CHAPTER 4

Behavior and Complications of Hepatocellular Adenoma During Pregnancy and Puerperium: A Retrospective Study and Systematic Review

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Abstract

Background

Hepatocellular adenomas (HCA) are benign liver tumors at risk of hemorrhage. The influence of pregnancy on HCA growth and potential bleeding remains unclear. This study investigates HCA-associated behavior and bleeding complications during or shortly after pregnancy.

Methods

(I) Single center retrospective cohort study of HCA during and after pregnancy. (II) Systematic literature review.

Results

The retrospective study included 11 patients, of which 4 with HCA ≥5 cm. In only two patients HCA showed growth during pregnancy. In this local cohort, no HCA-related hemorrhages occurred during median follow-up of 34 months (interquartile range 19-58 months). The systematic review yielded 33 studies, totaling 90 patients with 99 pregnancies. Of 73 pregnancies without prior HCA-related intervention, 39 HCA remained stable (53.4%), 11 regressed (15.1%), and 23 (31.5%) progressed. Fifteen HCA-related hemorrhages occurred in HCA measuring 6.5-17.0 cm. Eight patients experienced bleeding during pregnancy, two during labor and five postpartum.

Discussion

Although hemorrhage of HCA during or shortly after pregnancy is rare and only reported in HCA ≥6.5 cm, it can be fatal. Pregnancy in women with HCA, regardless of size, warrant a close surveillance strategy. Observational studies on behavior and management of HCA ≥5 cm during and immediately after pregnancy are needed.

Introduction

Hepatocellular adenomas (HCA) are rare, benign liver tumors. HCA can be complicated by bleeding (15-20%) and malignant transformation (4-5%). These complications are related to tumor diameter, and typically occur in HCA ≥5 cm.[1–6] HCA growth can be stimulated by estrogen, either of endogenous (*i.e.* from adipose tissue) or exogenous origin.[1,6–8] Consequently, obesity or weight loss and chronic use or cessation of oral contraceptive pills (OCP) can either lead to HCA stimulation or regression.[7,9,10]

HCA are classified into subtypes, diagnosed through either immunohistochemistry or molecular analyses with specific morphological and etiological features, clinical characteristics, and behaviors.[2,6] Inflammatory HCA (I-HCA; 40-55% of HCA), hepatocyte nuclear factor 1a (*HNF1A*) inactivated HCA (H-HCA; 30-40% of HCA) rarely bleed or show malignant transformation, beta-catenin activated HCA (b-HCA; 10%) are at risk for malignant transformation to hepatocellular carcinoma (HCC). Importantly, half of b-HCA are hybrid b-catenin/inflammatory HCA (b-IHCA).[6] Finally, sonic hedgehog and roof plate spondin-2 HCA have been identified, the former being prone for hemorrhage.[6,11] U-HCA is diagnosed if analyses cannot identify any subtype. Pregnancy-associated estrogen increase may lead to HCA growth and potentially (lethal) hemorrhage.[12] Risk of gestational HCA hemorrhage, however, is largely unknown. Consequently, diagnostic strategy, follow-up, and management of HCA during pregnancy, remain controversial, especially in HCA ≥5 cm.

Current guidelines provide limited recommendations regarding diagnostics, treatment, or mode of delivery on HCA diagnosed prior to or during pregnancy.[13–16] We reviewed our records to evaluate the behavior, complications, and outcome of HCA during gestation and puerperium at our center. Subsequently, a literature review was performed to compare our data with the current literature.

Methods

This study consists of two sections: (1) a single center retrospective study; and (2) a systematic review of the current literature. This study was approved by the local medical ethical committee (METc2020/064-UMCG/RR2020000071).

Retrospective analysis of HCA during pregnancy and puerperium

Electronic patient files of patients with HCA diagnosed prior to or during pregnancy during January 2010-December 2020 were retrospectively investigated. HCA size and number were extracted from radiology reports. HCA size on either cross-sectional imaging or ultrasound (US) was reported during diagnosis, latest observation before pregnancy, latest observation during pregnancy, and last observation. If no recorded measurement during pregnancy was available, measurements up to two weeks post-partum were used. Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 were applied.[17] Paraphrased criteria are: "complete regression" defined by disappearance of all tumors, "regression" defined by ≥30% regression, "growth" defined by ≥20% increase in diameter, and "stable" defined by neither sufficient growth for being classified as "growth" nor sufficient regression for "regression". Extraction of all measurements was supervised by a radiologist (R.J.D.H.). Lastly, HCA related complications, invasive treatments, methods of delivery, and duration of follow-up were extracted.

Statistical analyses

Continuous variables were described using the median with interquartile range (IQR) or range, whereas nominal and ordinal variables were described using totals, frequencies, and percentages. The statistical analyses were performed using IBM SPSS statistics v23.0 (SPSS Inc., Chicago, IL, USA).

Systematic review on HCA during pregnancy and puerperium

A systematic literature search was performed by two investigators using pre-specified search terms within the electronic bibliographic databases of MEDLINE, EMBASE, and Web of Science, from inception with the latest search on July 10th 2020. Manual reference checks of accepted papers in recent reviews and included papers were performed to supplement the electronic searches. The review protocol was registered at the International Prospective Register of Systematic Reviews; CRD42020181650.[18] Literature search and screening, and data extraction and appraisal were performed in duplicate by M.P.D.H. & C.S.S.

Literature screening

Case reports, case series, and cohort studies from English-language journals were included if they reported on HCA during pregnancy. Reports with missing HCA size were included to reduce publication bias. Bibliographic filters were applied for exclusion of conference abstracts, non-English articles, systematic reviews, and animal studies. Duplicates were excluded manually. Two investigators first independently screened titles and abstracts, and thereafter full texts. Duplicate removal and article screening was performed using the web based, open-access software CADIMA.[19] No blinding strategies were employed. A third investigator (V.E.M.) resolved discrepancies.

Data extraction and critical appraisal

The retrospective study adhered to Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[20] The design, conduct, and reporting of the review were according to Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines.[21] Data were independently extracted in duplicate from included articles in a standardized form. Surgical interventions and HCA size were quoted if explicit reporting of resected hepatic segments or absolute HCA size was missing. Data were presented on a per pregnancy base. Individual patients from cohort studies were pooled together with case reports and case series if sufficient information was provided and reported separately if not. Separately reported cases were excluded from data synthesis but included in the discussion of data. Two independent investigators appraised levels of evidence using the Oxford Centre for Evidence-based Medicine Level of Evidence (OCEBM) scale, the Newcastle-Ottawa Scale (NOS), and the Enhancing the Quality and Transparency of Health Research Network consensus-based Clinical Case Reporting (EQUATOR-CARE) guidelines.[22–25]

Definitions

HCA size behavior in the included studies was extracted and categorized into growing, stable, or regressing. RECISTv1.1 definitions were applied if possible.[17] Extraction of all measurements was supervised by a radiologist (R.J.D.H.).

Results

Retrospective analysis of HCA during pregnancy and puerperium

From a total cohort of 332 HCA patients, 11 patients were identified with HCA diagnosed either prior to or during pregnancy (**Table 1**). All patients had a history of OCP use. Median (IQR) age of diagnosis was 26 years (25-30). Two patients were diagnosed with hepatic adenomatosis (*i.e.* ≥10 HCA). Five HCA with subtype analysis on histopathology were diagnosed as I-HCA, and one I-HCA was diagnosed on contrast-enhanced magnetic resonance imaging (CE-MRI). Other patients had a median (IQR) of 2 HCA (1-3). Median (IQR) size at diagnosis was 27 mm (24-63), and prior to pregnancy 28 mm (14-63). Four out of 11 patients had HCA >5 cm (36.4%). Two HCA grew during pregnancy; both HCA <5 cm. All HCA among the four patients with HCA >5 cm showed stable behavior during pregnancy. Postpartum, 6 HCA were stable, and 5 regressed (complete regression in two patients). There were 2 Cesarean sections (CS), 1 due to HCA size (67 mm), and 1 because of fetal breech position. No HCA induced hemorrhages were observed during the median (IQR) follow-up period of 34 months (19-58). No (minimally) invasive treatments for HCA were performed prior to or during pregnancy. No relation was observed between HCA behavior after pre-pregnancy OCP cessation and HCA behavior during or after pregnancy.

Systematic review of the literature on HCA during pregnancy and puerperium

Quantity and quality of included evidence

Among 311 unique articles identified in the search, 33 fell within the scope of the study (**Figure 1**). Twenty-eight case reports and case series were included.[12,26–53] Five cohort studies were included.[3,12,54–56] All included cohort studies scored ≥6on the NOS and provided OCEBM level three evidence. None of the included case series adhered to CARE guidelines. Data from 28 case reports or series and one cohort study were pooled, resulting in 90 patients during 99 pregnancies (**Table 2**).[12,26–53] OCP status was reported in most studies (79%).[26,28,30,42–45,52] Four cohort studies reported insufficient information on patient characteristics, HCA size, and HCA behavior for reporting and pooling of individual patients.[3,54–56] One case report and one cohort study reported on hepatocyte

nuclear factor 1a maturity onset diabetes of the young (HNF1A-MODY)-associated HCA.[40,55] One cohort study described glycogen storage disease (GSD)-associated HCA.[56]

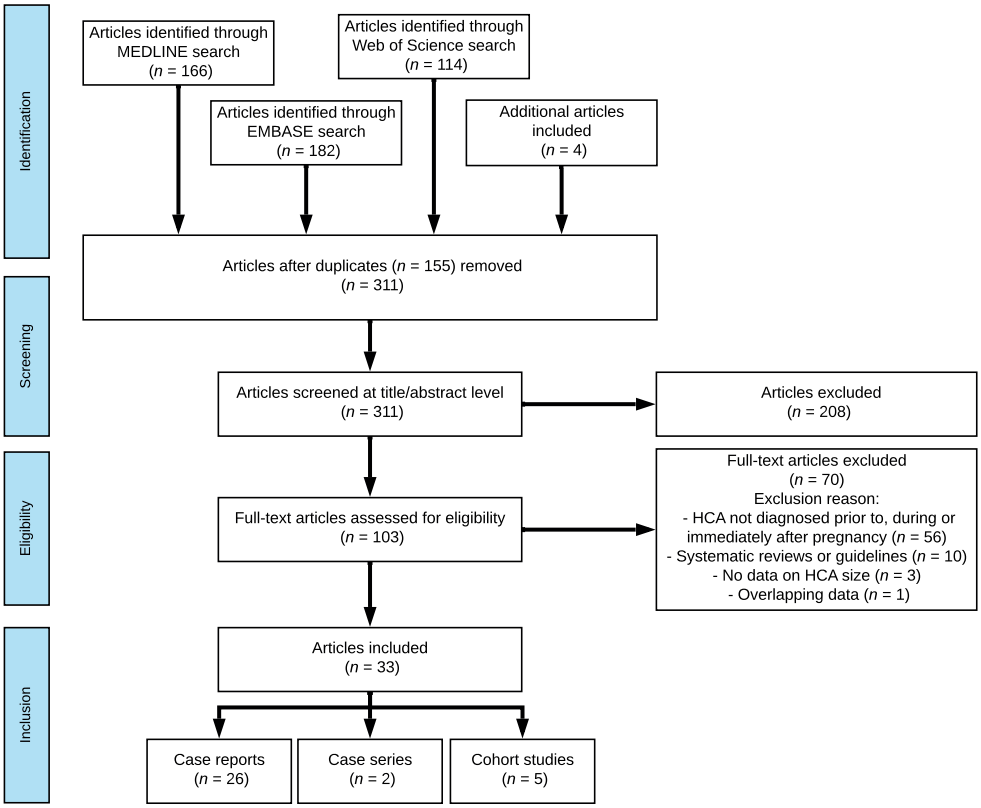

Figure 1. Flowchart of systematic literature search.
Abbreviations: HCA, hepatocellular adenoma.

Table 1. Overview of baseline, gestational, and postpartum characteristics of patients with HCA during pregnancy

Case ID	Age of diagnosis (years)	No. of HCA	HCA Subtype	Timing of HCA diagnosis	HCA size at diagnosis (mm)	HCA size last observation prior to pregnancy (mm)	HCA size during pregnancy (mm, trimester)	HCA behavior during pregnancy	HCA behavior postpartum	HCA size postpartum (mm)	Follow-up postpartum (months)	HCA bleeding complication	Mode of delivery & indication for CS
A	37	4	I-HCA	Prior to pregnancy	63	63	67, 3rd trimester	Stable	Stable	67	34	None	CS, HCA size
B	26	1	I-HCA*	Prior to pregnancy	104	82	91, 3rd trimester	Stable	Stable	66	19	None	Vaginal
C	26	2	No subtype analysis	Prior to pregnancy	15	14	36, 3rd trimester	Growth	Stable	19	69	None	Vaginal
D	17	1	N/A	Prior to pregnancy	27	28	Unobservable	N/A	Regression	18	24	None	Vaginal
E	31	3	I-HCA	Prior to pregnancy	62	62	57, 3rd trimester	Stable	Stable	51	2	None	Vaginal
F	24	>10	I-HCA	Prior to pregnancy	36	30	31, 3rd trimester	Stable	Stable	31	67	None	Vaginal
G	26	3	N/A	Prior to pregnancy	24	11	11, 3rd trimester	Stable	Complete regression	4	9	None	Vaginal
H	30	>10	I-HCA	Prior to pregnancy	24	24	31, 2 weeks postpartum	Growth	Regression	18	58	None	Vaginal
I	26	1	N/A	Prior to pregnancy	27	16	14, 3rd trimester	Stable	Regression	9	47	None	CS, breech position
J	28	1	N/A	Prior to pregnancy	18	10	Unobservable	Complete regression	Complete regression	0	29	None	Vaginal
K	25	2	I-HCA	3rd week gestation	63	63	71, 3rd trimester	Stable	Stable	65	58	None	Vaginal

Abbreviations: OCP, oral contraceptive pill; HCA, hepatocellular adenoma; I-HCA, inflammatory hepatocellular adenoma. *HCA subtype diagnosis made on contrast-enhanced magnetic resonance imaging.

Table 2. Behavior of HCA during gestation and puerperium of all studies included in the systematic review

Author (year)	Patient ID-pregnancy	Timing of HCA diagnosis	Largest HCA at diagnosis (cm)	No. of HCA	HCA behavior after OCP stop	HCA behavior during pregnancy	HCA diameter at start (cm)	HCA diameter at end (cm)	Behavior postpartum
				HCA <5 cm					
Cobey (2004)[26]	1-1	Prior to pregnancy	-	1	-	-	-	4.0	Stable
	1-2	Prior to pregnancy	4.0	1	-	Growth	4.0	10.7	Growth
Fujita (2006)[27]	2	Prior to pregnancy	3.0	2	-	Growth (Surgery + RFA)	3.0	4.0	Regression
Wilson (2011)[28]	3	During, 3rd trimester	3.4	3	-	Stable	-	-	Stable
Noels (2011)[29]	4	Prior to pregnancy	All <5 cm	3	Stable (Surgery)	Stable	-	-	-
Noels (2011)[29]	5-1	Prior to pregnancy	<5 cm	1	Regression	Stable	-	-	Regression
	5-2	Prior to pregnancy	<5 cm	1	Regression	Stable	-	-	Regression
Noels (2011)[29]	6-1	Prior to pregnancy	All <5 cm	"Multiple"	-	Growth to >5 cm	3.2	7.5	Regression & stable
	6-2	Prior to pregnancy	All <5 cm	"Multiple"	-	Growth to >5 cm	4.0	-	Regression & stable
Noels (2011)[29]	7	Prior to pregnancy	All <5 cm	"Multiple"	Regression	Stable	-	-	-
Noels (2011)[29]	8-1	Prior to pregnancy	All <5 cm	3	-	Growth, <5 cm	-	-	Regression
	8-2	Prior to pregnancy	All <5 cm	3	-	Stable	-	-	-
Noels (2011)[29]	9-1	During, unreported	≥5 cm	1	-	Growth to >5 cm	-	-	Regression
	9-2	During, unreported	≥5 cm	1	-	N/A (RFA)	-	-	Not visible on US
Noels (2011)[29]	10	Prior to pregnancy	All <5 cm	"Multiple"	Stable (Surgery)	Stable	-	-	Regression
Noels (2011)[29]	11	Prior to pregnancy	<5 cm	1	Regression	-	-	-	Regression
Klompenhouwer (2017)[30]	12	Prior to pregnancy	4.6	-	-	Growth	4.6	6.5	Regression
Klompenhouwer (2017)[30]	13	Prior to pregnancy	3.0	-	-	Stable	3.0	3.0	Stable
Gaspersz (2020)[12]	14-61	Prior to pregnancy	All <5 cm	-	Regression *n*=26 Stable *n*=14 N/A *n*=11	Regression 22% Stable 53% Growth 25% (TAE *n*=1)	2.3 (1.9-3.9)[§]	Growth of 1.4 (0.8-1.9)[§]	All uncomplicated

*TAE procedure prior to pregnancy. #RFA during 1st trimester. †Co-occurring HNF1A-MODY. ‡Two TAE and one electroporation procedures prior to pregnancy. § Median (IQR). Abbreviations: HCA, hepatocellular adenoma; OCP, oral contraceptives; MRI, magnetic resonance imaging; CE-CT, contrast-enhanced computed tomography; US, ultrasound; TAE, transarterial embolization; RFA, radiofrequency ablation; HNF1A-MODY; hepatocyte nuclear factor 1A maturity onset diabetes of the young; LT, liver transplantation.

Table 2. Behavior of HCA during gestation and puerperium of all studies included in the systematic review (continued)

Author (year)	Patient ID-pregnancy	Timing of HCA diagnosis	Largest HCA at diagnosis (cm)	No. of HCA	HCA behavior after OCP stop	HCA behavior during pregnancy	HCA diameter at start (cm)	HCA diameter at end (cm)	Behavior postpartum
			HCA 5-10 cm						
Antoniades (1975)[31]	62	Postpartum	6.5	1	-	-	-	-	N/A, resected
Lansing (1976)[32]	63	Postpartum	7.5	1	-	-	-	-	N/A, resected
Hibbard (1976)[33]	64	During, 3rd trimester	"⅓ of right hepatic lobe"	1	-	-	-	-	N/A, death
Kent (1977)[34]	65	During, 3rd trimester	7.0	1	-	-	-	-	-
Kent (1977)[34]	66	During, labor	"½ of right hepatic lobe"	1	-	-	-	-	-
Kent (1978)[35]	67	During, labor	"⅓ of right hepatic lobe"	1	-	-	-	-	N/A, death
Monks (1986)[36]	68	During, 3rd trimester	8.0	1	-	-	-	-	N/A, resected
Terkivatan (2000)[36]	69	During, 1st trimester	9.0	1	-	N/A (Surgery)	9.0	-	N/A, resected
Jabbour (2005)[38]	70	Prior to pregnancy	6.0	3	-	Growth (Surgery)	-	-	N/A, resected
Santambrogio (2009)[39]	71	Prior to pregnancy	5.0	1	-	Growth to ≥5 cm	5.0	12.0	N/A, LT
Wilson (2011)[28]	72	Prior to pregnancy	5.0	"Multiple"	-	Stable (Surgery)	-	-	N/A, resected
Noels (2011)[29]	73	Prior to pregnancy	One ≥5 cm	2	Regression	Stable	-	-	-
Noels (2011)[29]	74	Prior to pregnancy	One ≥5 cm	3	Stable (Surgery)	Stable	-	-	Not visible on US
Noels (2011)[29*]	75-1	Prior to pregnancy	One ≥5 cm	2	Growth (TAE)	Stable	-	-	Regression & stable
	75-2	Prior to pregnancy	One ≥5 cm	2	Growth (TAE)	Stable	-	-	-
Noels (2011)[29#]	76	Prior to pregnancy	One ≥5 cm	"Multiple"	No OCP	Stable (RFA)	-	-	Regression (RFA)

Table 2. Continued

Author (year)	Patient ID-pregnancy	Timing of HCA diagnosis	Largest HCA at diagnosis (cm)	No. of HCA	HCA behavior after OCP stop	HCA behavior during pregnancy	HCA diameter at start (cm)	HCA diameter at end (cm)	Behavior postpartum
Jeannot (2012)[40 †]	77	During, 2nd trimester	6.0	>30	-	-	-	-	-
Scheffer (2014)[41 ‡]	78	Prior to pregnancy	5.2	1	Stable (TAE & EP)	Regression	6.9 cm^3	5.2 cm^3	-
Gryspeerdt (2017)[42]	79	During, 2nd trimester	9.0	1	-	- (Surgery)	9.0	-	N/A, resected
Sanford (2020)[43]	80	During, 3rd trimester	6.5	1	-	-	-	-	Regression (TAE)
			HCA ≥10cm						
Baird (1971)[44]	81	During, 3rd trimester	16.0	1	-	-	-	-	N/A, death
Motsay (1972)[45]	82	Postpartum	10.0	1	-	-	-	-	N/A, resected
Stenwig (1975)[46]	83	During, 3rd trimester	10.0	1	-	-	-	-	N/A, resected
Hayes (1977)[46]	84	Postpartum	10.0	1	-	-	-	10.0	N/A, death
Stock (1985)[48]	85	During, 1st trimester	18.0	1	-	Growth (Abortion)	-	-	Necrosis after abortion, resection
Tsang (1989)[49]	86	During, 2nd trimester	15.0	3	-	-	-	-	N/A, resected
al-Otaibi (1995)[50]	87	Postpartum	17.0	1	-	-	-	-	Regression
Hill (1997)[51]	88	During, 2nd trimester	10.0	3	-	Stable (Resection)	-	-	N/A, resected
Stoot (2006)[52]	89	During, 3rd trimester	10.0	4	-	-	-	10.0	-
Bernstein (2019)[53]	90	During, 3rd trimester	16.1	1	-	-	-	-	Regression (TAE + Resection)

*TAE procedure prior to pregnancy. #RFA during 1st trimester. †Co-occurring HNF1A-MODY. ‡Two TAE and one electroporation procedures prior to pregnancy. § Median (IQR). Abbreviations: HCA, hepatocellular adenoma; OCP, oral contraceptives; MRI, magnetic resonance imaging; CE-CT, contrast-enhanced computed tomography; US, ultrasound; TAE, transarterial embolization; RFA, radiofrequency ablation; HNF1A-MODY; hepatocyte nuclear factor 1A maturity onset diabetes of the young; LT, liver transplantation.

Table 3. Treatment and outcomes of HCA induced hemorrhage in studies included in the systematic review

Author (year)	Patient ID-pregnancy	Largest HCA at diagnosis (cm)	No. of HCA	Timing of HCA induced hemorrhage	Treatment	Postoperative course	Maternal outcome	Fetal outcome
				HCA 5-10 cm				
Antoniades (1975)[31]	62	6.5	1	5 Weeks postpartum	Segment resection	Uncomplicated	Alive	Alive
Lansing (1976)[32]	63	7.5	3	9 Days postpartum	Lobectomy	Uncomplicated	Alive	Alive
Hibbard (1976)[33]	64	"⅓ of right hepatic lobe"	1	3rd Trimester	None, patient deceased	No surgery performed	Death	Death
Kent (1977)[34]	65	7.0	1	3rd Trimester	Tumor shelled out	Uncomplicated	Alive	Alive
Kent (1977)[34]	66	"½ of right hepatic lobe"	1	During labor	None, patient deceased	No surgery performed	Death	Alive
Kent (1978)[35]	67	"⅓ of right hepatic lobe"	1	During labor	None, patient deceased	No surgery performed	Death	Death
Monks (1986)[36]	68	8.0	1	3rd Trimester	Segment resection	Postoperative transfusions	Alive	Alive
Santambrogio (2009)[39]	89	12.0	1	1 Day postpartum	Primary: gauze packing	Uncomplicated	Alive	Alive
					Secondary: liver transplantation	Uncomplicated		
Sanford (2020)[43]	80	6.5	1	3rd Trimester	Primary: gauze packing, cautery coagulation, TAE	Uncomplicated	Alive	Alive
					Secondary: gauze removal & segment resection	Liver abscess, percutaneous drainage (led to pulmonary & right external iliac vein embolism)		
					Tertiary: segment resection	Uncomplicated		

Table 3. Continued

Author (year)	Patient ID-pregnancy	Largest HCA at diagnosis (cm)	No. of HCA	Timing of HCA induced hemorrhage	Treatment	Postoperative course	Maternal outcome	Fetal outcome
				HCA ≥10 cm				
Baird (1971)[44]	81	16.0	1	3rd Trimester	Hysterectomy & mattress sutures	Intraoperative death	Death	Death
Stenwig (1975)[46]	83	10.0	1	3rd Trimester	Segment resection	Uncomplicated	Alive	Death
Hayes (1977)[47]	84	10.0	1	5 Days postpartum	Gauze packing	Death 7 days postoperative	Death	Alive
Tsang (1989)[49]	86	15.0	1	2nd Trimester	Primary: gauze packing & arterial ligation Secondary: tumor shelled out	Uncomplicated	Alive	Abortion
al-Otaibi (1995)[50]	87	17.0	4	2 Weeks postpartum	Segment resection	Unreported	Alive	Alive
Stoot (2006)[52]	89	10.0	1	3rd Trimester	TAE postpartum	Uncomplicated	Alive	Alive

Abbreviations: HCA, hepatocellular adenoma; TAE, transarterial embolization.

Table 4. Indications and outcomes of elective invasive procedures of studies included in the systematic review

Author (year)	Patient ID-pregnancy	Largest HCA at diagnosis (cm)	No. of HCA	Timing of invasive procedure	Procedure type	Indication for procedure	Procedure outcome	Procedure related complications
				HCA <5 cm				
Cobey (2004)[26]	1-1	-	1	Postpartum, 1 year	"Resection"	HCA growth	Full resection	Uncomplicated
	1-2	4.0	1	Postpartum, 1 year	"Resection"	HCA growth	Full resection	
Fujita (2006)[27]	2	3.0	2	During, 2nd trimester	Enucleation + RFA	HCA growth	Residual HCA stable	-
Wilson (2011)[28]	3	3.4	3	During, 3rd trimester	Percutaneous biopsy	Tumor diagnosis	HCA diagnosis	Severe HCA induced hemorrhage requiring 2 surgeries and ICU. Fetus and mother survived.
Noels (2011)[29]	4	All <5 cm	3	Prior to pregnancy	Lap. s2/3 resection	Unreported	Residual HCA stable	-
Noels (2011)[29]	5	All <5 cm	"Multiple"	Prior to pregnancy	Lap. s3/6 resection	Unreported	Residual HCA stable	Uncomplicated
Noels (2011)[29]	9-1	≥5 cm	1	Prior to 2nd pregnancy	RFA	HCA size	No residual HCA	Uncomplicated
Gaspersz (2020)[12]	1 patient	All <5 cm	-	During, 2nd trimester	1 case: TAE	HCA growth	Stable at 5.1 cm	Subphrenic abscess, drainage
Motsay (1972)[45]	82	5.2	1	Postpartum, 3 weeks	Right "lobectomy"	Pain	Full resection	

Table 4. Continued

Author (year)	Patient ID-pregnancy	Largest HCA at diagnosis (cm)	No. of HCA	Timing of invasive procedure	Procedure type	Indication for procedure	Procedure outcome	Procedure related complications
				HCA 5-10 cm				
Terkivatan (2000)[37]	69	9.0	1	1: During, 1st trimester 2: During, 1st trimester	1: Percutaneous biopsy 2: s2/3 resection	1: Tumor diagnosis 2: HCA size	1: HCA/well differentiated HCC diagnosis 2: Full resection	1: Uncomplicated 2: Uncomplicated
Jabbour (2005)[38]	70	6.0	3	During, 2nd trimester	Open "partial right resection"	HCA growth	Full resection	Uncomplicated
Wilson (2011)[28]	72	5.0	"Multiple"	During, 2nd trimester	Lap. s2/3 + 6 resection	HCA size	Full resection	-
Noels (2011)[29]	74	One ≥5 cm	3	Prior to pregnancy	s4 resection	Unreported	Residual HCA stable	-
Noels (2011)[29]	75-1	One ≥5 cm	2	Prior to pregnancy	TAE	Unreported	Residual HCA stable & regression	-
	75-2	One ≥5 cm	2	Prior to pregnancy	TAE	Unreported	Residual HCA stable & regression	-
Noels (2011)[29]	76	One ≥5 cm	"Multiple"	During, 1st trimester	RFA	HCA growth	RFA: regression, other stable	Uncomplicated
Gryspeerdt (2017)[42]	79	9.0	1	During, 2nd trimester	Lap. s2/3 resection	HCA size	Full resection	Uncomplicated
Sanford (2020)[43]	80	6.5	1	Postpartum, 4 months	Converted lap. S2/3 resection	Residual collection	Full resection	Uncomplicated

Table 4. Continued

Author (year)	Patient ID-pregnancy	Largest HCA at diagnosis (cm)	No. of HCA	Timing of invasive procedure	Procedure type	Indication for procedure	Procedure outcome	Procedure related complications
				HCA ≥10 cm				
Scheffer (2014)[41]	78	10.0	1	Prior to pregnancy	1: 2 x TAE 2: Electroporation	HCA size	1: No effect on HCA diameter 2: 90% size reduction	Uncomplicated, uncomplicated pregnancy
Stock (1985)[48]	85	18.0	1	1: During, 1st trimester 2: During, 1st trimester 3: Six weeks after termination	1: Fine needle aspiration 2: Abortion 3: Partial left "segmentectomy"	1: Tumor diagnosis 2: HCA size 3: Tumor necrosis	1: HCA diagnosis 2: No effect on diameter. Hemorrhagic tumor congestion & necrosis 3: Full Resection	1: Uncomplicated 2: Uncomplicated 3: Uncomplicated
Hill (1997)[51]	88	10.0	3	During, 2nd trimester	Open s2-4 + 8 resection	HCA size	Full resection	Uncomplicated
Bernstein (2019)[53]	90	16.1	1	1: Postpartum, 6 days	1: TAE	1: HCA size	1: Some necrosis	1: Infected post-necrotic hematoma, drainage
				2: Postpartum, 2 months	2: "Partial hepatectomy"	2: epigastric pain & residual HCA	2: Full resection	2: uncomplicated

Abbreviations: HCA, hepatocellular adenoma; TAE, transarterial embolization; RFA, radiofrequency ablation; lap, laparoscopic; HCC, hepatocellular carcinoma; ICU, intensive care unit admittance.

Table 5. Mode and outcomes of delivery of all studies included in the systematic review

Author (year)	Patient ID-pregnancy	Largest HCA at diagnosis (cm)	No. of HCA	HCA hemorrhage during pregnancy	Mode of delivery & indication for CS	Maternal Outcome	Fetal outcome
			HCA <5 cm				
Cobey (2004)[26]	1-1	-	1	None	Vaginal delivery	Alive	Alive
	1-2	4.0	1	None	CS: HCA size	Alive	Alive
Fujita (2006)[27]	2	3.0	1	None	Vaginal delivery	Alive	Alive
Wilson (2011)[28]	3	3.4	2	Biopsy induced, 3rd trimester	CS: circulatory shock after HCA biopsy	Alive	Alive
Noels (2011)[29]	4	All <5 cm	3	None	Vaginal delivery	Alive	Alive
Noels (2011)[29]	5-1	<5 cm	1	None	Vaginal delivery	Alive	Alive
	5-2	<5 cm	1	None	Vaginal delivery	Alive	Alive
Noels (2011)[29]	6-1	One ≥5 cm	"Multiple"	None	CS: indication unreported	Alive	Alive
	6-2	One ≥5 cm	"Multiple"	None	CS: indication unreported	Alive	Alive
Noels (2011)[29]	7	All <5 cm	"Multiple"	None	Vaginal delivery	Alive	Alive
Noels (2011)[29]	8-1	All <5 cm	3	None	Vaginal delivery	Alive	Alive
	8-2	All <5 cm	3	None	Vaginal delivery	Alive	Alive
Noels (2011)[29]	9-1	≥5 cm	"Multiple"	None	Vaginal delivery	Alive	Alive
	9-2	≥5 cm	"Multiple"	None	Vaginal delivery	Alive	Alive
Noels (2011)[29]	10	All <5 cm	"Multiple"	None	CS: indication unreported	Alive	Alive
Noels (2011)[29]	11	<5 cm	1	None	Vaginal delivery	Alive	Alive
Klompenhouwer (2017)[30]	12	4.6	-	None	Unreported	Alive	Alive
Klompenhouwer (2017)[30]	13	3.0	-	None	Unreported	Alive	Alive
Gaspersz (2020)[12]	14-61	All <5 cm	-	None	Vaginal delivery *n*=45 CS *n*=6, unrelated to HCA	All alive	All alive

Table 5. Continued

Author (year)	Patient ID-pregnancy	Largest HCA at diagnosis (cm)	No. of HCA	HCA hemorrhage during pregnancy	Mode of delivery & indication for CS	Maternal Outcome	Fetal outcome
			HCA 5-10 cm				
Antoniades (1975)[31]	62	6.5	1	Postpartum	Vaginal delivery	Alive	Alive
Lansing (1976)[32]	63	7.5	1	Postpartum	Vaginal delivery	Alive	Alive
Hibbard (1976)[33]	64	"⅓ of right hepatic lobe"		3rd Trimester	No delivery	Death	Death
Kent (1977)[34]	65	7.0	1	3rd Trimester	CS: circulatory shock	Alive	Alive
Kent (1977)[34]	66	"½ of right hepatic lobe"	1	During labor	Vaginal delivery (complicated)	Death	Alive
Kent (1978)[35]	67	"⅓ of right hepatic lobe"	1	During labor	Vaginal delivery (complicated)	Death	Death
Monks (1986)[36]	68	8.0	1	3rd Trimester	CS: circulatory shock & failure to progress	Alive	Alive
Terkivatan (2000)[37]	69	9.0	1	None	Vaginal delivery	Alive	Alive
Jabbour (2005)[38]	70	6.0	3	None	Vaginal delivery	Alive	Alive
Wilson (2011)[28]	72	5.0	"Multiple"	None	Vaginal delivery	Alive	Alive
Noels (2011)[29]	73	One ≥5 cm	2	None	Vaginal delivery	Alive	Alive
Noels (2011)[29]	74	One ≥5 cm	3	None	Vaginal delivery	Alive	Alive
Noels (2011)[29]*	75-1	One ≥5 cm	2	None	Vaginal delivery	Alive	Alive
	76-2	One ≥5 cm	2	None	Vaginal delivery	Alive	Alive
Noels (2011)[29]#	76	One ≥5 cm	"Multiple"	None	Vaginal delivery	Alive	Alive
Jeannot (2012)[40]†	77	6.0	>30	None	Vaginal delivery	Alive	Alive
Scheffer (2014)[41]‡	78	5.2	1	None	Vaginal delivery	Alive	Alive
Gryspeerdt (2017)[42]	79	9.0	1	None	Vaginal delivery	Alive	Alive
Sanford (2020)[43]	80	6.5	1	3rd Trimester	CS: circulatory shock	Alive	Alive

Table 5. Continued

Author (year)	Patient ID-pregnancy	Largest HCA at diagnosis (cm)	No. of HCA	HCA hemorrhage during pregnancy	Mode of delivery & indication for CS	Maternal Outcome	Fetal outcome
			HCA ≥10 cm				
Baird (1971)[44]	81	16.0	1	3rd Trimester	No delivery	Death	Death
Motsay (1972)[45]	82	10.0	1	None	Vaginal delivery	Alive	Alive
Stenwig (1975)[46]	83	10.0	1	3rd Trimester	CS: circulatory shock & fetal bradycardia	Alive	Death
Hayes (1977)[47]	84	10.0	1	Postpartum	CS: pre-eclampsia & fetal distress	Death	Alive
Stock (1987)[48]	85	18.0	1	None	No delivery	Alive	Abortion
Tsang (1989)[49]	86	15.0	3	2nd Trimester	Spontaneous abortion	Alive	Abortion
al-Otaibi (1995)[50]	87	17.0	1	Postpartum	Unreported	Alive	Alive
Hill (1997)[51]	88	10.0	3	None	CS: failure to progress	Alive	Alive
Stoot (2006)[52]	89	100	4	3rd Trimester	Vaginal delivery (induced after hemorrhage)	Alive	Alive
Santambrogio (2009)[39]	71	12.0	1	Postpartum	CS: abruptio placentae	Alive	Alive
Bernstein (2019)[53]	90	16.1	1	None	CS: HCA size	Alive	Alive

*TAE procedure prior to pregnancy. #RFA during 1st trimester. †Co-occurring HNF1A-MODY. ‡Two transarterial embolization and one electroporation procedures prior to pregnancy. Abbreviations: HCA, hepatocellular adenoma; CS, cesarean section.

Results from pooled data

Response to gestation and puerperium of non-bleeding HCA

Ninety patients during 99 pregnancies with non-bleeding HCA were pooled (**Table 2**). Besides patients 76 and 88, and five out of 48 patients in a cohort study, all had a history of OCP use (92%).[12,29,51] HCA was diagnosed prior to pregnancy in 67 patients with 74 pregnancies (75%). HCA was diagnosed during pregnancy in 18 patients, including 11 in the third trimester and two during labor. HCA was diagnosed postpartum in five patients.

HCA behavior without prior intervention was observed during 73 pregnancies. HCA were ultimately treated in four of these pregnancies (**Tables 2, 3, 4; patients 2, 70, 72 and one of patients 14-61**). Untreated HCA remained stable in 39 (53.4%) pregnancies. Eleven HCA demonstrated spontaneous regression (15.1%). Twenty-three HCA demonstrated growth (31.5%), seven exceeding 5 cm in size (patients 1, 6-1, 6-2, 9-1, 71, and two of patients 14-61). HCA in patient 71 demonstrated the most remarkable growth, progressing from 5 to 12 cm.[39] Postpartum HCA behavior was observed in 18 pregnancies and showed growth on one occasion (patient 1).The remainder of HCA demonstrated either stability or regression.

Fifty-one of the 99 studied pregnancies (patients 14-61) were derived from a prospective cohort study focusing solely on HCA <5 cm.[12] This observational study investigated 48 women during 51 pregnancies with HCA evaluations by US at 14 (±3), 20, 26, 32, and 38 weeks of gestation, and 6-12 weeks postpartum. It was the only study applying RECISTv1.1 criteria. Median (IQR) HCA size was 2.3 cm (1.9-3.9) prior to pregnancy. The cohort included 2 H-HCA, 16 I-HCA, 12 U-HCA, and 18 HCA without subtype determination. There were no HCA-related indications for Cesarean section. HCA demonstrated growth in 13 pregnancies (25%), exclusively during the second and third trimester. No bleedings were reported.

HCA induced bleeding during pregnancy and puerperium

Fifteen HCA bleeding episodes were reported in HCA sized 6.5-17 cm (**Table 3**). Eight bleedings occurred during pregnancy, two during labor, and five postpartum. In all 15 patients the bleeding episode was the presenting symptom of their HCA. Seven out of eight HCA-related hemorrhages during pregnancy occurred in the third

trimester. The two bleeding cases occurred during labor in HCA measuring "⅓ to ½ of right hepatic lobe".[34,35] HCA subtype could not be related to bleeding. Only one bleeding I-HCA was observed (case 79).[42] Four out of five HCA induced postpartum bleedings occurred during the first two weeks after delivery.

Three patients deceased before any intervention could be performed. Bleeding treatment was successful in 10 out of 12 remaining cases (**Table 3**). Four patients underwent primary gauze packing with secondary segment resection (*n*=2) or secondary liver transplantation (*n*=1), one patient deceased prior to secondary surgery. Other interventions were primary segment resection (*n*=6), transarterial embolization (TAE) (*n*=1), and mattress sutures (*n*=1). Although the hemorrhage incidence was low in pooled pregnancies, mortality was reported. Fatal outcome was observed in five out of 15 mothers and five out of 15 fetuses, including one abortion in the second trimester. Three pregnancies had fatal outcome for both mother and fetus.

Outcome of invasive interventions during pregnancy

Three reports described percutaneous HCA biopsy during pregnancy. Two were safely performed during 12 weeks of gestation (**Table 4; patients 69 & 85**).[37,48] One biopsy (**Table 4; patient 3**) in a 3.4 cm HCA at 32 weeks of gestation was complicated by severe hepatic hemorrhage.[28] Treatment consisted of emergency laparotomy with CS, and hepatic gauze packing. Shortly after, second look laparotomy was performed with simultaneous HCA resection, followed by short intensive care unit admittance. Both mother and the newborn survived.

Seventeen patients underwent HCA-related invasive procedures prior to, during, or after pregnancy during 18 pregnancies (**Table 4**). Seven pregnancies featured prior treatment: 3 patients with TAE (one with successive percutaneous electroporation), three with hepatic resection, and one with percutaneous radiofrequency ablation (RFA). Six patients underwent hepatic surgery during pregnancy, five of whom during the second trimester. Indications for surgery were HCA size ≥5 cm in four patients and HCA growth in two. Postpartum interventions were performed in two patients. Right lobectomy was performed in patient 84 due to postpartum abdominal pain.[45] TAE was performed in patient 90 resulting in necrosis and infected hematoma with residual HCA, necessitating partial hepatectomy.[53] Patients 84

and 90 account for the observed intervention-related complications: a subphrenic abscess, and an infected hematoma; both were treated by percutaneous drainage.[45,53]

Safety of vaginal delivery

Ninety-five deliveries were observed in 99 pregnancies. Two pregnancies had fatal outcome for the mother and unborn child due to hemorrhage, and two pregnancies were aborted (one spontaneous). Of full-term pregnancies, 73 (77%) resulted in vaginal delivery (**Table 5**). There were 19 CS for varying indications, with among them eight emergency procedures. Fourteen patients with HCA ≥5 cm delivered vaginally. Hepatic hemorrhage during labor occurred twice (patients 66 & 67), resulting in maternal and fetal death in the latter patient.[34,35] HCA size of these two patients spanned "⅓ to ½ of the right liver lobe". Method of delivery was unreported in three pregnancies.[30,50]

Results from non-pooled data

One single center retrospective study reported surgical interventions and outcomes in 122 HCA patients.[3] The report included nine patients with HCA during pregnancy and observed "moderate progression" without reporting actual size.

Another retrospective cohort study on hepatic adenomatosis reported 29 out of 36 included females (81%) with pregnancy prior to HCA diagnosis.[54] Four patients became pregnant after HCA diagnosis. In one patient, HCA progression was observed after pregnancy. Information on HCA size during pregnancy was not reported. One patient presented with uncontrollable and ultimately lethal hemorrhage in an undiagnosed 15 cm-sized HCA during pregnancy (pregnancy stage and comorbidities were unreported). One patient underwent resection of the largest HCA prior to pregnancy. HCA size, surgical outcomes, and behavior of remnant HCA were missing. It included six *HNF1A* germline mutated patients but did not report on pregnancies in this subgroup.

HCA due to metabolic disease

Two studies reported solely on metabolic disease associated HCA. A retros-pective study on 24 HNF1A-MODY patients with hepatic adenomatosis reported on fourteen pregnancies in eight women without bleeding complications.[55] Three patients had

imaging available: stable disease was observed twice, and regression once. HCA size was not reported. One patient experienced pre-pregnancy hemorrhage (and regression thereafter) in a 7 cm HCA following ovarian stimulation.

The other report described 32 GSD type I patients during pregnancy and included four HCA cases.[56] Two patients showed increase in HCA size or number and one patient had stable disease. Clinical course and HCA size of the latter patient was not reported. There were no HCA-related complications.

Discussion

This study aimed to evaluate HCA behavior, bleeding complications, mode of delivery, and outcomes of invasive treatment during pregnancy and puerperium. It concerned both a retrospective cohort study and a systematic review. The retrospective study included 11 patients, of whom 4 had HCA ≥5 cm. In two patients, HCA growth was observed during pregnancy; both in HCA <5 cm. All HCA with available subtype identification were diagnosed as I-HCA. No complications occurred during pregnancy, puerperium, or postpartum follow-up.

A systematic review was performed to compare our data with the current literature, especially regarding HCA size and bleeding risk association, including 29 studies. Ninety patients (99 pregnancies) in whom HCA were diagnosed before, during, or after pregnancy were reported. HCA remained stable in 39/73 treatment-naive pregnancies (53.4%). Eleven HCA demonstrated spontaneous regression (15.1%). Twenty-three HCA demonstrated growth (31.5%), seven exceeding >5 cm diameter. Fifteen cases of HCA–associated hemorrhage were included, none occurred in the first trimester and all HCA measuring ≥6.5 cm.[33,34,36,43,44,46,49,52] Eight HCA bled during gestation, seven in the third trimester. The remaining seven bleeding cases occurred during labor (n=2) or postpartum (n=5).

Prior studies have observed HCA regression, especially in large HCA, after OCP cessation or weight loss due to estrogen level reduction.[7,9] Strong regression after estrogen level reduction might arguably predict HCA behavior during pregnancy. Yet, this relationship was neither observed in the systematic review, nor in the retrospective study.[12,29]

The current manuscript concerns the second systematic review on HCA during or after pregnancy. The other review focused on focal nodular hyperplasia, hepatic hemangiomas, HCA, and HCC during and after pregnancy, including literature up to 2004.[26] The authors identified 26 reports on HCA and added one local case, totaling 27 pregnancies. The study already reported six postpartum bleeding HCA – yet this potentially hazardous period remains underexposed in clinical practice.[13] Postpartum HCA bleeding might result from HCA regression and necrosis by postpartum declining estrogen levels. Larger HCA might regress and necrotize more extensively causing HCA membrane rupture, yet not all postpartum bleeding HCA showed necrosis.[32]

Accurate HCA diagnosis is vital for optimal management. HCA are diagnosed best non-invasively through CE-MRI (sensitivity 92-97% and specificity 91-100%).[57–60] Pregnancy, however, is still considered a contraindication for CE-MRI by most radiologists because fetal exposure to contrast agents may potentially lead to various skin conditions, stillbirth, and neonatal death.[61] MR exposure itself during the first trimester may be safe but many clinical practice guidelines remain restrictive and await further evidence. Hence, gestational liver tumor diagnosis can be performed through unenhanced MRI in the second or third trimester and thereafter monitored by US (or MRI). Gold standard remains histopathology, although biopsy-associated hepatic hemorrhage may occur (patient 3). Biopsies should therefore only be performed in selected cases with severe treatment implications, and only during early gestation.

Multiple invasive treatment strategies were applied. Elective, uncomplicated, hepatic resections were performed up to the second trimester.[27,28,37,38,42,51] No minimally invasive strategy was identified as superior due to limited observations. Three patients were treated by US-guided RFA: two during pregnancy (patients 2 & 75) and one prior to the second pregnancy (patient 9-2).[27,29] TAE proved less effective with more complications. These observations are anecdotal and cannot be extrapolated to definite conclusions. Previous series have demonstrated effectiveness and safety for TAE and RFA in HCA patients.[62,63]

Several risk factors for symptomatic HCA bleeding, have been identified including diameter ≥5 cm, exophytic growth, hemorrhage observed on imaging, presence of central or peripheral arteries on imaging, sonic hedgehog subtype, and hepatic parenchymal

steatosis >30%.[6,64] Especially H-HCA are less likely to bleed.[6] We suggest not to include HCA subtype into treatment consideration, as this would implicate invasive (biopsy) as well as non-invasive (CE-MRI) diagnostics with its accompanying risk of gestational complications. However, HCA treatment may be considered in selected cases in which one or more risk factors are present. Drafting of a strict treatment algorithm is warranted but unfortunately not feasible with the currently available data. Nevertheless, several recommendations can be made.

(1) Management and surveillance of HCA in pregnancy should always be individualized and performed by a multidisciplinary team.[13] A well-performed observational cohort study by Gaspersz *et al.* prospectively followed 51 pregnancies with HCA <5 cm (median HCA size 2.3 cm) without bleeding complications.[12] In the current literature review, hemorrhage was only observed in women with HCA ≥6.5 cm in size. Although a reasonable estimate of the true risk of HCA hemorrhage in relation to size during pregnancy remains unknown, it seems safe to apply a watchful waiting strategy to women with HCA up to 5-6.5 cm. Close surveillance with US every 6 weeks should be mandatory, however, for any pregnant woman with HCA, regardless of size.

(2) Treatment of bleeding HCA during pregnancy should be decided by bleeding severity and gestational term. TAE may be preferred over surgery in minor, intra-tumoral bleedings during the first or second trimester. Surgery, however, is indicated when intra-abdominal, and especially third trimester, bleeding occurs. Fetal monitoring during surgery is essential, and an obstetrician/gynecologist should be on standby for emergency delivery when signs of fetal or patient (circulatory) distress are observed. Pre-emptive treatment, for example by TAE or surgery, may be considered in women who wish to become pregnant in case of large HCA (*e.g.* size ≥6,5-10cm) but only after evaluating HCA size/behavior for at least six months after OCP cessation and lifestyle changes/weight loss. Management and surveillance should always be individualized and performed by a multidisciplinary team.

(3) If high diagnostic suspicion for malignancy arises, unenhanced MRI may be performed from the second trimester onwards. Postpartum confirmation by CE-MRI or biopsy of equivocal tumors is recommended.

(4) Pre-emptive (minimally) invasive treatment of HCA during pregnancy cannot be recommended due to potential risks of teratogenic effects of (anesthesia accompanying) surgery or TAE-associated radiation, and risk of surgery induced (premature) labor without strong evidence for any benefit.

The systematic review is limited by a publication bias of included studies and patients. Substantial underreporting of HCA patients with successful and uncomplicated pregnancies is most likely. Another potential limitation is the inclusion of only retrospective studies, except one report.[12] The quality of included retrospective studies was appraised as moderate to high. The information on HCA behavior only warranted limited conclusions as exact HCA size was only systematically analyzed in the prospective study.[12] None of the included case reports adhered to CARE guidelines, however, all patients were sufficiently described for data pooling.

Concluding, most pregnancies with HCA did not demonstrate HCA-related bleeding complications, and hemorrhage was only observed in HCA ≥6.5 cm. Current guidelines provide limited recommendations for pregnant HCA patients.[13–16] Pregnant HCA patients should be referred to centers with sufficient experience on complex hepatobiliary pathology, (radiological) intervention facilities, and adequate supportive care infrastructure. Close surveillance and adequate diagnostic and treatment escalation decided by a multidisciplinary team is recommended. The current findings warrant a prospective observational cohort study on behavior and treatment strategies of HCA ≥5 cm during gestation and puerperium.

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