Introduction

Antiphospholipid syndrome (APS) predominantly affects young women and there has been a growing awareness of this condition amongst obstetricians and gynecologists over the last 15 years. In this chapter we discuss the association between APS and adverse pregnancy outcome and present some of the dilemmas in the management of on-going pregnancies in women with APS. Although clinicians are becoming increasingly familiar with these management options, knowledge of the pathogenesis of poor pregnancy outcome in APS remains incomplete, and in the last part of this chapter we outline some of the areas of research in this rapidly evolving field.

Making the Diagnosis of APS

The criteria for the classification of APS are well described [1] and it is critical that these are applied strictly to avoid inappropriate management of patients [2]. Similarly, even in those with a robust diagnosis, all adverse pregnancy outcomes should not be entirely attributed to the syndrome as there are numerous other associations with poor outcome that may be causative or contributory, for example, cervical incompetence, “unexplained” intrauterine death. It is therefore essential to apply good clinical judgment in each individual case to avoid interventions that may be unnecessary or even harmful.

The Effect of Pregnancy on APS

Pregnancy is a hypercoagulable state and women with APS are at increased risk of thrombosis unless thromboprophylaxis or anticoagulation is adequate. Some studies have demonstrated that a significant proportion of pregnant patients still have thrombotic episodes despite thromboprophylaxis [3, 4]. These patients need long-term anticoagulation with warfarin aiming for an international normalized ratio (INR) of at least 2.0–2.9 [5]. Pregnancy can also exacerbate pre-existing
thrombocytopenia, and this may be further compounded by medication because aspirin and heparin administered during pregnancy may cause thrombocytopenia. Thromboprophylaxis, full anticoagulation, and the management of thrombocytopenia in pregnant women with APS are discussed in more detail below.

The Effect of APS on Pregnancy

APS and Early Pregnancy Complications

Many cases of APS are diagnosed following investigation of recurrent miscarriage. The association between APS and recurrent miscarriage is well known [6–9], with second trimester loss being particularly common [10]. The prospective fetal loss rate in primary APS is reported to be 50% to 75% [11, 12]. In patients with systemic lupus erythematosus (SLE) and secondary APS some studies suggest this may be as high as 90% [13, 14], although this is likely to be an overestimate. It has been suggested that the risk of fetal loss is directly related to the antibody titer [15, 16], but this is certainly not true of all cases. Some studies have shown maternal IgG aCL to be a particularly reliable predictor of miscarriage [17, 18]. Although this makes theoretical sense as this subfraction of antibodies can cross into the fetoplacental circulation [19], many women with recurrent miscarriage have IgM aCL antibodies only. It is impossible to predict which women will develop complications in pregnancy, and some women with persistently elevated aPL titers and a history of thromboses and/or thrombocytopenia will have no obstetric complications at all. Previous poor pregnancy outcome remains the most important predictor of future risk [20–22].

APS and Late Pregnancy Complications

In pregnancies that do not end in miscarriage or fetal loss, there is a high incidence of early onset pre-eclampsia (PET) [23–26] and intrauterine growth restriction (IUGR) [20, 27], placental abruption [28], and premature delivery [29, 30]. Because patients with APS form a heterogeneous group, the incidence of these complications varies between units. Indeed it is now clear that the substantial differences in APS patient populations in studies of pregnancy inevitably results in large differences in reported adverse pregnancy outcomes, and whilst attempts are being made to define management in certain subgroups, many recommendations are not strictly evidence based [31, 32]. Those units which manage women with systemic manifestations of APS have a higher incidence of complications in pregnancy [33], whilst those which recruit women predominantly from recurrent miscarriage clinics have a lower incidence of these complications [34, 35]. It is essential to appreciate these differences in order to critically appraise the literature, advise women appropriately, and rationalize therapy [36]. In a recent study from our own unit, 35 pregnancies in women with primary APS resulted in a live birth in 32 cases (91%) with a mean gestation of 38.4 (27.5–42) weeks and a mean birth weight of 2895 ± 165 g. Complications included miscarriage in 3 cases (9%), fetal growth restriction in 4 cases (12%), placental abruption in 1 case (3%), pre-eclampsia in 2 cases (6%), pre-term delivery in 8 cases (24%), and maternal thrombotic events in 5 cases (14%). Labor was induced in 8 (25%) cases and delivery was by Caesarean section in 19
cases. Five (16%) babies required neonatal intensive care [37]. A summary of the outcomes in APS pregnancies reported in the main studies is shown in Table 44.1.

The early prediction of women with APS who are likely to develop complications in pregnancy remains a challenge. Several studies have recommended uterine artery Doppler waveform analysis in these women [38, 39]. In a study of APS pregnancies, bilateral uterine artery notches at 22–24 weeks gestation represented a likelihood ratio for prediction of pre-eclampsia of 12.8 [95% confidence interval (CI), 2.2-75] with a sensitivity of 75% and a specificity of 94% and a negative predictive value of 94%, and similar statistics were obtained for the prediction of fetal growth restriction [40]. Other studies in APS pregnancies have confirmed the reassuring nature of absence of bilateral uterine artery notches at even lower gestations [41]. Histological evidence of impaired trophoblast migration in placental bed biopsies from women showing these high resistance Doppler waveforms has been reported [42], although the extent of uteroplacental pathology does not always correlate with the severity of maternal or fetal disease.

Therapeutic Options in APS Pregnancies

Many therapeutic options have been tried in APS pregnancies and the risks and benefits of each form of therapy continue to be an active area of debate [43]. A meta-analysis of therapeutic trials in pregnant women with APS has recently been published but the conclusions need to be interpreted with caution due to the small number of patients in most studies, differences in diagnostic laboratory methods, and variable inclusion criteria [44]. The most commonly used medications are aspirin, heparin, warfarin, and steroids. A summary of the side-effects of these drugs is shown in Table 44.2. Pre-conceptual review of medication is useful as it allows clinicians to place each patient in a risk category and treat her accordingly. These individualized treatment regimes limit the problems associated with polypharmacy in pregnancy and enable resources to be invested appropriately.

Aspirin

Women with APS are advised to take low-dose aspirin (75 mg daily) in pregnancy. The rationale for this is aspirin-mediated inhibition of thromboxane, increased vasodilation, and subsequent reduced risk of thromboses in the placenta and else-

Table 44.1. Pregnancy outcomes in different populations of women with antiphospholipid syndrome.

<table>
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<tr>
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<tbody>
<tr>
<td>Pregnancies (n)</td>
<td>82</td>
<td>60</td>
<td>53</td>
<td>150</td>
</tr>
<tr>
<td>Population</td>
<td>Predominantly systemic</td>
<td>Predominantly systemic</td>
<td>Predominantly recurrent miscarriage</td>
<td>All recurrent miscarriage</td>
</tr>
<tr>
<td>PET (%)</td>
<td>51</td>
<td>18</td>
<td>3</td>
<td>11</td>
</tr>
<tr>
<td>IUGR (%)</td>
<td>31</td>
<td>31</td>
<td>11</td>
<td>15</td>
</tr>
<tr>
<td>Preterm delivery (%)</td>
<td>37</td>
<td>43</td>
<td>8</td>
<td>24</td>
</tr>
</tbody>
</table>

Adapted from Ref. 36.
where. However, the use of aspirin in APS pregnancies has never been subjected to a randomized trial, although several non-randomized studies suggest it is beneficial [45–47], and there are animal data to support this [48]. In low risk APS pregnancies, that is, no previous thromboses or miscarriages, a randomized controlled trial of aspirin versus no aspirin failed to show any benefit of treatment [49]. Damage to the developing trophoblast occurs early in pregnancy and therefore if aspirin is used it is likely to be of most benefit if administered from the pre-conceptual period as use of aspirin from the mid-trimester onwards has been shown to be of no benefit in reducing the incidence of adverse pregnancy outcome in high risk groups [50]. Treatment is usually continued at least until delivery if not into the puerperium. Low-dose aspirin does not affect the use of regional anesthesia during labor. Renal and hepatic impairment do not occur with this dose of aspirin and bronchospasm is exceptionally rare affecting a minority of asthmatics. There are no adverse fetal or neonatal effects from the use of low-dose aspirin.

**Heparin**

Women with APS and a previous history of thromboembolism are treated with heparin as thromboprophylaxis in pregnancy. For those with recurrent pregnancy loss or previous adverse pregnancy outcome but without a history of thromboembolism, there is as yet no consensus of opinion [51]. Some studies have suggested that heparin therapy in addition to aspirin may contribute to improved fetal outcome [52]. One group has shown improved fetal outcome using heparin [53] or LMWH alone [54]. Most specialist units caring for pregnant women with APS use aspirin and low-molecular-weight heparin (LMWH) together in women with a history of thrombosis or second trimester loss, and there is some evidence of improved pregnancy outcome with the use of heparin in women with recurrent first trimester loss [55, 56], although not all studies have shown a benefit in this subgroup [57]. Those women who wish to take LMWH during pregnancy for fetal indications, for example, recurrent miscarriage, previous intrauterine death, pre-

**Table 44.2. Therapeutic options in antiphospholipid syndrome pregnancies.**

<table>
<thead>
<tr>
<th>Maternal side effects</th>
<th>Fetal side effects</th>
<th>Breastfeeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>Gl disturbances</td>
<td>Safe</td>
</tr>
<tr>
<td>Warfarin</td>
<td>Gl disturbances</td>
<td>Teratogenic</td>
</tr>
<tr>
<td></td>
<td>Hypersensitivity</td>
<td>Hemorrhage</td>
</tr>
<tr>
<td></td>
<td>Hemorrhage</td>
<td>Miscarriage</td>
</tr>
<tr>
<td>Heparin</td>
<td>Osteoporosis</td>
<td>Safe</td>
</tr>
<tr>
<td></td>
<td>Thrombocytopenia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hemorrhage/bruising</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hypersensitivity</td>
<td></td>
</tr>
<tr>
<td>Prednisolone</td>
<td>Infection</td>
<td>Safe</td>
</tr>
<tr>
<td></td>
<td>Diabetes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hypertension</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Osteoporosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Peptic ulceration</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Muscle wasting</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cushing’s syndrome</td>
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<tr>
<td></td>
<td>Depression/psychosis</td>
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eclampsia, or fetal growth restriction, usually receive once daily thromboprophylactic doses. However, those with previous thromboses are often given high dose thromboprophylaxis in the form of twice daily administration (e.g., Enoxaparin 40 mg SC b.i.d.) to minimize the risk of recurrent thromboses during pregnancy which might necessitate treatment with either therapeutic doses of LMWH or oral anticoagulation with warfarin. Whether LMWH is being administered for fetal or maternal indications or both, the potential benefits of treatment should be balanced against the risk of heparin-induced osteoporosis [58-60]. The problem of osteoporosis is compounded by concomitant use of steroid medication, and indeed by pregnancy itself [61-63]. LMWHs are commonly used in APS patients because of the convenience of once daily administration (in most cases), the improved antithrombotic (áXa) to anticoagulant (áIIa) ratio, the decreased risk of heparin-induced thrombocytopenia, and the probable decreased risk of heparin-induced osteoporosis [64]. However, there have been small case series reporting osteoporotic fractures with LMWH administered in therapeutic doses [65]. Systematic review of all studies of LMWH use in pregnancy confirms a very low (0.09%) risk of osteoporosis [66]. Although Factor Xa levels may be used to monitor LMWH [67], experience has shown that doses are virtually never altered as a result [60], and therefore it is not necessary to measure Factor Xa levels routinely [68]. LMWH administration is omitted at least 12 hours prior to elective delivery, but in case urgent delivery is necessary, reversal with protamine sulphate is possible. The molecular weight of unfractionated heparin ranges from 12–15 kDa and that of LMWH from 4–5 kDa therefore neither preparation is able to cross the placenta. Heparin is not excreted into breast milk [69].

**Warfarin**

When there has been a thrombotic event in the index pregnancy despite heparin thromboprophylaxis, or in women with a history of previous cerebrovascular thromboses, the risk of recurrence is sufficiently high to consider antenatal administration of warfarin [70]. In practice the use of warfarin is avoided in the first trimester unless a woman develops transient ischemic attacks or other thrombotic events at that time. This is because, unlike heparin, warfarin does cross the placenta and is potentially teratogenic producing a typical embryopathy characterized by nasal hypoplasia, stippled epiphyses, rhizomelia (short proximal limbs), digital dysplasia, eye abnormalities, and developmental delay [71]. The exact incidence of these anomalies is unknown largely due to case-reporting bias. Review of the literature suggests that it is between 2% to 4% [72], but there appears to be a dose dependent incidence of complications with a higher number of complications in pregnant women receiving more than 5 mg per day [73, 74]. Patients require close supervision and regular INR estimates maintaining values between 2.0–2.5. It must be remembered that the maternal INR does not accurately reflect the fetal coagulation status and animal studies show that the risk of fetal intravascular hemorrhage is still present despite optimum maternal control [75]. The fetus is therefore at risk throughout pregnancy during the period of warfarin administration [76]. A fortnight before planned delivery, warfarin is discontinued and either an intravenous infusion of unfractionated heparin or therapeutic doses of subcutaneous LMWH is commenced. This allows sufficient time for clearance of warfarin by both mother and fetus to occur. Every attempt should be made to avoid rapid reversal of war-
farin anticoagulation with vitamin K at the time of delivery as this makes subsequent anticoagulation in the post-natal period difficult. There is no evidence to suggest that fetal outcome is improved with the use of warfarin. There is no significant excretion of warfarin into breast milk [77, 78].

**Steroids**

In the past, high dose steroids (greater than or equal to 60 mg daily) were used to suppress lupus anticoagulant (LA) and anticardiolipin antibodies (aCL) and some studies reported improved fetal survival [79, 80]. However, these therapeutic regimes resulted in considerable maternal morbidity including gestational diabetes, hypertension, and sepsis, and subsequent studies failed to show an improvement in pregnancy outcome [46, 81]. Cowchock et al demonstrated that aspirin and heparin gave equivalent fetal outcomes when compared with aspirin and steroids with significantly less maternal morbidity [52], and more recently there have been suggestions that steroid use may be detrimental to fetal outcome by promoting pre-term delivery [82]. Therefore the use of steroids in APS pregnancies has been abandoned except for the treatment of maternal thrombocytopenia or co-existent SLE for which prednisolone is still first line therapy. Regular blood glucose monitoring is required with long-term administration of steroids. Patients requiring more than 7.5 mg prednisolone daily for more than 2 weeks prior to delivery should be given intra-partum intravenous hydrocortisone 100 mg t.i.d.. Breastfeeding is rarely contraindicated, although women taking greater than 60 mg prednisolone with healthy term babies may consider bottle-feeding because of the theoretical risk of neonatal hypothalamic–pituitary adrenal suppression at these high doses.

**Others**

Immunosupression with azathioprine, intravenous immunoglobulin [83–85], plasma exchange [86], and interleukin-3 therapy [87] have all been tried in APS pregnancies. Due to the cost of immunoglobulin therapy, this treatment has previously been limited to salvage therapy in women who develop complications despite treatment with aspirin and heparin [88]. Initial reports using a 2 g/kg course of intravenous immunoglobulin administered in divided doses over 2–5 days in the second or early third trimester in pregnancies complicated by IUGR suggested a temporary improvement in uteroplacental Doppler waveforms [89]. More recently, a randomized controlled trial of intravenous immunoglobulin versus aspirin and heparin in 40 women with APS associated recurrent miscarriage showed a live birth rate of only 57% in the immunoglobulin group compared with 84% in the aspirin and heparin group [90]. Thus, although initially promising, immunoglobulin therapy does not appear to be beneficial in APS pregnancies.

**Management of APS Pregnancies at St. Thomas’ Hospital**

St. Thomas Hospital is a national referral center for APS and there is a weekly antenatal clinic for pregnant women with APS. Many of these women are well known to
the rheumatology and hematology services and this allows pre-conceptual counseling in most cases. At this visit women undergo a risk assessment and future therapy is planned. Many women with APS have related disorders also addressed at that time, for example, SLE or thrombocytopenia. Apart from the standard pre-pregnancy advice, for example, folic acid, women who are not already taking aspirin are advised to start from the pre-conceptual period onwards until delivery. LMWH is offered to women who are taking long-term oral anticoagulation, those with previous thrombotic events and those with 1 or more previous second trimester losses. LMWH is administered immediately after ultrasound confirmation of a viable intrauterine pregnancy, but not pre-conceptually in order to limit the time of heparin usage. Women are regularly reviewed by a multi-disciplinary team and the frequency of visits depends on the presence of any complications and practical issues such as commuting distance.

As well as routine aspects of ante-natal care offered to all pregnant women, for example, screening for chromosomal abnormalities and mid-trimester ultrasound examination of the fetus, women with APS are offered Doppler analysis of uterine artery wave forms at 20 and 24 weeks gestation. In the third trimester, “high risk” women with APS, for example, abnormal Doppler assessment of the uterine arteries or previous late pregnancy complications, are offered 4 weekly scans, whereas those at the milder end of the APS spectrum, for example, recurrent first trimester losses only, are offered scans at 28 and 34 weeks gestation. In cases with suspected fetal growth restriction, biophysical profiles are performed to further assess fetal well being. LMWH is discontinued at 20 weeks gestation in women with a history of recurrent first trimester miscarriage alone and normal uterine artery Dopplers at this time as the benefits of LMWH have not been demonstrated beyond this gestation in this sub-group of patients. In the other women, LMWH is continued up to the time of delivery and for 6 weeks afterwards [91]. Those with previous thromboses taking long-term anticoagulant therapy are converted back to warfarin after delivery.

Women have direct access to hospital 24 hours a day and inpatients are regularly reviewed by a multi-disciplinary team. Women who develop pre-eclampsia are managed according to the standard hospital protocol. A specialist team of midwives care for these high risk pregnancies and this provides continuity of care. Obstetric anesthetists are involved when planning delivery especially in women who are fully anti-coagulated. A bereavement counseling service is provided by consultant obstetricians, specialist midwives, and neonatologists where appropriate.

Pathogenesis of Adverse Pregnancy Outcome in APS

The safe and successful treatment of pregnant women with APS lies in understanding the etiology of this condition and the mechanism by which complications in pregnancy may arise. As yet there are many more questions than answers [92]. Most research has been in the form of drug trials and conclusions have been largely unconvincing due to small numbers, poor study design, and variable entry criteria and outcome measures. More recently there has been a shift in emphasis to more laboratory based research using models for trophoblast development and molecular
biological techniques to determine various aspects of antibody–endothelial interactions [93].

**Early Pregnancy Failure**

Early pregnancy failure is likely to be due to impaired development of the trophoblast and failure to establish an effective fetoplacental circulation. The factors governing trophoblast invasion and early placental development are multiple and complex. Some factors specific to APS pregnancies have been well characterized, in particular \( \beta_2 \)-glycoprotein I (\( \beta_2 \)-GPI) [94]. In addition, aPL have been shown to directly alter trophoblastic hormone production and invasiveness in in vitro models [95], and, more interestingly, that LMWH restores trophoblast differentiation and invasiveness [96]. However, many others factors are also involved. It is likely that growth factors [97, 98], cytokines [99], integrins [100, 101], cell adhesion molecules [102, 103], and class I major histocompatibility complex antigens [104] are all instrumental. The effect of aPL on the function of these molecules has yet to be established.

**Late Pregnancy Failure**

Late pregnancy complications are likely to arise from damage to the uteroplacental vasculature. After 15 weeks gestation the vasculosyncitial membrane is porous enough for IgG antibodies to be able to cross into the fetal circulation. High concentrations of IgG antibodies have been eluted from placenta from women with aPL-positive sera with poor pregnancy outcomes [19]. Whether these aPL themselves are directly responsible for structural and/or functional damage to the placental vessels or whether they act indirectly via another secondary mechanism is unclear. It has been difficult to extrapolate antibody data from animal studies to clinical experience in humans [105, 106]. Some studies have suggested that aPL are involved in oxidant mediated damage to the vascular endothelium [107]. However, in order to recognize endothelial cells, aPL antibodies require the presence of certain co-factors [108, 109], the best characterized of which are \( \beta_2 \)-GPI [110] and prothrombin [111]. Much work has been done in this area but few conclusions drawn. Histological examination of placenta from APS pregnancies often show thromboses of the uteroplacental vasculature and placental infarction [112]. There may be decidual vasculopathy characterized by fibrinoid necrosis and atherosis of decidual vessels [113]. These findings suggest thrombotic damage to the fetoplacental circulation, and whilst some groups have published data to support this [114–116], others disagree [117, 118]. Another possibility is that placental dysfunction and subsequent fetal demise in APS pregnancies are secondary to the maternal vasculopathy which is thought to also affect placental bed vessels, and not to primary antibody mediated fetoplacental events at all. In this way, APS related adverse pregnancy outcome may be similar to that which occurs in women with pre-eclampsia without an underlying vasculopathy [119], or those with hereditary thrombophilias [120, 121]. Although the mechanisms causing utero-placental dysfunction in these pregnancies has attracted much interest in the last decade, recent research in a murine model suggests that the complement system has a major role in APS-related adverse pregnancy outcome [122].
Summary

Pregnant women with APS are at risk of complications at all stages of pregnancy. They require specialist care and a team approach involving obstetricians, obstetric physicians, rheumatologists, hematologists, neonatologists, and specialist midwives. Close monitoring of the various aspects of the condition may reduce maternal morbidity and improve fetal outcome. Therapeutic options include aspirin, LMWH, and, less commonly, warfarin and steroids.

The pathogenesis of the adverse pregnancy outcome in APS has not yet been fully elucidated although there is active research in this field. Until this is ascertained, we must accept that many aspects of management are purely empirical and it is our duty to counsel women thoroughly such that they understand the risks and benefits of the treatment options they are offered.

References


