CHAPTER SAMPLER

Key Topics in Obstetric Medicine

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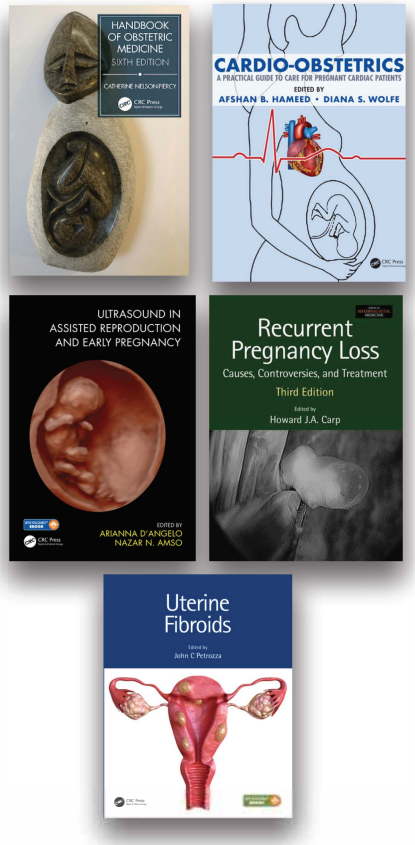

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CHAPTER 10

Renal disease

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Physiological adaptation (Table 10.1)

- There is a dramatic dilatation of the urinary collecting system during pregnancy. This may be the result of ureteral smooth muscle relaxation induced by progesterone or compression of the ureters by the enlarging uterus or iliac vessels. Caliceal and ureteral dilatation is more pronounced on the right.
- The 'physiological hydronephrosis' of pregnancy can be dismissed as normal up to a pelvicaliceal diameter of about 2 cm.
- Renal plasma flow (RPF) rises very early in pregnancy and increases to 60%–80% by the second trimester of pregnancy.
- RPF falls throughout the third trimester but is still maintained at 50% greater than pre-pregnancy values at term.
- Glomerular filtration rate (GFR) also increases significantly and creatinine clearance rises by about 50%. This results in a fall in the serum urea and creatinine levels. The upper limit of normal in pregnancy is 77 μmol/L.
- The use of estimated GFR from the Modification of Diet in Renal Disease formula is not recommended for use in pregnancy.
- Protein excretion is increased and the upper limit of normal in pregnancy is taken as 300 mg/24 hours or a protein creatinine ratio (PCR) of 30 mg/mmol.
- Microscopic haematuria, in the absence of proteinuria, renal impairment or infection, is not uncommon in pregnancy and may relate to bleeding from small venules in dilated collecting systems. If renal ultrasound (US) is normal, no further investigation is required unless the haematuria persists postpartum.
- An isolated finding of leucocytes (probably related to vaginal discharge) in the urine is also common and not indicative of urinary tract infection.
- There is physiological sodium (and water) retention during pregnancy; 80% of pregnant women develop some oedema, especially towards term, so it is usually not a pathological sign. The pregnant woman has a decreased ability to excrete a sodium and water load and this is most marked near term.
- Renal secretion of vitamin D, renin and erythropoietin are all increased in pregnancy.

Table 10.1 – Physiological renal changes in pregnancy

Physiological variable	Direction of change	Percentage increase or normal range for pregnancy
RPF	↑	60%–80%
GFR	↑	55%
Creatinine clearance	↑	120–160 mL/min
Protein excretion	↑	<300 mg/24 hour
Urea	↓↓	2.0–4.5 mmol/L
Creatinine	↓↓	25–77 μmol/L
Bicarbonate	↓↓	18–22 mmol/L
Uric acid	↑↓	With gestation (see Appendix A.2)

Urinary tract infection

This may be divided into the following:

- Asymptomatic bacteriuria
- Acute cystitis
- Acute pyelonephritis

Although urinary tract infection (UTI) is a common and important problem in pregnancy, it should never be assumed to be the cause of abdominal pain and/or proteinuria before further investigation (see Chapter 16) to confirm or refute the diagnosis is undertaken.

Asymptomatic bacteriuria

Incidence

- This affects 4%–7% of pregnant women, of whom up to 40% will develop symptomatic UTI and 30% acute pyelonephritis if untreated in pregnancy.
- Women who have a history of previous UTI and are found to have bacteriuria have a tenfold increased risk of developing cystitis or acute pyelonephritis in pregnancy.

Pathogenesis

- About 75%–90% of bacteriuria in pregnancy is due to *Escherichia coli*, probably derived from the large bowel.
- Colonization of the urinary tract results from ascending infection from the perineum and may be related to sexual intercourse.

Diagnosis

- Most women with asymptomatic bacteriuria are infected during early pregnancy. Very few subsequently acquire asymptomatic bacteriuria.
- Bacteriuria is only considered significant if the colony count exceeds 100,000/mL on a mid-stream urine (MSU) specimen.
- Urine culture resulting in a non-significant or mixed growth should be repeated on a fresh MSU specimen.
- Dipsticks for nitrites and leukocyte esterase may be used to help exclude UTI.

Management

- Because dilation of the upper renal tract during pregnancy increases the risk of pyelonephritis (see later), asymptomatic bacteriuria should be treated.
- Treating asymptomatic bacteriuria reduces the risk of preterm delivery and low birthweight babies.
- The choice of antibiotic depends on the sensitivities of the causative organism.
- Amoxycillin and the cephalosporins are safe and appropriate antibiotics for use in pregnancy. Treatment with cefalexin 500 mg b.d. is effective against the majority of urinary pathogens.
- Nitrofurantoin 100 mg thrice daily and trimethoprim 200 mg b.d. are safe alternatives. Nitrofurantoin used in the last few weeks of pregnancy carries a theoretical risk of neonatal haemolytic anaemia. Trimethoprim should be avoided in the first trimester due to its anti-folate action.
- Long-acting sulphonamides should be avoided in the last few weeks of pregnancy because they increase the risk of neonatal kernicterus.
- Treatment for 3 days is sufficient for asymptomatic bacteriuria. Regular urine cultures should be taken following treatment to ensure eradication of the organism. About 15% of women will have recurrent bacteriuria during their pregnancy and require a second course of antibiotics.

Acute cystitis

Incidence

Cystitis complicates about 1% of pregnancies.

Clinical features

- These include urinary frequency, urgency, dysuria, haematuria, proteinuria and suprapubic pain.
- UTI in pregnancy is more common in women with diabetes (both pre-existing and gestational), in those receiving systemic corticosteroids or other immunosuppression and in those with a history of previous recurrent UTIs (with or without structural renal abnormalities).

Pathogenesis

See the subsection 'Asymptomatic bacteriuria'. Most infections are due to *E. coli*.

Diagnosis

- This is confirmed by the finding of significant bacteriuria (see subsection 'Asymptomatic bacteriuria') following culture of an MSU specimen.
- Microscopy of the urine may reveal organisms, white cells and occasionally red cells, but the false-positive rate is very high and is no longer recommended for the diagnosis of UTI.
- The presence of nitrites and leukocytes is suggestive but not diagnostic of UTI.

Management

- This is the same as for asymptomatic bacteriuria (see earlier).
- Antibiotic therapy is guided by sensitivities of the organism. If the organism is resistant to penicillins, cephalosporins, nitrofurantoin and trimethoprim, then ciprofloxacin may be appropriate, but this is not used as first-line therapy in pregnancy as it has caused arthropathy in animal studies.
- Antibiotics should be continued for 5–7 days.
- Several non-pharmacological manoeuvres may help prevent recurrent infection in those women troubled by UTIs in pregnancy. These include:
  - Increasing fluid intake. This ensures frequent voiding and a high-volume dilute urine, all of which reduce the risk of symptomatic infection.
  - Emptying the bladder following sexual intercourse. This 'washes away' organisms massaged up the urethra from the perineum into the bladder during coitus, before they have a chance to replicate in urine within the bladder.
  - Double voiding (to ensure no residual urine is left in the bladder following micturition).
  - The perineum should be cleaned from 'front to back' following defaecation to minimize the risk of bowel organisms colonizing the urethra.

Acute pyelonephritis

Incidence

- This complicates 1%–2% of pregnancies.
- It is more common in pregnancy because of the physiological dilatation of the upper renal tract.

Clinical features

- These include fever, loin and/or abdominal pain, vomiting, rigors, as well as proteinuria, haematuria and concomitant features of cystitis (see earlier).
- Like cystitis, it is more common in women with diabetes, those on steroid or immunosuppressive therapy and those with previous recurrent UTIs.

Other risk factors include:

- Polycystic kidneys
- Congenital abnormalities of the renal tract (e.g. duplex kidney or ureter, reflux nephropathy)

- Neuropathic bladder (e.g. in those with spina bifida or multiple sclerosis)
- Urinary tract calculi

Pathogenesis

See the subsection 'Asymptomatic bacteriuria'. Most infections are due to *E. coli*. Cultures yielding significant growths of mixed organisms should prompt a search for underlying renal calculi.

Diagnosis

- This is confirmed by the finding of significant bacteriuria (see earlier) following culture of an MSU specimen.
- Differential diagnosis includes pneumonia (especially right lower lobe), viral infections, cholecystitis and biliary colic, pre-eclampsia, acute appendicitis, gastroenteritis, placental abruption and a degenerating uterine fibroid (see also Chapter 16, Tables 16.12 and 16.17.)
- Investigation in women with fever should include blood cultures, a full blood count, renal function, liver function, CRP (C-reactive protein) and a lactate.

Pregnancy

- Acute pyelonephritis increases the risk of preterm labour at least in part because of associated pyrexia.
- There is also evidence for an increased risk of low birthweight babies, but this is partly related to an increase in preterm delivery.

Management

- This should be undertaken in hospital.
- Once the diagnosis is suspected and urine and blood culture samples obtained, antibiotic treatment with appropriate intravenous (i.v.) antibiotics should begin immediately, before awaiting the results of urine and blood culture or sensitivities.
- Intravenous penicillins or cephalosporins (e.g. amoxicillin/clavulanic acid, cefuroxime) are usually the first choice, although in the case of septicaemia or resistant organisms or women who are allergic to both penicillins and cephalosporins, an aminoglycoside such as gentamicin may be used. More frequent dosing is usually required in pregnancy because of increased renal clearance.
- Antibiotics should be given i.v. for at least 24 hours, when they may be changed to an appropriate oral formulation. Antibiotics should be continued for a period of at least 2 weeks.
- Renal function should be checked regularly since acute kidney injury (AKI) may complicate acute pyelonephritis in pregnancy, especially if there is associated sepsis.
- Intravenous fluids may also be required if the woman is volume depleted as a result of inadequate intake, vomiting or sweating.
- An US examination of the kidneys should be undertaken to exclude hydronephrosis, congenital abnormalities and renal calculi.

Prophylaxis

- Women who usually take antibiotic prophylaxis against UTIs should continue this in pregnancy.
- Suitable regimes in pregnancy include low-dose amoxycillin or low-dose oral cephalosporins (cephalexin 250 mg) or nitrofurantoin 50 mg o.d., but depend on the sensitivities of the usual infecting organisms. The prophylactic agent may need to be changed in pregnancy if there is intervening infection with a resistant organism.
- Once a woman has had two or more confirmed and documented UTIs in pregnancy, renal US should be performed and antibiotic prophylaxis considered.

Urinary tract infection—points to remember

- UTI is more common in pregnancy.
- Asymptomatic bacteriuria should be treated because there is a significant risk of acute pyelonephritis.
- Acute pyelonephritis increases the risk of preterm labour.
- Acute pyelonephritis should be managed in hospital with i.v. antibiotics.
- Once antibiotic treatment has rendered the urine sterile, regular MSU specimens are necessary to exclude reinfection.
- Amoxycillin and cephalosporins are appropriate antibiotics for the treatment and prevention of UTI in pregnancy.
- Gentamicin may be required for severe or resistant infections.
- Investigations in cases of pyrexia and suspected acute pyelonephritis should include MSU, blood cultures, full blood count, renal function, CRP, lactate and a renal US.

Chronic kidney disease

Pregnancy

Effect of pregnancy on chronic kidney disease

The risks include:

- Accelerated decline in renal function
- Escalating hypertension during pregnancy
- Worsening proteinuria during pregnancy
- A flare/relapse of glomerulonephritis (particularly with lupus)

Increased proteinuria is a physiological response to pregnancy and may not necessarily indicate superimposed pre-eclampsia or deteriorating renal disease.

It also results from withdrawal of angiotensin-converting enzyme inhibitors/ angiotensin receptor blockers before or in early pregnancy.

Effect of chronic kidney disease on pregnancy

The risks include:

- Miscarriage
- Pre-eclampsia
- Fetal growth restriction (FGR)
- Preterm delivery
- Fetal death

Factors influencing outcome

- The outcome of pregnancy and any adverse effect on underlying chronic kidney disease (CKD) are both influenced by the presence and severity of hypertension
- Presence and degree of proteinuria
- Presence and degree of renal impairment (see later)
- Underlying cause of CKD (see later)

In general, women without hypertension or renal impairment prior to conception have successful pregnancies and pregnancy does not adversely influence the progression of the kidney disease.

Degree of renal impairment

- Absolute creatinine levels may be misleading if allowance is not made for the size, age and ethnicity of the woman. For example, a plasma creatinine level of 200 μmol/L in a woman weighing 50 kg represents a greater reduction in renal function than the same level in a woman weighing 80 kg.
- Renal disease is classified by stages of CKD according to estimated GFR in mL/ min as follows:

– CKD 1	>90
– CKD 2	60–89
– CKD 3a	45–59
- CKD 3b	30–44
– CKD 4	15–29
– CKD 5	<15

- Women with severe renal impairment (CKD 4–5, serum creatinine >250 μmol/L) or on dialysis are usually advised against pregnancy.

Table 10.2 – Effect of pregnancy on renal impairment (percentage of affected women)

	CKD 1	CKD 2	CKD 3	CKD 4–5
Creatinine fall in pregnancy <10%		35	50	58
CKD stage shift or RRT start (%)	8	13	16	20
Percentage reduction in eGFR (estimated glomerular filtration rate) at 6 months post-partum	8	15	23	67
Loss of 25% eGFR/RRT at 1 year		23	35	86

Abbreviations: RRT, renal replacement therapy; eGFR, estimated glomerular filtration rate

Effect of pregnancy on renal impairment

- Women with more severe renal impairment (CKD 3–5) are more likely to have an accelerated decline and/or a permanent worsening of renal function as a result of pregnancy (Table 10.2).
- Initially in many the usual increase in GFR occurs, leading to a fall in the serum creatinine level early in pregnancy. However, the serum creatinine level usually begins to rise to and beyond pre-pregnancy levels during the late second trimester and third trimester.
- A lack of the normal physiological fall in serum creatinine is a poor prognostic sign (Table 10.2).

Effect of degree of renal impairment on pregnancy outcome

- Women with more severe renal impairment are at increased risk of adverse pregnancy outcome and complications – especially pre-eclampsia, FGR and preterm delivery (Table 10.3).

Table 10.3 – Effect of degree of renal impairment on pregnancy outcome (percentage of affected women)

	CKD 1	CKD 2	CKD 3	CKD 4–5
Pre-eclampsia	18	20	21	40
SGA (small for gestational age) (<10th centile)	10	33	32	64
Preterm delivery (<37 weeks)	25	48	60	88
NICU (neonatal intensive care unit) admission	10	41	30	48

Abbreviations: SGA, small for gestational age; NICU, neonatal intensive care unit.

- Polyhydramnios (and the accompanying risks of preterm rupture of the membranes and cord prolapse) may complicate pregnancies where the maternal urea level is >10 mmol/L. This results from fetal polyuria due to the osmotic load from the high maternal urea level.
- Once the maternal urea level is >20 mmol/L, there is a risk of fetal death. Dialysis for fetal indications is recommended once the urea level is >17 mmol/L.

Specific types of renal disease

Glomerulonephritis

- The type of glomerulonephritis has less impact on pregnancy outcome than the presence of hypertension proteinuria and level of renal impairment. Most pregnancies are successful. Those with hypertension are at increased risk of superimposed pre-eclampsia.
- In those with normal renal function at conception, pregnancy does not affect the course of renal disease or the occurrence of end-stage renal failure. Hypertension and proteinuria accelerate the rate of decline in renal function, whether or not a woman has been pregnant.

Reflux nephropathy

- This is one of the most common renal diseases in women of childbearing age.
- Women with reflux nephropathy should be screened regularly for UTI and treated promptly if it occurs.
- Reflux nephropathy may be inherited as an autosomal dominant condition, and therefore offspring of affected mothers should be screened with a micturating cystogram, as US may miss the diagnosis. It is common to start prophylactic antibiotics if there is suspicion that the child may have reflux nephropathy.

Diabetic nephropathy (see also Chapter 5)

- Adverse pregnancy outcome and maternal complications are doubled compared to pregnant women with diabetes without nephropathy.
- The specific risks are UTI, pre-eclampsia, proteinuria and oedema that may be severe but usually revert after delivery to pre-pregnancy levels.
- Nephrotic syndrome can be severe with marked hypoalbuminaemia and the associated risks of pulmonary oedema and thrombosis.
- Anaemia is often out of proportion to the degree of renal impairment and may become severe in pregnancy. This is due to a combination of deficient erythropoietin secretion in the presence of renal impairment and haemodilution.

Systemic lupus erythematosus nephritis

See Chapter 8.

Polycystic kidney disease

- This is an autosomal dominant disorder usually presenting in the fourth decade with hypertension, recurrent UTIs, haematuria or renal impairment. Some

asymptomatic women are aware of their diagnosis because of affected family members and positive screening. Women may remain undiagnosed throughout pregnancy.
- Loin pain and haematuria may occur without UTI, related to bleeding into a renal cyst, or may occur in the absence of these complications.
- PCKD (polycystic kidney disease) may be associated with polycystic liver disease and subarachnoid haemorrhage from intracranial aneurysms. Liver cysts may enlarge during pregnancy and those with a family history of intracranial aneurysms should be screened for aneurysms prior to pregnancy.
- Since PCKD is an autosomal dominant disorder, there is a 50% chance of transmission to the affected woman's offspring.

Management of pregnancies complicated by CKD

- Management should begin with pre-pregnancy counselling. Assessment of renal function, proteinuria and blood pressure enables accurate counselling and provides a baseline with which to compare trends in pregnancy.
- Obstetricians and physicians who have expertise in the care of renal disease in pregnancy should jointly manage women with CKD.
- In view of the increased risk of pre-eclampsia, treatment with low-dose aspirin from the first trimester should be advised.
- Careful monitoring and control of blood pressure both pre-pregnancy and antenatally is important. Treatment for hypertension is no different from the management of pregnant women without CKD (see Chapter 1); targets for treatment are >110/70 and <135/85. Good control of hypertension is important to preserve renal function.
- Regular assessment of renal function by serum creatinine and proteinuria by PCR is essential.
- It is also important to monitor electrolyte, serum albumin, bicarbonate, haemoglobin and platelet levels.
- In women with vitamin D deficiency and CKD, the use of active vitamin D metabolites (1α-hydroxy-cholecalciferol or 1,25-dihydroxycholecalciferol) is required as there is deficient 1α hydroxylation in the kidney.
- The fetus should be monitored with regular US assessment of growth and liquor volume. Doppler assessment of uterine artery blood flow at 20–24 weeks and placental growth factor (see Chapter 1) is useful to predict pre-eclampsia and FGR and assessment of the umbilical flow is useful in the presence of FGR.

Renal biopsy in pregnancy

- Indications for renal biopsy during pregnancy are mostly limited to early gestations where the result of the biopsy is likely to influence or change the management (i.e. before 28 weeks' gestation where a diagnosis of a steroid- or chemotherapy-responsive lesion is suspected). Indications include:
  - Pre-existing but undiagnosed nephrotic syndrome
  - New-onset nephrotic syndrome <16–20 weeks with no other features of pre-eclampsia
  - Strong suspicion of treatable underlying cause of AKI/CKD e.g. lupus, rejection in allograft

- Other causes of AKI and proteinuria should be excluded prior to biopsy and the blood pressure must be adequately controlled. Other causes include:
  - Renal vein thrombosis (excluded with Doppler US of renal veins)
  - Obstruction (excluded with US)
  - Infection (excluded with MSU)
  - Pre-eclampsia (excluded clinically or if <16 weeks)

Diagnosis of superimposed pre-eclampsia

- Superimposed pre-eclampsia should be considered.
- In a women with proteinuric CKD if she develops new hypertension (systolic BP >140 mm Hg and/or diastolic BP >90 mm Hg) or maternal organ dysfunction after 20 weeks' gestation.
- In a women with chronic hypertension and proteinuria, if she develops maternal organ dysfunction after 20 weeks' gestation.
- In women with chronic hypertension and proteinuria who develop sustained severe hypertension (systolic BP >160 mm Hg and/or diastolic BP >110 mm Hg or doubling of antihypertensive agents) and/or a substantial rise in proteinuria (doubling of PCR compared to early pregnancy).
- Angiogenic markers (PlGF±sFlt-1) (see Chapter 1) are particularly useful in women with CKD and pre-existing proteinuria and hypertension.
- Admission should be considered if the woman develops worsening hypertension, deteriorating renal function or proteinuria, superimposed pre-eclampsia or polyhydramnios.

Chronic kidney disease—points to remember

- Women with CKD are at increased risk of pre-eclampsia, FGR, preterm delivery and caesarean section; the perinatal mortality rate is increased.
- These obstetric complications and the risk of permanent deterioration in renal function are increased by the CKD stage and presence and severity of proteinuria or hypertension.
- An increase in the degree of proteinuria is very common in pregnancy and does not necessarily imply pre-eclampsia or worsening renal disease.
- Management should include regular monitoring of blood pressure, renal function and fetal well-being.
- In view of the increased risk of pre-eclampsia, treatment with low-dose aspirin should be advised, especially in those with hypertension and renal impairment or a previous poor obstetric history.

Pregnancy in dialysis patients

- Fertility is reduced in women on haemodialysis or chronic ambulatory peritoneal dialysis (CAPD). The pregnancy rate is about 1 in 200 women per year.
- Fertility and the chance of successful pregnancy outcome are improved with daily dialysis.
- Poor prognostic features for pregnancy in dialysis patients include:

- Age >35 years
- More than 5 years on dialysis
- Delayed diagnosis of pregnancy (leading to late increase in dialysis times)

Effect of pregnancy on renal replacement therapy

- Anaemia is exacerbated by pregnancy. Transfusion requirements increase. Erythropoietin and i.v. iron may be safely used and increased in pregnancy.
- Pregnancy is associated with markedly increased requirements for dialysis.
- Doses of heparin may need to be increased to prevent clotting of dialysis lines.
- Pregnancy causes fluctuations in fluid balance and blood pressure.
- Doses of vitamin D and calcium may need to be reduced.

Effect of dialysis on pregnancy

- The risks include:
  - Miscarriage
  - Intrauterine death
  - Hypertension and pre-eclampsia
  - Preterm labour
  - Preterm rupture of membranes
  - Polyhydramnios related to uraemia
  - Placental abruption
- Full heparinization requirements during haemodialysis increase the risk of bleeding.
- The specific problems with CAPD include peritonitis and limitation in the volume of exchanges in later pregnancy.

Management

- In women on haemodialysis, the duration and/or the frequency of dialysis must be increased to more than 20 hours/week, and often dialysis on 5–6 days per week.
- The aim should be to maintain the pre-dialysis urea at <17 mmol/L.
- Recent studies using intensified haemodialysis regimes with daily dialysis and >36 hours per week have achieved live birth rates of 85%.
- Dietary restrictions can usually be lifted, although continued adherence to fluid restriction is important to avoid large fluid shifts during dialysis.

Renal transplant recipients

- Women receiving renal transplants should be counselled that as renal function returns to normal (usually rapidly after successful transplantation), ovulation, menstruation and fertility also resume.
- Women desiring pregnancy are usually advised to delay pregnancy until 1 year after transplantation, by which time the graft function has stabilized and

maintenance levels of immunosuppressive drugs will have been reached, thus minimizing any risk to the fetus.
- Graft survival is improved for recipients of living, related donors compared to cadaveric donors.
- Successful pregnancy outcome for those transplant recipients who become pregnant and do not miscarry before 12 weeks is now >95%.
- Pregnancy outcome and effects on the renal allograft are both dependent on the baseline serum creatinine level and the presence of hypertension and proteinuria; the poorer the graft function at conception, the higher the risk of complications and deterioration in graft function.

Pregnancy

Effect of pregnancy on renal transplants

- Pregnancy has no adverse long-term effect on renal allograft function or survival in women with baseline creatinine levels <100 μmol/L.
- For women who enter pregnancy with a serum creatinine level >130 μmol/L, renal graft survival is only 65% at 3 years.
- Renal allografts adapt to pregnancy in the same way as normal kidneys and exhibit an increase in GFR and collecting-system dilatation. As with native kidneys, the GFR may decrease again in the third trimester.
- As with other causes of renal impairment, the risk of deterioration in renal function is increased in those with higher baseline serum creatinine, hypertension and/or proteinuria.
- More than 10% of women are likely to develop new long-term problems following pregnancy, although whether this is as a direct result of pregnancy is difficult to ascertain. The risk of long-term problems is higher in women developing pregnancy complications prior to 28 weeks' gestation.

Effect of renal transplants on pregnancy

- Outcome is optimal in those without hypertension, proteinuria or recent episodes of graft rejection and in those with normal or near-normal renal function (serum creatinine level <125 μmol/L).
- The chance of successful outcome beyond 12 weeks is 97% with a baseline creatinine level <125 μmol/L, but this is reduced to 75% if the baseline creatinine level is >125 μmol/L.
- The complication rate is higher for women with diabetes and for those with poor graft function.
- The risks of pre-eclampsia, FGR and preterm delivery are increased in the presence of renal impairment and hypertension. The incidence of a complicated pregnancy overall is about 50% and includes:
  - Hypertension/pre-eclampsia (20%–30%)
  - FGR (20%–30%)
  - Preterm delivery (45%–60%)
  - Infection, especially UTI
  - Graft rejection (2%)

Antenatal management

- Women should be jointly managed by nephrologists and obstetricians with expertise in the care of pregnant renal transplant recipients.
- Careful monitoring and control of blood pressure is important.
- Regular assessment of renal function and proteinuria is essential.
- A full blood count and liver function tests should also be checked regularly. Anaemia is common and haematinics should be prescribed. Maternal hypocalcaemia and hypercalcaemia are both potential problems, and calcium status should be carefully monitored. Doses of calcium and vitamin D may need to be altered in pregnancy.
- An MSU specimen should be taken and sent at each visit and any infection treated promptly. Some women require prophylactic antibiotics.
- The fetus should be monitored with regular US assessment of growth and Doppler assessment of uterine and umbilical circulation.
- Provided proteinuria is not accompanied by deteriorating renal function or hypertension, this is not an indication for delivery.
- The differential diagnoses of deteriorating renal function include:
  - Reversible causes e.g. infection (e.g. UTI), dehydration, obstruction
  - Pre-eclampsia
  - Calcineurin inhibitor (CNI) (tacrolimus/cyclosporin) nephrotoxicity
  - Acute and/or chronic rejection
- The features of acute rejection include:
  - Deteriorating renal function
  - Fever
  - Oliguria
  - Graft swelling and tenderness
  - Altered echogenicity of renal parenchyma and blurring of corticomedullary junction on US
- Definitive diagnosis of rejection is only possible with renal transplant biopsy.

Immunosuppressive therapy

- Women should be counselled pre-pregnancy about any necessary required changes in their drugs.
- They need reassurance regarding the relative safety of their drugs, as reduction or cessation of immunosuppressive therapy may provoke rejection.
- The levels of immunosuppressive drugs are maintained at pre-pregnancy levels. Regimes vary but include treatment with

Drugs safe in pregnancy	Drugs to avoid in pregnancy
– Prednisolone	–Mycophenolate mofetil (MMF)
– Azathioprine	–Sirolimus (rapamycin)
– Tacrolimus	
– Cyclosporin	

- The commonest combination used outside pregnancy is MMF plus tacrolimus.
- MMF is contraindicated in pregnancy as there is an increased risk of malformations (see Chapter 8). Provided graft function is stable, MMF is replaced with azathioprine prior to conception. Women are then advised to wait 3 months before conceiving to ensure continued stability.
- Side effects of prednisolone and azathioprine are discussed in Chapters 4 and 8, respectively.
- Azathioprine dose may be monitored via maternal white cell count.
- Both CNIs cyclosporin and tacrolimus appear to be safe for use in pregnancy and breastfeeding. Plasma levels should be measured regularly and doses may need to be increased in pregnancy. The risk of diabetes is increased with tacrolimus.
- Sirolimus is avoided if possible because of known toxicity in animals. Few data are available in human pregnancy and a potent adverse effect on wound healing is reported; however, successful pregnancies have been reported.

Delivery

- Caesarean section is only required for obstetric indications, although the overall section rate (50%–60%) is increased compared to background rates, largely because of increased rates of preterm delivery. The renal allograft does not obstruct vaginal delivery. If caesarean section is required this should ideally be performed by a consultant obstetrician, following previous discussion with a member of the surgical transplant team. A vertical incision on the abdomen is often used to avoid injury to the allograft.
- Prophylactic antibiotics should be given to cover any surgical procedure, including episiotomy.
- Parenteral steroids are necessary to cover labour if the woman is on maintenance steroids (see Chapter 4).

Neonatal problems

These are largely related to preterm delivery but also include the following:

- Transient reduced levels of T and B lymphocytes in neonates exposed to CNIs that normalize in a few months.
- Breastfeeding is not contraindicated with maternal use of tacrolimus, azathioprine or prednisolone. Breastfeeding does not slow the decline of infant tacrolimus levels from levels present at birth.

Acute kidney injury

Incidence

- AKI is uncommon in pregnancy (1%–3%), often undiagnosed, and in the United Kingdom most commonly associated with pre-eclampsia and postpartum haemorrhage.
- In the developing world, AKI is more common and remains a common cause of maternal mortality.

Renal transplants—points to remember

- If graft function is normal, pregnancy outcome is excellent and there is no adverse long-term effect on renal allograft function or survival.
- The chance of successful pregnancy outcome is reduced and the risk of long-term deterioration in graft function increased with poor baseline graft function.
- Pregnancy outcome is optimal in those without hypertension, proteinuria or recent episodes of graft rejection.
- The doses of immunosuppressive drugs are maintained at pre-pregnancy levels, but CNI doses may need to increase to maintain therapeutic levels.
- Prednisolone, azathioprine, cyclosporin and tacrolimus are safe for use in pregnancy and breastfeeding without any reported increase in the risk of congenital malformations. MMF and sirolimus are contraindicated.
- The risks of pre-eclampsia, graft rejection, FGR, preterm delivery and infection are increased.
- Caesarean section is only required for obstetric indications, but the rate is increased.
- Prophylactic antibiotics should be given for recurrent UTIs and to cover any surgical procedure.

- In the developed world, AKI is much less dangerous than iatrogenic fluid overload, particularly in the context of pre-eclampsia.

Clinical features

- AKI most commonly presents in the postpartum period.
- Anuria is unusual and should prompt a search for urinary retention, a blocked urinary catheter or damage to the ureters.
- Oliguria, especially intra- and postpartum, is common and does not indicate AKI. AKI is defined as a serum creatinine of >77 umol/L.
- Urea may rise in isolation following corticosteroid administration; this does not indicate AKI.
- The serum sodium level is low; there may be hyperkalaemia and a metabolic acidosis.
- Oliguria may be followed by a period of polyuria. This may occur physiologically after delivery or in the recovery phase of acute tubular necrosis.
- There may be evidence of pre-existing CKD.

Pathogenesis (see also Chapter 16, Table 16.13)

The causes of AKI in pregnancy include the following:

- *Infection*: Septic abortion, puerperal sepsis, rarely acute pyelonephritis
- *Blood loss*: Postpartum haemorrhage, abruption
- *Volume contraction*: Pre-eclampsia, eclampsia, hyperemesis gravidarum, diarrhoea
- *Post-renal failure*: Ureteric damage or obstruction
- *Drugs*: Non-steroidal anti-inflammatory drugs (NSAIDs), antibiotics

In many of these situations, there is an associated coagulopathy. The constellation of AKI, microangiopathic haemolytic anaemia and thrombocytopenia may be due to the following:

- Pre-eclampsia (see Chapter 1)
- Haemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome (7% have AKI) (see Chapter 11)
- Thrombotic thrombocytopenic purpura/haemolytic uraemic syndrome (HUS) (see Chapter 14)
- Acute fatty liver of pregnancy (see Chapter 11)

The commonest cause of AKI in the context of pre-eclampsia is HELLP syndrome (about 50%).

Diagnosis

- The underlying cause of AKI may be obvious, for example, in the case of abruption and postpartum hemorrhage, although abruption occurs in 16% of women with HELLP syndrome and this may be the true underlying cause.
- Blood loss may not be recognized or may be underestimated, and the diagnosis only made after clinical examination for signs of volume depletion (tachycardia, reduced skin turgor, reduced capillary refill, JVP (jugular venous pressure) not visible, dry tongue) or upon the finding of a low central venous pressure (CVP). Hypotension may be absent or masked by coexistent pre-eclampsia.
- The differentiation between pre-renal (volume depletion or blood loss) and renal (acute tubular or cortical necrosis) causes is important, since the treatment of each is different.
- Often AKI is seen postpartum, where there are features of pre-eclampsia with thrombocytopenia and differentiation of HELLP syndrome from HUS may be difficult.
- Pointers to HELLP syndrome, which is far more common, are abnormal liver function, a coagulopathy (not seen in HUS) and a lower grade haemolysis.
- Pointers to HUS are profound thrombocytopenia and florid microangiopathic haemolytic anaemia and the finding of abnormalities of complement.

Management

- This depends on the underlying cause, but in all cases accurate assessment of fluid balance, usually with a urinary catheter is essential. Measurements of fluid input and output should be made hourly. Venous blood gas, lactate, electrolytes and serum creatinine twice daily if creatinine rising.
- The treatment of pre-renal failure is adequate replacement of blood and fluid losses. Diuretics should be avoided until volume depletion has been corrected.
- NSAIDs should be avoided/discontinued.
- Any associated coagulopathy must be treated (see Chapter 14).
- Once volume depletion has been excluded or treated, fluids are infused at a rate of 20 mL/hour (to allow for insensible losses) plus the volume of the previous hour's urine output. This can be averaged out over 24 hours to allow for i.v. drug administration and equates to about 500 mL plus the total output of the previous day.

- Fluid overload must be prevented, especially in pre-eclampsia, because of the susceptibility of these women to pulmonary oedema (see Chapter 1).
- There is no place for 'fluid challenges' in the context of euvolaemia or a high or normal CVP.
- Acute tubular necrosis is reversible and supportive management is continued until recovery is apparent.
- Plasmapheresis is not needed for HELLP syndrome, which usually improves with conservative therapy. It is the treatment of choice for TTP (*thrombotic thrombocytopenic purpura*).

- Eculizumab is a recombinant, humanized, monoclonal antibody directed against C5. It has replaced plasma exchange as the gold standard in the management of complement-mediated primary aHUS (atypical hemolytic uremic syndrome).
- Dialysis may become necessary in AKI to prevent or treat uraemia, acidosis, hyperkalaemia or fluid overload, but a requirement for long-term renal replacement therapy is very unusual.

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2

The Cardio-Obstetric Team

Diana S. Wolfe

KEY POINTS

- Care of a pregnant woman with cardiac disease requires collaboration between various disciplines
- The multidisciplinary team bridges the gap in communication, promoting appropriate care of the pregnant cardiac patient
- Academic, administrative, and logistic support is needed to create a cardio-obstetric team at a given institution
- A "Triad" solution to improve maternal mortality due to cardiovascular disease includes patient education, universal cardiovascular disease screening, and a multidisciplinary team approach
- Advocacy for establishing a cardio-obstetric team should continue at local and national levels

Introduction

The concept of team effort to care for a patient is not novel, especially when there is a high risk of morbidity and mortality. The goal is to bring together skill sets from maternal-fetal medicine (MFM), cardiology, anesthesia, neonatology, and other subspecialties as needed to optimize patient care. Cardiovascular disease in pregnancy is the number one indirect obstetric cause of pregnancy-related mortality ratio in the United States [1]. The 2006–2010 pregnancy-related mortality ratio was 16.0 deaths per 100,000 live births, a total of 14.6% due to cardiovascular conditions and 11.8% due to cardiomyopathy [1]. Improved data collection of severe maternal morbidity and maternal near-miss (SMM/MNM) has illustrated that cardiac disease is a significant contributing indicator in the United States [2]. The definition of SMM/MNM has evolved from the initial WHO definition that attempted to establish a comparable description across facilities to encourage health quality improvement [13]. The 2011 SMM/MNM definition includes five disease-specific, four management, and seven organ dysfunction−based criteria including cardiovascular dysfunction. In the United States, the Centers for Disease Control and Prevention (CDC) uses a large all-payer hospital inpatient care database for SMM/MNM surveillance. These indicators are based on three guiding principles [3]:

1. State-level availability of data in most states, territories, and large metropolitan areas
2. Presence of an established evidence base in the literature
3. Quality of the indicator was sufficient for population level surveillance and the planning and evaluation of public health interventions

A validation study of the CDC SMM/MNM index was applied to 67,468 deliveries across 16 California hospitals and found a sensitivity of 0.99 and a positive predictive value of 0.44 [4]. The American College of Obstetricians and Gynecologists (ACOG) and the Alliance for Innovation on Maternal Health updated the 2009 set of 25 CDC SMM/MNM indicators [3]. Based on the revised 21 indicator index, rates for the majority of SMM/MNM indicators increased in the United States between 1993–2014 [4]. Acute myocardial infarction was among those indicators that increased. This information implies the need for public health surveillance and clinical audit to ultimately improve quality obstetric care. A team of experts is required to care for complex obstetric patients including the cardiac pregnant patient.

Multidisciplinary Team

The *cardio-obstetric team* comprises a multidisciplinary team of the patient, physicians, nurses, and administration that includes the following team members at the minimum: MFM, cardiology, anesthesia, neonatology, labor and delivery (L&D), and critical care staff. The approach mirrors the "heart team" model, traditionally known as a team of cardiologists and cardiothoracic surgeons who manage most at-risk cardiac surgical patients [5]. The pregnancy heart team is now employed internationally, and outlined in the most recent European Society of Cardiology Guidelines [6]. The mobilization of this framework came from the devastating findings of the U.S. maternal mortality rate in recent years whereby cardiac disease is the number one contributor in the United States [1]. Due to the complexity of the cardiac pregnant patient, an exchange of expertise and knowledge among experts including MFM and cardiology is strongly advisable to optimize maternal and fetal outcomes.

Our Experience

At Einstein/Montefiore in the Bronx, New York, we created an MFM–Cardiology outpatient joint program in February 2015 in response to the rising contribution of cardiovascular conditions to pregnancy-related morbidity and mortality [1]. The aim was to establish a multidisciplinary program to optimize the care of high-risk pregnant patients with known or suspected cardiac disease. In these instances, there is a real potential for communication barriers or gaps in care when specialists individually see patients at different times, locations, and/or health systems.

To create a cardio-obstetric team, an institution needs administrative and academic support from both departments, i.e., obstetrics and gynecology and cardiology. The office space where patients are seen is a key component because it has to be designed to accommodate both maternal and fetal testing. The logistics including billing are often a challenge because each specialty and its staff are most accustomed to their own needs for detailed physical exam and testing. However, a collaborative environment can be established with administrative support from both specialties. Trainee participation is key to modeling this multidisciplinary work and therefore academic support to build this into fellows' required rotations is recommended. In addition to the outpatient setting described, an inpatient team is essential for management of the pregnant cardiac patient.

At Einstein/Montefiore we have established an outpatient cardio-obstetric team that is composed of both MFM and cardiology attendings and fellows who see patients together in the same space at least 3 times per month. The cardiologists include subspecialists in interventional cardiology, noninvasive imaging, and congenital heart disease. The space where we see our patients has multiple expert areas within cardiology including pulmonary hypertension, heart failure, electrophysiology, and so on. Our office is able to provide a risk assessment through both maternal and fetal assessment. We have cardiac testing readily available including echocardiogram, EKG, pacemaker interrogation, and other vascular studies including lower extremity Doppler studies. We utilize sonograms and Doppler tones to assess fetal well-being as well as fetal echocardiography study within the same space. Our examination rooms consist of a gynecology table with the appropriate lighting and examination tools to provide for our pregnant patients and also to serve our postpartum and preconception patients. In this environment, as a team, together we have the ability to establish risk assessment each trimester (Table 2.1) and commence delivery planning. For our postpartum

TABLE 2.1

Sample Pregnancy Follow-Up Checklist

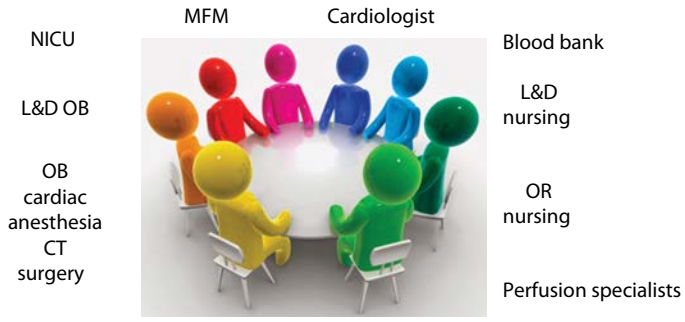
	Frequency of Follow-Up		
	Cardiologist	**Laboratory**	**Diagnostic Testing**
First trimester	☐ Once ☐ Every 4 weeks ☐ Every 2 weeks ☐ Every week	☐ BNP ☐ CBC ☐ TSH ☐ INR ☐ Other	☐ EKG ☐ Echocardiogram ☐ Holter monitor ☐ Exercise stress test ☐ Other
☐ Pregnancy termination			
Second trimester	☐ Once ☐ Every 4 weeks ☐ Every 2 weeks ☐ Every week	☐ BNP ☐ CBC ☐ TSH ☐ INR ☐ Other	☐ EKG ☐ Echocardiogram ☐ Holter monitor ☐ Exercise stress test ☐ Other
☐ Anesthesia consultation ☐ Multidisciplinary meeting ☐ Delivery planning ☐ Contraception plan			
Third trimester	☐ Once ☐ Every 4 weeks ☐ Every 2 weeks ☐ Every week	☐ BNP ☐ CBC ☐ TSH ☐ INR ☐ Other	☐ EKG ☐ Echocardiogram ☐ Holter monitor ☐ Other
☐ Contraception ☐ Medication review ☐ Follow-up plan with cardiology			
Postpartum	☐ 1 week ☐ 2 weeks ☐ 4 weeks	☐ BNP ☐ CBC ☐ TSH ☐ INR ☐ Other	☐ EKG ☐ Echocardiogram ☐ Holter monitor ☐ Other

Abbreviations: BNP, B-type natriuretic peptide; CBC, complete blood count; TSH, thyroid stimulating hormone; INR, international normalized ratio; EKG, electrocardiogram.

and preconception patients, reproductive life planning and birth control counseling is emphasized. The team demonstrates their collaboration to the patient, delivering the same message, clarifying any confusion while they are counseled in person by both MFM and cardiology. In addition to our outpatient team, we have an inpatient cardio-obstetric team where the delivery plans are finalized. We meet monthly in the cardiac intensive care conference room. All members of the team are represented to review the major concerns and exchange an understanding of both cardiac and obstetric risks (Figure 2.1). We use a template (see Figure 2.2) to present the case and a review checklist as a reminder of all aspects of the intrapartum and peripartum time period.

The checklist begins with a description of the pathophysiology of the patient and a review of their cardiac history including surgeries and any comorbidities. Step 2 is to review of all imaging studies. This will raise any major concerns and culminate an exchange of thoughts from MFM, cardiology, anesthesia, and L&D staff to think through the possible scenarios during labor and delivery. This leads to the next steps, which involve choosing timing and location of delivery. At Einstein/Montefiore, most of our patients deliver by 39 weeks at our larger location, where we have a cardiac intensive care unit (CICU) and therefore cardiology consult available 24/7. Very few patients require delivery outside of L&D, that is, main operating room or CICU. Your institution should assess the safest place for these patients and consider where and when all equipment and experts are readily available. We deliver our patients at 39 weeks or earlier due to need for a scheduled delivery where the most skilled experts, including nursing, for the specific cardiac pathology are available. The L&D nurse at our institution is not telemetry trained and therefore we often have two nurses monitoring our patient—obstetrics and CICU nursing. Equipment is readily available on L&D to manage indwelling pacemakers and implantable defibrillators, as an example. For the rare case that may require delivery outside of the L&D unit, cesarean delivery and neonatal trays are housed adjacent to or inside the patient's room for any unforeseen emergency. Cardiac medications and those on L&D for various indications are reviewed with the team to assess their

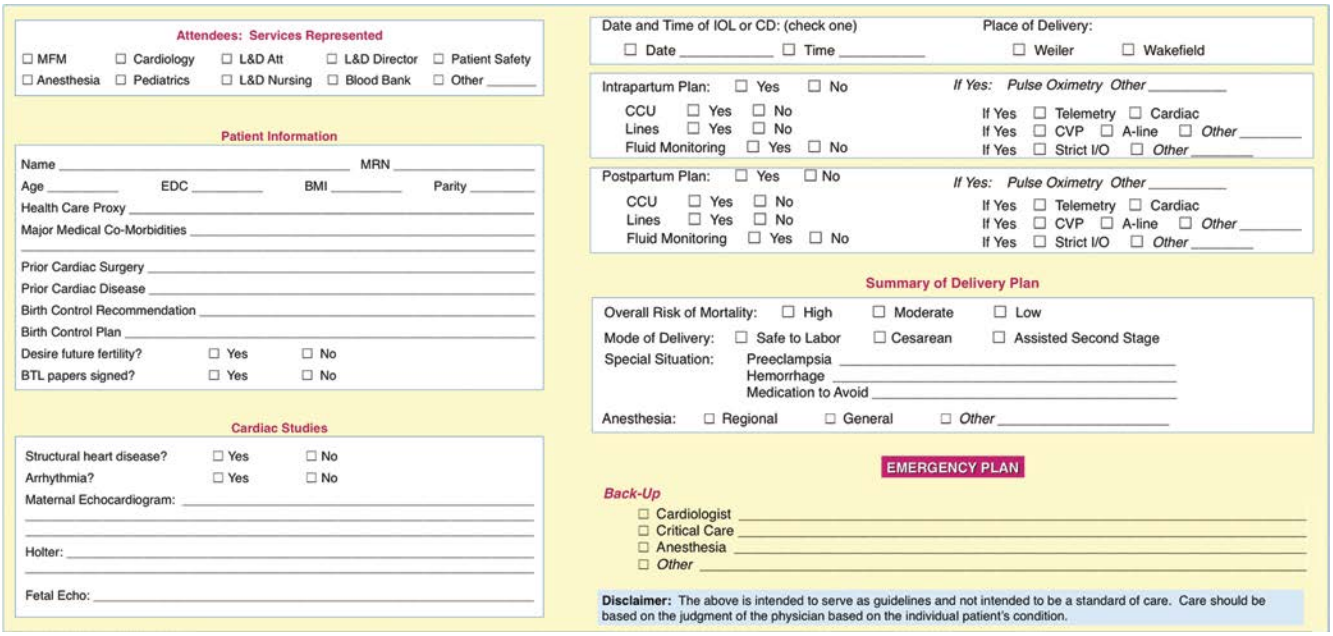
(a)



(b)

Team Member	Role
Maternal-fetal medicine	1. Present the patient 2. Present obstetric concerns 3. Determine safe management in labor and postpartum
Cardiologist	1. Present the cardiac pathophysiology 2. Review the cardiac studies with team 3. Determine safe management in labor and postpartum
Neonatology	Availability for receival of fetus at time of delivery
Blood bank	All blood products available
Labor and delivery OB staff	Availability to deliver patient
Labor and delivery OB Nursing	Coordinate 1:1 nursing at delivery and postpartum
Cardiac and obstetric Anesthesia	Tailor safe anesthesia plan, cardiac monitoring
OR nursing	Coordinate delivery and cardiac monitoring
Cardiothoracic surgery	Availability where risk of CT surgery warranted
Perfusion specialists	Availability where risk of heart failure elevated

FIGURE 2.1 Cardio-obstetric team: (a) Personnel; (b) roles.



Attendees: Services Represented

☐ MFM ☐ Cardiology ☐ L&D Att ☐ L&D Director ☐ Patient Safety
☐ Anesthesia ☐ Pediatrics ☐ L&D Nursing ☐ Blood Bank ☐ Other _____

Patient Information

Name _____ MRN _____
Age _____ EDC _____ BMI _____ Parity _____
Health Care Proxy _____
Major Medical Co-Morbidities _____
Prior Cardiac Surgery _____
Prior Cardiac Disease _____
Birth Control Recommendation _____
Birth Control Plan _____
Desire future fertility? ☐ Yes ☐ No
BTL papers signed? ☐ Yes ☐ No

Cardiac Studies

Structural heart disease? ☐ Yes ☐ No
Arrhythmia? ☐ Yes ☐ No
Maternal Echocardiogram: _____
Holter: _____
Fetal Echo: _____

Date and Time of IOL or CD: (check one) Place of Delivery:
☐ Date _____ ☐ Time _____ ☐ Weiler ☐ Wakefield

Intrapartum Plan: ☐ Yes ☐ No *If Yes: Pulse Oximetry Other* _____
CCU ☐ Yes ☐ No If Yes ☐ Telemetry ☐ Cardiac
Lines ☐ Yes ☐ No If Yes ☐ CVP ☐ A-line ☐ *Other* _____
Fluid Monitoring ☐ Yes ☐ No If Yes ☐ Strict I/O ☐ *Other* _____

Postpartum Plan: ☐ Yes ☐ No *If Yes: Pulse Oximetry Other* _____
CCU ☐ Yes ☐ No If Yes ☐ Telemetry ☐ Cardiac
Lines ☐ Yes ☐ No If Yes ☐ CVP ☐ A-line ☐ *Other* _____
Fluid Monitoring ☐ Yes ☐ No If Yes ☐ Strict I/O ☐ *Other* _____

Summary of Delivery Plan

Overall Risk of Mortality: ☐ High ☐ Moderate ☐ Low
Mode of Delivery: ☐ Safe to Labor ☐ Cesarean ☐ Assisted Second Stage
Special Situation: Preeclampsia _____
Hemorrhage _____
Medication to Avoid _____
Anesthesia: ☐ Regional ☐ General ☐ *Other* _____

EMERGENCY PLAN

Back-Up
☐ Cardiologist _____
☐ Critical Care _____
☐ Anesthesia _____
☐ *Other* _____

Disclaimer: The above is intended to serve as guidelines and not intended to be a standard of care. Care should be based on the judgment of the physician based on the individual patient's condition.

FIGURE 2.2 Multidisciplinary labor and delivery planning list.

maternal and neonatal safety in collaboration with pharmacy specialists and the neonatal team. Postpartum need for cardiac medications should be individualized for nursing mothers based on the indications and compatibility with breastfeeding.

I recommend advocating for a cardio-obstetric team within your community to increase referrals to your institution and ultimately to establish safe motherhood. Suggestions include speaking at Grand Rounds within your home institution as well as your city and region. Creation of continuing medical education courses within your community can attract the attention of providers and lead to positive collaborations. An emphasis on patient education and why screening for cardiovascular disease should be universal for all pregnant and postpartum patients is beneficial. Patient education should include a review of the normal physiological changes and symptoms that occur in pregnancy, including its impact on the heart. Patients with cardiac disease need to be advised about warning signs that should prompt them to seek medical attention, because benign symptoms of pregnancy may mimic worsening cardiac disease. In addition, patients need to be counseled that a cesarean delivery is not an absolute requirement for all patients with cardiac disease, and that a normal spontaneous vaginal delivery and breastfeeding postpartum are optimal [7].

The Triad

A triad solution (Figure 2.3) including patient education, cardiovascular screening, and the multidisciplinary team has been proposed to address maternal mortality and morbidity associated with cardiovascular disease of pregnancy [7]. Preconception counseling for all women with known heart disease is recommended. Review of their reproductive goals and an understanding of their disease and potential physiologic cardiac changes in a future pregnancy is recommended [8,9]. A contraceptive plan is essential to optimize

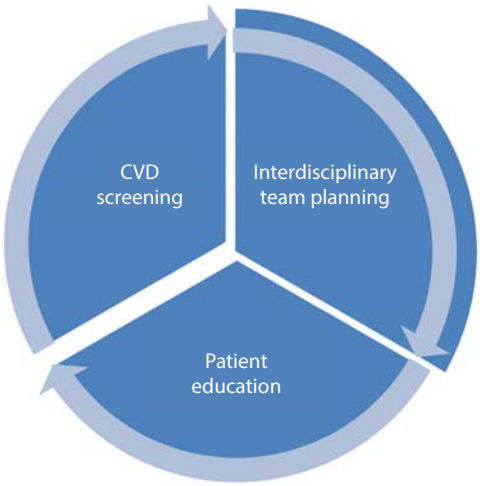


FIGURE 2.3 Triad algorithm: Patient education, screening, maternal cardiology team.

pregnancy planning and birth spacing [10]. This counseling can be done in a multidisciplinary setting whereby a cardiologist and MFM subspecialist can assess the patient's options together. The third aspect of the triad is a cardiovascular screening toolkit that has been proposed by the California Maternal Quality Care Collaborative based on a retrospective review of peripartum cardiomyopathy case deaths [11]. This screening tool is used to identify pregnant and postpartum patients at risk for cardiovascular disease who therefore need to be referred to the maternal cardiology team. It is well established that many symptoms of pregnancy overlap common symptoms of heart disease. The challenge of distinguishing between the two has been proposed in Table 6.1 of the Practice Bulletin on Pregnancy and Heart Disease, ACOG [12]; see Chapter 6 of this book.

Conclusion

High-risk cardiac patients contemplating pregnancy or who are currently pregnant should have expedited, streamlined evaluation by cardiology and MFM specialists. The team approach as supported by ACC/AHA guideline includes collaboration with cardiology, MFM/obstetricians, anesthesiologists, cardiothoracic surgery, and additional subspecialists as needed. The cardio-obstetric team (Figure 2.1) and the multidisciplinary planning list (Figure 2.2) provide key components needed to create a cardio-obstetric team and how to utilize available resources to achieve an appropriate level of care for the pregnant cardiac patient.

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19

Safety Aspects of Ultrasound Scanning

Kelly Tilleman

Brief History on the Covering and Cleaning of the Endovaginal Probe

In the mid-1990s, the American Institute of Ultrasound in Medicine invoked a multidisciplinary task force to tackle the reprocessing of vaginal ultrasound probes between patients. Although very few scientific data existed on the microbial contamination of the probes at that time, it was quite obvious that cleaning the probe with detergent/water should be the cornerstone of the disinfection, since the probes could not be autoclaved as vaginal specula could. The use of chemical disinfection could provide an additional margin of safety and would help in the further reduction in microbial load; however, there were at that time concerns on the toxicity of the chemicals used to both the patient and the sonographers [1]. Ultrasound covers were already routinely used at that time; however, the effectiveness of this barrier in daily clinical practice was not well known. Although these covers sometimes showed small ruptures or breaks after the clinical investigation, a true estimate of the failure rate was unknown. An early study by Rooks et al. [2] demonstrated an 8.3% perforation rate in probe covers and a 1.7% perforation rate in latex condoms by performing a standard leak test by filling the covers or condoms with water. This study already showed the superior quality of condoms, which were a cheaper alternative than the commercially available probe covers. A large study by Milki and Fisch [3] tested more than 800 nonlubricated latex condoms that were used as ultrasound covers and demonstrated a perforation rate of 2%. Although these data were known at that time, apparently not all practitioners routinely disinfected the probes after use because they did not observe any obvious blood or vaginal secretions on the probe, and so it was concluded that the use of a cover was sufficient.

Because of the perforation rate of covers and condoms, both the study of Milki and Fisch [3] and Rooks et al. [2] clearly underlined the use of a germicidal spray or the use of a soaked cloth for disinfection after removal of the cover, since the possibility of microscopic bacterial contamination could not be excluded.

Endovaginal Probe as Semicritical Device

Semicritical devices come directly in contact with mucous membranes or nonintact skin, and these devices should be free from all microorganisms; however, small numbers of bacterial spores are permissible. Since the use of probe covers in transvaginal (TV) ultrasounds made it possible to keep the probe from directly contacting the patient, the ultrasound probe was actually first categorized as a noncritical device. When probe covers were introduced in routine ultrasound practices and changed between every patient, it was considered that a low-level disinfection (LLD) would be sufficient. Since several studies clearly demonstrated that the probe covers were prone to perforation, the guideline for disinfection from the Centers for Disease Control and Prevention (CDC) recommended that even if probe covers were used, the ultrasound probe was to be defined as a semicritical device; thus, the probe had to be first cleaned and subsequently a high-level disinfection (HLD) had to be performed (recommendation 10a; [4]) to ensure the removal of all microorganisms.

Bacterial Contamination of Endovaginal Ultrasound Probe

Results in the literature determine that HLD disinfection is necessary to make sure that ultrasound probes are free of contaminated bacterial flora. Almost all TV probes show bacterial growth when

sampled after removal of the probe cover and before disinfection or even after LLD [5]. The microbial testing reveals mostly environmental contaminants, microorganisms originating from vaginal or skin flora. Even after manual disinfection, nosocomial pathogens like *Staphylococcus aureus*, *Klebsiella pneumonia*, *Pseudomonas* spp., or *Escherichia coli* can be identified on ultrasound probes [5–7]. Ngu et al. [6] identified a large portion of isolates containing *S. aureus*, and one of these isolates was found to be methicillin-resistant *S. aureus* (MRSA). Additionally, causative agents of urinary tract infections like *S. aureus*, *S. haemolyticus*, *S. saprophyticus*, and *E. faecium* can be found on TV transducers after manual LLD [6]. Likewise, Westerway et al. [8] showed remaining species derived from normal skin flora of environmental organisms after LLD. When ultrasound probes in this study were subsequently subjected to manual HDL, no bacterial contamination could be found. The authors of these studies already discussed the variability in the residual contamination after manual disinfection, related to the sonographer's compliance with disinfecting procedure. Studies that have included automated disinfection illustrate this to be superior to manual HLD disinfection. The risk for bacterial contamination after manual disinfection was 2.9-fold higher than the risk after automated disinfection using a Trophon EPR automated system in the study of Buescher et al. [5]. Similarly, the use of a disinfection apparatus using ultraviolet-C (UVC) light (Antigermix device) resulted in TV probes where neither bacterial nor viral flora could be detected [9]. Not only can pathogenic microorganisms reside on ultrasound transducers, reports on the presence of human papillomavirus (HPV) gained interest in more recent literature.

Human Papillomavirus Contamination of Endovaginal Ultrasound Probe

The gynecological environment can become contaminated by HPV from health-care workers' hands and gloves. There is, however, conflicting evidence for HPV transmission, and while skin-to-skin and mucosa-to-mucosa contact, predominantly by sexual intercourse, is the most frequent route of transmission, other routes might be involved [10]. HPV can persist in the environment and on medical equipment even after disinfection. The close contact between the transvaginal probe and the cervix uteri or vaginal wall can be a potential risk for transmission of sexually transmitted infections, such as HPV [11].

HPV persists on the probe after disinfection with LLD despite the covering of the probe; thus, LLD is clearly inadequate for preventing contamination of the ultrasound probe [11]. This study found 3.5% HPV DNA positive samples of which 6% were positive for HPV 53, 16, 58, and 31. When the results were analyzed in a successive mode, it was shown that HPV 58 was detected in three out of four subsequent samples suggesting a persistent probe contamination despite each disinfection round. In the second study period, 2.8% were HPV DNA positive, and again, high-risk HPV 53 was detected in the positive samples. Similarly, the study from Ma et al. [12] observed that 7.5% of the TV ultrasound transducers were positive for HPV after disinfection using T-Spray, a quaternary ammonia-based spray.

Not only are ultrasound transducers or handles prone to contamination risk, but the vast majority of gynecological equipment is apparently contaminated with HPV [10].

And even when chemicals are used that are categorized as HLD, they seem to be ineffective against HPV [13,14]. This means that the current guidelines for HLD might not be sufficient in eradicating HPV from TV probes. Although HPV DNA detection does not mean HPV virulence, and consequently, no infectivity of HPV is shown in any of the previously mentioned cross-sectional studies, it is clear that HPV is quite difficult to eliminate.

Recent data show two validation studies using an automated disinfection machine for the complete removal of microorganisms and HPV: one apparatus uses UVC (Antigermix device) [13], and one uses sonicated hydrogen peroxide (Trophon EPR) [14]. These reports present preclinical efficacy for removal of HPV by using a hard surface carrier test in comparison to using chemicals that have been classified as HLD by the CDC (recommendation 10a; [4]). The results of the studies undoubtedly show the possibility for these two automated devices to completely remove and inactivate HPV, as these are the only studies including an HPV infectivity assay [13,14]. See further Table 19.1.

TABLE 19.1

Overview of Cross-Sectional Studies Cited on the Risk of Probe Contamination Following Endovaginal Ultrasound from the Bacterial or Viral Perspective

Study Details	Setting, Population, and Load Tested	Covers Used	Disinfection Used	Method of Sampling	Results	Remarks and Conclusions
Ngu et al. [6]	Single center, prospective study, cross-sectional study, 77 samples GDHO, 75 GDHH • Bacterial contamination	Type of transducers used: not specified, covers used: not specified	The probe: first cleaned with detergent and water, dried with paper towel, then soaking 2.4% GD (GDHO) or automated disinfection using Trophon EPR (using hydrogen peroxide) where both handle and probe are disinfected (GDHH)	Cotton swab dipped in tryptone soya broth, identification by VITEK device (biomérieux)	80.5% of GDHO versus 5.3 of GDHH showed contamination, most of them associated with health-care infections (*Staphylococcus aureus* and one MRSA)	Ultrasound transducer handles might become contaminated if they are not disinfected HLD methods should include disinfecting the entire transducer. Automated disinfection is more effective than manual disinfection
Buescher et al. [5]	Prospective randomized controlled clinical study, 120 samples pre- and postdisinfection using manual disinfection, 120 samples after Trophon EPR disinfection • Bacterial contamination	TV: transducer covers: not specified	Manual (Mikrozid-sensitive wipes containing quaternary ammonium compounds), Trophon EPR (using hydrogen peroxide)	Polywipe premoistened sponge swabs incubated overnight at 36°C applied to blood-and MacConkey-Agar overnight incubated, next MALDI-TOF analysis for identification	95.4% of the samples before disinfection were positive. After automatic disinfection: 8.6% contaminated, after manual disinfection: 21.2% contaminated	Disinfection reduces bacterial contamination, and automated disinfection shows advantages over manual disinfection
Westerway et al. [8]	Prospective blinded single center study (two ultrasound units), 171 samples were taken before disinfection and after LLD and after LLD and HLD Sampling was also done on the ultrasound unit and on coupling gel • Bacterial contamination	TV: latex condom TA: vinyl cover	Manual LLD using an alcohol-based wipe or HLD by immersion in 2.4% GD	Culture swabs were plated on nutrient agar and incubated at 37°C overnight. CFU were counted and subsequently identified by MALDI-TOF or by PCR	60% TA and 14% TV were positive after removal of the cover. After LLD, 3% (TA) and 4% (TV) were positive. No contamination detected in TV after LLD and HLD	HLD is more effective than LLD. The ultrasound apparatus (keyboard, cord) needs disinfection. Gels are a source of bacterial contamination

(*Continued*)

TABLE 19.1 (*Continued*)

Overview of Cross-Sectional Studies Cited on the Risk of Probe Contamination Following Endovaginal Ultrasound from the Bacterial or Viral Perspective

Study Details	Setting, Population, and Load Tested	Covers Used	Disinfection Used	Method of Sampling	Results	Remarks and Conclusions
Casalegno et al. [11]	Single center, prospective study, two study periods; period 1: 200 samples, period 2: 217 samples • Viral (HPV) contamination	TV: disposable probe cover (93/42/EEC CE mark)	Disinfection wipes (sani-cloth active) (containing quaternary ammonium compounds)	Sampling by dry swab, subsequently submerged in EMEM transport medium; DNA extraction (NucliSens easyMAG), genotyping via microarrays (Genomica SAU)	Period 1: 3.5% HV DNA positive Period 2: 2.5% HPV DNA positive	LLD is not sufficient for complete disinfection. HPV DNA detection ≠ HPV virulence. Dry swabbing could result in sensitivity loss for HPV detection
Ma et al. [12]	Two-part cross-sectional study: 2 periods: part 1 (surveillance): 120 samples; part 2: 14 samples originating from TV ultrasound probes used in known HPV+ females • Viral (HPV) contamination	Latex condom	Disinfection with T-spray containing quaternary ammonia	Cotton wool swabs, DNA extraction (QIAamp DNA mini kit), PCR (PGMY09–11)	Part 1: 7.5% HPV positive; Part 2: 21.4% HPV positive	Most positive HPV samples were in the first 20 days of the study. Possibly a more thorough disinfection was performed when staff were aware of the study
Gallay et al. [10]	Cross-sectional study in two centers (public hospital and private setting), 179 samples on gynecological equipment and surfaces • Viral (HPV) contamination	No data	HLD, no further specification	Sampling by flocked swabs submerged in 1 mL PBS saline DNA extraction and identification using real-time PCR (Anyplex II HPV28 test)	18% of samples were HPV DNA positive	Detection of HPV more frequent in samples from private center. Lamp, glove box, specula, and gel tubes were positive for HPV DNA

Abbreviations: CFU, colony-forming units; EMEM, Eagle's minimum essential medium; GD, glutaraldehyde; GDHH, glutaraldehyde disinfection head and handle; GDHO, glutaraldehyde disinfection head only; HLD, high-level disinfection; LLD, low-level disinfection; MRSA, methicillin-resistant *Staphylococcus aureus*; MALDI-TOF, matrix-assisted laser desorption ionization-time of flight; TA, transabdominal; TV, transvaginal.

Clinical Practice in Endovaginal Ultrasound Disinfection

Disinfectants Used

When looking at the literature, a wide variety of chemicals are used for disinfecting ultrasound probes: solutions containing glutaraldehyde, quaternary ammonium salts, peracetic acid, and hydrogen peroxide. All these solutions have to bear a disinfecting activity and be compatible with the functionality of the transducer. Some chemicals can shorten the lifespan of the probe, and insufficient rinsing after using these chemicals can result in a higher risk for irritation to the patient due to damage of the mucosa. HLD chemicals are tested for the removal of bacterial species; however, some studies have shown that glutaraldehyde and orthophthalaldehyde do not have virucidal activity against certain HPV types [13,14]. Nonchemical alternatives, like UVC (Antigermix device) or treatments with H_2O_2 nanodroplets (Trophon EPR automated system) have therefore gained interest and have been shown to be effective in completely disinfecting the probe and removing all bacterial and viral contamination [5,9].

Many hospitals have an infection control department in charge of procedures concerning the overall cleanliness in the hospital, sanitization, and sterilization. It is important to contact this department for information on the disinfectants to be used on semicritical devices such as TV ultrasound probes. On an individual basis, a sonographer could also contact the manufacturer of the disinfectants and the ultrasound machines to get information about utilization of the disinfecting agents and kits.

The Sonographers' Performance

The limited amount of studies on the effectiveness of manual disinfection of TV transducers clearly shows that there is an operator link to the quality of the disinfection. In most studies, the staff was aware of the study, and this aids the compliance to the standard operating procedure (SOP) for disinfection of the probe. Although the cleaning and disinfection of an ultrasound probe might seem futile in the broader package of sonographers' tasks, there is a risk that the disinfection fails simply due to lack of education and training. Knowledge of the disinfecting agents used, compliance to disinfection SOP, especially considering the contact exposure time of the disinfecting chemicals on the probe, and a short literature overview of the possible remaining bacterial and viral load on the probes after disinfecting will reduce the risk of contamination and support the patient safety in ultrasound practice. The study of Ngu et al. [6] clearly showed the importance of the disinfection of the ultrasound handle alongside of the disinfection of the probe. Likewise, data from Buescher et al. [5] showed that disinfection of the handle and the probe (e.g., during automated disinfection) resulted in a 91.4% success rate of disinfection, where manual disinfection had a 78.8% success rate. Finally, Westerway et al. [8] demonstrated high levels of bacterial contamination on the ultrasound unit (keyboards, probe wire) and ultrasound gel. Although most contamination originated from human commensals and environmental species, there was evidence of potential pathogenic species on the keyboard of the ultrasound machine.

Step-by-Step Manual Disinfection Procedure

After the scan has been performed, use new gloves to perform the disinfection procedure and remove the probe cover. First clean the probe by removing any visible remaining residues by using a paper towel or an impregnated cloth (Figure 19.1a). A simple paper towel can already remove 40%–45% of the bacterial load. The use of physiological saline solution reduces the microorganisms further to 76%, and water-soap can eliminate up to 96% of the bacteria [15]. When a soaked cloth has been used, the probe has to be carefully rubbed dry using a paper towel. Next, disinfect the probe by immersing the probe in an HLD agent (Figure 19.1b). If immersing is not possible, then gently rubbing the probe with an impregnated cloth is necessary. It is important to check the desired contact time of the chemical used in order to sufficiently decontaminate the surface (Figure 19.1c). Finally, leave the probe to dry. Next, use new gloves to disinfect the handle of the ultrasound probe. Additionally, disinfect the ultrasound apparatus (keyboard and wire) in

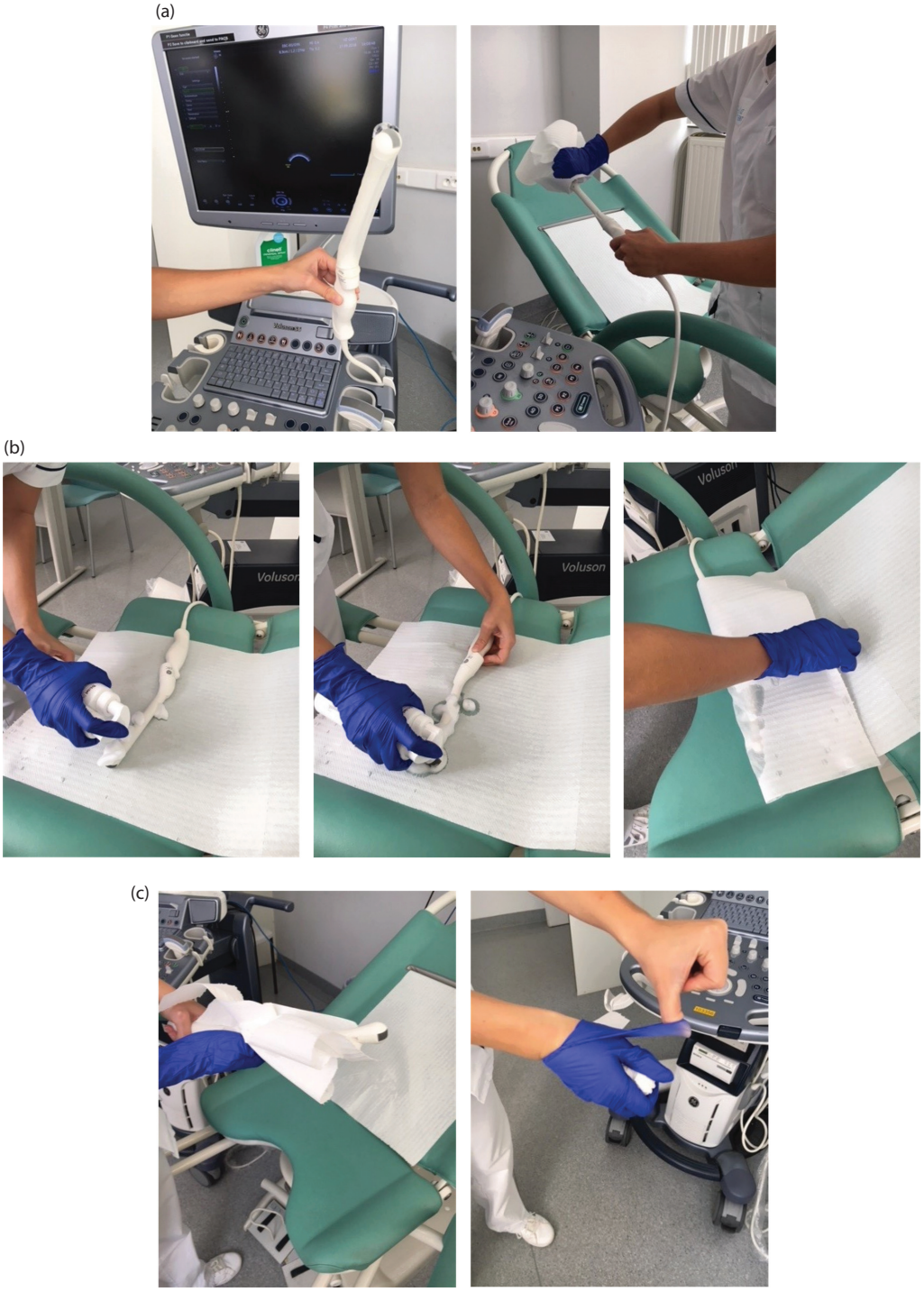

FIGURE 19.1 A step-by-step example of a disinfection protocol: (a) Remove the probe cover and first clean the probe by removing any visible remaining residues by using a paper towel or an impregnated cloth. (b) Disinfect the probe by immersing or covering the probe in a high-level disinfection agent and respect the contact time or gently rub the probe with an impregnated cloth according to the manufacturer's guidelines. (c) If necessary when soaking or covering has been executed, remove the disinfectant with a paper cloth and leave the probe to dry. After disinfecting the probe, new gloves should be used to manually disinfect the handle, the cord, and/or the keyboard.

between patients and, if possible, use single-dose coupling gels. Endorse a vigorous hand hygiene protocol while performing the ultrasound procedure, and take care that during or after the disinfection procedure the transducer, the handle, or the ultrasound unit are not recontaminated.

Conclusion and Published Guidelines

Although there is a limited number of studies in the literature on the disinfection of ultrasound probes, it is clear that recently this subject has gained interest. It is clear that TV probes require HDL disinfection, whereas abdominal probes could still be considered noncritical devices, as abdominal probes do not come directly in contact with mucous membranes or nonintact skin. For the latter, an LLD is sufficient [4].

In order to find out if your disinfection protocol is effective and your staff is adhering to the protocol, a simple practical audit can be carried out. A disinfection exercise was carried out in our fertility department where a total of 71 samples of TV ultrasound probes were analyzed. The samples were taken during a daily practice ultrasound program for controlled ovarian stimulation in fertility patients. After removal of the cover and HLD disinfection, ultrasound probes were sampled by pressing down and rolling the head of the transducer onto a RODAC (replicate organism detection and counting) dish. After 48 hours, mass spectrometry analysis was used for identification of the bacterial residual load. Results showed that the majority of the probes (60.5% [43/71]) were negative, and an average 1.9 colony forming units (CFUs) (min: 0; max: 42) were detected. The majority of the bacterial contaminants originated from skin flora or from environmental contamination, being coagulase-negative staphylococci, micrococci, and *Corynebacterium* sp. (unpublished data from Ghent University Hospital). It was clear that although our protocol consisted of a validated HLD method, the performance of the disinfection procedure among the staff was quite different. A dedicated periodic training in manual disinfection was recommended to aid the consistency of the procedure and to contribute to patient safety. Moreover, an automatic disinfection omits the operator variability of the manual disinfection procedure, additionally reducing the risk for the subsequent use of contaminated ultrasound probes.

Since national guidelines and legislation regulating disinfection procedures vary throughout Europe, the European Society of Radiology Ultrasound Working Group recently published best recommendations on infection prevention and control in ultrasound [16]. The paper is a coherent overview of the transmission risk of infection through ultrasound procedures and describes the normal skin microbial flora and potential pathogens varying from site to site in the human body. There are extensive definitions of the decontamination procedures, and recommendations on disinfection are unambiguously listed. Likewise, the World Federation for Ultrasound in Medicine and Biology (WFUMB) published their guidelines for cleaning transvaginal ultrasound transducers between patients [17]. This document cites relevant disinfecting chemicals and explains how they are effective in eradicating certain bacterial and viral species and spores. Precautions while using these chemicals are mentioned alongside recommendations on the practicalities of disinfection, and automatic disinfection systems (UVC) (Antigermix device) or Trophon EPR are explained [17]. As ultrasound practitioners do not always know which patients carry transmissible pathogens or who may be susceptible to acquiring infections, implementation of clear disinfection recommendations will reassure patients and contribute to their quality of care [16]. Additionally, it is advisable to keep information in the medical file of the disinfection products used and the sonographer or nurse performing the disinfection. These data should be part of traceability and general record keeping.

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18

Obstetric Outcomes after Recurrent Pregnancy Loss

Rakefet Yoeli-Ullman, Howard J.A. Carp, and Shali Mazaki-Tovi

Introduction

Recurrent pregnancy loss (RPL) is one of the most challenging conditions in reproductive medicine for patients and physicians alike. The overwhelming majority of research conducted in this field explores the etiologies, methods of prediction, and treatment for prevention of this frustrating condition. The conventional view is that once the patient with previous RPL passes the first trimester, the risk of major complications is not significantly increased. However, over the last decade evidence has emerged demonstrating a link between RPL and several complications of pregnancy including preterm birth, pre-eclampsia, fetal growth restriction, gestational diabetes mellitus, fetal anomalies, placental abruption, and perinatal mortality. The rationale for this association hinges on several observations: (i) Both recurrent pregnancy loss and several complication of pregnancy share similar risk factors and predisposing conditions, (ii) observational studies have highlighted the relationship between these two conditions, (iii) epidemiological studies have identified recurrent pregnancy loss as a significant and independent risk factor for several complications of pregnancy, and (iv) similar treatments have been shown to be effective for both recurrent pregnancy loss and some of the complications of pregnancy. This chapter presents the available evidence for the association between recurrent pregnancy loss and several common and important complications of pregnancy, to suggest a plausible explanation(s) for this association and to critically appraise the literature.

Spontaneous Preterm Labor

Contradicting evidence exists regarding the association between spontaneous preterm birth and recurrent pregnancy loss (Table 18.1). Several studies do not distinguish between induced and spontaneous preterm birth. Furthermore, both RPL and several complications of pregnancy that are frequently managed with iatrogenic preterm induction of labor (e.g., preeclampsia, fetal growth restriction, etc.) share the same risk factors, thus adding an additional layer of complexity in the attempt to decipher the genuine relationship between these conditions.

Hughes et al. [1] examined the obstetric outcome in 88 women with a past history of three or more consecutive pregnancy losses and compared the results to a control group drawn from their local obstetric population. The rate of preterm delivery (12.5%) was no different than the control group. Sheiner et al. [2] conducted a population-based study in which all singleton pregnancies were assessed in women with and without two or more consecutive recurrent miscarriages. The study included 154,294 singleton deliveries. Of these deliveries, 7503 occurred in patients with recurrent miscarriage. Spontaneous preterm birth did not differ significantly between the two groups, although the rate of preterm premature rupture of membranes (PPROM) was significantly higher in the study group compared to controls (6.5% vs. 5.6%, respectively; $p < 0.001$).

Two randomized trials of special note were conducted in which the rate of preterm birth was relatively low compared to the general population. Schleussner et al. [3] conducted a multicenter, randomized controlled trial including 449 women with at least two consecutive early miscarriages or one late miscarriage. Women in the intervention group received 5000 IU of dalteparin sodium for up to 24 weeks'

TABLE 18.1

Association between RPL and Spontaneous Preterm Labor

	Study Group (*n*)	Control (*n*)	PTL in Study Group (%)	PTL in Controls (%)	*p*	Comments
Hughes et al. [1]	88	12,590	11/88 (12.5%)	1075/12,590 (8.5%)	NS	
Cozzolino [40]	53	65	6/53 (11.3%)	1/65 (1.5%)	$p = 0.05$	OR 8.17; CI 0.95−70.1
Sheiner [2]	$n = 7503$	$n = 146{,}791$	6.5%	5.6%	$p < 0.001$	PPROM
Schleussner [3]	Total = 449 Study group (dalteparin) $n = 226$ Control (no treatment) $n = 223$	No control	Total: 38/449 (8.5%) Study group: 20/226 (8.8%) Control: 18/223 (8%)	No control		
Kaandorp [4]	Total ongoing pregnancies $n = 200$ Aspirin+ nadroparin $n = 69$ Aspirin $n = 61$, Placebo $n = 70$	No control	Total: 11/200 (5.5%) Aspirin+ nadroparin: 7/69 (10.1%) Aspirin: 1/61 (1.6%) Placebo: 3/70 (4.3%)			
Shapira [47]	Total $n = 306$ Primary RPL $n = 123$ Secondary RPL $n = 183$	No control	Total: 47/306 (15.3%) Primary RPL: 26/123 (21.1%) Secondary RPL: 21/182 (11.5%)			
Reginald [5]	$n = 175$	Normal population	28%		$p < 0.05$	
Tulppala [6]	$n = 63$	No control	9.7%			
Jivraj [7]	$n = 162$	$n = 24{,}699$	22/162 (13%)	959/24,699 (3.9%)	$p < 0.01$	
Thom [8]	$n = 583$	$n = 2820$	63/583 (11.1%)	220/2820 (7.8%)		RR 1.5; 95% CI 1.1−2.1
Brown [16]	One previous miscarriage $n = 6105$ Two previous miscarriages $n = 1813$ ≥ 3 previous miscarriages $n = 978$	$n = 44{,}308$				One: OR 1.7; CI 1.52−1.83 Two: OR 2.0; CI 1.73−2.37 ≥ 3: OR 3; CI 2.47−3.70
Hammoud [17]	One previous miscarriage $n = 5973$ Two miscarriages $n = 908$ Three or more miscarriages $n = 225$	$n = 52{,}280$	One: 527/5973 (8.8%) Two: 90/908 (9.9%) Three or more: 32/225 (14.2%)	3552/52,280 (6.8%)	$p < 0.001$	

gestation. The rate of preterm birth was 8.8% in the study group and 8% in the controls ($p = 0.24$), a rather low rate by any standard. Similarly, Kaandorp et al. [4] reported the results of a randomized trial that included 364 women who had a history of unexplained recurrent miscarriage and were attempting to conceive or were less than 6 weeks pregnant. Participants were randomly allocated to receive 80 mg of aspirin plus subcutaneous nadroparin daily, 80 mg of aspirin alone, or placebo. The rate of preterm birth was 10.1%, 1.6%, and 4.3%, respectively. In a pooled analysis, the rate of preterm birth was only 5.5%, a very low rate for the general population in the Netherlands, where the study was conducted.

In contrast, others have found an association between preterm birth and recurrent pregnancy loss. Reginald et al. [5], in a retrospective observational cohort study, assessed the results of 175 pregnancies in 97 recurrently miscarrying women whose subsequent pregnancy progressed beyond 28 weeks. The results were not compared with a control group attending the same hospital, but with standard figures from Scotland between the years 1973–1979. A significantly higher prevalence of preterm deliveries was found. Tulppala et al. [6] conducted a prospective study of 63 women with recurrent miscarriage and presented the results of a detailed investigative protocol, including antiphospholipid syndrome. The rate of preterm delivery (9.7%) appeared to be increased. Unfortunately, the results were not compared to any control population. Jivraj et al. [7] studied a cohort of 162 women with recurrent miscarriage compared to the local control population from 1992 to 1998. Among a total of 162 pregnancies that progressed beyond 24 weeks gestation in women with a history of recurrent miscarriage, there were 22 (13%) preterm deliveries compared with 959 (3.9%) in the 24,699 controls ($p < 0.01$). Thom et al. [8] analyzed Washington State birth certificate records for 1984–1987 to examine the association between spontaneous abortion, recurrent miscarriage, and adverse outcomes in the subsequent live birth. The results of 638 women with three or more miscarriages were compared to those of women with no prior spontaneous abortions ($n = 3099$). Women with recurrent pregnancy loss had a higher risk of delivery at less than 37 weeks' gestation (relative risk 1.5; 95% confidence interval [CI] 1.1–2.1). Importantly, several epidemiological studies have identified recurrent preterm birth as a significant risk factor for preterm birth [9–15].

Two more recent studies have supported the association between preterm birth and recurrent pregnancy loss by demonstrating a "dose-dependent effect." Brown et al. [16] examined live singleton births using data from the United States Collaborative Perinatal Project. Compared with women with no history of miscarriage, women who had one, two, or three or more previous abortions were 1.7 (95% CI 1.52–1.83), 2.0 (95% CI 1.73–2.37), and 3.0 (95% CI 2.47–3.70) times more likely to have preterm birth (defined as delivery <37 weeks of gestation), respectively. These results remained significant after control for obstetric and medical history and lifestyle and demographic factors. Hammoud et al. [17] analyzed data from the perinatal database collected from the state of Schleswig-Holstein, Germany. During the years 1991–1997 there were 170,254 deliveries and 59,386 nulliparas with singleton pregnancies. Among the 59,386 (38%) nulliparous patients included, 5973 (10.1%) had a history of one miscarriage, 908 (1.5%) had a history of two previous miscarriages, and 225 (0.4%) had a history of three or more previous miscarriages. The risk of preterm delivery increases with the increasing number of previous spontaneous miscarriages. Compared to women with no history of miscarriages (3552/6.8%), women who had one (527/8.8%), two (90/9.9%), or three (32/14.2%) previous abortions were more likely to have preterm birth ($p < 0.001$). A similar increase was found in the rate of PPROM: controls: 1354/2.6% versus one 192/3.2%, two 46/5.1%, and three 15/6.7% previous miscarriages ($p < 0.001$). Logistic regression analysis was performed correcting for smoking status, maternal age, and obesity. Patients with a history of three or more previous miscarriages had a risk of preterm delivery of more than twice that of women with no such history (OR 2.46; CI = 1.68–3.60).

Although the cause of the association between recurrent pregnancy loss and preterm birth has not been elucidated, there are several possible explanations. Uterine evacuation, by either mechanical dilatation or osmotic dilatation of the cervix, may explain the association. Saccone et al. [18] reported the results of a systematic review and meta-analysis of 36 studies (1,047,683 women). Women with a history of uterine evacuation had a significantly higher risk of preterm birth (5.7% vs. 5.0%; OR 1.44; 95% CI 1.09–1.90) than controls. The authors concluded that a prior surgical uterine evacuation is an independent risk factor for preterm birth. Similar findings were reported by Lemmers et al. [19] from a systematic review and meta-analysis of 21 studies including 1,853,017 women. Lemmers et al. [19] asked whether dilatation and curettage (D&C) increases the risk of subsequent preterm birth. D&C increased the odds ratio (OR) for

preterm birth. The OR was 1.29 (95% CI 1.17–1.42) if a 37-week cutoff was used. This risk was 1.69 (95% CI 1.20–2.38) for 32 weeks and 1.68 (95% CI 1.47–1.92) for 28 weeks of gestation. The risk remained increased when the control group was women with medically managed miscarriage or induced abortion (OR 1.19; 95% CI 1.10–1.28). When women with multiple D&Cs were compared to women with no D&C, the OR for preterm birth (>37 weeks) was 1.74 (95% CI 1.10–2.76). For spontaneous preterm birth, the OR was 1.44 (95% CI 1.22–1.69). Collectively, these data may suggest a causal relationship between prior surgical uterine evacuation and subsequent preterm birth. Additional risk factors that have been implicated in both RPL and preterm birth are uterine malformation [20] and infections (i.e., bacterial vaginosis and endocervical infections) [21].

Preeclampsia and Pregnancy-Induced Hypertension

Hughes et al. [1] examined the obstetric outcome in 88 women with a past history of three or more consecutive pregnancy losses and compared the results to a control group drawn from their local obstetric population (see Table 18.2). The rate of preeclampsia appeared to be similar in both groups (2.3% vs. 2.6%, respectively). Similarly, Jivraj et al. [7], who studied a cohort of 162 women with recurrent miscarriage compared to local controls, found no difference in the rate of pregnancy-induced hypertension or preeclampsia (6.7%) between the two groups. Sheiner et al. [2] reported a similar rate of preeclampsia in 7503 pregnant women with RPL and 146,791 controls (3.5% in both groups; OR 1; 95% CI 0.9–1.2). Of note, there was a significant difference in the rate of severe preeclampsia between the pregnant women with and without RPL (1.6% vs. 1.1%; OR 1.5; 95% CI 1.3–1.8; $p < 0.001$)

Consistent with these reports, several recent multicenter randomized trials have found a low rate of preeclampsia in patients with RPL. Schleussner et al. [3] reported that the rate of preeclampsia was 3/226 women in the intervention group (treated with 5000 IU of dalteparin sodium) and 6/223 in the controls (1.3% vs. 2.6%; $p = 0.74$). Kaandorp et al. [4] reported that the rate of preeclampsia was 2.9%, 1.6%, and 1.4% in pregnant women with a history of unexplained recurrent miscarriage treated with daily 80 mg of aspirin plus nadroparin, 80 mg of aspirin alone, or placebo, respectively. Of note, there was only one case of HELLP syndrome out of 364 participants.

Trogstad et al. [22] conducted a cohort study based on the Norwegian Mother and Child Cohort Study, a large population-based pregnancy cohort. The sample consisted of 20,846 singleton pregnancies in nulliparous women between the years 1999–2005. The authors found an increased risk of preeclampsia following three or more miscarriages but not after one or two miscarriages. The association was statistically significant only when combined with a history of infertility treatment (OR 2.4; 95% CI 1.11–5.18). Further support for the association between RPL and preeclampsia came from Weintraub et al. [23] who reported a case-control study designed to evaluate the prevalence of pregnancy complications in a live birth preceding the appearance of recurrent miscarriages. Women who had at least two consecutive spontaneous miscarriages after one live birth ($n = 58$) were matched with controls, women without recurrent miscarriages ($n = 232$). A statistically significant higher rate of preeclampsia (mild and severe) was found in a live birth preceding recurrent miscarriages than in the matched controls (10.3 vs. 3.9%; $p = 0.04$).

The association between preeclampsia and unexplained recurrent miscarriages may be due to endothelial dysfunction. Germain et al. [24] determined brachial arterial reactivity and factors related to endothelial dysfunction, such as circulating cholesterol, uric acid, nitrites, L-arginine, vascular endothelial growth factor, and soluble vascular endothelial growth factor receptor-1, in women with previous healthy pregnancies ($n = 22$), patients with severe preeclampsia ($n = 25$), and patients with RPL ($n = 29$). A significant decrease in endothelium-dependent dilatation was found in the preeclampsia (40%) and RPL (45%) groups compared to the controls (4.5%). In addition, lower serum nitrites and higher cholesterol were found in both study groups as compared to control subjects.

An additional putative mechanism linking preeclampsia and recurrent pregnancy loss is obesity. Obesity has been associated with both recurrent pregnancy loss [25,26] and preeclampsia [27,28]. A two- to fourfold higher prevalence of preeclampsia has been reported in obese patients [29]. A meta-analysis focusing on maternal BMI and preeclampsia has shown that the risk of preeclampsia is doubled with each 5–7 kg/m^2

TABLE 18.2

Association between RPL and Preeclampsia/Pregnancy-Induced Hypertension

	Study Group (*n*)	Control (*n*)	Rate of PET/PIH in Study Group (%)	Rate of PET/PIH in Control (%)	*p*	Comments
Hughes et al. [1]	88	$N = 15{,}590$	2/88 (2.3%)	333/15,590 (2.1%)	NS	PET
Jivraj [7]	162	$N = 24{,}699$	13/162 (8%)	2643/24,699 (10.7%)	NS	Hypertensive related disorders
Sheiner [2]	7503	$N = 146{,}791$	Mild PET: 3.5% Severe PET: 1.6%	Mild PET 3.4% Severe PET 1.1%	NS $P < 0.001$	
Schleussner [3]	Total: 449 Dalteparin: 226 Control (no RX): 223	No control	Total: 9/449 (2%) Study group: 3/226 (1.3%) Control: 6/223 (2.6%)			PET
Kaandorp [4]	Ongoing pregnancies: 200 Aspirin+ nadroparin: 69 Aspirin: 61 Placebo: 70	No control	Total: 4/200 (2%) Aspirin+ nadroparin: 2/69 (2.9%) Aspirin: 1/61 (1.6%) Placebo: 1/70 (1.4%)			PET
Shapira [47]	Total: $n = 306$ Primary RPL $n = 123$ Secondary RPL $n = 183$	No control	Total: 20/306 (6.5%) Primary RPL: 9/123 (7.4%) Secondary RPL: 11/183 (6%)			
Trogstad [22]	Total: 3159 One miscarriage: 2556 Two miscarriages: 473 $\geq$3 miscarriages: 130	$N = 17{,}687$	Total: 165/3159 (5.2%) One: 133/2556 (5.2%) Two: 21/473 (4.4%) Three: 11/130 (8.5%)	956/17687 (5.4%)	NS	
Cozzolino [40]	53	65	PIH: 2/53 (3.8%) PET: 1/53 (1.9%)	PIH 2/65 (3.1%) PET 1/65 (1.5%)	NS NS	
Weintraub [23]	58	232	6/58 (10.3%)	9/232 (3.9%)	$P = 0.04$	PET in the pregnancy preceding RPL

increase in BMI [30]. Several explanations have been proposed to explain the association between obesity and RPL: (i) Excess adipose tissue can produce a hypoxic state by increasing the concentrations of glycosylated hemoglobin and decreasing the affinity for oxygen. This relative hypoxemia may cause abnormal placentation leading to miscarriage in severe cases and preeclampsia if more moderate [31]. (ii) Subclinical inflammation is a hallmark of obesity, and an exaggerated inflammatory response may predispose women to both preeclampsia and recurrent pregnancy loss. (iii) Obese pregnant women have a three- to tenfold higher risk of preexisting hypertension or diabetes compared to those of normal weight.

Finally, several common and important pathophysiological mechanisms and predisposing factors have been implicated in both conditions including antiphospholipid syndrome [32], thrombophilia [33,34], endocrine disorders [35], fetal and maternal genetic mismatch [36], and immunologic abnormalities [37,38].

Intrauterine Growth Restriction and Small for Gestational Age

Hughes et al. [1] examined the obstetric outcome in 88 women with a past history of three or more consecutive pregnancy losses and compared the results to a control group drawn from their local obstetric population (see Table 18.3). The prevalence of small for gestational age (SGA) infants (3.4%) was no different than the control group. Sheiner et al. [2] conducted one of the largest population-based studies regarding the association between RPL and intrauterine growth restriction (IUGR)/SGA. This study included 7503 patients with recurrent miscarriage and 146,791 controls. The rate of IUGR was identical (2%) in both groups.

As with other complications of pregnancy, there is evidence to support the association between IUGR and RPL. Reginald et al. [5], in a retrospective observational cohort study, assessed the results of 175 pregnancies in 97 recurrently miscarrying women whose subsequent pregnancy progressed beyond 28 weeks. The results were compared with standard figures from Scotland between the years 1973–1979. They reported a 30% incidence of intrauterine growth restriction representing a relative risk of 3 compared to the standard Scottish population. Tulppala et al. [6] conducted a prospective study in 63 women with recurrent miscarriage. The results were not compared to any control population. The prevalence of fetal growth restriction (20%) appeared to be increased. Similarly, Thom et al. [8] quoted a relative risk (RR) of 2.0 (95% CI 1.4–2.8) for IUGR.

Basso et al. [9] analyzed a Danish population-based registry consisting of 45,449 women having a live birth preceded by one or more spontaneous miscarriages and a random sample of 9752 women with two consecutive live births. They reported an increased risk for IUGR in patients with two or more miscarriages (OR 1.4; 95% CI 1.2–1.6). Similarly, Jivraj et al. [7], who studied a cohort of 162 women with recurrent miscarriage compared to local controls, found a significant difference in the rate of SGA in patients with or without RPL (13% vs. 2.1%, respectively).

Preeclampsia SGA or IUGR may have similar causes, including failure of physiologic transformation of the spiral arteries, an antiangiogenic state, endothelial cell dysfunction, and an increased maternal intravascular inflammatory response. Thus, the same factors that predispose patients with RPL to developing preeclampsia may affect fetal growth and cause IUGR. Notably, it has been proposed that the presence of altered metabolic states including obesity, insulin resistance, and dyslipidemia predisposes pregnant women to develop preeclampsia, while the absence of these metabolic alterations will result in an SGA or IUGR neonate [39].

Gestational Diabetes Mellitus

Cozzolino et al. [40] performed a retrospective cohort study investigating adverse pregnancy outcomes in women with RPL ($n = 53$) compared to a control group of couples attending a low-risk antenatal unit ($n = 65$) (see Table 18.4). Women with previous RPL had a significantly increased risk of gestational diabetes with 12 cases (22.6%) in the study group and 3 cases (4.6%) in the control group (OR 6.04; 95% CI 1.60–22.76; $p = 0.007$). Romero et al. [41] used fructosamine as an indicator of mean blood glucose

TABLE 18.3

Association between RPL, IUGR, and SGA

	Study Group (*n*)	Control (*n*)	IUGR in Study Group	IUGR in Controls	*p*	Comments
Hughes et al. [1]	88	12,590	3/88 (3.4%)	180/12,590 (1.4%)	NS	
Sheiner [2]	7503	146,791	2%	2%	NS	
Cozzolino [40]	53	65	4/53 (7.5%)	3/65 (4.6%)	NS	
Schleussner [3]	Total: 449 Dalteparin: 226 Control (no RX): 223	No control	Total: 11/449 (2.4%) Dalteparin: 5/226 (2.2%) Control: 6/223 (2.6%)			IUGR or placental insufficiency
Kaandorp [4]	Total ongoing pregnancies: 200 Aspirin+ nadroparin: 69 Aspirin: 61 Placebo: 70	No control	Total: 18/200 (9%) Aspirin+ nadroparin: 6/69)8.7%(Aspirin: 7/61 (11.5%) Placebo: 5/70 (7.1%)			
Shapira [47]	Total: 306 Primary RPL: 123 Secondary RPL: 183	No control	Total: 14/306 (4.5%) Primary RPL: 11/123 (8.9%) Secondary RPL: 3/183 1.6%)			
Reginald [5]	175	Normal obstetric population	30%			Prevalence of IUGR was 3 times higher in study group compared to controls
Tulppala [6]	63	No controls	20%			
Thom [8]	631	$N = 3065$	60/631 (9.5%)	141/3065 (4.6)	RR 2.0, CI 1.4–2.8	
Basso [9]	45,449	9752				Increased risk for IUGR with $\geq$2 miscarriages OR 1.4; CI 1.2–1.6
Jivraj [7]	162	24,699	21/162 (13%)	523/24,699 (2.1%)	$<$0.001	

TABLE 18.4

Association between RPL and Gestational Diabetes Mellitus

	Study Group (*n*)	Control (*n*)	GDM in Study Group	GDM in Controls	*p*	Comments
Cozzolino [40]	53	65	12/53 (22.6%)	3/65 (4.6%)	$P = 0.007$	OR 6.04; CI 1.60–22.76
Romero [41]	117	117	3/117 (2.5%)	0/117	NS	GDM defined according to fructosamine levels
Vaquero [42]	Total $n = 82$ Prednisone and aspirin $n = 29$ IVIG $n = 53$	No control	Total 5/63 (7.9%) Prednisone and aspirin 3/22 (14%) IVIG 2/41 (5%)			
Shapira [47]	Total $n = 306$ Primary RPL $n = 123$ Secondary RPL $n = 183$	No control	Total 43/306 (14%) Primary RPL 24/123 (19.5%) Secondary RPL 19/183 (10.4%)			
Hughes [1]	$N = 88$	$N = 12{,}590$	15/88 (17%)	359/12,590 (2.8%)	$P < 0.05$	
Sheiner [2]	$N = 7503$	$N = 146{,}791$	8.6%	4.3%	$P < 0.001$	
Tulppala [6]	$N = 63$	No control	22.8%			
Jivraj [7]	$N = 162$	$N = 24{,}699$	3/162 (1.8%)	198/24,699 (0.8%)	NS	

in a study including 117 women with unexplained RPL, and no more than one live birth, and 117 age-matched controls with at least one full-term uncomplicated pregnancy and no more than one pregnancy loss. The mean fructosamine concentration was higher in women with RPL (224.1 ± 28.79 μmol/mL) compared with controls (188.9 ± 19.3 μmol/mL, $P < 0.001$). This difference persisted when RPL patients and controls were stratified according to BMI. However, the proportion of women with elevated fructosamine (>285 μmol/L) was similar in RPL patients and controls.

Vaquero et al. [42] reported the results of a prospective, two-center trial study that included 82 women with RPL and antiphospholipid syndrome. Twenty-nine were treated with prednisone and low-dose aspirin in one center and 53 received IVIG in the other center. In the prednisone plus low-dose aspirin-treated patients, gestational diabetes was found significantly more often than in the IVIG-treated group (14% vs. 5%, $p < 0.05$). Clearly one cannot exclude the diabetogenic effect of prednisone to account for this finding. The association between RPL and gestational diabetes has also been reported by Hughes et al. [1] (study group 17% vs. 2.8% in controls, $p < 0.05$) and Sheiner et al. [2] (study group 8.6% vs. 4.3% in controls, $p < 0.001$).

The molecular mechanism(s) that may account for the association between RPL and gestational diabetes has not been fully determined. However, an interesting publication may shed new light on this relationship. Andraweera et al. [43] investigated the association of the fat mass and the obesity associated gene (FTO) rs9939609 single nucleotide polymorphism with recurrent miscarriage. This was a candidate gene association study including 202 Sinhalese women with two or more first trimester miscarriages and no living children and 202 age- and ethnicity-matched women with no history of miscarriage and having two or more living children. The prevalence of the AA genotype and A allele of the FTO rs9939609 single nucleotide polymorphism was increased in women with recurrent miscarriage compared with the controls (AA: OR 3.8; 95% CI 1.8–8.0; $p = 0.0002$; A: OR 1.6; 95% CI 1.2–2.2; $p = 0.002$).

Fetal Anomalies

The data regarding the association between RPL and congenital anomalies are scarce. Thom et al. [8] examined the Washington State birth certificate records and included 638 women with three or more miscarriages and a control group of women with no prior miscarriages ($n = 3099$). Women with RPL had a higher risk of delivering a child with congenital malformations (RR 1.8; 95% CI 1.1–3.0). The Recurrent Miscarriage Immunotherapy Trialists Group trial [44] showed an anomaly rate of 4%, which is higher than expected in the general population. Schoenbaum et al. [45] reviewed 5003 records of consecutive deliveries in 1975 and 1976 at the Boston Hospital for Women and analyzed singleton deliveries at 27 weeks' gestation or greater. They compared women with exactly one prior proximate induced or spontaneous abortion with women of similar gravidity or parity with no prior pregnancy losses. The offspring of women with a proximate miscarriage had an increased incidence of congenital malformations. Finally, there are a few case reports reporting that chromosomal aberrations lead to both RPL and fetal anomalies [46]. Today, with the advances in ultrasonic detection of fetal malformations, many patients elect to terminate the pregnancy. Consequently, today the incidence of anomalies at birth may not be higher than in the general population.

Placental Abruption

Only two case-control studies have compared the incidence of placental abruption in patients with and without RPL. Neither Thom et al. [8] nor Sheiner et al. [2] found an increased risk of placental abruption in women with RPL. However, if both studies are pooled the common odds ratio for abruption is significant: 5.8 (CI 5.1–6.6).

In contrast to the report of Sheiner et al. [2] and the aforementioned pooled analysis, two multicenter randomized trials have found a very low prevalence of placental abruption in patients with RPL. Schleussner et al. [3] reported that the prevalence of placental abruption was 0/226 women in the intervention group (treated with 5000 IU of dalteparin) and 1/223 in the controls (0% vs. 0.4%; $p = 0.5$). Kaandorp et al.

[4] did not find a single case of placental abruption in a study that included of 364 patients with RPL. Of note, Kaandorp et al. [4] excluded patients with aPL from the study.

The group of Shapira et al. [47], in a retrospective cohort study of 420 patients with two or more consecutive pregnancy losses, found no significant difference in the incidence of abruption in the subsequent (index) pregnancy in 162 primary aborters and 258 secondary aborters (2.4% and 0.5%, respectively; $p = 0.3$).

Perinatal Mortality

Only a few studies have reported on the association between prenatal death and RPL, and none has reported an increased risk of this complication. Hughes et al. [1] reported that perinatal mortality rate was 0/88 (0%) in women with a past history of three or more consecutive pregnancy losses and 0.46% in the control group. Jivraj et al. [7] reported a perinatal mortality rate of 2/162 (1.2%) in women with recurrent miscarriage compared to 247/24,699 (1.0%) in controls. Importantly, Jivraj et al.'s [7] study only included pregnancies that progressed beyond 24 weeks' gestation. Sheiner et al. [2] conducted the largest population-based study addressing the association between RPL and perinatal death. The prevalence of perinatal mortality was 1.7% among 7503 patients with recurrent miscarriage and 1.4% in 146,791 controls ($p = 0.12$).

Van Oppenraaij et al. [49] reported the results of several studies in which the rate of perinatal mortality was determined in women with a single miscarriage. These studies found an increased risk of intrauterine fetal death (OR 1.9; 95% CI 1.1–3.6) and an increased risk of neonatal death (OR 2.2; 95% CI 1.1–4.8) [8,45,48]. As previously mentioned, this higher risk for perinatal mortality was not found in studies including patients with two or more miscarriages.

Conclusions

Patients with RPL seem to be at increased risk for developing several complications of pregnancy. Nevertheless, this conclusion should be interpreted with caution because (i) the syndromic nature of RPL (i.e., multiple etiologies and numerous underling mechanisms of disease) critically hampers the external validity of many studies, (ii) the available data are insufficient to claim cause and effect, (iii) the literature is sparse and the findings in the literature are inconsistent, and (iv) there are no interventional studies comparing patients with and without RPL to determine whether treatment for the prevention of gestational complications is effective in this set of patients. Despite these limitations, we recommend active prenatal care and not to regard these patients as "low risk." The role of preventative treatment for obstetric complications (e.g., low-dose aspirin for the prevention of preeclampsia, or frequent sonographic cervical length measurements to prevent preterm labor) is debatable. Prospective and interventional, well-designed studies are necessary in order to identify RPL patients at increased risk for obstetric complications and provide individualized and effective treatment.

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3

Dietary Factors and Uterine Fibroids

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Dietary factors may play a role in fibroid etiology due to their potential to modify endogenous hormones as well as their inflammatory effects; however, few studies have examined diet and UL risk, and few clear dietary associations have been established. Characteristics of the peer-reviewed studies that have examined dietary factors and uterine fibroids though June 2016 are provided in Table 3.1, and the observed associations are summarized in Table 3.2.

Fruits and Vegetables

Fruits and vegetables contain vitamins, minerals, antioxidants and phytochemicals that may decrease fibroid risk. One of the most consistent associations between diet and fibroid risk has been with fruit and vegetable consumption (Table 3.3). The prospective Black Women's Health Study (BWHS) cohort and case-control studies in China and Italy all reported decreased risk of fibroids with fruit and vegetable intake [1–4]. Specifically, the BWHS reported a statistically significant decreased risk with total fruits and vegetables combined, with a stronger association for fruits than vegetables, which appeared to be driven by a significant inverse association with citrus fruits [2]. He et al. also reported a significant inverse association with total fruit and vegetable intake [1], while Shen et al. reported significant inverse associations for broccoli, cabbage, Chinese cabbage, tomatoes and apples [4], and Chiaffarino et al. reported a significant inverse association with fresh fruit and green vegetable consumption [3]. Animal data have suggested that lycopene, a carotenoid with strong antioxidant properties, decreases fibroid risk [5]. However, in both case-control and cohort studies, lycopene, other carotenoids, vitamins C and E, folate and fiber did not explain the decreased risk observed with fruits and vegetables [2,6,7]. The BWHS observed an inverse association with dietary vitamin A and fibroids risk that appeared to be driven by preformed vitamin A, not pro-vitamin A carotenoids [2]. In contrast, a cross-sectional study in the National Health and Nutrition Examination Survey examined serum micronutrient levels and reported higher serum vitamin A concentrations among women with fibroids compared to those without, but no serum difference was observed for other carotenoids or micronutrients [8].

Dietary Fat

Trans fat intake influences circulating levels of IL-6, IL-1β, TNF-α and other inflammatory markers [9–11], and markers including IL-6, IL-1 and TNF-α have been reported to influence the secretion of enzymes that digest endometrial extracellular matrices [12]. In contrast, dietary intake and plasma levels of omega-3 fatty acids have been inversely associated with inflammatory cytokines, including IL-6, TNF-α and TNF-α receptors [13,14]. Omega-6 fatty acids have also been hypothesized to reduce fibroid risk through their anti-inflammatory properties. However, few studies have examined the associations between dietary fats and fibroid risk [3,7,15]. The BWHS examined the association between dietary fats and fibroid risk, reporting statistically significant increased risks of fibroids with intake of specific long-chain omega-3 fatty acids but no significant associations with total fat or other fat subtypes [15]. However, no associations between dietary fats and fibroids were observed in a cross-sectional study of Japanese women enrolled through a health check-up program [7] or in an Italian case-control study that examined butter, margarine and oil intake [12].

Dairy Foods

Dairy foods also contain multiple components that may protect against fibroids through their anti-tumorigenic and

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TABLE 3.1

Summary of Previous Observational Studies on Dietary Factors and Fibroid Risk

Author/Year	Study Name/Type	Number of Fibroid Cases and Controls or Total Study Population	Dietary or Biomarker Assessment Method	Exposure(s) Evaluated	Exposure Categorization	Adjustment Variables
Questionnaire-based dietary assessment						
Shen 2016 [4]	Hospital-based case-control study, Nanjing, China	600 fibroid cases; 600 controls	Questionnaire	Green tea, honey, coffee, green onions, vitamin D, garlic, strawberries, grapes, cranberries, blueberries, walnuts, pomegranate, broccoli, cabbage, cauliflower, Chinese cabbage, turnip, tomatoes, watermelon, pawpaw, lemon, onions, apples	Frequent, occasional, no consumption	Age, education
Wise 2014 [15]	Prospective cohort 2001–2009, Black Women's Health Study	2,695 incident fibroid cases; 12,044 participants at start of follow-up	85-item food frequency questionnaire (FFQ)	Total fat, saturated fat, monounsaturated fat, polyunsaturated fat, omega-6 fatty acid intake, omega-3 fatty acid intake, ratio of omega-6 to omega-3 fatty acids, trans fats, all fish/seafood, dark-meat fish, other fish/seafood	Quintiles of intake for fats; Quartiles of intake for fish/seafood	Age, questionnaire cycle, energy intake, age at menarche, parity, age at first birth, years since last birth, ever use of oral contraceptives, age at first oral contraceptive use, alcohol, smoking, body mass index (BMI), education, occupation, income, marital status, US region of residence
He 2013 [1]	Hospital-based case-control study, Beijing, China	73 fibroid cases; 210 controls	Short-form FFQ	Cereals, soy, meat, fish, dairy food, eggs, vegetables and fruits, desserts, fried food, salty food	High (more than 3 days/week), intermediate (1–2 days/week), low (never/less than 1 day/week) consumption	Age, gravidity, parity
Wise 2011 [2]	Prospective cohort 1997–2009, Black Women's Health Study	6,627 incident fibroid cases; 22,583 participants at start of follow-up	68-item FFQ (1995) and 85-item FFQ (2001)	Total fruits and vegetables, vegetables (total, cruciferous, green leafy, yellow–orange), fruit (total, citrus, cantaloupe, apples, pears and bananas, orange and grapefruit juice), vitamin A (total, dietary, pro-vitamin A, preformed retinol), vitamin C (total, dietary), vitamin E (total, dietary), folate (total, dietary), carotenoids (lycopene, alpha-carotene, beta-carotene, carotene, beta-cryptoxanthin, lutein/zeaxanthin), fiber (total, insoluble, soluble)	Various categories of intake for foods (i.e., <1/day, 1/d, 2–3/d, 4+/day); Quintiles of intake for nutrients	Age, time period, energy intake, parity, age at first birth, years since last birth, ever use of oral contraceptives, age at first oral contraceptive use, BMI, smoking, current alcohol intake, multivitamin use, education, income, marital status, US region of residence

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TABLE 3.1 (*Continued*)

Summary of Previous Observational Studies on Dietary Factors and Fibroid Risk

Author/Year	Study Name/Type	Number of Fibroid Cases and Controls or Total Study Population	Dietary or Biomarker Assessment Method	Exposure(s) Evaluated	Exposure Categorization	Adjustment Variables
Wise 2010 [16]	Prospective cohort 1997–2007, Black Women's Health Study	5,871 incident fibroid cases; 22,120 participants at start of follow-up	68-item FFQ (1995) and 85-item FFQ (2001)	Dairy foods (total, high-fat, low-fat, milk, high-fat milk, low-fat milk, cheese, ice cream, yogurt, butter), soy (total soy foods, soy milk, tofu, soy/veggie burgers), calcium, phosphorus, calcium-to-phosphorus ratio, dietary vitamin D, butyric acid intake	Various categories of intake for foods (i.e., <1/day, 1/d, 2/d, 3/d, 4+/day); Quintiles of intake for nutrients	Age, time period, energy intake, age at menarche, parity, age at first birth, years since last birth, ever use of oral contraceptives, age at first oral contraceptive use, vigorous exercise, BMI, smoking, alcohol intake, diabetes, education, occupation, income, marital status, geographic region
Radin 2010 [31]	Prospective cohort 1997–2007, Black Women's Health Study	5,800 incident fibroid cases; 22,861 participants at start of follow-up	68-item FFQ (1995) and 85-item FFQ (2001)	Glycemic load, glycemic index	Quintiles	Age, questionnaire cycle, energy intake, servings of dairy foods, age at menarche, current use of hormonal contraception, BMI, diabetes, current alcohol consumption, smoking, vigorous physical activity, current US region of residence, marital status, household income, occupation, education, parity, age at first birth, years since last birth
Nagata 2009 [7]	Hospital based case-control study, Gifu, Japan	54 fibroid cases; 231 controls	169-item FFQ	Total energy, fat (total, SFA, MUFA, PUFA), dietary fiber, soya isoflavones, alcohol (total, beer/light beer, other types of liquor)	Tertiles	Age, BMI, smoking, number of live births, age at menarche
Terry 2008 [6]	Prospective cohort 1991–2001, Nurses' Health Study II	6,302 incident fibroid cases; 82,512 participants at start of follow-up	130-item FFQ (assessed in 1991, 1995 and 1999)	Lycopene, alpha-carotene, beta-carotene, beta-cryptoxanthin, lutein/zeaxanthin	Quintiles	Age, age at menarche, infertility, marital status, ancestry, age at first oral contraceptive use, parity, age at first birth, time since last birth, BMI, diastolic blood pressure, antihypertensive therapy, calories

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TABLE 3.1 (*Continued*)

Summary of Previous Observational Studies on Dietary Factors and Fibroid Risk

Author/Year	Study Name/Type	Number of Fibroid Cases and Controls or Total Study Population	Dietary or Biomarker Assessment Method	Exposure(s) Evaluated	Exposure Categorization	Adjustment Variables
Wise 2004 [30]	Prospective cohort 1997–2001, Black Women's Health Study	2,177 incident fibroid cases; 22,885 participants at start of follow-up	68-item FFQ	Alcohol consumption status, current alcohol consumption, years of alcohol consumption, type of alcohol (beer, wine, liquor), coffee (caffeinated, decaffeinated), tea, soft drinks, caffeine	Various categories of intake (i.e., cups/day: almost never, <1, 1, 2, 3, 3 or more)	Age, time period, age at menarche, age at first birth, years since last birth, use of oral contraceptives, education, smoking, current alcohol consumption, BMI
Chiaffarino 1999 [3]	Hospital-based case-control study, Milan, Italy	843 fibroid cases; 1,557 controls	Questionnaire	Milk, beef and other red meat, liver, carrots, green vegetables, fresh fruit, eggs, ham, fish, cheese, whole-grain foods, butter, margarine, oil, coffee, tea, alcohol	High, intermediate, low	Age, education, marital status, parity, BMI, smoking, calendar year at interview
Biomarker-based exposure assessment						
Baird 2013 [25]	Health plan-based cross-sectional study, National Institute for Environmental Health Sciences Uterine Fibroid Study	674 participants with fibroids; 362 participants without fibroids	Plasma levels using radioimmunoassay	25-hydroxyvitamin D	Linear term and 5-ng/mL categories	Age, age at menarche, full-term pregnancies after age 24 years, BMI, physical activity, ethnicity
Paffoni 2013 [27]	Infertility clinic-based case-control study, Milan, Italy	128 fibroid cases; 256 controls	Serum levels using radioimmunoassay	25-hydroxyvitamin D_3	Continuous (ng/mL) and categorical (<10 ng/mL, 10–19.9 ng/mL, 20+ ng/mL)	BMI, parity, ethnicity
Sabry 2013 [26]	Outpatient clinic-based cross-sectional study, Sohag, Egypt	104 participants with fibroids; 50 participants without fibroid	Serum levels using radioimmunoassay	25-hydroxyvitamin D_3	Continuous (ng/mL)	Stratification by ethnicity
Martin 2011 [8]	Population-based cross-sectional study, 2003–2004 National Health and Nutrition Examination Survey	68 participants with fibroids; 819 participants without fibroids	Serum blood levels	Beta-carotene, vitamin A, vitamin B_6, vitamin B_{12}, vitamin C, vitamin E, folate	Tertiles	Age, race, BMI, education, parity, oral contraceptive use, age at first birth, age at last birth
Atkinson 2006 [29]	Health plan-based case-control study, Washington, US	170 fibroid cases; 173 controls	Urinary excretion of phytoestrogens measured using gas chromatography-mass spectrometry	Isoflavones and lignans	Continuous (nmol/mg Cr^x) and quartiles	Age, BMI, race, family history of uterine fibroids, mean lignin or isoflavone excretion

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TABLE 3.2

Summary of Associations between Selected Dietary Factors and Uterine Fibroids

Dietary Factor	Summary of Association(s)	References
Fruits and vegetables	Consistently decreased risk	[1–4]
Carotenoids	No associations	[2,6]
Fats	No associations overall, suggestion of increased risk with specific long chain omega-3 fatty acids	[3,7,15]
Dairy	Inconsistent	[1,3,16]
Dietary vitamin D	No associations	[4,16]
Plasma vitamin D	Consistently decreased risk	[25–27]
Fish	Inconsistent	[1,3,15,28]
Soy	No associations	[1,7,16]
Meat	Inconsistent	[1,3]
Alcohol	Suggestion of increased risk among beer drinkers	[3,7,30]

anti-inflammatory effects [16,17], as well as through influences on circulating estrogens [18]. In mouse models, a milk diet has been demonstrated to reduce markers of oxidative and inflammatory stress, including tumor necrosis factor alpha and IL-6 [17]. In addition, milk consumption has also been shown to increase circulating insulin-like growth factor-I (IGF-I) levels [19–21], and IGF-I has been shown to promote fibroid cell proliferation in culture [22,23]. Baird et al. has reported a suggestive inverse association between high circulating IGF-I levels and fibroid prevalence [24]. The BWHS has examined the association between dairy intake and fibroids, reporting a reduced risk of fibroids with increasing consumption, with similar associations observed for low-fat and high-fat dairy foods [16]. In contrast, case-control studies in China and Italy reported no significant associations with dairy foods [1], milk or cheese [3]. Wise et al. also examined vitamins, minerals and fatty acids commonly found in dairy foods but, after adjustment for total dairy intake, did not observe significant associations with any of these dietary factors [16].

Vitamin D

Although human levels of vitamin D are primarily derived from sun exposure, vitamin D is naturally occurring in some foods such as fatty fish, liver and eggs, while other foods, such as milk or orange juice, are fortified with vitamin D. Dietary vitamin D was not associated with fibroid risk in the BWHS or a China-based case-control study [4,16]. However, given that only a small portion of vitamin D comes from diet, plasma levels may be a more accurate indicator of an individual's vitamin D level, and three cross-sectional studies have reported a reduced risk of fibroids among women with higher levels of plasma vitamin D [25–27].

Fish

Four studies conducted in three different geographic regions have examined fish intake. While fish can be rich in polyunsaturated fats, it also can be a source of toxin exposure—particularly persistent organic pollutants (POPs) and other phytoestrogenic compounds. A case-control study from China reported no association between fish consumption and fibroid risk [1], while an Italian case-control study reported a protective effect of fish consumption on fibroid risk [3]. In the US, the BWHS observed the suggestion of an increased risk with consumption of dark-meat fish [15]. In the midwestern US, consumption of sport fish, which are known to be high in a number of POPs, was marginally associated with increased fibroid risk [28]. The varied types of fish consumed in different countries, assorted preparation methods

TABLE 3.3

Main Results from Studies Evaluating the association(s) between Fruit and Vegetable Intake and Uterine Fibroids

Author/Year	Selected exposure(s)	Multivariable Hazard Ratio (HR) or Odds Ratio (OR) and 95% Confidence Intervals (CI)	Serving Categories
Shen 2016 [4]	Broccoli	OR = 0.55; 95% CI = 0.32–0.96	Continuous servings
	Cabbage	OR = 0.45; 95% CI = 0.21–0.95	
	Chinese cabbage	OR = 0.31; 95% CI = 0.10–0.95	
	Tomato	OR = 0.45; 95% CI = 0.24–0.85	
	Apple	OR = 0.41; 95% CI = 0.21–0.81	
He 2013 [1]	Vegetables and fruits	OR = 0.4; 95% CI = 0.2–0.9	High vs. low consumption (reference)
Wise 2011 [2]	Total fruits and vegetables	HR = 0.90; 95% CI = 0.82–0.98	≥4 servings/day vs. <1/day (reference)
	Total vegetables	HR = 0.97; 95% CI = 0.89–1.05	≥2 servings/day vs. <4/week (reference)
	Cruciferous	HR = 0.97; 95% CI = 0.89–1.06	≥6 servings/week vs. <1/week (reference)
	Green leafy	HR = 0.93; 95% CI = 0.85–1.01	≥6 servings/week vs. <1/week (reference)
	Yellow-orange	HR = 1.00; 95% CI = 0.92–1.09	≥6 servings/week vs. <1/week (reference)
	Total fruits	HR = 0.89; 95% CI = 0.81–0.98	≥2 servings/day vs. <2/week (reference)
	Citrus	HR = 0.92; 95% CI = 0.86–1.00	≥3 servings/week vs. <1/month (reference)
	Cantaloupe	HR = 0.95; 95% CI = 0.86–1.04	≥3 servings/week vs. <1/month (reference)
	Apples, pears and bananas	HR = 0.98; 95% CI = 0.89–1.08	≥3 servings/week vs. <1/month (reference)
	Orange and grapefruit juice	HR = 1.02; 95% CI = 0.93–1.12	≥1 serving/day vs. <1/month (reference)
Chiaffarino 1999 [3]	Green vegetables	OR = 0.5; 95% CI = 0.4–0.6	Third vs. first tertile (reference)

and differing POP burdens across studies make the interpretation of these results challenging.

Soy

Soy intake has been examined in populations with high and low intakes of soy products with no clear association. In a case-control study in Japan, no significant association was observed between soy isoflavones and fibroid risk [7]. Soy intake was also not associated with fibroid risk in a case-control study in China or in the BWHS in the US [1,16].

Meat

Only two studies have examined meat intake in relation to fibroid risk, with inconsistent results. Chiaffario et al. observed a significant increased risk of fibroids with higher beef and other red meat consumption [3] while He et al. observed no association between meat intake and fibroid risk [1].

Alcohol

Alcohol consumption has been associated with an increased risk of fibroids in two of three studies that have examined this association. The BWHS reported significantly higher risks of fibroids among women who were current drinkers and those who had consumed alcohol for a longer period of time. This association was strongest for beer consumption [30]. Nagata et al. also observed an increased risk of fibroids with increasing alcohol consumption that was strongest among beer drinkers [7]. An Italian case-control study observed no association between alcohol intake and fibroids; however, wine was the alcohol consumed by 90% of women included in this study, with only a small proportion consuming beer [3].

In summary, few studies have examined the associations between dietary factors and fibroid risk and the majority of these studies have been cross-sectional in design—severely reducing the ability to draw temporal cause and effect conclusions. To date, consistent associations between diet and fibroid risks are limited to two consistent discoveries: a reduced risk with higher fruit and vegetable intake (although the primary food contributors remain to be determined) and increased risk with lower vitamin D levels (although the impact of sun versus food sources remains unclear). Much more research is needed to clarify the role of other dietary factors in relation to fibroid risk. Given the prevalence of fibroids and the effects on women's lives, understanding the impact of this modifiable group of risk or preventive factors would have a large clinical and public health impact.

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