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Review

Biologics in pregnancy – for the obstetrician

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Key content
- The authors discuss commencing biologics in pregnancy and the potential side effects. Infection is a particular risk, which may be atypical or present atypically.
- While there is no evidence of teratogenicity, these drugs cross the placenta and neonatal cord drug levels may exceed those of maternal drug levels.
- If possible, anti-tumour necrosis factor (TNF) agents should be discontinued midtrimester but the gestation to which each drug can be used is slightly different.
- Neonates exposed in utero to anti-TNF agents beyond the recommended gestation should not be given live attenuated vaccines for the first 6 months of life and any infections promptly treated.
- Data are lacking on the long-term effects of biologics on children exposed in utero. However, the benefits of controlling active autoimmune disease in the mother often outweigh the small risk to the exposed infants.

Learning objectives
- To know the biologics most commonly used in pregnancy.
- To understand the literature regarding safety of the common biologics in pregnancy.
- To be able to counsel a woman taking a biologic about the potential benefits and risks of taking it at different gestations.
- To be able to counsel a woman receiving biologics in pregnancy about vaccinations for her baby after birth.

Ethical issues
- Biologic agents are relatively new drugs that are being increasingly used in young women because of their perceived 'fertility sparing' benefits despite a lack of high quality evidence.
- Most women who have been prescribed biologics are often refractory to other treatments, and therefore these agents are required for disease control. The decision to continue or discontinue these drugs in pregnancy, especially late pregnancy, is particularly contentious.
- The long-term effect of biologics on infants exposed in utero is not known and the decision to use these drugs has to be balanced against the risk of severe maternal flares.

Keywords: biologics / infection / pregnancy / screening / vaccination

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Introduction

What are biologics and when are they used?

The term 'biologics' encompasses a wide variety of biologic molecules that include both human and murine monoclonal antibodies and soluble cytokine receptors. Commonly available examples that obstetricians may come across include infliximab, adalimumab, etanercept and rituximab; all of these are commonly used to treat young women with rheumatic diseases and a breadth of other immune-mediated conditions, including Crohn's disease, idiopathic thrombocypenic purpura, psoriasis and asthma.

Different biologic agents work at different sites, for example, to interfere with cytokine function (anti-tumour necrosis factor [TNF] agents, interleukin [IL]-1 and IL-6 inhibitors), to inhibit T-cell function via inhibition of the 'second signal' (blocking of CD80 and CD86 molecules) and to deplete B-cells (anti-CD20, that is rituximab). The classes of these biologics, examples and indications of the more commonly used agents are presented in Table 1.[1–8] All of these molecules cross the placenta to varying degrees and therefore have the potential to affect the fetus. However, the peglylated anti-TNF agent certolizumab does not cross the placenta quite so efficiently and may become the mainstay of

Table 1. Biologics and their uses

Type (*examples*)	Mode of action	Common indications
Anti-TNF agents *(infliximab, etanercept, adalimumab, golimumab, certolizumab)*	TNF is often present at high concentrations at any site of inflammation; anti-TNFs are engineered to block its formation thereby effectively ameliorating any inflammatory process.	Rheumatoid arthritis, juvenile idiopathic arthritis, psoriasis, psoriatic arthritis, ankylosing spondylitis, inflammatory bowel disease*, Wegener's* granulomatosis, sarcoidosis*.[1]
Anti-IL-1 *(anakinra)*	Provides competitive inhibition of IL-1 by binding to any IL-1 receptors in a wide variety of tissues. IL-1 is particularly involved in cartilage degradation and bone resorption.	Neonatal-onset multisystem inflammatory disorders, rheumatoid arthritis. It is less efficacious when compared to anti-TNF agents for the treatment of rheumatoid arthritis and therefore prescribed less frequently.[2]
Anti-IL-6 *(tociluzumab)*	Binds to soluble and membrane-bound IL-6 receptors, almost completely blocking the transmembrane signaling of IL-6 thereby inhibiting differentiation of T-helper cells and reducing B-cell activation and reduces acute-phase reactants.[3]	Rheumatoid arthritis refractory to anti-TNF agents and unable to tolerate B-cell depletion therapy (NICE guidelines),[4] juvenile idiopathic arthritis and Castleman's disease.
T-cell stimulator/inhibitor *(abatacept)*	Cytotoxic T lymphocyte-associated antigen 4 immunoglobulin fusion protein (CTLA-4 Ig) competes with CD28 to bind to CD80:86 thereby preventing the second signal required for full T-cell activation.[5]	Severe rheumatoid arthritis despite conventional disease-modifying anti-rheumatic drugs,[6] juvenile idiopathic arthritis.
B-cell depleting agents *(rituximab, belimumab)*	Rituximab is a chimeric monoclonal antibody against the protein CD20, primarily found on the surface of immune system B cells, and results in its destruction.[7]	Non-Hodgkin's lymphoma, chronic lymphocytic leukaemia, immune thrombocytopenic purpura, rheumatoid arthritis, granulomatosis with polyangiitis (i.e. Wegener's and microscopic polyangiitis).
	Belimumab inhibits B-cell activating factor, also known as B-lymphocyte stimulator.	Systemic lupus erythematosus and Sjögren's syndrome.[8]

*Etanercept is not effective for the treatment of Wegener's granulomatosis, inflammatory bowel disease and sarcoidosis.

biologic therapy in women of childbearing age in the very near future.[9]

The focus of this article will be on anti-TNF agents because these are the most commonly used drugs, and where most data pertaining to pregnancy are available. The evidence for other biologic agents is less robust and therefore many of these agents will have been discontinued prior to pregnancy.

Common side effects and precautions necessary for pregnant women

Unlike traditional drugs, biologics have a different classification to their adverse effect profile.[10] Clinicians caring for pregnant women will need to be specifically aware of the heightened risk of infections (Type γ reactions – immune or cytokine imbalance syndromes). All biologics are potent suppressors of various components or pathways of the immune system. Studies have demonstrated an increased vulnerability to infections.[11,12] Reactivation of latent infections, particularly tuberculosis (TB), can occur; hence guidelines are in place to screen and empirically treat any person at risk of latent TB prior to treatment with any biologic agent, particularly anti-TNF agents.[13] Infections may present atypically and there should be a high index of suspicion in screening for infections and aggressively treating any patient with an infection.

For similar reasons, it is advised that a person starting any biologic has all their vaccinations completed because any live vaccinations (for example, Bacillus Calmette–Guérin [BCG], measles, mumps, rubella [MMR], yellow fever, oral polio and rotavirus vaccinations) are contraindicated once a person is started on biologics.[14,15]

A woman commencing a biologic agent in pregnancy should undergo the same screening measures and vaccinations as a nonpregnant person, with the exception of live vaccinations. Chemoprophylaxis is needed in those with latent TB starting anti-TNF therapy; this is guided by a Respiratory Physician; in the UK this is usually with isoniazid with or without rifampicin, both of which are drugs that can be used in pregnancy.[13]

Certain malignancies are more common in those receiving anti-TNF therapy. Though not currently included in the UK guidelines, other national guidelines advocate screening for cervical cancer prior to commencing anti-TNF therapy.[16] Commencing anti-TNF therapy in those with a prior history of malignancy and those with premalignant conditions, for example human papillomavirus, should be undertaken with caution.[14] Pregnancy or the postpartum interval would be

Box 1. Case 1

A 32-year-old woman with erosive rheumatoid arthritis on adalimumab is referred by her rheumatologist for prepregnancy counselling. She has been told that this might not be a safe medication in pregnancy and could potentially lead to fetal malformations. In the past, she had been advised to discontinue the medications 6 months prior to becoming pregnant. On adalimumab, she is back to cycling and doing yoga. Prior to this medication she was on high doses of steroids, had Cushingoid features, yet remained stiff and had spent quite a lot of time off work. She has been told that once pregnant, her rheumatoid arthritis will 'melt away' and she will not need medication. It is best if she 'puts up with the pain' for a few months in order to have a safe and healthy pregnancy. How would you advise her?

ideal windows for opportunistic cervical screening in women on anti-TNF therapy.

If a woman is receiving a biologic infusion for the very first time in the antenatal setting, the team will need to be aware of the risk of immediate hypersensitivity-type reactions (Type β reactions); these are rare (3–5%) but may present as severe bronchospasm.[10] Type α reactions, as a result of the release of cytokines, are common and usually present as fever, headaches and myalgias. This is different from the well-publicised life-threatening cytokine storm from the Phase I trial of TGN1412 (a super-agonist CD28 T-cell co-stimulatory molecule) (Box 1).[17]

Anti-TNF use in early pregnancy

Teratogenicity of anti-TNF agents

In 2007, Carter et al.[18] first presented their work utilising the US Food and Drug Administration (FDA) Database (voluntary postmarketing reporting of any adverse events) to link anti-TNF use and VACTERL (vertebral, anal, cardio, tracheo-esophageal, renal, limb) type anomalies. This work was eventually published in 2009 amid heavy criticism, as there was emerging data on its safety from specialised biologic registries.[18] Of the 41 cases of congenital anomalies found in the offspring of women taking anti-TNF agents (the total number of pregnancies exposed to anti-TNF was not available), only one child fulfilled the VACTERL classification of having three of more of the anomalies described and none of the children had chromosomal anomalies excluded. Moreover, many of the anomalies included in the publication were commonly occurring anomalies, such as cardiac defects, hypospadias and limb anomalies, not specific for the VACTERL association and occur in 3–5% in the general population.[19] In addition, many of the women who were taking anti-TNF medications were on concurrent immunosuppressants, often methotrexate, which is teratogenic. Other factors such as maternal disease activity and lifestyle factors may also contribute to the risk of fetal anomalies but none of these factors were addressed by the FDA database study.[20]

Nevertheless, the negative publicity associated with the use of anti-TNF in pregnancy has led many rheumatologists and their specialty association's guidelines to advise the cessation of these agents prior to pregnancy. The British Society of Rheumatology (BSR) 2010 guidelines have suggested continuation of anti-TNF agents could be considered (in both male and female patients) if the risks of stopping treatment are perceived to be high.[14] Similarly, they have also suggested that clinicians should consider discontinuing a woman's anti-TNF agents once she is pregnant. These agents could be continued during pregnancy if the risks of cessation and subsequent flares are perceived to be unacceptably high.[14] In 2011, a published survey of rheumatologists and obstetricians in the UK showed that more than 90% of rheumatologists but only 54% of obstetricians would discontinue anti-TNF therapy during pregnancy.[21]

Fortunately, more recent publications from biologic databases (and large observational studies) have been reassuring with regards to the risk of teratogenicity and many authors now conclude that the risk of fetal malformations seen are similar to that of the general population.[22–31]

Anti-TNF use in fertility treatments

As the nationwide UK survey demonstrates, obstetricians appear to be more comfortable with the use of anti-TNF agents in pregnancy. The underlying reason for this could be that a number of fertility services are utilising anti-TNF agents, particularly adalimumab, to attempt to increase the chances of successful outcome by correcting the cytokine imbalances seen in women who require assisted conception.[32] Small observational studies from a single centre have shown that adalimumab (in combination with immunoglobulin) improves the rates of pregnancy in women undergoing in vitro fertilisation.[33]

With reassuring data emerging on the safety of anti-TNF in early pregnancy, it is often the practice now to encourage all women to continue on their anti-TNF therapy while attempting to conceive. For many, cessation of these drugs – particularly if there is a prolonged interval between drug cessation and successful conception – could result in recurrent active disease, which in itself is a barrier to a pregnancy.

Women with active disease in pregnancy have a higher risk of complications including features of placental-insufficiency, that is pre-eclampsia, fetal growth restriction, small-for-gestational-age infants and intrauterine demise.[20] Discussion of these risks and the higher risk of preterm birth (both

Box 2. Case 2

A 28-year-old woman with a long history of seronegative spondyloarthopathy refractory to conventional disease-modifying anti-rheumatic drugs presents at 22 weeks of gestation with back pain so severe that she is now wheelchair-bound. She discontinued her etanercept more than 6 months prior to conception. In early pregnancy, she developed a severe flare that was refractory to large doses of oral prednisolone.
What would your approach be to her management?

spontaneous and iatrogenic) and operative deliveries are often seen in women with connective tissue diseases. The risk will need to be individualised to each woman's underlying disease, severity of disease activity and consequences of the disease.[34]

As part of prepregnancy counselling, it is important to review all the woman's other medications to ensure that she is on 'pregnancy-friendly' drugs[34] and that an appropriate plan is made for pain relief options and vitamin supplements. Other consequences of chronic inflammatory conditions, such as the increased risk of venous thromboembolic disease, should be assessed and plans made for the antenatal and postnatal management of this as required.

Transplacental transfer and accumulation of anti-TNF drugs in the neonate

At present, the biggest concern of anti-TNF use in pregnancy relates to the transplacental transfer that occurs predominantly after 20 weeks of gestation. There are two factors that influence this: the efficiency of the transplacental transfer, which is dependent on the molecular structure of the Fc portion of the anti-TNF molecule, and the half-life of the drug used.[1]

As anti-TNF agents are immunoglobulins (Ig), transplacental transfer increases exponentially as the pregnancy progresses with maximal active transplacental transfer occurring after 28 weeks of gestation. Immunosuppression of the neonate is of major concern, though small observational studies have not demonstrated an increased risk of infections.

Infliximab, adalimumab and golimumab are IgG1 monoclonal antibodies of the IgG1 subclass that are actively transported across the placenta from the late second trimester onwards. The transfer across the placenta is initially limited by the cytotrophoblasts which then develop Fc receptors by 14 weeks of gestation. Transport is increasingly efficient as pregnancy progresses. By term, active transportation across the placental barrier ensures that drug levels in the neonate are often in excess of those in the maternal circulation. Moreover, the very long half-lives of adalimumab and infliximab (8–20 days) have led to very high levels (98–400% of maternal drug levels) of the active drug detected in the cord blood of the neonate (Table 2).[34–39]

To ensure that low levels of anti-TNF, or none at all, are detected in the cord blood, the latest BSR guidelines recommend that infliximab be discontinued by 16 weeks of gestation, and entanercept and adalimumab be discontinued by the third trimester.[40]

Table 2. Accumulation of anti-TNF agents in the neonate

Anti-TNF agent	Half-life (days)[1]	Cord blood to maternal serum concentrations (%)	Suggested gestation to discontinue (weeks)
Etanercept[35,36]	4	3.6–7.4	30–32
Infliximab[37–39]	8–10	83–400	21–22
Adalimumab[39]	10–20	98–293	26–28
Certolizumab[39]	14	1.5–24.0	28–32*

*Safe to continue throughout pregnancy.
Adapted from Soh and Nelson-Piercy[34], with permission from the British Society of Rheumatology. © 2015 British Society of Rheumatology.

Etanercept has a shorter half-life; with its modified Fc portion, it does not bind as effectively to the cytotrophoblasts. Therefore, transplacental passage of etanercept to the neonate is less efficient. Cord etanercept levels are much lower at only 3.6–7.4% of maternal drug levels.[35,36]

Pegylated anti-TNF agent, certolizumab, is now being touted as the 'pregnancy-friendly' anti-TNF agent. This is because its molecular structure prohibits active transplacental transport and therefore it is reliant on slow diffusion across the placental barrier to reach the developing fetus. However, it has a half-life of 14 days and the levels detected in the cord blood have varied from 1.5–24.0% of maternal drug levels (<2 microgram/ml).

Specific concerns about transplacental transfer to the neonate

Development of the neonatal immune system

In animal studies, the offspring of macaque monkeys exposed to golimumab at doses significantly higher than human treatment doses did not show any changes in the lymphoid tissues of the thymus, spleen and lymph nodes.[41]

Neonatal response to vaccinations

In a small observational study on neonates exposed to infliximab in the third trimester, none of the children had any immune deficits. At 6 months, these infants had normal immunoglobulin levels and appropriate response antibody

titres to tetanus and *Haemophilus influenzae* vaccinations.[42] Therefore all neonates should undergo routine vaccinations (with the exception of live vaccines like the rotavirus vaccine and BCG vaccine), even when exposed to anti-TNF agents after 22 weeks of gestation. However, if the neonate is exposed beyond the recommended gestation, the BSR guidelines advise against immunisation of the neonate for the first 7 months of life.[40]

Disseminated infection after live vaccination of the neonate

There is a single case report published of a 4.5-month-old infant in London who died of probable disseminated TB following maternal infliximab use in pregnancy.[43] The mother had inflammatory bowel disease and received her last infliximab infusion just two weeks prior to delivery. Cord infliximab levels were not quantified but the infant failed to thrive and progressively deteriorated following BCG vaccination at 3 months of age. On autopsy of the infant, multiple non-caseating granulomata with inflammation were found in the lungs, liver and dura. These nodular massess were typical of those seen in disseminated mycobacterial infections though the Ziehl-Neelson staining for acid-fast bacilli were equivocal. There was no evidence of TB within the family or recent close contacts. Therefore it was concluded that the disseminated TB seen in the neonate was a result of the recent BCG vaccination of the immunosuppressed infant.[43]

Live vaccinations are not recommended in severely immunocompromised individuals. Completion of routine vaccination is recommended in anticipation of commencing any anti-TNF agents or other biological agents in adults. Hence, it would seem logical that any neonate exposed in utero to anti-TNF agents beyond the recommended gestation (Table 2) should not have any live vaccinations for the first 6 months of life. The immature neonatal reticuloendothelial system takes about 6 months to clear any maternal antibodies transferred transplacentally.

Commencing or continuing anti-TNF agents in pregnancy

The decision to start or to continue anti-TNF agents in pregnancy has to be individualised. The issues to consider are:

- Whether there any other therapeutic options with better safety data in pregnancy.
- The severity of the woman's inflammatory disease, the likelihood of a relapse and potential effects on the fetus if a relapse were to occur.

This is a decision that needs to be made with input from a multidisciplinary team including obstetricians, specialty physicians, midwives, neonatologists and the woman herself, particularly if exposure to anti-TNF agents will continue beyond the recommended gestation.

In the case of one young woman (Box 2), seronegative spondyloarthropathies are particularly refractory to non-biological agents. Large doses of steroids seldom produce the desired clinical effect and can result in other unwanted side effects of increased risk of ascending infections, excessive weight gain and the development of gestational diabetes and/or gestational hypertension. Non-steroidal anti-inflammatory drugs may be of some benefit, but should not be continued beyond the second trimester.

Additionally, the negative effect of constant pain and poor mobility may adversely affect the young woman's mood and perceptions on her ability to cope with her pending motherhood. She would be at greater risk of mental health issues during this vulnerable time.

In the case described here (Box 2), after careful discussion with the patient, we would recommend that she should resume her etanercept. If she feels clinically improved and able to contemplate a short period off of anti-TNF therapy again, then we would aim to discontinue the drug by 32 weeks of gestation and hope that her disease remains under control. It is possible that even a short therapeutic trial would provide sufficient benefit to this young woman to discontinue the drug for the next 6–8 weeks, pending the delivery of her baby.

The woman's etanercept can be resumed almost immediately after delivery. If she has a wound from a caesarean section or a perineal tear/episiotomy, then withholding it for a few days while the wound heals would be advised to minimise the risk of infection.

We would encourage women to breastfeed on all biologic agents. These drugs are IgG molecules, and it is predominantly IgA that is excreted in breast milk. Being large proteinaceous molecules, these drugs are unlikely to survive the passage through the infant's gastrointestinal tract to achieve drug levels of any therapeutic significance (or to cause any adverse effects). Studies involving anti-TNF agents in breast milk have been singularly reassuring (Table 3).[9,35–39,43–50]

B-cell depleting agents: rituximab and belimumab

Like anti-TNF agents, B-cell depleting agents are also immunogloubulins that cross the placenta from the second trimester onwards, resulting in transient cytopenias and neonatal B-cell depletion that can persist for up to 6 months.[46,47,51] Nevertheless, there were only four cases of neonatal infections according to the data in the rituximab global drug safety database (n = 153); all of these were thought to be unrelated to rituximab exposure.[45] These infants also appear to mount good responses to vaccinations

Table 3. Summary of the effect of common biologics on the fetus/neonate when exposed in utero

Drug	Effect on organogenesis	Effect with mid-trimester/third trimester use	Precautions needed
Etanercept[35,36]	Registries of biologic use in pregnant women have not demonstrated an increased incidence of fetal anomalies.	Transplacental transfer occurs at an attenuated rate due to the modified Fc portion of the molecule.	Not to have live vaccines administered (rotavirus and BCG) in the first 6 months of life if in utero exposure continued beyond suggested gestation (Table 2).
Infliximab[37,38] Adalimumab[9,38]		Active transplacental transfer of these anti-TNF agents with risk of neonatal immune suppression if drugs are continued throughout pregnancy.	
Certolizumab[39,44]		Passive diffusion of drug means lower levels are achieved in the neonate.	
Rituximab[45,47]	No teratogenic effect in animals. Only 2 of the 253 pregnancies had congenital anomalies.	Animal studies have shown a reduction in the density of lymphoid tissue B–lymphocytes, which has no long-term effect on the offspring.[48,49]	Prompt assessment and treatment for any suspected infections.
Belimumab	No teratogenic effect in animals.	Transient cytopenias lasting weeks to months; B-cell depletion for up to 6 months in exposed neonates.[45,46,50]	

administered.[46,47,51] Despite these reassuring data, it is still recommended that any exposed infant should have a prompt assessment and treatment of any infections and full blood count to exclude any cytopenias.

Despite the absence of any data to indicate teratogenicity, manufacturers still recommend avoiding pregnancy for 12 months after the last dose of rituximab. Rituximab is often used as a 'remission-inducing' drug in many vasculitides and systemic lupus erythematosus, so cessation of the drug and establishing the woman on a 'pregnancy-friendly' maintenance regimen seems a sensible therapeutic option. The addition of other 'pregnancy-friendly' disease-modifying agents, for example azathioprine and hydroxychloroquine, may help maintain disease remission after the discontinuation of rituximab.

Belimumab is the first systemic lupus erythematosus-targeted therapy developed in recent years. Its effects in reducing the density of lymphoid tissue in animal studies are similar to the effects seen in rituximab.[37,38] Despite these effects, the exposed offspring have normal growth and

Box 3. Take home messages

1. There is no evidence that biologic agents are teratogenic.
2. Cessation of biologics in anticipation of a planned pregnancy is inadvisable because of the long lag time to conception, leading to the risk of flares just before pregnancy.
3. Flares of the disease are more harmful to both the mother and the fetus, leading to placental insufficiency manifesting as poor fetal growth, pre-eclampsia, preterm delivery or even intrauterine demise.
4. The decision to continue biologic agents in pregnancy needs to be individualised depending on alternative and effective 'pregnancy-friendly' drugs to treat the disorder, and the risk of flares off the biological agent.
5. Trial cessation of biologics should be attempted in the late second trimester – depending on the agent (Table 2) and the underlying disease.
6. Women on biologics are at a much greater risk of infections, and these infections may present atypically.
7. Biologics can be resumed almost immediately after delivery.
8. Women on biologics should be encouraged to breastfeed.
9. Infants who have been exposed in utero to anti-TNF agents beyond the suggested gestation should not be immunised with live vaccines (rotavirus and BCG) for the first 6 months of life. All non-live vaccinations are safe and should be undertaken.
10. Infants who have been exposed to B-cell depleting agents in the late second trimester may have transient cytopenias and absent B-lymphocytes in the circulation.

neurodevelopment.[37] The manufacturer, GlaxoSmithKline, has set up a pregnancy registry.[52]

The take home messages have been summarised in Box 3.

The future: what other information is needed?

There is still limited information from databases on indications for biologic use, disease activity in pregnancy, end organ damage and its correlation with pregnancy outcomes both maternal and neonatal. Prospective studies and drug registries need to be carefully tailored to collect these data, which could potentially alter how clinicians approach the use of biologics in pregnancy.

Longitudinal studies looking at the offspring exposed in utero to biologics would be useful to determine the speed at which the infant's immune system recovers from exposure to biologics and whether there is a longer term effect, for example an increased risk of childhood malignancies, severe infections or drug-induced autoimmune diseases, which are all potential side effects of these drugs in adults.

In the meantime, the clinicians caring for pregnant women on biologics should feel more reassured with their use in pregnancy. Ongoing biologic use is preferable to a severe flare of the disease, which may be refractory to other agents. A heightened awareness of its adverse effects, especially infections, and a planned trial of discontinuing the drug in the mid-trimester will likely ensure the best outcomes for both the mother and her baby.

Contribution to authorship

Both authors contributed to drafting the article and revising it critically for important intellectual content, and final approval of the version to be published.

Disclosures of interests

None to declare

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Supporting Information

Single Best Answer questions are available for this article at https://stratog.rcog.org.uk/tutorial/tog-online-sba-resource

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