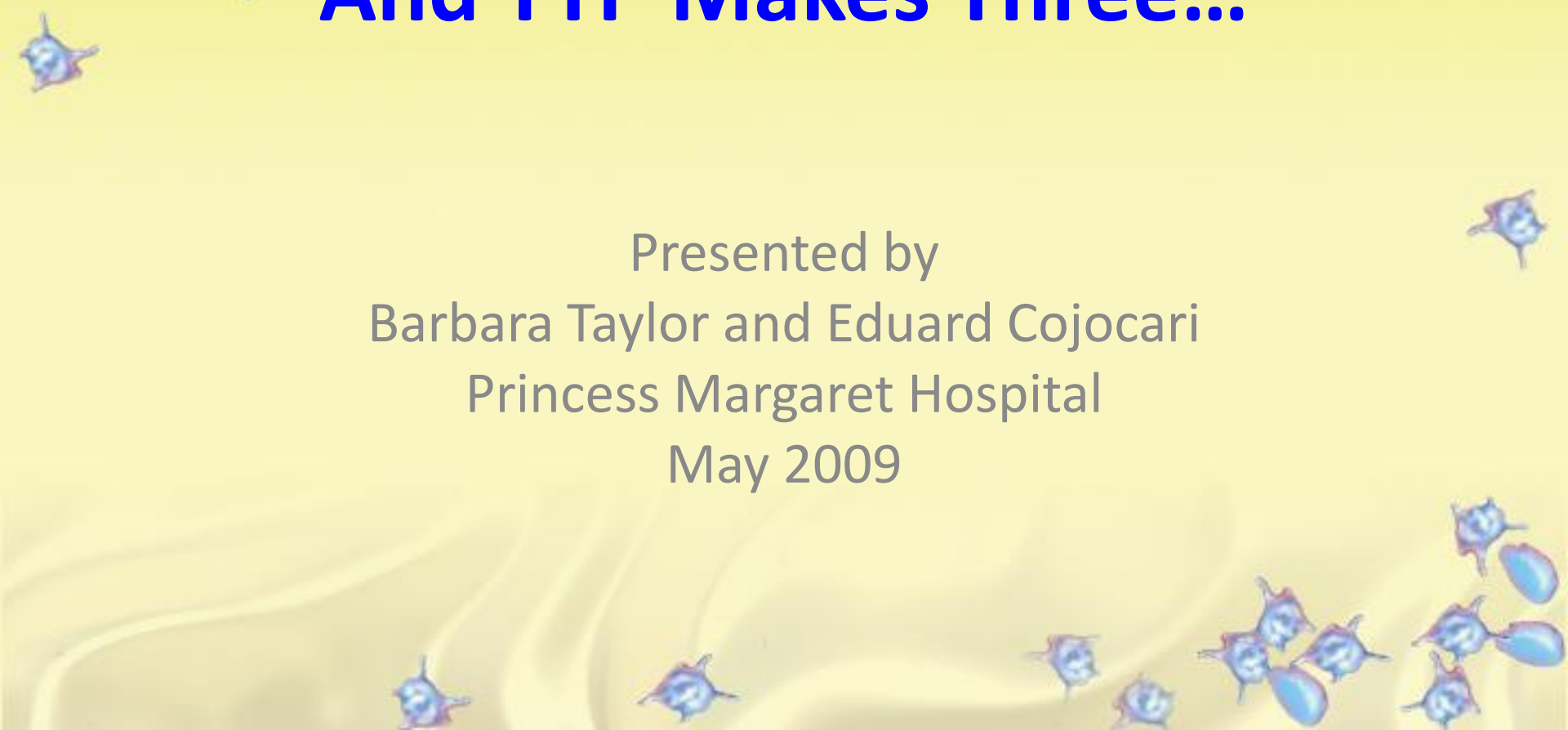




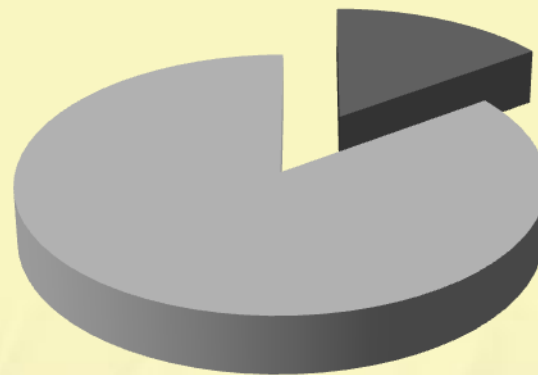
And TTP Makes Three...

Presented by
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Princess Margaret Hospital
May 2009



Incidence of TTP in general population

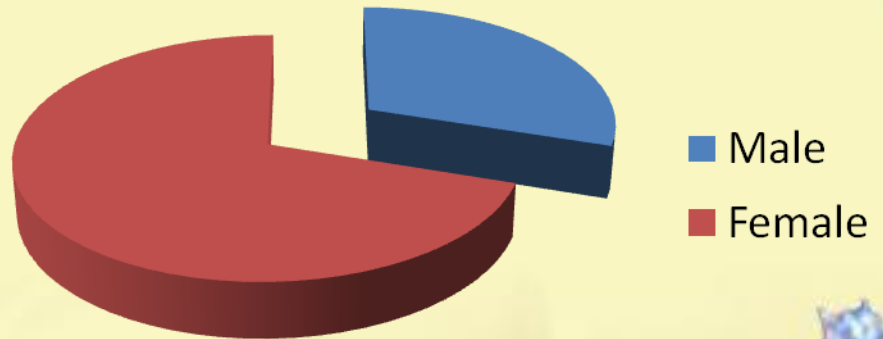
- The incidence rate is 3.7 cases per 1 million.
- Survival rate is **80-90%** with early diagnosis and treatment.



■ Mortality
■ Survival

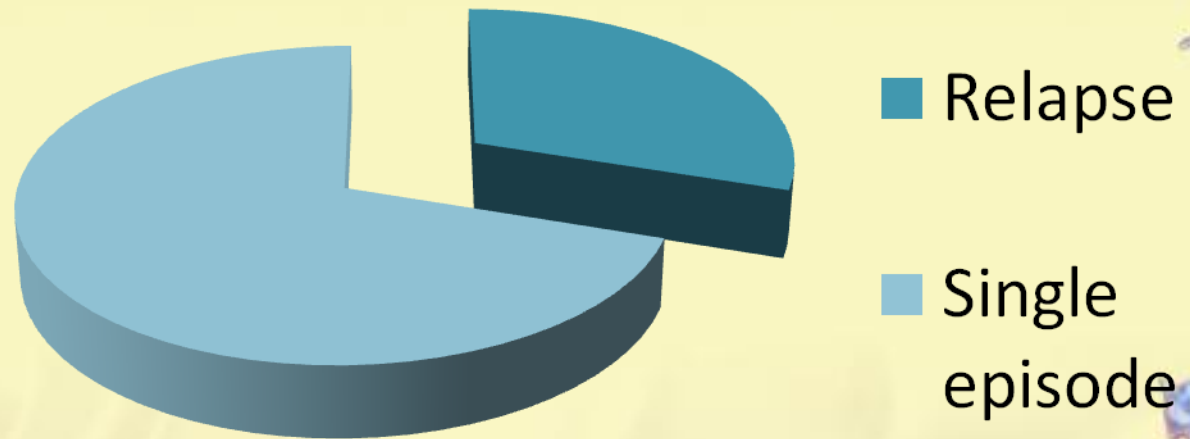
Incidence of TTP in general population

- Twice as many women as men (2)
- most often 20 –50 years old



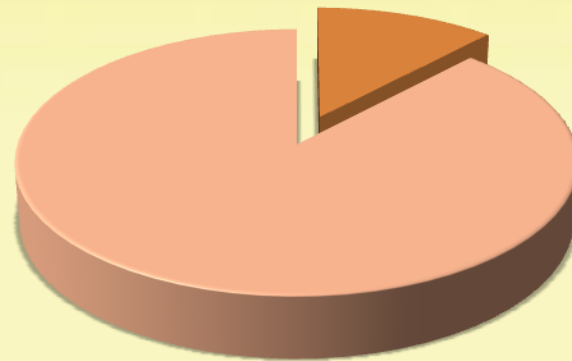
Incidence of TTP in general population

- One third of the TTP patients experience a relapse within the following 10 years.



Incidence of TTP in pregnancy

- **12-31%** of the TTP cases occur in pregnancies and postpartum period;

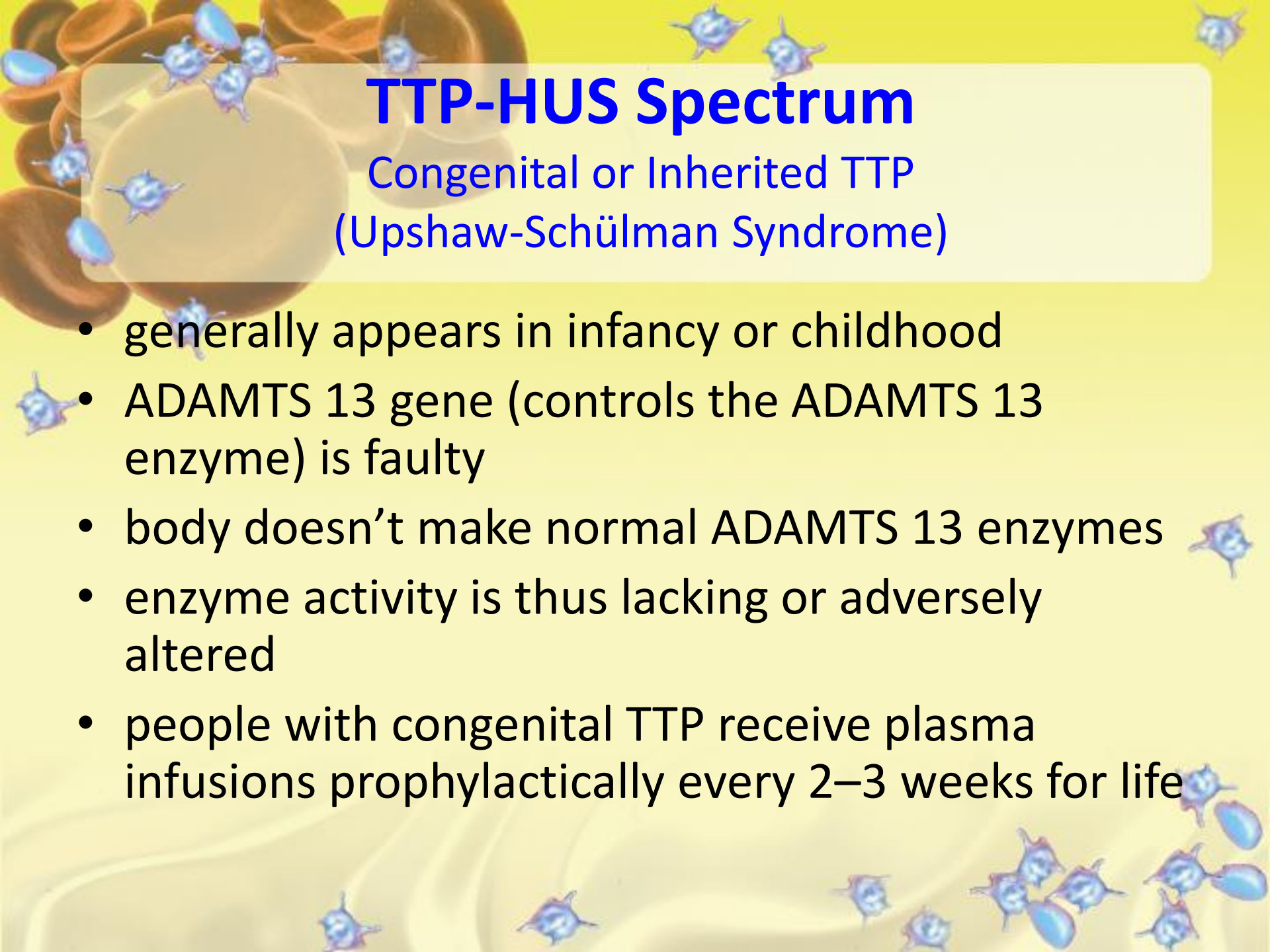


- TTP affects approximately **1 in 20,000** to **1 in 70,000** pregnancies.

The background features a yellow gradient with several blue, star-shaped platelets and orange, biconcave disc-shaped red blood cells scattered throughout. A white rounded rectangle is positioned at the top, containing the title text.

Etiology: ADAMTS 13 and TTP

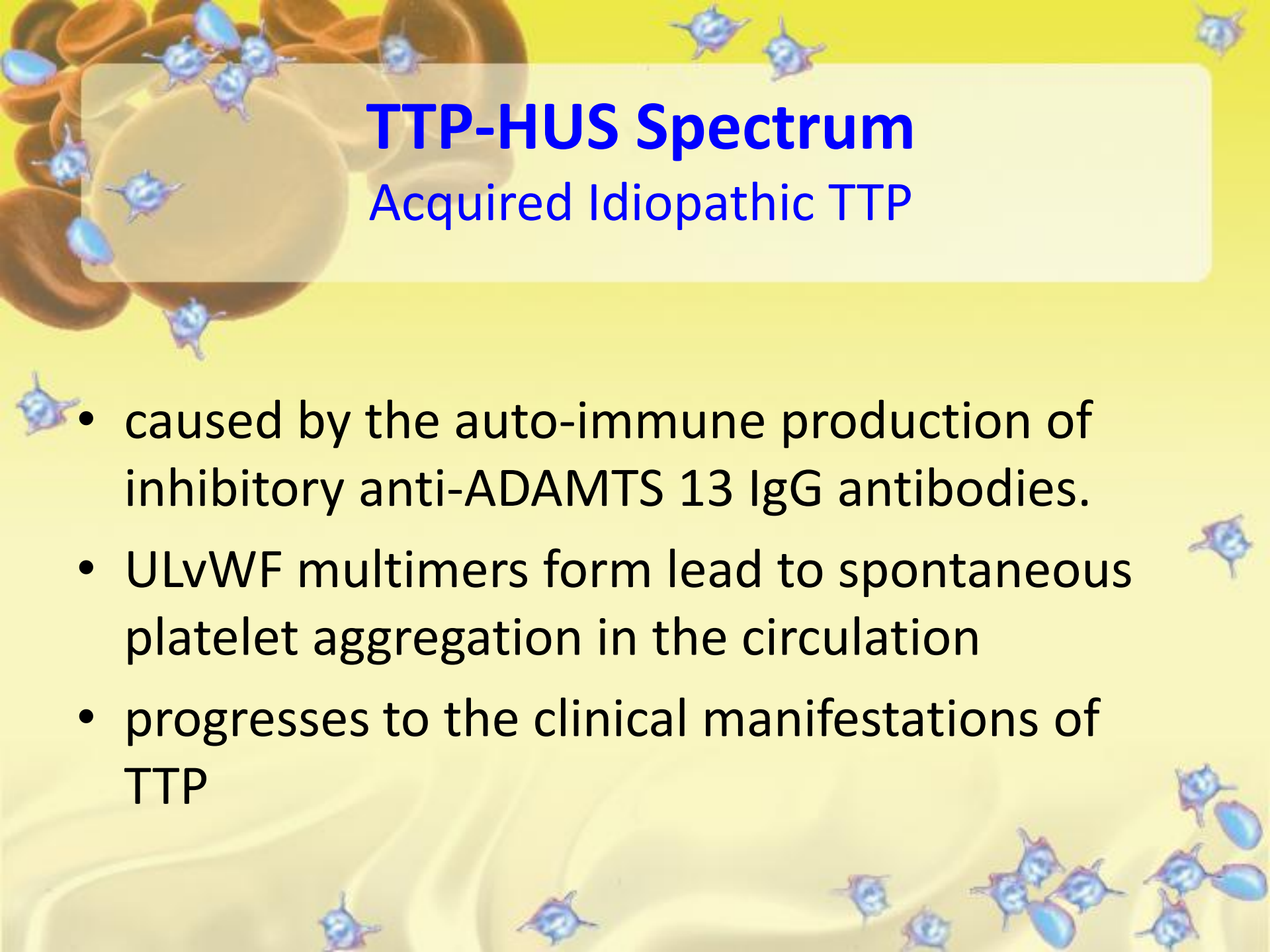
- ADAMTS13 is an enzyme synthesized mainly in the liver.
- cleaves **Ultra Large von Willebrand Factor (ULvWF)** multimers.
- vascular injury triggers the release of the ULvWF multimers from endothelial cells into the blood stream in long “strings”.
- platelets aggregate around the multimers and if uncleaved by ADAMTS 13, would grow into platelet rich thrombi.
- these thrombi would block the arterioles and capillaries
- platelets used to form the thrombi lower the circulating platelets.
- RBCs trying to pass through the narrowed vessels rupture (5)



TTP-HUS Spectrum

Congenital or Inherited TTP
(Upshaw-Schülman Syndrome)

- generally appears in infancy or childhood
- ADAMTS 13 gene (controls the ADAMTS 13 enzyme) is faulty
- body doesn't make normal ADAMTS 13 enzymes
- enzyme activity is thus lacking or adversely altered
- people with congenital TTP receive plasma infusions prophylactically every 2–3 weeks for life



TTP-HUS Spectrum

Acquired Idiopathic TTP

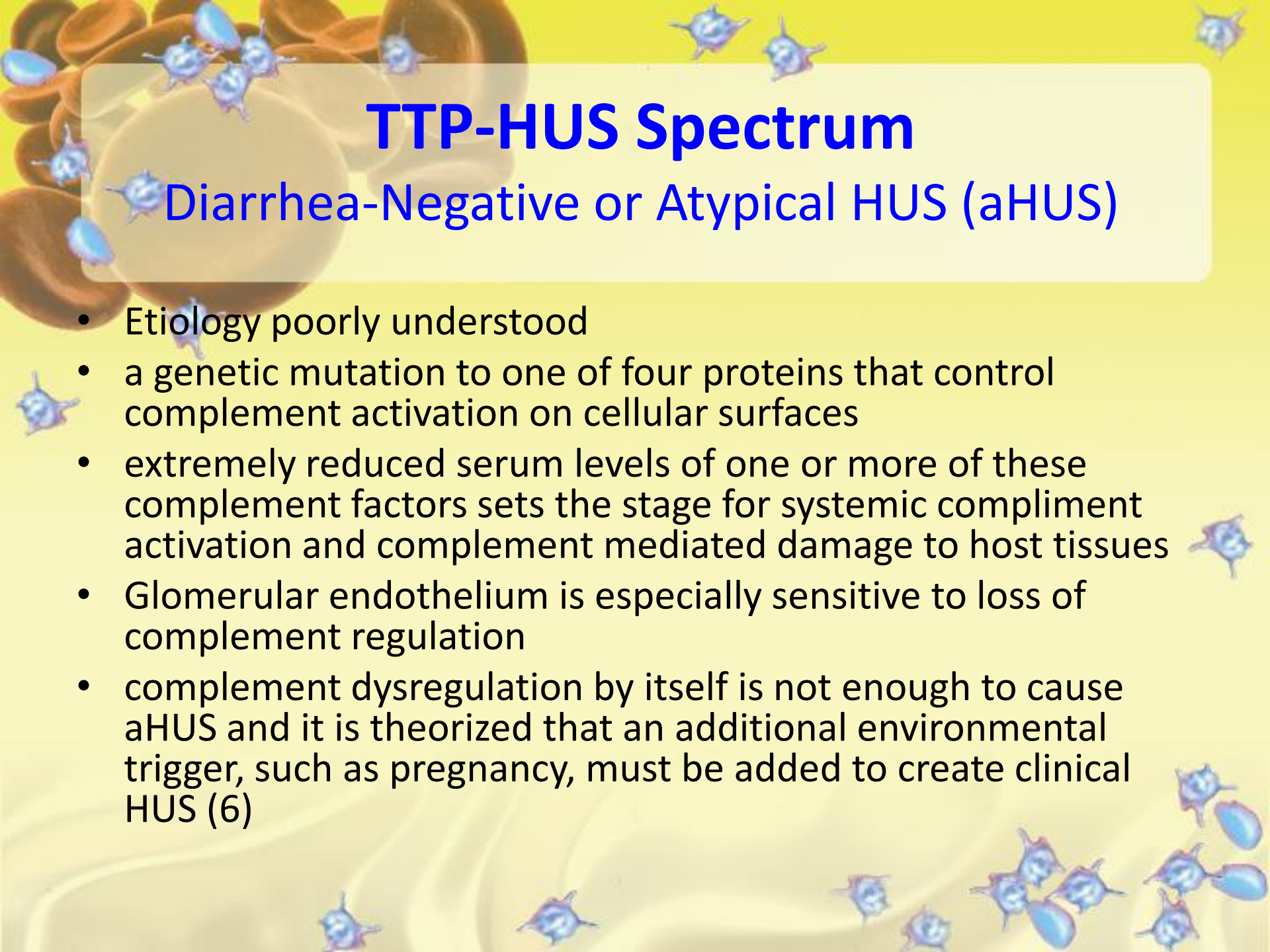
- caused by the auto-immune production of inhibitory anti-ADAMTS 13 IgG antibodies.
- ULvWF multimers form lead to spontaneous platelet aggregation in the circulation
- progresses to the clinical manifestations of TTP



TTP-HUS Spectrum

Diarrhea-Associated HUS (D+HUS)

- mostly seen epidemically in childhood or sporadic outbreaks
- bacterial toxin Shigella dysenterian (primarily the strain E.coli0157:H7 in North America) causes a gastrointestinal infection and hemorrhagic colitis
- Shiga toxins then released into the circulation and localizes in the kidney where there are a lot of receptors for it
- here the toxin causes necrosis of the renal endothelium
- substance is thus freed that starts coagulation abnormalities leading to HUS (6).

The background features a light yellow gradient with several clusters of red blood cells (orange and brown) and blue, spiky, star-shaped cells scattered throughout. A large, semi-transparent white rounded rectangle is positioned in the upper left, containing the title and subtitle.

TTP-HUS Spectrum

Diarrhea-Negative or Atypical HUS (aHUS)

- Etiology poorly understood
- a genetic mutation to one of four proteins that control complement activation on cellular surfaces
- extremely reduced serum levels of one or more of these complement factors sets the stage for systemic complement activation and complement mediated damage to host tissues
- Glomerular endothelium is especially sensitive to loss of complement regulation
- complement dysregulation by itself is not enough to cause aHUS and it is theorized that an additional environmental trigger, such as pregnancy, must be added to create clinical HUS (6)

The background features a yellow gradient with several blue, star-shaped platelets and red blood cells scattered throughout. A large, semi-transparent white rounded rectangle is positioned in the upper left, containing the title text.

Theorized Causes of TTP in Pregnancy

- normal late pregnancy coagulation changes predispose to the development TMA's (thrombotic microangiopathies) in susceptible women:
- increased concentrations of pro-coagulant factors
- decreased fibrinolytic activity
- reduced endothelial thrombomodulin
- decreased activity of ADAMTS 13 (7)



Theorized Causes of TTP in Pregnancy

- “In some mothers with a mutation in their complement regulatory proteins, pregnancy has precipitated aHUS” (8)
- Progesterin levels associated with pregnancy may instigate TTP (9)
- “A pregnancy associated rise in vWF was concluded to have caused a first time bout of TTP in a 22 year old with congenital TTP” (10)
- pre-pregnancy anti-phospholipid antibody syndrome is suspected to predispose to the development of TTP in pregnancy (11)



Types of TTP-HUS During Pregnancy

- **Idiopathic acquired TTP** is the type commonly seen in pregnancy
- **Congenital TTP** in pregnancy is extremely rare
- **D-HUS and aHUS** rarely occur in pregnancy, but a few cases have been reported

The background features a yellow gradient with several 3D illustrations of red blood cells (orange and biconcave) and platelets (small, blue, star-shaped cells). A semi-transparent white box with a yellow border is positioned at the top, containing the title.

Diagnosis of TTP-HUS During Pregnancy

In the 2-nd or 3-rd trimester the diagnosis can be obscured by several conditions :

- **gestational thrombocytopenia** is primarily dilutional (expanded plasma volume) and resolves after delivery without treatment (Plt = 100,000 –150,000)
- severe **pre-eclampsia** or **eclampsia** causes hypertension, thrombocytopenia, peripheral edema, and proteinuria in 2-nd half of pregnancy

The background features a light yellow gradient with several 3D-rendered red blood cells and blue platelets scattered throughout. A semi-transparent white rounded rectangle is positioned at the top, containing the title text.

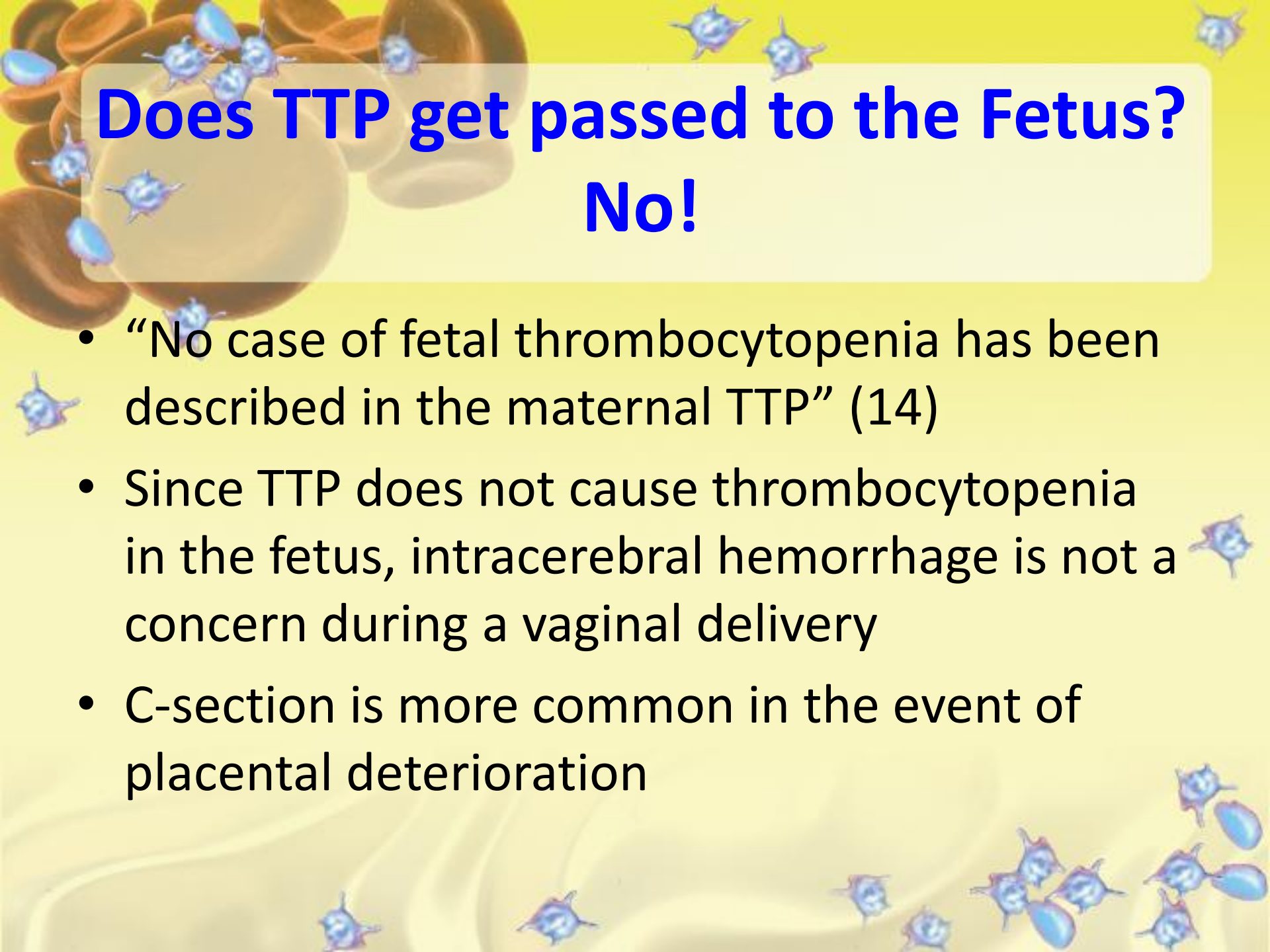
Diagnosis of TTP-HUS During Pregnancy

- a unique pre-eclampsia state called **Hemolysis, Elevated Liver enzymes, and Low Platelets (HELLP)** can also be confused with TTP
- unlike TTP, HELLP does not cause a fever, ADAMTS 13 activity doesn't drop, and resolves quickly postpartum (11)
- unlike TTP, HELLP causes RUQ abdominal pain

The background features a light yellow gradient with several 3D-rendered red blood cells and platelets. The red blood cells are depicted as biconcave discs in shades of orange and red, while the platelets are smaller, blue, and disc-shaped. Some platelets are shown with small protrusions, suggesting they are in motion or interacting with the red blood cells.

Diagnosis of TTP-HUS During Pregnancy

- ADAMTS 13 activity of less than 5 % is diagnostic of idiopathic TTP
- ADAMTS 13 assays are helpful but must be done at specialized labs and require considerable time and expertise to perform
- Since time is of the essence in initiating treatment for a pregnant patient with TTP, they are of value only to confirm the TTP diagnosis reflectively
- The current goal is to develop bedside assay for ADAMTS 13 (13)



Does TTP get passed to the Fetus?

No!

- “No case of fetal thrombocytopenia has been described in the maternal TTP” (14)
- Since TTP does not cause thrombocytopenia in the fetus, intracerebral hemorrhage is not a concern during a vaginal delivery
- C-section is more common in the event of placental deterioration



Is a TA (Therapeutic Abortion) Recommended in TTP?

Acquired TTP

Not in responsive stable TTP...

- “Pregnancy does not impair the response to plasmapheresis and termination of pregnancy does not alter the clinical course of the disease” (15)

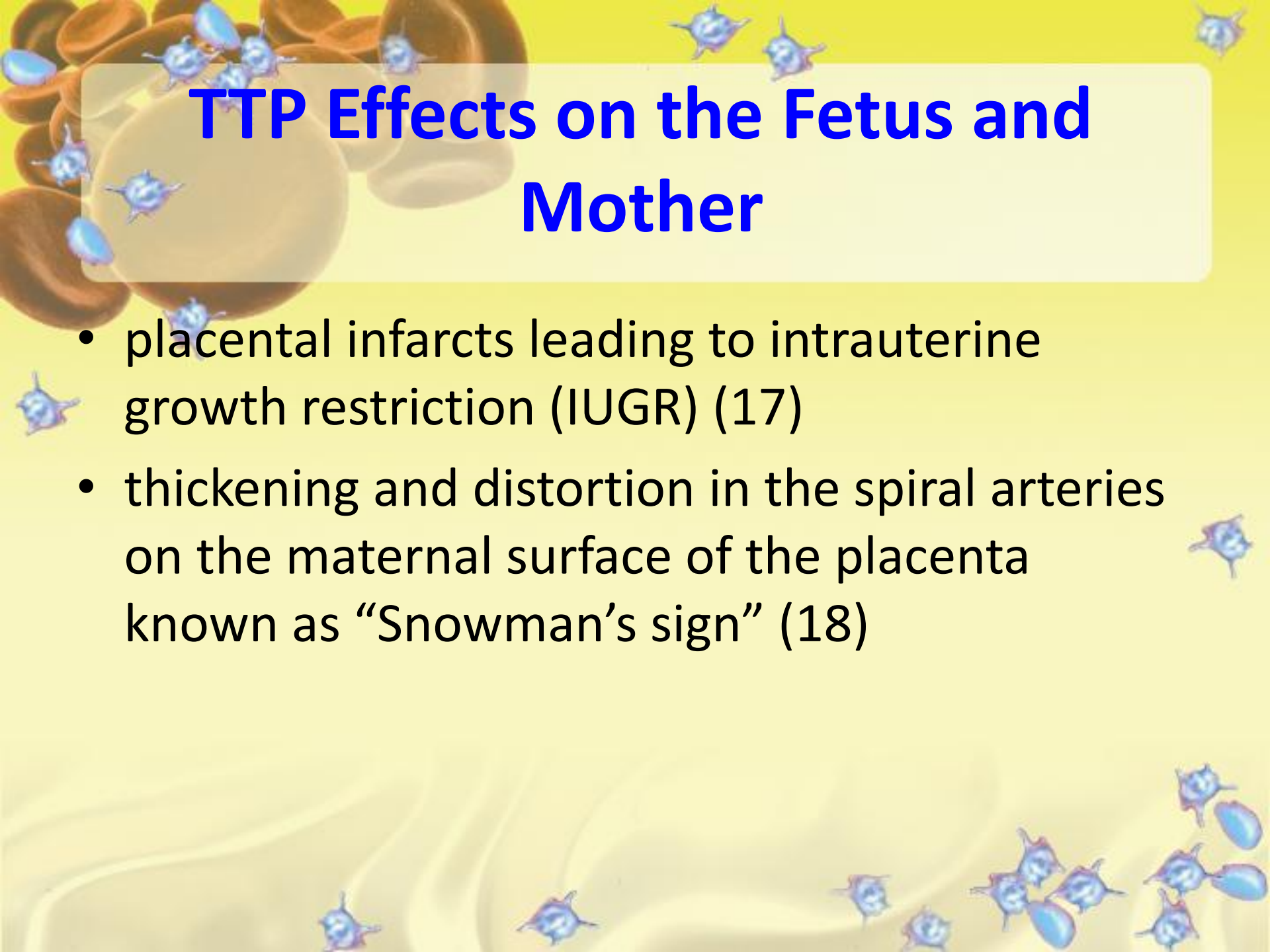


Is a TA (Therapeutic Abortion) Recommended in TTP?

Congenital TTP

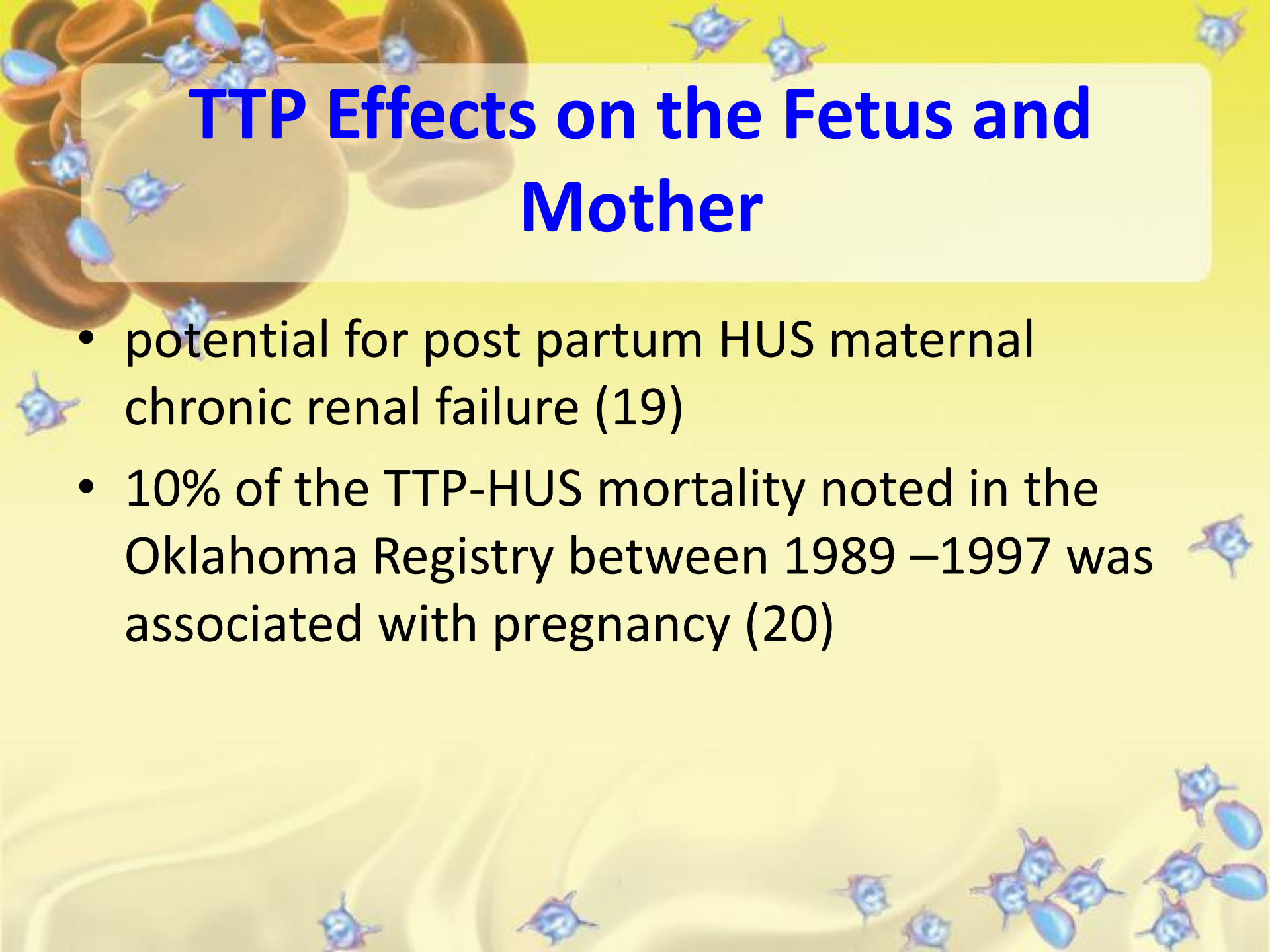
Maybe ...

- “Reports of women with congenital TTP-HUS have described more frequent and more severe episodes during pregnancy” (16)



TTP Effects on the Fetus and Mother

- placental infarcts leading to intrauterine growth restriction (IUGR) (17)
- thickening and distortion in the spiral arteries on the maternal surface of the placenta known as “Snowman’s sign” (18)

The background of the slide features a light yellow gradient with several clusters of red blood cells and platelets. The red blood cells are depicted as biconcave discs in shades of orange and brown, while the platelets are smaller, blue, and star-shaped. These elements are scattered across the slide, with a higher concentration in the top-left and bottom-right corners.

TTP Effects on the Fetus and Mother

- potential for post partum HUS maternal chronic renal failure (19)
- 10% of the TTP-HUS mortality noted in the Oklahoma Registry between 1989 –1997 was associated with pregnancy (20)

The background features a cluster of red blood cells and platelets in the upper left corner, and a group of platelets in the lower right corner. The rest of the background is a light yellow gradient with faint, larger-scale wavy patterns.

Treatment for Acquired Idiopathic TTP in Pregnancy

- plasma exchange promptly to “replenish the deficient ADAMTS 13 and remove some of the pathogenic auto-antibodies” (21)
- PLEX also removes large complexes of von Willebrand protein from the blood (22)

The background of the slide features a microscopic view of blood components. In the upper left, there is a cluster of red blood cells (erythrocytes) and several platelets (thrombocytes). The platelets are small, blue, and have a characteristic biconcave shape with some surface projections. The overall background is a light yellowish-green color with a subtle, wavy pattern.

Treatment for Acquired Idiopathic TTP in Pregnancy

- plasma infusion of 30 ml/kg/day if exchange is delayed (23)
- prescription for PLEX is 1.5 plasma volumes (PV) daily tapering gradually to 1 PV at tolerated intervals as the platelets normalize



Treatment for Congenital TTP in Pregnancy

- possible increase in the volume and frequency of plasma infusions for women with congenital TTP during pregnancy (24)
- in conjunction with PLEX/plasma infusion possible prophylactic low dose aspirin once platelets increase to 50,000 (25)
- possible Dipyridamole to keep the blood vessels open (26)



Treatment of Non-Responding and Refractory Idiopathic TTP in Pregnancy

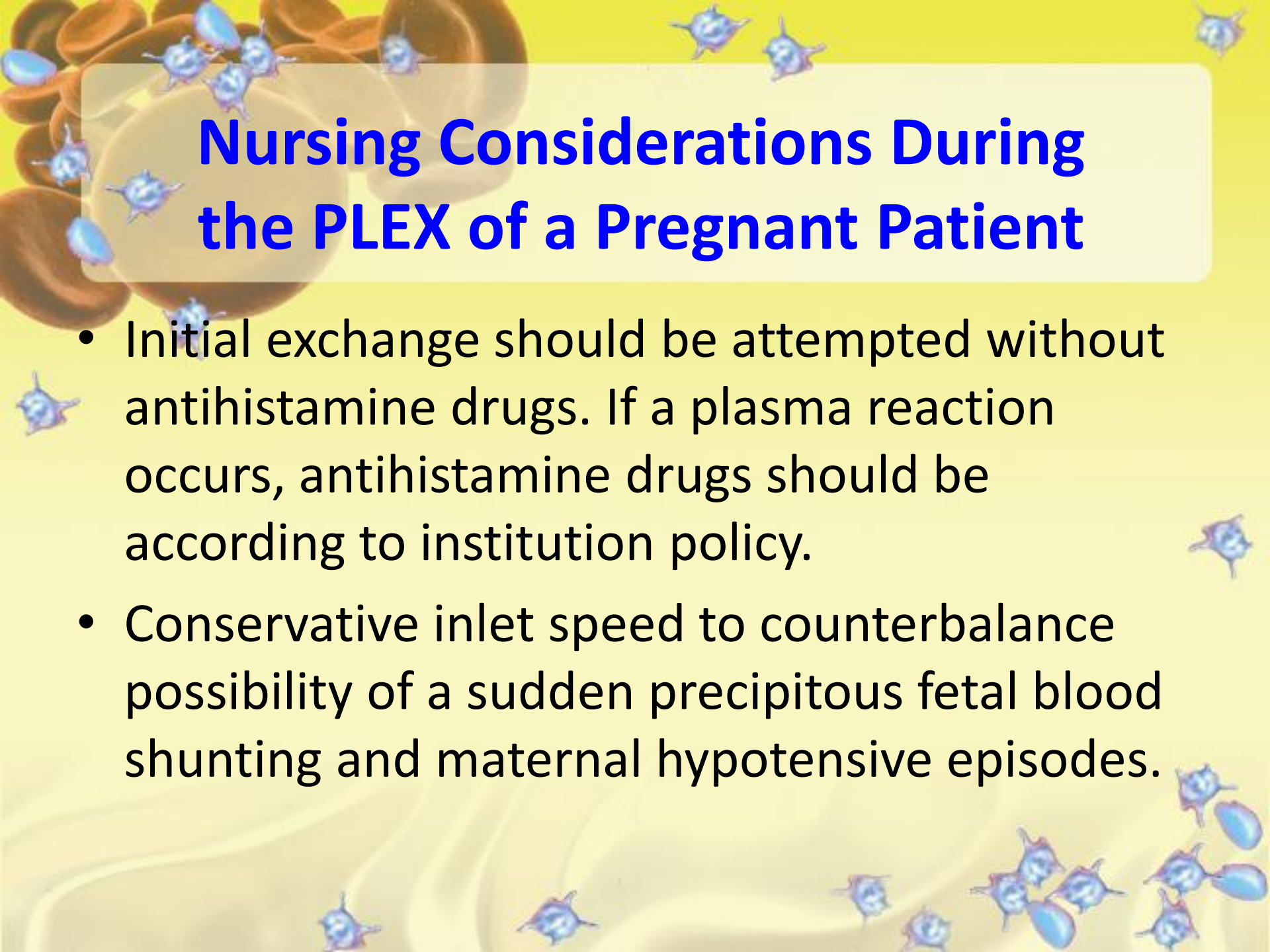
Conservative

- intensification of PLEX either by increasing frequency to Q12H or volume amount to 2 PV (27)
- cytotoxic immunosuppressants such as Rituximab, Vincristine and Cyclophosphamide are and **not recommended** in pregnancy.



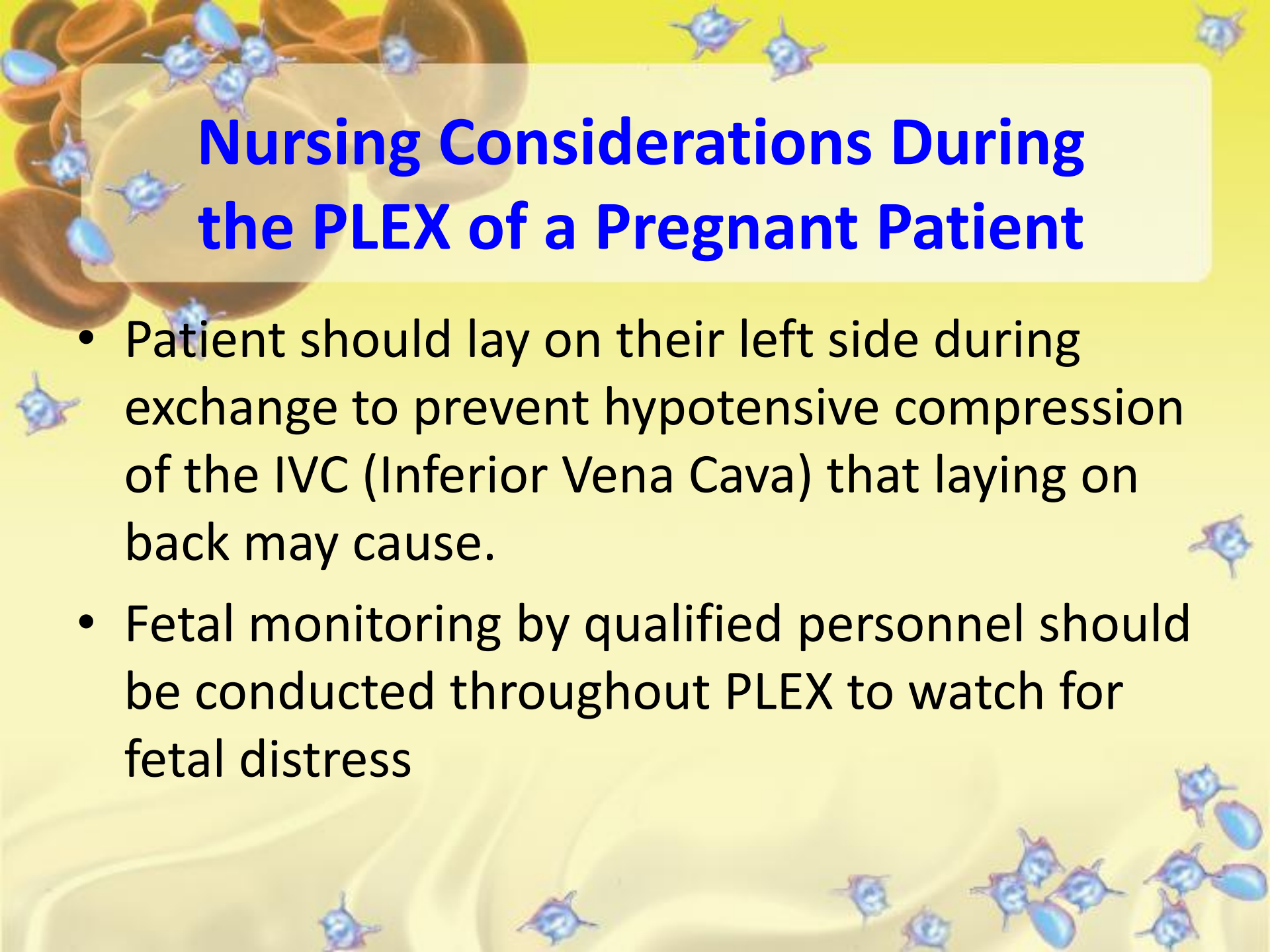
Treatment of Non-Responding and Refractory Idiopathic TTP in Pregnancy

- corticosteroid immunosuppressants such as prednisone are **not recommended** because the benefit is unproven and the multiple side effects.
- Splenectomy **should be postponed** until after delivery because an anesthetic can bring on premature labour



Nursing Considerations During the PLEX of a Pregnant Patient

- Initial exchange should be attempted without antihistamine drugs. If a plasma reaction occurs, antihistamine drugs should be according to institution policy.
- Conservative inlet speed to counterbalance possibility of a sudden precipitous fetal blood shunting and maternal hypotensive episodes.



Nursing Considerations During the PLEX of a Pregnant Patient

- Patient should lay on their left side during exchange to prevent hypotensive compression of the IVC (Inferior Vena Cava) that laying on back may cause.
- Fetal monitoring by qualified personnel should be conducted throughout PLEX to watch for fetal distress



What is the Risk of Recurrence in Future Pregnancies?

- it is very like that all women with congenital TTP will have a recurrence of the TTP –HUS in any other pregnancies.
- normal future pregnancies are expected for women who had shiga-toxins HUS during a pregnancy

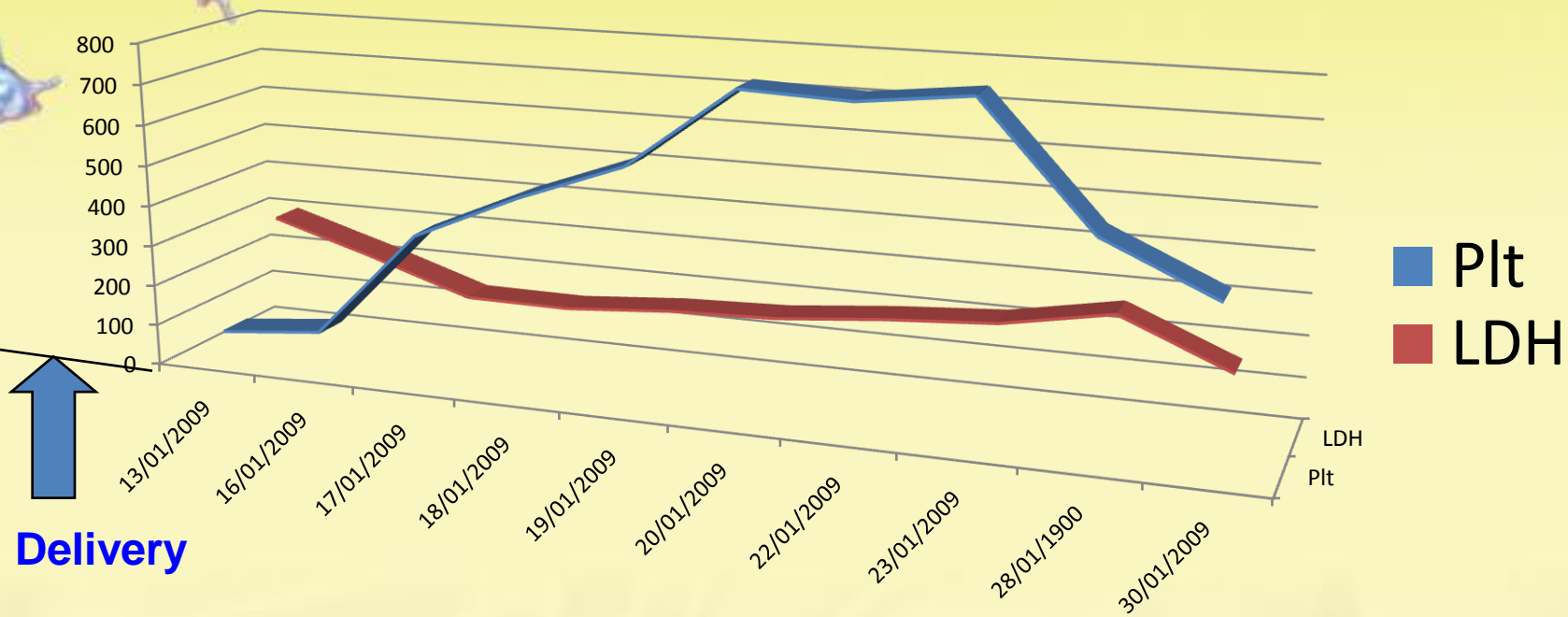
The background features a light yellow gradient with several 3D-rendered red blood cells and blue platelets scattered throughout. A semi-transparent white box with a thin blue border is positioned in the upper left quadrant, containing the title text.

What is the Risk of Recurrence in Future Pregnancies?

- acquired TTP during pregnancy may recur, but seems to be uncommon (according to the Oklahoma Registry data),
- aHUS? (28)

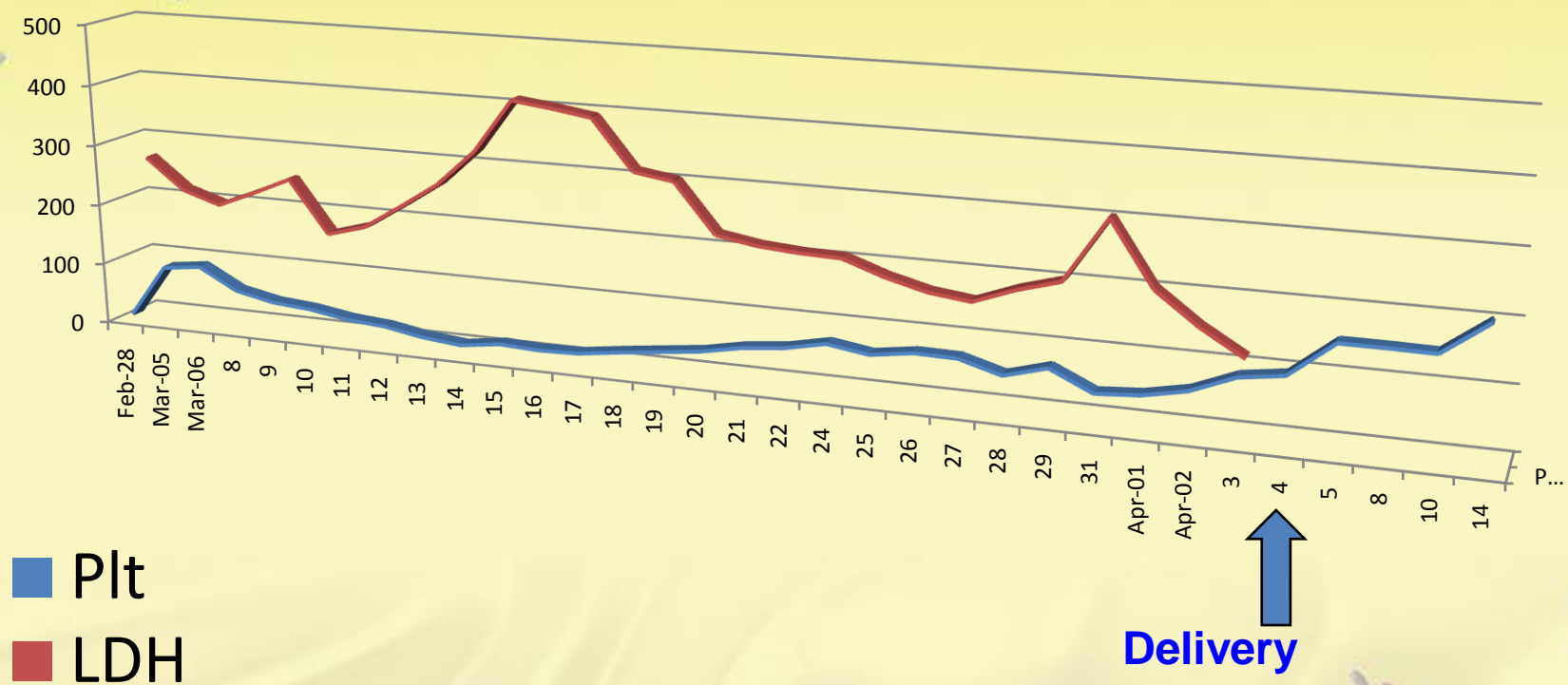
Patient S.A.

Plt and LDH Postpartum Trend

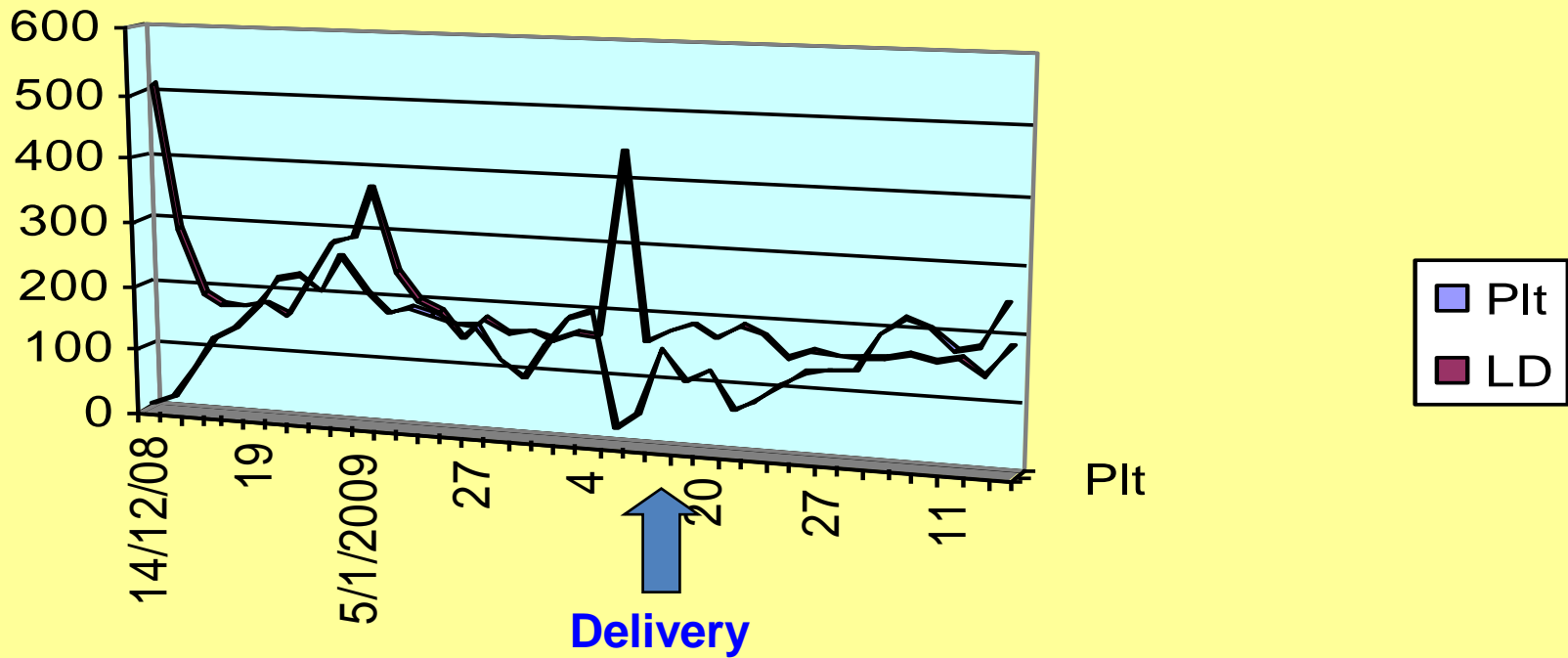


Patient C.Z.

Plt and LDH trend



Patient S.I. Plt and LDH trend

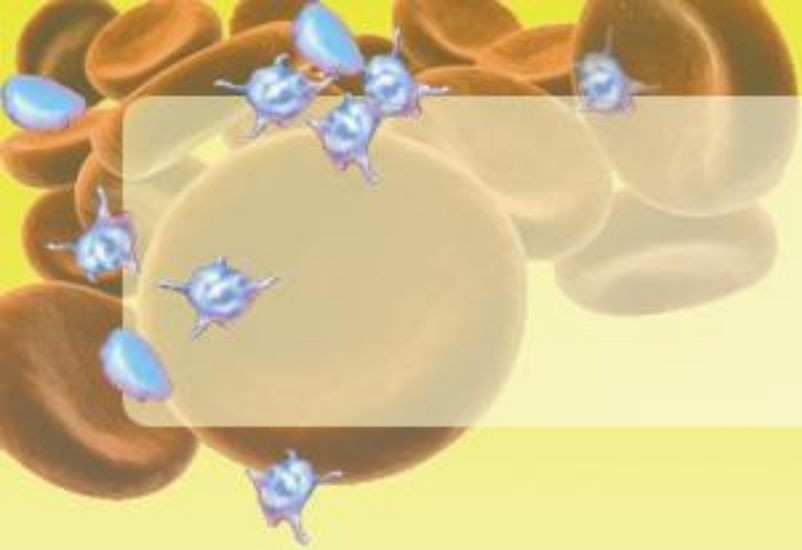


The Final Product



The Final Product

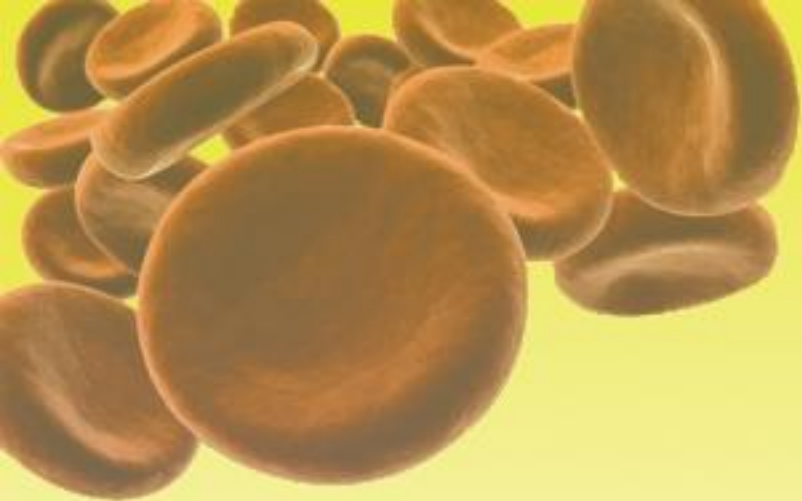






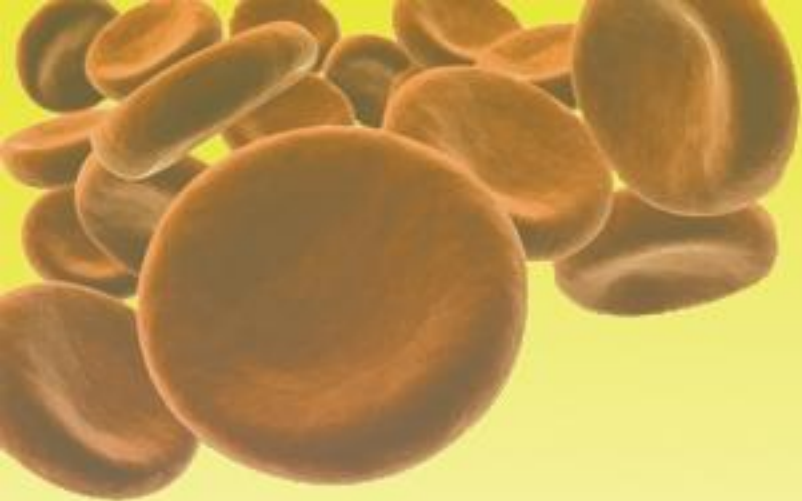
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