OUTCOME OF PREGNANCY AFTER EXPOSURE TO RADIOIODINE IN UTERO

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ABSTRACT

Objective: Radioiodine (\(^{131}\)I) therapy is absolutely contraindicated in pregnancy yet reports of inadvertent exposure continue to appear in the literature. In this review, we discuss the risks of fetal exposure and prevention strategies in the light of current guidelines.

Methods: We performed a literature search on MEDLINE using the terms radioiodine, I-131, toxicity, complications and pregnancy and chose the most relevant studies for this review.

Results: Before implantation, the major concern is miscarriage and death of the embryo above a radiation threshold of 100mGy (10 rads). Exposure to \(^{131}\)I at this very early stage of pregnancy is unlikely to result in major malformations or thyroid dysfunction in surviving embryos. Exposure later in pregnancy i.e. during thyroidogenesis (from 10 weeks gestation) and organogenesis (from 2 weeks gestation) at similar radiation thresholds may result in fetal thyroid ablation, birth defects and in later life, growth retardation and reduction in IQ. In addition to these deterministic effects, radiation at any dose may increase the risk of cancer (stochastic effect) and recent evidence indicates an increased risk of thyroid cancer many years after in utero exposure.

Conclusions: Clinicians treating women of child-bearing age with radioiodine need to be aware of the risks of fetal exposure to radioiodine and take all measures to avoid inadvertent exposure during pregnancy.
INTRODUCTION

Radioiodine ($^{131\text{I}}$) has been successfully employed for the treatment of benign and malignant thyroid disease for more than 50 years but must be strictly avoided in pregnancy because of detrimental effects on the developing fetus. Inadvertent exposure during pregnancy may occur because pregnancy testing was not carried out or was falsely reassuring. This inadvertent exposure is most likely in the first trimester, the crucial period of organogenesis, when the patient does not yet realize she is pregnant. It then becomes necessary to quantify the absorbed dose to the fetus in order to estimate the potential health risks and advise the mother appropriately. The gestational age at the time of exposure and the radiation dose are important determinants of potential harm to the fetus. This review will consider the risks of harm to the developing fetus after $^{131\text{I}}$ exposure in utero. Potential risks to the mother have been reviewed previously (1).

ESTIMATING THE ABSORBED FETAL $^{131\text{I}}$ DOSE

The dose to the developing embryo or fetus resulting from inadvertent radioiodine administration during early pregnancy can vary considerably. The fetus is exposed to radiation from $^{131\text{I}}$ circulating in the mother’s blood, transit of radioiodine through the urinary and gastro-intestinal tract and from uptake in thyroid tissue. The absorbed dose by the fetus is not only dependant upon the activity of radioactivity administered but also on uptake and distribution of isotope which varies with gestational age. If radioiodine is administered for hyperthyroidism in the first 8 weeks following conception the fetal whole body dose would be in the range of 0.048mGy/MBq to 0.083mGy/MBq (0.18rad/mCi to 0.31rad/mCi) depending on the model assumptions (2). So for a typical 400MBq (10.8mCi) administration the resulting fetal dose would be 19 -33mGy (1.9- 3.3 rads). The model assumes normal renal function; patients with renal impairment will have reduced $^{131\text{I}}$ clearance and higher thyroid uptake (2).

Berg et al 2008 (3) reported two cases where radioiodine was given during the 20th gestational week. In the first case 500MBq (13.5mCi) was administered as treatment for hyperthyroidism and resulted in a fetal whole body dose of 100mGy (10 rads) and a fetal thyroid dose of 600mGy (60 rads). The baby was alive and well apart from complete absence of thyroid function. In the second case 3700MBq (100mCi) was administered for thyroid cancer. The dose to the fetal thyroid was also estimated to be 600mGy (60 rads); in this case the fetus did not survive, most likely due to a combination of recent anaesthesia, hypothyroidism prior to the radioiodine and the administered radiation dose. It should be noted that the lethal dose to the fetus is based upon the total fetal exposure rather than the higher absorbed dose to the fetal thyroid.

The risks to the developing fetus based on the estimated absorbed dose are summarised in Table 1 using data contained in the International Commission on Radiological Protection (ICRP) Publication 90 (4). Fetal risks before implantation are based exclusively on animal studies as there is no human data available. Risks at 8-15 weeks post-conception are based on data derived from Japanese atomic bomb survivors and are consistent with animal studies. The risks pertaining to the various stages of development are outlined in greater detail below although it must be emphasised that the likelihood of these effects is still uncertain. The potential risk of radiation-induced harm from exposures of 10 mGy (1 rad) in the first trimester is estimated at 0-1 cases per 1000 (5).
FETAL RISKS

1. Pre-implantation exposure (up to 2 weeks following conception)

The very early embryo is made up of only a few cells which are not yet specialised. Radiation damage to a critical number of progenitor cells at this stage will result in failure to implant, miscarriage and death of the embryo (6). If the embryo survives, however, it is unlikely to be malformed as organogenesis has not yet commenced. Thus there have been no reports of birth defects in children born to mothers who received $^{131}$I before the 10th week of pregnancy (7) and good outcomes after unintentional exposure have been reported (8). The fetal thyroid will not be affected from exposures prior to the 10th week of gestation (see below).

Management
It is recommended that physicians managing patients inadvertently exposed to $^{131}$I consult with experts in radiation dosimetry about fetal dose estimation. This will usually be the hospital medical physicist (Medical Physics Expert, MPE). Detailed information for assessing fetal doses from medical exposures are available from the International Commission on Radiological Protection (ICRP) and other authorities will provide assistance including in the US; the Conference of Radiation Control Program Directors (CRCPD), the Health Physics Society (HPS), and in UK; Administration of Radioactive Substances Advisory Committee (ARSAC).

There are minimal risks if the estimated exposure to the embryo or fetus is <50 mGy (5 rads) (see Table 1). Absorbed doses of 50-500 mGy (5-50 rads) may increase the risk of failure to implant slightly. Greater doses will result in larger risks of embryonic death but those that survive will probably have no significant adverse effects. Based on animal studies, the lethal dose resulting in the death of 50% of embryos ($LD_{50}$) is 1 Gy (100 rads) (4); see Table 1. Mothers can be reassured that if their pregnancies persist, the outcome is likely to be good.

2. Exposure during thyroid development

Radioiodine readily crosses the placenta and will be concentrated in the fetal thyroid from approximately 10-11 weeks after conception (9). This corresponds to the time the developing thyroid starts to synthesize thyroid hormones. Administration of activities of 550 MBq (15 mCi) or less at 10 weeks of gestation appears not to severely affect fetal thyroid function (10). Activities higher than this after 10 weeks are likely to result in ablation of the infant’s thyroid gland causing fetal hypothyroidism (3,11).

Management
The advice of the MPE should be sought to estimate the absorbed fetal radiation dose (12). A clear explanation of the consequences of thyroid ablation for the developing fetus and for later life must be provided for the mother and an informed decision taken regarding her wish to continue the pregnancy. Fetal doses of <100mGy (10 rads) which equate to an activity of <500 MBq (13.5mCi) do not justify termination because of radiation exposure (3,13). For patients receiving radioiodine for Graves’ disease, a lethal absorbed total dose of 1 Gy (100 rads) to the fetus would be achieved by a treatment activity of 5GBq (135 mCi) (3). The situation is more
complex for thyroid cancer patients as the absorbed fetal dose will depend on the size of the maternal thyroid remnant, uptake by any metastases and the gestational age of the mother. Activities to achieve a lethal dose to the fetus are likely to be in excess of 5GBq (135 mCi) because of the faster clearance of $^{131}$I in athyroidal patients.

Assuming the pregnancy continues, replacement thyroxine should be started without delay in order that the neonate avoids any impairment of neurological development. Mothers may be started on thyroxine in doses high enough to maintain circulating levels at the high end of the normal range. Even so, transplacental passage of maternal thyroxine may not always be sufficient to maintain normal thyroxine levels in the fetus and the neonate may still be hypothyroid at birth (11).

Potassium iodide given immediately after radioiodine exposure can significantly reduce the fetal thyroid uptake of $^{131}$I (14). This intervention is ineffective if given more than 12 hours after radioiodine administration (15). This treatment should not be prolonged because of the risk of inducing massive fetal goitre.

3. Exposure during organ development

(i) Brain

Radiation can impair the developmental events occurring at the time of exposure. The potential risk depends on the radiation dose absorbed and the sensitivity of the tissue. These deterministic effects occur above a given radiation threshold. Data from atomic bomb survivors indicate that ionising radiation at 8-15 weeks gestation may significantly affect brain development leading to IQ loss or mental retardation (16). The average IQ loss is approximately 25-30 points per Gy (100 rads) above 100 mGy (10 rads). In the 16-25 week stage of gestation, the brain is less sensitive and the average IQ loss is estimated to be 13-20 points per Gy above 700 mGy (70 rads) (17). Beyond about 26 weeks, the fetal brain is less sensitive to radiation exposure. Figurative memory was found to be impaired in a case report of a patient inadvertently exposed to 500 MBq (10.8mCi) $^{131}$I at 20 weeks gestation (3). In addition to the direct radiation effects outlined above, radioiodine-induced hypothyroidism in the fetus (see section 1) or mother may also impair neurodevelopment and may not be evident until years later (18).

(ii) Congenital malformations

The risk of congenital malformation is considered to be minimal after in utero exposures of 50 mGy (5 rad) or less but rises significantly over control levels at doses above 150 mGy (15 rads) (2). The type of malformation is determined by the stage of development at which the radiation occurs.

(iii) Growth

Permanent impairment of physical growth has been noted in atomic bomb survivors with radiation doses above 1 Gy (100 rads) particularly when exposure occurs in the first trimester of pregnancy. This results in a 3-4% reduction in height at aged 18 years for radiation doses greater than 1 Gy (100 rads) (17).

(iv) Thyroid cancer
Whilst $^{131}$I administration to adults is not associated with an increased risk of thyroid cancer, data from the Chernobyl accident suggest that *in utero* exposure may be associated with a small increased risk (19). In a cross-sectional study of 2,582 Ukrainian mothers pregnant at the time of the accident, 7 cases of thyroid carcinoma and 1 case of Hurthle cell cancer were identified amongst the offspring by screening. Estimated odds ratio per gray for thyroid cancer approximately 20 years after the accident was 11.66. No radiation risks were identified for other thyroid diseases.

(v) Other cancers

The probability of radiation-induced cancer effects increase as radiation dose rises but can theoretically occur at any radiation dose and are termed “stochastic” effects. An *in-utero* dose of 100 mGy (10 rads) will significantly increase the risk of cancer (leukaemia and solid tumours) in childhood with a life-time fatal cancer risk estimated at 1-2% (4). However, estimates of lifetime cancer risks are very uncertain.

*Management*

As discussed above, the absorbed radiation dose to the fetus needs to be estimated in conjunction with the MPE in order to assess the potential risks to fetal development. Patients will need counselling based on this information in order to make informed decisions regarding continuation of the pregnancy.

**PREVENTATIVE STRATEGIES**

Prevention relies on excluding pregnancy in women about to receive radioiodine. Strategies for doing so are outlined in current practice guidelines. The American Association of Clinical Endocrinologists (AACE) states “before radioactive iodine treatment, a negative pregnancy test should be obtained in all women of childbearing age, and pregnancy should be postponed after such therapy (20).” The American College of Radiology (ACR) recommends using one of four criteria to exclude pregnancy (21):

1. A negative $\beta$-hCG result obtained within 72 hours prior to administration of the pharmaceutical
2. Documented history of hysterectomy
3. Postmenopausal state with absence of menstrual bleeding for 2 years
4. Premenarche in a child of 10 years or younger

The Society of Nuclear Medicine procedure guideline for therapy of thyroid disease with radioiodine states that females of child-bearing age should routinely be tested for pregnancy *within 72 hours or less* before I-131 treatment (22). However, if the patient’s history clearly indicates that pregnancy is impossible, the treating physician may omit the pregnancy test. In UK, the Royal College of Physicians guidelines on the use of radioiodine simply state “if necessary, a pregnancy test should be performed to confirm that the patient is not pregnant at the time of radioiodine administration (12).” Similar statements appear in the European guidelines (23).

There are important differences in the sensitivity of serum versus urine $\beta$-hCG in the detection of pregnancy and this is not fully taken into account in the guidelines. Typically serum $\beta$-hCG becomes
detectable by 11 days post-conception whereas urine hCG is positive 15-17 days after conception (24,25). Thus urine hCG, the standard pregnancy test, may be falsely negative in a gestation of less than 15 days.

Another approach is to ask the patient to abstain from sexual activity for at least 2 weeks prior to $^{131}$I therapy in order to cover the period before the $\beta$-hCG becomes detectable. This is broadly in line with the recommendation of the Endocrine Society which states “It is considered routine to question women who are potentially fertile about possible pregnancy before administration of any radioisotope, and blood samples for determination of $\beta$–hCG are routinely taken. However, there is an approximate 1-wk interval after fertilization before this test becomes positive, so in addition some therapists suggest abstinence be documented for this interval.” (26) This cautious approach addresses the risk of radiation-induced failure to implant and miscarriage rather than the risk of malformation which will be very low before 10 weeks gestation (see above).

An alternative strategy would be to incorporate the 10 day rule into the current guidelines which only permits radiopharmaceuticals during the 10 days after the onset of the menstrual period (27, 8). However, even this approach is not foolproof in a patient with an irregular menstrual cycle as is often the case in patients with thyroid disease. Nevertheless, the authors believe that for a woman with regular menstrual cycles this is the most practicable approach. This approach relies on the patient providing an accurate menstrual and sexual history. Whatever approach is taken, a full discussion with the patient needs to be undertaken taking account of the risks of malformation and miscarriage. Written consent must be obtained prior to administration of radioiodine and some authorities will include a declaration by the patient that she is definitely not pregnant.

Many patients using contraception will underestimate the risk of failure with these methods and pregnancies may still ensue. (13). Most authorities recommend avoiding conception for six months following radioiodine (12,20,21). This is not based on potential radiation effects in any new pregnancy but rather to be sure that the hyperthyroidism or cancer is well controlled so that if further treatment with radiiodine was needed, the patient would not be pregnant. It is felt that six months is a reasonable time to stabilise the disease. It should be noted that the principle that the absorbed dose to the fetus should not exceed 1 mGy (0.1 rad) could be achieved by avoiding pregnancy for far less than 6 months. The risk resulting from an absorbed dose of 1 mGy (0.1 rad) is approx 1:20,000 and is comparable to that resulting from variations in natural background irradiation.

**SUMMARY**

Fetal exposure to radioiodine before implantation will increase the risk of miscarriage and death of the embryo in a dose-dependent manner, but surviving embryos will probably escape any major malformations or thyroid problems. Exposure during thyroid development, from 10 weeks of gestation onwards, will result in fetal hypothyroidism and fetal thyroid ablation needing lifelong thyroxine replacement. Birth defects may occur when exposure occurs during organogenesis and there is also an increased risk of growth delay and mental retardation later in childhood.

In addition to these deterministic effects, evidence from survivors of the Chernobyl accident who were exposed to $^{131}$I in utero indicates an increased lifetime risk of thyroid cancer and possibly other
cancers. Current guidelines to avoid exposure in pregnancy are not sufficiently explicit and need to incorporate reference to the 10 day rule.

REFERENCES

Table 1: Fetal risks from $^{131}$I exposure in utero

<table>
<thead>
<tr>
<th>Absorbed dose by fetus</th>
<th>Before implantation (up to 2 weeks gestation)*</th>
<th>During organogenesis (2-7 weeks gestation)</th>
<th>During thyroid development (from 10 -12 weeks gestation)**</th>
<th>During fetal development (16 weeks onwards)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.05 –0.5 Gy (5-50 rads)</td>
<td>Slight increase in miscarriage rates</td>
<td>Slight increased risk of malformations Growth retardation possible</td>
<td>Depressed or absent thyroid function at birth</td>
<td>Deterministic effects unlikely but potential stochastic risk for thyroid cancer</td>
</tr>
<tr>
<td>&gt;0.5 Gy (50 rads)</td>
<td>Fetal dose of 1 Gy (100 rads) will kill 50% embryos* Surviving embryos unlikely to have major malformations</td>
<td>Substantial increased risk of major malformations including neurological defects above threshold of 0.1-0.2 Gy (10-20 rads).</td>
<td>Fetal thyroid ablation Dose to fetal thyroid highest during the sixth month of gestation</td>
<td>Miscarriage risk may increase. Birth defects may increase. Growth retardation possible. Reduction in IQ especially at higher doses.</td>
</tr>
</tbody>
</table>

Note: The potential stochastic effects occur at all gestational ages

*Data based on animal studies.
**Fetal risks from 8-15 weeks are based on Japanese atomic bomb survivors and are in agreement with animal studies.