Maternal-Fetal Evidence Based Guidelines

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Maternal-Fetal Evidence Based Guidelines

THIRD EDITION

EDITED BY

VINCENZO BERGHELLA, MD, FACOG

Director, Division of Maternal-Fetal Medicine
Professor, Department of Obstetrics and Gynecology
Sidney Kimmel Medical College of Thomas Jefferson University
Philadelphia, Pennsylvania, USA

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To Paola, Andrea, Pietro, Mamma, and Papá,

For giving me the serenity, love, and strength at home now, then,
and in the future to fulfill my dreams and spend my talents as best as possible.

To all those who loved the first and second editions

To my mentors and to my mentees who have been so passionate
and supportive about these books

To the health of mothers and babies

And—as I often toast—to the next generation!

Contents

Introduction

Welcome to the third edition of our evidence-based books on obstetrics and maternal-fetal medicine! I am indebted for your support! I can't believe how much praise we have gotten for these companion volumes. Your words of encouragement have kept me and all the collaborators, past and present, going now for well over a decade (we are indebted to contributors to previous editions of this text for their work). It has been extremely worthwhile and fulfilling. You are making me happy! In return, I hope we are helping you and your patients toward ever better evidence-based care of pregnant women and their babies and, therefore, better outcomes. Indeed, maternal and perinatal morbidities and mortalities throughout the world are improving.

To me, pregnancy has always been the most fascinating and exciting area of interest as care involves not one, but at least two persons—the mother and the fetus—and leads to the miracle of a new life. I was a third-year medical student when, during a lecture, a resident said, "I went into obstetrics because this is the easiest medical field. Pregnancy is a physiologic process, and there isn't much to know. It is simple." I knew from my "classical" background that "obstetrics" means to "stand by, stay near," and that indeed pregnancy used to receive no medical support at all.

After more than 25 years of practicing obstetrics, I now know that although physiologic and, at times, simple, obstetrics and maternal-fetal medicine can be the most complex of the medical fields: Pregnancy is based on a different physiology than for nonpregnant women, can include any medical disease, require surgery, etc. It is not so simple. In fact, ignorance can kill—in this case, with the health of the woman and her baby both at risk. Too often, I have gone to a lecture, journal club, rounds, or other didactic event to hear presented only one or a few articles regarding the subject without the presenter reviewing the pertinent best review of the total literature and data. It is increasingly difficult to read and acquire knowledge of all that is published, even just in obstetrics, with about 3000 scientific manuscripts published monthly on this subject. Some residents or even authorities would state at times that "there is no evidence" on a topic. We indeed used to be the field with the worst use of randomized trials [1]. As the best way to find something is to look for it, my coauthors and I searched for the best evidence. On careful investigation, indeed there are data on almost everything we do in obstetrics, especially on our interventions. Indeed, our field is now the pioneer for numbers of meta-analyses and extension of work for evidence-based reviews [2]. Obstetricians are now blessed with lots of data and should make the best use of it.

The aims of this book are to summarize the best evidence available in the obstetrics and maternal-fetal medicine literature and make the results of randomized controlled trials (RCTs) and meta-analyses of RCTs easily accessible to guide clinical care. The intent is to bridge the gap between knowledge (the evidence) and its easy application. To reach these goals, we reviewed all trials on effectiveness of interventions in obstetrics. Millions of pregnant women have participated in thousands of properly conducted RCTs. The efforts and sacrifice of mothers and their fetuses for science should be recognized at least by the physicians' awareness and understanding of these studies. Some of the trials have been summarized in more than 600 *Cochrane* reviews with hundreds of other meta-analyses also published on obstetrical topics (Table 1). All of the *Cochrane* reviews, as well as other meta-analyses and trials in obstetrics and maternal-fetal medicine, were reviewed and referenced. The material presented in single trials or meta-analyses is too detailed to be readily translated to advice for the busy clinician who needs to make dozens of clinical decisions a day. Even the Cochrane Library, the undisputed leader for evidence-based medicine efforts, has been criticized for its lack of flexibility and relevance in failing to be more easily understandable and clinically readily usable [3]. It is the gap between research and clinicians that needed to be filled, making sure that proven interventions are clearly highlighted and are included in today's care. Just as all pilots fly planes under similar rules to maximize safety, all obstetricians should manage all aspects of pregnancy with similar, evidenced-based rules. Indeed, only interventions that have been proven to provide benefit should be used routinely. On the other hand, *primum non nocere*: interventions that have clearly been shown to be not helpful or indeed harmful to mother and/or baby should be avoided.

Table 1 Obstetrical Evidence

More than 600 current *Cochrane* reviews
Hundreds of other current meta-analyses
More than 1000 RCTs
Millions of pregnant women randomized

Another aim of this book is to make sure the pregnant woman and her unborn child are not marginalized by the medical community. In most circumstances, medical disorders of pregnant women can be treated as in nonpregnant adults. Moreover, there are several effective interventions for preventing or treating specific pregnancy disorders.

Evidence-based medicine is the concept of treating patients according to the best available evidence. Although George Bernard Shaw said, "I have my own opinion, do not confuse me with the facts," this can be a deadly approach, especially in medicine, and compromise two or more lives at the same time in obstetrics and maternal-fetal medicine. What should be the basis for our interventions in medicine? Meta-analyses of RCTs provide a comprehensive summary of the best research data available. As such, they provide the best guidance for "effective" clinical care [4]. It is unscientific and unethical to practice medicine, teach, or conduct research without first knowing all that has already been proven [4]. In the absence of trials or meta-analyses, lower-level evidence is reviewed. This book aims at providing a current systematic review of all the best evidence so that current practice and education as well as future research can be based on the full story from the best-conducted research, not just the latest data or someone's opinion (Table 2).

These evidence-based guidelines cannot be used as a "cookbook" or a document dictating the best care. The knowledge from the best evidence presented in the guidelines needs to be integrated with other knowledge gained from clinical judgment, individual patient circumstances, and patient preferences to lead to best medical practice. These are guidelines, not rules. Even the best scientific studies are not always perfectly related to any given individual, and clinical judgment must still be applied to allow the best "particularization" of the best knowledge for the individual, unique patient. Evidence-based medicine informs clinical judgment but does not substitute it. It is important to understand, however, that greater clinical experience by the physician actually correlates with inferior quality of care if not integrated with knowledge of the best evidence [5]. The appropriate treatment is given in only 50% of visits to general physicians [5]. At times, limitations in resources may also limit the applicability of the guidelines but should not limit the physician's knowledge. Guidelines and clinical pathways based on evidence not only point to the right management, but also can decrease medicolegal risk [6]. We aimed for brevity and clarity. Suggested management of the healthy or sick mother and child is stated as straightforwardly as possible for everyone to easily understand and implement (Table 3). If you find the *Cochrane* reviews, scientific manuscripts, and other publications difficult to "translate" into care of your patients, this book is for you. We wanted to prevent information overload.

Table 2 Aims of This Book

Improve the health of women and their children
"Make it easy to do it right"
Implement the best clinical care based on science (evidence), not opinion
Education
Develop lectures
Decrease disease, use of detrimental interventions, and therefore costs
Reduce medicolegal risks

Table 3 This Book Is For

Obstetricians
Midwives
Family medicine and others (practicing obstetrics)
Residents
Nurses
Medical students
Maternal-fetal medicine attendings
Maternal-fetal medicine fellows
Other consultants on pregnancy
Lay persons who want to know "the evidence"
Politicians responsible for health care

On the other hand, "everything should be made as simple as possible, but not simpler" (A. Einstein). Key management points are highlighted at the beginning of each guideline and in bold in the text. The chapters are divided into two volumes, one on obstetrics and one on maternal-fetal medicine; cross-references to chapters in *Obstetric Evidence Based Guidelines* have been noted in the text where applicable. Please contact us (vincenzo.berghella @jefferson.edu) for any comments, criticisms, corrections, missing evidence, etc.

I have the most fun discovering the best ways to alleviate discomfort and disease. The search for the best evidence for these guidelines has been a wonderful, stimulating journey. Keeping up with evidence-based medicine is exciting. The most rewarding part, as a teacher, is the dissemination of knowledge. I hope, truly, that this effort will be helpful to you, too.

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How to "Read" This Book

The knowledge from RCTs and meta-analyses of RCTs is summarized and easily available for clinical implementation. Relative risks and 95% confidence intervals from studies are quoted sparingly. Instead, the straight recommendation for care is made if one intervention is superior to the other with the percentage improvement often quoted to assess degree of benefit. If there is insufficient evidence to compare to interventions or managements, this is clearly stated.

References: Cochrane reviews with 0 RCT are not referenced, and instead of referencing a meta-analysis with only one RCT, the actual RCT is usually referenced. RCTs that are already included in meta-analyses are not referenced for brevity and because they can be easily accessed by reviewing the meta-analysis. If new RCTs are not included in meta-analysis, they are obviously referenced. Each reference was reviewed and evaluated for quality according to a modified method as outlined by the U.S. Preventive Services Task Force (http://www.ahrq.gov):

I	Evidence obtained from at least one properly designed randomized controlled trial.
II-1	Evidence obtained from well-designed controlled trials without randomization.
II-2	Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group.
II-3	Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments could also be regarded as this type of evidence.
III (Review)	Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

These levels are quoted after each reference. For RCTs and meta-analyses, the number of subjects studied is stated, and, sometimes, more details are provided to aid the reader to understand the study better.

List of Abbreviations

AA	artery-to-artery
AAN	American Academy of Neurology
AAP	American Academy of Pediatrics
AASLD	American Association for the Study of Liver Diseases
Ab	antibody
AC	abdominal circumference
ACA	anticardiolipin antibody
ACCM	American College of Critical Care Medicine
ACE	angiotensin-converting enzyme
ACOG	American College of Obstetricians and Gynecologists
ACR	acute cellular rejection
ACR	American College of Rheumatology
ACS	acute chest syndrome
ADHD	attention deficit hyperactivity disorder
ADP	atopic dermatitis of pregnancy
ADR	autonomic dysreflexia
AED	antiepileptic drug
AEDF	absent end-diastolic flow
AEP	atopic eruption of pregnancy
AF	amniotic fluid
AFE	amniotic fluid embolism
AFI	amniotic fluid index
AFP	alpha-fetoprotein
AFV	amniotic fluid volume
Ag	antigen
AGA	appropriate for gestational age
AHA	American Heart Association
aHR	adjusted hazard ratio
AIDS	acquired immune deficiency syndrome
AII	angiotensin type II
AIT	alloimmune thrombocytopenia
ALI	acute lung injury
ALT	alanine aminotransferase
ANA	antinuclear antibodies
APA	American Psychiatric Association
APS	antiphospholipid syndrome
aPT	activated prothrombin time
aPTT	activated partial thromboplastin time
ARDS	adult respiratory distress syndrome
AROM	artificial rupture of membranes
ARPV	airway pressure release ventilation
ART	antiretroviral therapy
ART	assisted reproductive technologies
ASA	aspirin
ASD	atrial septal defect
ASD	autism spectrum disorder
AST	aspartate aminotransferase
ATIII	antithrombin III
ATLS	Advanced Trauma Life Support
ATS	American Thoracic Society
AV	artery-to-vein
AVD	assisted vaginal delivery
AZT	zidovudine
BAD	bipolar disorder
BCG	bacille Calmette-Guerin
BHI	biphasic human insulin
BIAsp	biphasic insulin aspart
bid	"bis in die," i.e., twice per day
BMI	body mass index
BP	blood pressure
BPD	biparietal diameter
BPD	bronchopulmonary dysplasia
bpm	beats per minute
BPP	biophysical profile
BPS	biophysical profile score
BUN	blood urea nitrogen
CAP	community-acquired pneumonia
CBC	complete blood count
CCAM	congenital cystic adenomatoid malformation
CCTG	computerized cardiotocography
CD	cesarean delivery
CD	Crohn's disease
CDC	Centers for Disease Control
CDH	congenital diaphragmatic hernia
CF	cystic fibrosis
CFC	chlorofluorocarbon
CFU	colony-forming unit
cGH	comparative genomic hybridization
CGRP	calcitonin gene-related peptide
CHB	congenital heart block
CHD	congenital heart defect
CHF	congestive heart failure
CHIPS	Control of Hypertension in Pregnancy Study
CHTN	chronic hypertension
CL	cervical length

CLIA	Clinical Laboratory Improvement Amendments
CMV	cytomegalovirus
CNS	central nervous system
CPAM	congenital pulmonary airway malformation
CPAP	continuous positive airway pressure
CPR	cardiopulmonary resuscitation
CPR	cerebroplacental ratio
CPS	capsular polysaccharide
CPS	complex partial seizure
CRF	chronic renal failure
CRI	chronic renal insufficiency
CRL	crown-rump length
CS	corticosteroid
CSD	cortical spreading depression
CSE	combined spinal epidural
CSF	cerebrospinal fluid
CSII	continuous subcutaneous insulin infusion
CST	contraction stress test
CT	computerized tomography
CT	connective tissue
CTG	cardiotocography
CTPA	computed tomography pulmonary angiography
CTZ	chemo-receptor trigger zone
CVS	chorionic villus sampling
CVS	congenital varicella syndrome
D&E	dilation and evacuation
DAA	direct-acting antiviral agent
DBP	diastolic blood pressure
DC/DA	dichorionic/diamniotic
DES	diethylstilbestrol
DHHS	Department of Health and Human Services
DIC	disseminated intravascular coagulation
DIF	direct immunofluorescence
DM	diabetes mellitus
DMPA	depot medroxyprogesterone acetate
DNA	deoxyribonucleic acid
DNS	dysplastic nevus syndrome
DPI	dry powder inhaler
DPL	diagnostic peritoneal lavage
DRVVT	dilute Russell's viper venom time
DV	ductus venosus
DVP	deepest vertical pocket
DVT	deep vein thrombosis
DZ	dizygotic
EASL	European Association for the Study of the Liver
EBV	Epstein-Barr virus
ECDC	European Centre for Disease Prevention and Control
ECMO	extracorporeal membrane oxygenation
EC-MPS	enteric-coated mycophenolate sodium
ECT	electroconvulsive therapy
ECV	external cephalic version
ED	emergency department
EDC	estimated date of confinement
EDD	estimated date of delivery (synonym of EDC)
EDF	end-diastolic flow
EFW	estimated fetal weight
EIA	enzyme immunoassay
EKG	electrocardiogram
ELISA	enzyme-linked immunosorbent assay
EM	electron microscopy
EM	expectant management
EN	enteral nutrition
EPCOT	European Prospective Cohort on Thrombophilia
EPDS	Edinburgh Postnatal Depression Scale
EPS	extrapyramidal symptom
EPT	expedited partner therapy
ERCP	endoscopic retrograde cholangiopancreatography
ESLD	end-stage liver disease
ESRD	end-stage renal disease
FAST	focused abdominal sonogram for trauma
FBS	fetal blood sampling
FD	fetal distress
FDA	Food and Drug Administration
FDC	fixed-dose combination
FEV1	forced expiratory volume in one second
FFN	fetal fibronectin
FGR	fetal growth restriction
FHM	familial hemiplegic migraine
FHR	fetal heart rate
FHT	fetal heart tracing
FISH	fluorescent in situ hybridization
FKCG	fetal kinetocardiogram/ tissue Doppler echocardiography
FLM	fetal lung maturity
FMAIT	fetal maternal alloimmune thrombocytopenia
FNAIT	fetal and neonatal alloimmune thrombocytopenia
FOB	father of baby
FPG	fasting plasma glucose
FPR	false positive rate
FSBS	fetal scalp blood sampling
FSE	fetal scalp electrode
FSI	foam stability index
FTS	first-trimester screening
FVC	forced vital capacity
FVL	factor V Leiden
g	grams
GA	gestational age
GBS	group B streptococcus
GBS	Guillain–Barré syndrome
GDM	gestational diabetes
GERD	gastroesophageal reflux disease
GFR	glomerular filtration rate
GHB	gamma-hydroxybutyrate

GHTN	gestational hypertension
GI	gastrointestinal
GISP	Gonococcal Isolate Surveillance Project
GTC	generalized tonic clonic
GTT	glucose tolerance test
GWG	gestational weight gain
HAART	highly active antiretroviral therapy
HAV	hepatitis A virus
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HC	head circumference
HCG	human chorionic gonadotroponin
Hct	hematocrit
HCV	hepatitis C virus
HD	hemodialysis
HD	Hodgkin's disease
HDU	high-dependency unit
HELLP	hemolysis, elevated liver enzymes, and low platelet count
HES	hydroxyethyl starch
HFA	hydrofluoroalkane
HG	hyperemesis gravidarum
Hgb	hemoglobin
HIE	hypoxic-ischemic encephalopathy
HIT	heparin-induced thrombocytopenia
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HPA	hypothalamic–pituitary–adrenal
HPA	human platelet antigen
HR	heart rate
HSV	herpes simplex virus
HTN	hypertension
IAAT	immunosorbent agglutination assay test
IALE	International League Against Epilepsy
IBD	inflammatory bowel disease
IBW	ideal body weight
ICH	intracranial hemorrhage
ICP	intrahepatic cholestasis of pregnancy
ICS	immunochromatographic strip
ICS	Intensive Care Society
ICU	intensive care unit
IDSA	Infectious Diseases Society of America
IGRA	interferon gamma-release assay
IH	impetigo herpetiformis
IM	intramuscular
INR	international normalized ratio
IOL	induction of labor
IPAA	ileal pouch–anal anastomosis
IPV	inactivated polio vaccine
ISS	injury severity score
IUD	intrauterine device
IUFD	intrauterine fetal demise
IUGR	intrauterine growth restriction (synonym of FGR)
IUPC	intrauterine pressure catheter
IV	intravenous
IVC	inferior vena cava
IVDU	intravenous drug use
IVF	intravenous fluids
IVH	intraventricular hemorrhage
L&D	labor and delivery
L/S	lecithin/sphingomyelin
LA	lupus anticoagulant
LABA	long-acting β-agonist
LAGB	laparoscopic adjustable gastric baning
LB	lamellar body
LBW	low birth weight
LBW	low birth weight (infants)
LCR	ligase chain reaction
LFT	liver function tests
LGA	large for gestational age
LGV	lymphogranuloma venereum
LMP	last menstrual period
LMW	low molecular weight
LMWH	low-molecular-weight heparin
LR	likelihood ratio
LSD	lysergic acid diethylamide
LSD	lysosomal storage disease
LTRA	leukotriene receptor antagonist
MA/MC	monoamniotic
MAC	mycobacterium avium complex
MAOI	monoamine oxidase inhibitor
MAS	meconium aspiration syndrome
MC/DA	monochorionic diamniotic
MCA	middle cerebral artery
MCV	mean corpuscular volume
MD	mean difference
MDD	major depressive disorder
MDI	metered-dose inhaler
MDI	multiple-dose insulin
MDQ	Mood Disorders Questionnaire
MDR	multidrug-resistant
MFM	maternal–fetal medicine
MHC	major histocompatibility complex
MI	myocardial infarction
MM	malignant melanoma
MMF	myco-phenolate mofetil
MMR	measles–mumps–rubella
MOM	multiple of the median
MPA	mycophenolic acid products
MRCP	magnetic resonance cholangiopancreatography
MRI	magnetic resonance imaging
MRU	magnetic resonance urography
MSAFP	maternal serum alpha-fetoprotein
MSH	melanocyte-stimulating hormone

MTHFR	methylenetetrahydrofolate reductase
MTX	methotrexate
MVI	prenatal multivitamin
MVP	maximum vertical pocket
MZ	monozygotic
n/v	nausea and/or vomiting
NA	not available
NA-ACCORD	North American AIDS Cohort Collaboration on Research and Design
NAAED	North American Antiepileptic Drug
NAAT	nucleic acid amplification test
NAEPP	National Asthma Education and Prevention Program
NAIT	neonatal alloimmune thrombocytopenia
NAS	neonatal abstinence syndrome
NBPP	neonatal brachial plexus palsy
NCHS	National Center for Health Statistics
NEC	necrotizing enterocolitis
NG	nasogastric
NHL	Non–Hodgkin's lymphoma
NICU	neonatal intensive care unit
NIH	National Institutes of Health
NIH	nonimmune hydrops
NIS	National Inpatient Sample
NNRTI	non-nucleoside reverse transcriptase inhibitor
NODM	new-onset diabetes mellitus
NOTES	natural orifice translumenal endoscopic surgery
NPH	neutral protamine Hagedorn
NRFHR	nonreassuring fetal heart rate
NRFHT	nonreassuring fetal heart testing
NRFS	nonreassuring fetal status
NRI	norepinephrine reuptake inhibitor
NRT	nicotine replacement therapy
NRTI	nucleoside reverse transcriptase inhibitor
NS	nephrotic syndrome
NS	normal saline
NSAIDS	nonsteroidal anti-inflammatory drugs
NSCIA	National Spinal Cord Injury Association
NST	nonstress test
NSVD	normal spontaneous vaginal delivery
NT	nuchal translucency
NTD	neural tube defect
NTDB	National Trauma Data Banks
NTPR	National Transplantation Pregnancy Registry
NVP	nausea and vomiting of pregnancy
OB	obstetrician
OCT	oxytocin challenge test
OCT	oxytocin contraction test
OGTT	oral glucose tolerance test
OPV	oral live polio vaccine
OR	odds ratio
OR	operating room
OSA	obstructive sleep apnea
OTC	over the counter
PAPP-A	pregnancy-associated plasma protein-A
PC	platelet count
PC	protein C
PCA	patient-controlled analgesia
PCI	percutaneous coronary intervention
PCP	phencyclidine
PCP	Pneumocystis carinii pneumonia
PCR	polymerase chain reaction
PCWP	pulmonary capillary wedge pressure
PD	peritoneal dialysis
PDA	patent ductus arteriosus
PE	pulmonary embolus
PEA	pulseless electrical activity
PEFR	peak expiratory flow rate
PEP	polymorphic eruption of pregnancy
PER	prophylaxis effective rate
PET	positron emission tomography
PFP	pruritic folliculitis of pregnancy
PFT	pulmonary function tests
PG	pemphigoid gestationis
PG	phosphatidylglycerol
PG	plasma glucose
PGL	persistent generalized lymphadenopathy
PGM	prothrombin gene mutation
PI	protease inhibitor
PI	pulsatility index
PICC	peripherally inserted central catheter
PID	pelvic inflammatory disease
PK	pharmacokinetic
PL	pregnancy loss
PlGF	placental growth factor
PMCD	perimortem cesarean delivery
PN	parenteral nutrition
PNC	prenatal care
PNM	perinatal mortality
po	"per os," i.e., by mouth
PP	prurigo of pregnancy
PP-13	placental protein-13
PPD	purified protein derivative
PPH	postpartum hemorrhage
PPHN	persistent pulmonary hypertension of the newborn
PPI	proton-pump inhibitor
PPROM	preterm premature rupture of membranes

PR	per rectum
pRBC	packed red blood cells
PRCD	planned repeat cesarean delivery
PROM	preterm rupture of membranes
PS	protein S
PS	pulmonic stenosis
PSI	Pneumonia Severity Index
PSV	peak systolic velocity
PT	prothrombin time
PTB	preterm birth
PTL	preterm labor
PTT	partial thromboplastin time
PTU	propylthiouracil
PUBS	percutaneous umbilical blood sampling
PUPPP	pruritic urticarial papules and plaques of pregnancy
PUQE	pregnancy-unique quantification of emesis/nausea
PVR	pulmonary vascular resistance
PW	pulsed wave
qd	once a day
qhs	before bedtime
qid	four times per day
QS	quadruple screen
RBC	red blood cell
RCT	randomized controlled study
RCVS	reversible cerebral vasoconstriction syndrome
RDS	respiratory distress syndrome
RDW	red blood cell distribution width
REDF	reverse end-diastolic flow
RI	resistive index
RNA	ribonucleic acid
ROM	rupture of membranes
ROSC	return of spontaneous circulation
RPR	rapid plasma reagin
RR	relative risk
RR	respiratory rate
RR	risk ratio
Rx	treatment
S/D	systolic/diastolic
SAB	spontaneous abortion
SABA	short-acting β-agonist
SBP	systolic blood pressure
SC	subcutaneous
SCI	spinal cord injury
SCRN	Stillbirth Collaborative Research Network
SD	striae distensae
SDA	strand-displacement amplification
SDP	single deepest pocket
SEE	Syphilis Elimination Effort
SFDT	Sabin–Feldman dye test
SG	striae gravidarum
SGA	small for gestational age
SIDS	sudden infant death syndrome
SJS	Stevens–Johnson syndrome
SLE	systemic lupus erythematosus
SLICC	Systemic Lupus International Collaborating Clinics
SNRI	serotonin-norepinephrine reuptake inhibitor
SPTB	spontaneous preterm birth
SQ	subcutaneous
SSC	Surviving Sepsis Campaign
SSKI	saturated solution of potassium iodide
SSRI	selective serotonin reuptake inhibitor
STD	sexually transmitted diseases (synonym of STI)
STI	sexually transmitted infections
STS	second-trimester screening
SUDEP	sudden unexpected death in epilepsy
SVC	superior vena cava
SVR	systemic vascular resistance
SVR	sustained virologic response
TB	tuberculosis
TBG	thyroid-binding globulin
TBII	thyroid-stimulating hormone-binding inhibitory immunoglobulin
TCA	tricyclic antidepressant
TDD	total daily dose
TG	*Toxoplasma gondii*
TH	therapeutic hypothermia
THC	tetrahydrocannabinol
tid	three times per day
TIV	trivalent inactivated vaccine
TMA	transcription-mediated amplification
TNF	tumor necrosis factor
TOL	trial of labor
TOLAC	trial of labor after cesarean
TPO	thyroid peroxidase
TRAb	TSH receptor antibody
TRALI	transfusion-related acute lung injury
TRAP	twin reversal arterial perfusion
TSH	thyroid-stimulating hormone
TSI	thyroid-stimulating immune globulins
TST	tuberculin skin testing
TTTS	twin–twin transfusion syndrome
TVU	transvaginal ultrasound
U/S (or u/s)	ultrasound
UA	umbilical artery
UC	ulcerative colitis
UDCA	ursodeoxycholic acid
UFH	unfractionated heparin
UPC	urinary protein creatinine
USPSTF	U.S. Preventative Services Task Force
UTI	urinary tract infection
V/Q	ventilation/perfusion

VAS	vibroacoustic stimulation	**VTE**	venous thromboembolism
VBAC	vaginal birth after cesarean	**VV**	vein-to-vein
		vWD	von Willebrand disease
VC	vital capacity	**vWF**	von Willebrand factor
VDRL	venereal disease research laboratory	**VZIG**	varicella zoster immune globulin
VEGF	vascular endothelial growth factor	**VZV**	varicella zoster virus
		WBC	white blood cell
VIG	vaccinia immune globulin	**WHO**	World Health Organization
VKA	vitamin K antagonist		
VL	viral load	**WIHS**	Women's Interagency HIV Study
VPA	valproic acid		
VSD	ventricular septal defect	**XDR**	extensively drug-resistant

Contributors

James A. Airoldi Department of Obstetrics and Gynecology, Division of Maternal-Fetal Medicine, St Luke's University Health Network, Bethlehem, Pennsylvania

Joshua H. Barash Department of Family and Community Medicine, Thomas Jefferson University Hospital, Philadelphia, Pennsylvania

Madeleine A. Becker Department of Psychiatry and Human Behavior, Division of Consultation-Liaison Psychiatry, Psychosomatic Medicine Fellowship, Thomas Jefferson University Hospital, Philadelphia, Pennsylvania

Meriem K. Bensalem-Owen University of Kentucky, Lexington, Kentucky

Vincenzo Berghella Department of Obstetrics and Gynecology, Division of Maternal-Fetal Medicine, Sidney Kimmel Medical College of Thomas Jefferson University, Philadelphia, Pennsylvania

Meredith Birsner Department of Obstetrics and Gynecology, Division of Maternal-Fetal Medicine, Sidney Kimmel Medical College of Thomas Jefferson University, Philadelphia, Pennsylvania

Rupsa C. Boelig Department of Obstetrics and Gynecology, Division of Maternal-Fetal Medicine, Sidney Kimmel Medical College of Thomas Jefferson University, Philadelphia, Pennsylvania

Ryan K. Brannon Drexel University College of Medicine, Philadelphia, Pennsylvania

Edward M. Buchanan Department of Family and Community Medicine, Thomas Jefferson University Hospital, Philadelphia, Pennsylvania

Elyce Cardonick Division of Maternal-Fetal Medicine, Robert Wood Johnson Medical School New Brunswick, New Jersey

Laura Carlson Department of Obstetrics and Gynecology, Division of Maternal-Fetal Medicine, University of North Carolina School of Medicine, Chapel Hill, North Carolina

Nahida Chakhtoura Eunice Kennedy Shriver National Institute of Child Health and Human Development, Bethesda, Maryland

Ann Chandy Department of Psychiatry and Human Behavior, Thomas Jefferson University Hospital, Philadelphia, Pennsylvania

Suneet P. Chauhan Eunice Kennedy Shriver NICHD Maternal-Fetal Medicine Units Network, Bethesda, Maryland and McGovern Medical School, University of Texas Health Science Center, Houston, Texas

Melissa Chu Lam Department of Obstetrics and Gynecology, St. Luke's University Health Network, Bethlehem, Pennsylvania

Katherine Connolly Department of Obstetrics, Gynecology and Reproductive Sciences, Division of Maternal Fetal Medicine, Icahn School of Medicine at Mount Sinai, New York, New York

Dana Correale Private Practice, Cheshire Dermatology, Cheshire, Connecticut

Raja Dhanekula Department of Medicine, Division of Gastroenterology, Sidney Kimmel Medical College, Thomas Jefferson University, Philadelphia, Pennsylvania

Jeffrey Ecker Department of Obstetrics and Gynecology, Division of Maternal Fetal Medicine, Massachusetts General Hospital, Boston, Massachusetts

Jonathan M. Fenkel Department of Medicine, Division of Gastroenterology, Sidney Kimmel Medical College, Thomas Jefferson University, Philadelphia, Pennsylvania

Henry L. Galan Department of Obstetrics and Gynecology, Division of Maternal-Fetal Medicine, Colorado Institute for Maternal and Fetal Health, University of Colorado Hospital, Aurora, Colorado

Maria A. Giraldo-Isaza Florida Perinatal Associates, Obstetrix Medical Group, Inc, Tampa, Florida

Megan Gooding College of Health and Human Services, George Mason University, Fairfax, Virginia

Nora Graham Department of Obstetrics and Gynecology, Thomas Jefferson University Hospital, Philadelphia, Pennsylvania

Ibrahim A. Hammad Department of Obstetrics and Gynecology, Division of Maternal Fetal Medicine, University of Utah Health Sciences Center, Salt Lake City, Utah

Christopher R. Harman Department of Obstetrics, Gynecology and Reproductive Sciences, University of Maryland Medical Center, Baltimore, Maryland

Edward J. Hayes Department of Obstetrics and Gynecology, Division of Maternal-Fetal Medicine, Aurora Baycare Medical Center, Greenbay, Wisconsin

Michelle R. Hayes Department of Obstetrics and Gynecology, Division of Maternal-Fetal Medicine, Aurora Baycare Medical Center, Greenbay, Wisconsin

Paniz Heidari Department of Obstetrics and Gynecology, Sidney Kimmel Medical College of Thomas Jefferson University, Philadelphia, Pennsylvania

Steven K. Herrine Division of Gastroenterology and Hepatology, Thomas Jefferson University, Philadelphia, Pennsylvania

Katherine Husk Department of Urogynecology and Reconstructive Pelvic Surgery, University of North Carolina, Chapel Hill, North Carolina

Sushma Jwala Department of Obstetrics and Gynecology, Division of Maternal-Fetal Medicine, Obstetrix Medical Group of Washington, Seattle, Washington

Priyadarshini Koduri Division of Maternal-Fetal Medicine, Antenatal Resource Center, Advocate Illinois Masonic Medical Center, Chicago, Illinois

Elisabeth J. S. Kunkel Division Consultation-Liaison Psychiatry, Department of Psychiatry and Human Behavior, Thomas Jefferson University, Philadelphia, Pennsylvania

Augusto Lauro Liver and Multiorgan Transplant Unit, St. Orsola University Hospital, Bologna, Italy

Jason B. Lee Department of Dermatology and Cutaneous Biology, Sidney Kimmel Medical College, Thomas Jefferson University, Philadelphia, Pennsylvania

Dawnette Lewis Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, Mount Sinai St. Luke's Hospital, New York

Melisa Lott Division of Maternal-Fetal Medicine, Women's and Children's Institute, Geisinger Health System, Danville, Pennsylvania

A. Dhanya Mackeen Division of Maternal-Fetal Medicine, Women's and Children's Institute, Geisinger Health System, Danville, Pennsylvania

Lucio Mandalà HPB Unit, La Maddalena Cancer Center, Palermo, Italy

Tracy A. Manuck Department of Obstetrics and Gynecology, Division of Maternal-Fetal Medicine, University of North Carolina, Chapel Hill, North Carolina

Amber S. Maratas Department of Family and Community Medicine, Thomas Jefferson University Hospital, Philadelphia, Pennsylvania

Giancarlo Mari Department of Obstetrics and Gynecology, University of Tennessee Health Science Center, Memphis, Tennessee

Ignazio R. Marino Department of Surgery, Sidney Kimmel Medical College, Thomas Jefferson University, Philadelphia, Pennsylvania

Sally Mathias Department of Neurology, University of Kentucky, Lexington, Kentucky

Rebekah McCurdy Department of Obstetrics and Gynecology, Division of Maternal-Fetal Medicine, Sidney Kimmel Medical College, Thomas Jefferson University, Philadelphia, Pennsylvania

Maria Teresa Mella Department of Obstetrics, Gynecology and Reproductive Sciences, Division of Maternal Fetal Medicine, Icahn School of Medicine at Mount Sinai, New York

M. Kathryn Menard Department of Obstetrics and Gynecology, Division of Maternal-Fetal Medicine, University of North Carolina School of Medicine, Chapel Hill, North Carolina

Rebecca J. Mercier Department of Obstetrics and Gynecology, Division of General Obstetrics and Gynecology, Sidney Kimmel Medical College Thomas Jefferson University, Philadelphia, Pennsylvania

Srikanth Nagalla Department of Medicine, Division of Hematology/Oncology, UT Southwestern Medical Center, Dallas, Texas

Mariam Naqvi Department of Obstetrics and Gynecology, Division of Maternal Fetal Medicine, Massachusetts General Hospital, Boston, Massachusetts

A. Marie O'Neill Rowan University School of Osteopathic Medicine, Stratford, New Jersey

Kelly M. Orzechowski Department of Obstetrics and Gynecology, Division of Maternal Fetal Medicine, Virginia Hospital Center, Arlington, Virginia

Luis D. Pacheco Department of Obstetrics/Gynecology, Division of Maternal Fetal Medicine and Department of Anesthesiology, Division of Surgical Critical Care, The University of Texas Medical Branch, Galveston, Texas

Michael J. Paglia Division of Maternal-Fetal Medicine, Women's and Children's Institute, Geisinger Health System, Danville, Pennsylvania

Leonardo Pereira Department of Obstetrics and Gynecology, Division of Maternal-Fetal Medicine, Oregon Health and Science University, Portland, Oregon

Lauren A. Plante Department of Obstetrics and Gynecology, Division of Maternal-Fetal Medicine and Department of Anesthesiology, Drexel University College of Medicine, Philadelphia, Pennsylvania

Sarah Poggi The Brock Perinatal Diagnostic Center Alexandria, Virginia

Timothy J. Rafael Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, Mount Sinai Beth Israel Hospital, New York

Uma M. Reddy Eunice Kennedy Shriver National Institute of Child Health and Human Development, Bethesda, Maryland

Shane Reeves Division of Maternal-Fetal Medicine, Colorado Institute for Maternal and Fetal Health, University of Colorado, Aurora, Colorado

Amanda Roman Department of Obstetrics and Gynecology, Division of Maternal-Fetal Medicine, Sidney Kimmel Medical College, Thomas Jefferson University, Philadelphia, Pennsylvania

Sharon Rubin Department of Internal Medicine, Division of Cardiology, Pennsylvania Hospital, University of Pennsylvania, Philadelphia, Pennsylvania

Antonio F. Saad Department of Obstetrics/Gynecology, Division of Maternal Fetal Medicine, The University of Texas Medical Branch, Galveston, Texas

Joya Sahu Department of Dermatology and Cutaneous Biology, Sidney Kimmel Medical College, Thomas Jefferson University, Philadelphia, Pennsylvania

Jacques E. Samson Department of Obstetrics and Gynecology, University of Tennessee Health Science Center, Memphis, Tennessee

Corina N. Schoen Department of Obstetrics and Gynecology, Division of Maternal Fetal Medicine, Baystate Medical Center, Springfield, Massachusetts

Neil S. Seligman Division of Maternal Fetal Medicine, Strong Memorial Hospital, University of Rochester, Rochester, New York

Kathryn Shaia Department of Obstetrics, Gynecology and Reproductive Sciences, Icahn School of Medicine at Mount Sinai, New York

William R. Short Division of Infectious Diseases, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania

Stephen Silberstein Jefferson Headache Center, Thomas Jefferson University, Philadelphia, Pennsylvania

Nazanin E. Silver Department of Psychiatry and Human Behavior, Thomas Jefferson University Hospital, Philadelphia, Pennsylvania

Robert M. Silver Department of Obstetrics and Gynecology, University of Utah, Salt Lake City, Utah

Neil Silverman Department of Obstetrics and Gynecology, Division of Maternal-Fetal Medicine, David Geffen School of Medicine at UCLA, Los Angeles, California

Giuliana Simonazzi Department of Medical and Surgical Sciences, Division of Obstetrics and Prenatal Medicine, St. Orsola Malpighi Hospital, University of Bologna, Bologna, Italy

Marcela C. Smid Department of Obstetrics and Gynecology, Division of Maternal-Fetal Medicine, University of North Carolina, Chapel Hill, North Carolina

David M. Stamilio Department of Obstetrics and Gynecology, Division of Maternal Fetal Medicine, University of North Carolina, Chapel Hill, North Carolina

Joanne Stone Department of Obstetrics, Gynecology and Reproductive Sciences, Division of Maternal Fetal Medicine, Icahn School of Medicine at Mount Sinai, New York, New York

Robert A. Strauss Department of Obstetrics and Gynecology, Division of Maternal-Fetal Medicine, University of North Carolina, Chapel Hill, North Carolina

Danielle L. Tate Department of Obstetrics and Gynecology, University of Tennessee Health Science Center, Memphis, Tennessee

Jorge E. Tolosa Department of Obstetrics and Gynecology, Division of Maternal-Fetal Medicine, Oregon Health and Science University, Portland, Oregon and Departamento de Obstetricia y Ginecologia, Centro Nacer, Salud Sexual y Reproductiva, Facultad de Medicina, Universidad de Antioquia, Medellín, Colombia

Tino Tran Department of Obstetrics and Gynecology, Crozer-Keystone Medical Center, Chester, Pennsylvania

Oscar A. Viteri Department of Obstetrics, Gynecology and Reproductive Sciences, Division of Maternal-Fetal Medicine, McGovern Medical School, University of Texas Health Science Center, Houston, Texas

Tal E. Weinberger Thomas Jefferson University Hospital, Philadelphia, Pennsylvania

Shuhan Zhu Department of Neurology, Boston University School of Medicine, Boston, Massachusetts

13

Pregnancy after liver and other transplantation

Ignazio R. Marino, Lucio Mandalà, and Augusto Lauro

KEY POINTS

- The best outcomes in pregnancy after liver transplant occur in patients with the following:
  - Good general health ≥1 year since transplant
  - Minimal or no proteinuria (<1 g/24 hours)
  - Creatinine <1.5 mg/dL
  - Well-controlled or no hypertension
  - No evidence of recent graft rejection
  - **Stable immunosuppressive regimen and liver function**
- Potential maternal and fetal complications include **preterm birth, preeclampsia, fetal growth restriction, and low birth weight**.
- Pregnancy in and of itself does not affect previously stable hepatic allograft function.
- The effect of **comorbid conditions (i.e., diabetes, hypertension)** should be considered and their **management optimized**.
- **Transplant recipients should have their baseline kidney function** (creatinine, 24-hour urine collection for total protein) **assessed**.
- Maintenance of current immunosuppression in pregnancy is usually recommended except for **mycophenolic acid products, for which fetal risks should be discussed and alternatives sought**.
- Summary of **management options in Table 13.4**.

PREGNANCY AFTER LIVER TRANSPLANTATION

Introduction and Historic Notes

Since the first human liver transplant performed in 1963 by Thomas Starzl (University of Colorado) [1], many advances in surgical techniques and immunosuppressive therapy have helped to increase the numbers of women who undergo allogenic organ transplantation each year. In 1978, Walcott [2] documented the first known pregnancy in a liver transplant recipient, which resulted in a successful delivery with both mother and infant in excellent health. Many times, a transplanted organ normalizes a woman's hormonal imbalance and restores fertility, thus offering the prospect of pregnancy and providing many women with end-stage organ disease a chance to conceive and bear children. As a result, among liver transplant recipients, a higher survival rate and a return to a good quality of life have been achieved. In 1991, the National Transplantation Pregnancy Registry (NTPR) was established at Thomas Jefferson University in Philadelphia, Pennsylvania, to analyze pregnancy outcomes in solid-organ transplant recipients [3].

Definition/Symptoms and Signs of ESLD

Liver transplantation (LTx): treatment of choice for all nonneoplastic end-stage liver diseases and for selected patients with nonresectable hepatic malignancies.

End-stage liver disease (ESLD): any hepatic disease that jeopardizes the survival or that seriously modifies the quality of life of the patient and for which the transplant is the only therapy because no other medical or surgical treatment exists that is able to provide a reasonable chance of recovery.

Before undergoing LTx, some patients remain in quite good clinical condition. There may be individual variations in terms of hospital care requirements. As the liver disease progresses, symptoms such as encephalopathy, weakness, and lethargy become more frequent. Intractable ascites, GI bleeding, peripheral edema, anorexia, jaundice, pruritus and cholestasis, peritonitis, and pneumonia may also develop. Often the patient is severely malnourished.

Indications

Although **chronic hepatitis C infection** (HCV) represents the leading indication for LTx in the United States, **autoimmune hepatitis** is probably the most frequent reason for transplantation among young female recipients who may become pregnant after transplant [4].

Epidemiology

Approximately one third of all patients who have undergone LTx are women, and about 75% of female recipients are of reproductive age [4]. The incidence indicates that more than 14,000 women of reproductive age are living in the United States after liver transplantation (LTx), and another 500 undergo LTx each year [5].

Pathophysiology

Women with decompensated liver disease commonly have menstrual dysfunction: Infertility is common in women with ESLD because of hypothalamic–pituitary–gonadal dysfunction, which decreased ovulation [6,7] and affects up to 50% of these patients. In fact, menstrual abnormalities may be the first signs of liver disease in females with chronic liver disease. In cirrhotic state, hypothalamic–pituitary dysfunction is associated with an inadequate response to the gonadotropin-releasing hormone agonists and clomiphene citrates as well as diminished gonadotrophin release relative to the reduced levels of circulating sex steroids [8]. Furthermore, serum levels of estradiol and testosterone are increased in patients with porto-systemic shunts. Thus pregnancy in decompensated cirrhosis is very uncommon. A successful transplant almost uniformly leads to a **prompt return to normal menstrual cycles and to reproductive functions** because of the recovery of the gonadotrophic function [8–11]. This is an important component of the restoration of normality of life for patients of childbearing age, and it is evidenced by the increasing number of post-transplantation pregnancies reported worldwide [12–24].

Preconception Counseling and Timing of Pregnancy

Pregnancy after liver transplant should be considered as a high-risk pregnancy and monitored closely by a team of transplant hepatologists and experts in obstetrics and maternal-fetal medicine. Female liver transplant recipients who are planning to become pregnant should be **counseled on contraception and optimal timing of pregnancy, proper vaccinations, and risks associated with immunosuppressive therapy**.

For this reason **an appropriate contraceptive plan should be recommended. Oral contraceptives are relatively contraindicated** in women with liver transplant because of many theoretical complications, such as the risk of thromboembolism, cholestasis, exacerbated hypertension, and interference in cyclosporin metabolism [7]. Although **intrauterine devices** may initially increase the risks of infection especially in immunocompromised women, their use is probably safe and **should be recommended**.

Many medications used for post-transplant immunosuppression have potential effects during pregnancy and breast-feeding. **The risks and benefits of each medication should be reviewed with patients contemplating pregnancy, and regimens should be tailored accordingly** [see below].

Ideally, **patients should be vaccinated prior to transplantation against influenza, pneumococcus, hepatitis B, and tetanus**. Alternatively, they should be vaccinated prepregnancy.

The optimal timing of conception post-transplant is controversial, but current recommendations suggest **waiting for at least one year after transplantation** based on rejection risks and to allow stabilization of allograft function and of immunosuppressive regimen [7–8,20] even though the shortest interval from OLTx to conception reported in the literature is three weeks [24]. Immunosuppressive agents are at their nadir one year post liver transplantation, and thus risk of allograft rejection is low at that time. Furthermore, renal and liver functions tend to stabilize during that period. Thus it is ideal to delay pregnancy until the patient is on a maintenance immunosuppression one to two years after transplantation to **minimize fetal exposure to high doses of immunosuppressants**. When choosing the timing of pregnancy after OLTx, **several factors should be considered**:

- **a.** Good general health ≥1 year since transplant.
  1. Risk of acute graft rejection
  2. Risk of acute infection that might impact the fetus (cytomegalovirus [CMV] acute infection is most common within 6–12 months post-transplant)
- **b.** Proteinuria and creatinine level.
  1. None or minimal proteinuria (<1 g/24 hours)
  2. Serum creatinine <1.5 mg/dL
- **c.** Rejection and immunosuppression.
  1. No evidence of recent graft rejection (in the past year)
  2. Stable immunosuppression regimen (stable dosing)
- **d.** Stable liver function.
  1. Patients with stable liver function generally have a low risk for opportunistic infections
- **e.** Maternal age.
- **f.** Medical noncompliance.

Comorbidity and Risk Factors

The outcome in liver transplant recipients from selected publications is shown in **Table 13.1**. The main comorbidity, risk factors about patient, graft, and fetus complications described in the English literature are also described below.

Hepatitis Virus Reactivation

Even if autoimmune hepatitis is the most frequent reason for transplantation among young female recipients who may become pregnant after transplant, a reactivation of viral hepatitis is considered one of the most serious risks for both mother and child.

For hepatitis B, for example, vertical transmission is reported between 10% and 20% of HBsAg-positive (HBeAg-negative) nontransplant mothers without immunoprophylaxis. It is recommended to vaccinate and give IVIg to all newborns born to HBsAg-positive women within 12 hours of birth as the hepatitis B virus (HBV) neonatal infection risks with these interventions decreases to less than 10% [25] (Chapter 30).

The rate of maternal-fetal HCV transmission in OLTx recipients is still unclear, requiring additional analysis. The vertical infection rate in pregnant HCV RNA-positive subjects is around 3% to 5% (in absence of other viral coinfections) [26]. A well-documented risk factor for HCV vertical transmission is maternal high viral load. Therefore, special attention should be given to patients with high viral load post-transplant (Chapter 31).

Hypertension and Renal Insufficiency

The immunosuppression regimen based on calcineurin inhibitors (cyclosporine and tacrolimus) is associated with an increased incidence of hypertension and renal insufficiency in the post-transplantation population. The pathogenesis is related to endothelial cell dysfunction and decreased endogenous nitric oxide production, causing renal dysfunction and hypertension: The side effect for the post-LTx pregnant women is an increased incidence of preeclampsia [6,21]. The same treatment with **calcium channel blockers** used in the nontransplant population is recommended [27].

Diabetes

The incidence of new-onset diabetes mellitus (NODM) is approximately **15%** among liver transplant recipients [28]. The immunosuppressive therapy plays an important role even if the impact of steroids is controversial. Most of the authors agree to **limit the use of steroids as much as possible and to reduce calcineurin inhibitors** at the minimum needed dose. The management of NODM is essentially similar to that of diabetes in the nontransplant population. NODM is associated with obesity, insulin resistance, insulin secretory defect, and subsequent development of type II diabetes in the offspring. Modern treatment protocols during pregnancy include **strict glycemic control** by a combination of diet and medications (Chapters 4 and 5). Traditionally, insulin therapy has been considered the gold standard for management of diabetes because of its efficacy in achieving better glucose control and the fact that it does not cross the placenta [29].

CMV Acute Infection

CMV infection represents one of the most common types of infection within six to 12 months in the post-transplant population, and it is very dangerous in early pregnancy because it is responsible for congenital malformation (microcephaly, cerebral palsy, sensorineural deafness) or congenital liver disease with an incidence of 10% to 15% of infected pregnancies. It is advisable to **screen all transplant recipients with CMV IgG and IgM**. If IgM positive, avidity testing should

Table 13.1 Fetal and Maternal Outcomes in Liver Transplant Recipients from Selected Studies

Author	No. of Pregnancies	Live Birth Rate (%)	Spontaneous Abortions (%)	Preterm (%)	Graft Dysfunction (%)	Cesarean Rate (%)	Birth Weight <2500 g (%)	Maternal Deaths (%)	Neonatal Deaths (%)
Alvaro E	30	66.6	26.6	NA	10	42	NA	0	6
Armenti VT	205	73	19	35	7	35	34	0	0
Dashpande NA	450	76.9	6.2	39.4	NA	44.6	NA	NA	NA
Christopher V	71	71	19	NA	17	40	20	4	NA
Coffin CS	20	70	5	27	5	38	NA	0	6
Dei Malatesta MF	285	78	NA	31	10	43	23	4	4
Jabiry-Zieniewicz Z	39	100	0	31	8	80	20	0	0
Jain AB	49	100	0	4	25	47	9	10	6
Nagy S	38	63	NA	29	17	46	17	17	0
Sibanda N	16	69	13	50	NA	62	57	NA	NA
Total	1203	76.7	7.95	30.8	12.37	47.76	25.7	4.3	3.1

Source: Adapted from Hammound GM, Almashhrawi AA, Ahmed KT et al. *World J Gastroenterol*, 19, 7647–51, 2013.

be performed (Chapter 47). The use of antiviral agents in the management of CMV infection during pregnancy remains controversial [8] (Chapter 47).

Acute Cellular Rejection
Acute cellular rejection (ACR) rate in the post-LTx pregnancies is reported **between 2% and 8%** [3,8,23] and **occurs during the earlier phases of pregnancy. Immunosuppression therapy should be maintained and monitored during pregnancy by serum levels** as a reduction or discontinuation may lead to rejection of the transplanted organ. **When acute rejection is suspected, an ultrasound-guided percutaneous liver graft biopsy is strongly recommended** and should be associated with a Doppler ultrasound study of the graft in order to exclude anatomic source of graft dysfunction. The ACR treatment includes adjustment of immunosuppressive medications and **use of steroids as antirejection therapy**.

Infrarenal Aortic Graft
One death due to aortic graft clotting by external compression from the gravid uterus has been reported [27]. For this reason, patients with infrarenal aortic graft should be monitored with color Doppler ultrasonography during pregnancy.

Pregnancy Complications (Table 13.1)

Preterm Birth and Low Birth Weight
The risk of prematurity is up to 50%, and the mean gestational age at delivery ranges between 36 and 37 weeks [3–5,20].

Intrauterine Growth Restriction
Intrauterine growth restriction (IUGR) is estimated to occur in about 20% of liver transplant recipients and is associated with perinatal morbidity and mortality (Chapter 45).

Table 13.2 FDA Classification of Risk of Immunosuppressive Drug in Pregnancy

Drugs	Pregnancy Category
Corticosteroids	B
Cyclosporin	C
Sirolimus	C
Tacrolimus	C
Azathioprine	D
Mycophenolate mofetil	D

Table 13.3 Selected Immunosuppressive Agents and Their Side Effects

Immunosuppressant	Side Effect
Prednisone[a]	Glucose intolerance
Azathioprine[a]	Leukopenia
Cyclosporine[a,b]	Hypertension, nephrotoxicity
Tacrolimus[a,b]	Hypertension, nephrotoxicity, neurotoxicity, glucose intolerance, myocardial hypertrophy
Mycophenolate Mofetil	GI disturbance
Sirolimus[a,b]	Leukopenia, thrombocytopenia, hyperlipidemia

[a]There have been no known teratogenic effects.
[b]Follow with blood levels.

Table 13.4 Pregnancy after Liver Transplantation: Management Options

Prepregnancy
- Patients should defer conception for at least one year after transplantation, with adequate contraception.
- Assessment of graft function (organ specific):
  - Recent liver biopsy
  - Proteinuria (24-hour collection for total protein)
  - Hepatitis B and C status (HBsAg; Hep. C Antibody)
  - *CMV, toxoplasmosis, herpes simplex status (IgG, IgM)*
- Maintenance immunosuppression options:
  - Azathioprine
  - Cyclosporine
  - Tacrolimus
  - Corticosteroids
  - *Mycophenolate mofetil (**avoid as feasible**)*
  - *Enteric-coated mycophenolate sodium (**avoid as feasible**)*
  - Sirolimus
- The effect of comorbid conditions, (i.e., diabetes, hypertension) should be considered and their management optimized.
- Vaccinations should be given if needed (i.e., rubella, etc.) (Chapter 38).
- Explore etiology of original disease.
- Discuss genetic issues if relevant.
- Discuss the effect of pregnancy on renal allograft function.
- Discuss the risks of intrauterine growth restriction, preterm birth, low birth weight, etc.

Prenatal
- Pregnancy in and of itself does not affect previously stable allograft function.
- Accurate early diagnosis and dating of pregnancy.
- Baseline laboratory tests should include:
  a. Liver enzymes (ALT and AST)
  b. Creatinine and bilirubin
  c. Immunosuppression medication (e.g., cyclosporine or tacrolimus) level
  d. 24-hour urinary protein and creatinine clearance
  e. Urine analysis and urine culture
  f. CMV, HSV, and Toxoplasma IgM and IgG
  g. HBsAg, HBsAb, HepCAb

Timing of repeat laboratory testing of at least tests a–e should be once every trimester until 32 weeks.
- Fetal surveillance.
- Monitor for hypertension and nephropathy.
- Careful surveillance for preeclampsia.
- Early screening for gestational diabetes.

Labor and delivery
- Vaginal delivery is optimal; cesarean delivery for obstetric reasons.

Post-natal
- Monitor immunosuppressive drug levels for at least one month postpartum, especially if dosages increased during pregnancy.
- Surveillance for rejection with biopsy if it is suspected.
- Breast-feeding discussion.
- Contraception counseling.

Preeclampsia
The incidence of hypertension and preeclampsia is approximately 20% in OLTx recipients and seems to occur mainly in patients taking **cyclosporine**, probably because of the related endothelial cell dysfunction, and less commonly with tacrolimus [3–6,23,27]. The management of preeclampsia is the same as in the nontransplant population (Chapter 1).

Abnormal Blood Chemistry and Liver Function Tests
In most series, **pruritus and cholestasis** seem to be the most frequent symptoms described in pregnancies after LTx. Differential diagnosis with ACR should be considered in all cases. HELLP syndrome and anemia have been reported [5].

Immunosuppression Therapy: Drugs and Their Side Effects

There is no consensus on the optimal maintenance regimen for transplant pregnant recipients. The use of immunosuppressive therapy after liver transplantation is unavoidable even taking into consideration the potential risks of the exposure of infants to immunosuppressive medications. **All immunosuppressive medications cross the placenta** and enter into fetal circulation and could potentially have effects in utero. Despite the fact that immunosuppressive agents such as Azathioprine, Cyclosporine, and Mycophenolic acid were teratogenic in animals, the risk of birth defects was not statistically different between those who received immunosuppressive medications and those who did not. Patients treated with either calcineurin inhibitors (**cyclosporine or tacrolimus**) **should have serial blood tests in pregnancy to follow medication levels** and to assess hepatic and renal function while avoiding unnecessary toxicity. Recent studies have reported an association between administration of **mycophenolic acid products (MPA) [myco-phenolate mofetil (MMF) and enteric-coated mycopheno-late sodium (EC-MPS)]** to transplant recipients and an increased risk of adverse outcomes in pregnancy-like specific pattern of **birth defects**. In 2007, the package inserts of MMF and EC-MPS included a change from pregnancy category C to **category D** [30–33]. The warning states that females of potential childbearing age must use contraception while taking MPA because its use during pregnancy is associated with increased rates of pregnancy loss and congenital malformations. Pregnancy outcomes with exposure to sirolimus remain limited: Reported to the NTPR are three liver recipients with three pregnancies (two live births, one spontaneous abortion) [3]. The Food and Drug Administration (FDA) classification of risk medication and their categories in pregnancy is reported in **Table 13.2**. Selected immunosuppressive drugs and their side effects are reported in **Table 13.3**.

Workup and Management

A summary of the suggested key points is in **Table 13.4**.

In case of elevations of liver function tests and/or bilirubin, an ACR should be ruled out. Evaluation of rejection includes liver ultrasound with Doppler to exclude anatomic sources of graft dysfunction. **Liver biopsy to diagnose rejection is *not* contraindicated in pregnancy.** Because of an increased risk of carbohydrate intolerance caused by the administration of prednisone or tacrolimus, **patients should be screened with glucose tolerance tests in the first trimester, followed by routine screening between 24 and 28 weeks**.

Antepartum Testing

A dating **ultrasound** should be performed in the first trimester. Ultrasound study should be performed every trimester with detailed fetus anatomy in the second trimester and serial assessment of fetal growth in the third trimester [3,19,34].

Weekly nonstress tests can begin at 32 weeks unless medical or obstetric complications indicate earlier testing.

Table 13.5 Pregnancy Outcomes among Solid-Organ Transplant Recipients

	Kidney[a]	Pancreas–Kidney	Liver	Heart	Lung
Maternal factors (*n* = pregnancies)	(987)	(75)	(287)	(103)	(30)
Mean transplant-to-conception interval (years)	3.6–6.1	3.0–5.5	5.7 ± 4.9	6.0 ± 4.7	3.6 ± 3.3
Hypertension during pregnancy	56%–65%	28%–95%	32%	39%	53%
Diabetes during pregnancy	4%–12%	0%–5%	7%	2%	23%
Infection during pregnancy	19%–23%	23%–62%	26%	13%	21%
Preeclampsia	30%–32%	27%–32%	22%	18%	17%
Rejection episode during pregnancy	1%–2%	0%–14%	7%	11%	6%
Graft loss within two years of delivery	8%–10%	18%–19%	7%	4%	14%
Outcomes (*n*)[b]	(1017)	(77)	(293)	(106)	(32)[c]
Therapeutic abortions	0.8%–8.4%	4%–5%	4%	5%	16%
Spontaneous abortions	12%–26%	9%–28%	18%	30%	28%
Ectopic	0.4%–1%	0%–3%	0.3%	2%	0
Stillborn	2%–3%	0	1.7%	1%	0
Live births	70.8%–76%	69%–86%	76%	62%	56%
Live births (*n*)	(762)	(58)	(221)	(66)	(18)
Mean gestational age (weeks)	35–35.8	34.2–34.8	36.4 ± 3.5	36.8 ± 2.6	33.9 ± 5.2
Preterm birth (<37 weeks)	52%–53%	65%–83%	42%	38%	61%
Mean birth weight (g)	2470–2547	1934–2263	2674 ± 796	2600 ± 568	2206 ± 936
Low birth weight (<2500 g)	42%–46%	50%–68%	34%	39%	61%
Cesarean section	43%–58%	61%–69%	41%	40%	31%
Neonatal deaths, % (*n*) (within 30 days of birth)	1%–2%	(1)	(1)	0	(2)[b]

Source: Adapted from Coscia LA, Constantinescu S, Moritz MJ et al. Report from the National Transplantation Pregnancy Registry (NTPR): Outcomes of pregnancy after transplantation. In: Cecka JM, Terasaki PI, eds. *Clinical Transplants* Los Angeles: UCLA Terasaki Foundation Laboratory. 65–85, 2011.

[a]Range of incidence due to different immunosuppressants.

[b]Includes twins, triplets, quadruplets.

[c]Includes one triplet pregnancy: one spontaneous abortion at 14 weeks and two born at 22 weeks and died within 24 hours of birth.

Labor and Delivery Issues

Patients who have received steroids during the antepartum period in the equivalent of more than 20 mg of prednisone for more than three weeks should receive "stress dose" steroids (i.e., hydrocortisone 100 mg IV every eight hours × 24 hours).

Cesarean delivery should be performed only for obstetric indications.

Breast-Feeding

Data collected from the NTPR [3] indicated no adverse outcomes in infants who were breast-fed during maternal cyclosporine use. Azathioprine seems also to be safe with breast-feeding. Nevertheless, mothers may be discouraged to breast-feed in the first few months post transplantation when immunosuppressive therapy is at high serum levels. The American Academy of Pediatrics advises that breast-feeding mothers can use prednisone and other glucocorticoids safely. Infant exposure to tacrolimus in milk is very low, and subsequently, **maternal tacrolimus therapy may be compatible with breast-feeding**.

PREGNANCY AFTER OTHER TRANSPLANTATIONS

For pregnancy after **renal transplantation**, please see Chapter 17.

Table 13.5 shows pregnancy **outcomes in kidney, kidney/pancreas, liver, heart, and lung recipients** for comparison [3]. Female heart transplant recipients are able to maintain pregnancy with the majority resulting in a live birth. Not all rejections are treated as some are low-grade. Maternal survival, independent of pregnancy-related events, should be considered as part of prepregnancy planning.

By comparison, lung recipients have a higher incidence of more significant rejection as well as graft loss in the peripartum period with smaller newborns. Successful pregnancy is possible post lung transplantation. Analyses of a larger number of cases may help to identify trends in pregnancy after lung transplantation. Whether long-term maternal survival is impacted by pregnancy warrants further study.

Intestinal transplantation has shown steady improvements in graft and patient survival over the past 20 years and is rapidly becoming more established worldwide [35]. The first pregnancy after intestinal transplant was described in 2006 [36], followed later by few other reports [37–40] with 100% success rate. Specific to this procedure, there are two factors affecting the transplant to be considered in case of pregnancy: higher need of immunosuppressants and absorptive function of transplanted bowel. Close monitoring of renal function and of the graft by endoscopies and biopsies must be performed during the pregnancy in order to prevent episodes of rejection or enteritis, preserving the fetus by temporary malnutrition.

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