

## Pneumonia and pregnancy

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Community acquired pneumonia (CAP) is recognised as a common problem that carries a substantial morbidity and mortality. The burden of disease falls mainly on people at the extremes of age and the occurrence of CAP in young adults is uncommon. Nevertheless, pneumonia in young adults can be severe and fatal.<sup>1</sup> In the pregnant patient, pneumonia is the most frequent cause of fatal non-obstetric infection.<sup>2</sup>

Concern that pneumonia occurring in a pregnant patient may be more frequent, exhibit atypical features, run a more severe course, or be more difficult to treat than in a non-pregnant patient is not unusual. Underlying these concerns are the recognised physiological and immunological changes that occur during pregnancy which may compromise the mother's ability to respond to an infection. Added to this are concerns for the health of the fetus.

### Changes in pregnancy

Alterations in cellular immunity have been widely reported and are aimed primarily at protecting the fetus from the mother. These changes include decreased lymphocyte proliferative response, especially in the second and third trimesters, decreased natural killer cell activity, changes in T cell populations with a decrease in numbers of circulating helper T cells, reduced lymphocyte cytotoxic activity, and production by the trophoblast of substances that could block maternal recognition of fetal major histocompatibility antigens.<sup>3–7</sup>

In addition, hormones prevalent during pregnancy—including progesterone, human chorionic gonadotropin, alpha-fetoprotein and cortisol—may inhibit cell mediated immune function.<sup>6</sup> These changes could theoretically increase the risk from infection, particularly by viral and fungal pathogens.

Anatomically, the enlarging uterus causes elevation of the diaphragm by up to 4 cm and splaying of the thoracic cage. A 2.1 cm increase

in the transverse diameter of the chest and a 5–7 cm increase in the circumference of the thoracic cage has been reported.<sup>8</sup> These changes may decrease the mother's ability to clear secretions. The decrease in functional residual capacity, increase in oxygen consumption, and increase in lung water that occur during pregnancy add to the vulnerability of the lung to injury from infection. Obstetric and anaesthetic interventions, including endotracheal intubation, pose further risks, not least from aspiration pneumonia.<sup>9</sup>

### Incidence

A true estimate of the incidence of pneumonia during pregnancy is difficult to obtain. The few studies of pneumonia during pregnancy are mostly retrospective and include few cases (table 1). Based on these studies, a marked variation in incidence over the years is evident. A very high incidence was reported in the years before 1965 ranging from 6.3 per 1000 deliveries to 8.5 per 1000 deliveries.<sup>10–11</sup> This had decreased in the 1970s and early 1980s to 0.44–0.78 per 1000 deliveries, presumably due to the introduction of antibiotics and improvements in obstetric care.<sup>12–13</sup> More recently, an incidence of 1.2–2.7 per 1000 deliveries has been reported.<sup>14–16</sup> It has been proposed that this increase in incidence is a reflection of the higher proportion of pregnant women with chronic medical conditions.<sup>14</sup> However, patients in these study cohorts are not directly comparable and the varying proportions with documented illicit drug use (14–52%) and HIV seropositivity (4–27%) may not simply be the result of time trends.<sup>13–15</sup>

At the Nottingham City Hospital, a large teaching hospital in the Trent region of the UK, there were only six cases of pneumonia in pregnant women in the 5 years from 1995 to 2000, based on computer records. In that time there were approximately 27 800 deliveries giving an estimated incidence of 0.2 per 1000 deliveries.

Perhaps, more importantly, the incidence rates of pneumonia during pregnancy reported in recent studies do not differ materially from the estimated incidence of CAP in young non-pregnant adults. A population study conducted in Finland estimated the age specific incidence of CAP per year for persons aged 15–59 years as 6 per 1000 population. The incidence was higher in men than in women.<sup>17</sup> Similarly, Foy *et al* estimated the incidence per year for

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Table 1 Incidence and mortality of pneumonia in pregnancy

Author	No. of cases	Incidence per 1000 deliveries	Drug use	HIV positive	Maternal mortality	Preterm delivery
Finland <sup>10</sup>	164	6.3	NR	NR	18/74 (24%)	32/74 (43%)
Hopwood <sup>11</sup>	23	8.5	NR	NR	2/23 (8.7%)	NR
Benedetti <sup>12</sup>	39	0.44	NR	NR	0/39 (0%)	3/20 (15%)
Madinger <sup>13</sup>	25	0.78	5/25 (20%)	1/25 (4%)	1/25 (4%)	9/21 (43%)
Berkowitz <sup>14</sup>	25	2.7	13/25 (52%)	3/11 (27%)	0/25 (0%)	1/18 (6%)
Richey <sup>15</sup>	71	1.2	10/71 (14%)	2/56 (4%)	2/71 (3%)	1/71 (1%)
Yost <sup>16</sup>	133	1.5	NR	NR	0/133 (0%)	14/107 (13%)

NR = not reported

subjects aged 15–59 as 5–8 per 1000 population while Woodhead *et al* reported an estimate of 5 per 1000 for subjects aged 15–79 years.<sup>18 19</sup>

- The incidence of pneumonia in pregnancy is not materially different from that in non-pregnant adults.

### Mortality

Pneumonia has been cited as the third most frequent cause of indirect obstetric death in North America.<sup>20</sup> However, in the Report on Confidential Enquiries into Maternal Deaths in the UK 1994–6, of 134 indirect deaths—that is, deaths resulting from previous existing disease or disease that developed during pregnancy and which was not due to direct obstetric causes but which was aggravated by the physiological effects of pregnancy—which is equivalent to a rate of 6.1 per 100 000 pregnancies, only six were due to pneumonia. Three patients were known to have cystic fibrosis, one had varicella pneumonia, one was in a methadone maintenance programme, and one occurred 3 days after delivery in an otherwise healthy mother. In addition, there were three deaths due to pneumococcal sepsis but none of these patients had evidence of pneumonia. Therefore, even taking into account patients with cystic fibrosis, maternal death from pneumonia is rare in the UK. This is reflected in the reported maternal mortality of 0–4% in recent studies, which approximates the mortality from CAP in hospitalised non-pregnant adults. There are no data available for direct comparison. However, based on hospital studies of CAP, overall mortality in adults is in the region of 10–15% with older people bearing the brunt of the disease.<sup>21</sup> Mortality of 5.7% was reported in a BTS multicentre study of hospitalised adults aged 16–74 years compared with 0–1% in young ambulatory adults with CAP.<sup>22 23</sup>

- Mortality from pneumonia in pregnancy is similar to rates in non-pregnant adults.

### Fetal outcome

There is persuasive evidence to indicate that fetal outcome is affected by maternal pneumonia. Mothers with pneumonia are significantly more likely to deliver before 34 weeks gestation, with preterm delivery occurring in up to 43% of cases.<sup>24</sup> Prostaglandin production or the host's inflammatory response to infection may be responsible. In addition, infants born to mothers with pneumonia weigh significantly less.<sup>24</sup> One study found a difference of 150 g in the birth weight of infants born to mothers with pneumonia compared with controls.<sup>16</sup> Similarly, the frequency of low birth weight infants (2500 g or less) was higher in cases than in controls (16% *v* 8%). There is no firm evidence of any difference in perinatal mortality based on studies conducted over the last two decades.

- Mothers with pneumonia are more likely to deliver early and have infants of lower birth weight than other pregnant women.

### Risk factors

No significant differences in maternal age and parity have been identified between women who have pneumonia during pregnancy and those who do not.<sup>16</sup> The risk of pneumonia during pregnancy appears to be lowest in the first trimester with only 0–16% of cases occurring during this period. Mean gestational age at admission for pneumonia ranges from 24 to 31 weeks.<sup>13 16</sup>

Benedetti *et al*<sup>12</sup> noted that 19 of 37 pregnant patients with pneumonia (47%) had a haemoglobin of 10 g/dl or less and hence highlighted the possibility of anaemia as a risk factor for pneumonia.<sup>12</sup> This finding was not supported by Richey *et al*<sup>15</sup> who found eight of 71 patients in their series (11%) had anaemia on admission. On the other hand, a quarter of their cases (n=17) were noted to have a history of asthma. More recently, in a case control study of 59 women and 118 controls, both anaemia—measured as a haematocrit of 30% or less on admission—and a history of asthma were found to be independently associated with a fivefold increased risk for the development of pneumonia on multivariate analysis.<sup>24</sup>

The same study also found that women with pneumonia were more likely to be receiving betamethasone to enhance fetal lung maturity. The suggestion that antepartum corticosteroids given to reduce morbidity and mortality in the premature neonate may be a risk factor for development of maternal pneumonia is supported by another case control study involving 37 cases and 74 controls.<sup>25</sup> This showed that the use of antepartum corticosteroids is associated with a higher rate of infectious disease (64.8% cases *v* 17.5% controls), with serious bacterial infections occurring in nine (24.3%) of the cases, including four pneumonias in previously healthy subjects.

Tocolytic agents given to induce labour have been associated with the development of pneumonia.<sup>24</sup> They also increase the risk of respiratory insufficiency due to pneumonia through the promotion of pulmonary oedema.<sup>26</sup> It has therefore been recommended that they are not used in pregnant patients with pneumonia.<sup>27</sup>

Smoking is a recognised risk factor for the development of pneumonia and invasive pneumococcal disease in non-pregnant adults.<sup>28 29</sup> A dose-response relationship has been shown; 20–32% of women with pneumonia in pregnancy are reported to smoke.<sup>13 15</sup> Although not formally examined, it would be reasonable to expect smoking to confer at least the same risks for the development of pneumonia in pregnant mothers as in other adults.

- Established risk factors for pneumonia in pregnancy include anaemia, asthma, antepartum corticosteroids given to enhance fetal lung maturity, and the use of tocolytic agents to induce labour.

### Diagnosis

The diagnosis of pneumonia in an otherwise healthy adult without pre-existing cardiorespiratory illness is usually straightforward. Symptoms of dyspnoea, fever and cough, when

present, help point to the correct diagnosis. However, initial misdiagnosis in pregnant patients is not uncommon. Yost *et al*<sup>6</sup> found that 14 of 133 cases (10.5%) had incorrect initial diagnoses. These included two patients who were thought to have pyelonephritis and two others who underwent surgery for suspected appendicitis. Similarly, in a series of 25 cases studied by Madinger *et al*,<sup>13</sup> five (20%) were initially misdiagnosed (one was initially treated for suspected pyelonephritis, two had surgery for suspected appendicitis, and two were thought to have preterm labour with no predisposing cause identified).

The difficulties in diagnosis during pregnancy reflect the complexity of distinguishing between symptoms related to physiological changes and more sinister symptoms of disease. Patients themselves may attribute symptoms of pneumonia to pregnancy and hence defer consultation. Dyspnoea is a common symptom during pregnancy. It is experienced by 50% of women at 19 weeks gestation and up to 76% at 31 weeks.<sup>30</sup> It may be distinguished in that physiological dyspnoea characteristically begins early in pregnancy and improves or plateaus as term approaches. It does not interfere with daily activities and rarely occurs at rest. Chest discomfort may also occur in the later stages of pregnancy, possibly due to the mechanical effects of the uterus on the diaphragm.<sup>31</sup> It may be difficult to distinguish it from other causes of chest discomfort.

In patients with dyspnoea that appears out of keeping with the expected symptoms related to pregnancy, pneumonia must be considered. Other possible causes include asthma, pulmonary embolism, amniotic fluid embolism, air embolism, and aspiration pneumonitis. Cough is not usually a symptom of pregnancy and should arouse clinical suspicion of an underlying cause. Clinical signs should be sought, although crepitations at the lung bases may occasionally be heard in pregnancy, presumably due to atelectasis from the raised diaphragm compressing the lower lung fields.<sup>32</sup> Even in patients with symptoms consistent with a lower respiratory tract infection and unilateral chest signs, radiologically proven pneumonia is confirmed in only 39% of cases.<sup>19</sup> Ultimately, a firm diagnosis of pneumonia can only be made with the aid of a chest radiograph.

#### CHEST RADIOLOGY

It is estimated that radiation doses to the mother from a standard departmental posteroanterior chest radiograph, performed with a grid to reduce scatter and a peak voltage for the beam of 90–120 kV, is 5–30 mRad. The absorbed dose for the uterus and fetus is 100 times less (about 300 µRad).<sup>33</sup> A lateral chest radiograph results in greater exposure (maternal dose 150–250 mRad) and is not usually required. The differential diagnosis of alveolar shadowing with specific reference to pregnancy includes non-cardiogenic pulmonary oedema in pre-eclampsia and eclampsia, pulmonary oedema secondary to tocolytic agents, aspiration pneumonitis and, rarely, choriocarcinoma

with pulmonary metastases which may present as small or large ill defined foci mimicking pneumonia.<sup>34</sup>

- Misdiagnosis or delay in diagnosis of pneumonia is common in pregnancy.
- A firm diagnosis of pneumonia can only be made with the aid of a chest radiograph.

#### Pathogens

There have not been any detailed studies focusing specifically on the microbial agents involved in pneumonia during pregnancy. The available data are derived mainly from observational (often retrospective) studies where only routine microbiological investigations were employed. Sputum and blood cultures were the main pillars of diagnosis, while serological tests were employed inconsistently. Accepting these limitations, the range of pathogens identified from four recent studies mirrors the experience in studies of hospitalised non-pregnant adults with CAP (table 2).

#### BACTERIAL AND ATYPICAL PATHOGENS

*Streptococcus pneumoniae* is the most common organism identified, followed by *Haemophilus influenzae*. Infection with *Legionella* sp has been documented but is rare. Based on the few cases reported, it is generally felt that there is no increase in the risk of infection during pregnancy and possibly no difference in severity of disease. Treatment with erythromycin has proved successful.<sup>35</sup> *Mycoplasma pneumoniae* might be expected to be more common, particularly in this age group. Incomplete serological testing and seasonality may explain the relatively low frequency reported in these studies. Human infection with *Coxiella burnetii* (Q fever) results mainly from aerosols which are generated by farm animals when they give birth or abort as the bacteria multiply and reach high concentrations in the placenta of mammals. Cases present most commonly with respiratory symptoms.<sup>36</sup> Human to human transmission of infection through aerosolisation of *C burnetii* during delivery of the fetus and placenta can occur.<sup>37</sup> *C burnetii* has been isolated from the placentas of asymptomatic women and the organism has been reported to cause abortions and stillbirths. The largest reported series of patients with Q fever comes from France. Of 1383 infections identified over a 13 year period, 15 patients had Q fever during pregnancy.<sup>38</sup> These patients reported significantly more contact with farm or newborn animals than other patients with acute Q fever. Fetal outcome was poor; in 10 the fetus

Table 2 Pathogens implicated in pneumonia during pregnancy: from four studies (n=161)<sup>12-15</sup>

Pathogen	No (%)
<i>Streptococcus pneumoniae</i>	28 (17%)
<i>Haemophilus influenzae</i>	9 (5.5%)
<i>Mycoplasma pneumoniae</i>	5 (3%)
<i>Legionella</i> sp	2 (1.2%)
<i>Staphylococcus aureus</i>	2 (1.2%)
Influenza A virus	2 (1.2%)
Others	14 (9%)
Unknown	99 (61%)

aborted, in three the infant was born prematurely, and in only two was pregnancy normal. Hence, although Q fever in pregnancy is rare, there are important issues regarding transmission and fetal outcome.

Overall, the clinical presentation of these infections during pregnancy has not been found to display features that are different from infection in non-pregnant adults. In adult CAP it is now recognised that clinical features cannot be used to differentiate confidently between the likely respiratory pathogens, and there is no indication that this position is any different in pregnancy.<sup>23</sup>

#### VIRUSES

##### *Influenza virus*

There are three antigenically distinct types of influenza myxoviruses that cause human disease: types A, B and C. Type A is usually associated with epidemic disease and, historically, has been implicated in causing severe disease in pregnant patients. In the 1918 epidemic maternal mortality was 30–50% while in the Asian flu epidemic of 1957–8 half of all women of child bearing age who died were pregnant, representing 10% of all influenza deaths.<sup>39–40</sup> Mortality was highest in women in the third trimester.<sup>39</sup> Post mortem studies showed that pregnant women most commonly died from fulminant primary viral pneumonia whereas non-pregnant patients died from secondary bacterial infection.<sup>41</sup> Importantly, since 1958 influenza epidemics have not been associated with increased morbidity or mortality in pregnant women.

Influenza A virus can pass through the placenta.<sup>40</sup> Whether influenza can cause congenital malformations is under debate. Circulatory defects and central nervous system malformations have been described. However, a review of the literature did not reveal convincing evidence for a definite association with pregnancy.<sup>42</sup>

##### *Varicella virus*

Chickenpox is an uncommon disease in adults with an annual incidence in people aged 15 years and over in England and Wales of 82–183 per 100 000.<sup>43</sup> Trends of an increase in the proportion of cases occurring in adults over the last two decades have been reported in the UK and USA, although they have not been substantiated in Scotland.<sup>43–45</sup> The incidence in pregnancy is estimated at 5–10 per 10 000 pregnancies.<sup>46–47</sup> In the tropics varicella is more common with 20–50% of cases occurring in young adults.<sup>48–49</sup>

Whether varicella pneumonia occurs more frequently and runs a more fulminant course in pregnant women is unclear. Paryani *et al*<sup>50</sup> reported pneumonia in four (9%) of 43 pregnant women with chickenpox while Baren *et al*<sup>51</sup> observed one case of pneumonia in 28 pregnant women (3.6%). These data are similar to the rate of pneumonia in non-pregnant adults of 5–14%

There are no differences in the clinical manifestation of varicella pneumonia between pregnant and non-pregnant adults. Mortality

from varicella pneumonia is approximately 11% in non-pregnant adults and ranges from 2% to 35% in pregnant women, with prospective series reporting lower mortality rates.<sup>53</sup> A recent review of the subject concluded that the data on the severity of varicella in pregnancy are conflicting, with some data indicating no difference from non-pregnant adults while other data suggest that pregnant women with varicella pneumonia have a higher mortality.<sup>53</sup> The third trimester appears to be the time of highest incidence and is when the disease is most severe.<sup>54–56</sup> This may be related to the prominent changes in cell mediated immunity at this time.

The effects of maternal varicella infection on the fetus are complex and are related to the timing of infection. Intrauterine infection may occur in 8.7–26% of cases.<sup>55–57</sup> Whether or not there is an increased risk of fetal death is unclear. A useful review on the subject has been prepared by the UK Advisory Group on Chickenpox.<sup>53</sup>

##### *Other viruses*

There are case reports of pneumonia as a result of rubeola, infectious mononucleosis, and hantavirus infection in pregnant women.<sup>58–61</sup> These reports depict patients with severe disease and complications, perhaps reflecting publication bias. The true incidence and severity of these infections during pregnancy is unknown.

#### FUNGI

Fungal infection, notably coccidioidomycosis, may rarely complicate pregnancy. The alterations in maternal cell mediated immunity may be contributory, although firm evidence is lacking.

The estimated incidence of coccidioidomycosis in historical reports has been as high as one per 1000 pregnancies.<sup>62</sup> More recently, Wack *et al*<sup>63</sup> identified only 10 cases of coccidioidomycosis out of 47 120 pregnancies between 1979 and 1985. There appears to be a greater risk of dissemination associated with high mortality if infection is acquired during the third trimester.<sup>62–63</sup>

Cryptococcal infection usually presents as meningitis and presentation as isolated pneumonia in immunocompetent adults is a rare event. Recently, five cases of isolated cryptococcal pneumonia have been reported in pregnant women.<sup>64–65</sup> The clinical presentations of pneumonia ranged from insidious cough and increasing dyspnoea to severe pleuritic chest pain of sudden onset. There were no reported deaths.

There have also been a number of case reports of blastomycosis in pregnancy.<sup>66–69</sup> These are rare events and the impact of pregnancy on them, and vice versa, is not clear.<sup>62</sup>

#### **Impact of HIV infection**

Bacterial infections are the most common respiratory complications in patients with HIV infection.<sup>70</sup> In the cohort studied in the Pulmonary Complications of HIV Infection Study the

incidence of bacterial pneumonia was 5.5 per 100 person years compared with a rate of 5.1 per 100 person years for *Pneumocystis carinii* pneumonia (PCP).<sup>71</sup> Others have reported a bacterial pneumonia rate of up to 12.5 per 100 person years, significantly higher than in HIV negative patients.<sup>72-73</sup> The CD4+ lymphocyte count is strongly associated with the occurrence of both PCP and bacterial pneumonia, with infection becoming increasingly likely at CD4+ lymphocyte counts below 500/mm<sup>3</sup>.<sup>73</sup> Bacteraemia rates of about 30% are not uncommon in HIV positive patients.<sup>71-74</sup> Generally, *S pneumoniae* is the most common organism identified, although a recent series found *P aeruginosa* to be more common.<sup>74</sup>

The prevalence of HIV infection in mothers living in London has risen more than fivefold between 1988 and 1996, from 0.032% to 0.19%. Elsewhere in the UK and in Scotland prevalence is low and has been relatively stable over the same time period (1996 figures 0.016% and 0.025%, respectively).<sup>75</sup> The majority of mothers (58%) are probably infected heterosexually abroad. A recent Swiss cohort study comparing HIV infected pregnant and non-pregnant women found a trend towards a higher rate of any AIDS defining event in pregnant women (rate ratio 1.92, 95% confidence interval 0.80 to 4.64). Recurrent bacterial pneumonia was the only AIDS defining event which was significantly more common in pregnant women (rate ratio 7.98, 95% confidence interval 1.73 to 36.8).<sup>76</sup>

Case reports of PCP complicating pregnancy have described maternal death as the most common outcome.<sup>77-79</sup> In a study of 20 women who died from AIDS during or within 1 year of completing a pregnancy, the observed mean interval between AIDS diagnosis and death in pregnant women with PCP was 59 days.<sup>79</sup> However, as elsewhere, there is a paucity of studies directly comparing respiratory infections in HIV infected pregnant and non-pregnant women. Based on current published literature, clinical presentation of disease is probably not altered.<sup>80</sup> Whether PCP complicating pregnancy runs a more severe course is unclear, as is the influence of highly active antiretroviral therapy on PCP in pregnancy.

An extensive literature on the effects of pregnancy on HIV infection and of HIV infection on fetal outcome exists which is beyond the scope of this review. Guidelines for the treatment of HIV infection in pregnant women are published elsewhere and are regularly updated ([www.hivatis.org](http://www.hivatis.org)).<sup>81</sup>

### Aspiration pneumonia and anaerobic infections

The pregnant woman is at risk from aspiration due to a variety of predisposing factors including progesterone induced relaxation of the gastro-oesophageal sphincter, delayed gastric emptying, and raised intragastric pressure due to abdominal compression by the uterus. Anaesthetic procedures add to the risk. Women who deliver by Caesarean section are recognised to be at higher risk of aspiration than those who deliver vaginally.<sup>82</sup>

Aspiration may present with features of airway obstruction due to foreign body inhalation or of a chemical pneumonitis causing pulmonary oedema, hypoxia and, occasionally, respiratory failure. The risk from pneumonitis is substantially increased if the aspirated fluid has a pH of less than 2.4. Contamination of the lower respiratory tract may result in anaerobic bacterial pneumonia, necrotising pneumonia, lung abscess, or empyema. There are no specific studies addressing the microbial agents implicated in aspiration pneumonia in pregnant women. At the same time, there is no good basis for assuming any difference from the situation in non-pregnant adults. Anaerobes such as the Gram positive cocci *Peptostreptococcus* and *Peptococcus* sp and the Gram negative bacilli *Fusobacteroides* and *Bacteroides* sp predominate in two thirds of cases.<sup>83</sup> These are usually penicillin sensitive apart from *Bacteroides* sp which are generally resistant to penicillin. Should aspiration pneumonia occur following prolonged stay in hospital, Gram negative enteric bacilli (including *Pseudomonas aeruginosa*) become more important, reflecting oropharyngeal colonisation by these bacteria.<sup>84</sup>

### Treatment

No antimicrobial agents are licensed for use in pregnancy. An informed assessment of the risks from infection compared with the risks of adverse drug effects on the fetus or mother is essential before the initiation of any antimicrobial agent. This is especially pertinent where treatment options are limited, the probability of adverse drug effects is uncertain, and the infection potentially severe without appropriate treatment. Data that are available on antimicrobial agents in pregnancy are summarised in table 3. Reports of teratogenicity need to be compared against a background incidence of major malformations in the general population of 2-3%.

#### ANTIBACTERIAL AGENTS

Updated guidelines from the British Thoracic Society for the management of CAP in adults are expected in 2001. Penicillins, macrolides (including newer ones), and cephalosporins are likely to be the main antibacterial agents recommended. These antibiotics have a good safety record in pregnancy. Avoidance of the quinolones, tetracyclines, chloramphenicol, and sulpha compounds, which are contraindicated in pregnancy, should not therefore pose a problem in the majority of cases.

A history of recent contact with farm or newborn animals should raise the possibility of Q fever pneumonia for which macrolides are a reasonable alternative to tetracyclines in the pregnant patient. If cover for anaerobic infection, particularly with *Bacteroides* sp, is required, as may be the case in suspected aspiration pneumonia, then co-amoxiclav is a useful alternative to metronidazole. Most Gram negative infections can be treated with cephalosporins. The aminoglycosides can be used if there is a strong indication, bearing in mind the risk of fetal toxicity to the auditory nerve. The

Table 3 Safety in pregnancy of selected antimicrobial agents commonly used to treat pneumonias

Class of antibiotic	Evidence regarding adverse effects	Safety in human pregnancy
Antibacterial agents		
Penicillins	Widely used without evidence of problems	Good
Cephalosporins	Widely used without evidence of problems	Good
Macrolides	Widely used without evidence of problems. Most information relates to erythromycin and less to clarithromycin or azithromycin	Good
Aminoglycosides	No published reports on fetal nephropathy after maternal gentamicin, however ability of premature infants to eliminate gentamicin seems to be dependent on gestational age <sup>91</sup>	Potential risk of nephropathy and ototoxicity. Maternal plasma levels should be carefully monitored if clear indication exists for its use
Sulphonamides	May cause kernicterus if given in late pregnancy. Of 2296 newborns exposed to co-trimoxazole during the first trimester, 126 (5.5%) major birth defects were observed, 98 expected <sup>92</sup>	Avoid. Insufficient information on high doses. Theoretical risk of neural tube defects with co-trimoxazole due to its folate antagonist activity
Quinolones	Arthralgia and tendonitis reported in adults but none following in utero exposure in human pregnancy <sup>91</sup>	Insufficient evidence of safety
Tetracyclines	Administration in the second or third trimesters can cause yellow-brown staining and banding of the teeth of the child and reversible growth retardation of the long bones <sup>91</sup>	Avoid, especially at or after 12 weeks
Metronidazole	Conflicting data. Some epidemiological studies suggest increased risk of malformations, stillbirths and low birth weight infants. Other studies totalling exposure to over 3000 newborns have found no increase in congenital anomalies <sup>91</sup>	Unclear
Antiviral agents		
Amantadine	Limited preclinical data in animals showed a possible association with cleft palate. In a study of 64 pregnancies five births with defects were reported <sup>93</sup>	Insufficient evidence of safety
Zanamivir	No information in humans. In animals high doses were not associated with malformation (GlaxoWellcome Summary of Product Characteristics, Relenza, 2000)	Insufficient evidence of safety. Theoretically safer than amantadine
Ribavirin	Teratogenic or embryolethal in nearly all animal species	Avoid
Aciclovir	Prospective register (1984–99) with data on 1246 pregnancies showed no increase in birth defects compared with the general population (GlaxoWellcome Medical Information, personal communication)	Use recommended in situations where risk from untreated infection is greater than risk of possible adverse effects e.g. life threatening varicella infections
Antifungal agents		
Amphotericin B	Case reports of fetal toxicity involving anaemia, transient acidosis with uraemia, and respiratory failure <sup>94</sup>	Use if benefit outweighs risk of fetal toxicity (usually maternal toxicity also present)
Itraconazole	Embryotoxic and teratogenic in laboratory animals. <sup>95</sup> Of 198 women exposed during the first trimester, 3.2% major malformations were seen <sup>95</sup>	Best avoided. Manufacturer recommends contraception during and for one menstrual cycle after stopping treatment
Fluconazole	Embryotoxic and teratogenic in high doses in rats. Multiple congenital abnormalities reported with high dose use in humans. Possible dose dependent teratogenicity <sup>94</sup>	Avoid

pneumococcal vaccine is not recommended for pregnant women or those who are breast feeding.<sup>85</sup>

#### ANTIVIRAL AGENTS

Although amantadine has been used in treating influenza in the past, the newer neuraminidase inhibitors are probably to be preferred.<sup>86</sup> However, as efficacy and safety have not yet been established, routine use of these agents for the treatment of influenza in pregnancy cannot be recommended.

The influenza vaccine is not recommended for pregnant women who would not otherwise qualify for immunisation according to Department of Health guidelines.<sup>87</sup> The low risk of maternal morbidity and mortality, plus the uncertain (though probably minimal) effects of the vaccine on the fetus, support this recommendation. If immunisation is warranted, avoidance of the first trimester where possible would be prudent.

Recommendations for the treatment of varicella pneumonia in pregnancy have been prepared by the UK Advisory Group on Chickenpox.<sup>53</sup> Intravenous aciclovir is the preferred option. Although this drug is not currently approved for use in pregnancy, the risks from withholding treatment probably

outweigh the risks from adverse drug effects to the fetus or mother.

#### ANTIFUNGAL AGENTS

The Infectious Diseases Society of America has recently issued practice guidelines for the management of different fungal infections.<sup>88–90</sup> However, in view of the few cases reported, the optimal treatment for these conditions in pregnancy is unknown. Amphotericin B has been used to treat coccidioidomycosis in pregnancy with success. Indeed, in view of the risk of disseminated infection, treatment with amphotericin B should be considered in all women diagnosed with coccidioidomycosis during the third trimester of pregnancy or immediately in the postpartum period.<sup>89</sup>

#### Conclusion

Our current knowledge of pneumonia during pregnancy is based largely on small cohort studies, which are mostly retrospective in design, and isolated case reports. This reflects the relative rarity of the condition. A large prospective study examining the microbial aetiology with detailed tests would be desirable but would be difficult to organise. Some studies have compared pregnant women with pneumonia and pregnant women without pneumonia

to establish risk factors related to the development of pneumonia and the effect of pneumonia on pregnancy. However, there have been no studies directly comparing pneumonia in pregnant and non-pregnant women. Hence, there is no information on whether pneumonia is any different in pregnant women and non-pregnant adults. Current evidence suggests that no material differences exist. There is certainly no convincing evidence that the documented changes in the immune system result in clinically significant immunosuppression with increased susceptibility to respiratory tract infection. Management strategies developed for non-pregnant adults can therefore be broadly applied to pregnant women as well, with modifications to take into account issues of toxicity to the fetus.

- 1 Simpson JC, Macfarlane JT, Watson J, et al. A national confidential enquiry into community acquired pneumonia deaths in young adults in England and Wales. *Thorax* 2000;55:1040-5.
- 2 Kaunitz AM, Hughes JM, Grimes DA, et al. Causes of maternal mortality in the United States. *Obstet Gynecol* 1985;65:605-12.
- 3 Baley JE, Schacter BZ. Mechanisms of diminished natural killer cell activity in pregnant women and neonates. *J Immunol* 1985;134:3042-8.
- 4 Bulmer R, Hancock KW. Depletion of circulating T lymphocytes in pregnancy. *Clin Exp Immunol* 1977;28:302-5.
- 5 Chardonens X, Jeannot M. Lymphocyte-mediated cytotoxicity and humoral antibodies in human pregnancy. *Int Arch Allergy Appl Immunol* 1980;61:467-71.
- 6 Lederman MM. Cell-mediated immunity and pregnancy. *Chest* 1984;86:6-9S.
- 7 Sridama V, Pacini F, Yang SL, et al. Decreased levels of helper T cells: a possible cause of immunodeficiency in pregnancy. *N Engl J Med* 1982;307:352-6.
- 8 Nyhan D, Quigley C, Bredin CP. Acute respiratory failure in pregnancy due to staphylococcal pneumonia. *Ir Med J* 1983;76:320-1.
- 9 MacLennan FM. Maternal mortality from Mendelson's syndrome: an explanation? *Lancet* 1986;i:587-9.
- 10 Finland M, Dublin TD. Pneumococcal pneumonias complicating the pregnancy and puerperium. *JAMA* 1939;250:1027-32.
- 11 Hopwood HG. Pneumonia in pregnancy. *Obstet Gynecol* 1965;25:875-9.
- 12 Benedetti TJ, Valle R, Ledger WJ. Antepartum pneumonia in pregnancy. *Am J Obstet Gynecol* 1982;144:413-7.
- 13 Madinger NE, Greenspoon JS, Ellrodt AG. Pneumonia during pregnancy: has modern technology improved maternal and fetal outcome? *Am J Obstet Gynecol* 1989;161:657-62.
- 14 Berkowitz K, LaSala A. Risk factors associated with the increasing prevalence of pneumonia during pregnancy. *Am J Obstet Gynecol* 1990;163:981-5.
- 15 Richey SD, Roberts SW, Ramin KD, et al. Pneumonia complicating pregnancy. *Obstet Gynecol* 1994;84:525-8.
- 16 Yost NP, Bloom SL, Richey SD, et al. An appraisal of treatment guidelines for antepartum community-acquired pneumonia. *Am J Obstet Gynecol* 2000;183:131-5.
- 17 Jokinen C, Heiskanen L, Juvonen H, et al. Incidence of community-acquired pneumonia in the population of four municipalities in eastern Finland. *Am J Epidemiol* 1993;137:977-88.
- 18 Foy HM, Cooney MK, Allan I, et al. Rates of pneumonia during influenza epidemics in Seattle, 1964 to 1975. *JAMA* 1979;241:253-8.
- 19 Woodhead MA, Macfarlane JT, McCracken JS, et al. Prospective study of the aetiology and outcome of pneumonia in the community. *Lancet* 1987;i:671-4.
- 20 Visscher HC, Visscher RD. Indirect obstetric deaths in the state of Michigan 1960-1968. *Am J Obstet Gynecol* 1971;109:1187-96.
- 21 Lim WS, Lewis S, Macfarlane JT. Severity prediction rules in community acquired pneumonia: a validation study. *Thorax* 2000;55:219-23.
- 22 British Thoracic Society and Public Health Laboratory Service. Community-acquired pneumonia in adults in British hospitals in 1982-1983: a survey of aetiology, mortality, prognostic factors and outcome. *Q J Med* 1987;62:195-220.
- 23 Marrie TJ, Peeling RW, Fine MJ, et al. Ambulatory patients with community-acquired pneumonia: the frequency of atypical agents and clinical course. *Am J Med* 1996;101:508-15.
- 24 Munn MB, Groome LJ, Atterbury JL, et al. Pneumonia as a complication of pregnancy. *J Matern Fetal Med* 1999;8:151-4.
- 25 Rotmensch S, Vishne TH, Celentano C, et al. Maternal infectious morbidity following multiple courses of beta-methasone. *J Infect* 1999;39:49-54.
- 26 Maccato M. Respiratory insufficiency due to pneumonia in pregnancy. *Obstet Gynecol Clin North Am* 1991;18:289-99.
- 27 Goodrum LA. Pneumonia in pregnancy. *Semin Perinatol* 1997;21:276-83.
- 28 Nuorti JP, Butler JC, Farley MM, et al. Cigarette smoking and invasive pneumococcal disease. Active Bacterial Core Surveillance Team. *N Engl J Med* 2000;342:681-9.
- 29 Almirall J, Bolibar I, Balanzo X, et al. Risk factors for community-acquired pneumonia in adults: a population based case-control study. *Eur Respir J* 1999;13:349-55.
- 30 Milne JA, Howie AD, Pack AI. Dyspnoea during normal pregnancy. *Br J Obstet Gynaecol* 1978;85:260-3.
- 31 Burlew BS. Managing the pregnant patient with heart disease. *Clin Cardiol* 1990;13:757-62.
- 32 Zeldis SM. Dyspnea during pregnancy. Distinguishing cardiac from pulmonary causes. *Clin Chest Med* 1992;13:567-85.
- 33 Diethelm L, Xu H. Diagnostic imaging of the lung during pregnancy. *Clin Obstet Gynecol* 1996;39:36-55.
- 34 Libshitz HI, Baber CE, Hammond CB. The pulmonary metastases of choriocarcinoma. *Obstet Gynecol* 1977;49:412-6.
- 35 Tewari K, Wold SM, Asrat T. Septic shock in pregnancy associated with legionella pneumonia: case report. *Am J Obstet Gynecol* 1997;176:706-7.
- 36 Pebody RG, Wall PG, Ryan MJ, et al. Epidemiological features of *Coxiella burnetii* infection in England and Wales: 1984 to 1994. *Commun Dis Rep CDR Rev* 1996;6:R128-32.
- 37 Raoult D, Stein A. Q fever during pregnancy: a risk for women, fetuses and obstetricians. *N Engl J Med* 1994;330:371-?
- 38 Raoult D, Tissot-Dupont H, Foucault C, et al. Q fever 1985-1998. Clinical and epidemiologic features of 1383 infections. *Medicine (Baltimore)* 2000;79:109-23.
- 39 McKinney WP, Volkert P, Kaufman J. Fatal swine influenza pneumonia during late pregnancy. *Arch Intern Med* 1990;150:213-5.
- 40 Larsen JW Jr. Influenza and pregnancy. *Clin Obstet Gynecol* 1982;25:599-603.
- 41 Hollingsworth HM, Pratter MR, Irwin RS. Acute respiratory failure in pregnancy. *J Intensive Care Med* 1989;4:11-34.
- 42 MacKenzie JS, Houghton M. Influenza infections during pregnancy: association with congenital malformations and with subsequent neoplasms in children, and potential hazards of live virus vaccines. *Bacteriol Rev* 1974;38:356-70.
- 43 Miller E, Vardien J, Farrington P. Shift in age in chickenpox. *Lancet* 1993;341:308-9.
- 44 Gray GC, Palinkas LA, Kelley PW. Increasing incidence of varicella hospitalizations in United States Army and Navy personnel: are today's teenagers more susceptible? Should recruits be vaccinated? *Pediatrics* 1990;86:867-73.
- 45 Sloan DS, Burlison A. Shift in age in chickenpox. *Lancet* 1992;340:974.
- 46 Stagno S, Whitley RJ. Herpesvirus infections of pregnancy. Part II: Herpes simplex virus and varicella-zoster virus infections. *N Engl J Med* 1985;313:1327-30.
- 47 Fox GN, Strangarity JW. Varicella-zoster virus infections in pregnancy. *Am Fam Physician* 1989;39:89-98.
- 48 Weller TH. Varicella and herpes zoster. Changing concepts of the natural history, control, and importance of a not-so-benign virus. *N Engl J Med* 1983;309:1434-40.
- 49 Weller TH. Varicella and herpes zoster. Changing concepts of the natural history, control, and importance of a not-so-benign virus. *N Engl J Med* 1983;309:1362-8.
- 50 Paryani SG, Arvin AM. Intrauterine infection with varicella-zoster virus after maternal varicella. *N Engl J Med* 1986;314:1542-6.
- 51 Baren JM, Henneman PL, Lewis RJ. Primary varicella in adults: pneumonia, pregnancy, and hospital admission. *Ann Emerg Med* 1996;28:165-9.
- 52 Straus SE, Ostrove JM, Inchauste G, et al. NIH conference. Varicella-zoster virus infections. Biology, natural history, treatment, and prevention. *Ann Intern Med* 1988;108:221-37. (Published erratum appears in *Ann Intern Med* 1988;109:438-9.)
- 53 Nathwani D, Maclean A, Conway S, et al. Varicella infections in pregnancy and the newborn. A review prepared for the UK Advisory Group on Chickenpox on behalf of the British Society for the Study of Infection. *J Infect* 1998;36(Suppl 1):59-71.
- 54 Esmonde TF, Herdman G, Anderson G. Chickenpox pneumonia: an association with pregnancy. *Thorax* 1989;44:812-5.
- 55 Smego RA Jr, Asperilla MO. Use of acyclovir for varicella pneumonia during pregnancy. *Obstet Gynecol* 1991;78:1112-6.
- 56 Chandra PC, Patel H, Schiavello HJ, et al. Successful pregnancy outcome after complicated varicella pneumonia. *Obstet Gynecol* 1998;92:680-2.
- 57 Mouly F, Mirlisse V, Meritet JF, et al. Prenatal diagnosis of fetal varicella-zoster virus infection with polymerase chain reaction of amniotic fluid in 107 cases. *Am J Obstet Gynecol* 1997;177:894-8.
- 58 Stein SJ, Greenspoon JS. Rubella during pregnancy. *Obstet Gynecol* 1991;78:925-9.
- 59 Biem J, Roy L, Halik J, et al. Infectious mononucleosis complicated by necrotizing epiglottitis, dysphagia, and pneumonia. *Chest* 1989;96:204-5.
- 60 Korones SB. Uncommon virus infections of the mother, fetus, and newborn: influenza, mumps and measles. *Clin Perinatol* 1988;15:259-72.

- 61 Gilson GJ, Maciulla JA, Nevils BG, *et al.* Hantavirus pulmonary syndrome complicating pregnancy. *Am J Obstet Gynecol* 1994;171:550-4.
- 62 Catanzaro A. Pulmonary mycosis in pregnant women. *Chest* 1984;86:14-8S.
- 63 Wack EE, Ampel NM, Galgiani JN, *et al.* Coccidioidomycosis during pregnancy. An analysis of ten cases among 47,120 pregnancies. *Chest* 1988;94:376-9.
- 64 Ely EW, Peacock JE Jr, Haponik EF, *et al.* Cryptococcal pneumonia complicating pregnancy. *Medicine (Baltimore)* 1998;77:153-67.
- 65 LaGatta MA, Jordan C, Khan W, *et al.* Isolated pulmonary cryptococcosis in pregnancy. *Obstet Gynecol* 1998;92:682-4.
- 66 Chakravarty A, Salgia R, Mason E, *et al.* Pneumonia and infraorbital abscess in a 29-year-old diabetic pregnant woman. *Chest* 1995;107:1752-4.
- 67 MacDonald D, Alguire PC. Adult respiratory distress syndrome due to blastomycosis during pregnancy. *Chest* 1990;98:1527-8.
- 68 Ismail MA, Lerner SA. Disseminated blastomycosis in a pregnant woman: review of amphotericin B usage during pregnancy. *Am Rev Respir Dis* 1982;126:350-3.
- 69 Neiberg AL, Mavromatis F, Fayyad A. Blastomyces dermatitidis treated during pregnancy: report of a case. *Am J Obstet Gynecol* 1977;128:911-2.
- 70 Wallace JM, Rao AV, Glassroth J, *et al.* Respiratory illness in persons with human immunodeficiency virus infection. The Pulmonary Complications of HIV Infection Study Group. *Am Rev Respir Dis* 1993;148:1523-9.
- 71 Hirschtick RE, Glassroth J, Jordan MC, *et al.* Bacterial pneumonia in persons infected with the human immunodeficiency virus. Pulmonary Complications of HIV Infection Study Group. *N Engl J Med* 1995;333:845-51.
- 72 Baril L, Astagneau P, Nguyen J, *et al.* Pyogenic bacterial pneumonia in human immunodeficiency virus-infected inpatients: a clinical, radiological, microbiological, and epidemiological study. *Clin Infect Dis* 1998;26:964-71.
- 73 Wallace JM, Hansen NI, Lavange L, *et al.* Respiratory disease trends in the Pulmonary Complications of HIV Infection Study cohort. Pulmonary Complications of HIV Infection Study Group. *Am J Respir Crit Care Med* 1997;155:72-80.
- 74 Afessa B, Green B. Bacterial pneumonia in hospitalized patients with HIV infection. The pulmonary complications, ICU support, and prognostic factors of hospitalized patients with HIV(PIP) study. *Chest* 2000;117:1017-22.
- 75 Nicoll A, McGarrigle C, Brady AR, *et al.* Epidemiology and detection of HIV-1 among pregnant women in the United Kingdom: results from national surveillance 1988-96. *BMJ* 1998;316:253-8.
- 76 Weisser M, Rudin C, Battagay M, *et al.* Does pregnancy influence the course of HIV infection? Evidence from two large Swiss cohort studies. *J Acquir Immune Defic Syndr Hum Retroviro* 1998;17:404-10.
- 77 Hicks ML, Nolan GH, Maxwell SL, *et al.* Acquired immunodeficiency syndrome and *Pneumocystis carinii* infection in a pregnant woman. *Obstet Gynecol* 1990;76:480-1.
- 78 Minkoff H, deRegt RH, Landesman S, *et al.* *Pneumocystis carinii* pneumonia associated with acquired immunodeficiency syndrome in pregnancy: a report of three maternal deaths. *Obstet Gynecol* 1986;67:284-7.
- 79 Koonin LM, Ellerbrock TV, Atrash HK, *et al.* Pregnancy-associated deaths due to AIDS in the United States. *JAMA* 1989;261:1306-9.
- 80 Saade GR. Human immunodeficiency virus (HIV)-related pulmonary complications in pregnancy. *Semin Perinatol* 1997;21:336-50.
- 81 Carpenter CC, Fischl MA, Hammer SM, *et al.* Antiretroviral therapy for HIV infection in 1998: updated recommendations of the International AIDS Society USA Panel. *JAMA* 1998;280:78-86.
- 82 Krantz ML, Edwards WL. The incidence of nonfatal aspiration in obstetric patients. *Anesthesiology* 1973;39:359.
- 83 Macfarlane JT. Acute respiratory infections in adults. In: Brewis RAL, Corrin B, Geddes DM, Gibson GJ, eds. *Respiratory medicine*. London: WB Saunders, 1995: 705-46.
- 84 American Thoracic Society. Hospital-acquired pneumonia in adults: diagnosis, assessment of severity, initial antimicrobial therapy, and preventive strategies. A consensus statement. *Am J Respir Crit Care Med* 1996;153:1711-25.
- 85 Departments of Health. Pneumococcal infection. In: Salisbury DM, Begg NT, eds. *Immunisation against infectious disease*. London: HMSO, 1996: 167-72.
- 86 Gubareva LV, Kaiser L, Hayden FG. Influenza virus neuraminidase inhibitors. *Lancet* 2000;355:827-35.
- 87 Departments of Health. Influenza. In: Salisbury DM, Begg NT, eds. *Immunisation against infectious disease*. London: HMSO, 1996: 113-20.
- 88 Chapman SW, Bradsher RW Jr, Campbell GD Jr, *et al.* Practice guidelines for the management of patients with blastomycosis. Infectious Diseases Society of America. *Clin Infect Dis* 2000;30:679-83.
- 89 Galgiani JN, Ampel NM, Catanzaro A, *et al.* Practice guideline for the treatment of coccidioidomycosis. Infectious Diseases Society of America. *Clin Infect Dis* 2000;30:658-61.
- 90 Saag MS, Graybill RJ, Larsen RA, *et al.* Practice guidelines for the management of cryptococcal disease. Infectious Diseases Society of America. *Clin Infect Dis* 2000;30:710-8.
- 91 NHS Northern and Yorkshire Regional Drug and Therapeutics Centre. *Antibiotics: use in pregnancy review*. National Teratology Information Service, July 2000.
- 92 Briggs GG, Freeman RK, Yaffe SJ. Trimethoprim. In: *Drugs in pregnancy and lactation*. Baltimore, Maryland: Williams and Wilkins, 1998: 1061-2.
- 93 Hurlburt KM. *ReproRisk system*. Englewood, Colorado: Micromedex Inc (edition expires end 2000).
- 94 King CT, Rogers PD, Cleary JD, *et al.* Antifungal therapy during pregnancy. *Clin Infect Dis* 1998;27:1151-60.
- 95 Bar-Oz B, Moretti ME, Bishai R, *et al.* Pregnancy outcome after in utero exposure to itraconazole: a prospective cohort study. *Am J Obstet Gynecol* 2000;183:617-20.