

Review Article:**Respiratory diseases in pregnancy****Srikanti Raghu, Surya Kiran Pulivarthi***Department of TB and Chest diseases, Guntur Medical College, Government Fever Hospital, Guntur***ABSTRACT**

Pulmonary diseases are one of the major indirect causes of maternal deaths. Pregnancy is a unique physiological state during which changes occur in all systems of the body to meet metabolic needs of both the mother and growing fetus. Enlarging uterus and increasing hormonal levels cause changes in volumes and mechanics of lungs. Understanding the basic physiology of the cardiovascular and respiratory changes during pregnancy along with the pathology of disease processes are vital in making therapeutic decisions. Pre-existing conditions like asthma, tuberculosis, and acute illnesses like pneumonia, acute respiratory distress syndrome (ARDS), pneumothorax can have calamitous effect on mother and child health. Continual foetal monitoring throughout pregnancy is very important in early recognition of foetal jeopardy.

Key words; *Pregnancy, Pulmonary Diseases, Lung Mechanics, Asthma, Tuberculosis*

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INTRODUCTION

In 2013 Globally, there were 289000 maternal deaths. Of these, (n=50,000;17%) India and Nigeria (n=40,000;14%) accounted for one-third of maternal deaths.¹ Pulmonary diseases are one of the major indirect causes of maternal death. Significant physiological changes occur in pregnancy to meet metabolic needs of both mother and foetus in-situ. Getting an insight of such changes is important in making therapeutic decisions.

PHYSIOLOGICAL CHANGES OF RESPIRATORY SYSTEM IN PREGNANCY**First trimester changes**

Nasal congestion occurs at an early stage of first trimester (first 12 weeks) due to hyperaemia and glandular hyperplasia, but reaches peak at late stage in pregnancy and often disappears within 48 hours of delivery. Nasal congestion and resultant mouth breathing

reduces concentrations of inhaled nitric oxide (NO), a potent mediator of pulmonary vascular tone, produced primarily in the maxillary sinuses; contributing to complications associated with snoring.² Increased progesterone level is the primary cause for hyperventilation, augmented by an increased metabolic rate and carbon dioxide production in response to enlarging uterus and increasing weight. Early in the first trimester there is an increase in the subcostal angle of the rib cage and the circumference of the lower chest causing diaphragm to move up.

In first trimester, there is a 20% - 30% decrease in mean functional residual capacity (FRC), 3.7% decrease in mean expiratory reserve volume (ERV) and increase of nearly 9.7% mean tidal volume. Whereas residual volume (RV) shows a decrease of 21.4%, minute volume (MV) and vital capacity (VC) show an increase of 1.9% and 3.5% respectively.³ Closing volume and closing capacity change minimally during pregnancy. Diffusing capacity

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of lung for carbon monoxide capacity (DLCO) is highest in the first trimester due to increase in cardiac output and intravascular volume, leading to increased recruitment of the capillary surface area. Respiratory exchange ratio (V_{CO_2}/V_{O_2}) is unchanged or slightly increased. Arterial oxygen tension (PaO_2) increases slightly during the first trimester, as an important adaptation to facilitate oxygen transfer across the placenta. There is no change in the alveolar-arterial oxygen gradient throughout pregnancy.³

Second trimester changes

In the second trimester (13-28 weeks), mean expiratory reserve volume (ERV) decreases by 7% and mean RV decreases by 15.3%.³ As the pregnancy progresses to term, MV gradually increases by 5.4% and VC increases by 3.7%. DLCO decreases from 24 to 27 weeks with no further reduction thereafter due to decrease in haemoglobin. Closing volume shows no change during pregnancy. Closing capacity shows a progressive linear increase at the beginning of 2nd trimester. Minimal increase in resting minute ventilation (V_E), important for gaseous exchange occurs.³

Third trimester changes

During third trimester (29-40 weeks) progressive relaxation of the ligamentous attachments of the ribs broadens the subcostal angle by about 50%, from 68° to 103° , which causes increase in transverse chest diameter by 5-7 cm and anteroposterior diameter by 2 cm. Enlarging uterus causes upward displacement of diaphragm by 4 cm. But the diaphragmatic excursion remains normal because of increased anteroposterior and transverse diameters of chest wall, decreased abdominal muscle tone and widening of subcostal angle.⁴ Chest wall changes returns to normal within 6 months of delivery, although the costal angles remain widened.

Spirometry show significant reduction in mean FRC (40%-55%) at 6 months gestation, which

progressively declines as pregnancy continues. The mean ERV shows decrease of 10% with maximum decrease in 3rd trimester. There is maximum increase in the tidal volume (TV) at term. RV gradually decreases in third trimester with 24.7% decrease. There is increase in mean MV by 9.6% and mean VC by 8.1%.⁵

PaO_2 decreases from 106 mm in first trimester to 102 mm Hg near term; arterial carbon dioxide tension ($PaCO_2$) falls and arterial pH increases due to physiological hyperventilation resulting in respiratory alkalosis with compensatory renal excretion of bicarbonate. Throughout pregnancy, pH is maintained at 7.42 to 7.46 without much variations from normal but bicarbonate levels are least in late pregnancy (18-22 mg/dL). These adaptations help to thrive through changes that occur in pregnancy.⁵

RESPIRATORY PHYSIOLOGY DURING LABOUR

Respiratory responses during parturition are greatly affected by stage of labour and the response to pain and anxiety. Acute hyperventilation imposed on chronic hyperventilation may cause dangerous elevation of pH to 7.6 or higher. During labour, severe pain and anxiety may lead to rapid shallow breathing with alveolar hypoventilation, atelectasis and hypoxaemia. Higher values of MV close to maximum voluntary ventilation are noted during second stage of labour. Oxygen consumption during contractions doubles or may even become threefold (upto 750 mL/min).⁶

Relative hypoventilation between contractions may have grave implications of foetal hypoxaemia which justifies liberal use of oxygen in order to keep maternal oxygen saturation at 95% or greater. Adequate pain relieving narcotics or epidural analgesia blunts ventilatory response and gas exchange abnormalities associated with active labour.

PULMONARY DISORDERS IN PREGNANCY

Clinical presentation and management of pulmonary diseases in pregnant women is almost similar to non-pregnant with few notable exceptions. Pulmonary disorders commonly presents with breathlessness, various conditions causing dyspnoea are shown in Table 1.

Asthma

Bronchial asthma is one of the most common conditions complicating the pregnancy. Pregnancy is a heterogeneous immune state affecting the course of the asthma, during which the latter may worsen or improve or remain stable with equal distribution. Prevalence of bronchial asthma in pregnancy is about 8%-12%. Around 12.6 % of patients with bronchial asthma experience exacerbation of the medical condition and 6% may require hospital admissions.⁷ Exacerbations are more commonly clustered around end of the second trimester and early third trimester.

Bronchial asthma is safe during pregnancy if controlled. Uncontrolled asthma is associated with increased complications like pregnancy induced hypertension, preeclampsia, intrauterine

growth retardation (IUGR), low birth weight, premature birth, increased elective caesarian delivery and poor perinatal outcomes.⁸ Exacerbations during first trimester are associated with increased risk of congenital malformations.⁹

Diagnosis of bronchial asthma during pregnancy is similar to that done in nonpregnant state, which includes history, clinical examination, and pulmonary function tests (PFT). The PFT and clinical evaluation should be done in pregnant asthmatics once in every month to assess severity and course of bronchial asthma, as severe asthma is associated with poor perinatal outcomes. Recently management plan according to fraction of exhaled nitric oxide (FeNO) has promising effects on management of bronchial asthma but further studies are required to establish its effectiveness.¹⁰

Management of bronchial asthma during pregnancy is almost similar to non pregnant counterparts. Patient education, avoidance of triggers and written action plan are the foremost important aspects of bronchial asthma management. Patient should be educated about course of the bronchial asthma management. Patient should be educated about course of the bronchial asthma, risk of exacerbations, and benefits of adherence to medications.

Goals of bronchial asthma management include decreasing the use of short acting beta-2 agonists (SABA), preventing the exacerbations and maintaining near normal lung function. Non adherence to the treatment is one of the common risk factors for poor control of asthma during pregnancy. SABA are used as rescue medications whenever required as they are not associated with any adverse perinatal outcomes.¹¹ Long acting beta-2 agonists (LABA) are used in step up therapy only if asthma is not controlled by medium or low dose inhaled corticosteroids (ICS). High dose

Table 1: Differential diagnosis of dyspnoea during pregnancy

Dyspnoea of pregnancy
Allergic rhinitis
Bronchial asthma
Tuberculosis
Pneumonia
Influenza
Anaemia
Interstitial lung disease
Pleural diseases
Pulmonary thromboembolism
Amniotic fluid embolism
Pneumothorax
Gestational trophoblastic disease
Peripartum cardiomyopathy
Drugs e.g., tocolytics (β_2 agonists) induced pulmonary oedema

corticosteroids are associated with side effects. All ICS except budesonide are classified as FDA class C while budesonide is classified as class B. Even though theophylline is included in FDA class C, it is not preferred during pregnancy due to its low therapeutic index, frequent monitoring of drug levels and toxic effects. Levels above 10 µg/mL are required for therapeutic effects and at levels above 20 µg/mL toxic effects are seen. Systemic corticosteroids are associated with more adverse effects than inhaled and should be used only in moderate and severe bronchial asthma. Use of systemic corticosteroids in early pregnancy is associated with cleft lip, cleft palate, preeclampsia and gestational diabetes. Their use during pregnancy should outweigh against adverse effects. Muscarinic antagonists like ipratropium bromide are used in exacerbations along with SABA. Leukotriene antagonists and mast cell stabilizers can be used as controller medication (FDA class B) except zileuton (class C), as their use has shown to decrease exacerbations and are safe during pregnancy. Moteleukast is a preferred leukotriene modifier. Omalizumab (FDA class B) can be used in pregnant asthmatics with elevated immunoglobulin E (IgE) levels and

positive testing for perennial antigens whose condition cannot be improved with medium dose ICS and LABA. Sparse data are available regarding the safety of omalizumab during pregnancy. Hence, it is uncertain to start omalizumab during pregnancy and whether to continue during pregnancy if it is started before.¹² Safety profile of commonly used anti asthmatic drugs in pregnancy are shown in Table 2.¹³

Treatment of acute severe asthma in pregnancy is almost similar to nonpregnant counterparts. Initially the patients should be treated with inhaled albuterol or salbutamol 2.5 mg for every 20 min followed by systemic corticosteroids. Inhaled ipratropium bromide can be added to this regimen. They are monitored for every 30-60 minutes. Treating maternal hypoxia and continuous foetal monitoring are more important. Further management depends on clinical condition. Both inhaled and intravenous magnesium sulphate can be used in severe asthma and it has the added advantage of tocolytic. This dual effect is used in preeclamptic asthmatics.¹⁴

Indomethacin should not be used, because it may cause bronchospasm and premature

Table 2: FDA classification of different medications used in pregnant women with bronchial asthma¹³

Drugs	FDA Category
Short acting β ₂ agonists	C
Long acting β ₂ agonists	C
Ipratropium bromide	B
Inhaled corticosteroids (except budesonide)	C
Budesonide	B
Montelukast and zafirlukast	B
Zileuton	C
Systemic corticosteroids	C
Theophylline	C
Omalizumab	B
Mast cell stabilizers	B

Category A=Human studies fail to demonstrate fetal harm; Category B = animal studies fail to demonstrate harm, but no human studies or animal studies demonstrate risk not shown in human studies; Category C = animal studies demonstrate risk or insufficient data available, drugs may be used if benefit outweighs risk; Category D = human studies demonstrate risk, drugs may be used if benefits justify the risks; X, contraindicated in pregnancy

FDA = Food and Drug Administration

closure of ductus arteriosus. Prostaglandin F_{2α} and ergometrine compounds may cause severe bronchospasm, hence should be avoided. Oxytocin and prostaglandin E₁ and E₂ can be used safely. Fentanyl is the preferred agent to treat pain than morphine due to its safer profile and histamine release by the latter. Upper respiratory tract viral infections, gastroesophageal reflux disease, and rhinitis of pregnancy should be treated promptly as they are associated with increased exacerbations during pregnancy.¹⁵

Tuberculosis

Risk factors for tuberculosis (TB) in pregnancy include positive family history or past history of TB, residence in area of high prevalence of TB, human immunodeficiency virus (HIV) co-infection. Performing chest radiograph after 12 weeks, early morning sputum examination, and fiberoptic bronchoscopy are useful in early diagnosis of TB in pregnancy. Xpert MTB/RIF is being explored for early diagnosis of TB especially in the areas of high HIV prevalence.¹⁶

Treatment of TB in pregnancy is similar to that administered to nonpregnant women. Streptomycin is contraindicated because of auditory and vestibular defects in fetus. Breast feeding is not contraindicated in women taking anti-TB treatment.¹⁷

Pneumonia

Pneumonia is one of the important causes of indirect maternal mortality, most common organisms being *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Mycoplasma pneumoniae*. Clinical presentation is similar to that of non-pregnant woman but risk of respiratory failure and empyema is increased.¹⁸ Decreased cell mediated immunity results in increased severity of infections due to viral and fungal organisms. Patient presents with dyspnoea. Respiratory rate is not increased significantly in pneumonia.

Patients with suspected pneumonia should get a chest radiograph with abdominal shield. Delay in diagnosis may be associated with morbidity. Other investigations are sputum microscopy, sputum culture and serologic tests.

Quinolones and tetracyclines should be avoided in pregnancy. Prophylaxis with varicella zoster virus (VZV) immunoglobulin should be given to pregnant woman with history of exposure to VZV. Acyclovir should be given within 96 hours if the disease occurs.¹⁹

Influenza

It is most common viral infection in pregnancy resulting in increased morbidity and mortality. Risk of hospitalization for an acute cardiopulmonary illness is three to four times more likely in third trimester than for a non-pregnant or postpartum woman. Influenza (H1N1) should be suspected in patients not responding to routine antibiotics and in extensive pneumonia or respiratory failure. Increased risk of preterm delivery or a low-birth weight infant, severe pneumonia, maternal deaths have been observed.²⁰

Management includes prevention and supportive care. Prevention is by providing pregnant women with the yearly influenza vaccine. American College of Obstetrics and Gynecology (ACOG) recommends that pregnant women can be vaccinated during all the three trimesters with inactivated intramuscular vaccine with 95% of them recommending it in second and third trimester.²⁰ Antipyretics should be used for the treatment of fever as these not only reduces foetal tachycardia, but are also been associated to be a protective agent against congenital abnormalities. Dehydration should be avoided. The use of antiviral medications in pregnancy is controversial. Neuraminidase inhibitors (zanamivir, oseltamivir) are also used in the treatment.

GASTRIC ASPIRATION

Gastric aspiration is one of the leading cause of ARDS during pregnancy. Reduced oesophageal lower sphincter tone, delayed gastric emptying and increased intraabdominal pressure are causes of increased gastric aspiration during pregnancy.²¹

AMNIOTIC FLUID EMBOLISM

Amniotic fluid embolism most commonly occurs during labour and delivery. Amniotic fluid enters into the vascular circulation through endocervical veins or uterine tears.²² It produces acute pulmonary hypertension, both by obstructing the pulmonary vessels and by causing vascular spasm by particulate cellular contents or humoral factors. Acute left ventricular dysfunction may also occur, either secondary to the initial pulmonary embolic event or in response to humoral events mediated by cytokines.

Presentation includes sudden onset of shortness of breath, hypoxemia, cardiogenic shock often associated with seizures. Uncommon presentations include disseminated intravascular coagulation (DIC) and foetal distress. There is no specific investigation to confirm the diagnosis of amniotic fluid embolism. Differential diagnosis include placental abruption, tension pneumothorax, myocardial ischaemia, pulmonary thromboembolism and septic shock. Diagnosis is based on clinical presentation. Foetal squames in wedge pulmonary capillary aspirate have been used for diagnosis but this is an invasive method.²³

Treatment is mainly supportive. Oxygen supplementation, ventilatory support and maintaining adequate circulatory support. DIC and ARDS are common complications in survivors;. 50% of patients die within first hour, due to cardiac arrest. Hypotension and hypoxaemia may cause neurological damage in survivors but is rare.

PULMONARY THROMBOEMBOLIC DISEASE

Most common time of occurrence of pulmonary thromboembolism disease is early postpartum period. Left leg is the most common site of deep vein thrombosis (DVT) in pregnant woman due compression of left iliac vein by gravid uterus.²⁴ Ventilation-perfusion scan is performed with low radiation exposure and low dose helical computed tomography (CT).²⁵

Heparin is the drug of choice. Low molecular weight (LMW) heparins are preferred as they do not cross placenta and have no effects on foetus. Inadvertent use of thrombolytics may cause haemorrhagic complications.

Clinical features include prolonged bleeding at injection sites, haemorrhage from gastrointestinal (GI) tract and signs of bruising before delivery. Bleeding from suture sites, postpartum haemorrhage in spite of hard contracted uterus are manifestations of DIC after delivery.

The most valuable screening test is thrombin time as it is rapid and prolonged if fibrinogen is depleted. Other investigations include measurement of fibrin degradation products (FDP) which is an indirect evidence of fibrinolysis. In fibrinolytic process, low platelet count is diagnostically more significant than finding raised FDP level.

Management is similar to nonpregnant state. Replacement of blood and coagulation factors is important in management of DIC.

ACUTE RESPIRATORY DISTRESS SYNDROME

Risk of ARDS increases in pregnancy. Gastric aspiration is an important cause. Other causes of ARDS during pregnancy are amniotic fluid embolism, preeclampsia, choriamnionitis, pneumonias, and trophoblastic embolism, sepsis and air embolism.²⁶ Respiratory alkalosis

results in decreased placental perfusion. Supplemental oxygen should be given to maintain saturation. Maternal acidosis is well tolerated by the foetus; delivery of the foetus improves the outcome of both mother and the fetus. Epidural anesthesia decreases oxygen demand. Pregnancy should be considered in women of child bearing age with ARDS.

PREECLAMPSIA AND PULMONARY OEDEMA

Preeclampsia is a multisystem system disorder of unknown aetiology characterized by development of hypertension to the extent of 140/90 mm Hg or more with proteinuria after the 20th week in a previously normotensive and nonproteinuric woman.²⁷ About 3% of people with preeclampsia may develop pulmonary oedema, especially, those who are chronically hypertensive and obese, particularly in early post- partum period.²⁷ Aggressive intrapartum fluid replacement in a preeclamptic patient is the most common cause. Other less contributing causes include reduced serum albumin, systolic and diastolic dysfunction. Concomitant conditions like sepsis, placental abruption may aggravate the condition.

Mainstay of treatment includes restriction of fluids, cautious administration of diuretics without compromising output and placental perfusion. Inotropes and ventilatory support are to be given if necessary. Definitive treatment of preeclampsia is delivery of foetus.

TOCOLYTICS AND PULMONARY OEDEMA

Tocolytics are used to decrease uterine contractions in preterm labour. Beta2-agonists like nifedipine, indomethacin, magnesium sulphate may cause pulmonary oedema. Beta-adrenergic stimulation causes hypotension and decreased osmotic pressure. Glucocorticoids are given during preterm labor to enhance foetal lung maturity. Prolonged exposure to corticosteroids, beta 2-agonists causes left

ventricular dysfunction causing pulmonary oedema.²⁸

Diagnosis of tocolytic induced pulmonary oedema is based on clinical presentation in appropriate setting of tocolytic use. No specific investigation establishes diagnosis of tocolytic induced pulmonary oedema.

Mainstay of the treatment includes discontinuation of tocolytics where rapid resolution is seen. Other supportive treatment includes diuresis, cardio-pulmonary evaluation. Alternative diagnosis should be considered if pulmonary oedema doesnot resolve within 12-24 hours of stopping the drug.

PERIPARTUM CARDIOMYOPATHY AND PULMONARY OEDEMA

Peripartum cardiomyopathy is an idiopathic cardiomyopathy which occurs most commonly in third trimester or early postpartum period, in absence of other causes of cardiomyopathy.²⁹ Pulmonary oedema due to peripartum cardiomyopathy occurs around labour or early postpartum period due to increased cardiac output.

Treatment includes afterload reduction with diuretics and anticoagulants. Angiotensin converting enzyme (ACE) inhibitors should not be used in pregnancy. Recovery usually occurs after 6 months. Some patients develop progressive cardiac failure. Intravenous immunoglobulin (IVIG), bromocriptine are other therapeutic options. Cardiac transplantation may be considered in some patients with progressive cardiac failure.

GESTATIONAL TROPHOBLASTIC DISEASE

Pulmonary embolism is the most common complication during evacuation of uterus for benign mole or hydatidform mole, which may cause pulmonary hypertension or pulmonary oedema.³⁰ Choriocarcinoma associated with molar pregnancy produce

discrete nodules. Pleural effusion may occur occasionally.

OVARIAN HYPERSTIMULATION SYNDROME

Ovarian hyperstimulation syndrome (OHS) is most common with use of gonadotropins rather than clomiphene citrate to stimulate ovulation for in vivo fertilization. Ascites, pleural effusion on both sides may occur due to increased capillary permeability.³¹ Correction of fluid loss, draining effusion is mainstay of the treatment. Respiratory failure may occur due to large effusion, shock and acute renal failure due to volume depletion.

PLEURAL DISEASES

Small asymptomatic pleural effusions are common during postpartum period due to increased blood flow and decreased colloid osmotic pressure during pregnancy.³² Spontaneous pneumothorax and pneumomediastinum are reported due to valsalva maneuvers resulting in patients presenting with chest discomfort and dyspnoea during or immediately after delivery. Preeclampsia, choriocarcinoma may also cause pleural effusions.

OBSTRUCTIVE SLEEP APNOEA

Sleep disordered breathing (SDB) during pregnancy ranges from simple snoring to Obstructive sleep apnoea (OSA). Pregnancy associated physiological changes may aggravate the underlying SDB. OSA may worsen in late pregnancy, coupled with the development of hypertension.³³ OSA is risk factor for development of preeclampsia. Nocturnal hypoxaemia may adversely affect the foetus, and poor foetal growth has been documented in these patients. Treatment with nasal continuous positive airway pressure is safe and effective.³⁴

PULMONARY VASCULAR DISEASES

Pregnancy is contraindicated in patients with primary pulmonary hypertension. Pulmonary arterio-venous (A-V) malformations may expand and there may be an increased likelihood of bleeding.³⁵ Idiopathic haemoptysis during pregnancy is attributed to hyperaemia from dilated normal bronchial arteries.

TRANSFUSION RELATED ACUTE LUNG INJURY

Transfusion related acute lung injury (TRALI) is a major concern amongst transfusion medicine clinicians as it is acclaimed to be the leading cause of transfusion-associated mortality. It is a syndrome consisting of non-cardiogenic pulmonary oedema with hypoxia and respiratory distress occurring during or within 6 hours of transfusion.³⁶ The two-hit hypothesis proposes that, the adhesion of primed neutrophils to pulmonary endothelial cells (first hit) followed by the subsequent activation of both cells by antibodies or inflammatory mediators present in transfused blood (second hit)⁴ causes capillary leakage that may result in TRALI. Donations from persons with previous history of transfusions or previous pregnancies are often implicated to contain antibodies to class II-human leucocyte antigens and to human neutrophil antigens, which may justify the antibody-mediated TRALI. Various substances accumulated during the prolonged storage of red blood cells or platelets are suspected to elicit antibody-negative TRALI.³⁷

Several risk factors acknowledged in patients with TRALI are massive transfusion, mechanical ventilation, sepsis, haematological malignancies, end stage liver disease and cardiac surgery, primary pulmonary hypertension (PPH).³⁸

Laboratory investigation of TRALI include detection of any leucocyte antibodies [(HNA)

human leucocyte antigen (HLA) class I and HLA class II] in the patient (transfusion recipient) and the associated donations in all blood products transfused within 6 hours of the recognition of TRALI or to seek corroborative evidence that the detected antibody can react with an available corresponding antigen on the target cell.³⁹ The combination of the (GIFT) and (GAT) is an effective approach for detecting polymorphonuclear reactive antibodies in serum or plasma which have the advantage of detecting antibodies to HNA and also detect antibodies to HLA class I, and possibly HLA class II antibodies.⁴⁰ Many of the assays employed are based upon testing donors and recipients prior to solid organ transplantation and these techniques are highly sensitive in order to detect the presence of any antibodies in donor or recipient sera that could be clinically relevant. HLA antibody screening is often the first step in many TRALI investigations when screening patients and associated donor samples, as it is widely available.

TRALI is a complex syndrome. The risk of TRALI can be reduced by the adoption of predominantly male donor plasma, screening women for HLA antibodies, and the selective deferral of donors with antibodies.

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