Predictors of Outcome Patterns in Infants Diagnosed with Congenital Ovarian Cysts

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ABSTRACT

Introduction:

Variable management practices complicate the identification of the optimal treatment strategy for infants diagnosed with ovarian cysts during the fetal period. Most fetal ovarian cysts remain asymptomatic in the neonatal period. However, they have been associated with complications including ovarian torsion and subsequent loss of the ovary. Early surgical intervention has been proposed to mitigate the risk of ovarian loss. Alternatively, ovarian cysts have also been observed to regress spontaneously after birth using serial ultrasounds. Without a standardized observation period or strict indications for surgical intervention, many patients with congenital ovarian cysts undergo surgery despite their benign nature. This thesis sought to identify the incidence and predictors of spontaneous resolution of congenital ovarian cysts, to describe factors associated with surgical management, and to evaluate whether surgical or non-surgical management is associated with an increase in ovarian preservation.

Methods:

There are two main studies in this thesis: a systematic review and a pan-Canadian retrospective cohort study. The systematic review was performed to examine the incidence and predictors of spontaneous resolution of congenital ovarian cysts within the first year of life. The impact of surgical or non-surgical management on ovarian preservation was also described. The national pan-Canadian retrospective cohort study was then conducted at ten pediatric surgical institutions to evaluate the effects of various treatment strategies on outcomes of patients with congenital ovarian cysts. Prenatal and postnatal sonographic cyst characteristics were collected and compared between patients who underwent surgical management versus observation for a

minimum of 3 months, and Kaplan-Meier analysis was used to assess the overall time to cyst resolution. Stepwise multivariate logistic regression analysis was used to determine independent clinical predictors of surgical management. Multivariate logistic regression was also used to compare the incidence of ovarian preservation between patients who were initially observed and those who underwent early surgery.

Results:

Seventy studies including 1,635 patients were included in the systematic review. A meta-analysis was not performed due to heterogeneity in the management strategies and reporting of results. The systematic review revealed that surgery was more likely to be performed in patients with complex ovarian cysts or cysts with diameters >40mm. The majority of surgical interventions resulted in oophorectomy, or loss of the ovary. Approximately 80% of ovaries with complex cysts managed non-surgically were not detected on follow-up ultrasound, indicating inevitable ovarian loss. These findings call into question whether early surgery in patients with congenital ovarian cysts does in fact mitigate the risk of ovarian loss. However, most studies were underpowered with high heterogeneity and numerous biases. The incidence of spontaneous ovarian cyst resolution at one year of age in our Canadian sample of 189 patients was 61.9%. Median time to postnatal cyst resolution was 124 days (95% CI 111 – 166 days). A total of 57 patients underwent surgical intervention for an ovarian cyst, 43 of whom underwent an oophorectomy. No significant difference was found in the odds of ovarian preservation between patients who underwent early surgery and those who were initially observed (OR 3.06, 95% CI 0.86 – 13.2), regardless of sonographic complex features or size.

Conclusions:

There is limited high-quality evidence and substantial heterogeneity in the management strategies employed to treat congenital ovarian cysts. Study findings suggest the majority of congenital ovarian cysts are asymptomatic and spontaneously resolve. Early surgical intervention does not seem to increase the incidence of ovarian preservation, and observation may be a safe management strategy.

RÉSUMÉ

Introduction :

Il est difficile d'identifier la prise en charge optimale pour le traitement des enfants recevant un diagnostic de kyste ovarien durant la gestation, compte tenu du large éventail de pratiques courantes. La plupart des kystes ovariens demeurent asymptomatiques durant la période néonatale. Cependant, ces derniers sont associés à certaines complications telles que les torsions annexielles et la perte d'ovaire qui peut en résulter. Une option thérapeutique proposée est la prise en charge chirurgicale rapide afin de mitiger le risque de perte annexielle. Parallèlement, les kystes ovariens peuvent aussi régresser de façon spontanée après la naissance, tel qu'observé par échographies séquentielles. Étant donné le manque de consensus sur la période d'observation standard ainsi que sur les indications chirurgicales à suivre, plusieurs patientes ayant des kystes congénitaux passent sous le scalpel malgré la nature bénigne de leur kyste. La thèse présente a pour but d'identifier l'incidence et les prédicteurs de résolution spontanée de kystes annexiels, de décrire les facteurs associés au besoin de chirurgie ainsi que d'évaluer l'impact de traitement chirurgical ou non sur la conservation d'ovaire.

Méthodes :

La thèse présente comprend deux études principales : une revue systématique et une étude de cohorte rétrospective pancanadienne. La revue systématique avait pour but de déterminer l'incidence et les prédicteurs de résolution spontanée de kystes ovariens dans l'année suivant la naissance. L'impact de traitement chirurgical ou non-chirurgical sur la conservation de l'annexe a aussi été étudié. L'étude de cohorte rétrospective nationale pancanadienne a ensuite été menée dans dix établissements de chirurgie pédiatrique afin d'évaluer les effets de diverses stratégies de

traitement sur les résultats des patientes atteintes de kystes ovariens congénitaux. Les caractéristiques échographiques prénatales et postnatales des kystes ont été recueillies et comparées entre les patients ayant subi une prise en charge chirurgicale par rapport à une approche d'observation pendant au moins 3 mois, et une analyse de Kaplan-Meier a été utilisée pour évaluer le temps global de résolution des kystes. Une analyse de régression logistique multivariée pas à pas a été utilisée pour déterminer les prédicteurs cliniques d'une prise en charge chirurgicale. La régression logistique multivariée a également été utilisée pour comparer l'incidence de conservation ovarienne entre les patientes initialement observées et celles qui ont subi une intervention chirurgicale précoce.

Résultats:

Soixante-dix études portant sur 1 635 patients ont été incluses dans la revue systématique. Une méta-analyse n'a pas été réalisée en raison d'une hétérogénéité importante dans les stratégies de prise en charge et la communication des résultats. La revue systématique a révélé qu'une intervention chirurgicale était plus probable chez les patientes ayant des kystes ovariens complexes ou d'un diamètre de > 40 mm. La majorité des chirurgies menaient à une ovariectomie. De plus, environ 80 % des ovaires avec des kystes complexes gérés de manière non-interventionnelle n'ont pas été détectés lors de l'échographie de suivi, indiquant une perte ovarienne inévitable. Ces résultats remettent en question l'idée qu'une intervention chirurgicale précoce chez les patientes atteintes de kystes ovariens congénitaux atténuerait réellement le risque de perte ovarienne. Cela étant dit, la plupart des études manquaient de puissance avec une forte hétérogénéité et de nombreux biais. L'incidence de résolution spontanée de kystes ovariens dans notre échantillon canadien de 189 patientes était de 61,9 %. Le délai médian de résolution

postnatale du kyste était de 124 jours (IC à 95 % 111 – 166 jours). Au total, 57 patientes ont subi une intervention chirurgicale pour un kyste ovarien, dont 43 ont subi une ovariectomie. Aucune différence significative n'a été trouvée dans les chances de préservation ovarienne entre les patientes ayant subi une chirurgie précoce et celles qui ont été initialement observées (OR 3,06, IC à 95 % 0,86 - 13,2), indépendamment des caractéristiques complexes échographiques ou de la taille.

Conclusion:

Il existe une hétérogénéité substantielle et peu de données probantes de haute qualité quant aux stratégies de prise en charge utilisées pour traiter les kystes ovariens congénitaux. Les études suggèrent que la majorité des kystes ovariens congénitaux sont asymptomatiques et se résolvent spontanément. Les interventions chirurgicales précoces ne semblent pas augmenter l'incidence de la préservation ovarienne, et la prise en charge par observation peut être une stratégie considérée sécuritaire.

THESIS FORMAT

This thesis is presented in manuscript-based format in compliance with the guidelines and specifications detailed by the Faculty of Graduate and Postdoctoral Studies at McGill University. It includes two distinct manuscripts that are either in preparation or have already been submitted for publication. The first manuscript is a systematic review that is being prepared for submission to the *Journal of Pediatric Surgery*. The second manuscript is a pan-Canadian retrospective cohort study that was for published in *Annals of Surgery.*

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I am also extremely thankful for Dr. Maida Sewitch, who generously accepted to co-supervise and guide me through my research. Dr. Sewitch has taught me the importance of rigorous research methodology, and her input and feedback have been instrumental in allowing me to complete my thesis. Her enthusiasm, constant availability, and relentless encouragement were so appreciated, and I am extremely grateful.

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ORIGINAL CONTRIBUTIONS

The work presented in this thesis represents original contributions and adds to the body of knowledge for all pediatric general surgeons. This work highlights the natural history of congenital ovarian cysts and clinical outcomes after surgical and non-surgical management of patients diagnosed with these cysts. The thesis includes the most recent and comprehensive systematic review conducted on the predictors of clinical outcomes of congenital ovarian cysts. This thesis also includes the largest multicenter study evaluating the effect of management strategy choices on the clinical outcomes of patients with congenital ovarian cysts, and provides data that support non-surgical management as a safe option, which does not negatively affect the rate of ovarian preservation. While I have received support from my supervisors and co-authors for each study, the data presented in the following chapters represents my original work.

AUTHOR CONTRIBUTIONS

I have made a substantial contribution to each of the individual manuscripts listed below and played an active role in the study design, data acquisition, data analysis, and preparation of the manuscript. My contributions were performed under the guidance of my supervisors, Dr. Maida Sewitch and Dr. Sherif Emil, and in collaboration with the co-authors listed below. The contributions of each individual author within each manuscript is listed below.

1. Fetal ovarian cysts: a systematic review of determinants of prenatal and postnatal management

Study conception*:* Nadia Safa, Maida Sewitch, Cassandra Poirier, Elena Guadagno, Robert Baird, Pramod Puligandla, Sherif Emil
Data acquisition: Nadia Safa, Cassandra Poirier Elena Guadagno
Analysis and interpretation of data: Nadia Safa, Maida Sewitch, Cassandra Poirier, Elena Guadagno, Robert Baird, Pramod Puligandla, Sherif Emil
Drafting of manuscript: Nadia Safa, Maida Sewitch, Elena Guadagno, Sherif Emil
Critical revision of manuscript: Nadia Safa, Maida Sewitch, Cassandra Poirier, Elena Guadagno, Robert Baird, Pramod Puligandla, Sherif Emil

2. Treatment and outcomes of congenital ovarian cysts: a study by the Canadian Consortium for Research in Pediatric Surgery (CanCORPS)

Study conception: Nadia Safa, Natalie Yanchar, Pramod Puligandla, Maida Sewitch, Robert Baird, Elena Guadagno, Sherif Emil
Data acquisition: Nadia Safa, Natalie Yanchar, Robert Baird, Niamh Campbell, Rati Chadha, Christopher Griffiths, Manvinder Kaur, Annie Le-Nguyen, Ahmed Nasr, Elena Guadagno
Analysis and interpretation of data: Nadia Safa, Natalie Yanchar, Pramod Puligandla, Maida Sewitch, Robert Baird, Sherif Emil
Drafting of manuscript: Nadia Safa, Maida Sewitch, Sherif Emil
Critical revision of manuscript: Nadia Safa, Natalie Yanchar, Pramod Puligandla, Maida Sewitch, Robert Baird, Mona Beaunoyer, Niamh Campbell, Rati Chadha, Christopher Griffiths, Sarah Jones, Manvinder Kaur, Annie Le-Nguyen, Ahmed Nasr, Nelson Piché, Hannah Piper, Pascale Prasil, Rodrigo LP Romao, Lisa VanHouwelingen, Paul Wales, Elena Guadagno, Sherif Emil

CHAPTER 1 – INTRODUCTION

Incidence of Fetal Ovarian Cysts

Prior to the widespread use of ultrasound as a reliable and accurate imaging modality for the ovary, the frequency of ovarian cysts was believed to be low in the pediatric population. Fetal ovarian cysts were first described by Valenti in 1975.[1] Since that time, technical advancements in ultrasonography have led to an increased detection rate of ovarian cysts.[2] Kirkinen reviewed 21,000 pregnancies and reported sonographic evidence of ovarian cysts in 8 fetuses, leading to the widely accepted estimated incidence of prenatally diagnosed ovarian cysts of 1 in 2,625 births.[3] Autopsy series of stillborn and neonatal deaths have demonstrated that ovarian cysts are even more common, and can be found in a much as one-third of female newborns.[4, 5] Clinically significant fetal ovarian cysts are less common, but nevertheless they are still the most common abdominal cysts in female neonates.[6]

Development of the Ovary

The fetal ovary, once thought of as quiescent until puberty, is hormonally responsive as early as the second trimester of pregnancy.[7] It is the active site of follicle formation and maturation, which occurs secondary to maternal and fetal hormones, including maternal and fetal estrogens, placental human chorionic gonadotropin (hCG), and fetal pituitary gonadotropins (follicle-stimulating hormone [FSH] and lutenizing hormone [LH]).

The ovary is comprised of three different embryonic tissues: (1) mesenchyme, (2) germinal epithelium, and (3) germ cells.[8, 9] Proliferation of germ cells (oogonia) begins at 6-8 weeks of gestation, and continues until they enter meiotic division and are transformed into

oocytes.[9, 10] Follicular development is initiated at 16-20 weeks under the influence of placental gonadotropins.[4, 10] First, *oocytes* become surrounded by granulosa cells, which are derived from the *germinal epithelium*. Subsequently *mesenchyme cells* surround the developing follicle and form the theca, which are the endocrine cells of the ovary. Therefore, all three embryonic components join together to comprise the primary follicle. These follicles continue to grow in size and number in response to ongoing placental hormonal stimulation and activation of the hypothalamic-pituitary-ovary axis, an important hormonal axis responsible for regulating ovarian hormonal production. Mature follicles, known as graffian follicles, can be found as early as 28 weeks.[11] After birth, a decrease in maternal hCG and estrogen levels occurs due to removal of maternal hormones. However, fetal gonadotropins, LH and FSH, continue to rise until approximately 3-4 months of age when the hypothalamus and pituitary become sensitive to the decrease in estrogen levels.[12] A negative feedback mechanism is then activated and leads to a decrease in LH and FSH around 4-6 months. These levels remain relatively low throughout childhood until puberty when the hypothalamic-pituitary-ovary axis is activated again.

Pathogenesis of Fetal Ovarian Cysts

Fetal ovarian cysts are the most common intra-abdominal cyst observed in the female fetus. The timeline of folliculogenesis correlates with the natural history of fetal ovarian cyst development. The influence of maternal and fetal hormones promotes the development of fetal ovarian cysts. The majority can be identified in the third trimester, although the earliest reported fetal ovarian cyst was identified at 19 weeks.[13] Three theories exist linking fetal ovarian cyst formation to hormonal stimulation; they involve (1) fetal gonadotropins, (2) placental hCG, and (3) an immature hypothalamic-pituitary-ovarian axis (gonadostat).[7, 11, 14] The first theory is that a

precocious peak in fetal gonadotropins between the 20th and 30th week leads to increased stimulation of the follicles and subsequent cyst formation. This hypothesis is supported by evidence of an increased risk of cyst formation seen with fetal hypothyroidism, which is thought to result in non-specific pituitary stimulation by elevated thyroid-stimulating hormone.[13, 15-17] The second theory associates hCG with ovarian cysts. Increased cyst formation has been observed in pregnancies complicated by gestational diabetes, Rh isoimmunization, and preeclampsia, and all these conditions are associated with increased production of gonadotropins by the placenta.[4, 18] The third theory suggests that an immature hypothalamic-pituitary-ovarian axis may be associated with fetal ovarian cyst formation. Normally, maturation of this hormonal axis takes place in the third trimester. Full-term newborns with a mature axis respond to low postnatal levels of estrogen with a negative feedback mechanism that results in a decrease of FSH and LH hormone levels. In premature infants or in infants with an immature gonadostat, inadequate negative feedback results in ongoing elevated levels of FSH and LH. This can lead to ovarian hyperstimulation and promote ovarian cyst formation.[19, 20]

Complications of Ovarian Cysts

Fetal ovarian cysts are often asymptomatic at birth. Occasionally they present in neonates as asymptomatic abdominal masses detected during a routine physical examination. Despite their benign nature, fetal ovarian cysts can be associated with a variety of complications in the prenatal and postnatal period, including mass effect, torsion, rupture, bowel obstruction, and death.

Mass Effect

Large ovarian cysts may cause compression of fetal intra-abdominal organs. Concern for thoracic compression and consequent pulmonary hypoplasia has been reported in association with large fetal ovarian, as well as compression of retroperitoneal structures such as the ureter or vena cava.[3, 9, 20-22]

Torsion & Intracystic Hemorrhage

The most common complication is ovarian torsion. It is caused by rotation of the ovary, and occasionally the fallopian tube, with the vascular pedicle on its axis, resulting in arterial, venous, or lymphatic obstruction (Figure 3). This often leads to hemorrhagic infarction and necrosis, although intracystic hemorrhage may occur spontaneously in the absence of torsion. Rarely, chronic ovarian torsion can lead to de-vascularization and result in auto-amputation of the ovary. Most of these free-floating cysts slowly atrophy and eventually undergo resorption, but a minority persist as calcified remnants.

Torsion is rare in the postnatal period, and usually occurs in the antenatal period or during birth.[23-25] The most common presenting symptom of ovarian torsion is lower abdominal pain.[9] Other symptoms in an infant include abdominal distension, vomiting, feeding intolerance, or general irritability. A systematic review and meta-analysis reported that the overall incidence of ovarian torsion is approximately 20%, and is more common in larger cysts > 40 mm in diameter.[26] However, it has been reported in cysts as small as 22 mm in diameter.[26-28] Length of the vascular pedicle has also been proposed as a predictor of intracystic hemorrhage and torsion.[14, 29]

Cyst Rupture

A rare complication is rupture of an ovarian cyst.[30-33] It most commonly occurs in the antenatal period or during delivery. Patients who present with peritonitis due to hemoperitoneum from the ruptured cyst are usually considered surgical emergencies. However, three ruptured cysts have been reported in infants who remained asymptomatic in the postnatal period, and were followed with serial ultrasounds until the cysts resolved.[3, 32, 33]

Bowel Obstruction

Bowel obstruction occurs most commonly due to adhesions caused by a torsed, necrotic ovary.[34] Large cysts may also present in utero with polyhydramnios due to proximal gastrointestinal compression.[35, 36] Rarely, bowel perforation may occur resulting in a surgical emergency.[34, 37]

Death

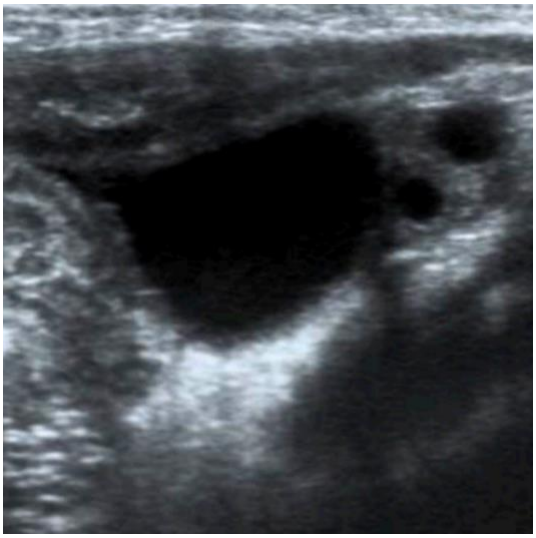
Death secondary to ovarian cyst complications is rare. Currently, 8 cases have been reported in the literature of infant deaths related to torsion since 1969.[38-44] Cause of death was most commonly attributed to hypovolemic shock and bleeding diathesis secondary to uncontrollable hemorrhage within the ovarian cyst.

Imaging Appearances

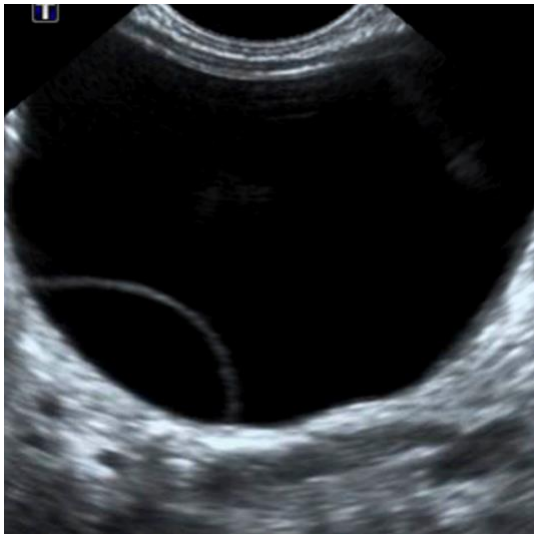
Ultrasound is the imaging modality of choice for diagnosis and follow-up of fetal ovarian cysts, both in the prenatal and postnatal period. The diagnosis of a fetal ovarian cyst is based on the following criteria: (1) presence of a uniformly-shaped cystic structure located on one side of the fetal abdomen, (2) integrity of the urinary and gastrointestinal tracts, and (3) female sex of the fetus.[13, 14]

Nussbaum et al. is credited as the earliest group to categorize fetal ovarian cysts as simple or complex.[45] The sonographic features of simple ovarian cysts are: anechoic, round, unilocular, more often intra-abdominal rather than intra-pelvic, and thin-walled (**Figure 1**). Occasionally a simple cyst may have one septation. A "daughter cyst" sign is reported to be pathognomonic for a simple ovarian cyst with a 100% specificity and 82% sensitivity, and is defined as a small, round, anechoic structure within a cyst (**Figure 1B**).[46, 47] The sonographic features of complex cysts are: heterogeneous with echogenic components, thick-walled, containing free-floating material or debris, intracystic septations, intracystic fluid-fluid level, or retracted blood clots (**Figure 2**). Some complex cysts may have a solid appearance or solid components, corresponding to an organized hematoma. This can lead to difficulty differentiating the cyst from a malignancy.[48] The presence of ascites in association with an ovarian cyst raises the possibility of a ruptured cyst.[45, 49]

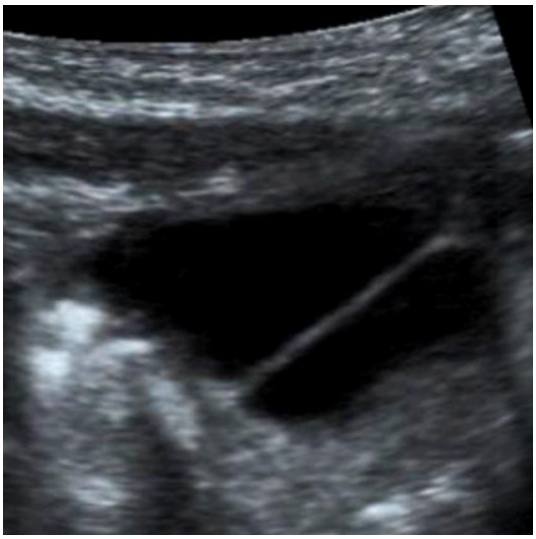
Figure 1. Simple ovarian cyst



A Simple ovarian cyst

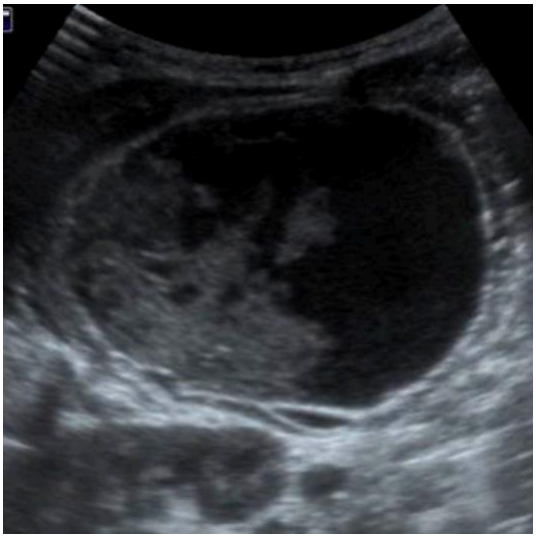


B Daughter cyst sign

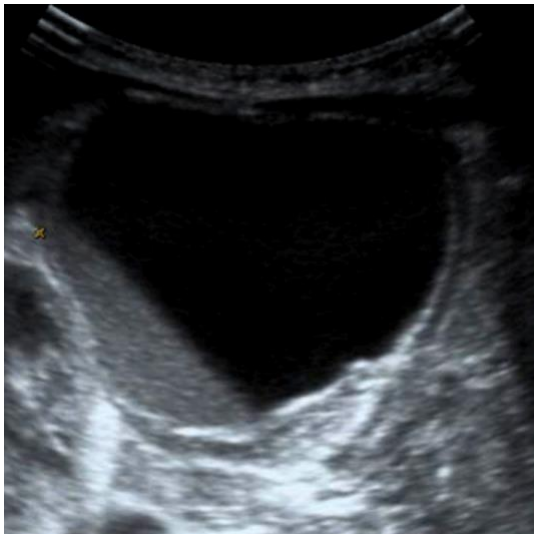


C Simple ovarian cyst with single septation

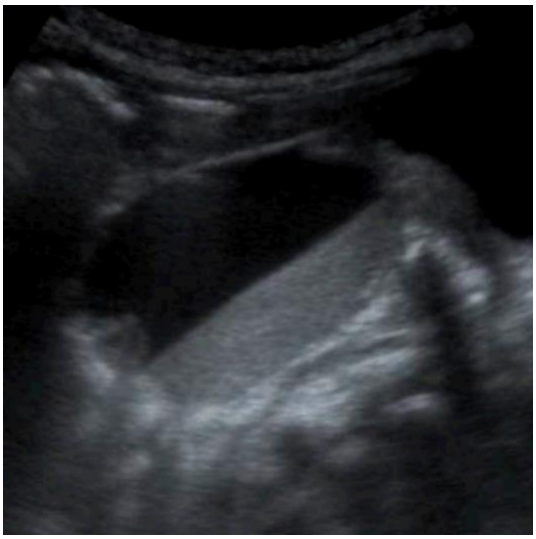
Figure 2. Complex ovarian cyst



A Internal debris/echoes



B Fluid-fluid level



C Fluid-level with solid component

Sonographic findings of ovarian torsion are related to the duration and degree of torsion, complete or incomplete vascular obstruction, and the presence of intracystic hemorrhage. The presence of vascular flow on Doppler imaging does not exclude ovarian torsion, as it may represent vascular proliferation within the cyst wall and fibrotic tissue congestion around the cyst.[50]

Rarely, necrosis can lead to self-amputation of the ovary. This is identified on ultrasound as a free mobile abdominal mass, usually described as a "wandering mass", and it is commonly associated with progressive dystrophic calcifications.[50, 51] Resorption and involution of the cystic mass may also present as a mobile calcified abdominal mass. Another important image finding is a change in position of the ovary, compared to prior ultrasounds, which indicates a free-floating ovary.[50]

Magnetic resonance imaging (MRI) is useful for further characterization of the ovarian cyst in cases where acoustic access is limited by maternal habitus, fetal position, or low volume of amniotic fluid.[6] MRI is also useful for confirming intact urinary and gastrointestinal tracts and confirming the sex of the fetus, all of which are criteria for the diagnosis of an ovarian cyst. Lastly, in the context of sonographic findings that raise the suspicion for a malignancy, such as a solid lesion or a complex cyst with internal calcifications.

Differential Diagnoses of Fetal Intra-Abdominal Cysts

The differential diagnosis for a fetal intra-abdominal cyst is broad, and includes renal cyst, ureterocele, urachal anomalies, dilated bowel, meconium cyst, enteric duplication cyst, lymphangioma, choledochal cyst, and cystic neuroblastoma [6]. The diagnosis can be narrowed by identifying surrounding anatomy, recognizing the cyst location within the abdomen or pelvis,

and characterizing the organ of origin. For example, a classical five-layered cyst wall with alternating hyperechoic and hypoechoic layers, also known as a "gut signature", is highly suggestive of a duplication cyst.[14] However, layers can be obscured on ultrasound and a gut signature can be missed or mistaken for a thickened cyst wall. Although it can be quite challenging to identify the organ of etiology for a fetal intra-abdominal cyst due to confines of the fetal abdomen, recognition of pertinent imaging findings can help distinguish fetal ovarian cysts from other fetal abdominal cystic origins.

Management of Fetal Ovarian Cysts

Delivery Plan

Historically, immediate delivery by prompt cesarean section was suggested for fetuses diagnosed in utero with ovarian torsion to avoid soft tissue dystocia or cyst rupture during delivery.[52] However, this recommendation was based on anecdotal case reports. Currently cesarean deliveries are recommended for obstetrical indications only.[14]

Treatment Options

The controversy surrounding the treatment of ovarian cysts is longstanding. Most ovarian cysts detected in the prenatal or neonatal period are small and asymptomatic. The expectation for nearly all simple ovarian cysts is that they will resolve spontaneously after birth with the removal of the fetus from the maternal hormonal milieu. Simple ovarian cysts < 40 – 50 mm in diameter should be followed with serial ultrasound and managed non-surgically given the high likelihood of spontaneous resolution.[12]

What is more controversial is the management of large simple cysts (> 40-50 mm in diameter) and complex cysts. There is a paucity of high quality prospective data to show that the

risk of non-surgical management is higher than the risk of immediate surgery. As a result, there are two general schools of thought regarding the management of large or complex fetal ovarian cysts in the neonate: surgical and non-surgical management. The major goal of both surgical treatment and non-invasive monitoring by ultrasound is optimal ovarian preservation. However, the long-term outcome and risk to future fertility is unknown for both management strategies.

Surgical Management

Experts who advocate for elective surgical intervention for large or complex cysts in the neonatal period base this recommendation on the presumption that surgery will decrease the risk of ovarian torsion and other secondary complications associated with the cyst. Though there is conflicting evidence regarding whether larger cysts are at a higher risk of torsion compared to smaller cysts, a surgical intervention attempts to decrease the size of the cyst to decrease this risk of torsion. Ultimately, avoiding torsion and other cyst complications results in improved ovarian preservation, and avoids ovarian loss, for which the long-term fertility risks are largely unknown. However, the majority of perinatal ovarian torsions occur in the antenatal period, therefore it is unlikely that postnatal surgery will decrease the rate of torsion.[23, 25] Additionally, many surgeons recommend operating on all complex cysts, even if ovarian preservation is not expected, to prevent complications such as intracystic hemorrhage, cyst rupture, and intestinal obstruction. It remains unclear whether the risk of early intervention, specifically the risk of anesthesia-related complications in the developing neonate, outweighs the risk of such rare, but severe complications.[53]

A variety of surgical approaches exist for the treatment of a newborn with an asymptomatic ovarian cyst. Given that the majority of torsion events occur antenatally, some experts recommend intrauterine cyst aspiration to mitigate the incidence of ovarian torsion and

eliminate the need for postnatal surgery. This strategy has been advocated for simple cysts larger than 40 mm.[54] However, experience with this procedure is limited, and potentially severe complications such as cyst rupture and peritonitis preclude its widespread acceptance.[55] Furthermore, ongoing hormonal stimulation in the maternal environment can lead to cyst recurrence. Some experts would rather perform an ultrasound-guided aspiration in the postnatal period to circumvent the risks associated with prenatal aspiration and still avoid postnatal surgery.[56] The advantage of postnatal aspiration is that it enables preservation of ovarian tissue while obviating some of the iatrogenic complications associated with fetal cyst aspiration. Nevertheless, it is still associated with risks, including limited visualization of the cyst and adjacent organs depending on infant positioning. This is especially important in the context of a misdiagnosed ovarian cyst where a lethal outcome can ensue.[57] To avoid misdiagnosis and potentially lethal complications, laparoscopic aspiration has been recommended.[58] Although general anesthesia is unavoidable with this management strategy, the procedure is minimally invasive, it allows for complete visualization of the intra-abdominal cavity with confirmation of the diagnosis, and the ovaries can still be preserved. Laparoscopy has rapidly gained more support than laparotomy among pediatric surgeons, likely due to its potential advantages of improved cosmesis, shorter hospital stay, decreased ileus, and reduced postoperative pain.[59-61] However, both laparoscopy and laparotomy have been shown to be safe and effective in the surgical management of neonatal ovarian cysts. The advantage of laparoscopy and laparotomy is the ability to perform additional procedures, including detorsion of the ovary, cystectomy when the ipsilateral ovarian parenchyma appears viable, and oophorectomy or salpingo-oophorectomy when no viable ovarian tissue is detected or when there is involvement of the fallopian tube.[60]

Despite the intention to spare ovarian tissue in patients with both simple and complex cysts and prevent torsion, many surgical interventions result in oophorectomy, particularly in complex cysts. A systematic review and meta-analysis of 954 fetuses demonstrated that ovarian loss due to oophorectomy occurred in 25% of patients that underwent surgical management. Moreover, complex cysts (OR 35.1, 95% CI 17-72.7) and cysts ≥ 40 mm (OR 58.9, 95% CI 19.2 – 181) were statistically significantly associated with an increased risk of ovarian loss with surgical management. The macroscopic appearance of necrosis makes it difficult to appreciate any viable ovarian tissue, therefore ovary-sparing surgery may become more challenging to perform. Moreover, some studies have reported viable ovarian tissue in surgical specimens, indicating that the intra-operative appearance of ovarian necrosis may not reflect the true viability of the ovarian tissue.[28, 62]

Non-Surgical Management

Justification for non-surgical management is based on the benign nature of fetal ovarian cysts, and that the expected outcome is usually spontaneous resolution after birth. Non-surgical management consists of serial ultrasound follow-ups of the cyst and avoids a potentially unnecessary surgery. In most cases, particularly for simple cysts, ovarian parenchyma persists after spontaneous resolution of the ovarian cyst.[24] Even large cysts > 50 mm, including one cyst measuring 87 mm in diameter, have been documented to spontaneously resolve.[27, 63] There have been documented disappearances of the ipsilateral ovary after spontaneous cyst resolution, which most likely represents resorption and involution of the cyst after perinatal torsion.[24, 64]

Despite the success of this "wait-and-see" approach for both simple and complex cysts, some ovarian cysts fail to undergo spontaneous resolution after months of monitoring. In these situations, an operation is sometimes necessary to confirm the diagnosis or to remove a persistent

cyst. No standardized "waiting" period or ultrasound surveillance protocols have been established for the longitudinal follow-up of infants with fetal ovarian cysts. There are reports of cysts being observed up to two years without complications until complete resolution.[65] Therefore, the indications for surgical intervention in cysts that fail non-surgical management vary widely among surgeons and centers.

Thesis Objectives

The objectives of this Master's thesis were:

1. To identify the known clinical and sonographic predictors influencing surgical versus non-surgical management strategies for fetal ovarian cysts
2. To determine the incidence of spontaneous ovarian cyst resolution in the first year after birth
3. To examine whether early surgical intervention is associated with increased ovarian preservation compared to non-surgical management.

To accomplish these objectives:

1. I conducted a systematic review to determine the clinical predictors that have influenced the management strategies of fetal ovarian cysts. The systematic review also compared ovarian preservation between surgical and non-surgical management.
2. I conducted a national multicenter retrospective cohort study involving ten centers across Canada. I reported the national incidence of spontaneous cyst resolution and incidence of complications secondary to ovarian cysts in the first year after birth. Additionally, I examined predictors of management strategies and

compared the incidence of ovarian preservation in the first year of age between patients who underwent surgical and non-surgical management.

The thesis is structured as follows: Chapter 1 provides background on the pathogenesis of congenital ovarian cysts and a review of the current literature on the known management strategies used for patients with congenital ovarian cysts. Chapter 2 is the systematic review manuscript, followed by a short Chapter 3 that connects the first manuscript to the second. The retrospective cohort study comprises Chapter 4. This is then followed by a discussion of the research methods and results in Chapter 5. Finally, Chapter 6 provides the conclusions of the thesis. Inevitably, there will be some degree of repetition throughout the work. Please note that each manuscript (Chapters 2 and 4) has its own reference list and associated Tables and Figures. The master reference list at the end of the thesis pertains to Chapters 1, 3, and 5 only.

CHAPTER 2 – FETAL OVARIAN CYSTS: A SYSTEMATIC REVIEW OF DETERMINANTS OF PRENATAL AND POSTNATAL MANAGEMENT (MANUSCRIPT #1)

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Abstract

Background: Variable management practices complicate the identification of optimal treatment strategies for infants diagnosed with ovarian cysts during the fetal period.

Methods: A systematic search of eight databases was performed according to PRISMA guidelines (CRD42019125172) for studies describing surgical and non-surgical management of fetal ovarian cysts. Data on clinical predictors, including sonographic cyst character and size, and long-term outcomes were extracted. Patients who underwent intrauterine aspiration (IUA) were examined separately.

Results: Of 8,392 references, 70 studies (1985 – 2019) were included. All were observational case series except 4 cohort studies and 1 randomized controlled trial. Outcomes of 1,681 fetal ovarian cysts in 1,635 patients were reported. In 36 studies, cyst echogenicity and size >4-5 cm were associated with higher risks of ovarian torsion, leading to surgical intervention. In 17 studies, there was no association between cyst size or sonographic character and perinatal outcome. Between 73-80% of ovaries with complex cysts managed non-surgically were undetected on follow-up ultrasound, indicating ovarian atrophy. Cyst management was not standardized across the included studies. 20 studies examined 118 patients after IUA, including an RCT that did not demonstrate a reduction in postnatal intervention after IUA compared with in utero observation.

Conclusions: Cyst size and complex sonographic character are the major determinants of perinatal management decisions. However, the low-quality evidence and substantial heterogeneity in management strategies prevent the development of robust recommendations for the management of fetal ovarian cysts.

1. Introduction

Antenatal ovarian cysts were first described by Valenti et al. in 1975, and since that time, great advances in ultrasound have led to an increased frequency of diagnosis, with an estimated incidence of approximately1 in 2,500 births.[1, 2] Ovarian cysts are generally benign in nature, occurring as a result of stimulation from maternal estrogen, placental HCG, and fetal gonadotropins.[3] After birth, decreased hormonal stimulation and maturation of the hypothalamic-pituitary-ovary axis leads to an expected spontaneous regression of the cyst within 4 to 6 months.[2]

Although their natural tendency is to regress after birth, fetal ovarian cysts are associated with several complications including compression of various intra-abdominal organs, intracystic hemorrhage, cyst rupture, and ovarian torsion. The most common complication is ovarian torsion, which may result in loss of the ovary, fallopian tube, or both and can affect future fertility.[4, 5] Despite the increase in the number of cysts reported in the literature, there remains uncertainty regarding their prenatal and postnatal management.

The two main management strategies for fetal ovarian cysts are surgical or radiological intervention and observation. The risk of ovarian loss due to cyst complications has led some to advocate for early surgical intervention in the postnatal period in an attempt to preserve ovarian tissue. Others recommend initial observation and non-surgical management, arguing that intervention is unlikely to lead to ovarian preservation. Frequently, the necrotic state of the ovaries or the close adherence of the cyst to the remnant ovarian tissue results in oophorectomy despite the intention of ovarian tissue preservation. Management decisions are most commonly driven by cyst size or sonographic character of the cyst, but strong indications for prenatal or postnatal interventions have not yet been validated. Therefore, there is persistent controversy

regarding surgical indications, and a lack of standardized management guidelines for these babies.

The aims of this systematic review were to critically evaluate the published literature, summarize the clinical predictors for and outcomes following surgical and non-surgical management of infants with prenatally diagnosed ovarian cysts, and compare ovarian preservation between surgical and non-surgical management strategies.

2. Methods

2.1 Study Design

A systematic review was conducted in accordance with the Tri-Council Policy Statement on Ethical Conduct for Research Involving Humans; institutional ethics approval was not required. The study protocol was registered *a priori* on the International Prospective Register of Systematic Reviews (PROSPERO) on August 29, 2019 (CRD42019125172).

2.2 Search Strategy

The search strategy, detailed in Appendix 1, was developed in collaboration with a senior medical librarian (EG). The following databases were searched from inception until July 23, 2019: Medline (Ovid), Embase (Ovid), Cochrane (Wiley), Global Health (Ovid), Global Index Medicus (WHO), Africa-Wide Information (Ebsco), CINAHL (Ebsco) and Web of Science (Clarivate Analytics). The systematic literature search identified studies which included variations of the terms “abdominal cyst” or “ovarian cyst” in the fetal and/or neonatal population, found in the subject headings as well as text words in the title, abstract, or keyword fields. No time or language limits were applied to the search. Animal studies were excluded. Given that a diagnosis in utero is usually presumptive, and other intra-abdominal cysts such as

mesenteric cysts or enteric cysts cannot be ruled out with absolute certainty on antenatal ultrasound, the search included intra-abdominal cyst variants. In addition to studies located through the searches, the list was augmented by searching the reference list of each selected study to find further papers.

2.3 Eligibility criteria

Eligibility was based on the study providing a description of the natural history of fetal ovarian cysts and a comparison of predictors for surgical and non-surgical management. Only full-text studies that reported a prenatal diagnosis of ovarian cyst were considered for inclusion. Editorials, commentaries, letters, case reports with fewer than three fetal ovarian cysts, and prior systematic reviews were excluded. Studies in which the cysts were diagnosed after birth or where time of diagnosis was unclear were excluded. Surgical case series that included only patients undergoing surgical treatment were also excluded. The primary outcome of interest was surgical or non-surgical management for fetal ovarian cysts. Secondary outcomes included ovarian tissue preservation, ovarian torsion, resolution of cyst in utero or after birth, IUA, postnatal aspiration, change in sonographic character, and any other complications attributable to the presence of a fetal ovarian cyst.

2.4 Screening process and data extraction

After return of search results and removal of duplicates, two independent reviewers (NS, CP) performed a first screen based on titles and abstracts using the online Rayyan tool (https://rayyan.qcri.org/cite).[6] A third independent reviewer (SE) was available to resolve discrepancies or conflicts. Subsequently, the same two independent reviewers (NS, CP) performed full-text screening based on the eligibility criteria, as well as data extraction using a pre-established data extraction template. Study characteristics extracted were author, year,

country of origin, and study design. Patient characteristics were also extracted including: gestational age at diagnosis, radiologic imaging modalities, prenatal and postnatal cyst size and sonographic character, and age at surgery. Outcomes extracted included: spontaneous resolution of cyst in utero or after birth, status of ipsilateral ovary after cyst resolution, surgery, type of surgical intervention (ovary-sparing or not), postnatal aspiration, IUA, change in sonographic character from simple to complex, ovarian torsion, and length of follow-up. Sonographic character was defined based on Nussbaum's classification of neonatal ovarian cysts into two groups, which is the most widely used classification of ovarian cyst character: (1) simple cysts, which are usually anechoic, round, unilocular and thin-walled, and (2) complex cysts, which are usually thick-walled and heterogeneous, containing hyperechoic elements, free-floating or solid material, or intracystic septations.[7] Ovarian preservation was defined as ovary-sparing surgical intervention or sonographic evidence of an ipsilateral ovary after spontaneous cyst resolution. A clinical variable was identified as an indication for a particular management strategy only if it was reported as such, or if the study reported a specific management protocol based on specific cyst criteria. Cysts that underwent IUA were evaluated separately with regards to cyst characteristics and subsequent outcomes after the procedure. Study results were reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[8]

2.5 Data analysis

Due to the heterogeneous nature of included studies in terms of surgeon- and center-specific management strategies and length of follow-up as well as the poor level of evidence of the majority of studies, a meta-analysis was not performed. The results were synthesized and summarized in a qualitative fashion, and the overall trends in management were described.

2.6 Risk of bias assessment

Risk of bias assessment was performed using the Methodological Index for Non-Randomized Studies (MINORS) tool, which was designed and validated to assess the methodological quality for surgical studies where randomization is not always possible or feasible.[9] The tool can be used for non-comparative (8 items) and comparative studies (12 items). Each item is scored 0 (not reported), 1 (reported but inadequate), or 2 (reported and adequate), with a global ideal score of 16 for non-comparative studies and 24 for comparative studies. MINORS assessment was reported for each study and the cumulative risk-of-bias was displayed in tabular format. For randomized controlled trials (RCTs), the Cochrane Collaboration risk-of-bias tool (RoB 2), which assesses bias in five distinct domains and results in an overall risk-of-bias judgement, was used.[10]

3. Results

3.1 Search results and study characteristics

The literature search revealed a total of 8,392 titles, of which 7,610 were non-duplicated titles. Of these, 194 were deemed highly or possibly relevant and fully appraised, of which 124 (64%) were excluded (Appendix 2). In total 70 studies were included[11-80] (Figure 1) that examined 1,681 ovarian cysts (median 18, range 3 – 82) in 1,635 fetuses (median 17, range 3 – 81).

A summary of the characteristics of included studies is presented in Table 1. Among the 70 studies, 65 were case series, 5 of which were multicenter, 4 were cohort studies, and 1 was an RCT. Maximum follow-up duration ranged from 3 months to 9 years, with 20 studies (29%) following patients longer than 1 year after birth. All patients were monitored using ultrasound, with 10 studies reporting additional utilization of MRI to assist in cyst characterization [40, 47, 48, 56,

[63-65, 67, 69, 72] and 2 studies using CT.[65, 74] Various combinations of cyst size and/or sonographic characteristics were used as indications for surgical or non-surgical management. The exact indications for surgery varied among studies. All studies intervened surgically for patients with symptoms secondary to the presence of an ovarian cyst. Four studies examined ovarian preservation after spontaneous cyst resolution or surgical intervention, with three of these studies conducting long-term follow-up (i.e., over 1 year). A summary of the fetal ovarian cyst outcomes can be found in Table 2. IUA was performed in 113 fetuses from 19 studies, and cyst characteristics and outcomes are shown in Table 3.

3.2 Clinical predictors of surgical vs non-surgical management

3.2.1 Cyst size

Twenty-six studies considered that larger cyst size presented a risk for complications if left untreated, and therefore used cyst size as an indication for surgical intervention to prevent potential future torsion and preserve the ovary.[11, 13, 14, 19, 22, 25-27, 30, 32, 38, 39, 48, 49, 51, 59, 60, 63, 64, 66, 68, 70, 71, 73, 74, 77] The size cut-offs for what was considered a large cyst that required an intervention varied between the studies. One study implemented a size cut-off for surgical intervention of 80 mm for simple cysts and 30 mm for complex cysts.[34] Another study operated on all simple cysts greater than 20 mm in diameter.[46] Marino used receiver-operating characteristic (ROC) curves to determine the predictive ability of mean and maximum cyst diameters for postnatal management, which they reported were 45 and 47 mm respectively.[78] This was based on a series of 38 patients, 12 of which underwent surgery and 26 that regressed spontaneously.

Four studies compared large cysts to small cysts on complications and surgical intervention.[25, 38, 48, 77] Giorlandino reviewed the outcomes of 42 cysts in 41 fetuses who were followed after birth, 30 of which were anechoic simple cysts.[25] They reported a statistically

significant difference in diameter between simple cysts that underwent a complication and subsequent surgery compared to those that resolved spontaneously (5.7 ± 1.2 vs 3.8 ± 1.2, p = 0.001), with a statistically significantly higher risk of surgical management in cysts 50 mm or greater in diameter (p = 0.01). Zampieri reported on 57 patients with antenatal simple ovarian cysts ranging between 27 to 75mm in diameter.[48] A diameter of > 50mm was statistically significantly associated with surgical intervention. All 24 neonates with cysts >50 mm underwent surgery, sixteen of those for immediate complications after birth, namely ovarian torsion (6 patients) and intracystic hemorrhage (10 patients). The other 8 patients had a cyst greater than 70 mm in diameter, and underwent surgery to avoid future complications. The remaining 33 cysts, all with diameters less than 50 mm, spontaneously resolved within 6 months of life. Similarly, Mittermayer reported a statistically significantly higher mean diameter of cysts in those that required surgical treatment compared to those that resolved spontaneously (6.8 ± 2.4 vs 3.3 ± 0.08, p < 0.01). More recently, Husen found that torsion occurred more often in ovarian cysts with a size ≥40mm (11/18 vs 11/63), p = 0.001).[77]

In contrast, twelve studies found no association between cyst size and outcome.[23, 24, 31, 35, 43, 44, 47, 52, 61, 62, 76, 79] Shimada's review of 16 ovarian cysts found no correlation between cyst size and torsion rate; the mean diameter of cysts that resolved was 44.2 ± 12.8 mm versus that of cysts with torsion was 44.6 ± 12.1 mm.[47] Similarly, Karakuş did not encounter prenatal torsion in simple ovarian cysts larger than 40 mm.[61] More recently, Tyraskis argued that size alone is not the only criterion for surgical intervention, reporting that larger cysts can spontaneously regress under observation with serial ultrasounds. In that series, 44% of patients with cysts > 40 mm resolved spontaneously.[76] They found no difference in the incidence of torsion between cysts > 40 mm (25%) to those ≤ 40 mm (10%) (p = 0.26). Furthermore, logistic regression using cyst

measurements demonstrated no statistically significant difference in the rate of both torsion and surgery with increasing cyst size.

3.2.2 Cyst character

In eleven studies, all complex or echogenic cysts regardless of size were treated surgically.[21, 25-27, 34, 35, 46, 49, 66, 70, 74] The indication for surgical intervention was that complex sonographic features were indicative of torsion or intracystic hemorrhage, so surgery was performed in an attempt to salvage ovarian tissue in that context. Monnery-Noché described a series of 37 complex cysts out of 67 prenatally diagnosed ovarian cysts, all of which were managed surgically.[46] Intraoperatively, 33 (89%) cysts were torsed, and 4 (11%) cysts were hemorrhagic; salpingo-oophorectomy or oophorectomy was performed in 29 (78%) patients. In another study, ten patients with complex cysts (diameter range 40 to 73 mm) underwent surgery between the 1st and 4th months of life.[35] In all patients, the ovaries were no longer viable, and an oophorectomy was performed. Nakamura also managed all cysts with complex features surgically.[70] They did not demonstrate that cyst character on the first prenatal ultrasound was associated with a higher incidence of ovarian torsion ($p = 0.07$).

One study reported the indication for surgery was a documented change in cyst echogenicity at birth from anechoic to echogenic, representing a change in cyst character from simple to complex after birth.[17] They reviewed twelve fetal ovarian cysts, of which 4 underwent elective surgery. In three patients with prenatal evidence of intracystic echoes suggestive of a complex cyst, a conservative approach was taken, and all resolved spontaneously. This was reportedly due to a resorption of a prenatally twisted ovary. All three patients remained asymptomatic in the postnatal period.

One study managed all complex ovarian cysts with serial ultrasounds for up to 3 months, and those that failed to regress or increased in size were operated.[61] In their series of 38 ovarian cysts, 11 cysts were complex and managed non-surgically, with seven of them resolving within the 3 months of postnatal follow-up. Three cysts did not regress and underwent cystectomy. One patient presented with a complication related to the cyst, namely intestinal obstruction, and underwent an emergent laparotomy. Despite the majority of cysts spontaneously resolving, three of these patients presented with abdominal pain, vomiting, and abdominal distension at 9, 11, and 12 months, respectively. Intraoperatively, all three patients had a bowel obstruction with a necrotic ovary adherent to either a jejunal or ileal segment, and all underwent oophorectomy with adhesiolysis.

Three studies included 8 complex cysts managed non-surgically that resolved spontaneously after an observation period of 12 months or more.[32, 38, 43] The longest reported time to cyst resolution was reported by Mittermayer, who reported resolution of 4 complex cysts at 12, 18, 19, and 24 months. Kwak reported the resolution of a complex ovarian cyst after 16 months, despite a documented increase in cyst size after birth.[43]

Five studies managed complex cysts with serial ultrasounds only.[32, 40, 41, 53, 62] Luzzatto described spontaneous involution of 10 out of 13 complex cysts, with a longer mean time to resolution (8 months) compared to simple cysts (3.5 months).[32] The remaining three complex cysts failed to regress and were operated at 6, 8, and 17 months of age. Those patients remained asymptomatic throughout the long follow-up duration, and did not experience complications secondary to the complex ovarian cyst. Another study reported spontaneous resolution of four out of five complex cysts within 6 months of age, with only one complex cyst requiring oophorectomy at 1 month for torsion.[53] Foley followed eleven patients prenatally and postnatally

with ultrasounds.[41] Postnatal scans revealed that seven of ten prenatal simple cysts became complex. Out of eight postnatal complex cysts, 2 cysts were managed with surgery at 7 and 8 months, respectively. The first cyst had failed to regress, and in the second, parental concern prompted laparoscopic intervention. None of the patients developed symptoms such as abdominal distension, vomiting, or intestinal obstruction during the follow-up period. Enríquez found that complex ovarian cysts in patients that are asymptomatic may be followed with regular sonography with good outcomes.[40] Eleven prenatally diagnosed complex cysts resolved without surgery.

3.2.3 Symptoms secondary to fetal ovarian cysts

Among the 695 ovarian cysts that underwent postnatal surgery and postnatal aspiration, 6% (43/695) were operated due to clinical symptoms or signs attributable to presence of the ovarian cyst. The remaining patients were asymptomatic at the time of surgery. Symptoms included abdominal distension, vomiting, feeding intolerance, and signs included peritonitis, and respiratory insufficiency due to mass effect from the cyst. All patients with symptoms or signs secondary to the cyst presented early in the neonatal period except three patients, who presented with intestinal obstruction secondary to a necrotic ovarian cyst after a long period of observation at 9, 11, and 12 months, respectively.

3.2.4 Failure of non-surgical management

Twelve studies reported on 21 cysts that underwent surgery after having failed non-surgical management.[19, 20, 22, 32, 35, 41, 60-62, 65, 67, 78] The observation period was at least 4 months and consisted of follow-up with serial ultrasounds. Follow-up time ranged between 4 – 24 months (median 7 months). Indications for surgery included persistence of the cyst, suspicion of auto-amputation in a complex cyst, increased cyst size, and concern for postnatal torsion. One

patient underwent surgery at 7 months for a complex cyst because of parental concern for future complication.

3.3 Ovarian preservation after surgical versus non-surgical management

3.3.1 Ovarian preservation after surgical intervention

Of 695 cysts managed surgically, details on the type of procedure were provided for 88% (614/695) cysts. Among them, 41% (252/614) cysts were managed with an ovary-sparing procedure, namely with a cystectomy, surgical drainage, or postnatal aspiration. Only 20 patients from 13 studies with cysts that were managed surgically had an auto-amputated cyst discovered intra-operatively.[13, 19-21, 27, 30, 32, 36, 40, 61, 76, 78] Therefore, those patients were not candidates for ovary-sparing surgery. All of these cysts had sonographic complex features detected postnatally.

While the majority of studies were able to perform ovary-sparing procedure for at least one cyst in their series, 13 studies reported that no ipsilateral ovaries were salvageable in any of their patients who underwent surgical management for a complex ovarian cyst.[13, 17, 24, 25, 32, 36, 38, 40, 41, 47, 51, 54, 60] Giorlandino reported on 27 cysts that were managed operatively, none of which had any identifiable ovarian tissue at the time of surgery.[25] Except for 2 cysts operated on for increasing size, all patients had evidence of torsion on prior ultrasounds, with 24 torsions confirmed intra-operatively. Surgery consisted of oophorectomy or salpingo-oophorectomy in all patients. Similarly, in Chiaramonte's series, despite the success of ovarian preservation in 4 out of 5 surgically-managed simple cysts, all 10 patients with complex cysts underwent an oophorectomy because no viable ovarian tissue was detected.[35] In a comparative series, Enriquez reported on 17 complex cysts managed either surgically (7 cysts) or observed with serial ultrasounds (10 cysts).[40] All surgical interventions resulted in oophorectomy or salpingo-oophorectomy, while all the observed complex cysts spontaneously resolved without surgery.

Alternatively, Zampieri successfully performed an ovary-sparing surgery for all 24 neonates who were managed surgically, including 16 with cysts complicated by torsion or intracystic hemorrhage. Similarly, Comparetto managed 16 patients surgically with ovarian-sparing cystectomies despite the presence of cyst complications. However, these complications were apparent immediately after birth. Therefore, there was no initial observation period and surgery was performed early.

Two studies reported that viable ovarian tissue was detected in the surgical specimen of 4 patients. Galiner reported such findings in two hemorrhagic cysts that underwent surgery.[44] In another study, Papic identified a single postnatal torsion out of 25 patients that were managed conservatively with serial ultrasound. The cyst was a simple 78mm cyst on initial postnatal ultrasound, but it developed a fluid debris level and torsion was present at operation, and subsequently an oophorectomy was performed. However, normal viable ovarian tissue was identified on pathology. In another three complex cysts that were managed early with surgery, torsion was present intra-operatively in all three patients, and oophorectomy was performed. Pathology reports identified areas of normal viable ovarian tissue in all three surgical specimens.

3.3.2 Long-term follow-up of ovaries

Of the twenty studies that followed patients for more than 1 year after birth, three detailed longitudinal ultrasound examinations to evaluate the state of the adnexa after non-surgical management.[32, 41, 50] One study conducted follow-up at an average of 3.5 years of age (range 3 months and 9 years) for 19 patients whose ovarian cysts were managed conservatively or with postnatal aspiration.[32] All 9 patients with simple cysts at birth demonstrated evidence of two viable ovaries with no residual cysts, while only one ovary was detected in 8 out of 10 patients with complex cysts. A second study reported follow-up data on fourteen of the 21 patients

included in the study, who were followed for an average of 6.6 years (range 1.3 – 11.6 years).[50] Eight of 11 patients (73%) with a complex cyst on the first postnatal scan had only one ovary detected, whereas both ovaries were detected in all patients with simple cysts on postnatal scans. In a third study, 6 out of 8 patients with complex cysts at first postnatal scan had only one ovary detected at follow-up, 5 of which had ovarian loss demonstrable at 1 year.[41]

One study examined the status of the ipsilateral ovary beyond 1 year of age in patients who underwent both surgical and non-surgical management.[44] In this series of 79 patients, twenty-four had hemorrhagic complex cysts that were managed non-surgically. Of those patients, 19 had no detectable ipsilateral ovary either on laparoscopy or by ultrasound beyond the age of 1 year. Furthermore, out of a total of 55 hemorrhagic cysts included in their study, 76.4% had no detectable ovary at the time of surgery or on ultrasound examination during the postnatal follow-up period.

One study compared ovarian preservation between patients that underwent immediate surgical intervention and those that underwent surgery after failure of an initial period of observation.[62] Of the 25 cysts that were managed with initial observation, 13 cysts failed observation and underwent surgery due to failure of cyst resolution or concern for postnatal ovarian torsion. The mean observation time prior to surgery was 12 weeks (range 3 – 64 weeks). Overall, they found no statistically significant difference in ovarian preservation between the two groups (initial observation: 75% vs early surgery: 89%, $p = 0.577$), and they concluded that a period of observation does not adversely affect the rates of ovarian preservation.

3.4 Intrauterine cyst aspiration

Prenatal aspiration is a management strategy aimed at preventing future cyst complications such as torsion. The timing of intervention varied during the gestation period.

Four studies cited the controversy surrounding aspiration, and performed it only for cysts large enough that had the possibility to impair spontaneous delivery or fetal development, but no size cut-off was specified.[35, 37, 43, 72] Eight studies reported a specific size cutoff for prenatal aspiration; 30 mm in two studies,[33, 75] 35 mm in 1 study,[57] 40 mm in 2 studies,[29, 67] and 50 mm in 3 studies.[25, 36, 72] Four studies specified only anechoic cysts were eligible for the procedure.[25, 36, 38, 75] However, twelve complex cysts were aspirated in five studies, with a total of 8 cysts successfully resolving in the postnatal period without further intervention.[29, 40, 57, 64, 76] Higher incidence of torsion was reported for simple cysts that were managed expectantly compared to those that underwent prenatal aspiration (2/10; 20% vs 0/7; 0%).[67]

Various indications contributed to the decision to intervene postnatally after prenatal aspiration, and included a change in sonographic character from simple to complex features, cyst recurrence, increase in size, and sonographic evidence of torsion. Two patients from different studies required a second aspiration postnatally prior to regression of the ovarian cyst.[23, 67] One underwent aspiration of a simple cyst that recurred was subsequently diagnosed with an ileal atresia, and underwent surgery in the postnatal period.[29]

Two studies compared postnatal outcomes for ovarian cysts that underwent aspiration to those that did not. Bagolan et al. reported a lower incidence of postnatal surgery in patients who underwent prenatal aspiration of a simple ovarian cyst ≥ 50mm (2/12; 14%) compared to a historical control group of cysts that were not aspirated in utero (12/14; 85%) (p =0.002).[36] Those two patients underwent oophorectomy for postnatal ultrasound signs of torsion. In 2018, Diguisto et al. performed an RCT comparing need for postnatal intervention following prenatal aspiration in patients with simple ovarian cysts ≥ 30mm.[75] They reported that intrauterine aspiration was associated with a higher incidence of in-utero involution of the cyst compared to

non-interventional prenatal management (47.1% vs 18.5%, RR 2.54, 95% CI 1.07-6.05) and a lower incidence of oophorectomy (3% vs 22.2%, RR 0.13, 95% CI 0.02-1.03). However, no difference was found in overall postnatal interventions between the two groups (20.6% vs 37%, RR 0.55, 95% CI 0.24-1.27).

3.5 Methodological quality

Using the Oxford Centre for Evidence-Based Medicine (OCEBM), all studies were graded as Level 3 or 4 studies, except for one study by Sanna et al., which was an RCT and graded as Level 2.[80, 81] The MINORS scores for the methodological quality are presented in Table 4, and the cumulative MINORS scores are displayed in Figure 2. Fifty-four of the 69 observational studies were non-comparative prospective or retrospective case series with an average MINORS score of 9.3 ± 1.5 (out of 16). The remaining 15 studies were comparative case series or cohort studies. Two studies used historical comparative groups, while the remainder used contemporary comparative groups. None of these studies used factors to match their comparative groups, and only one third of studies described baseline characteristics of the comparative groups. The average MINORS score for the comparative observational studies was 14.4 ± 1.8 (out of 24). Overall, the majority of studies had adequate follow-up information, and appropriate endpoints. Most collected data retrospectively, and only one third had a clearly stated aim. The overall risk of bias for the RCT was scored ‘low’ in all 5 domains of the RoB2 tool.

4. Discussion

Management of fetal ovarian cysts continues to be an area of controversy. The literature does not allow for definite conclusions or management recommendations owing to the heterogeneity in management across centers. However, our findings suggest that cyst size > 40-

50 mm and complex sonographic features are the most common indications for surgical intervention on an asymptomatic fetal ovarian cyst. Additionally, despite the intention to preserve ovarian tissue, surgical intervention for a complex ovarian cyst usually results in removal of an already necrotic ipsilateral ovary. Our findings confirm the need for continued investigation of the perinatal outcomes of fetal ovarian cysts and offer possibilities for future potential study.

4.1 Clinical predictors of management strategies

Cyst size and complex sonographic character are the major determinants of perinatal management decisions, with large and complex cysts having a high likelihood for surgery. However, as much of the current literature stems from case series reporting high complication rates and thus the need for surgical intervention, postnatal surgery may be overestimated. Furthermore, there is evidence that with time, fetal ovarian cysts, both simple and complex, may regress in the postnatal period irrespective of size or sonographic character, and that this regression may take up to 24 months.[38, 43, 82] In a previous systematic review that examined the outcomes of fetal ovarian cysts, Bascietto reported that a majority of cysts regress and resolve spontaneously, with a pooled proportion of 53.8% (95% CI 46 – 61.5%).[83] Overall, postnatal surgery occurred in approximately 40% of patients with ovarian cysts. However, as is the case in observational studies, management strategies are not performed randomly and are based on many factors, including the comfort level of a surgeon to continue observing a patient. To date, non-surgical management of fetal ovarian cysts has been reported with successful outcomes in a majority of patients, but studies are limited by small sample size, retrospective study design, and lack of standardized management protocols.[32, 41] Cyst size and sonographic character may

influence management decisions, but these clinical variables have not been validated as indications for immediate surgical management or non-surgical management.

The decision to classify an ovarian cyst as having failed non-surgical management is controversial. Spontaneous resolution of a fetal ovarian cyst is thought to correlate with the rise and fall of gonadotropin levels within the first 4 months of life.[84] Therefore, the justification for the observational approach lies in the expectation that fetal ovarian cysts will regress and resolve by 4-6 months after birth.[2] However, there is no standard observation period reported in the literature to guide non-surgical management. Moreover, no study addressed the need for a standardized ultrasound surveillance schedule for patients with fetal ovarian cysts. Frequent surveillance is especially important when considering timing of a surgical intervention, as studies have indicated that the duration of torsion is more associated with subsequent ovarian loss rather than the event itself. In the majority of patients, the decision to classify a cyst as having failed non-surgical management is up to the surgeon who is treating the patient. Out of all the cysts that underwent surgical management, only 6 % (43/695) were operated on due to acute symptoms, while the remainder were asymptomatic and underwent surgery based on other clinical predictors of presumed complications, including surgeons' individual comfort levels, parental choice, and other variables that could not be ascertained from the data. It is difficult to make assumptions about what the perinatal and long-term outcomes of those cysts would have been had non-surgical management been the strategy of choice. A standardized ultrasound surveillance protocol, especially after birth, is necessary to detect early signs of cyst complications and increase the potential of salvaging ovarian tissue via a surgical intervention. However, given the low rate of symptoms secondary to fetal ovarian cysts and that the majority of symptoms present themselves within the first 4 weeks of life, an initial observation period of 4-6 months may allow

surgeons to better appreciate the natural history of these asymptomatic cysts and avoid an unnecessary operation in the neonatal period for these infants.

4.2 Ovarian preservation

The recommendation for early surgical intervention on an asymptomatic fetal ovarian cyst lies in the inherent fear that ovarian tissue may be lost as a result of ovarian torsion. Loss of an ovary may have profound deleterious effects on future fertility and endocrine function, though studies addressing this topic are scarce and limited to adult series.[85] Nevertheless, despite the general appeal of ovarian preservation techniques, surgery for the majority of cysts demonstrating complex features or evidence of torsion usually results in oophorectomy or salpingo-oophorectomy. A review by Brandt reported 92% of neonatal ovaries with torsion had evidence of torsion present on the first postnatal ultrasound, suggesting that the majority of torsion events occur in utero.[20] This is supported by more recent studies which further highlight that even the earliest surgical intervention would fail to preserve the ovary.[35, 41, 62, 67, 76] Moreover, pathology reports have indicated the presence of viable ovarian tissue in complex cysts that have been surgically removed despite a macroscopic appearance of necrosis.[32, 62, 86]

Only one study investigated the effects of an observation period on neonatal ovarian preservation and found no statistically significant difference between the group that underwent immediate surgery compared with the group that was primarily observed (89% (8/9) vs 75% (6/8), $p = 0.577$).[62] Half of the neonates in the study were spared from an operation without compromising the rate of ovarian preservation. Therefore, while the goal of preserving ovarian tissue is important, the decision to operate early may not lead to a higher chance of saving the ipsilateral ovary. Furthermore, avoiding unnecessary exposure to general anesthesia for these

already vulnerable neonates is increasingly relevant as concerns over neurodevelopmental sequelae of anesthesia grow in the pediatric literature.[87, 88]

4.3 Role of intrauterine aspiration

A lack of clinical equipoise exists regarding the value of IUA for fetal ovarian cysts as a way to prevent future complications and increase the rate of ovarian preservation.[83, 89, 90] Proponents of the procedure believe that since the majority of torsions occur antenatally, IUA may mitigate this risk and subsequently decrease the risk of ovarian loss. Published in 2018, the first randomized controlled trial assessing the efficacy of IUA in anechoic fetal ovarian cysts reported that more postnatal interventions were necessary in the expectantly-managed group compared with those that underwent IUA, but this difference was not statistically significantly different (RR 0.55, 95% CI 0.24 – 1.27).[75] IUA is associated with numerous risks, including intracystic bleeding, infection of the amniotic cavity, and premature labor, although they are quite rare.[21, 37] Additionally, approximately 7% of fetal cystic abdominal masses are misdiagnosed as ovarian cysts, with the differential diagnosis including intestinal duplication, omental cyst, mesenteric cyst, choledochal cyst, hydronephrosis, and renal cyst.[29, 36, 57, 91] Some experts advocate for IUA not only as a successful treatment, but also a tool that may aid in the precision of the diagnosis through analysis of the hormones in the cyst fluid.[57] Others are critical, stating that the procedural risks outweigh the benefits of cyst fluid analysis.[21, 37, 89]

The success of the procedure is dependent on the favorable positioning of the cyst with no overlaying bowel to facilitate clear access for safe aspiration.[76] Furthermore, recurrence of the cyst after prenatal aspiration has been reported as high as 76%, likely due to ongoing hormonal stimulation in utero.[57] Lastly, given that the procedure is not frequently performed, the expertise may not be widely available. Notably, no complications secondary to the procedure occurred in

the 31 patients who underwent IUA in the RCT. IUA may be considered for especially large fetal ovarian cysts if there is a risk for impairing spontaneous labor or compromise of fetal organs leading to bowel obstruction or impaired venous flow. However, given the lack of evidence on the effectiveness of IUA over expectant prenatal management to prevent further postnatal interventions, it is difficult to generate robust conclusions or recommendations for the widespread implementation of this procedure.

4.4 Limitations of the included studies

Apart from one randomized controlled trial on the effect of prenatal aspiration on the outcome of fetal ovarian cysts, the majority of study designs were retrospective case series or cohort studies with substantial heterogeneity and high risk of bias. First, the majority of studies were limited by a small sample size, with over half reporting on less than 20 patients each, a lack of appropriate control groups, and variability in the frequency of prenatal and postnatal ultrasound evaluations. Second, the indications for surgical or non-surgical management were at the discretion of the surgeon, and therefore not random, increasing the potential for confounding by indication. This type of confounding occurs in observational studies when the indication for a specific exposure is also a possible cause of the outcome, thereby distorting the association between exposure and outcome. In this context, the presence of complex cyst features is associated with both surgical management and a higher chance of ovarian loss. Only one included study performed a logistic regression analysis to adjust for possible confounders, but logistic regression still does not eliminate bias due to confounding by indication.[76] Historical controls were used in two studies, increasing the potential for selection bias. Finally, in studies that performed IUA, the variability in timing of the procedure, lack of consistent inclusion and exclusion criteria, and lack of appropriate control groups limit the generalizability of the results.

4.5 Limitations of this review

There are several limitations in this systematic review. Studies were heterogeneous in terms of their inclusion criteria, years of study, sample size, length of follow-up, and choices of management strategies, which limited the ability to draw robust conclusions on the predictors influencing the management for fetal ovarian cysts. Management decisions were based on many clinical factors and different surgeons and centers had different thresholds for surgical management, thereby decreasing the generalizability of a single-institution study finding. Our review is also at risk of reporting bias, as we were only able to include the most commonly reported predictors for surgical and non-surgical management. Nevertheless, our study presents a critical and comprehensive review of the reported predictors and clinical indications for surgical and non-surgical management in fetuses diagnosed with ovarian cysts, as well as a review of ovarian preservation after cyst management.

5. Conclusion

The current literature on fetal ovarian cysts is largely comprised of low-quality studies with substantial heterogeneity and numerous biases. Despite the weakness of the evidence, one can cautiously make several conclusions about prenatally diagnosed ovarian cysts. Spontaneous regression is common in both simple and complex cysts. Some cysts will result in ovarian torsion and loss of the ovary, and most of these torsion events occur prenatally. Postnatal torsion and other postnatal complications are rare. Clear surgical indications aimed at optimizing ovarian preservation are lacking.

Despite the increased detection of prenatal ovarian cysts, their rarity makes large cohort studies difficult to execute. Multicenter studies investigating the natural history of prenatally

diagnosed ovarian cysts and prospectively evaluating standardized management strategies are necessary to create evidence-based approaches to this entity.

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Table 1. Summary of studies on prenatally diagnosed ovarian cysts included in systematic review

Study	Country	Study design	No. fetuses (No. ovarian cysts) *	GA at diagnosis (weeks) †	Cyst diameter (mm) †	Age at surgery	Follow-up time
Kirkinen (1985)	Finland	single institution retrospective case series	8 (9S;1C)	32 – 41	mean 47 (25 – 100)	3 – 8 d	1 wk – 6 mo
Collet (1987)	France	single institution retrospective case series	6 (2S;4C)	NS	mean 60 (20 – 80)	5 – 10 d	1 mo – 1 yr
Gaudin (1988)	France	single institution retrospective case series	11 (6S;6C)	29 – 39	NS	5 – 21 d	NS
Ikeda (1988)	Japan	single institution retrospective case series	9 (9)	median 34 (32 –36)	mean 44.6 (22 – 70)	3 – 49 d	1 – 12 mo
Lindeque (1988)	South Africa	single institution prospective case series	7 (7S)	NS	mean 51.4 (30 – 70)	NS	2 – 3 mo
Volpe (1988)	Italy	single institution retrospective case series	13 (7S;8C)	median 34(30 – 37)	mean 46.3 (29 – 80)	< 1 mo	NS
Calisti (1989)	Italy	single institution retrospective case series	11 (8S;3C)	mean 33 (27 – 39)	mean 41.2 (23 – 70)	NS	1 – 12 mo
D'Addario (1990)	Italy	multicenter (four) retrospective case series	25 (17S;10C)	mean 33.5 (30 – 41)	28 – 70	NS	NS
Suita (1990)	Japan	single institution retrospective case series	15 (15)	31– 40	mean 42.1 (20 – 70)	3 d – 6 mo	1 yr
Brandt (1991)	Canada	single institution retrospective case series	25 (18S;9C)	mean 33 (28 – 38)	mean 46 (20 – 80)	birth – 7 mo	3 – 13 mo
Meizner (1991)	Israel	single institution retrospective case series	15 (13S;6C)	19 – 37	NS	NS	2 – 6 mo
Hengster (1992) ‡	Austria	single institution retrospective case series	5 (2S;4C)	median 35 (29 – 40)	45.8 ± 24.1	within 1 mo	NS
Müller-Leisse (1992) ‡	Germany	multicenter (five) retrospective case series	43 (38S;5C)	28 –39	15 – 115	1 d – 4 mo	up to 3 yr
Spence (1992) ‡	Canada	single institution retrospective case series	5 (5S)	median 34 (27 – 37)	mean 50.2 (27 – 75)	1 wk – 6 mo	3 – 12 mo
Giorlandino (1993)	Italy	single institution retrospective case series	41 (30S;12C)	28 – 38	mean 50	2 – 7 d	NS
Sapin (1994)	France	single institution retrospective case series	21 (20S;3C)	28 – 38	mean 48 (20 – 75)	NS	NS
Bailez (1997) ‡	Argentina	single institution retrospective case series	17 (9S;9C)	NS	all cysts > 50	NS	4 mo – 5 yr

Bakri (1997)	France	single institution retrospective case series	6 (6S)	29 –39	mean 44.1 (30 – 63)	NS	NS
Ghisoni (1998)	Italy	single institution retrospective case series	33 (20S;17)	mean 34 (29 – 39)	mean 48 (20 – 101)	within 1 mo	1 yr
González (1999)	Spain	single institution retrospective case series	17 (8S;9C)	26 – 35	25 – 100	within 75 d	6 mo
Mazneikova (1999)	Bulgaria	single institution retrospective case series	11 (7S;4C)	32 – 36	30 – 56	6 d – 3 mo	NS
Luzzatto (2000)	Italy	single institution retrospective case series	27 (18S;9C)	mean 33 (28 – 36)	mean 43.4 (24 – 77)	birth – 17 mo	3 mo – 9 yr
Perrotin [(a)] (2000)	France	single institution technical report	3 (3S)	median 32 (29 – 32)	mean 41	NS	NS
Perrotin [(b)] (2000)	France	single institution retrospective case series	24 (16S;8C)	mean 32 (22 – 40)	43 ± 17	NS	9 mo
Chiaramonte (2001)	Italy	single institution retrospective case series	24 (17S;10C)	32 – 39	28 – 80	1 – 12 mo	12 mo
Bagolan (2002)	Italy	single institution prospective case series (historical comparator)	71 (48S;24C)	mean 33.6 (23 – 39)	NS	0 – 2 mo	NS
Heling (2002)	Germany	single institution retrospective case series	64 (46S;18C)	median 35 (26 – 40)	NS	0 – 0.5 mo	NS
Mittermayer (2003) [‡]	Austria	single institution retrospective case series	56 (31S;26C)	mean 32 (24 – 38)	42 ± 22	0 – 20 d	24 mo
Comparetto (2005)	Italy	single institution retrospective case series	32 (32S)	mean 34 (32 – 37)	27 – 75	NS	1 – 5 yr
Enríquez (2005)	Spain	single institution prospective case series (historical comparator)	18 (18C)	32 – 39	NS	NS	15 mo
Foley (2005)	Australia	single institution retrospective case series	11 (10S;1C)	second to third trimester	39.7 (7 – 70)	7 – 8 mo	1 mo – 6 yr
Antolín (2006)	Spain	single institution retrospective case series	16 (11S;6C)	mean 33 (28 – 36)	median 40 (20 – 80)		NS
Kwak (2006)	South Korea	single institution retrospective case series	16 (13S;5C)	mean 33.5 (30 – 38)	46.5 (33 – 78)	1 – 3 wk	1 – 24 mo
Galinier (2008)	France	single institution retrospective case series	79 (55S;27C)	median 32 (26 – 39)	median 43.5 (20 – 90)	NS	median 11 mo (6 – 72 mo)
Godinho (2008)	Portugal	single institution retrospective case series	5 (4S;1C)	mean 31.6 (29 – 35)	mean 38.2 (29 – 60)	within 1 mo	NS

Monnery-Noché (2008) ‡	France	single institution retrospective case series	65 (30S;37C) §	median 33 (24 – 39)	median 40 (70 – 130)	median 3 d (0 – 119 d)	median 3 mo (11 d – 6 yr)
Shimada (2008)	Japan	single institution retrospective case series	16 (11S;5C)	30 – 37	42.6 ± 12.3	within 10 mo	2 – 11 mo
Zampieri (2008)	Italy	single institution retrospective case series	57 (57S)	mean 34 (32 – 37)	mean 50 (27 – 75)	NS	1 – 5 yr
Akin (2010) ‡	Turkey	multicenter (two) retrospective case series	18 (12S;6C)	32 – 38	50.7 ± 13.9	1 – 23 d	NS
Ben-Ami (2010)	Israel	single institution retrospective case series	20 (16S;7C)	mean 33 (28 – 37)	42.4 ± 16.2 (10 – 60)	44.2 ± 40.5 d	6.6 ± 4 yr
Eleftheriades (2010)	Greece	single institution retrospective case series	7 (6S;2C)	mean 32+3 (32+1 – 32+4)	mean 37 (27 – 61)	NS	NS
Aqrabawi (2011) ‡	Jordan	single institution prospective case series	8 (8)	NS	30 – 100	NS	6 mo – 1 yr
Dimitraki (2012)	Greece	single institution retrospective case series	16 (12S;5C)	mean 32.4 (30 – 37)	mean 37.7 (21 – 73.5)	1 mo	3 – 12 mo
Gaspari (2012)	France	multicenter (three) prospective case series	5 (5S)	all diagnosed > 32 weeks	51.4 ± 8.05	1 – 3 mo	1.5 – 6.7 yr
Malek-Mellouli (2012)	Tunisia	single institution retrospective case series	3 (3S)	NS	67.3 ± 21.9	NS	NS
Nemec (2012)	Austria	single institution retrospective case series	11 (9S;4C)	mean 32+3 (23 – 36+5)	41.6 ± 16.4	NS	NS
Noia (2012)	Italy	single institution retrospective case series	13 (13S;2C)	mean 32 (27 – 36)	50.8 ± 13.3	5 mo	2 mo – 3 yr
Sànchez (2012)	Mexico	single institution retrospective case series	10 (10S)	median 32 + 1 (30+5 – 33)	median 36 (19 – 53)	NS	2 yr
Moreno (2012)	Spain	single institution retrospective case series	10 (11)	30 – 39	38.2 ± 22.1	< 1 mo	6 mo
Turgal (2013) ‡	Turkey	single institution retrospective case series	20 (14S;6C)	mean 28.4 (23 – 37)	39.3 ± 20.1	2 – 4 mo	2 – 9 mo
Karakuş (2014)	Turkey	single institution retrospective case series	37 (27S;11C)	33.1 ± 3.2	10 – 60	3 – 12 mo	3 – 12 mo
Papic (2014) ‡	USA	single institution retrospective cohort study	16 (5S;11C)	NS	47 ± 17.6	12 ± 16 wk	NS
Pujar (2014)	India	single institution retrospective case series	37 (37S)	NS	NS	NS	3 – 12 mo
Açikgöz (2015) ‡	Turkey	single institution retrospective case series	17 (17)	30 ± 6.4	39.8 ± 13.4	NS	NS

Akman (2015)	Turkey	single institution retrospective case series	4 (4C)	30 ± 37	45.5 ± 6.7	1 – 11 mo	NS
Balanescu (2015)	Romania	single institution retrospective case series	7 (3S;4C)	NS	55 ± 25.3	< 1 mo	NS
Jwa (2015)	Japan	single institution retrospective case series	21 (17S;4C)	33.9 ± 2.3	37.4 ± 10.4	1 d – 4 mo	NS
Kumru (2015) ‡	Turkey	single institution retrospective case series	8 (5S;3C)	30.1 ± 5.6	38.4 ± 18.6	< 1 mo	2 – 9 mo
Marchitelli (2015) ‡	France	single institution retrospective case series	17 (17)	NS	NS	NS	NS
Nakamura (2015)	Japan	single institution retrospective cohort study	31 (21S;10C)	median 32 (22 – 37)	median 47 (17 – 79)	NS	NS
Thakkar (2015) ‡	UK	single institution retrospective case series	34 (34)	NS	NS	NS	NS
Catania (2016) ‡	Italy	single institution retrospective case series	25 (10S;15C)	median 33 (22 – 39)	NS	NS	mean 5 yr
Aydin (2017) ‡	Turkey	single institution retrospective case series	18 (18S)	NS	54 ± 26.4mm	NS	2.6 ± 2.8 yr
Manjiri (2017)	India	single institution retrospective case series	25 (14S;11C)	NS	NS	1 – 6 wk	6 – 12 mo
Diguisto (2018)	France	two-arm randomized control trial	61 (61S)	28 – 39	median 42	< 1 mo	NS
Tyraskis (2018)	UK	multicenter (three) retrospective cohort study	37 (28S;9C)	NS	NS	NS	NS
Husen (2019) ‡	Netherlands	single institution retrospective case series	81 (49S;32C)	median 32.8 (23.9 – 38.3)	11 – 85	NS	NS
Marino (2019)	Italy	single institution retrospective case series	38 (20S;18C)	NS	mean 33.1 (12 – 71)	median 2.5 mo (birth – 24 months)	2 yr
Rialon (2019) ‡	Canada	single institution retrospective cohort study	19 (19)	35 ± 2	51 ± 3	NS	24 ± 49 mo
Sanna (2019) ‡	UK	single institution retrospective case series	33 (33)	NS	NS	NS	NS

Only first author name of each study given. NS: not stated; GA: gestational age; S: simple; C: complex; d: days; wk: weeks; mo: months; yr: years
* Number of ovarian cysts presented by prenatal cyst character on ultrasound if applicable
† Median/mean (range), range, mean ± standard deviation
‡ Only patients with prenatal ovarian cysts extracted
§ Only postnatal cyst character available

Table 2. Outcomes of Fetal Ovarian Cysts

	Spontaneous Resolution		Postnatal Intervention*		Ovarian Preservation		
Study	**In Utero**	**Total**	**Aspiration**	**Surgery**	**Surgical†**	**Non-Surgical**	**Ovarian Torsion**
Kirkinen	NA	60 % (6/10)	NA	40 % (4/10)	75% (3/4)	NA	10 % (1/10)
Collet	NA	33% (2/6)	NA	67% (4/6)	25% (1/4)	NA	33% (2/6)
Gaudin	NA	50% (6/12)	NA	50% (6/12)	0% (0/6)	NA	50% (6/6)
Ikeda	NA	33% (3/9)	NA	56% (5/9)	20% (1/5)	NA	33% (3/9)
Lindeque	NA	71% (5/7)	NA	29% (2/7)	50% (1/2)	NA	14% (1/7)
Volpe	33% (5/15)	53% (8/15)	NA	70% (7/10)	43% (3/7)	NA	27% (4/15)
Calisti	18% (2/11)	64% (7/11)	NA	44% (4/9)	0% (0/4)	NA	27% (3/11)
D'Addario	44% (11/25)	56% (14/25)	NA	44% (11/25)	NA	NA	NA
Suita	NA	53% (8/15)	NA	47% (7/15)	43% (3/7)	NA	26% (4/15)
Brandt	4% (1/27)	52% (14/27)	NA	38% (10/26)	10% (1/10)	NA	22% (6/27)
Meizner	NA	47% (9/19)	NA	32% (6/19)	50% (3/6)	NA	32% (6/19)
Hengster	NA	17% (1/6)	NA	83% (5/6)	20% (1/5)	NA	67% (4/6)
Müller-Leisse	10% (4/39)	36% (14/39)	NA	71% (25/35)	60% (15/25)	NA	19% (8/39)
Spence	NA	60% (3/5)	NA	40% (2/5)	0% (0/2)	NA	0% (0/5)
Giorlandino	NA	29% (11/38)	NA	71% (27/38)	0% (0/27)	NA	63% (24/38)
Sapin	NA	10% (2/21)	33% (7/21)	57% (12/21)	42% (5/12)	NA	21% (4/21)
Bailez	NA	6% (1/18)	39% (7/18)	56% (10/18)	10% (1/10)	NA	50% (9/18)
Bakri	NA	33% (2/6)	NA	67% (4/6)	50% (2/4)	NA	33% (2/6)
Ghisoni	20% (4/20)	50% (10/20)	NA	63% (10/16)	60% (6/10)	NA	67% (5/20)
González	NA	29% (5/17)	NA	71% (12/17)	17% (2/12)	NA	52% (9/17)
Mazneikova	36% (4/11)	72% (8/11)	NA	43% (3/7)	33% (1/3)	NA	9% (1/11)
Luzzatto	NA	63% (17/27)	7% (2/27)	30% (8/27)	0% (0/8)	53% (9/17)	NA
Perrotin (b)	13% (3/24)	42% (10/24)	NA	67% (14/21)	21% (3/14)	NA	42% (10/24)
Chiaramonte	NA	44% (12/27)	NA	56% (15/27)	27% (4/15)	NA	37% (10/27)
Bagolan	NA	60% (35/58)	NA	38% (22/58)	0% (0/22)	NA	55% (32/58)
Heling	28% (17/61)	54% (33/61)	NA	64% (28/44)	57% (16/28)	NA	8% (5/61)
Mittermayer	14% (8/58)	74% (43/58)	2% (1/58)	21% (12/58)	0% (0/12)	NA	21% (12/58)
Comparetto	NA	50% (16/32)	NA	50% (16/32)	100% (16/16)	NA	19% (6/32)
Enríquez	NA	59% (10/17)	NA	41% (7/17)	0% (0/7)	0% (0/10)	12% (2/17)
Foley	NA	81% (9/11)	NA	18% (2/11)	0% (0/2)	55% (5/9)	18% (2/11)
Antolín	24% (4/17)	65% (11/17)	NA	46% (6/13)	50% (3/6)	NA	NA
Kwak	6% (1/17)	65% (11/17)	NA	38% (6/16)	33% (2/6)	NA	24% (4/17)
Galinier	NA	44% (36/82)	12% (10/82)	48% (39/82)	15% (6/39)	72% (26/36)	39% (32/82)

Godinho	NA	60% (3/5)	NA	40% (2/5)	50% (1/2)	NA	NA
Monnery-Noché	NA	4% (3/67)	NA	96% (64/67)	47% (30/64)	NA	54% (36/67)
Shimada	13% (2/16)	56% (9/16)	NA	50% (7/14)	0% (0/7)	NA	19% (3/16)
Zampieri	NA	58% (33/57)	NA	42% (24/57)	100% (24/24)	NA	11% (6/57)
Akin	NA	17% (3/18)	NA	83% (15/18)	7% (1/15)	NA	28% (5/18)
Ben-Ami	NA	43% (10/23)	9% (2/23)	30% (7/23)	71% (5/7)	60% (6/10)	57% (4/7)
Eleftheriades	NA	88% (7/8)	NA	13% (1/8)	0% (0/1)	NA	13% (1/8)
Aqrabawi	NA	100% (8/8)	NA	0% (0/8)	NA	NA	NA
Dimitraki	18% (3/17)	94% (16/17)	NA	7% (1/14)	0% (0/1)	NA	6% (1/17)
Gaspari	NA	NA	100% (5/5)	40% (2/5)	0% (0/2)	NA	20% (1/5)
Malek-Mellouli	NA	67% (2/3)	NA	33% (1/3)	100% (1/1)	NA	0% (0/3)
Nemec	NA	75% (9/12)	NA	25% (3/12)	67% (2/3)	NA	8% (1/13)
Sànchez	40% (4/10)	90% (9/10)	NA	0% (0/10)	NA	NA	0% (0/10)
Moreno	NA	91% (10/11)	NA	9% (1/11)	NA	NA	0% (0/11)
Turgal	35% (7/20)	90% (18/20)	NA	15% (2/13)	0% (0/2)	NA	10% (2/20)
Karakuş	NA	71% (27/38)	NA	29% (11/38)	73% (8/11)	NA	5% (2/38)
Papic	NA	31% (5/16)	NA	69% (11/16)	36% (4/11)	NA	NA
Pujar	14% (5/37)	68% (25/37)	NA	38% (12/32)	75% (9/12)	NA	9% (3/32)
Açikgöz	NA	71% (10/14)	NA	29% (4/14)	NA	NA	21% (3/14)
Akman	NA	50% (2/4)	NA	50% (2/4)	50% (1/2)	50% (1/2)	50% (2/4)
Balanescu	NA	43% (3/7)	NA	57% (4/7)	50% (2/4)	NA	42% (3/7)
Jwa	28% (4/14)	64% (9/14)	10% (1/10)	40% (4/10)	100% (4/4)	NA	14% (2/14)
Kumru	25% (2/8)	75% (6/8)	NA	33% (2/6)	100% (2/2)	NA	25% (2/8)
Marchitelli	12% (2/17)	12% (2/17)	NA	13% (2/15)	NA	NA	NA
Nakamura	10% (3/31)	55% (17/31)	NA	50% (14/28)	79% (11/14)	NA	13% (4/31)
Thakkar	60% (20/34)	74% (25/34)	NA	14% (2/14)	NA	NA	NA
Catania	9% (2/23)	22% (5/23)	NA	86% (18/21)	NA	NA	NA
Aydin	NA	33% (6/18)	NA	67% (12/18)	33% (4/12)	NA	0% (0/18)
Manjiri	NA	56% (14/25)	NA	44% (11/25)	9% (1/11)	NA	16% (4/25)
Diguisto	NA	63% (15/24)	NA	37% (10/27)	40% (4/10)	NA	NA
Tyraskis	34% (12/35)	80% (28/35)	9% (2/23)	22% (5/23)	60% (3/5)	7% (2/28)	14% (5/35)
Husen	10% (8/81)	67% (54/81)	NA	25% (20/81)	NA	NA	27% (22/81)
Marino	32% (12/38)	68% (26/38)	NA	46% (12/26)	8% (1/12)	NA	29% (11/38)
Rialon	NA	5% (1/19)	NA	94% (18/19)	NA	NA	NA
Sanna	30% (10/33)	79% (26/33)	NA	22% (5/23)	NA	NA	NA

Only first author name of each study given. Patients undergoing intrauterine aspiration not included.
NA: not applicable or not reported
* Number of cysts that underwent postnatal intervention (cyst aspiration or surgery) among those still persisting after birth.
† Number of ipsilateral ovaries spared in patients with cysts that underwent surgical intervention.

Table 3. Summary of studies on intrauterine aspiration of fetal ovarian cysts

Author	No. fetuses (No. cysts)	Cyst diameter (mm)	Change in character *	In utero resolution	Total resolution	Ovarian torsion	Postnatal surgery & indication	Oophorectomy
D'Addario	2 (2S)	NS	NS	-	0	NS	2 (100 %) no indication stated	NS
Müller-Leisse	4 (4S)	NS	1 (25 %)	0	3 (75 %) †	NS	1 (25 %) change in character	NS
Giorlandino	4 (4S)	61 ± 16	no	0	4 (100 %)	0	-	-
Sapin	2 (2S)	55 ± 7.1	no	2 (100 %)	2 (100 %)	0	-	-
Ghisoni	14 (9S;6C)	55.5 ± 12.5	no	NS	14 (93 %)	0	1 (7 %) diagnostic error ‡	-
Perrotin(a)	3 (3S)	41 ± 5.3	no	2 (67 %)	3 (100 %)	0	-	-
Chiaramonte	1 (1S)	60	no	-	0	NS	NS	NS
Bagolan	14 (14S)	all ≥ 50	2 (14 %)	NS	12 (86 %)	2 (14 %)	2 (14 %) ovarian torsion	2 (14 %)
Heling	3 (3S)	61.7 ± 24.7	no	1 (33 %)	1 (33 %)	NS	2 (67 %) cyst size	0
Mittermayer	2 (2S)	66 ± 15.7	no	0	2 (100 %)	0	-	-
Enríquez	1 (1C)	26	no	0	1 (100 %)	0	-	-
Kwak	1 (1S)	43	1 (100 %)	-	0	0	1 (100 %) intracystic bleeding	1 (100 %)
Nemec	1 (1S)	NS	no	-	0	0	1 (100 %) cyst size	0
Noia	13 (12S;2C)	52.5 ± 12.6	no	5 (38 %)	NS	2 (15 %) §	1 (8 %) ovarian torsion	NS
Açikgöz	3 (1S;2C)	74 ± 26.8	no	0	2 (67 %)	NS	1 (33 %) no indication stated	0
Jwa	7 (7S)	43.9 ± 3.8	no	0	7 (100 %) ‖	0	0	0
Catania	2 (2S)	all ≥ 50	no	-	0	0	2 (100 %) cyst size	0
Diguisto	34 (34S)	all ≥ 30	2 (6 %)	16 (47 %)	23 (72 %)	NS	7 (21 %) multiple indications ¶	1 (3 %)
Tyraskis	2 (1S;1C)	99.5 ± 3.5	no	-	0	1 (50 %)	2 (100 %) cyst size	1 (50 %)

NS: not stated; -: not applicable; S: simple; C: complex. * Change in ultrasound character of ovarian cyst from simple to complex appearance after aspiration. † One cyst was aspirated again in postnatal period at 2.5 months old prior to resolution. ‡ Prenatal diagnostic error – case of ileal atresia. § Torsion detected pre-aspiration. ‖ One cyst was aspirated again in postnatal period at age 2 days old prior to resolution. ¶ Indications determined a priori: symptomatic cyst, cyst measuring ≥ 50mm, non-involution of cyst at 3 months post-partum, suspected ovarian torsion

Table 4. Risk-of-bias assessment using MINORS tool

	1.Clearly stated aim	2.Consecutive patients	3.Prospective data	4.Appropriate endpoints	5.Unbiased evaluation	6.Appropriate follow-up	7.Loss of follow-up <5%	8.Sample size calculation	9.Adequate control group	10.Contemporary groups	11. Baseline equivalence	12.Appropriate statistics	Total Score
1985. Kirkinen, et al.	0	1	1	2	0	2	2	0	-	-	-	-	8
1987. Collet, et al.	1	1	1	2	0	2	2	0	-	-	-	-	9
1988. Gaudin, et al.	1	1	1	2	0	2	2	0	-	-	-	-	9
1988. Ikeda, et al.	0	1	1	2	0	1	2	0	-	-	-	-	7
1988. Lindeque, et al.	2	2	2	2	0	2	2	0	-	-	-	-	12
1988. Volpe, et al.	1	1	1	2	0	2	2	0	-	-	-	-	9
1989. Calisti, et al.	0	2	1	2	0	2	1	0	-	-	-	-	8
1990. D'Addario, et al.	0	2	1	2	0	2	2	0	-	-	-	-	9
1990. Suita, et al.	0	2	1	2	0	2	2	0	-	-	-	-	9
1991. Brandt, et al.	0	2	1	2	0	2	2	0	-	-	-	-	9
1991. Meizner, et al.	0	2	1	2	0	2	2	0	-	-	-	-	9
1992. Hengster, et al.	0	1	1	2	0	2	2	0	-	-	-	-	8
1992. Muller-Leisse, et al.	0	1	1	2	0	2	2	0	-	-	-	-	8
1992. Spence, et al.	1	2	1	2	0	2	2	0	-	-	-	-	10
1993. Giorlandino, et al.	2	2	1	2	0	2	2	0	0	2	0	1	14
1994. Sapin, et al.	2	2	1	2	0	2	2	0	-	-	-	-	11
1997. Bailez, et al.	1	2	1	2	0	1	2	0	-	-	-	-	9
1997. Bakri, et al.	0	2	1	1	0	2	2	0	-	-	-	-	8
1998, Ghisoni, et al.	1	2	1	2	0	2	2	0	-	-	-	-	10
1999. Gonzalez, et al.	0	2	1	2	0	2	2	0	-	-	-	-	9
1999. Mazneikova, et al.	1	2	1	2	0	2	2	0	-	-	-	-	10
2000. Luzzatto, et al.	1	2	1	2	0	2	2	0	-	-	-	-	10
2000. Perrotin, et al. (a)	0	1	1	2	0	1	2	0	-	-	-	-	7
2000. Perrotin, et al. (b)	2	2	1	2	0	2	2	0	-	-	-	-	11
2001. Chiaramonte, et al	1	2	1	2	0	2	2	0	-	-	-	-	10
2002. Bagolan, et al.	2	2	2	2	0	2	2	0	1	0	0	1	14
2002. Heling, et al.	1	2	1	2	0	2	2	0	-	-	-	-	10
2003. Mittermayer, et al.	2	2	1	2	0	2	2	0	-	-	-	-	11
2005. Comparetto, et al.	2	2	1	2	0	2	2	0	-	-	-	-	11
2005. Enríquez, et al.	1	0	1	2	0	2	2	0	1	0	1	0	10

2005. Foley, et al.	1	2	1	2	0	2	1	0	-	-	-	-	9
2006. Antolin, et al.	2	2	1	2	0	2	2	0	-	-	-	-	11
2006. Kwak, et al.	1	2	1	2	0	2	1	0	-	-	-	-	9
2008. Galinier, et al.	2	2	1	2	0	2	2	0	-	-	-	-	11
2008. Godinho, et al.	1	2	1	2	0	2	2	0	-	-	-	-	10
2008. Monnery-Noche, et al.	2	2	1	2	0	2	2	0	0	2	1	1	15
2008. Shimada, et al.	2	2	1	2	0	2	2	0	-	-	-	-	11
2008. Zampieri, et al.	2	2	1	2	0	2	2	0	1	2	0	1	15
2010. Akin, et al.	1	2	1	2	0	2	2	0	-	-	-	-	10
2010. Ben-Ami, et al.	1	2	1	2	0	2	2	0	1	2	1	1	15
2010. Eleftheriades, et al.	0	2	0	2	0	1	2	0	-	-	-	-	7
2011. Aqrabawi, et al.	1	2	2	2	0	2	2	0	-	-	-	-	11
2012. Dimitraki, et al.	0	2	1	2	0	2	2	0	-	-	-	-	9
2012. Gaspari, et al.	2	2	1	2	0	2	2	0	-	-	-	-	11
2012. Malek-Mellouli, et al.	0	0	0	2	0	2	2	0	-	-	-	-	6
2012. Nemec, et al.	1	1	1	2	0	2	0	0	-	-	-	-	7
2012. Noia, et al.	2	2	1	1	0	2	2	0	-	-	-	-	10
2012. Sanchez, et al.	2	2	1	2	0	2	2	0	-	-	-	-	11
2013. Moreno, et al.	1	2	1	2	0	2	2	0	-	-	-	-	10
2013. Turgal, et al.	1	2	1	2	0	2	2	0	0	2	0	1	13
2014. Karakuş, et al.	1	2	1	2	0	2	2	0	-	-	-	-	10
2014. Papic, et al.	2	2	1	2	0	2	2	0	1	2	1	1	16
2014. Pujar, et al.	1	2	1	2	0	2	2	0	0	2	0	0	12
2015. Açikgöz, et al.	0	2	1	2	0	1	2	0	-	-	-	-	8
2015. Akman, et al.	0	0	0	2	0	2	2	0	-	-	-	-	6
2015. Balanescu, et al.	1	2	1	1	0	1	2	0	-	-	-	-	8
2015. Jwa, et al.	1	2	1	2	0	2	2	0	-	-	-	-	10
2015. Kumru, et al.	2	2	1	2	0	2	2	0	-	-	-	-	11
2015. Marchitelli, et al.	2	2	1	1	0	0	1	0	-	-	-	-	7
2015. Nakamura, et al.	2	2	1	2	0	2	2	0	1	2	1	1	16
2015. Thakkar, et al.	1	2	1	2	0	1	2	0	-	-	-	-	9
2016. Catania, et al.	2	2	1	2	0	2	2	0	-	-	-	-	11
2017. Aydin, et al.	0	2	1	2	0	2	2	0	0	2	1	1	13
2017. Manjiri, et al.	0	2	1	2	0	2	2	0	-	-	-	-	9
2018. Tyraskis, et al.	2	2	1	2	0	2	1	0	2	2	1	1	16
2019. Husen, et al.	2	2	1	2	0	2	2	0	0	2	1	1	15
2019. Marino, et al.	2	2	1	2	0	2	2	0	1	2	1	1	16
2019. Rialon, et al.	2	2	1	2	0	2	2	0	1	2	1	1	16
2019. Sanna, et al.	0	2	1	2	0	2	0	0	-	-	-	-	7

Figure Legend

Figure 1 – PRISMA diagram of included studies reporting on predictors of management for fetal ovarian cysts

Figure 2 – Cumulative risk-of-bias of studies using MINORS tool

Figure 1[93]

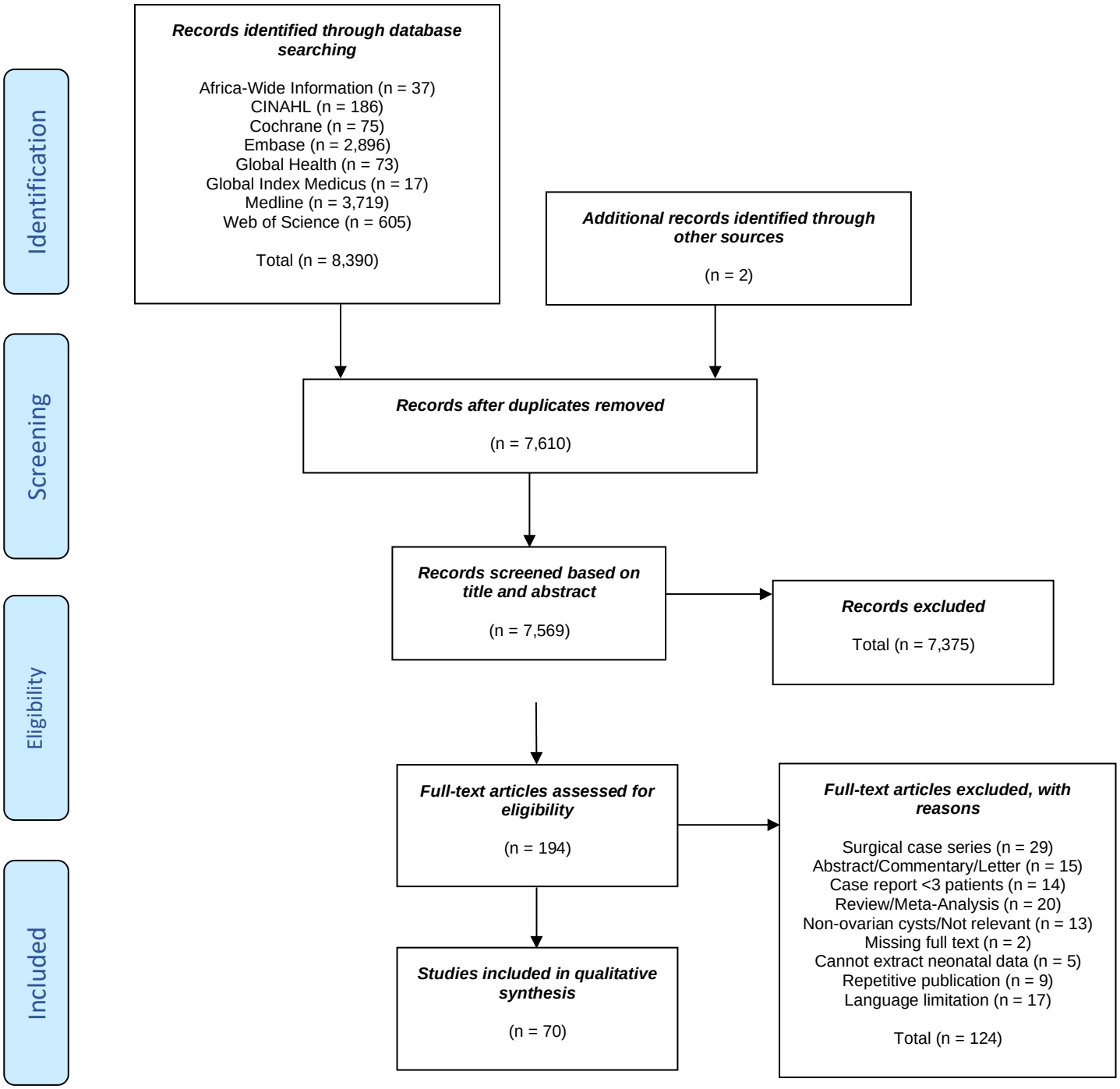
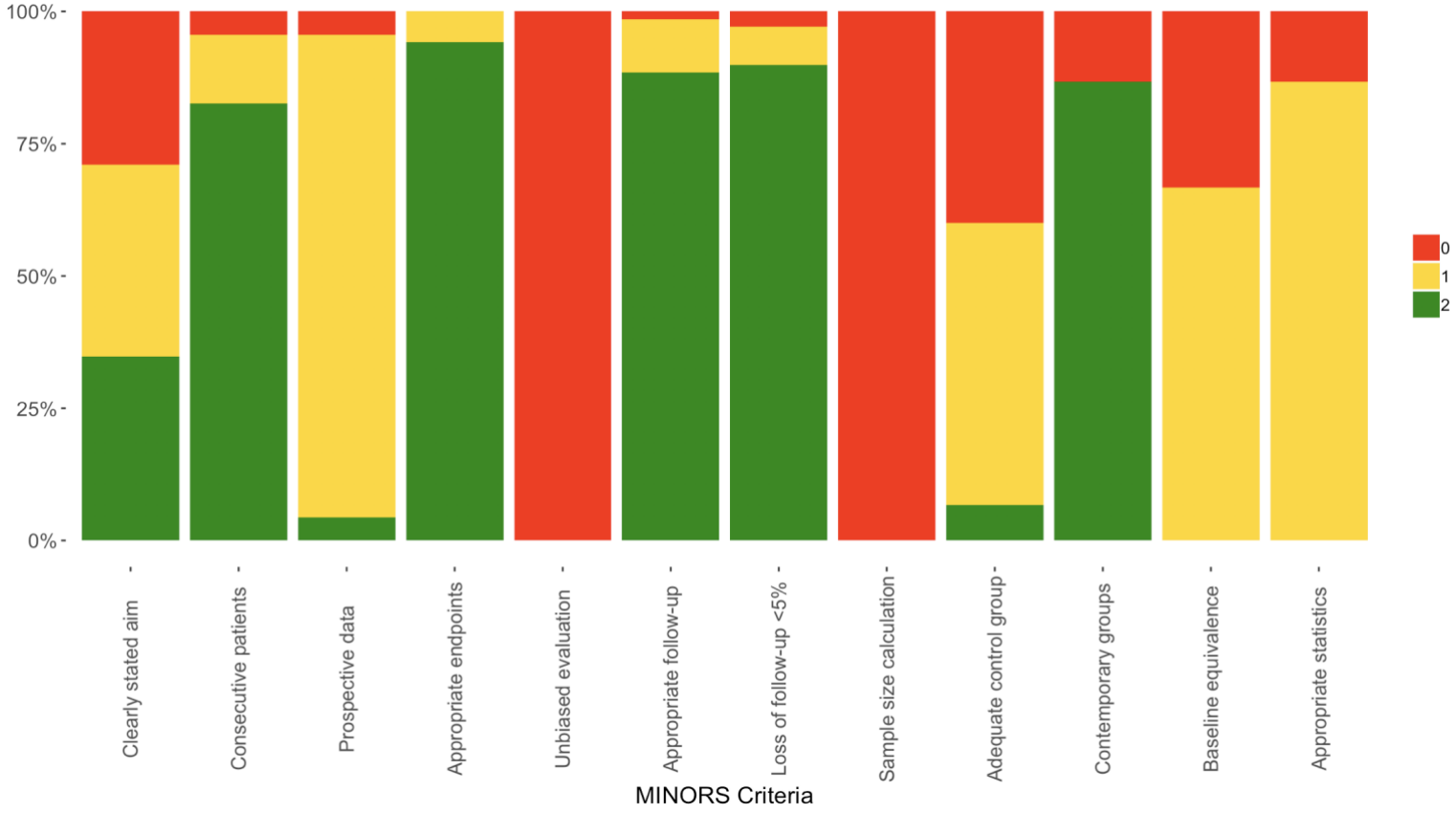

Identification
Screening
Eligibility
Included
Records identified through database searching
Africa-Wide Information (n = 37)
CINAHL (n = 186)
Cochrane (n = 75)
Embase (n = 2,896)
Global Health (n = 73)
Global Index Medicus (n = 17)
Medline (n = 3,719)
Web of Science (n = 605)
Total (n = 8,390)
Additional records identified through other sources
(n = 2)
Records after duplicates removed
(n = 7,610)
Records screened based on title and abstract
(n = 7,569)
Records excluded
Total (n = 7,375)
Full-text articles assessed for eligibility
(n = 194)
Full-text articles excluded, with reasons
Surgical case series (n = 29)
Abstract/Commentary/Letter (n = 15)
Case report <3 patients (n = 14)
Review/Meta-Analysis (n = 20)
Non-ovarian cysts/Not relevant (n = 13)
Missing full text (n = 2)
Cannot extract neonatal data (n = 5)
Repetitive publication (n = 9)
Language limitation (n = 17)
Total (n = 124)
Studies included in qualitative synthesis
(n = 70)

Figure 2


100%
75%
50%
25%
0%
Clearly stated aim
Consecutive patients
Prospective data
Appropriate endpoints
Unbiased evaluation
Appropriate follow-up
Loss of follow-up <5%
Sample size calculation
Adequate control group
Contemporary groups
Baseline equivalence
Appropriate statistics
MINORS Criteria
0
1
2

Appendix 1. Full MEDLINE search strategy

Eight databases were searched from inception until July 23, 2019. For brevity, Medline is shown as the main search.

Medline [Ovid] (July 23, 2019)

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily <1946 to Present>

1	exp Ovary/	89120
2	exp Ovarian Neoplasms/	80559
3	exp Abdomen/	104711
4	(ovar* or abdom* or intraabdom* or gastrointestin* or biliar* or spleen* or splenic* or mesenter* or enteric* or choledoch* or parovar* or paratubal* or (hydatid* adj4 morgagn*) or duplicat* or gastric or adrenal or intestin* or jujen* or duoden* or ileu* or ilial* or colon or colonic or omphalomesent* or ((corpus or corpora) adj2 (lutea* or luteu*))).tw,kf.	1903223
5	or/1-4	1986305
6	((fetal* or fetus* or foet* or feto* or fetu or prenatal* or pre-natal* or antenatal* or ante-natal* or perinat* or peri-nat* or postnat* or post-nat*) adj5 (cyst or cysts or cystic or lesion* or mass* or pseudocyst* or sclerocys*)).tw,kf.	7396
7	5 and 6	1425
8	Ovarian Cysts/	6711
9	Cysts/	37011
10	limit 9 to yr="1966 - 1967"	917
11	Ovarian Diseases/	5898
12	limit 11 to yr="1966 - 1967"	198
13	Mesenteric Cyst/	871
14	Choledochal Cyst/	1613
15	Parovarian cyst/	210
16	Ovarian Diseases/dg	528
17	Torsion Abnormality/dg	791
18	((ovar* or abdom* or intraabdom* or gastrointestin* or biliar* or spleen* or splenic* or mesenter* or enteric* or choledoch* or parovar* or paratubal* or (hydatid* adj4 morgagn*) or duplicat* or gastric or adrenal or intestin* or jujen* or duoden* or ileu* or ilial* or colon or colonic or omphalomesent* or follic* or ((corpus or corpora) adj2 (lutea* or luteu*))) adj2 (cyst or cysts or cystic or pseudocyst* or sclerocys*)).tw,kf.	17577
19	8 or 10 or (or/12-18)	23352
20	Fetus/	76859
21	exp Fetal Diseases/	66817
22	exp Fetal Development/	89108
23	"embryonic and fetal development"/	22638
24	limit 23 to yr="1984 - 2004"	20637
25	embryonic development/	19909
26	limit 25 to yr="1984 - 2004"	2908
27	exp Fetal Monitoring/	8504

28	exp Prenatal Diagnosis/	71634
29	Amniocentesis/	7745
30	limit 29 to yr="1971 - 1972"	381
31	exp Perinatal Care/	9390
32	Puerperium/	24118
33	limit 32 to yr="1966 - 1970"	828
34	Prenatal Care/	25983
35	Intensive Care Units, Neonatal/	13557
36	Intensive Care, Neonatal/	5393
37	exp Infant, Newborn/	587128
38	(fetal* or fetus* or foet* or feto* or fetu or prenatal* or pre-natal* or antenatal* or ante-natal* or perinat* or peri-nat* or postnat* or post-nat* or newborn* or new-born* or neonat* or neo-nat* or pre-matur* or premie* or preemie* or preterm? or pre-term? or postmatur* or post-matur* or nicu? or intrauterine* or intra-uterin* or embryo* or puerperium* or postpartum* or post-partum* or VLBW* or ELBW* or ((very-low or extrem* low*) adj3 (birth-weight or birthweight))).tw,kf.	1203240
39	(fetal* or fetus* or foet* or prenatal* or neonat* or neo-nat* or perinat*).jw.	64020
40	(or/20-22) or 24 or (or/26-28) or (or/30-31) or (or/33-39)	1562165
41	19 and 40	3349
42	7 or 41	4191
43	(Animals/ or Models, Animal/ or Disease Models, Animal/) not ((Animals/ or Models, Animal/ or Disease Models, Animal/) and Humans/)	4568134
44	((animals or animal or canine* or cat or cats or dog or dogs or feline or hamster* or mice or monkey or monkeys or mouse or murine or pig or pigs or piglet* or porcine or primate* or rabbit* or rats or rat or rodent* or sheep*) not (human* or patient*)).ti,kf.	2072945
45	42 not (43 or 44)	3727
46	remove duplicates from 45	3723

CHAPTER 3 – TRANSITION FROM CLINICAL KNOWLEDGE TO CLINICAL PRACTICE

In the previous chapter, I described a systematic review of the literature on the clinical predictors influencing management strategies of congenital ovarian cysts and compared the incidence of ovarian preservation between surgical and non-surgical management. The principal findings were that cyst diameter > 40 mm and complex sonographic characteristics are major determinants of surgical management, and that surgical management resulted in loss of the ipsilateral ovary in the majority of surgeries, regardless of cyst size or characteristics. However, the majority of studies that reported the clinical outcomes of patients with congenital ovarian cysts were underpowered and varied greatly in their implementation of surgical and non-surgical management strategies. These limitations preclude establishing reliable clinical recommendations.

With this knowledge, I set out to study our own population of pediatric patients with congenital ovarian cysts at McGill University. However, as with most research involving pediatric patients with congenital pathologies, the small number of patients at one institution can limit the ability to draw robust conclusions. Furthermore, published literature on this subject has largely consisted of single-institution case series, and our goal was to contribute new original and high-quality data that could lead to meaningful changes in the application of management strategies. Therefore, under the auspices of a newly formed consortium in Canada called the Canadian Consortium for Research in Pediatric Surgery (CanCORPS), I collaborated with study investigators from ten institutions to collect data from pediatric hospital centers across the country to create a database consisting of female infants with congenitally diagnosed abdominal cysts.[66] I then designed a multi-institutional retrospective cohort study of patients who were

diagnosed with congenital ovarian cysts and reported the incidence of spontaneous resolution of ovarian cysts as well as the predictors of surgical management. Finally, I also sought to determine whether surgical or non-surgical management was associated with an increase in ovarian preservation.

CHAPTER 4 – TREATMENT AND OUTCOMES OF CONGENITAL OVARIAN CYSTS: A STUDY BY THE CANADIAN CONSORTIUM FOR RESEARCH IN PEDIATRIC SURGERY (CANCORPS) (MANUSCRIPT #2)

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Short running title: Outcomes of Congenital Ovarian Cysts

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Conflicts of interest: The authors have no relevant conflicts of interest.

Abstract

Background: Wide variability exists in the treatment of congenital ovarian cysts. The effects of various treatment strategies on outcomes, specifically ovarian preservation, are not known.

Methods: Female infants diagnosed with congenital intra-abdominal cysts between 2013- 2017 at 10 Canadian pediatric surgical centres were retrospectively evaluated. Sonographic characteristics, median time to cyst resolution, and incidence of ovarian preservation were compared between patients who underwent surgical and non-surgical management. Subgroup analyses were performed in patients for complex cysts and cysts ≥40mm in diameter.

Results: The study population included 189 neonates. Median gestational age at diagnosis and median maximal prenatal cyst diameter were 33 weeks and 40mm, respectively. Cysts resolved spontaneously in 117 patients (62%), 14 (7%) prenatally and the remainder at a median age of 124 days. Intervention occurred in 61 patients (32%), including prenatal aspiration (2, 3%), ovary-sparing resection (14, 23%) or oophorectomy (45, 74%). Surgery occurred at a median age of 7.4 weeks. Independent predictors of surgery included postnatal cyst diameter ≥ 40mm (OR 6.19, 95% CI 1.66 – 35.9) and sonographic complex cyst character (OR 63.6, 95% CI 10.9 – 1232). There was no significant difference in the odds of ovarian preservation (OR 3.06, 95% CI 0.86 – 13.2) between patients who underwent early surgery (n=22) and those initially observed for at least 3 months (n=131).

Conclusion: Most congenital ovarian cysts are asymptomatic and spontaneously resolve. Early surgical intervention does not seem to increase ovarian preservation.

1. Introduction

Ovarian cysts are the most common cystic abdominal mass necessitating referral to a pediatric surgeon, with an estimated incidence of 1 in 2,625 live births.[1, 2] Most ovarian cysts detected in the prenatal period are asymptomatic and thought to be the result of maternal hormonal stimulation. Many of these cysts can be observed with serial ultrasounds until they resolve or regress spontaneously.[3, 4] However, tremendous variability exists in the evaluation and management of these lesions.[5-8]

Despite their benign nature, fetal ovarian cysts have been associated with complications, including torsion and hemorrhage.[9] Early surgical intervention has been proposed as a way to mitigate the risk of ovarian loss due to such complications. However, despite the intention to spare ovarian tissue, most surgical interventions result in oophorectomy.[10]

Although non-surgical management has succeeded in many patients, no standardized observation period or surveillance protocols have been established for the longitudinal follow-up of infants with fetal ovarian cysts. There are reports of cysts being observed for up to two years until complete resolution.[11] Moreover, there is a paucity of literature comparing the long-term outcomes and risks of non-surgical and surgical management.

We investigated the management strategies and outcomes of congenital ovarian cysts in a national sample of Canadian patients. The primary objectives were to (1) determine the incidence of spontaneous cyst resolution, (2) identify the clinical and sonographic predictors of intervention for fetal ovarian cysts, and (3) examine whether early surgical intervention is associated with increased ovarian preservation compared to observation alone.

2. Methods

2.1 Study setting

This study was conducted by the Canadian Consortium for Research in Pediatric Surgery (CanCORPS). Ten of the 15 CanCORPS institutions participated in the study. The study protocol was approved at the sponsor site (Montreal Children's Hospital; MP-37-2019-4977) and at each participating center. A data-sharing agreement was approved by all institutional review boards.

2.2 Study Design

A retrospective cohort study was conducted among all live-born female infants diagnosed with a congenital ovarian cyst over a 5-year period from January 1, 2013 to December 31, 2017. Congenital ovarian cysts were defined as ovarian cysts identified between 22 weeks gestation to 3 months of age. Patients were excluded if there was incomplete sonographic documentation of prenatal or postnatal cyst trajectory, and if the cyst was ultimately of non-ovarian origin. Data for all patients were collected until documented resolution of the ovarian cyst, surgical intervention, or the patient reached one year of age, which was then defined as the point of last follow-up. Data collected included maternal and patient characteristics, prenatal and postnatal sonographic findings, and outcomes including whether the cyst resolved spontaneously or whether an intervention occurred. Study data were entered and managed using REDCap (Research Electronic Data Capture) software hosted at the Montreal Children's Hospital.[12, 13] Data entered were validated at each individual institution and centrally for completeness and accuracy.

2.3 Independent Variables

Maternal characteristics, including age, gravida, and associated conditions influencing maternal hormones (e.g. obesity, diabetes mellitus, assisted reproduction), and patient characteristics, including prematurity, birth weight, prenatal or postnatal age at diagnosis, were

evaluated as possible predictors of outcomes. We examined sonographic data collected from both prenatal and postnatal ultrasounds including largest cyst diameter less than 40 mm or 40 mm and greater, cyst wall thickness, presence of septations, loculations, fluid-fluid level, debris, solid components, and the "gut signature" sign.[14] Congenital ovarian cysts were defined as complex if they had any of the following features: heterogeneity, echogenic solid components, thick walls, multiple septations, debris, or fluid-fluid levels.[15] Cysts without any of these features were classified as simple. A change in appearance on serial ultrasounds from a simple to a complex cyst was also recorded.

2.4 Outcomes

The outcomes of interest were defined at one year of age and included cyst resolution, interventional management, and ovarian preservation. Cyst resolution was defined as either the complete sonographic disappearance of the previously identified ovarian cyst or a decrease in ovarian cyst size to < 10 mm. An intervention was defined as a procedure performed to remove the cyst or diminish its size. This included percutaneous aspiration, ovarian-sparing surgical procedures such as cyst unroofing or cystectomy, or oophorectomy. Ovarian preservation was defined as the sonographic identification of a viable ipsilateral ovary after non-surgical management, or the surgical documentation of a visibly viable residual ovary in a patient who underwent operative management.

There was no standardized management protocol during the study period. Patients with asymptomatic ovarian cysts were categorized into two groups based on the intended management during the first 3 months of life: early surgical intervention or observation. This time point is based on literature describing a decline in maternal gonadotropin levels at approximately 3 months of age, corresponding to an expected spontaneous resolution of congenital ovarian

cysts.[16, 17] Patients with cysts that underwent prenatal resolution or a prenatal procedure, or a postnatal emergency surgical intervention were excluded, as an observation period was not applicable.

2.5 Statistical analyses

Frequencies and percentages as well as medians and interquartile ranges were used to describe categorical and continuous variables, respectively. Statistical significance between means was determined using Kruskal-Wallis test for continuous variables, and the χ^2 test for categorical variables, where applicable. Kaplan Meier curves were used to assess the overall time to cyst resolution and to compare resolution time between simple and complex ovarian cysts. Stepwise multivariate logistic regression analysis was used to determine independent clinical predictors of surgical management. The regression model included variables with a p-value of <0.25 on univariate analysis as well as variables previously reported to correlate with surgical intervention. Multiple logistic regression was also used to compare the incidence of ovarian preservation in patients with an initial observation period and those who underwent early surgical intervention. Subgroup analyses on ovarian preservation were performed in patients with complex cysts and cysts ≥ 40mm. A p-value less than 0.05 was considered statistically significant. All statistical analyses were performed by using R version 3.5.1.[18]

3. Results

3.1 Study population and overall outcomes

Over the 5-year study period, 247 female infants with congenital intra-abdominal cysts were identified **(Figure 1)**. After excluding 30 patients with missing prenatal or postnatal data, and 28 patients with non-ovarian cysts, 189 (76.5%) patients comprised the final sample. Of

these, 106 (56.1%) had simple cysts and 83 (43.9%) had complex cysts. **Table 1** displays the patient characteristics and interventions. Twenty-six patients (14%) were diagnosed postnatally within the first 3 months of age, while the remainder were diagnosed prenatally. A summary of patient outcomes is shown in **Figure 2.**

3.2 Cyst Resolution

Spontaneous cyst resolution occurred in 117 patients (117/189; 61.9%). Fourteen (7.4%) cysts resolved during the prenatal period, all simple cysts with a median diameter of 24 mm, while the remaining 103 (54.4%) cysts resolved postnatally within the first year of life. Median time to postnatal cyst resolution was 124 days (95% CI 111 – 166). Kaplan-Meier analysis **(Figure 3)** was used to compare time to cyst resolution between simple and complex cysts. Seventy-nine of 83 (95.2%) simple and 24 of 70 complex cysts (34.2%) resolved within one year of age. Median time to simple cyst resolution was 82 days compared to 320 days for complex cysts (log-rank $p<0.001$). At one year of age, thirteen patients (13/189; 6.8 %) had persistent ovarian cysts; 1 simple and 12 complex cysts.

3.3 Postnatal interventions

In total, 57 (30.1%) patients underwent postnatal intervention, including 14 open surgical procedures, 34 laparoscopic procedures, 8 laparoscopic converted to open procedures, and one percutaneous aspiration. Eleven patients had an auto-amputated ovary identified at the time of surgery. In total, 43 patients underwent oophorectomy/salpingo-oophorectomy, while 14 underwent an ovary-sparing procedure, including cystectomy, cyst unroofing, or percutaneous cyst aspiration. Of those who underwent surgical intervention, 47 were complex and 10 were simple cysts, with 40 (85%) complex and 3 (30%) simple cysts managed with an oophorectomy. The pathologic diagnosis of all surgical specimens was non-neoplastic benign cyst.

Table 2 compares the maternal, infant, and sonographic characteristics of patients undergoing early surgical intervention within 3 months of age to those observed. Surgery was performed at a median age of 39 days (IQR 53.5 days). Median cyst size was 55 mm (IQR 25.5 mm), nineteen (86%) were complex, while 3 (14%) were simple.

One patient underwent surgery due to parental request, and the remainder underwent surgery at the discretion of the treating surgeon due to persistence or enlargement of the cyst. Intra-operatively, of the three simple cysts, one that measured 69 mm had undergone torsion. Among the 19 complex cysts, torsion was identified in 15. Oophorectomy was performed in 17 of the 22 patients (77%).

Fifteen patients underwent elective surgery after a period of at least 3 months of observation **(Table 3)**. Median observation time prior to surgical intervention was 168 days (IQR 100). All 15 cysts were complex with a mean diameter of 44 mm (IQR 17.5 mm), and all fifteen patients underwent oophorectomy, with fourteen cysts demonstrating evidence of ovarian torsion intra-operatively.

A total of 20 patients underwent an emergent surgical intervention due to concerns that the ovarian cyst may be the cause of acute symptoms. The age at intervention ranged between 0 to 108 days (median 7.5 days). Twelve infants presented with abdominal distension and vomiting, and one with respiratory distress. Overall, 9 of the 20 patients (45%) who underwent an emergent intervention had an ovarian-sparing procedure, while the remainder had an oophorectomy.

3.4 Predictors of surgical management

Patients who underwent surgical management were compared to those who underwent non-surgical management **(Table 4).** Multiple logistic regression analysis identified the

independent predictors of surgical management as postnatal cyst diameter ≥ 40mm (OR 6.19, 95% CI 1.66 – 35.9) and sonographic characteristics of a complex cyst (OR 63.6, 95% CI 10.9 – 1232) **(Table 5)**.

A total of 32 simple ovarian cysts demonstrated a change in ultrasound pattern to that of a complex cyst. In all patients, the change in cyst character was first noticed on postnatal ultrasound at a median age of 5 days of life. Median cyst diameter was 51 mm (IQR 22.3 mm). Fourteen of these patients were observed, and 11 cysts completely resolved within the first year of life, while 3 persisted at the end of the follow-up period. The other 18 patients underwent surgical intervention at a median age of 42.5 days (IQR 153), three of which occurred emergently in the first week of life due to symptoms (respiratory distress, bowel obstruction, and abdominal distention, respectively). Fifteen (47%) patients that had changes in sonographic character of the ovarian cyst underwent oophorectomy. Change in cyst character was significantly higher in cysts ≥ 40 mm compared to those < 40 mm (44 % vs 15 %; p = 0.04).

3.5 Ovarian preservation

No significant difference in the odds of ovarian preservation between patients who underwent early surgery (n = 22) and those who were initially observed (n = 131) was identified on multiple logistic regression analysis (OR 3.06, 95% CI 0.86 – 13.2, p = 0.102), after adjusting for cyst diameter, cyst character, and change in sonographic character. Complex cyst character was the only variable independently associated with a lower odds of ovarian preservation regardless of intended treatment (OR 0.02, 95% CI 0.002 – 0.07). Subgroup analysis of patients with complex cysts, adjusted for cyst diameter, demonstrated no statistically significant difference in the odds of ovarian preservation based on intended treatment (OR 2.05, 95% CI

0.57 – 8.51), as did subgroup analysis of patients with cysts ≥ 40 mm, adjusted for cyst character (OR 4.46, 95% CI 1.00 – 25.1).

4. Discussion

With advances and increased availability of prenatal sonographic imaging, congenital ovarian cysts are identified relatively frequently. However, their management has remained a challenge due to the sparse availability of high-level evidence from which to draw robust management recommendations. The current study represents a national Canadian experience which includes the largest cohort of infants with congenital ovarian cysts to date. It is the first study to be conducted by a new national pediatric surgery research consortium, CanCORPS. The Consortium was founded in July 2018 and includes the largest 15 of the 18 academic pediatric surgical services in Canada. Since Canadian tertiary pediatric surgery practice, which would include diagnosis and management of congenital ovarian cysts, occurs only in such institutions, data obtained through CanCORPS is representative of national pediatric surgical practice patterns and outcomes.

The study accomplished its objectives:

The first objective was to identify the incidence of spontaneous cyst resolution in one year following birth. The study demonstrated a high rate of resolution of all congenital ovarian cysts, 62%. This is a very conservative estimate, since the rate may have been substantially higher if a prolonged period of observation had been employed for all of the operated patients. All asymptomatic simple cysts less than 40 mm in diameter resolved spontaneously, as has been previously reported.[5, 8, 19] All but 3 out of 20 simple cysts ≥ 40 mm in the study population also resolved, while the remainder underwent surgery before 3 months of age, two of which were

oophorectomies. We have also demonstrated that a complex cyst, indicative of prenatal ovarian torsion and necrosis, is neither an indication for early surgery nor a contraindication to prolonged observation, as complex cysts take a longer time to resolve. This finding reinforces those of previous smaller studies which have challenged the dictum of early surgery for complex cysts, and provides further evidence that long observation periods are both expected and safe.[5,20]

The second objective was to identify the clinical and sonographic predictors of intervention for congenital ovarian cysts. We identified larger cyst size and complex cyst character as significant predictors of surgical intervention. The justification for surgery in patients with large simple cysts is to prevent potential ovarian torsion.[4] A recent systematic review reported an increased risk of torsion in simple cysts greater than 40 mm compared with smaller simple cysts (OR 26.7, $p = 0.002$).[10] However, this systematic review presented cross-sectional but not longitudinal follow-up, data. As is seen in the present study, torsion events occur early.[7, 19] All 32 cysts that changed from having simple to complex sonographic characteristics demonstrated these changes on the first postnatal ultrasound at a median age of 5 days after birth. A review by Brandt et. al. on 257 ovarian cysts reported 92% of neonatal ovaries with torsion had evidence of torsion present on the first postnatal ultrasound, suggesting all in utero events.[9] Therefore, the concept of a larger simple cyst predisposing the ovary to postnatal torsion is not supported by the evidence.

Surgery is typically performed for complex cysts due to concerns about possible reversible ovarian torsion and potential complications from an intra-abdominal necrotic ovary. In the present study, surgery resulted in an oophorectomy rate of 85% for complex cysts, and we had no definitive sonographic proof of a long-term viable ovary in the other 15%. This reinforces the results of other studies, showing high oophorectomy rates in patients undergoing surgical

intervention because no normal or viable ovarian tissue was identified at the time of surgery.[4, 6, 8, 19-24] Therefore, ovarian torsion and complete loss of the ovary should be considered irreversible in the presence of a complex cyst.

There is little evidence to support the concept of potential long-term complications due to complex cysts left in the abdomen.[25] In the present study, 50% of symptomatic patients presented within the first week of life. This finding is in keeping with other studies showing the majority of symptomatic patients presented during the neonatal period.[6, 11] We did not observe any complications in patients with complex cysts undergoing continued follow-up during the first year of life. In addition, it was difficult to ascertain whether the cyst in fact explained the symptoms. For example, there was no consistent documentation of intestinal obstruction in patients who presented with abdominal distention based on our retrospective review.

Our third objective was to examine whether early surgical intervention, defined as an intervention before 3 months of age, is likely to result in increased ovarian preservation. Overall, we found no statistically significant difference in the incidence of ovarian preservation between the patients who were observed and those who underwent early surgical management. To our knowledge, only one other study specifically investigated the effect of an observation period on ovarian preservation.[7] It showed no difference in ovarian preservation rates (75% vs 89%, $p = 0.577$) and no difference in the percentage of auto-amputated ovaries at the time of surgery between their observation group and primary surgery group.[7] Therefore, the utility of even the earliest surgical intervention in saving the ovary is unproven. Surgical interventions that increase resource utilization but do not improve outcomes have been cited as major contributors to health care costs.[26,27] Moreover, concerns have been raised regarding unnecessary general anesthetics in infants and children.[28,29] These are additional reasons to limit interventions for congenital

ovarian cysts that do not increase ovarian preservation or improve patient outcomes. Given these findings, observation may be considered as a safe option that does not deleteriously affect the rate of ovarian preservation in the management of all asymptomatic congenital ovarian cysts.

Based on the findings in this present study, we can recommend against any early surgical intervention in asymptomatic babies with congenital ovarian cysts, regardless of size and cyst complexity. A period of observation of at least 3-6 months is safe in these infants, and allows for spontaneous resolution. Asymptomatic complex cysts can be observed through the first year of life.

This study has several limitations. Sonographic follow-up beyond one year of age was not available for our study cohort, and there is scant data on this important outcome in the literature.[20,30] Confounding by indication is possible because the presence of complex cyst features (i.e. the indication) is associated with both surgical management and a higher chance of ovarian loss. The retrospective study design limited our ability to collect data on all pertinent variables, and although attempts were made to control for confounding variables that were available in the dataset, residual confounding remains a possibility. However, the inclusion of ten hospital centers increases the external validity of the findings.

To address some of these limitations, we have created a proposed a pathway for the diagnosis and management of asymptomatic congenital ovarian cysts diagnosed between the beginning of the 3rd trimester of pregnancy and 3 months of age **(Figure 3)**. The pathway aims emphasizes management based on the trajectory of sonographic findings, rather than findings at any one point in time. The pathway aims to avoid early surgical intervention, allow an adequate period of observation, identify non-resolving cysts, and document the natural history and outcomes of all lesions. Prospective application of the pathway in a new CanCORPS longitudinal

follow- up study will allow further understanding of the natural history of these lesions, refine indications for intervention, and establish well-documented outcomes regardless of treatment modality.

5. Conclusions

The vast majority of congenital ovarian cysts, including most simple cysts and nearly half of complex cysts, resolve spontaneously during the first year of life. Many patients who undergo interventional management are still treated with oophorectomies despite the lack of evidence that surgical management increases the chance of saving the ovary. Observation is a safe option that may lead to the avoidance of unnecessary surgical procedures in young infants.

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Table 1. Clinical characteristics of study population (n = 189)

Characteristic	Total
Maternal age (years), median (IQR)	32 (8)
Gestational age at birth (weeks), median (IQR)	39 (3)
Gestational age at diagnosis (weeks), median (IQR)	33 (4)
Diagnosis	
Prenatal, n (%)	163 (86)
Postnatal, n (%)	26 (14)
Largest cyst diameter (mm) [a], median (IQR)	39 (33)
Cyst diameter < 40 mm, n (%)	91 (52)
Cyst diameter ≥ 40 mm, n (%)	84 (48)
Prenatal cyst resolution, n (%)	14 (7.4)
Initial sonographic characteristic	
Simple, n (%)	106/189 (56)
Complex, n (%)	83/189 (44)
Change in ultrasound character [b], n (%)	32/173 (18)
Prenatal cyst aspiration, n (%)	2 (1)
Postnatal Intervention, n (%)	57/173 (34)
Ovary-sparing intervention [c], n (%)	14/57 (25)
Oophorectomy/salpingo-oophorectomy, n (%)	43/57 (75)
Urgent procedure, n (%)	20/57 (35)
Intervention approach	
Laparotomy, n (%)	14/57 (25)
Laparoscopy, n (%)	34/57 (60)
Laparoscopy converted to laparotomy, n (%)	8/57 (14)
Percutaneous aspiration, n (%)	1/57 (1)

[a] Measured on postnatal ultrasound
[b] Change from simple to complex sonographic characteristics
[c] Percutaneous aspiration, cyst unroofing, cystectomy

Table 2. Comparison of characteristics based on treatment in first 3 months of life (n = 153)

Characteristic	**Early surgery (n = 22)**	**Initial observation (n = 131)**	**p value**
Maternal age (years), median (IQR)	33 (7)	31 (7)	0.503
Gestational age at birth (weeks), median (IQR)	39 (2)	39 (3)	0.265
Gestational age at diagnosis (weeks), median (IQR)	36 (4)	33 (4)	0.025
Postnatal diagnosis, n (%)	3 (13.6)	13 (9.9)	0.598
Largest cyst diameter (mm), median (IQR)	55 (25.5)	33 (22)	< 0.001
Sonographic character			< 0.001
Simple, n (%)	3 (13.6)	80 (61.1)	
Complex, n (%)	19 (86.4)	51 (38.9)	
Change in character, n (%)	9 (47.4)	20 (17.2)	0.003

[a] Patients excluded: prenatal resolution (n = 14), emergency intervention (n = 20), and prenatal aspiration (n = 2)

Table 3. Comparison of characteristics between patients who had successful cyst resolution after observation to patients who underwent surgical intervention after initial observation for a minimum of 3 months

Characteristic	**Successful observation (n = 103)**	**Failed observation (n = 15)**	**p value**
Largest cyst diameter (mm), median (IQR)	28 (18.5)	44 (17.5)	< 0.001
Complex cyst, n (%)	24 (23.3)	15 (100)	< 0.001
Days of observation, median (IQR)	99 (117.5)	168 (100)	< 0.001

Table 4. Comparison of clinical characteristics of patients undergoing observation versus intervention for asymptomatic ovarian cysts

Characteristic	**Observation (n = 103)**	**Intervention (n = 37)**	**p-value**
Maternal age (years), median (IQR)	31 (7)	33 (7)	0.285
Gestational age at birth (weeks), median (IQR)	39 (3)	39 (2)	0.133
Gestational age at diagnosis (weeks), median (IQR)	33 (4)	35 (4)	0.017 [c]
Postnatal diagnosis, n (%)	10 (9.7)	4 (10.8)	0.848
Largest cyst diameter (mm), median (IQR)	30 (17.5)	50 (21)	< 0.001 [c]
Sonographic character			< 0.001 [c]
Simple, n (%)	79 (76.7)	3 (8.1)	
Complex, n (%)	24 (23.3)	34 (91.9)	
Change in character, n (%)	11 (11.8)	14 (43.8)	< 0.001 [c]

[a] Patients excluded: prenatal resolution (n = 14), emergency intervention (n = 20), prenatal aspiration (n = 2), and persisted cyst after 1 year (n = 13)

Table 5. Logistic regression analysis of predictors of surgical management

Predictor	**Crude OR (95% CI)**	**Adjusted OR (95% CI)** [a]	**p-value**
Maternal age (years)	1.04 (0.96 – 1.13)	-	-
Gestational age at birth (weeks)	1.12 (0.98 – 1.34)	-	-
Gestational age at diagnosis (weeks)	1.19 (1.04 – 1.4)	1.24 (0.99 – 1.66)	0.084
Cyst diameter ≥ 40mm	12.1 (4.9 – 32.9)	6.19 (1.66 – 35.9)	0.012
Complex cyst	37.3 (12.1– 164.8)	63.6 (10.9 -1232)	< 0.001
Change in sonographic character	5.8 (2.29 –15.2)	-	-

Surgical intervention (n = 37) compared to observation (n = 103); reference is observation group
[a] Refers to stepwise multivariate logistic regression analysis; adjusted for gestational age at diagnosis, cyst diameter, and complex cyst character

Figure Legend

Figure 1 – Study population

Figure 2 –Management and outcomes of patients with congenital ovarian cysts (n = 189)

Figure 3 – Kaplan Meier survival analysis of time to resolution

Figure 4 – Management pathway for patients with congenital abdominal cysts

Figure 1

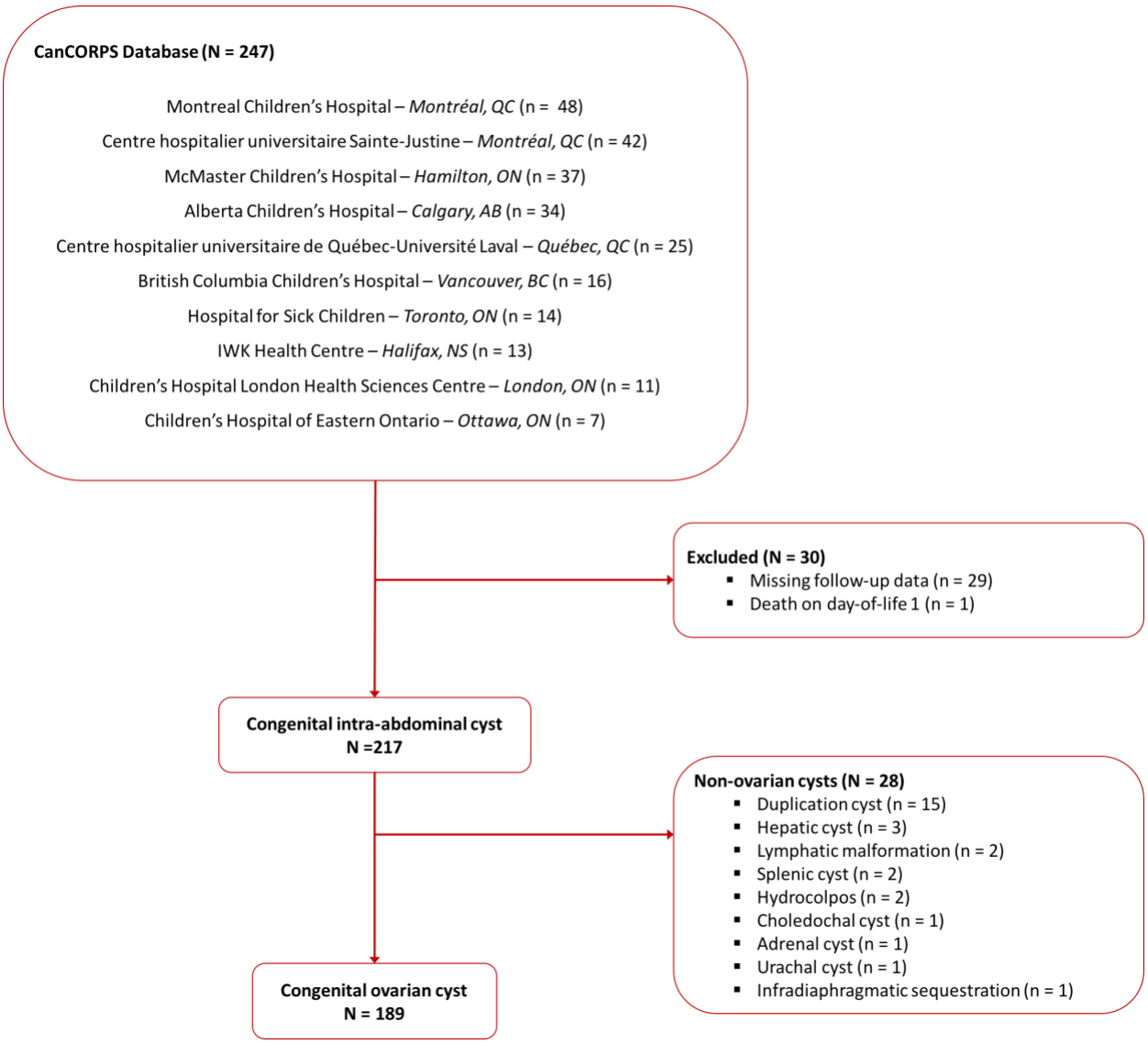

CanCORPS Database (N = 247)
Montreal Children's Hospital – Montréal, QC (n = 48)
Centre hospitalier universitaire Sainte-Justine – Montréal, QC (n = 42)
McMaster Children's Hospital – Hamilton, ON (n = 37)
Alberta Children's Hospital – Calgary, AB (n = 34)
Centre hospitalier universitaire de Québec-Université Laval – Québec, QC (n = 25)
British Columbia Children's Hospital – Vancouver, BC (n = 16)
Hospital for Sick Children – Toronto, ON (n = 14)
IWK Health Centre – Halifax, NS (n = 13)
Children's Hospital London Health Sciences Centre – London, ON (n = 11)
Children's Hospital of Eastern Ontario – Ottawa, ON (n = 7)
Excluded (N = 30)
Missing follow-up data (n = 29)
Death on day-of-life 1 (n = 1)
Congenital intra-abdominal cyst
N =217
Non-ovarian cysts (N = 28)
Duplication cyst (n = 15)
Hepatic cyst (n = 3)
Lymphatic malformation (n = 2)
Splenic cyst (n = 2)
Hydrocolpos (n = 2)
Choledochal cyst (n = 1)
Adrenal cyst (n = 1)
Urachal cyst (n = 1)
Infradiaphragmatic sequestration (n = 1)
Congenital ovarian cyst
N = 189

Figure 2

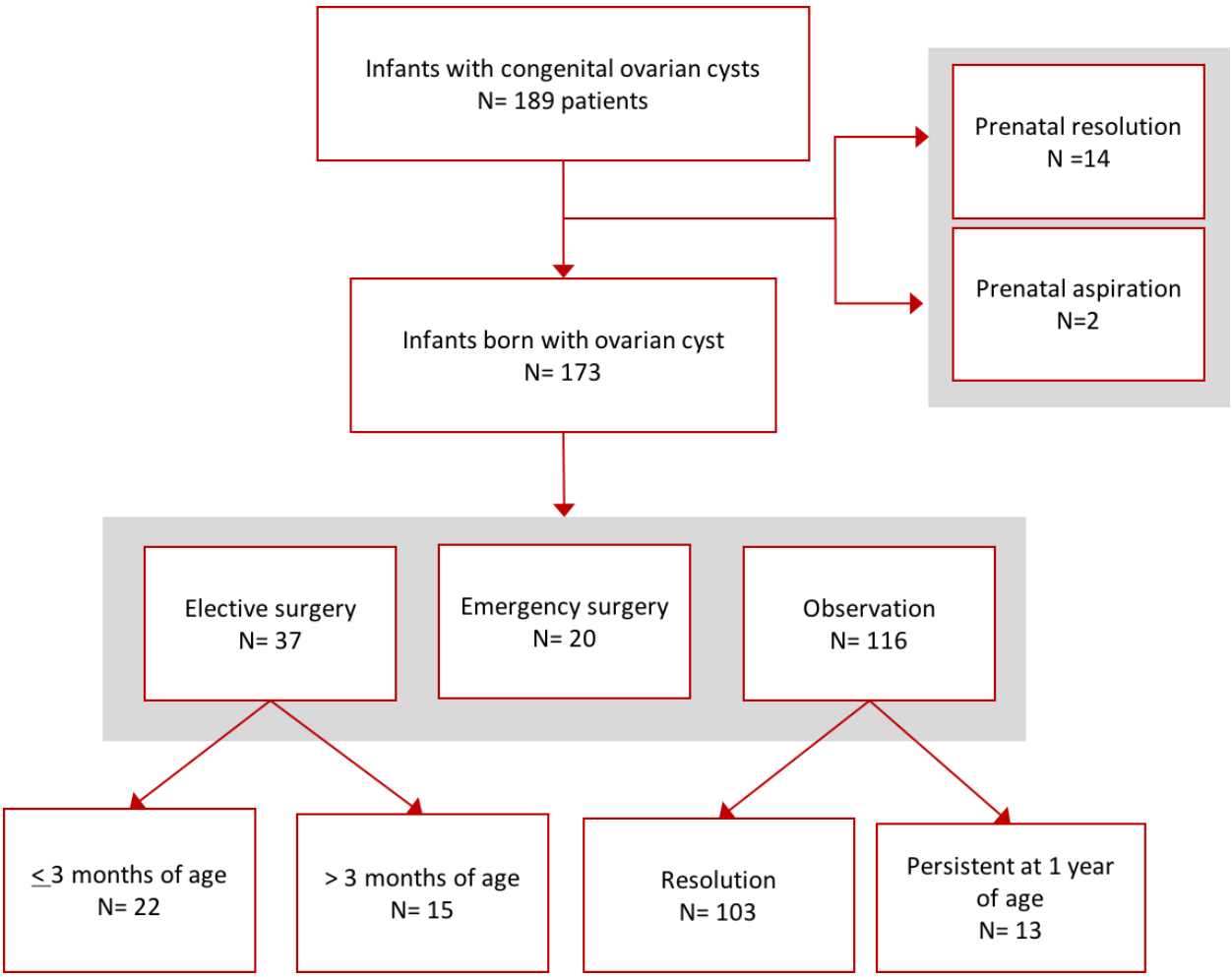
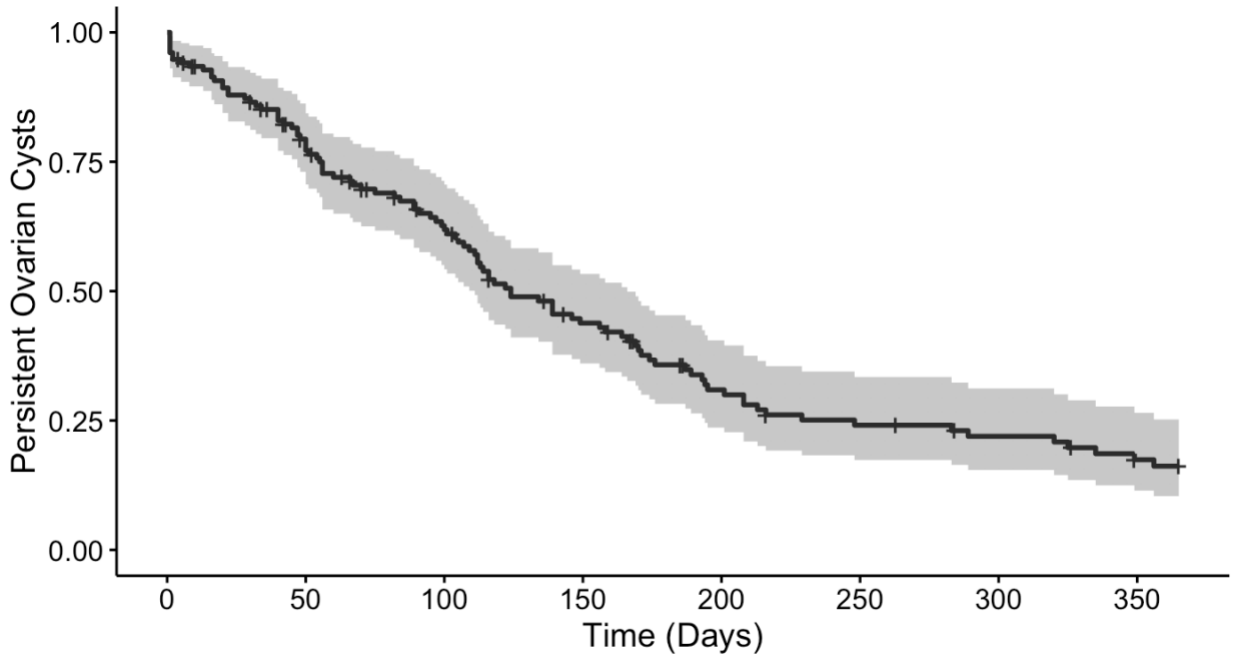

Infants with congenital ovarian cysts
N= 189 patients
Prenatal resolution
N =14
Prenatal aspiration
N=2
Infants born with ovarian cyst
N= 173
Elective surgery
N= 37
Emergency surgery
N= 20
Observation
N= 116
≤ 3 months of age
N= 22
> 3 months of age
N= 15
Resolution
N= 103
Persistent at 1 year of age
N= 13

Figure 3

A. Overall time to resolution for congenital ovarian cyst



B. Comparison of time to resolution between simple and complex congenital ovarian cysts

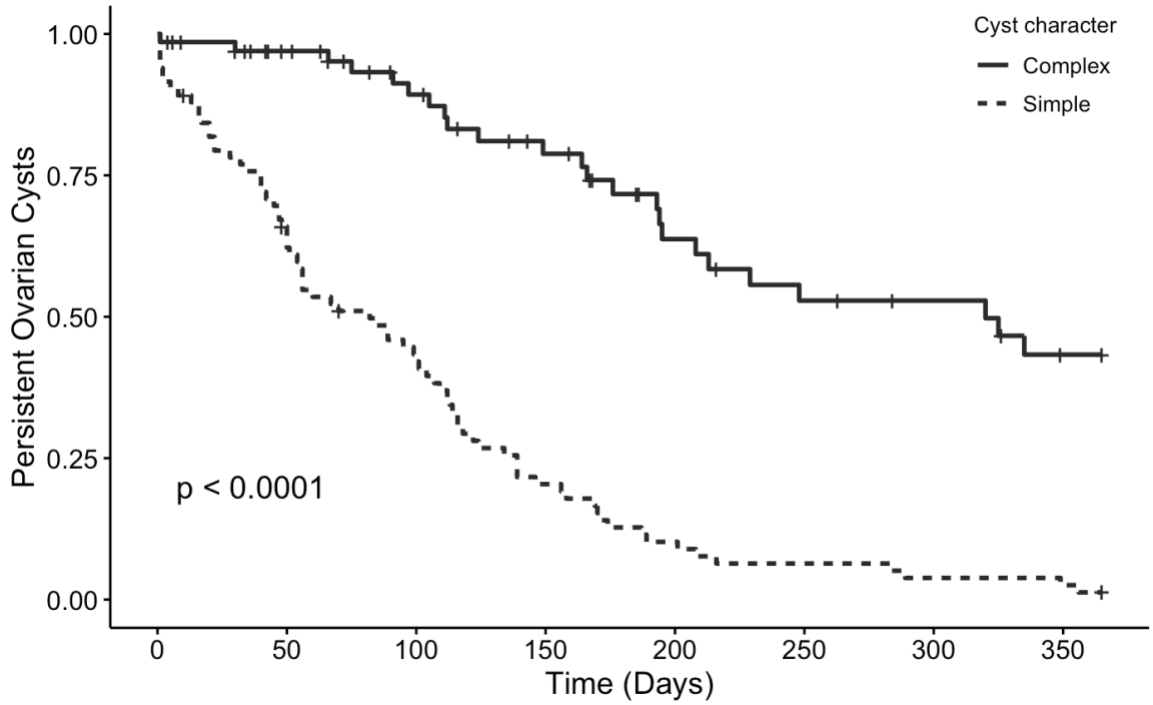
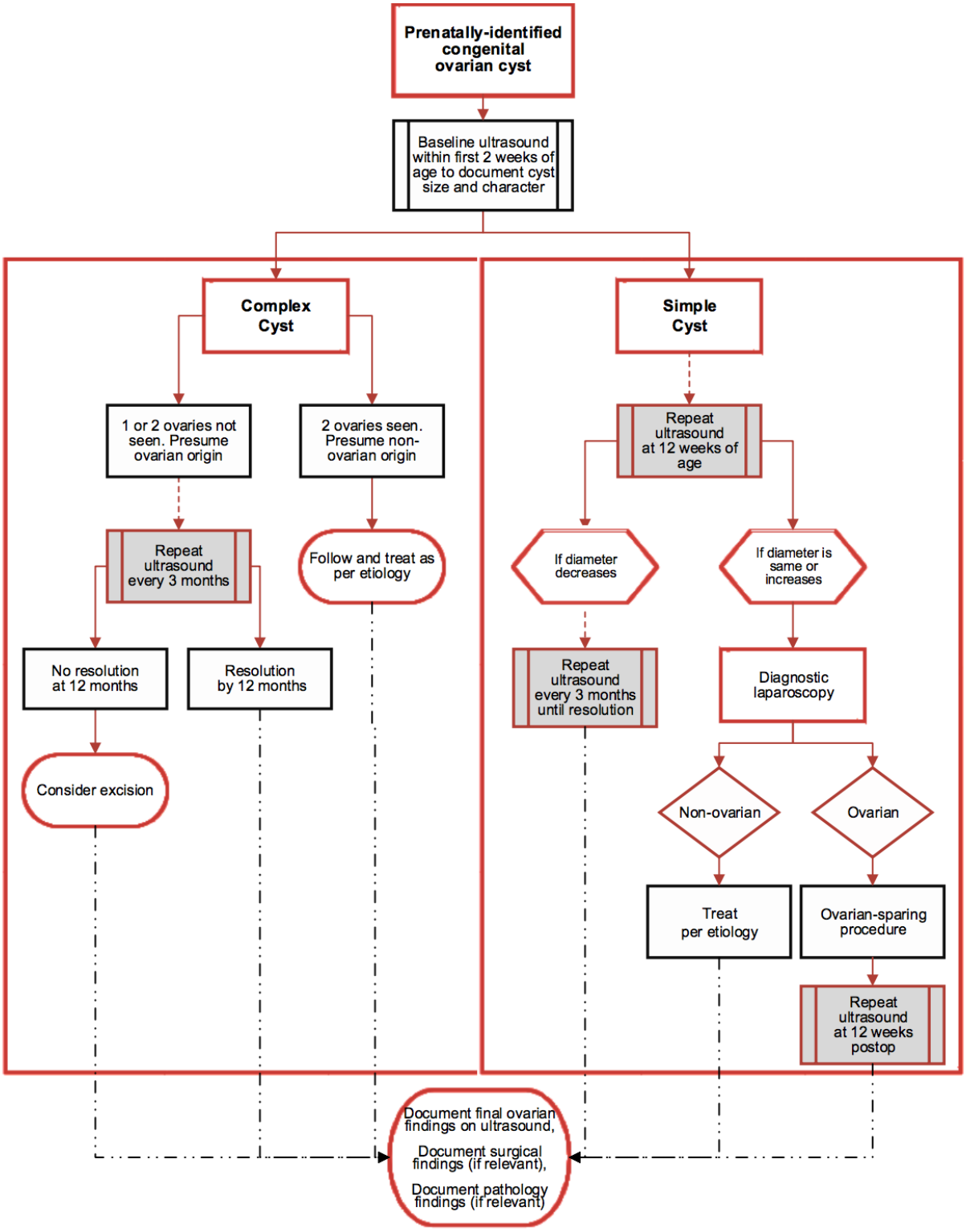


Figure 4


Prenatally-identified congenital ovarian cyst
Baseline ultrasound within first 2 weeks of age to document cyst size and character
Complex Cyst
Simple Cyst
1 or 2 ovaries not seen. Presume ovarian origin
2 ovaries seen. Presume non-ovarian origin
Repeat ultrasound every 3 months
Follow and treat as per etiology
No resolution at 12 months
Resolution by 12 months
Consider excision
Repeat ultrasound at 12 weeks of age
If diameter decreases
If diameter is same or increases
Repeat ultrasound every 3 months until resolution
Diagnostic laparoscopy
Non-ovarian
Ovarian
Treat per etiology
Ovarian-sparing procedure
Repeat ultrasound at 12 weeks postop
Document final ovarian findings on ultrasound,
Document surgical findings (if relevant),
Document pathology findings (if relevant)

CHAPTER 5 – DISCUSSION

In the first manuscript, I conducted a systematic review of 70 studies that included 1,635 patients. The majority of studies were single-institution retrospective case series and of low quality. The reporting of outcomes was heterogeneous, and the study methodologies differed with regards to the management strategies employed by the different hospital centers, including indications for surgical and non-surgical management. A previous systematic review on this subject was published in 2017, and those authors performed a meta-analysis using a random-effects model to estimate the incidence of cyst resolution and identify predictors of spontaneous cyst resolution and of surgical intervention. After rigorously reviewing the data of each included study in the present systematic review, I did not perform a pooled analysis with such heterogeneous data, as a meta-analysis would not contribute robust or generalizable conclusions. Rather, using the knowledge gained from the systematic review, I designed a retrospective cohort study to examine the realm of clinical practice in Canada for the management of patients with congenital ovarian cysts to address some of the remaining controversies.

The second manuscript is a retrospective cohort study that included ten pediatric surgical hospital centers across Canada to study the following: (1) to identify the incidence of spontaneous cyst resolution in one year following birth, (2) to identify the clinical and sonographic predictors of intervention on fetal ovarian cysts, and (3) to examine whether surgical intervention is associated with increased ovarian preservation compared to observation alone. A congenital ovarian cyst was defined as an abdominal cyst with confirmed ovarian origin that was documented during sonographic evaluation (prenatal or postnatal) or during an invasive or surgical intervention. As discussed in Chapter 1, the pathophysiology of ovarian cysts is attributed to maternal and fetal hormonal stimulation of fetal ovarian follicles that can be

stimulated as early as 19 weeks gestation and lead to ovarian cyst formation. The majority of ovarian cysts are identified in the third trimester. The hormone levels decrease with the maturation of the infant hypothalamic-pituitary axis at around 3-6 months of age, and this is usually accompanied by regression of the ovarian cyst.[11, 20] For the purposes of this study, a congenital ovarian cyst was defined as an ovarian cyst identified between 22 weeks gestation to 3 months of age. This definition not only is in keeping with the pathophysiological timeline for development and regression of these cysts, but also allows for the inclusion of patients who were not referred to a pediatric surgical center in the prenatal period for fetal consultation, and were only referred in the postnatal period.

In addition to obtaining ethics approval at McGill University, I worked with site investigators across the country to establish center-specific study protocols that would meet criteria for ethics approval at each respective hospital center. I created a REDCap database for data abstractors to enter and store the study data centrally in a centralized password-protected electronic system. A large emphasis was placed on identifying relevant study variables and creating clear definitions for each variable to decrease heterogeneity in data reporting between centers, since much of the sonographic surveillance and management is institution-specific and does not follow standardized guidelines. For example, if a cyst has one septation, it may be considered a complex cyst at one institution and classified as a simple cyst at another institution. Therefore, I collaborated with an investigator from each of the ten hospital centers to develop a list of clinically relevant variables that could easily be abstracted from hospital charts, and to create clear definitions for every variable. An abstractor manual was distributed to all participating centers so that all data abstractors extracting the data could refer to the agreed upon

definitions. I helped data abstractors navigate their center-specific hospital records and maternal referral patterns so that the data collection for this study could be complete and accurate.

The decision to separate patients into an early surgery versus observation group was two-fold. Firstly, for patients who underwent observation, it allowed use of Kaplan-Meier analysis to determine the median time to spontaneous cyst resolution, which was 124 days (95% CI 111-166 days) and similar to data previously reported.[26] Secondly, it allowed us to address whether surgical management for congenital ovarian cysts mitigates the risk of ovarian loss. This has always been an area of controversy because advocates for early surgical intervention claim there is a higher chance of preserving the ipsilateral ovary with early surgery. Yet this is mostly anecdotal, and previously published studies do not corroborate this claim. Importantly, our study shows that there is no increase in ovarian preservation when early surgery is performed compared with initially observing patients for at least 3 months (OR 3.06, 95% CI 0.86 – 13.2), irrespective of whether patients in the latter group undergo delayed surgery after a period of observation. Importantly, the 3-month observation period was again based on the pathophysiology of ovarian cyst formation and regression, specifically that a decline in hormonal levels at approximately 3 months of age corresponds to an expected spontaneous cyst resolution.[11, 20] Previous case series have described their intra-operative findings at the time of surgery and discussed that surgery may be futile because the ipsilateral ovary is already nonviable at the time of the operation, especially in the context of a large or complex cyst. However, the present cohort study is the first to demonstrate statistical evidence in support of this claim. [24, 28, 39] In fact, all fifteen of the patients who underwent elective surgery after a minimum three-month observation period were asymptomatic, had no complications associated with the cysts, and intra-operatively underwent an oophorectomy due to findings of either

ovarian torsion or a complex ovarian cyst. None of the ovaries were preserved, and while it is difficult to extrapolate what may have happened if no surgery was performed, it is important to emphasize that delayed surgery did not lead to salvage of the ovary. The present cohort study provides evidence that surgical interventions may increase resource utilization without providing improved outcomes, and recommends a more conservative approach that shifts management strategies towards sonographic surveillance rather than surgery for patients with congenital ovarian cysts.

It is important to highlight and discuss a major limitation present in all observational studies on the management of congenital ovarian cysts, and that is confounding by indication. As described in detail by Kyriacou and Lewis, confounding by indication occurs in observational studies when a treatment of interest is selectively used or not used in patients who develop the outcome of interest.[67] This would occur, for example, if cysts with complex sonographic characteristics are more likely to be operated on and are more likely to be associated with ovarian loss; in this instance, the cyst character influences both the decision to operate and the outcome of ovarian loss, and is not on the causal pathway. The ascertainment of the predictors for surgical and non-surgical management remains influenced by this bias.

Only one observational study included in the systematic review in Chapter 2 performed a logistic regression analysis to adjust for other possible confounders.[27] In designing the present cohort study, we performed a multivariate logistic regression analysis to control for confounders to examine the predictors of surgical versus non-surgical management. We also used logistic regression to determine whether early surgical or non-surgical management affected ovarian preservation. In doing so, we were able to challenge the dogma of early surgery for complex cysts and provide justification that observation is safe. Notably, few of the confidence intervals

for some of the odds ratios reported in the cohort study are really wide. With regards to ovarian preservation following early surgery and observation, while the 95% confidence interval for the odds ratio includes the null value (OR 3.06, 95% CI 0.86 – 13.2), most of the confidence interval is above 1. Thus we cannot say there is truly no difference in ovarian preservation between patients undergoing early surgery and those who are observed. A post-hoc power analysis demonstrated a power of 75%, meaning there is a 25% chance for a type II error. Despite our best efforts to include multiple centers across Canada, our sample size may be too small to draw conclusions with any degree of confidence, so we also recognize this study limitation. Finally, multivariate logistic regression cannot be used to control confounding by indication in observational studies, which is why it remains an important study limitation. Therefore, we cautiously suggest that the present retrospective cohort study contributes evidence in support of a conservative approach to patients with congenital ovarian cysts by demonstrating no statistically significant increase in ovarian preservation in patients who underwent surgery compared to those who were initially observed.

CHAPTER 6 – CONCLUSION

Congenital ovarian cysts are the most common cystic abdominal mass necessitating referral to a pediatric general surgeon. Surgical and non-surgical management are two main treatment strategies for congenital ovarian cysts, with the ultimate goal aimed at preserving the ipsilateral ovary. The findings of the systematic review show that cyst size and complex sonographic character are the major determinants of perinatal management decisions, with large and complex cysts having a higher likelihood for surgery. Although advocates for surgical intervention maintain that early surgery can lead to a higher rate of ovarian preservation, but the majority of published case series do not provide supportive evidence.

The retrospective cohort study is the largest observational study on the current management of patients with congenital ovarian cysts. In this study, we report that one year of observation of patients with congenital ovarian cysts, regardless of the presence of complex features on ultrasound, is safe and can result in spontaneous resolution of the cyst. Although the study is limited by confounding by indication, findings suggest that ovarian preservation is not increased with surgical intervention, and that observation of patients with congenital ovarian cysts is a safe option that may lead to favorable outcomes in the majority of patients.

Future directions for research will focus on designing a longitudinal study evaluating the clinical outcomes of infants with congenital ovarian cysts after implementing a standardized management protocol that specifies indications for early surgical intervention versus observation. We hope this future study will elucidate further the generally benign natural history of congenital ovarian cysts, and provide high-quality data on the viability of the ipsilateral ovary after surgical or non-surgical management.

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