



TITLE: Ionizing Radiation in Pregnant Women: A Review of the Safety and Guidelines

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CONTEXT AND POLICY ISSUES

During pregnancy it is possible that a disease condition may develop or a pre-existing condition may worsen. The incidence of cancer, is estimated to be in 1 in 1000 pregnancies.¹ There is a tendency for periodontal disease to develop or deteriorate possibly as a result of hormone fluctuations during pregnancy.² Cholesdocholithiasis is estimated to occur in up to 12% of pregnant women and may be associated with cholangitis and/or gallstones, both of which may be detrimental for the mother and the fetus.^{3,4} Deep vein thrombosis (DVT) is estimated to cause complications in 1 to 2 of 1000 pregnancies. In such circumstances, diagnostic and therapeutic procedures may need to be performed during pregnancy.

Several medical diagnostic tests and treatment procedures entail the use of ionizing radiation. Examples of these include dental X-rays, chest X-rays, computed tomography (CT) scans, positron emission tomography (PET) scan, fluoroscopy, and nuclear medicine procedures.⁵⁻⁷ When averaged over all individuals, the largest source of medical exposure to ionizing radiation results from chest or limb X-rays and dental X-rays.⁶ Radiation exposure to an individual is estimated to be 0.01 mSv for a dental X-ray, 0.1 mSv for a chest X-ray, 3 mSv for a mammogram and between 5 mSv and 30mSv for a CT scan depending on the area scanned.⁸

Ionizing radiation can cause detrimental effects if not used appropriately. The beneficial effects of ionizing radiation need to be balanced against the risks. During pregnancy the potential detrimental consequences of exposure to ionizing radiation include pregnancy loss, malformation or growth disturbances of the fetus, and carcinogenic effects.⁹ In recent times, concerns regarding the safety of ionizing radiation use have arisen from the increase in volume of medical procedures involving ionizing radiation and the high doses of radiation required in some procedures. There is some debate as to whether pre-operative or pre-procedural pregnancy tests should be universally offered to women of child bearing age who are expected to undergo diagnostic or therapeutic procedures involving ionizing radiation. There is a possibility that an individual at the early stage of pregnancy may not be aware of the pregnancy and may be inadvertently exposed to ionizing radiation from such procedures.

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The purpose of this report is to review the clinical evidence on safety and the evidence based guidelines on the use of ionizing radiation in pregnant women.

RESEARCH QUESTIONS

1. What is the clinical evidence regarding the safety of ionizing radiation in pregnant women?
2. What are the evidence-based guidelines regarding the use of ionizing radiation in pregnant women?

KEY FINDINGS

Four non-randomized studies suggest that overall, in most instances, there were no statistically significant differences in outcomes between the pregnant women exposed to diagnostic or therapeutic procedures involving ionizing radiation compared to those unexposed. However results need to be interpreted with caution considering the limitations of the studies.

The recommendations in the evidence based guidelines regarding the exposure to ionizing radiation during pregnancy were based on low level evidence. During pregnancy the use of diagnostic or therapeutic procedures involving ionizing radiation were not considered unsafe but it was recommended that risks and benefits be weighed and care be taken to minimize exposure to the fetus.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, ECRI, Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies, and guidelines. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2005 and May 11, 2015.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Pregnant women
Intervention	Ionizing radiation (e.g. radiation therapy, diagnostic tests)
Comparator	Alternate ionizing radiation interventions; Active comparators (e.g. non-ionizing radiation diagnostic tests such as magnetic resonance imaging [MRI]); No comparator
Outcomes	Q1: Safety outcomes (maternal and neonatal) Q2: Guidelines and recommendations regarding the use of these interventions
Study Designs	Health technology assessment (HTA), systematic review (SR), meta-analysis (MA), randomized controlled trial (RCT), non-randomized study (NRS) and evidence-based guideline

Exclusion Criteria

Studies were excluded if they did not satisfy the selection criteria, if they were duplicate publications, or were published prior to 2005. Case series and case reports were excluded. Guidelines which were not evidence based, did not adequately describe methods, or did not conduct a systematic review were excluded.

Critical Appraisal of Individual Studies

Critical appraisal of a study was conducted based on an assessment tool appropriate for the particular study design. The Downs and Black checklist¹⁰ was used for non-randomized studies and the AGREE checklist¹¹ was used for guidelines.

For the critical appraisal, a numeric score was not calculated. Instead, the strength and limitations of the study were described narratively.

SUMMARY OF EVIDENCE

Quantity of Research Available

A total of 729 citations were identified in the literature search. Following screening of titles and abstracts, 678 citations were excluded and 51 potentially relevant reports from the electronic search were retrieved for full-text review. Nine potentially relevant publications were retrieved from the grey literature search. Of these 60 potentially relevant articles, 46 publications were excluded for various reasons, while 14 publications met the inclusion criteria and were included in this report. These 14 publications were comprised of four NRSs^{2,12-14} and 10 guideline reports.¹⁵⁻²⁴ Of the 10 guideline reports, two reports^{21,22} were for two versions of the same guideline but the older version²¹ had some additional information regarding methodology, hence both publications were included. Appendix 1 describes the PRISMA flowchart of the study selection.

Summary of Study Characteristics

Characteristics of the included non-randomized studies and guidelines are summarized below and details are provided in Appendix 2 and 3.

Non-randomized studies

Four relevant non randomized studies^{2,12-14} were identified. All were cohort studies that compared pregnant women undergoing procedures involving exposure to ionizing radiation with pregnant women not exposed. Three studies¹²⁻¹⁴ were prospective and one study² was prospective but with some data collected retrospectively. Of the four studies, two studies^{12,13} involved pregnant woman who had been exposed to radiodiagnostic procedures in their first trimester and one study¹⁴ reported outcomes separately for the subgroup who were exposed in their first trimester. Hence outcome data for pregnant women exposed to ionizing radiation during the first semester were available from three studies. One study¹² was published in 2012 from Korea, one study¹³ was published in 2011 from Korea, one study¹⁴ was published in 2009 from Germany and one study² was published in 2007 from the United Kingdom (UK). In the studies, the number of pregnant women varied between 32 and 568 in the exposed groups and between 94 and 6807 in the unexposed groups. The mean or median ages varied between 29 and 32 years. In two studies,^{12,13} the exposed groups were comprised of pregnant women in their first trimester undergoing abdominal or lumbar radio diagnostic procedures,¹² and gastrointestinal radiography.¹³ In the other two studies,^{2,14} the exposed groups were comprised of pregnant women requiring Tc-99m scintigraphy,¹⁴ and dental X-rays.² The outcomes reported included gestational age at birth^{12,13} birth weight,^{2,12-14} preterm birth,^{2,13,14} neonatal complications or malformations,¹²⁻¹⁴ inter-uterine fetal death (IUFD),¹² neonatal intensive care unit (NICU) admission,¹² and termination of pregnancy.¹⁴

Guidelines

Ten publications¹⁵⁻²⁴ of nine relevant evidence based guidelines were identified. For one guideline, two publications^{21,22} were included as some information was also taken from the older publication.²¹ This guideline²² on thromboembolic disease in pregnancy and puerperium was published in 2015 by the Royal College of Obstetricians and Gynaecologists (RCOG), UK and the older version²¹ was published in 2007. One guideline¹⁹ on Hodgkin lymphoma was published in 2014 by the British Committee for Standards in Hematology. One guideline²³ on common breast problems was published in 2013 by the University of Michigan Health System, USA. Two guidelines^{17,24} on endoscopy were published in 2012 with one guideline²⁴ published by the European Society of Digestive Endoscopy (ESGE) and one guideline¹⁷ published by the American Society for Gastrointestinal endoscopy. One guideline¹⁵ on pulmonary embolism in pregnancy was published in 2012 by the American Thoracic Society (ATS). One guideline²⁰ on perioperative evaluation was published by the Brazilian Society of Cardiology in 2011. One guideline¹⁶ on laparoscopy for surgical problems during pregnancy was published in 2011 by the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES). One guideline¹⁸ on thyroid nodules was published in 2010 by the American Association of Clinical Endocrinologist (AACE), the Associazione Medici Endocrinology (AME) and the European Thyroid Association (ETA).

Summary of Critical Appraisal

The strength and limitations of the included non-randomized studies and guidelines are summarized below and details are provided in Appendix 4.

Non-randomized studies

Four relevant non-randomized studies^{2,12-14} were identified. All were prospective cohort studies. In one study,² however, the data on maternal dental history were collected retrospectively (postpartum), using a questionnaire. All four studies stated the objectives and inclusion criteria, described patient characteristics and outcomes and reported *P* values or 95% confidence intervals (CI). Exclusion criteria were mentioned in two studies^{2,12} and not in two studies.^{13,14} Intervention details were lacking in all four studies. In three studies^{2,12,13} it was unclear if there was adequate power to detect a difference and in one study¹⁴ the authors stated that the study had limited statistical power. In three studies¹²⁻¹⁴ the authors stated that there were no conflicts of interest and in one study² there was no mention of conflict of interest. Generalizability was limited as the studies pertained to a specific region in a specific country.

Guidelines

Ten publications¹⁵⁻²⁴ of nine relevant evidence-based guidelines were included. For the guideline with two publications^{21,22} only the most recent version²² will be referenced, though the older publication²¹ was used to identify additional methodological information. For all the guidelines the scope and purpose was stated, a systematic review was conducted, the method of formulation of recommendations was stated and the draft underwent a review process. Four guidelines^{15,19,22,24} were reviewed both internally and externally, three guidelines^{16,17,23} were internally reviewed and it was unclear if they were externally reviewed as well and two guidelines^{18,20} were reviewed but it was unclear if they were reviewed internally and/or externally. In six guidelines^{15,19,20,22-24} the guideline development group included clinicians from relevant areas of expertise depending on the guideline topic and in three guidelines¹⁶⁻¹⁸ the guideline development group included clinicians but their areas of expertise were unclear. Three guidelines^{15,18,20} considered cost implications and six guidelines^{16,17,19,22-24} did not. For all the guidelines, it was unclear if patient input was sought in developing the guidelines.

Summary of Findings

What is the clinical evidence regarding the safety of ionizing radiation in pregnant women?

Four relevant non randomized studies^{2,12-14} were identified. The findings are summarized below and the details are provided in Appendix 5.

Two studies^{12,13} reported on gestational age and birth weight and showed that there were no statistically significant differences between the exposed and unexposed groups (Table 2). One study¹⁴ showed that low birth weight at term was similar in the exposed and unexposed groups (Table 2). One study² showed that the odds of having a term low birth weight was higher in the exposed group compared with the unexposed group however the statistical significance was unclear as the 95% confidence interval (CI) started from one (Table 2). Two studies^{2,13} showed that for preterm birth, there were no statistically significant differences between the exposed and unexposed groups and in one study¹⁴ preterm birth was numerically higher in the unexposed group compared with the exposed group however the statistical significance of the difference

was not reported (Table 2). Three studies¹²⁻¹⁴ showed that with respect to malformation there was no statistically significant difference between the exposed and unexposed groups (Table 2). Besides the two studies^{12,13} which involved pregnant women exposed to radiodiagnostic procedures during the first trimester, a third study¹⁴ also reported on a subgroup exposed during the first trimester and showed that there was no statistically significant difference in birth defects between the exposed and unexposed groups (Odds ratio [OR] 0.75; 95% confidence interval [95% CI] 0.27 to 1.84). One study¹² showed that interuterine fetal death (IUFD) and admission to neonatal intensive care unit (NICU) were higher in the exposed group compared with the unexposed group, however the difference was not statistically significant (OR [95% CI] 4.7 [0.3 to 75.7], $P = 0.32$ for IUFD and 2.9 [1.0 to 9.4], $P = 0.06$ for NICU admission). In one study¹⁴ the elective termination of pregnancy was 4.9% in the exposed group and 1.9% in the unexposed group, however the statistical significance was not reported.

Table 2: Comparison of outcomes in pregnant women undergoing procedures involving exposure to ionizing radiation versus pregnant women not exposed

Outcome	Choi, ¹² 2012 ^a	Han, ¹³ 2011 ^a	Schaefer, ¹⁴ 2009	Daniels, ² 2007
Gestational age at birth (weeks)	39.5 vs 39.2 $P = 0.1$	40.7 vs 39.1 $P = 0.2$	NR	NR
Birth weight ^b (g)	3,321 vs 3,301 $P = 0.7$	3,277 vs 3,192 $P = 0.4$	3472 vs 3474 ^c $P = \text{NR}$	OR (95% CI): 1.9 (1.0 to 3.4) ^c
Preterm birth (< 37 weeks)	NR	6.2% vs 6.4% $P = 0.6$	3.8% vs 9.3% $P = \text{NR}$	OR (95% CI): 1.2 (0.8 to 1.8)
Malformation or birth defect	1.9 % vs 0.4% $P = 0.2$	3.1% vs 3.1% $P = 1.0$	OR (95% CI): 0.96 (0.38 to 2.18)	NR
CI = confidence interval, g = gram, NR = not reported, OR = odds ratio, vs = versus				
^a In the study pregnant women in their first trimester were exposed to radio diagnostic procedures				
^b Data indicate mean value unless stated otherwise				
^c Data for term low birth weight				

What are the evidence-based guidelines regarding the use of ionizing radiation in pregnant women?

Nine relevant evidence based guidelines^{15-20,22-24} were identified. They are summarized below and details are provided in Appendix 6.

One guideline²² on thromboembolic disease in pregnancy and puerperium recommended that in case of suspected pulmonary embolism (PE) without signs and symptoms of deep vein thrombosis, a ventilation/ perfusion (V/Q) lung scan or computerized tomography pulmonary angiogram (CTPA) should be conducted and in case of suspected PE and an abnormal chest X-ray, CTPA should take preference over V/Q scan (low level evidence). One guideline¹⁵ on PE in pregnancy, recommended that in case of suspected PE and a normal X-ray, lung scintigraphy should be performed rather than CTPA and if the V/Q scan is non-diagnostic and further testing is necessary, CTPA should be performed (low level evidence). One guideline²⁰ on perioperative evaluation recommended that for pregnant women with heart disease, chest X-rays can be taken, coronary cineangiography can be performed with abdominal protection and myocardial scintigraphy should be avoided. One guideline¹⁶ on laparoscopy for surgical problems during pregnancy recommended that contemporary multi detector CTs, which are associated with low

ionizing dose may be used (moderate level evidence) and administration of radionuclides for diagnostic purposes is general safe for both the mother and the fetus (low level evidence). Two guidelines^{17,24} on endoscopic procedures recommended that therapeutic endoscopic retrograde cholangiopancreatography (ERCP) is relatively safe during pregnancy and that care should be taken to minimize radiation exposure to the fetus and the mother (low level evidence). One guideline²³ regarding common breast problems recommended that for pregnant women imaging is relatively safe and should be generally performed (low level evidence). One guideline¹⁹ on Hodgkin lymphoma recommended that staging investigations in pregnant women should be individualized and fetal radiation exposure should be minimized (low level evidence), and that wherever possible radiation therapy should be postponed until after delivery (moderate level evidence). One guideline¹⁸ on thyroid nodules, recommended that during pregnancy use of radioactive agents for diagnosis or treatment should be avoided and that in women of child bearing age, a pregnancy test should be done before administration of radioactive iodine (moderate level evidence).

Limitations

The studies were non-randomized hence there is potential for selection bias. It was unclear if the studies had adequate power to detect a difference.

Not all outcomes were reported in all the studies and intervention details were lacking, hence comparison across studies was difficult. Details of exposure and the protective measures taken, if any, were lacking hence their effects on outcomes were unclear. It was unclear what dose of ionizing radiation and number of exposures would be considered detrimental. Concomitant medication was used in some studies and unclear if used in other studies hence confounding effects on results cannot be ruled out. Of the two studies that reported on medication use, in one study the usage was described for the exposed group but not for the unexposed group and in one study it was mentioned that medication use data were collected however no details were provided. Since it was unclear if medication use was similar in the two groups, this could result in further confounding. The underlying condition for which diagnostic or therapeutic procedures were required could also impact outcomes. Considering the potential confounders, it is difficult to ascertain to what extent the outcomes can be attributed to ionizing radiation alone. Hence results need to be interpreted with caution.

None of the four studies were conducted in Canada hence it is unclear if the results would be applicable in the Canadian setting. However, two studies were conducted in UK and Germany and the patient population is likely to be comparable to the Canadian population.

Of the nine guidelines, three guidelines focussed specifically on pregnant women and six guidelines were on a broad population with a section on pregnant women. The recommendations regarding the use of diagnostic and therapeutic procedures involving ionizing radiation during pregnancy were based on low level evidence.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

Four relevant non-randomized studies and nine evidence-based guidelines were identified.

Four non-randomized studies suggest that overall in most instances there is no statistically significant difference in outcomes between the pregnant women exposed to ionizing radiation

compared to those unexposed. However results need to be interpreted with caution considering the limitations of the studies.

The evidence based guidelines were for various conditions such as thromboembolic disease, digestive abnormalities, and cancers. Of the nine guidelines, three guidelines focussed specifically on pregnant women and six included a broad population with a section on pregnant women. The recommendations regarding the use of diagnostic and therapeutic procedures involving ionizing radiation during pregnancy were based on low level evidence. Use of diagnostic and therapeutic procedures during pregnancy was not considered unsafe but risk and benefits needed to be weighed and care was recommended to minimize exposure to the fetus. If possible, radiotherapy was recommended to be delayed until after delivery. There were some inconsistencies in the recommendations for the use of radioactive agents in pregnancy; one guideline considered it safe while another guideline recommended avoiding it during pregnancy and recommended conducting a pregnancy test before administering radioactive iodine in women of child bearing age.

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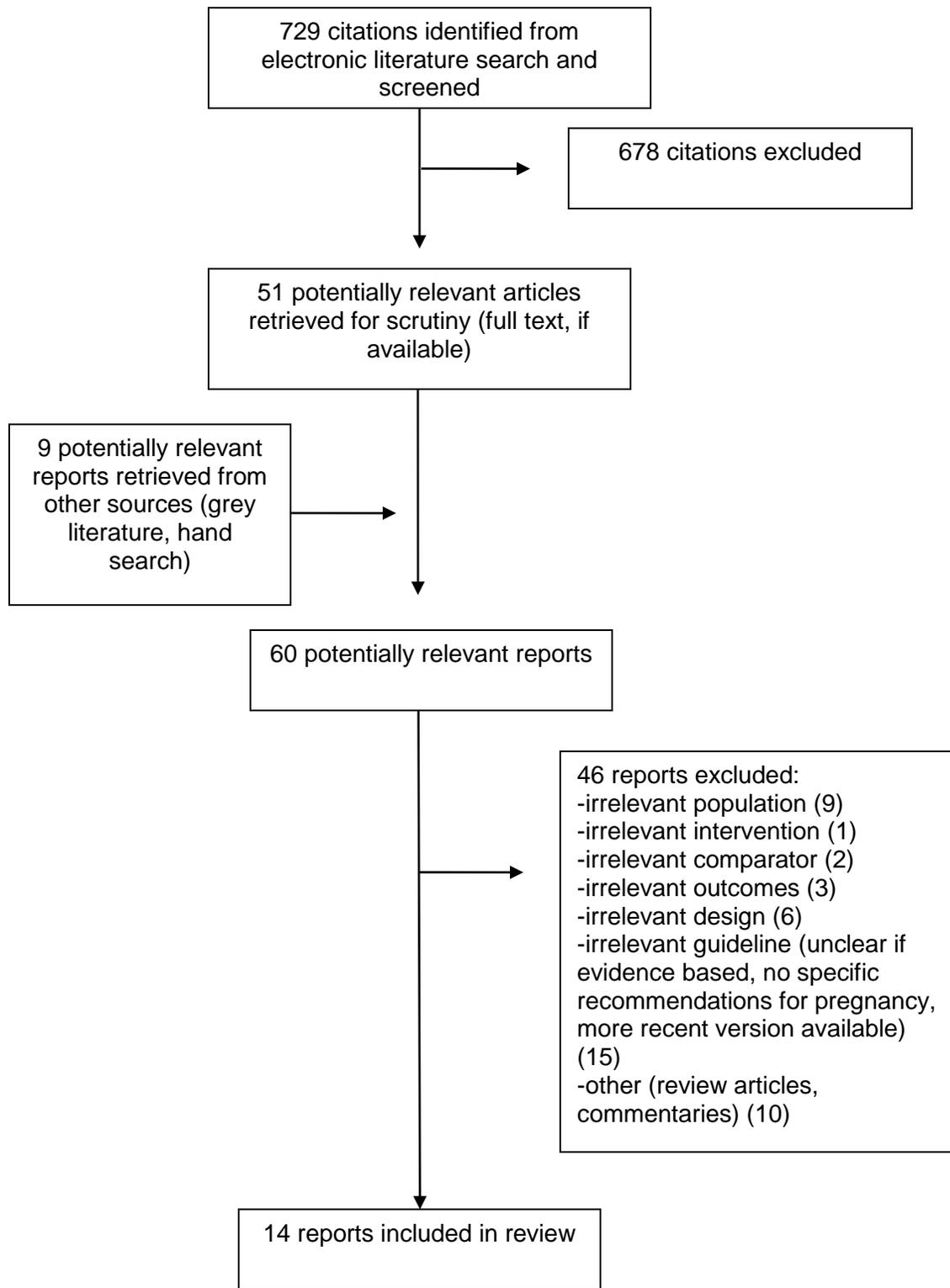
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ABBREVIATIONS

AACE	American Association of Clinical Endocrinologist
AME	Associazione Medici Endocrinologi
ASGE	American Society for Gastrointestinal Endoscopy
ATS	American Thoracic Society
BEL	best evidence level
CAPO	Committee on perioperative evaluation
CI	confidence interval
CT	computed tomography
CTPA	computerized tomography pulmonary angiogram
DVT	deep vein thrombosis
ERCP	endoscopic retrograde cholangiopancreatography
ESGE	European Society of Digestive Endoscopy
ETA	European Thyroid Association
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HL	Hodgkin lymphoma
IUFD	intrauterine foetal death
mSv	millisievert
NICU	neonatal intensive care unit
NR	not reported
OR	odds ratio
PE	pulmonary embolism
SAGES	Society of American Gastrointestinal and Endoscopic Surgeons
RCOG	Royal College of Obstetricians & Gynaecologists
RT	radiation therapy
SD	standard deviation
UGT	upper gastrointestinal tract
UK	United Kingdom
UMHS	Committee on perioperative evaluation
USA	United States of America
V/Q	ventilation/ perfusion
VTE	venous thromboembolism

APPENDIX 1: Selection of Included Studies



APPENDIX 2: Characteristics of Included Studies

First Author, Publication Year, Country	Study Design, Study period	Patient Characteristics, Sample Size ^a (N)	Comparison ^a	Outcomes ^a Measured
Non randomized studies				
Choi, ¹² 2012, Korea	Cohort – prospective Study period: NR	Singleton pregnant women (first trimester) requiring abdominal or lumbar radio diagnostic procedures without administration of radionuclide (N = 115) Age (mean ± SD) (years): 31.7± 3.8 Control: Age matched singleton pregnant women not exposed to radiation or any known teratogenic agent (N = 527) Age (mean ± SD) (years): 31.4 ± 3.7	Pregnant women exposed vs control (pregnant women not exposed)	Gestational age at birth, birth weight, IUFD, NICU admission, neonatal complications
Han, ¹³ 2011, Korea	Cohort - prospective Study period: March 2001 to February 2009	Pregnant women (first trimester) undergoing upper gastrointestinal radiography using radio-contrast media (N = 32) Age (mean ± SD) (years): 31.3 ± 3.5 Control: Age and gravidity matched pregnant women not exposed to radiation or any known teratogenic agent (N = 94) Age (mean ± SD) (years): 31.9 ± 4.1	Pregnant women exposed vs control (pregnant women not exposed)	Gestational age at birth, birth weight, pre-term birth, malformation
Schaefer, ¹⁴ 2009, Germany	Cohort study – prospective	Pregnant women exposed to Tc-99m scintigraphy (N =	Pregnant women exposed vs control (pregnant	Spontaneous abortion, elective

First Author, Publication Year, Country	Study Design, Study period	Patient Characteristics, Sample Size ^a (N)	Comparison ^a	Outcomes ^a Measured
	Study period: 1991 to 2008	122 Age (median [IQR]) (years): 32 (28 to 35) Control: Pregnant women not exposed to teratogenic agent (N = 366) Age (median IQR) (years): 31 (27 to 35)	women not exposed)	termination of pregnancy, birth weight, preterm birth, birth defect
Daniels, ² 2007, UK	Cohort study – prospective but with some data (dental history) collected retrospectively Study period: April 1991 to December 1992 (date of delivery)	Singleton pregnant women (N = 7375); (568 [7.7%] were exposed to dental X-rays and 6807 [92.3%] were not exposed) Age (mean ± SD) (years) : 28.9 ± 4.6	Pregnant women who received dental x-rays vs pregnant women who did not	Birthweight, preterm birth
IUFD = intrauterine foetal death, NICU = neonatal intensive care unit, NR = not reported, SD = standard deviation, UK = United Kingdom				

APPENDIX 3: Grading of Recommendations and Levels of Evidence

Guideline Society and/or Author, Year, Country, Topic	Recommendation grade	Level of Evidence
<p>RCOG²² 2015, UK</p> <p>Guidelines for thromboembolic disease in pregnancy and puerperium.</p>	<p>A. At least one meta-analysis, systematic reviews or randomised controlled trial rated as 1++, and directly applicable to the target population; or A systematic review of randomised controlled trials or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population and demonstrating overall consistency of results</p> <p>B. A body of evidence including studies rated as 2++ directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1++ or 1+</p> <p>C. A body of evidence including studies rated as 2+ directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2++</p> <p>D. Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2+” P. 31</p>	<p>1++ High-quality meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a very low risk of bias</p> <p>1+ Well-conducted meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a low risk of bias</p> <p>1– Meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a high risk of bias</p> <p>2++ High-quality systematic reviews of case–control or cohort studies or high-quality case–control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal</p> <p>2+ Well-conducted case–control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal</p> <p>2– Case–control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal</p> <p>3 Non-analytical studies, e.g. case reports, case series</p> <p>4 Expert opinion” P.31</p>
<p>British Committee for Standards in Haematology¹⁹ 2014, UK</p> <p>Guidelines for Hodgkin lymphoma</p>	<p>“Strong (Grade 1): Strong recommendations (Grade 1) are made when there is confidence that the benefits do or do not outweigh harm and burden. Grade 1 recommendations can be applied uniformly to most patients. Regard as "recommend".</p> <p>Weak (Grade 2): Where the magnitude of benefit or not is less certain a weaker Grade 2 recommendation is made. Grade 2 recommendations require judicious application to individual patients. Regard as "suggest".”</p> <p><i>From Section: Strength of recommendations</i></p>	<p>“(A) High: Further research is very unlikely to change confidence in the estimate of effect. Current evidence derived from randomised clinical trials without important limitations.</p> <p>(B) Moderate: Further research may well have an important impact on confidence in the estimate of effect and may change the estimate. Current evidence derived from randomised clinical trials with important limitations (e.g., inconsistent results, imprecision – wide confidence intervals or methodological flaws – e.g., lack of blinding, large losses to follow up, failure to adhere to intention to treat analysis), or very strong evidence from observational studies or case series (e.g., large or very large and consistent estimates of the magnitude of a treatment effect or demonstration of a dose–response gradient).</p> <p>(C) Low: Further research is likely to have an</p>

Guideline Society and/or Author, Year, Country, Topic	Recommendation grade	Level of Evidence															
		important impact on confidence in the estimate of effect and is likely to change the estimate. Current evidence from observational studies, case series or just opinion." <i>From Section: Quality of Evidence</i>															
UMHS, ²³ , 2013, USA Guideline for common breast problems.	1. Generally should be performed 2. May be reasonable to perform 3. Generally should not be performed	A. Randomized controlled trials B. Controlled trials, no randomization C. Observational trials D. Opinion of expert panel															
ASGE, ¹⁷ 2012, USA Guidelines for endoscopy in pregnant and lactating women	The GRADE system was used grading <table border="1" data-bbox="467 850 1417 1207"> <thead> <tr> <th>Symbol</th> <th>Quality of Evidence</th> <th>Explanation^a</th> </tr> </thead> <tbody> <tr> <td>++++</td> <td>High</td> <td>"Further research is very unlikely to change confidence in the estimate of effect."</td> </tr> <tr> <td>+++O</td> <td>Moderate</td> <td>"Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate."</td> </tr> <tr> <td>++OO</td> <td>Low</td> <td>"Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate."</td> </tr> <tr> <td>+OOO</td> <td>Very low</td> <td>"Any estimate of effect is very uncertain."</td> </tr> </tbody> </table> <p>^a <i>Explanations from Section: Definitions</i></p> <p>"The strength of individual recommendations is based on both the aggregate evidence quality and an assessment of the anticipated benefits and harms. Weaker recommendations are indicated by phrases such as "the Practice Committee suggests," whereas stronger recommendations are typically stated as "the Practice Committee recommends." " <i>From Section: Definitions</i></p>		Symbol	Quality of Evidence	Explanation ^a	++++	High	"Further research is very unlikely to change confidence in the estimate of effect."	+++O	Moderate	"Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate."	++OO	Low	"Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate."	+OOO	Very low	"Any estimate of effect is very uncertain."
Symbol	Quality of Evidence	Explanation ^a															
++++	High	"Further research is very unlikely to change confidence in the estimate of effect."															
+++O	Moderate	"Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate."															
++OO	Low	"Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate."															
+OOO	Very low	"Any estimate of effect is very uncertain."															
ATS, ¹⁵ 2012, USA Guidelines for evaluation of suspected pulmonary embolism in pregnancy.	GRADE was used to describe the level of evidence and rate the strength of evidence.																
ESGE, ²⁴ 2012, Europe Guidelines for radiation protection in digestive endoscopy.	"A" At least onemeta-analysis, systematic review, or RCT rated as 1 ++ and directly applicable to the target population or a systematic review of RCTs or a body of evidence consisting principally of studies rated as 1 + directly applicable to the target population and demonstrating overall	"1++" High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias 1+ Well conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias 1- Meta-analyses, systematic reviews, or RCTs															

Guideline Society and/or Author, Year, Country, Topic	Recommendation grade	Level of Evidence
	<p>consistency of results</p> <p>B A body of evidence including studies rated as 2 + + directly applicable to the target population and demonstrating overall consistency of results or extrapolated evidence from studies rated as 1++ or 1+</p> <p>C A body of evidence including studies rated as 1 – or 2+ directly applicable to the target population and demonstrating overall consistency of results or extrapolated evidence from studies rated as 2++</p> <p>D Evidence level 2–, 3 or 4 or extrapolated evidence from studies rated as 2 +” P. 410</p>	<p>with a high risk of bias</p> <p>2++ High quality systematic reviews of case – control or cohort studies; high quality case – control studies or cohort studies with a very low risk of confounding, bias, or chance and a high probability that the relationship is causal</p> <p>2+ Well conducted case – control or cohort studies with a low risk of confounding, bias, or chance and a moderate probability that the relationship is causal</p> <p>2- Case – control or cohort studies with a high risk of confounding, bias, or chance and a significant risk that the relationship is not causal</p> <p>3 Nonanalytic studies, e. g. case reports, case series</p> <p>4 Expert opinion” P. 409</p>
<p>CAPO and Brazilian Society of Cardiology,²⁰ 2011, Brazil</p> <p>Guidelines for perioperative evaluation.</p>	<p>Degree of recommendation:</p> <p>I “Benefit >>> Risk; the treatment/procedure must be indicated/ administered”</p> <p>IIa “Benefit >> Risk; the choice for the treatment/procedure may help the patient”</p> <p>IIb “Benefit > Risk; is not defined if the treatment/procedure can help the patient”</p> <p>III “Risk > Benefit; the treatment/procedure must not be performed since it does not help and may be harmful to the patient”</p> <p><i>From Section: Definitions</i></p>	<p>Level of Evidence:</p> <p>“A. Evidence in several populations from multiple randomized clinical trials or meta-analyses</p> <p>B. Evidence in a limited group of populations from single randomized clinical trial or non-randomized clinical studies</p> <p>C. Evidence in very limited group of populations from consensus and experts’ opinions, case reports and series”</p> <p><i>From Section: Definitions</i></p>
<p>SAGES,¹⁶ 2011, USA</p> <p>Guidelines for diagnosis, treatment and use of laparoscopy for surgical problems during pregnancy</p>	<p>GRADE System for Recommendations Based on the Quality of Evidence:</p> <p>“Strong - It is very certain that benefit exceeds risk for the option considered</p> <p>Weak - Risk and benefit well balanced, patients in differing clinical situations would make different choices, or benefits available but not</p>	<p>GRADE System for Rating the Quality of Evidence:</p> <p>“High quality - Further research is very unlikely to alter confidence in the estimate of impact</p> <p>Moderate quality - Further research is likely to alter confidence in the estimate of impact and may change the estimate</p> <p>Low quality - Further research is very likely to alter confidence in the estimate of impact</p>

Guideline Society and/or Author, Year, Country, Topic	Recommendation grade	Level of Evidence
	certain” <i>From Section: Definitions</i>	and is likely to change the estimate Very low quality - Any estimate of impact is uncertain” <i>From Section: Definitions</i>
AACE/ AME/ ETA, ¹⁸ 2010, USA & Europe Guidelines for diagnosis and management of thyroid nodules.	<p>A. “>1 conclusive level 1 publications demonstrating benefit >> risk”</p> <p>B. “No conclusive level 1 publication ≥1 conclusive level 2 publication demonstrating benefit >> risk”</p> <p>C. “No conclusive level 1 or 2 publication ≥1 conclusive level 3 publication demonstrating benefit >> risk OR No conclusive risk at all and no benefit at all”</p> <p>D. “No conclusive level 1, 2, or 3 publication demonstrating benefit >> risk Conclusive level 1, 2, or 3 publication demonstrating risk >> benefit”</p> <i>From Section: Definitions</i>	<p>1. “Well-controlled, generalizable, randomized trials Adequately powered, well-controlled multicenter trials Large meta-analyses with quality ratings All-or-none evidence”</p> <p>2. “Randomized controlled trials; limited body of data Well-conducted prospective cohort studies Well-conducted meta-analyses of cohort studies”</p> <p>3. “Methodologically flawed randomized clinical trials Observational studies Case series or case reports Conflicting evidence with weight of evidence supporting the recommendation”</p> <p>4. “Expert consensus Expert opinion based on experience “Theory-driven conclusions” “Unproven claims””</p> <i>From Section: Definitions</i>
AACE = American Association of Clinical Endocrinologist, AME = Associazione Medici Endocrinologi, ASGE = American Society for Gastrointestinal Endoscopy, CAPO = Committee on Perioperative Evaluation, ESGE = European Society of Digestive Endoscopy, ETA = European Thyroid Association, GRADE = Grading of Recommendations Assessment, Development and Evaluation, RCOG = Royal College of Obstetricians and Gynaecologists, SAGES = Society of American Gastrointestinal and Endoscopic Surgeons, UK = United Kingdom, UMHS = University of Michigan Health System, USA = United States of America		

APPENDIX 4: Summary of Study Strengths and Limitations

First Author, Publication Year, Country	Strengths	Limitations
Non randomized studies		
Choi, ¹² 2012, Korea	<ul style="list-style-type: none"> • Objectives were clearly stated. • Inclusion and exclusion criteria were stated. • Patient characteristics, interventions and outcomes were described, however details of interventions were not provided. • Prospective study • P values were provided • No participants were lost to follow up • Authors stated there were no conflicts of interest 	<ul style="list-style-type: none"> • Not randomized • Intervention description lacked details • Unclear if the study was adequately powered • Generalizability limited to participants who were referred to Korean Motherisk Program for teratogen risk counselling after undergoing radio diagnostic procedures and their matched unexposed controls.
Han, ¹³ 2011, Korea	<ul style="list-style-type: none"> • Objectives were clearly stated. • Inclusion was stated. • Patient characteristics, interventions and outcomes were described, however details of interventions were not provided. • Prospective study • P values were provided • Authors stated there were no conflicts of interest 	<ul style="list-style-type: none"> • Not randomized • Intervention description lacked details • Exclusion criteria not stated • Unclear if the study was adequately powered • Some were lost to follow up but similar in both groups (9.5% and 8.7% in the exposed and unexposed groups respectively) • Generalizability limited to participants who were referred to Korean Motherisk Program for teratogen risk counselling after inadvertently being exposed to x-rays and their matched unexposed controls.
Schaefer, ¹⁴ 2009, Germany	<ul style="list-style-type: none"> • Objectives were clearly stated. • Inclusion was stated. • Patient characteristics, interventions and outcomes were described, however details of interventions were not provided. • Prospective study • P values or 95% CI provided in most instances • No participants were lost to follow up • Authors stated there were no conflicts of interest 	<ul style="list-style-type: none"> • Not randomized • Intervention description lacked details • Exclusion criteria not stated • Limited power (as mentioned by the authors) • Generalizability limited. Information was collected by the Berlin Institute for Clinical Teratology by sending out requests to pregnant women or their physicians. The proportions of non-responders were 8.3% and 15.6% in the exposed and control groups respectively and the

First Author, Publication Year, Country	Strengths	Limitations
		responders and non-responders may have different characteristics
Daniels, ² 2007, UK	<ul style="list-style-type: none"> • Objectives were clearly stated. • Inclusion and exclusion criteria were stated. • Patient characteristics, interventions and outcomes were described, however patient characteristics in the exposed and unexposed groups were not provided separately and details of interventions were not provided. • Partially prospective with some data collected retrospectively • 95% CI provided • Unclear if the authors had any conflict of interest, there was no mention of conflict of interest. 	<ul style="list-style-type: none"> • Not randomized • Intervention description lacked details • Unclear if the study was adequately powered • Unclear if any participants were lost to follow up • Some data was collected retrospectively (mothers provided their dental history 33 months postpartum) hence potential for recall bias as • Generalizability limited to residents of Bristol, UK; also 85% of the eligible population participated and it is unclear if those who participated were different from those who did not
Guidelines		
RCOG, ²² 2013, and RCOG, ²¹ 2007, UK	<ul style="list-style-type: none"> • The scope and purpose were clearly stated. • Members of the Guideline development group appear to be from relevant areas such as obstetrics and gynaecology • Methodology: MEDLINE and PubMed databases searched, systematic review conducted, method used to formulate recommendations stated, draft reviewed internally and externally. • Recommendations were clear • Authors declared their conflicts of interest; one author had none to declare and one author had received a travel grant from industry. 	<ul style="list-style-type: none"> • Unclear if patient input was sought • Cost implications were not discussed.
British Committee for Standards in Haematology, ¹⁹ 2014, UK	<ul style="list-style-type: none"> • The scope and purpose were clearly stated. • The guideline development group comprised of individuals from relevant areas such as haematology, oncology, imaging. • Methodology: multiple data bases searched, systematic review conducted, methods used to formulate recommendations 	<ul style="list-style-type: none"> • Unclear if patient input was sought • Cost implications were not discussed.

First Author, Publication Year, Country	Strengths	Limitations
	<p>stated, draft reviewed internally and externally.</p> <ul style="list-style-type: none"> • Recommendations were clear • It was stated that the authors had no conflict of interest to declare 	
UMHS, ²³ 2013, USA	<ul style="list-style-type: none"> • The scope and purpose were clearly stated. • Members of the Guideline development group appear to be from relevant areas such as radiology, oncology, obstetrics and gynaecology • Methodology: MEDLINE database searched, systematic review conducted, method used to formulate recommendations stated, draft reviewed internally. • Recommendations were clear • Authors disclosed their conflicts of interest and there were none 	<ul style="list-style-type: none"> • Unclear if patient input was sought • Cost implications were not discussed
ASGE, ¹⁷ 2012, USA	<ul style="list-style-type: none"> • The scope and purpose were clearly stated. • Members of the Guideline development group were listed and appear to be from relevant areas (clinicians) • Methodology: MEDLINE database searched, systematic review conducted, method used to formulate recommendations stated, draft reviewed internally. • Recommendations were clear • Conflict of interest was declared by the authors: one author received speaker honorarium and one author received consultation honorarium from industry and the others had no financial relationships relevant for the report 	<ul style="list-style-type: none"> • Unclear if patient input was sought • Cost implications were not discussed.
ATS, ¹⁵ 2012, USA	<ul style="list-style-type: none"> • The scope and purpose were clearly stated. • The guideline development group comprised of individuals from relevant areas such as radiologists, nuclear medicine physicians, obstetrician, gynecologists, medical physicists and methodologist • Methodology: multiple databases 	<ul style="list-style-type: none"> • Unclear if patient input was sought

First Author, Publication Year, Country	Strengths	Limitations
	<p>searched, systematic review conducted, methods used to formulate recommendations stated, draft reviewed internally and externally.</p> <ul style="list-style-type: none"> • Cost implications were considered • Recommendations were clear • Authors disclosed their conflicts of interest 	
ESGE ²⁴ 2012, Europe	<ul style="list-style-type: none"> • The scope and purpose were clearly stated. • The guideline development group comprised of individuals from relevant areas such as endoscopists and medical physicists • Methodology: multiple databases searched, systematic review conducted, methods used to formulate recommendations stated, draft reviewed internally and externally. • Recommendations were clear • It was stated that the authors had no conflict of interest to declare 	<ul style="list-style-type: none"> • Unclear if patient input was sought • Cost implications were not discussed.
CAPO and Brazilian Society of Cardiology, ²⁰ 2011, Brazil	<ul style="list-style-type: none"> • The scope and purpose were clearly stated. • Members of the Guideline development group comprised of health sciences specialists with hands on and academic experience • Methodology: multiple databases searched, systematic review conducted, methods used to formulate recommendations stated, draft reviewed but unclear if internally and/ or externally. • Cost implications were considered • Recommendations were clear • Authors disclosed their conflicts of interest; most had no relevant financial relationships with industry, a few received speaker honorarium or consultation honorarium from industry 	<ul style="list-style-type: none"> • Unclear if patient input was sought
SAGES, ¹⁶ 2011, USA	<ul style="list-style-type: none"> • The scope and purpose were clearly stated. • Members of the Guideline development group were listed 	<ul style="list-style-type: none"> • Unclear if patient input was sought • Cost implications were not discussed.

First Author, Publication Year, Country	Strengths	Limitations
	<p>and appear to be from relevant areas (clinicians)</p> <ul style="list-style-type: none"> • Methodology: MEDLINE database searched, systematic review conducted, method used to formulate recommendations stated, draft reviewed internally. • Recommendations were clear • Authors were required to declare their conflicts of interest and real and potential conflicts were mitigated through mechanisms put in place by SAGES Conflict of Interest Task Force 	
<p>AACE/ AME/ ETA,¹⁸ 2010, USA & Europe</p>	<ul style="list-style-type: none"> • The scope and purpose were clearly stated. • Members of the Guideline development group were listed and appear to be from relevant areas (clinicians) • Methodology: multiple databases searched, systematic review conducted, methods used to formulate recommendations stated, draft reviewed but unclear if internally and/ or externally. • Cost implications were considered • Recommendations were clear • Authors disclosed their conflicts of interest; most had no relevant financial relationships with industry, a few received speaker honorarium or consultation honorarium from industry 	<ul style="list-style-type: none"> • Unclear if patient input was sought
<p>AACE = American Association of Clinical Endocrinologist, AME = Associazione Medici Endocrinologi, ASGE = American Society for Gastrointestinal Endoscopy, ATS = American Thoracic Society, CAPO = Committee on Perioperative Evaluation, ESGE = European Society of Digestive Endoscopy, ETA = European Thyroid Association, RCOG = Royal College of Obstetricians and Gynaecologists, SAGES = Society of American Gastrointestinal and Endoscopic Surgeons, UK = United Kingdom, UMHS = University of Michigan Health System, USA = United States of America</p>		

APPENDIX 5: Main Study Findings and Authors' Conclusions

First Author, Publication Year, Country	Main Findings and Authors' Conclusion																												
Non randomized studies																													
Choi, ¹² 2012, Korea	<p>Main Findings: Foetal and neonatal outcomes</p> <table border="1" data-bbox="472 600 1430 1188"> <thead> <tr> <th data-bbox="472 600 711 785">Outcome</th> <th data-bbox="711 600 950 785">Exposed to radio diagnostic procedures during pregnancy N = 104</th> <th data-bbox="950 600 1188 785">Not exposed to radio diagnostic procedures during pregnancy N = 485</th> <th data-bbox="1188 600 1430 785">P value</th> </tr> </thead> <tbody> <tr> <td data-bbox="472 785 711 816">IUFD, n (%)</td> <td data-bbox="711 785 950 816">1 (1.0)</td> <td data-bbox="950 785 1188 816">1 (0.2)</td> <td data-bbox="1188 785 1430 816">0.32</td> </tr> <tr> <td data-bbox="472 816 711 909">Gestational age at birth (weeks), (mean ± SD)</td> <td data-bbox="711 816 950 909">39.5 ± 1.1</td> <td data-bbox="950 816 1188 909">39.2 ± 1.6</td> <td data-bbox="1188 816 1430 909">0.12</td> </tr> <tr> <td data-bbox="472 909 711 972">Birth weight birth (g), (mean ± SD)</td> <td data-bbox="711 909 950 972">3,320.9 ± 424.7</td> <td data-bbox="950 909 1188 972">3,300.6 ± 428.7</td> <td data-bbox="1188 909 1430 972">0.66</td> </tr> <tr> <td data-bbox="472 972 711 1035">NICU admission, n (%)</td> <td data-bbox="711 972 950 1035">5 (4.9)</td> <td data-bbox="950 972 1188 1035">8 (1.7)</td> <td data-bbox="1188 972 1430 1035">0.06</td> </tr> <tr> <td data-bbox="472 1035 711 1127">Congenital malformation, n (%)</td> <td data-bbox="711 1035 950 1127">2 (1.9)</td> <td data-bbox="950 1035 1188 1127">2 (0.4)</td> <td data-bbox="1188 1035 1430 1127">0.15</td> </tr> <tr> <td data-bbox="472 1127 711 1188">Neonatal jaundice, n (%)</td> <td data-bbox="711 1127 950 1188">2 (1.9)</td> <td data-bbox="950 1127 1188 1188">11 (2.3)</td> <td data-bbox="1188 1127 1430 1188">0.59</td> </tr> </tbody> </table> <p data-bbox="472 1188 1430 1251">IUFD = intrauterine foetal death, NICU – neonatal intensive care unit, SD = standard deviation</p> <p>Authors' Conclusion: “Our results indicate that X-ray and computed tomography scan exposure involving abdominal irradiation without the administration of radionuclotides is not associated with adverse foetal and neonatal deterministic outcomes. Efforts are required to reduce the use of radiodiagnostic procedures for general check-ups in childbearing age women.” P. 513</p>	Outcome	Exposed to radio diagnostic procedures during pregnancy N = 104	Not exposed to radio diagnostic procedures during pregnancy N = 485	P value	IUFD, n (%)	1 (1.0)	1 (0.2)	0.32	Gestational age at birth (weeks), (mean ± SD)	39.5 ± 1.1	39.2 ± 1.6	0.12	Birth weight birth (g), (mean ± SD)	3,320.9 ± 424.7	3,300.6 ± 428.7	0.66	NICU admission, n (%)	5 (4.9)	8 (1.7)	0.06	Congenital malformation, n (%)	2 (1.9)	2 (0.4)	0.15	Neonatal jaundice, n (%)	2 (1.9)	11 (2.3)	0.59
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First Author, Publication Year, Country	Main Findings and Authors' Conclusion																											
Han, ¹³ 2011, Korea	<p>Main Findings: Neonatal outcomes</p> <table border="1" data-bbox="472 464 1419 989"> <thead> <tr> <th data-bbox="472 464 711 646">Outcome</th> <th data-bbox="711 464 950 646">Exposed to UGT barium fluoroscopy during pregnancy N = 32</th> <th data-bbox="950 464 1188 646">Not exposed to UGT barium fluoroscopy during pregnancy N = 94</th> <th data-bbox="1188 464 1419 646">P value</th> </tr> </thead> <tbody> <tr> <td data-bbox="472 646 711 737">Gestational age at birth (mean ± SD) (weeks)</td> <td data-bbox="711 646 950 737">40.7 ± 7.4</td> <td data-bbox="950 646 1188 737">39.1 ± 1.4</td> <td data-bbox="1188 646 1419 737">0.2</td> </tr> <tr> <td data-bbox="472 737 711 800">Birth weight (mean ± SD) (g)</td> <td data-bbox="711 737 950 800">3,277 ± 735</td> <td data-bbox="950 737 1188 800">3,192 ± 543</td> <td data-bbox="1188 737 1419 800">0.4</td> </tr> <tr> <td data-bbox="472 800 711 863">Pre-term birth (< 37 weeks) n (%)</td> <td data-bbox="711 800 950 863">2 (6.2)</td> <td data-bbox="950 800 1188 863">6 (6.4)</td> <td data-bbox="1188 800 1419 863">0.6</td> </tr> <tr> <td data-bbox="472 863 711 926">Major malformation</td> <td data-bbox="711 863 950 926">1 (3.1)</td> <td data-bbox="950 863 1188 926">3 (3.1)</td> <td data-bbox="1188 863 1419 926">1.0</td> </tr> <tr> <td data-bbox="472 926 711 989">Minor malformation</td> <td data-bbox="711 926 950 989">1 (3.1)</td> <td data-bbox="950 926 1188 989">2 (2.1)</td> <td data-bbox="1188 926 1419 989">1.0</td> </tr> </tbody> </table> <p data-bbox="472 989 1419 1020">SD = standard deviation, UGT = upper gastrointestinal tract</p> <p>Authors' Conclusion: "In conclusion, our small prospective cohort study of women suggests no association between inadvertent exposure to ionising radiation and barium sulphate during fluoroscopic barium swallow and adverse fetal outcomes." P. 586</p>				Outcome	Exposed to UGT barium fluoroscopy during pregnancy N = 32	Not exposed to UGT barium fluoroscopy during pregnancy N = 94	P value	Gestational age at birth (mean ± SD) (weeks)	40.7 ± 7.4	39.1 ± 1.4	0.2	Birth weight (mean ± SD) (g)	3,277 ± 735	3,192 ± 543	0.4	Pre-term birth (< 37 weeks) n (%)	2 (6.2)	6 (6.4)	0.6	Major malformation	1 (3.1)	3 (3.1)	1.0	Minor malformation	1 (3.1)	2 (2.1)	1.0
Outcome	Exposed to UGT barium fluoroscopy during pregnancy N = 32	Not exposed to UGT barium fluoroscopy during pregnancy N = 94	P value																									
Gestational age at birth (mean ± SD) (weeks)	40.7 ± 7.4	39.1 ± 1.4	0.2																									
Birth weight (mean ± SD) (g)	3,277 ± 735	3,192 ± 543	0.4																									
Pre-term birth (< 37 weeks) n (%)	2 (6.2)	6 (6.4)	0.6																									
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Minor malformation	1 (3.1)	2 (2.1)	1.0																									

First Author, Publication Year, Country	Main Findings and Authors' Conclusion																																
Schaefer, ¹⁴ 2009, Germany	<p>Main Findings: Pregnancy and Neonatal Outcomes</p> <table border="1" data-bbox="472 432 1419 1115"> <thead> <tr> <th data-bbox="472 432 711 554">Outcome</th> <th data-bbox="711 432 922 554">Exposed to Tc-99m during pregnancy N = 122</th> <th data-bbox="922 432 1166 554">Not exposed to Tc-99m during pregnancy N = 366</th> <th data-bbox="1166 432 1419 554">OR 95% (CI), P value</th> </tr> </thead> <tbody> <tr> <td data-bbox="472 554 711 646">Elective termination of pregnancy</td> <td data-bbox="711 554 922 646">6/122</td> <td data-bbox="922 554 1166 646">7/366</td> <td data-bbox="1166 554 1419 646">NR</td> </tr> <tr> <td data-bbox="472 646 711 709">Term birth weight (g)</td> <td data-bbox="711 646 922 709">3472</td> <td data-bbox="922 646 1166 709">3474</td> <td data-bbox="1166 646 1419 709">NR</td> </tr> <tr> <td data-bbox="472 709 711 772">Pre-term birth (<37 weeks)</td> <td data-bbox="711 709 922 772">4/105 (3.8%)</td> <td data-bbox="922 709 1166 772">30/322 (9.3%)</td> <td data-bbox="1166 709 1419 772">NR</td> </tr> <tr> <td data-bbox="472 772 711 835">All birth defects</td> <td data-bbox="711 772 922 835">9/108 (8.3%)</td> <td data-bbox="922 772 1166 835">28/323 (8.7%)</td> <td data-bbox="1166 772 1419 835">0.96 (0.38 to 2.18), P = 1</td> </tr> <tr> <td data-bbox="472 835 711 898">Major birth defects^a</td> <td data-bbox="711 835 922 898">4/108 (3.7%)</td> <td data-bbox="922 835 1166 898">12/323 (3.7%)</td> <td data-bbox="1166 835 1419 898">1.0 (0.23 to 3.38), P = 1</td> </tr> <tr> <td data-bbox="472 898 711 991">All birth defects (exposure during 1st trimester only)</td> <td data-bbox="711 898 922 991">7/105 (6.7%)</td> <td data-bbox="922 898 1166 991">28/323 (8.7%)</td> <td data-bbox="1166 898 1419 991">0.75 (0.27 to 1.84), P = 0.68</td> </tr> <tr> <td data-bbox="472 991 711 1115">Major birth defects^a (exposure during 1st trimester only)</td> <td data-bbox="711 991 922 1115">3/105 (2.9%)</td> <td data-bbox="922 991 1166 1115">12/323 (3.7%)</td> <td data-bbox="1166 991 1419 1115">0.76 (0.14 to 2.90), P = 1</td> </tr> </tbody> </table> <p data-bbox="472 1115 1419 1142">^aGenetic and chromosomal disorders excluded</p> <p>Authors' Conclusion: "This prospective observational study suggests that the inadvertent exposure to Tc-99m scintigraphy in early pregnancy is relatively safe for the fetus." P.161 "Diagnostic administration of radioisotopes during pregnancy should be critically weighed." P.165</p>	Outcome	Exposed to Tc-99m during pregnancy N = 122	Not exposed to Tc-99m during pregnancy N = 366	OR 95% (CI), P value	Elective termination of pregnancy	6/122	7/366	NR	Term birth weight (g)	3472	3474	NR	Pre-term birth (<37 weeks)	4/105 (3.8%)	30/322 (9.3%)	NR	All birth defects	9/108 (8.3%)	28/323 (8.7%)	0.96 (0.38 to 2.18), P = 1	Major birth defects ^a	4/108 (3.7%)	12/323 (3.7%)	1.0 (0.23 to 3.38), P = 1	All birth defects (exposure during 1 st trimester only)	7/105 (6.7%)	28/323 (8.7%)	0.75 (0.27 to 1.84), P = 0.68	Major birth defects ^a (exposure during 1 st trimester only)	3/105 (2.9%)	12/323 (3.7%)	0.76 (0.14 to 2.90), P = 1
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Daniels, ² 2007, UK	<p>Main Findings: Neonatal outcomes</p> <table border="1" data-bbox="472 1451 1338 1549"> <thead> <tr> <th data-bbox="472 1451 959 1486">Outcome</th> <th data-bbox="959 1451 1338 1486">OR (95% CI)</th> </tr> </thead> <tbody> <tr> <td data-bbox="472 1486 959 1522">Term low birth weight (N = 108), n (%)</td> <td data-bbox="959 1486 1338 1522">1.9 (1.0 to 3.4)^a</td> </tr> <tr> <td data-bbox="472 1522 959 1549">Preterm (N = 317), n (%)</td> <td data-bbox="959 1522 1338 1549">1.2 (0.8 to 1.8)^a</td> </tr> </tbody> </table> <p data-bbox="472 1549 1338 1633">^aOR was calculated using logistic regression and was adjusted for child's sex, birth order, maternal fish consumption, age, education, other dental history variables, prenatal smoking and alcohol use</p> <p>Authors' Conclusion: "Having x-rays taken during pregnancy was not associated with birthweight measured continuously but was associated with slightly increased odds of having a term, low birthweight baby. More detailed evaluation of the potential adverse effects of elective dental treatment during pregnancy, particularly dental x-rays, may be warranted." P.448</p>	Outcome	OR (95% CI)	Term low birth weight (N = 108), n (%)	1.9 (1.0 to 3.4) ^a	Preterm (N = 317), n (%)	1.2 (0.8 to 1.8) ^a																										
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APPENDIX 6: Guidelines and Recommendations

Guideline Society and/or Author, Year, Country	Recommendations
RCOG, ²² 2015, UK	<p>Guidelines for thromboembolic disease in pregnancy and puerperium.</p> <p>“In women with suspected PE who also have symptoms and signs of DVT, compression duplex ultrasound should be performed. If compression ultrasonography confirms the presence of DVT, no further investigation is necessary and treatment for VTE should continue. [C]</p> <p>In women with suspected PE without symptoms and signs of DVT, a ventilation/perfusion (V/Q) lung scan or a computerised tomography pulmonary angiogram (CTPA) should be performed. [C]</p> <p>When the chest X-ray is abnormal and there is a clinical suspicion of PE, CTPA should be performed in preference to a V/Q scan. [C]</p> <p>Alternative or repeat testing should be carried out where V/Q scan or CTPA is normal but the clinical suspicion of PE remains. Anticoagulant treatment should be continued until PE is definitively excluded. [C]</p> <p>Women with suspected PE should be advised that, compared with CTPA, V/Q scanning may carry a slightly increased risk of childhood cancer but is associated with a lower risk of maternal breast cancer; in both situations, the absolute risk is very small. [D]” P.2</p>
British Committee for Standards in Haematology ¹⁹ , 2014, UK	<p>Guidelines for Hodgkin lymphoma</p> <p>“Staging investigations and response evaluation should be tailored to the clinical presentation with radiology input to minimise fetal radiation exposure (1C).” <i>From Section: Management of HL in Pregnancy.</i></p> <p>“Wherever possible, RT should be delayed until post-delivery (1B).” <i>From Section: Management of HL in Pregnancy.</i></p>
UMHS, ²³ 2013, USA	<p>Guideline for common breast problems.</p> <p>“<u>Pregnant women</u>. If concerning indications, imaging is relatively safe and should be done [I C].” <i>From Section: Special populations</i></p>
ASGE, ¹⁷ 2012, USA	<p>Guidelines for endoscopy in pregnant and lactating women</p> <p>“The Practice Committee recommends that endoscopy during pregnancy should be done only when there is a strong indication and should be postponed to the second trimester whenever possible (+OOO).” <i>From Section: Recommendations</i></p> <p>Therapeutic endoscopic retrograde cholangiopancreatography (ERCP) is generally safe in pregnancy. The Practice Committee recommends that care be taken to minimize radiation exposure to the fetus (++OO) and risks to the mother (++OO).” <i>From Section: Recommendations</i></p>
ATS, ¹⁵ 2012, USA	<p>Guidelines for evaluation of suspected pulmonary embolism in pregnancy.</p> <p>“In pregnant women with suspected PE and a normal CXR, we recommend lung scintigraphy as the next imaging test rather than CTPA (strong</p>

Guideline Society and/or Author, Year, Country	Recommendations
	<p>recommendation, low quality evidence).” P. 636</p> <p>“In pregnant women with suspected PE and a nondiagnostic V/Q scan, we suggest further diagnostic testing rather than clinical management alone (weak recommendation, low quality evidence). In patients with a nondiagnostic V/Q scan in whom a decision is made to further investigate, we recommend CTPA rather than DSA (strong recommendation, very low quality evidence).” P. 636</p> <p>“In pregnant women with suspected PE and an abnormal CXR, we suggest CTPA as the next imaging test rather than lung scintigraphy (weak recommendation, very low quality evidence).” P. 636</p>
ESGE, ²⁴ 2012, Europe	<p>Guidelines for radiation protection in digestive endoscopy.</p> <p>“Therapeutic ERCP is relatively safe and effective during pregnancy when performed by experienced endoscopists with adapted techniques. Fluoroscopy requirements may be reduced by using specific ERCP techniques (Evidence level 3). A pregnancy test should be obtained before ERCP in women for whom there is doubt about pregnancy (Recommendation grade D). ERCP in pregnant women should be performed only with a therapeutic purpose (Recommendation grade A); it is probably best performed by experienced ERCP endoscopists during the second trimester of pregnancy, strictly following recommendations to decrease patient radiation dose and with an RP apron wrapped around the patient’s abdomen (Recommendation grade D).” P. 410</p>
CAPO and Brazilian Society of Cardiology, ²⁰ (2011, Brazil	<p>Guidelines for perioperative evaluation.</p> <p>Recommendations regarding tests in the preoperative period for pregnant patients with heart disease (Degree of recommendation I, Level of evidence C):</p> <p>“Chest X-ray can be used.</p> <p>Myocardial scintigraphy is not advised (exposure to radiation); gallium-97 scintigraphy is contraindicated.</p> <p>Coronary cineangiography can be performed using abdominal protection.” <i>From Section: Heart Disease and Pregnancy</i></p>
SAGES, ¹⁶ 2011, USA	<p>Guidelines for diagnosis, treatment and use of laparoscopy for surgical problems during pregnancy.</p> <p>Quality of evidence is categorized as high, moderate, low and very low and grade of recommendation is categorized as strong and weak.</p> <p>“Expeditious and accurate diagnosis should take precedence over concerns for ionizing radiation. Cumulative radiation dosage should be limited to 5-10 rads during pregnancy (Moderate; Strong).”</p> <p>“Contemporary multidetector CT protocols deliver a low radiation dose and may be used judiciously during pregnancy (Moderate; Weak).”</p> <p>“Administration of radionucleotides for diagnostic studies is generally safe for mother and fetus (Low; Weak).”</p> <p>“Intraoperative and endoscopic cholangiography exposes the mother and fetus to minimal radiation and may be used selectively during pregnancy. The lower abdomen should be shielded when performing cholangiography during</p>

Guideline Society and/or Author, Year, Country	Recommendations
	<p>pregnancy to decrease the radiation exposure to the fetus (Low; Weak).”</p> <p><i>From Section: Diagnosis and Workup</i></p>
<p>AACE/ AME/ ETA,¹⁸ 2010, USA & Europe</p>	<p>Guidelines for diagnosis and management of thyroid nodules.</p> <p>For thyroid nodules - benign by FNA biopsy: “Radioiodine is contraindicated in pregnant or breastfeeding women (Grade A; BEL 2).</p> <p>Always perform a pregnancy test before administration of radioiodine in women of childbearing age (Grade A; BEL 2).”</p> <p>For management of thyroid nodules during pregnancy: “Avoid use of radioactive agents for both diagnostic and therapeutic purposes (Grade A, BEL 2)”</p>
<p>AACE = American Association of Clinical Endocrinologist, AME = Associazione Medici Endocrinologi, ASGE = American Society for Gastrointestinal Endoscopy, ATS = American Thoracic Society, BEL = best evidence level, CAPO = Committee on Perioperative Evaluation, CT = computed tomography, CTPA = computerized tomography pulmonary angiogram, CXR = chest X-ray, ERCP = endoscopic retrograde cholangiopancreatography, ESGE = European Society of Digestive Endoscopy, ETA = European Thyroid Association, HL = Hodgkin lymphoma, PE = pulmonary embolism, RCOG = Royal College of Obstetricians and Gynaecologists, RT = radiation therapy, SAGES = Society of American Gastrointestinal and Endoscopic Surgeons, UMHS = University of Michigan Health System, USA = United States of America, V/Q = ventilation/ perfusion, VTE = venous thromboembolism</p>	