TITLE: Anaesthetic Agents in Pregnant Women Undergoing Non-Obstetric Surgical or Endoscopic Procedures: A Review of the Safety and Guidelines

DATE: 8 June 2015

CONTEXT AND POLICY ISSUES

It has been estimated that up to 2% of pregnant women require non-obstetric surgery that may be performed during any trimester of their pregnancy.\(^1\)\(^-\)\(^4\) Depending on the type of surgery and condition of the patient, non-obstetric surgery may be performed using multiple options for anesthetic agents for general anaesthesia (GA) or regional anaesthesia (RA).\(^2\)\(^,\)\(^4\) However, anaesthesia may present risks to both the mother and the fetus by increasing the potential for maternal and fetal hypoxia, adverse impact on fetal development, or loss of pregnancy.\(^1\)\(^,\)\(^2\)\(^,\)\(^4\) For this reason, proper anaesthesia management of the pregnant patient is particularly sensitive. To inform clinical practice decisions, it is important to identify whether certain anaesthetic agents or drugs are safer than others for use during surgery on pregnant patients, particularly during early pregnancy or in cases when the patient does not yet know she is pregnant.

The purpose of this report is to review the clinical evidence and evidence-based guidelines regarding the safety of anaesthesia in pregnant women undergoing non-obstetric surgical or endoscopic procedures.

RESEARCH QUESTIONS

1. What is the clinical evidence regarding the safety of anaesthetic agents in pregnant women undergoing non-obstetric surgical or endoscopic procedures?

2. What are the evidence-based guidelines regarding the use of anaesthetic agents in pregnant women undergoing non-obstetric surgical or endoscopic procedures?

KEY FINDINGS

One systematic review and one retrospective non-randomized study showed that adverse maternal and neonatal outcomes following surgery with anaesthesia are rare. The systematic review also reported that miscarriage or fetal loss and major birth defects were observed more
frequently when surgery was performed during the first trimester of pregnancy. The non-randomized study concluded that regional anaesthesia for laparotomic adnexal mass surgery during pregnancy may be associated with an increased risk of preterm labour. However, it is difficult to elucidate the impact of anaesthesia alone on pregnancy outcomes due to the influence of several confounding factors present in the included studies.

One evidence-based guideline was identified that recommends meperidine as the preferred agent for endoscopic procedures on pregnant women requiring moderate sedation, and that deep sedation for endoscopy should be administered by an anaesthesia provider.

METHODS

Literature Search Methods

A focused search (with main concepts appearing in title or major subject heading) was conducted on key resources including PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to the main focused search to limit the retrieval by study type. A second broader search (with main concepts appearing in the title, abstract or subject heading) was also included, however methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses 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 8, 2015.

Rapid Response reports are organized so that the evidence for each research question is presented separately.

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>
<thead>
<tr>
<th>Table 1: Selection Criteria</th>
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<tbody>
<tr>
<td><strong>Population</strong></td>
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<td><strong>Intervention</strong></td>
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<tr>
<td><strong>Comparator</strong></td>
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<tr>
<td><strong>Outcomes</strong></td>
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<td><strong>Study Designs</strong></td>
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</table>
Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2005. Guidelines with unclear methodology were also excluded.

Critical Appraisal of Individual Studies

The included systematic review was critically appraised using AMSTAR, the non-randomized study was evaluated using the Downs and Black checklist, and the guideline was assessed with the AGREE II instrument. Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described narratively.

SUMMARY OF EVIDENCE

Quantity of Research Available

A total of 553 citations were identified in the literature search. Following screening of titles and abstracts, 526 citations were excluded and 27 potentially relevant reports from the electronic search were retrieved for full-text review. Two potentially relevant publications were retrieved from the grey literature search. Of these potentially relevant articles, 26 publications were excluded for various reasons, while three publications met the inclusion criteria and were included in this report. Appendix 1 describes the PRISMA flowchart of the study selection.

Additional references of potential interest regarding the safety of anaesthetic agents in pregnant women undergoing caesarean section or fetal surgeries are provided in Appendix 5.

Summary of Study Characteristics

Detailed study characteristics are provided in Appendix 2.

Study Design

One systematic review (SR), one non-randomized study (a retrospective chart review), and one evidence-based guideline from the American Society for Gastrointestinal Endoscopy (ASGE) regarding the safety of anaesthetic agents in pregnant women undergoing non-obstetric surgical or endoscopic procedures were identified for inclusion in this report. The SR was based on a database search for the years 1966 to 2002 and identified 54 publications that met the inclusion criteria. The 54 studies included in the SR predominantly consisted of retrospective case series but also included retrospective registry, prospective cohort, and case control studies.

Country of Origin

The SR was published in 2005 and was performed by authors located in Canada and Israel, but the included references were English-language publications from multiple regions. The non-randomized study was conducted in Korea and published in 2006, and the ASGE guideline was produced in the United States in 2012.
Patient Population

Both the SR\textsuperscript{8} and the retrospective chart review\textsuperscript{9} included pregnant women in any trimester of pregnancy. The SR included women undergoing any kind of non-obstetric surgical intervention, while the retrospective chart review limited inclusion to pregnant women undergoing surgery for adnexal masses. The risk of including inevitably nonviable pregnancies in the retrospective chart review was reduced by excluding patients that had a record of pre-surgical vaginal bleeding or an absence of a fetal heartbeat on ultrasonography.\textsuperscript{9} The ASGE guideline\textsuperscript{10} is relevant to pregnant women in any trimester of pregnancy and lactating women undergoing gastrointestinal endoscopy.

Interventions and Comparators

The SR\textsuperscript{8} considered a combined intervention of non-obstetric surgery (elective or emergency) under anaesthesia (GA or RA; specific anaesthetic agents not reported). The surgical procedures reported in the included studies were appendectomy, cholecystectomy, laparoscopy, adnexal mass surgery, thyroidectomy, and “various”. The retrospective chart review\textsuperscript{9} included three intervention groups classified by type of surgery and anaesthetic method: GA for laparotomy, GA for laparoscopy, and RA for laparotomy. A non-surgical control group of pregnant women was also included for comparison. The ASGE guideline\textsuperscript{10} provides recommendations for the provision of anaesthesia and suggested agents for endoscopy of pregnant and lactating women.

Outcomes

Both included studies\textsuperscript{8,9} reported on maternal and neonatal outcomes; these included: maternal deaths, spontaneous abortion (or miscarriage; pregnancy loss prior to 20 weeks), fetal death (or stillbirth; pregnancy loss at 20 weeks or later), neonatal deaths, preterm labour, premature delivery or delivery induced by surgical procedure, congenital anomalies, and low birthweight. The ASGE guideline\textsuperscript{10} developers used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system to evaluate the evidence and assign a quality rating ranging from “very low quality” to “high quality”; the ratings are presented with the corresponding recommendations within the guideline.

Summary of Critical Appraisal

In general, the included studies had several limitations that affect interpretation of the results. A list of critical appraisal points is provided in Appendix 3.

The SR\textsuperscript{8} was based on a comprehensive search of the published literature; however, it was unclear whether a grey literature search was performed and the list of excluded studies was not provided. The selection criteria were explicit and clear; however, it was unclear whether the article selection and data extraction were performed independently by two authors. It was reported that the quality of the publications selected for the review was evaluated; however, the formal method used to perform this quality assessment and results for each study were not documented. The nature of the body of evidence available for this particular review, mostly retrospective case series, limited the strength of conclusions that can be made due to the absence of a control group; baseline risk of adverse pregnancy outcomes (e.g., first trimester pregnancy loss) was not considered when reporting the findings for pregnant patients who underwent surgery with anaesthesia. The authors did note the need for more studies that
address confounders, including: surgical and anaesthetic techniques, pre-existing maternal health and socioeconomic statuses, smoking status, and alcohol consumption. The abundance of confounding variables in such descriptive studies that were not adjusted for in any statistical analyses makes it impossible to attribute causality of outcomes to anaesthesia.

The retrospective chart review by Hong\(^9\) had clearly described objectives, patient characteristics, interventions, and outcomes. Patients in the intervention and control groups were selected from the entire hospital population over the same period, suggesting consistent and representative subject selection. The inclusion of a non-surgical control group helped to establish a baseline risk of adverse outcomes for pregnant women. The pregnancy outcome measures were appropriate and findings were clearly presented in a table. However, there were significant limitations associated with this study as a result of its design. Patients were not randomized to type of anaesthesia, which introduces confounding; choice of surgical and anaesthetic technique could have been influenced by uterine pathology or other clinical factors that may also have contributed to pregnancy outcomes. The safety outcomes were presented as totals per intervention group and were not consistently reported with additional relevant patient information. This was likely due to the small number of events in each group but limits interpretation of the results. Furthermore, RA was only used for laparotomic procedures and therefore can only be compared appropriately with the GA for laparotomy group; comparison between the RA for laparotomy group with the GA for laparoscopy group is not valid as these two groups differed in both surgical and anaesthetic techniques. There was a small number of patients that fit the inclusion criteria for this study (\(n = 235\)), and the number of patients in each intervention group differed substantially. As this was a retrospective study and patients were not prospectively recruited, no sample size calculation was performed to ensure that the study was appropriately powered. Therefore, it is unlikely that there were enough cases to detect a difference between groups if a difference truly exists.

The guideline by ASGE\(^10\) clearly described the target population and users, but the overall objectives and health questions of the guideline were not explicitly defined. The evidence used to support the recommendations was formally evaluated using a recognized and established tool (GRADE), and the method of recommendation development was also reported. However, a limited literature search of one database with an unspecified date range was performed and there were unclear selection criteria for included studies. In addition, the composition of the ASGE guideline development group with respect to medical specialties was not described, nor was it clear whether patient input was sought during guideline development, which may have limited the representativeness of perspectives informing the recommendations. The recommendations were easily identifiable and clearly separated by indication (e.g., relevant to pregnant women or lactating women), and reflected the benefits and risks of different anaesthesia options. However, there was no discussion of guideline implementation or reported process for updating the guideline.

**Summary of Findings**

A detailed summary of main study findings and guideline recommendations is provided in Appendix 4.

*What is the clinical evidence regarding the safety of anaesthetic agents in pregnant women undergoing non-obstetric surgical or endoscopic procedures?*
One SR\(^8\) and one retrospective chart review\(^9\) assessed the safety of non-obstetric surgical procedures performed under anaesthesia on pregnant women.

The SR by Cohen-Kerem et al.\(^8\) evaluated the maternal and neonatal outcomes following a variety of elective or emergency surgical procedures performed on pregnant women of any trimester. Findings were presented by surgical procedure rather than by type of anaesthesia; no comparison was made between alternative anaesthetic methods. Overall, reported adverse events for either the mother or the child were rare. One maternal death from a total of 12,542 surgical procedures was reported for a patient who experienced intra-abdominal hemorrhage two weeks post-laparoscopic cholecystectomy (18 weeks pregnant at time of surgery). The anaesthetic agent used in this case was not described. Post-surgical pregnancy loss and major birth defects were more commonly reported when surgery was performed in the first trimester than when considering the total rate for these outcomes when surgery was performed at any trimester of pregnancy. The event that occurred in the highest percentage of surgical cases was prematurity (597 of 7313; 8.2%).\(^8\)

The 10-year retrospective chart review by Hong\(^9\) examined the maternal and neonatal outcomes after surgery for adnexal masses by laparotomy under GA, laparoscopy under GA, or laparotomy under RA compared with each other and compared with a non-surgical pregnant control group. Women in all trimesters of pregnancy were included in the study; however, the majority of surgeries in all groups were performed during the first and second trimesters. No maternal deaths were reported. There was a statistically significantly higher rate of preterm labour requiring treatment with tocolytics in the group that received RA for laparoscopy (29 of 71; 29.6%) compared with GA for laparotomy (8 of 137; 5.8%), GA for laparoscopy (0 of 27), and the non-surgical control group (2614 of 80,527; 3.2%). In addition, the rate of premature delivery was significantly higher with surgery and anaesthesia compared with non-surgical controls; however, there was no statistically significant difference in these rates between the surgical groups. There were no statistically significant differences between surgical groups or between surgical and non-surgical controls in the rates of spontaneous abortion, fetal loss, neonatal death, congenital anomalies, or low birthweight.\(^9\)

What are the evidence-based guidelines regarding the use of anaesthetic agents in pregnant women undergoing surgical or endoscopic procedures?

One guideline from ASGE\(^10\) was identified regarding gastrointestinal endoscopy in pregnant and lactating women, including recommendations for the use of analgesics and anaesthetic agents. Based on what was classified as very low quality evidence from “two large studies” otherwise undefined, ASGE recommends meperidine as the preferred agent for procedures on pregnant women requiring moderate sedation. They also recommend that deep sedation should be administered by an anaesthesia provider; however, no guidance on specific agents was included in this recommendation. A general procedural consideration for endoscopy in pregnant women is that endoscopy should be delayed until the second trimester of pregnancy when possible, though it was unclear whether this suggestion was solely a result of risks associated with anaesthesia. Additional general principles for endoscopy in pregnancy were to use the lowest possible effective dose of sedative agents and to use drugs classified as Category B by the U.S. Food and Drug Administration. Drugs are classified as Category B when there is no evidence of harm to the fetus based on animal studies and adequate evidence from well-controlled human studies is absent, or when there is evidence of harm to the fetus from animal studies but these observations have not been made in well-controlled human studies. This guideline also notes that “none of the currently used anesthetic agents, when used in standard
concentrations at any gestational age, have been shown to have any teratogenic effect in humans.”

Limitations

The SR\(^8\) and the retrospective chart review\(^9\) were mainly limited by their non-randomized study designs that could not control for all relevant confounders; it is impossible to identify and separate the influence of anaesthesia alone from the impact of the surgical procedure and underlying maternal condition. This was also a limitation of the ASGE guideline,\(^10\) as the recommendations were based on evidence that was rated as “very low quality”, reflecting the paucity of well-controlled human studies.

The retrospective chart review\(^9\) identified a total of 235 adnexal mass surgical cases of 81,325 births for inclusion in the study, which were further divided into three smaller treatment groups. Given the rarity of the outcomes of interest, these groups were likely not large enough to identify a statistically significant difference between groups. Therefore, it is unclear whether there truly was no difference between the groups or whether the sample size was insufficient to show a difference.

Both studies inconsistently reported outcomes by trimester of pregnancy or specific anaesthetic agent(s) used.\(^8,9\) Likewise, the ASGE guideline\(^10\) does not present recommendations for particular trimesters of pregnancy. Therefore, these studies and guideline do not address whether certain anaesthetic agents are safer for use during surgery in early pregnancy.

Furthermore, confirmed pregnancy was an inclusion criterion for both the SR\(^8\) and the retrospective chart review\(^9\) which may have affected choice of anaesthesia for the surgical procedures, therefore the applicability of these study findings to cases in which pregnancy is not yet known is also unclear.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

One SR\(^8\) and one non-randomized study\(^9\) regarding the safety of anaesthetic agents in pregnant women undergoing non-obstetric surgical or endoscopic procedures were identified for inclusion in this report. No randomized controlled trials comparing different anaesthetic agents or techniques in pregnant women were identified. Major adverse maternal and neonatal outcomes were rare in both included studies. Results from the SR suggested that these events were more common when surgery was conducted during the first trimester of pregnancy.\(^8\) The authors of the retrospective chart review concluded that RA for laparotomic adnexal mass surgery during pregnancy may be associated with an increased risk of preterm labour. The retrospective nature of the non-randomized study and the SR (comprised mostly of retrospective case series) included in this report limits the conclusions that can be made about the impact of anaesthesia alone on the pregnancy outcomes. Since patients were not randomized to particular interventions, additional factors such as underlying maternal condition, type of surgery, and variable anaesthetic techniques likely confounded the findings. Therefore, the results should be interpreted with caution.

The ASGE guideline\(^10\) recommends meperidine as the preferred agent for endoscopic procedures on pregnant women requiring moderate sedation, and that deep sedation for endoscopy should be administered by an anaesthesia provider. Anaesthesia recommendations were not provided according to stage of pregnancy, but the guideline does suggest that
endoscopy should be deferred to the second trimester whenever possible. ASGE reports that in general, no anaesthetics have clearly been associated with teratogenic effects. This statement has been echoed in several review articles on this subject. Despite the absence of clear evidence of teratogenic effects of anaesthesia on humans, the potential risks of these agents for pregnant women undergoing surgery remain. As a result, it has been suggested to try to detect early pregnancies before exposing a patient to surgery and anaesthesia, avoid elective surgeries during pregnancy, ensure that the anaesthesia team is aware when a surgical patient is pregnant, inform patients of the potential risks of anaesthesia, and for all members of the clinical team to provide comprehensive case management.

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REFERENCES


APPENDIX 1: Selection of Included Studies

553 citations identified from electronic literature search and screened

526 citations excluded

27 potentially relevant articles retrieved for scrutiny (full text, if available)

2 potentially relevant reports retrieved from other sources (grey literature, hand search)

29 potentially relevant reports

26 reports excluded:
- irrelevant population (23)
- irrelevant intervention (1)
- irrelevant comparator (2)

3 reports included in review
# APPENDIX 2: Characteristics of Included Publications

## Table A1: Characteristics of Included Systematic Reviews and Meta-Analyses

<table>
<thead>
<tr>
<th>Primary Studies Included</th>
<th>Population Characteristics</th>
<th>Intervention</th>
<th>Comparator(s)</th>
<th>Clinical Outcomes, Length of Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohen-Kerem et al., 2005, Canada</td>
<td>Pregnant women, any trimester: N = 12,452 (includes overlap between registry studies)</td>
<td>Any surgical intervention, urgent or elective, under regional anaesthesia or general anaesthesia.</td>
<td>None necessary</td>
<td>Maternal and fetal death, delivery induced by surgical procedure, major birth defects, prematurity</td>
</tr>
<tr>
<td></td>
<td>Patients reported by trimester in 39 studies: First, n = 411; Second, n = 688; Third: n = 288</td>
<td></td>
<td></td>
<td>Length of follow up not reported.</td>
</tr>
</tbody>
</table>

AE = adverse event; mL = millilitres; N = number, RCT = randomized controlled trial

## Table A2: Characteristics of Included Clinical Studies

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Patient Characteristics</th>
<th>Intervention(s)</th>
<th>Comparator(s)</th>
<th>Clinical Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hong 2006&quot;⁷</td>
<td>Pregnant women, any trimester, undergoing surgery for adnexal masses, n = 235</td>
<td>GA for laparotomy, n = 137; GA for laparoscopy, n = 27; RA for laparotomy, n = 71</td>
<td>Groups compared with each other; Non-surgical pregnant patients, n = 80,527</td>
<td>Maternal death, spontaneous abortion, congenital anomalies, stillbirths, neonatal death, preterm labour, premature delivery, low-birthweight</td>
</tr>
</tbody>
</table>

EA = epidural anaesthesia; GA = general anaesthesia; N = number, RA = regional anaesthesia; RCT = randomized controlled trial; SA = spinal anaesthesia
### Table A3: Characteristics of Included Guidelines

<table>
<thead>
<tr>
<th>Target population</th>
<th>Intervention and Practice Considered</th>
<th>Major Outcomes Considered</th>
<th>Evidence collection, Selection and Synthesis</th>
<th>Evidence Quality and Strength</th>
<th>Recommendations development and Evaluation</th>
<th>Guideline Validation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnant and lactating women undergoing endoscopy</td>
<td>Anesthetics and analgesics used for gastrointestinal endoscopy</td>
<td>Safety</td>
<td>Search of electronic database (PubMed), hand-searches of published literature from reference lists and expert recommendation</td>
<td>Evidence quality assessment using GRADE; rating scheme provided</td>
<td>Expert consensus</td>
<td>Unspecified</td>
</tr>
</tbody>
</table>

ASGE = American Society for Gastrointestinal Endoscopy; GRADE = Grading of Recommendations Assessment, Development and Evaluation.
## APPENDIX 3: Critical Appraisal of Included Publications

### Table A4: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR²

<table>
<thead>
<tr>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
</table>
| Cohen-Kerem et al., 2005⁸ | • A priori protocol not provided  
• Unclear whether article selection and data extraction occurred in duplicate  
• Unclear whether a grey literature search was performed  
• List of excluded studies not provided  
• Scientific quality of the included studies not formally assessed  
• Likelihood of publication bias not addressed  
• No conflict of interest declarations |
| • Comprehensive literature search was performed  
• List and characteristics of included studies provided | |

### Table A5: Strengths and Limitations of Clinical Studies using Downs and Black⁶

<table>
<thead>
<tr>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
</table>
| Hong, 2006⁹ | • Study was not randomized  
• Study was not blinded  
• Estimates of the random variability in the data not provided  
• Exact probability values not provided  
• Most neonatal outcomes not presented only according to intervention group without describing additional confounding factors such as gestational age at time of surgery, elective versus emergency surgery, etc.  
• Small sample size likely insufficient to detect a difference between groups for rare outcomes; no sample size calculation done as this was a retrospective study |
| • Clearly described objectives, patient inclusion and exclusion criteria, interventions, and main outcomes to be measured  
• Representative selection of study subjects from entire hospital patient population  
• Surgical patients and non-surgical control patients recruited from the same population and over the same length of time  
• Patient demographics and distribution of confounding variables clearly described  
• Reliable compliance with intervention due to the study of a surgical intervention  
• Valid outcome measures used and main findings clearly reported |
### Table A6: Strengths and Limitations of Guidelines using AGREE II

<table>
<thead>
<tr>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASGE, 2012&lt;sup&gt;10&lt;/sup&gt;</td>
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<tr>
<td>• Clear population to whom the guideline is meant to apply (pregnant and lactating women; however, trimester of pregnancy not mentioned)</td>
<td>• Overall objectives and health questions of guideline not clearly described</td>
</tr>
<tr>
<td>• Target users of guideline clearly described</td>
<td>• Composition of guideline development group and role of each member of the committee not thoroughly described</td>
</tr>
<tr>
<td>• Evidence used to support recommendations evaluated using GRADE</td>
<td>• Unclear whether patient preferences have been sought</td>
</tr>
<tr>
<td>• Method used to formulate recommendations described</td>
<td>• Limited literature search performed (one database, search terms not provided</td>
</tr>
<tr>
<td>• Health benefits, side effects, and risks have been considered in formulating the recommendations</td>
<td>• Unclear data selection criteria</td>
</tr>
<tr>
<td>• Clear separation of guidelines for pregnant women versus lactating women</td>
<td>• Unclear process for guideline review and updating</td>
</tr>
<tr>
<td>• The different options for anaesthesia use during endoscopy are clearly presented and considered in recommendations</td>
<td>• No discussion of guideline implementation</td>
</tr>
<tr>
<td>• Key recommendations are easily identifiable</td>
<td>• Source of funding for guideline development not described</td>
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<tr>
<td>• Relevant financial disclosure statement for individual committee members provided</td>
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</tbody>
</table>

ASGE = American Society for Gastrointestinal Endoscopy; GRADE = Grading of Recommendations Assessment, Development and Evaluation.
APPENDIX 4: Main Study Findings and Guideline Recommendations

Table A7: Summary of Findings of Included Studies

<table>
<thead>
<tr>
<th>Main Study Findings</th>
<th>Author’s Conclusions</th>
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</thead>
<tbody>
<tr>
<td>Cohen-Kerem et al., 2005* (Systematic review)</td>
<td>“Using modern surgical and anesthetic techniques, the risk of maternal death appears to be very low. Surgery and general anesthesia do not appear to be major risk factors for spontaneous abortion…. Non-obstetric surgical procedures do not increase the risk for major birth defects. Hence, urgent surgical procedures should be performed when needed.” Pages 471 to 472</td>
</tr>
<tr>
<td>Maternal death: 1/12,542 procedures (0.006%)</td>
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<tr>
<td>Cause of maternal death: intra-abdominal hemorrhage at 2 weeks post-laparoscopic cholecystectomy (18 weeks pregnant at surgery)</td>
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<td>Miscarriage (&lt; 20 weeks) or fetal loss (≥ 20 weeks): first trimester, n = 43 (10.5%); all trimesters, n = 236 (5.8%)</td>
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<tr>
<td>Fetal loss: non-registry studies, n = 45 (2.5%); registry studies, 99/5405 (1.8%)</td>
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<tr>
<td>Delivery induced by procedure or underlying condition: 79/2282 (3.5%)</td>
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<tr>
<td>Prematurity: 597/7313 (8.2%)</td>
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<tr>
<td>Major birth defects: first trimester, 105/2663 (3.9%); all trimesters, 194/9879 (2.0%)</td>
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<tr>
<td>Hong 2006# (Retrospective chart review)</td>
<td>“Although this series has limitations, we confirmed that surgical patients with adnexal mass in pregnancy are faced with increased risks of preterm labor and premature delivery compared to the non-surgical population. We also believe that patients who receive regional anesthesia for laparotomy may be at increased risk of preterm labor compared with those given general inhalational anesthesia for laparotomy or laparoscopy. Therefore, when regional anesthesia for adnexal mass surgery is indicated in a pregnant patient, precautions should be taken to minimize the risk of postoperative preterm labor.” Page 215</td>
</tr>
<tr>
<td>Significantly higher rate of preterm labour in the RA for laparoscopy group compared with the other surgical groups, and between surgery groups and non-surgical controls: RA for laparotomy – 21/71 (29.6%) GA for laparotomy – 8/137 (5.8%) GA for laparoscopy – 0/27 (0%) Non-surgical pregnant patients – 2614/80,527 (3.2%)</td>
<td></td>
</tr>
<tr>
<td>Significant difference in rate of premature delivery between surgical groups and non-surgical controls (no difference between three surgery and anaesthesia groups): RA for laparotomy – 4/71 (5.6%) GA for laparotomy – 12/137 (8.8%) GA for laparoscopy – 2/27 (7.4%) Non-surgical pregnant patients – 3876/80,527 (4.8%)</td>
<td></td>
</tr>
<tr>
<td>Rates of spontaneous abortion similar among surgery groups and non-surgery control: RA for laparotomy – 4/71 (5.6%) GA for laparotomy – 6/137 (4.4%) GA for laparoscopy – 2/27 (7.4%) Non-surgical pregnant patients – 4624/80,527 (5.7%)</td>
<td></td>
</tr>
<tr>
<td>2 stillbirths reported only in the RA for laparotomy group (first trimester surgery, fetal losses at 22 and 31 weeks)</td>
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<tr>
<td>3 congenital anomalies (two Down’s syndrome, one cystic hygroma) reported only in the GA for laparotomy group (first trimester surgery)</td>
<td></td>
</tr>
</tbody>
</table>
Table A7: Summary of Findings of Included Studies

<table>
<thead>
<tr>
<th>Main Study Findings</th>
<th>Author’s Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>• 2 of 3 congenital anomalies led to therapeutic abortions (Down’s syndrome at 17.4 weeks, cystic hygroma at 12 weeks).</td>
<td></td>
</tr>
<tr>
<td>• No difference in rate of therapeutic abortions between surgery and non-surgery populations (1.28% vs. 1.26%)</td>
<td></td>
</tr>
<tr>
<td>• No significant differences among surgical groups or between surgery and non-surgery groups in rates of additional outcomes: congenital anomaly, neonatal death, low birthweight</td>
<td></td>
</tr>
<tr>
<td>• No maternal deaths</td>
<td></td>
</tr>
</tbody>
</table>

GA = general anaesthesia; RA = regional anaesthesia.

Table A8: Main Recommendations of the Included Guidelines

<table>
<thead>
<tr>
<th>Main Recommendations</th>
<th>Strength of Recommendations by GRADE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ASGE, 2012</strong></td>
<td></td>
</tr>
<tr>
<td>• “We suggest that for endoscopic procedures involving moderate sedation during pregnancy, meperidine is the preferred agent followed by small doses of midazolam as needed” Page 23</td>
<td>Very low quality; any estimate of effect is very uncertain</td>
</tr>
<tr>
<td>• “We recommend deep sedation, when needed, be administered by an anesthesia provider” Page 23</td>
<td></td>
</tr>
</tbody>
</table>

ASGE = American Society of Gastrointestinal Endoscopy; GRADE = Grading of Recommendations Assessment, Development and Evaluation.
APPENDIX 5: Additional References of Potential Interest

Safety of Anaesthesia for Caesarean Section


**Safety of Anaesthesia for Fetal Surgery**
