Costs and benefits of iodine supplementation for pregnant women in a mildly to moderately iodine-deficient population

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Iodine, IQ and Income: Exploring the potential costs and benefits of iodine supplementation for pregnant women in a mildly/moderately iodine deficient population.

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Summary

Background: The cognitive ability of an unborn baby may be irreversibly damaged as a result of their mother's mild iodine deficiency during pregnancy. A lower IQ has broad economic and societal cost implications as intelligence affects wellbeing, income, and educational outcomes. Despite pregnancy and lactation leading to increased iodine requirements, no UK recommendations on iodine supplementation have been issued to pregnant women. This paper seeks to highlight to public health policy makers the potentially large societal benefits of an iodine supplementation strategy. We explored the cost-effectiveness of iodine supplementation versus no supplementation for pregnant women in a mild to moderately iodine deficient population in which a population based iodine supplementation programme, for example universal salt iodisation, does not exist.

Methods: A systematic search of the economic literature that linked IQ and income was undertaken. Clinical data relating to iodine supplementation and IQ impact were taken from primary research. A decision tree was developed to compare the treatment strategies of iodine supplementation versus no iodine supplementation for pregnant women in a UK setting. Data supported assumptions were required to complete the analysis but the approach adopted was to limit the benefits of iodine supplementation and over-estimate its potential harms. The analysis was carried out from health service and societal perspectives and presented in terms of cost per IQ point gained.

Findings: In the preliminary model, iodine supplementation was cost saving from both health service (saving £199 per woman) and societal perspectives (saving £4,476 per woman) with a net gain of 1·22 IQ points. Base case results were robust to sensitivity analysis.

Interpretation: Iodine supplementation to pregnant women in a UK setting is potentially cost saving. This has implications for the 1·88 billion population in the 32 countries with iodine deficiency. Valuation of IQ points should factor in non-earnings benefits also. Limitations include lack of randomised controlled trial evidence of the effect of iodine supplementation on IQ and pregnancy complications in mildly iodine deficient populations.

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Introduction

Severe iodine deficiency in pregnancy is linked to impaired neurodevelopment of the unborn child, manifesting in a permanent loss of Intelligence Quotient (IQ) points and cretinism in some children.[1,2] A systematic review of iodisation programmes and trials in China reported an 8·7 (95% confidence interval 6·3 to 11·1) IQ point difference in children born to mothers in severely deficient regions with and without iodine supplementation during pregnancy and after birth.[2] However, there is strong evidence that this cognitive impairment is prevented by iodine supplementation in pregnancy.[1,2] While the cognitive consequences of *severe* iodine deficiency in pregnant women are established, the effect on mild iodine deficiency is less clear.[3] In two cohort studies in the UK and Australia, nine year old children of women who had a urinary iodine concentration suggestive of mild iodine deficiency during their pregnancy exhibited reduced educational outcomes[4] and decreased IQ scores[5] compared to children of iodine replete mothers. In contrast, a large Spanish cohort study, which undertook cognitive assessment of infants at a median age of 16 months, did not report a significant association between iodine supplementation and cognitive outcomes.[6]

The UK is one of a shrinking number of countries not to have adopted any iodine fortification of food or salt and it is now believed to have become mildly iodine deficient.[7] At present, no national guidance on iodine supplementation has been issued to pregnant women, even though pregnancy and lactation lead to increased iodine requirements.[8,9]

A lower IQ in infancy has broad future economic societal costs as cognitive development has effects on health outcomes, educational attainment, and lifetime earnings. A lower IQ is associated with a higher rate of mortality,[10] a higher risk of suicide,[11] psychiatric illness[12,13] and higher incidence of heart disease.[14,15] A higher IQ is postulated to have a positive effect on an individual's health improving behaviour [16] and those with higher childhood IQ scores are significantly more likely to have higher educational attainment and earnings by the age of 25.[17]

In this paper we report the results of a model-based economic evaluation using the best available data from existing published literature, a systematic literature search and expert clinical input. Because of the need for data supported assumptions to complete the analysis, the approach adopted was to limit the benefits of iodine supplementation and over-estimate its potential harms as far as possible. The objective of the economic evaluation is to compare the costs and benefits of a strategy of iodine supplementation for pregnant women in a mild to moderately iodine deficient population against no iodine supplementation.

Methods

Model Structure

A decision tree model was developed in TreeAgePro 2014 (TreeAge Software, Williamstown, MA) to represent two alternative strategies, iodine supplementation versus no iodine supplementation. The model pathways (see Figure 1) represent the alternative clinical pathways undertaken by pregnant women.

Clinical Data required for the model

Parameter values and their respective sources are listed in Table 1. Data for the probability of a pregnant woman in the UK being iodine deficient is based on the only UK data and refers to a selective cohort of women. The proportion of pregnant women in each iodine status category (mild/moderate (median urinary iodine concentration (UIC) of 50 to 149 µg/l) and severe (UIC<50 µg/l)) and the subsequent impact on a child's IQ were based on this cohort study which examined the association between iodine status during the first trimester of pregnancy and the IQ levels of their children at age nine.[5]

Cost data required for the model

The cost of iodine tablets is based on the cost of local supermarket multivitamin tablets for pregnant women (£3·50 for 30 tablets typically containing 140 or 150 µg of iodine).[19] A daily dose of 150 µg of iodine is recommended by the American Thyroid Association[20] and European Thyroid Association[21] for euthyroid pregnant and lactating women. Annual incremental health & services costs and public sector costs including education by a child's IQ category are taken from a study that looked at the costs associated with neurological impairment during the children's 11th year.[22] The incremental childhood cost of preterm birth and the healthcare cost associated with stillbirth are taken from published sources.[23, 24] Costs are discounted at the standard annual rate of 3·5%[25] and updated to 2013 prices using a subset of the Consumer Price Index covering price inflation in education, health and social protection.[26] Public sector costs included in the model consist of health and social services costs, and education costs.

Assumptions

The economic evaluation required a monetary value for an IQ point and this was determined through an additional systematic search of the literature carried out by the current authors which is reported in Appendix 1.

To complete the analysis some pragmatic assumptions were required informed by the literature and expert opinion. As far as possible, assumptions were conservative and in the direction that ensured the strategy of iodine supplementation would not be advantaged. Panel 1 & 2 lists our model assumptions.

Panel 1: Model Assumptions relating to the Women

- Women take daily iodine tablets 13 weeks pre-pregnancy, throughout pregnancy and an additional 26 weeks whilst breastfeeding. Cessation of iodine tablets occurs at the end of the lactation period or if there is a pregnancy loss event.
- Iodine supplementation will only benefit women who were iodine deficient pre-supplementation.
- All iodine deficient women will be iodine replete with supplementation and they adhere to taking the daily supplementation.
- IQ gains will be different depending on the severity of iodine deficiency pre-supplementation; the pre-supplementation iodine deficient women were sub classified into severe and mild/moderate iodine deficient categories (see Table 1).
- All pregnancies are singleton.

Panel 2: Model Assumptions relating to the Pregnancy Losses and Complications

- Women with early pregnancy losses take daily tablets for 23 weeks on average and women with late pregnancy loss take tablets for 47 weeks on average (these both include the 13 weeks of taking the iodine tablets pre pregnancy).
- 0·25%[27] of women of reproductive age suffer adverse thyroid dysfunction as a result of the iodine supplementation. In the absence of existing evidence, the type of thyroid dysfunction, precipitated by the iodine supplementation, in the population are split evenly into four following groups:
    - Overt Hyperthyroidism (undetectable thyroid-stimulating hormone (TSH) with raised free thyroxine (fT4))
    - Overt Hypothyroidism (elevated TSH with low fT4)
    - Subclinical Hypothyroidism (elevated TSH with normal fT4)
    - Isolated Hypothyroxinemia (normal TSH with low fT4)
- None of the thyroid dysfunctions were diagnosed and treated.
- There is an increased incidence of pregnancy losses and complications for each type of thyroid dysfunction caused by iodine supplementation. Only pregnancy complications incurring significant costs (pre-eclampsia, preterm birth before 37 completed weeks of gestation, and stillbirth loss after 24 completed weeks of gestation) are used in the model.
- While pre-eclampsia and preterm births often occur together, they are separate events in the model.
- The infants whose mothers suffered from overt and subclinical hypothyroidism, during pregnancy suffer from losses of cognition of 7 IQ points.[18] Based on equivalent neurodevelopmental test scores,[28] this is also assumed for infants whose mothers suffered Isolated Hypothyroxinemia during pregnancy. This assumption relates to the hypothyroidism that is induced by iodine supplementation in a small minority of women and in this case is not related to iodine deficiency.
- There is no gain in IQ for the children of mothers with the adverse thyroid dysfunction from iodine supplementation who were iodine deficient pre supplementation.

We carried out two separate analyses each adopting a different perspective. In the first analysis (Analysis 1) a Health Service perspective was adopted in which direct health service costs are considered. Analysis 2 considered a societal perspective which additionally takes into account education costs and the value of an IQ point itself.

For both analyses, we assumed IQ follows the conventional normal distribution with a mean of 100 and a standard deviation of 15. We used z tables to calculate the reduction in the proportion of children in the lower IQ categories as a result of iodine supplementation (see Appendix 3). The present value health and social services costs for the first sixteen years of life are calculated for children with a mild neurodevelopmental impairment (IQ scores of 82-92). This is also calculated for children with a moderate/severe neurodevelopmental disability (IQ scores of 81 and below), but with an additional cost of special education. These costs savings are then adjusted for survivors using UK life tables.[29]

The monetary value of an IQ point (Analysis 2 only) was identified by the systematic search carried out as part of this study (see Appendix 1).

Analysis 1 and 2 are both presented in terms of their disaggregated cost and outcomes in the form of a cost consequence analysis and IQ points gained are reported as natural units.

Sensitivity analysis

To investigate the robustness of the base case results we carried out a comprehensive sensitivity analysis in which the main motivation was to further disadvantage the effect of iodine supplementation in the model and assess the impact on the results (see Appendix 2 for details). The majority of the changes explored, for both Analysis 1 and 2, were arbitrary where, for example, any gains as a result of iodine supplementation were halved and any detrimental effects as a result of the supplementation were doubled. A probabilistic sensitivity analysis (PSA) is not appropriate in this case since we are already using estimates for the worst case scenario rather than using central mean estimates.

Role of funding source

No external funding source supported this project. All authors were employed by the University of Birmingham and carried out this work within their existing research work portfolios.

Results

The systematic search (see Appendix 1) showed that most of the studies valued an IQ point based on its effect on an individual's income. The issue of differences in scaling of IQ tests hindered the comparability across studies. The value of an IQ point, derived from the systematic search and applied to the unborn cohort, comes from the lifetime earnings premium of an additional IQ point. This is calculated to be £3297 (after adjustment with life tables).

Findings are presented in Table 2. Under base case assumptions, the results of both analyses show that the iodine supplementation strategy dominated (less costly and more effective) compared to no supplementation. Taking the NHS perspective where only health related costs were considered (Analysis 1), iodine supplementation was cost saving with an expected positive Net Present Value of £199 per expectant mother and an increase of an average 1·22 IQ points for the unborn infants. Taking a societal perspective (Analysis 2), iodine supplementation was cost saving with an expected positive Net Present Value of £4476 per expectant mother and an increase of an average 1·22 IQ points for the unborn infants.

The pregnant women for whom thyroid dysfunction was precipitated by iodine supplementation would have to each incur an average cost of over £91000 to negate the overall benefits arising from the iodine deficient pregnant women without thyroid dysfunction taking iodine supplementation in the model from the NHS perspective alone.

The sensitivity analysis supported the cost saving indication of base case results. Iodine supplementation remained cost saving in all the sensitivity scenarios undertaken with one exception: In Analysis 1 (health service perspective) where we assumed zero IQ gain for children of the previously mildly/ moderately iodine deficient mothers, the results suggested an additional cost of £42 per expectant mother for a gain of 0·17 IQ points for the unborn infants.

Discussion

This is the first study to estimate the cost-effectiveness of a policy of iodine supplementation during pregnancy and lactation in a population with mild iodine deficiency. The analyses showed iodine supplementation saved money and improved IQ. The results were supported by all the sensitivity analysis scenarios bar the most extreme scenario, in which supplementation of mildly iodine deficient children did not affect IQ.A key strength of the analysis was the use of very conservative assumptions to limit the benefits of iodine supplementation and potentially overestimate adverse outcomes arising from supplementation. Given the preliminary work for this study had shown that iodine in pregnancy was unequivocally cost saving, the objective of the analysis reported here was to explore the robustness of this indication by solely focussing on the worst case possible.

The monetary value of an IQ point used was also intentionally conservative and excluded voluntary work and any earnings that happen after the UK retirement age. These potentially act to underestimate the true monetary value associated with an additional IQ point. The IQ earnings premium used in the model is based on an estimate from a US study in which earnings came from the years 1974 and 1990. In today's technologically driven high skill economy, the earnings benefit from an additional IQ point may be more valuable for a worker than in previous decades.

Health and public sector costs relating to childhood neurological impairment were taken from a study which collected incremental costs over a one year period during mid-childhood.[23] The model assumed that these annual costs are the same for each year of childhood when in reality they are very likely to vary. Excluding these costs in the 'societal perspective' sensitivity analysis did not change the direction of the results. No account has been made of public sector savings resulting from IQ improvement at the upper end of the IQ scale.

For the present value of lifetime earnings, a real wage growth of 1% per year in the future was assumed.[30] However, the sensitivity analysis also considered a zero real wage growth scenario. This did not prevent the iodine supplementation intervention from remaining cost saving.

There are a number of limitations to this study. First, there is the argument that if the majority of the IQ gains will provide an absolute shift in the population IQ distribution, the relative IQ differences remain largely unchanged, negating most of the earnings advantages stemming for the gains in IQ points for workers. A possible response to this is that in general economies compete at a global level and the addition of a more intelligent workforce in the future should help with productivity linked earnings gains. Second, some women may already take supplementation, which would mean that the overall modelled benefits might be overstated, but the analysis sought to highlight the benefits of iodine supplementation to an individual compared to no supplementation.

The sensitivity analysis considered using a person's willingness to pay for an additional IQ point instead of the monetary value of an IQ point derived from earnings. This was done to allay any concerns about using earnings as a basis for the value of an IQ point. However, when the monetary value of an IQ point is excluded (NHS perspective), the result showed iodine supplementation was still cost saving.

A further possible weakness of the analysis is that there is no identification of iodine status at an individual level for the pregnant women and therefore, some wastage occurs when iodine sufficient women receive unnecessary supplementation. However, iodine supplementation for iodine replete expectant mothers with normal thyroid function is likely not to cause any harm in the vast majority of pregnancies; despite our assumptions of harm in our model, there has been no evidence thus far to suggest iodine supplementation induces thyroid dysfunction in pregnancy. Indeed, iodine is included in some proprietary pregnancy supplements. However, there has been some evidence of induction of thyroid dysfunction in the non-pregnant population.[27] Severe iodine deficiency has been associated with increases in pregnancy loss and complications; rectifying the iodine status of mildly/moderately iodine deficient women is likely to decrease rather than increase pregnancy loss although no studies have investigated this thus far. There is at present no acceptable test for assessment of individual iodine status, only tests for assessing population iodine status which involves urine collections from a large sample size, which are both cumbersome and costly. Furthermore the testing required for a targeted programme also causes delay when the evidence suggests the benefits are increased with earlier treatment.[31]

The limitations in the analysis relate to the limitations in the evidence. Whilst the evidence for the benefit of iodine supplementation in populations who are severely iodine deficient is clear,[1,2] the evidence of benefit in mildly iodine deficient populations has not been established.[3] Two of the three prospective studies of iodine supplementation in women from mildly iodine deficient areas have shown improvements in child cognition, but these are limited by a lack of randomisation, risk of bias and small sample sizes.[32,33] A large cohort study, with relatively short follow-up, provides evidence of potential harm;[6] maternal consumption of 150 μg/day or more of iodine from supplements was related to a 1·7-fold increase (95% confidence interval 0·9 to 3·0) in the odds of a child's mental scale score being less than 85 derived from the Bayley Scales of Infant Development test, but this was not statistically significant. We based the IQ gains on an observational study which was a cohort study comprising relatively highly educated older women.[5] This is a major limitation, but is the most robust information available in the absence of high quality experimental evidence. Although systematic reviews exist, none of them provide an IQ change in a mildly iodine deficient non-supplemented population.[2,3,34,35]

The use of different IQ tests across studies raises the question of the comparability of findings. Bath and colleagues[5] used the abbreviated form of the Wechsler Intelligence Scale for Children (WISC-IIIUK). The base case estimate, taken from the study by Zax and Rees,[36] used the Henmon-Nelson Test of Mental Ability. Since these two intelligence tests are not perfectly correlated, an individual may get a slightly different IQ score from each test. We explored this in the sensitivity analysis by modifying IQ gains and the results remained cost saving with one exception which was based on an extreme scenario.

In the absence of randomised controlled trial evidence, our model results strengthen the case for universal iodine supplementation - preconception, during pregnancy and lactation in mildly/moderately iodine deficient populations. We only considered iodine supplementation via tablets. Fortification of food with iodine is another way of attaining iodine sufficiency. However, food fortification alone may not be enough to achieve iodine sufficiency for pregnant women.[37]

Our findings have important implications worldwide. Thirty-two countries have mild or moderate iodine deficiency identified from surveys of the iodine status of school aged children.[38] These countries have a population of 1·88 billion and 241 million school aged children, thus the potential effects of introducing iodine supplementation in pregnancy could be substantial. The use of urinary iodine of school aged children to estimate the iodine status of pregnant women is likely to underestimate the prevalence of iodine deficiency during pregnancy.[39,40] Lower urinary iodine levels have been identified in pregnant women compared to school aged children, possibly due to a higher consumption of milk in children.[39] In addition, pregnant women have an increased iodine requirement.[41]

A randomised controlled trial (RCT) would provide the most robust evidence on which to base policy, however, such a study would require costly child developmental assessments. An RCT with iodine deficient pregnant mothers taking placebo iodine tablets has been described as unethical[9] given iodine supplementation in pregnancy is already recommended by many National and International bodies including the World Health Organization.[8] Based on the best available current evidence this study highlights the cost-effectiveness of an iodine supplementation strategy for pregnancy in the UK.

Contributors

TR and KJ had the idea for the study and designed the study. KJ was responsible for groundwork that led to the study being planned. KJ, KB and SC provided clinical data used in the model based analysis and clinical interpretation. MM carried out the literature review (Appendix 1) and the model based analysis and interpreted the results under the supervision of TR. PB provided advice on use of data and modelling techniques. MM and TR wrote the first draft. All authors commented on all drafts of the study. TR is the guarantor for the study.

Conflicts of Interest

KJ reports she is a member of the UK Iodine Group. All other authors declare that they have no conflicts of interest.

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Research in context

Evidence before this study

The UK is amongst 32 countries worldwide with evidence of iodine deficiency. Severe iodine deficiency during pregnancy is associated with a lower intelligence quotient (IQ) and developmental abnormalities in the children. These are reversible by iodine supplementation during pregnancy. The effects of mild or moderate iodine deficiency during pregnancy are less clear as there are no good randomised controlled trials of supplementation that have reported the outcome of child IQ. However, in two cohort studies in the UK and Australia, nine year old children of women who had a urinary iodine concentration suggestive of mild iodine deficiency during their pregnancy exhibited reduced educational outcomes and decreased IQ scores compared to children of iodine replete mothers. Controversy about the need for supplementation in pregnancy, the ethics of undertaking an RCT and the high cost of following-up and assessing large numbers of children makes a trial unlikely.

What this study adds

Using an economic model of best available evidence and using assumptions that do not favour iodine supplementation, we found that universal iodine supplementation pre-pregnancy and during pregnancy and lactation, would increase the child's IQ by 1·22 points, save the NHS and society £199 and £4476 per pregnant woman respectively.

Implications of all the available evidence

Current available evidence suggests that a policy of iodine supplementation during pregnancy would be beneficial.

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