase in consumption of milk, dairy desserts and butter across pregnancy ($p <$
206 0.05).

207 Infant results: The mUIC in (at least partially) breast fed infants ($n=49$) was $146\mu\text{g/L}$
208 (IQR $103-202\mu\text{g/L}$) and $156\mu\text{g/L}$ (IQR $103-247\mu\text{g/L}$) in formula fed infants ($n=31$).
209 There was no significant difference between (at least partially) breast fed and
210 formula fed infants and no difference between male and female infants. Only 24

211 babies were exclusively breastfed and this is below the cutoff recommended by
212 WHO as a sufficient group to analyse. However results were not significantly
213 different from partially breast fed or formula fed babies (147 µg/L, IQR 92-229)
214 There was also no significant difference in mUIC between the breast versus bottle
215 feeding mothers who supplied a postpartum sample.

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Discussion

This is the first survey of its kind in NI and one of the few studies to survey across pregnancy into the postpartum with offspring iodine status. Results suggest iodine deficiency among this cohort across pregnancy and beyond but not in the offspring.

The ATA has called for population surveys in different geographical regions to take account of differing environmental iodine levels. The UK has an estimated population of ~66 million of which ~20 % are females of childbearing age and there are ~seven million births/year.^{27, 28} The regions where iodine nutrition during pregnancy have previously been studied locally include four areas of England, Wales and the Republic of Ireland (RoI) (Table 4).^{3, 5, 14, 16-19} A further study in Scotland (which incorporated other UK areas online) relied on FFQ rather than population urinary iodine sampling.²⁰ The studies span nearly 25 years and are consistent in reporting median UIC below the recommended 150 µg/L in pregnancy with no pointers to improvement over this period.

The median UIC increased across the trimesters in our survey and fell in the postpartum period. The only other UK study, which surveyed across pregnancy showed a similar trend while the RoI study showed no change from a higher baseline but did replicate the precipitous fall as quickly as three days postpartum.^{16, 19} We found that, after correction for dilution with urinary creatinine, there was still an increase in urinary iodine across pregnancy. Reasons for this may include a change in iodine intake across pregnancy, lessening iodine sequestration by the maternal thyroid, placenta and breast with time and/or a residual dilution bias in early pregnancy.

Lower SES occupations were associated with lower ICR. The association of lower ICR with lack of family thyroid disease raises the possibility that knowledge about thyroid health may be a factor. We have reported, in abstract form, a separate local pregnant cohort in which 80% of women were not aware of the increased iodine requirements in pregnancy and 45% were unable to identify any iodine rich foods.²¹

Vomiting in 1st trimester was associated with lower levels of ICR throughout all the trimesters. This points to the importance of dietary iodine intake in early pregnancy and a possible legacy effect in later pregnancy.

We found that conventional cow's milk intake increased across pregnancy and correlated with ICR in keeping with other studies.^{16,19} Numbers were too small to comment on more expensive organic cow's milk, which is in keeping with our socio-economic cohort, but other studies have demonstrated lower levels of iodine content in organic milk by up to 40%.²² Although fish is also an iodine rich source in the UK and we found associations with ICR, overall fish consumption was low.

The most commonly used combined pregnancy supplements taken in 1st trimester contain ~140-150 µg iodine /tablet. Although mothers who took this had higher levels of ICR, levels remained below target. This is in keeping with other studies where pregnant women taking iodine supplements but living in an iodine deplete area have higher ICR than those not taking supplements, but their levels remain below that recommended by WHO. Supplementation in an iodine deplete area may therefore not be sufficient without also an iodine fortification or education program.^{14, 24-25} In the absence of any successes in improving dietary intake of our population in pregnancy, the argument for fortification at a population level, may become compelling.

We found that iodine status was sufficient in the offspring as a whole at six weeks to six months despite iodine deficiency in their mothers at that stage. There were no differences in iodine excretion between breast and formula feeding mothers. The breast and formula feeding offspring also had similar levels of UIC. These results are at variance with the RoI study which reported that both mothers and their offspring overall were iodine deficient at 3 days postpartum and that the formula fed babies had lower levels than breast fed babies.¹⁶ The authors suggested that the available formula feeds (containing 100-150 µg/L iodine) may be inadequate for iodine deplete regions or was in a form that did not permit satisfactory absorption. The babies in our cohort were sampled from 6 weeks so that feeding would be in the established phase and suggests no disadvantage for the formula fed group. Although the content of iodine in formula feeds have not changed significantly in the intervening years, other changes to the formula may have had a positive impact on absorption.

Strengths of our study include the large sample size including offspring along with dietary information. Weaknesses include recruitment in only one centre, although this is the largest maternity unit in NI serving 25% of all the births in the region. The higher than expected rate of reported planned pregnancy and use of iodine containing supplements at booking may also underestimate the underlying scale of iodine deficiency in our population.

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291 **Conclusions**

292 This cohort of pregnant women living in Northern Ireland are iodine deficient across
293 pregnancy and into the post-partum period, while the offspring are iodine sufficient
294 when feeding is established. The UK does not provide an iodine fortification
295 program nor offer routine iodine dietary or supplement advice in pregnancy and this
296 requires consideration by public health agencies.

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421 Table 1 Baseline Characteristics

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Baseline characteristics (n)	
Age (241)	Mean 30.3 years (SD 5.4)
Body Mass Index kg/m ² (224)	Mean 26.2 kg/m ² (SD 4.9)
Height cm (224)	Mean 163.7 cm (SD 6.5)
Weight kg (224)	Mean 70.1 kg (SD 13.9)
Occupation	
- Higher (92)	41.4%
- Intermediate (53)	23.9%
- Lower/UE/ill-defined (77)	34.7%
Deprivation Scores	
- 1 (Most affluent) (61)	25%
-2 (48)	20%
-3 (31)	13%
-4 (18)	8%
- 5 (Most deprived) (83)	34%
Smoking	
- Never (214)	88.8%
- Current (25)	10.4%
- Ex-smoker (2)	0.8%
Ethnicity	
- White Caucasian (238)	98.8%
- Black African (2)	0.8%
- Indian (1)	0.4%
Previous pregnancy	
- 0 (114)	47.3%
- 1-2 (106)	44.0%
- >2 (21)	8.7%
Previous miscarriage	
- Yes (74)	30.7%
- No (167)	69.3%
Planned pregnancy	
- Yes (189)	78.4%
- No (52)	21.6%

Diet		448
- Normal (225)	93.4%	449
- Vegetarian (6)	2.5%	
- Gluten free (6)	2.5%	450
- Other	1.6%	451
Nausea		452
- Yes (179)	79.2%	453
- No (47)	20.8%	454
Ongoing vomiting		
- Yes (65)	27.0%	455
- No (160)	66.4%	456
Family history of thyroid disease		457
- Yes (51)	21.2%	
- No (170)	70.5%	458
Iodine containing multivitamin		459
- Yes (127)	52.7%	460
- No (105)	43.6%	461
Season		
- Winter (151)	62.7%	462
- Summer (90)	37.3%	463

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Table 2: Trimester specific and offspring median UIC and ICR

Trimester	Number of samples	Median UIC µg/L (IQR)	Median ICR µg/g creatinine (IQR)
First (<14 weeks)	217	72.6 (36.7-122.4)	116.4 (71.0 – 216.2)
Second (18-22 weeks)	134	94.2 (53.0-173.8)	147.2 (93.7 – 252.5)
Third (28-32 weeks)	153	116.7 (62.9 – 194.7)	149.9 (94.2 – 237.0)
Postpartum (6 weeks-6 months)	88	89.7 (52.2-152.5)	60.2 (32.6-92.4)
Baby breastfed (at least partially)	49	146.2 (103.4-202.3)	
Baby formula fed	31	156.5 (102.9-247.0)	

Abbreviations: UIC- urinary iodine concentration; IQR- interquartile range; ICR- iodine: creatinine ratio

478 Table 3: First trimester associations between ICR and dietary habits derived from
 479 food frequency questionnaires

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Food group	% of cohort	ICR Mean (SD)	p value
Milk daily ml (n=197)			
- None	8	66.4 (1.7)	
- < 140	28	107.4 (2.1)	
- 140 – 279	30	126.0 (2.4)	
- 280 – 424	19	157.0 (2.2)	
- >425	15	147.2 (2.1)	0.002*
Full fat yoghurt (n=192)			
- Never or <1/month	59	113.1 (2.2)	
- 1/ week - fortnight	20	111.0 (2.3)	
- 2-3 times/week	12	209.5 (2.2)	
- ≥4 /week	9	146.7 (1.9)	0.004*
White fish (n=194)			
- Never or <1/month	51	104.3 (2.2)	
- 1/ fortnight	20	131.0 (2.1)	
- 1/ week	29	152.7 (2.2)	
- 2-3 times/week	2	118.1 (2.3)	0.036*
Eggs weekly (n=197)			
- 0	16	95.8 (2.0)	
- 1-2	53	121.7 (2.3)	
- 3- 4	26	128.7 (2.1)	
- >4	7	177.8 (2.7)	0.100

481 Mean value back transformed; ICR compared between frequency groups using one-way analysis
 482 of variance

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Table 4: Comparison of comparable iodine surveys of the British Isles (UK and Rep of Ireland)

	Year	No.	Trim.	mUIC	mICR	Milk Intake assoc	I Supp	Offspring UIC µg/L
SW England ⁵	1991-2	1040	1 st	91	110	-	0%	-
Rep of Ireland ¹⁶	1997	79 67 83 108 122	1 st 2 nd 3 rd PP* PP**	135 124 122 67 74	-	-	0%	n=108* -Breast: 100 -Formula: 43
NE England ¹⁷	2000-1	227	1 st	40% “borderline”		-	n/a	-
Wales ¹⁸	2002-6	383	1 st	117	-	-	n/a	-
Rep of Ireland ³	2004-5	54	1 st	45-68	-	-	n/a	-
SE England ¹⁴	2009	100	1 st	85	123	yes	42%	-
S England ¹⁹	2009-11	230	1 st 2 nd 3 rd	42 52 69	102 120 126	yes	3%	-
N Ireland Current	2014-5	217 134 153 88	1 st 2 nd 3 rd PP***	73 94 118 90	116 147 150 60	yes	53%	n=80*** Breast: 149 Formula:144

Trim-Trimester; mUIC- median urinary iodine concentration (Pregnant sufficiency≥150 µg/L; Not Pregnant ≥ 100 µg/L) ; mICR-median iodine: creatinine ratio (Pregnant sufficiency ≥150 µg/g creatinine); I Supp– iodine supplement; 3d= 3 days postpartum

* Postpartum 3 days; ** 6weeks; ***6 weeks to 6months

495 Figure: Proportion of cohort with sufficient Urinary Iodine Concentration (UIC) $\geq$
496 150 $\mu\text{g/L}$ in each trimester
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