Review Article

Obstetric Medicine

Obstetric Medicine
6(3) 105–111

DOI: 10.1177/1753495X13488771
obm.sagepub.com

SAGE

The use of thrombolytic therapy in pregnancy

Eric J Gartman

Abstract

The relative hypercoagulable state of pregnancy leads to an increased risk of thrombotic complications, of which some may be life-threatening or medically devastating. In the non-pregnant patient, the current guidelines suggest thrombolysis as the primary treatment in acute ischemic stroke, myocardial infarction when percutaneous intervention is unavailable, certain cases of mechanical valve thrombosis, and pulmonary embolism with hemodynamic compromise or shock. Given that clinical trial data regarding thrombolytic use in pregnant women are absent due to exclusion, the goal of this review is to summarize the available published data regarding the use of thrombolytic agents and subsequent outcomes and complications in pregnant women. Overall, the use of thrombolytic agents in pregnancy is associated with a relatively low reported complication rate, especially given the severe medical conditions for which they are indicated. The data would suggest that thrombolysis should be considered for appropriate indications similar to that of non-pregnant patients. However, caution should be exercised when drawing conclusions regarding maternal and fetal safety, given the lack of controlled clinical trials including pregnant women and the nature of the weak evidence level of the cumulative data presented in this review.

Keywords

Thrombolysis, pulmonary embolism, pregnancy complications, thrombosis

Coagulation in pregnancy and risk of thrombotic complications

Many significant physiologic changes occur in hemostasis during pregnancy that prevent substantial hemorrhage during delivery and allow for expansion of the maternal–fetal circulations at the utero-placental interface. Unfortunately, these necessary changes also are responsible for an increased risk of thrombotic complications during and after the pregnancy. During the pregnancy, and peaking at term and the immediate peri-partum period, there is a state of relative hypercoagulability – marked by an increase in the majority of pro-clotting factors, a reduction in natural thrombolytic activity, and a reduction in anticoagulant protein activity (e.g. activated protein C, protein S). Following delivery, these coagulation changes cease and normal hemostasis generally returns 3–4 weeks following delivery.[1–3]

Thrombotic complications during pregnancy are among the leading causes of maternal mortality worldwide, and are the main cause in many developed countries.[4,5] The hypercoagulable state of pregnancy augments the risk of certain complications more than others, with the most marked effect seen with venous-thromboembolic events (VTE) (Table 1).

Therapeutic standards of care and the use of thrombolysis in non-pregnant patients

The range of therapies available for thrombotic diseases has evolved greatly over the last several decades, and many strategies now include the use of systemic or locally directed thrombolytic agents. Given the devastating hemorrhagic complications that can accompany the administration of thrombolytics, the decision to employ them requires careful weighing of the known risks and benefits. In some conditions, there exists strong evidence to support usage as the primary treatment, while in others thrombolysis is reserved for those patients with hemodynamic compromise or imminent risk of death.

In acute ischemic stroke, intravenous thrombolysis is indicated as the primary therapy within a prescribed symptom-onset window, and has been shown to significantly increase the chances of complete or near-complete recovery at three months.[14] For acute myocardial infarction (MI), the use of systemic thrombolysis is still common in regions without ready access to percutaneous intervention technology, and its expedient use is associated with a very significant reduction in mortality.[15] In cases of thrombotic obstruction of prosthetic cardiac valves, due to the appreciable surgical mortality associated with this condition, the use of systemic thrombolysis is often chosen – especially in those who are at high risk for surgery or have right-sided prosthetic valves.[16]

Unfortunately, the evidence for the benefit of thrombolysis in acute VTE has not been demonstrated as clearly. Despite the paucity of solid evidence, all guidelines agree that thrombolysis should be given in acute pulmonary embolism presenting with significant hypotension or evidence of shock.[17,18] When the much more common presentation of hemodynamically stable VTE is encountered, the evidence to support the use of thrombolytics remains uncertain. A meta-analysis of available trials showed a non-statistically significant improvement in mortality and a significant increase in major bleeding events with the use of thrombolytics plus anticoagulation versus anticoagulation alone – which led to the recommendation against their use in patients without evidence of hypotension or shock.[18] It should be noted, however, that there was a large difference in major bleeding events depending on bleeding risk (6.2% versus 0.1%, high versus low-risk) – with high risk defined by a point system scoring for recent bleeding, anemia, renal insufficiency, prior pulmonary embolism (PE), cancer, and age >75.[19] Finally, there is debate regarding whether thrombolysis improves right ventricular function and pulmonary hemodynamics in a sustained fashion, and some have argued for this consideration to prevent the development of possible long-term altered cardio-pulmonary hemodynamics.[20,21]

Pharmacology and teratogenicity of thrombolytic agents

Given the significant complications that potentially can occur following the administration of thrombolytic agents, there understandably is

Pulmonary, Critical Care, and Sleep Medicine, Warren Alpert Medical School of Brown University, Memorial Hospital of Rhode Island, Pawtucket, RI, USA

Corresponding author:
Eric J Gartman, Pulmonary, Critical Care, and Sleep Medicine, Warren Alpert Medical School of Brown University, Memorial Hospital of Rhode Island, 111 Brewster Street, Pawtucket, RI 02860, USA.
Email: eric_gartman@brown.edu

Table 1. Risk of thrombotic complications in pregnancy.

Thrombotic complication	Incidence or relative risk in pregnancy	Incidence in non-pregnant women	References
Deep venous thrombosis	0.615/1000 (age <35) 1.216/1000 (age >35)	0.11–0.41/1000	6,7
Pulmonary embolism	0.33–1/1000	0–0.2/1000[a]	7,8
Cerebral infarction	RR 0.7 (antepartum) RR 8.7 (post-partum)	0.11/1000	9,10
Artificial valve thrombosis	39/1000 (warfarin)[b] 92/1000 (heparin)[b]	3–13/1000[b]	11,12
Myocardial infarction	0.1/1000	0.05/1000	10,13

[a]Age-dependent incidence (essentially zero incidence in women <18).
[b]Incidence expressed in those with an artificial cardiac valve.

Table 2. Molecular weights of thrombolytic agents.[23]

Thrombolytic agent	Molecular weight (Da)
Alteplase (rtPA)	59042.3
Urokinase	31126.5
Streptokinase	47286.7
Tenecteplase	58951.2
Reteplase	39589.6

Da: Daltons; rtPA: recombinant tissue plasminogen activator.

concern regarding their effects on fetal outcomes. There are no formal studies examining the effects of thrombolytics in human pregnancy outcomes, and pregnancy is a universal exclusion criterion in their clinical trials. Therefore, the basis for fetal safety must rely on what is known regarding drug entry into the placenta. Several factors determine transfer of molecules to the placenta – lipid solubility, pH, protein binding, and most importantly, molecular weight – with drugs with molecular weights greater than 1000 Da crossing poorly into the placenta.[22] As such, it is thought that all thrombolytic agents do not pass into the placenta (Table 2).

There is a similar dearth of quality data surrounding the issue of potential teratogenicity of these agents, although similar arguments as above suggest there is not a potential for effects. The known fetal outcomes reported in case reports and case series are presented below – and overwhelmingly show no obvious teratogenetic effects. Likewise, there is no evidence in animal studies to suggest adverse fetal effects due to these agents.[24]

Clinical experience with thrombolytic use in pregnancy

Search strategy

As stated previously, pregnant women are uniformly excluded from participation in clinical trials involving thrombolytics. As such, the information below represents the known reports and series discussing the use of thrombolysis in various conditions. A systematic review of the use of thrombolytics in pregnant women was performed by searching the electronic databases MEDLINE (from 1946) and the Cochrane Library up to March 2013. The search included MeSH terms 'thrombolytic therapy', 'pregnancy', and 'tissue plasminogen activator'; and included also were the search terms 'pregnan*', 'streptokinase', 'urokinase', 'tPA', 'tenecteplase', 'alteplase', 'thrombolytic', 'thrombolysis', and 'tissue plasminogen activator'. The references listed in the full text articles were reviewed to ensure additional citations were not missed. All publication types that reported the use of a thrombolytic agent for any indication in a pregnant woman, and described the outcome, were included in the review. In sum, a total of 56 articles were found, and included a cumulative total of 231 patients (Table 3). There have been no randomized or prospective trials involving the use of thrombolytics in pregnant women.

Deep vein thrombosis (DVT) and PE

Twenty-nine articles were found discussing the role of various thrombolytic agents in DVT and PE, with a total case population of 189. There exists significant heterogeneity in the thrombolytic agent used, the method of administration (e.g. systemic versus directed therapy), and clinical indication for which they were used. The largest series comprised 122 patients with DVT,[29] which found a major bleeding complication rate of 1.6%, no maternal deaths, and one fetal death. In the remaining 67 patients with VTE, there were no maternal deaths, three major bleeding events (all associated with streptokinase), two minor bleeding events (one rtPA, one streptokinase), and two deaths *in utero* (one after mother presented in shock, one after failed surgical embolectomy and subsequent rtPA administration).[25–28,30–53]

Acute stroke and other neurologic indications

Eleven articles have been published describing outcomes in 18 pregnant patients who received thrombolytics (majority rtPA) for various neurologic thrombotic complications (acute stroke, venous sinus thrombosis).[54–64] There were no maternal deaths attributed to thrombolytic administration (one death reported due to arterial dissection during angioplasty), no major bleeding events, four minor bleeding events, one preterm delivery with good outcome, and three fetal deaths/spontaneous abortions (one due to maternal death, one at six weeks gestation in a 40-year-old mother with polycythemia vera and essential thrombocytosis, one in first trimester in a mother with bacterial endocarditis leading to acute stroke).

Mechanical cardiac valve thrombosis and acute MI

Sixteen articles were found describing the outcomes in 24 cases of patients receiving thrombolytics for cardiac indications (23 mechanical valve thromboses, one acute MI).[65–80] In addition to considering the relatively high mortality associated with these conditions, the indications for choosing thrombolysis versus operative intervention were not clear in the majority of the reports, and thus may have played a role in some of the observed outcomes. There were two maternal deaths, five fetal deaths (two due to maternal death), two serious bleeding complications, and two minor bleeding complications.

Discussion

The relative hypercoagulable state of pregnancy that is necessary to allow for normal growth of a fetus and arrest hemorrhage during delivery unfortunately carries with it increased risk of thrombotic complications. Some of these complications occur more frequently than others, with some approaching relative risks 6–10 times above the non-pregnant state. While some of thrombotic events are medically manageable, occasionally these conditions present in a life-threatening state or one that may carry lifelong debility. As such, the use of active thrombolysis may be warranted regardless of the pregnancy to ensure the safety of the mother and the health of the child. That stated, given their potential to induce significant hemorrhage, thrombolytic agents

Table 3. Thrombolytic use in pregnancy by clinical indication.

DVT/PE[a]	*N*	Thrombolytic	Maternal/fetal complications	Comments
Pfeifer[25]	12	SK	NA	Cases were DVT
Hall[26]	1	SK	No long-term complications	Significant uterine hemorrhage; however, SK given for 41 h (including 3 hours after delivery)
Ludwig[27]	24	SK	No complications	DVT – 21 cases, PE – 3 cases
McTaggart[28]	1	SK	Mother alive, fetal death *in utero*	Mother presented in shock
Ludwig and Genz[29]	122[b]	SK	2 severe maternal bleeding events; 1 fetal death	All cases were treatment of DVT
Delclos and Davila[30]	1	UK	No complications	
Fagher et al.[31]	1	SK	Severe maternal bleeding; no fetal complications	SK given directly before and after delivery – total 29 hours.
Baudo et al.[32]	1	rtPA	No complications	
Flossdorf et al.[33]	1	rtPA	No complications	
Seifried et al.[34]	1	rtPA	No complications	
De Stefano et al.[35]	1	rtPA	No complications	Hepatic and portal vein thrombosis
Mazeika and Oakley[36]	1	SK	Moderate cervical hemorrhage, normal fetus	Utilized mechanical disruption of PE following SK infusion
Kramer et al.[37]	1	UK	No complications	
La Valleur et al.[38]	2	UK	No complications	Cases were DVT only
Grand et al.[39]	1	rtPA	No complications	Acute ileo-femoral vein thrombosis
Saviotti et al.[40]	1	rtPA	Minor uterine bleeding, no fetal complications	
Krishnamurthy et al.[41]	3	UK	No complications	DVT – 2 cases, PE – 1 case. UK delivered via directed catheter
Sofocleous et al.[42]	1	rtPA	Mother alive, fetal death *in utero*	rtPA administered via catheter after failed catheter embolectomy
Henrich et al.[43]	1	SK	No complications	Acute severe iliac vein thrombosis
Ahearn et al.[44]	1	rtPA	No complications	
Yap et al.[45]	1	rtPA	No complications	
Patel et al.[46]	1	rtPA	No complications	
Stefanovic et al.[47]	1	SK	Mild vaginal bleeding, no fetal complications	SK given for PE 12 hours after caesarean delivery
Trukhacheva et al.[48]	1	rtPA	No complications	
Bechtel et al.[49]	1	rtPA	No complications	rtPA administered via catheter after mechanical fragmentation
te Raa et al.[50]	1	SK	No complications	
Fasullo et al.[51]	1	rtPA	No complications	
Holden et al.[52]	3	SK/rtPA	No complications	Followed out for 2 years
Lonjaret et al.[53]	1	rtPA	No complications	
Neurologic uses[c]	***N***	**Thrombolytic**	**Maternal/fetal complications**	**Comments**
Niwa et al.[54]	1	rtPA	No complications	Direct treatment of superior sagittal sinus thrombosis via select venography
Elford et al.[55]	1	rtPA	Mild neurologic deficits, no fetal complications	rtPA administered via directed intra-arterial catheter
Dapprich and Boessenecker[56]	1	rtPA	Radiographic hemorrhagic transformation of infarction, almost complete recovery at 4 weeks, no fetal complications	No indication of timing of onset of symptoms prior to rtPA administration
Weatherby et al.[57]	1	rtPA	No complications	Direct treatment of cerebral venous sinus thrombosis
Johnson et al.[58]	1	rtPA	No complications	rtPA administered via directed intra-arterial catheter

(continued)

Table 3. Thrombolytic use in pregnancy by clinical indication.

Neurologic uses[c]	*N*	Thrombolytic	Maternal/fetal complications	Comments
Murugappan et al.[59]	8	rtPA/UK	Maternal: 1 death from dissection during angioplasty, 4 minor bleeding events/asymptomatic ICH; 3 fetal deaths/SAB (1 due to maternal death), 3 MTP, 2 healthy infants	2 SABs (6wk in 40yo mother with PCV/ET, first trimester mother with bacterial endocarditis)
Wiese et al.[60]	1	rtPA	No complications	
Leonhardt et al.[61]	1	rtPA	Maternal: residual effects of CVA; preterm delivery at 32 + 6 weeks – healthy infant at 1 year follow-up	
Yamaguchi et al.[62]	1	rtPA	No complications	
Li et al.[63]	1	rtPA	No complications	rtPA administered via directed intra-arterial catheter
Tassi et al.[64]	1	rtPA	No complications	
Cardiac uses[d]	***N***	**Thrombolytic**	**Maternal/fetal complications**	**Comments**
Witchitz et al.[65]	1	SK	Minor uterine hemorrhage, no other maternal/fetal complications	Mitral valve
Ramamurthy et al.[66]	1	SK	No complications	Mitral valve
Azzano et al.[67]	1	rtPA	Uterine hemorrhage and rethrombosis of valve leading to interruption of pregnancy and need for cardiac surgical intervention	Tricuspid valve
Schumacher et al.[68]	1	rtPA	No complications	Acute myocardial infarction
Fleyfel et al.[69]	1	rtPA	No complications	Mitral valve
Rinaldi et al.[70]	1	rtPA	No complications	Aortic valve
Abbadi[71]	1	SK	No complications	Mitral valve
Anbarasan et al.[72]	1	SK	No complications	Mitral valve
Nanas et al.[73]	1	rtPA	No complications	Mitral valve
Behrendt et al.[74]	1	rtPA	No complications	Aortic valve
Nassar et al.[75]	1	rtPA/SK	No complications	rtPA administered after presumed rethrombosis occurred after SK use
Sahnoun-Trabelsi et al.[76]	7	rtPA	Two maternal deaths, one severe non-fatal bleeding complication, three completed healthy pregnancies	Mix of mitral and aortic valve cases. Two deaths presented in shock and had failure of treatment.
Wei et al.[77]	1	rtPA	No complications	Pulmonic valve
Kaya et al.[78]	1	rtPA	No complications	Mitral valve
Ozer et al.[79]	3	rtPA	TIA – complete resolution, transient epistaxis; no fetal complications	Mitral valve
Srinivas et al.[80]	1	SK	No complications	Mitral valve
Totals (DVT/PE, Neurologic, Cardiac)	231 (189/18/24)		No maternal death from hemorrhage; six major (four SK, two rtPA), 10 minor bleeding events (six SK/UK, four rtPA)	

DVT: deep vein thrombosis; PE: pulmonary embolism: SK: streptokinase: UK: urokinase; rtPA: recombinant tissue plasminogen activator; ICH: intracranial hemorrhage; MTP: medical termination of pregnancy; CVA: cerebral vascular accident; SAB: spontaneous abortion; PCV/ET: polycythemia vera/essential thrombocytosis.

[a]Cases represent PE unless stated in comments.

[b]Unclear if this report included population from 1973 reference.

[c]Treatment of acute stroke via systemic intravenous thrombolysis unless otherwise stated in comments.

[d]Treatment of acute prosthetic valve thrombosis unless otherwise indicated in comments.

only should be considered in appropriate clinical scenarios and in the safest manner possible.

This review described the known reports and series regarding the use of thrombolytic drugs in pregnant patients for a variety of serious clinical scenarios. When examining the group as a whole, it is difficult to ascertain the maternal and fetal complication rates that would be strictly attributable to the use of thrombolysis alone, given that many of these patients clinically presented in shock, after surgical attempts at treatment, and with large burden of medical comorbidity (both before and after their thrombotic complication). It would seem reasonable to expect that both maternal and fetal complications will occur in a cohort of critically and/or chronically ill women, irrespective of the additional burden of thrombotic complications and thrombolytic treatment. That stated, the observed complication rates in these articles is low and in proportion or less than reports in non-pregnant patients who were generally much older, especially given the conditions that were being treated carry a high mortality even without the addition of the pregnancy.[14,81] There were only a few maternal deaths reported – with none being reported due to the thrombolytic treatment in the VTE or neurologic indications. There were 10 fetal losses reported, with the majority associated with maternal death, maternal presentation in shock, and significant maternal medical comorbidity. A mixture of thrombolytic agents was used in the articles described, with rtPA and streptokinase being the most common. There were low rates of bleeding complications overall, with 10 events occurring with streptokinase and urokinase (six minor, four major) and six events occurring with rtPA (four minor, two major). No deaths were reported due to bleeding.

These data are suggestive that the use of thrombolytic agents in pregnant women should be considered as similar as when they would be indicated in a non-pregnant patient. Given the comparison of complication rates presented, rtPA likely would be selected as the agent of choice for several reasons; and regardless, this generally is the only agent now used and widely available. There may be several reasons that rtPA demonstrates a lower complication profile. First, it is administered over a short time period, versus some of the reports with streptokinase being given over a period of days. Next, it has been reported that rtPA's mechanism of action is ideal for acute thrombotic events in which one would desire the pathologic clot to be dissolved, and not induce a systemic 'lytic' effect. It has been shown that rtPA has high affinity for plasminogen only in the presence of fibrin, thus affording this theoretical benefit of less systemic hemorrhage risk.[82] Lastly, compared to other thrombolytics, rtPA is purported not to induce antigenicity, thus allowing for repeated administration – which is particularly important in the cases of mechanical valve thrombosis.[82]

The available published data suggest the safety of these agents in pregnancy and that the observed complication rates are seemingly on-par with their use in non-pregnant patients. However, it must be stated that there is a lack of scientific rigor leading to these conclusions given the poor quality of evidence (i.e. case reports and case series). There is an inherent publication bias at this level of evidence, especially when the subject is surrounding a potentially life-threatening scenario. It is reasonable to assume that a clinician would be much less likely to offer for publication a case of thrombolysis used in pregnancy that led to catastrophic bleeding and maternal–fetal death. With that understood, however, all available evidence suggest that one should approach the treatment of these thrombotic complications in pregnant women in an identical fashion to the general population.

Funding

This review received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

References

1. O'Riordan MN and Higgins JR. Haemostasis in normal and abnormal pregnancy. *Best Pract Res Clin Obstet Gynaecol* 2003; 17: 385–396.
2. Bremme KA. Haemostatic changes in pregnancy. *Best Pract Res Clin Haematol* 2003; 16: 153–168.
3. Thornton P and Douglas J. Coagulation in pregnancy. *Best Pract Res Clin Obstet Gynaecol* 2010; 24: 339–352.
4. Greer IA. Thrombosis in pregnancy: maternal and fetal issues. *Lancet* 1999; 353: 1258–1265.
5. Khan KS, Wojdyla D, Say L, et al. WHO analysis of causes of maternal death: a systematic review. *Lancet* 2006; 367: 1066–1074.
6. Macklon NS and Greer IA. Venous thromboembolic disease in obstetrics and gynaecology: the Scottish experience. *Scott Med J* 1996; 41: 83–86.
7. Silverstein MD, Heit JA, Mohr DN, et al. Trends in the incidence of deep vein thrombosis and pulmonary embolism: a 25-year population-based study. *Arch Intern Med* 1998; 158: 585–593.
8. De Swiet M. Management of pulmonary embolus in pregnancy. *Eur Heart J* 1999; 20: 1378–1385.
9. Kittner SJ, Stern BJ, Feeser BR, et al. Pregnancy and the risk of stroke. *N Engl J Med* 1996; 335: 768–774.
10. Petitti DB, Sidney S, Quesenberry CP Jr, et al. Incidence of stroke and myocardial infarction in women of reproductive age. *Stroke* 1997; 28: 280–283.
11. Horstkotte D and Burckhardt D. Prosthetic valve thrombosis. *J Heart Valve Dis* 1995; 4: 141–153.
12. Chan WS, Anand S and Ginsberg JS. Anticoagulation of pregnant women with mechanical heart valves: a systematic review of the literature. *Arch Intern Med* 2000; 160: 191–196.
13. Webber MD, Halligan RE and Schumacher JA. Acute infarction, intracoronary thrombolysis, and primary PTCA in pregnancy. *Cathet Cardiovasc Diagn* 1997; 42: 38–43.
14. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. *N Engl J Med* 1995; 333: 1581–1587.
15. Boersma E, Maas AC, Deckers JW, et al. Early thrombolytic treatment in acute myocardial infarction: reappraisal of the golden hour. *Lancet* 1996; 348: 771–775.
16. Roudaut R, Roques X, Lafitte S, et al. Surgery for prosthetic valve obstruction. A single center study of 136 patients. *Eur J Cardiothorac Surg* 2003; 24: 868–872.
17. Jaff MR, McMurtry MS, Archer SL, et al. Management of massive and submassive pulmonary embolism, iliofemoral deep vein thrombosis, and chronic thromboembolic pulmonary hypertension: a scientific statement from the American Heart Association. *Circulation* 2011; 123: 1788–1830.
18. Kearon C, Akl EA, Comerota AJ, et al. Antithrombotic therapy for VTE disease: antithrombotic therapy and prevention of thrombosis, 9th ed: American college of chest physicians evidence-based clinical practice guidelines. *Chest* 2012; 141: e419S–494S.
19. Ruiz-Gimenez N, Suarez C, Gonzalez R, et al. Predictive variables for major bleeding events in patients presenting with documented acute venous thromboembolism. Findings from the RIETE registry. *Thromb Haemost* 2008; 100: 26–31.
20. Sharma GV, Burleson VA and Sasahara AA. Effect of thrombolytic therapy on pulmonary-capillary blood volume in patients with pulmonary embolism. *N Engl J Med* 1980; 303: 842–845.
21. Konstantinides S, Tiede N, Geibel A, et al. Comparison of alteplase versus heparin for resolution of major pulmonary embolism. *Am J Cardiol* 1998; 82: 966–970.
22. Syme MR, Paxton JW and Keelan JA. Drug transfer and metabolism by the human placenta. *Clin Pharmacokinet* 2004; 43: 487–514.
23. Knox C, Law V, Jewison T, et al. DrugBank 3.0: a comprehensive resource for 'omics' research on drugs. *Nucleic Acids Res* 2011; 39: D1035–1041.
24. Shepard TH. *Catalog of teratogenic agents*, 13th ed. Baltimore, MD: Johns Hopkins University Press, 2010.
25. Pfeifer GW. The use of thrombolytic therapy in obstetrics and gynaecology. *Australas Ann Med* 1970; 19: 28–31.

26. Hall RJ, Young C, Sutton GC, et al. Treatment of acute massive pulmonary embolism by streptokinase during labour and delivery. *Br Med J* 1972; 4: 647–649.
27. Ludwig H. Results of streptokinase therapy in deep venous thrombosis during pregnancy. *Postgrad Med J* 1973; 49: 65–67.
28. McTaggart DR and Ingram TG. Massive pulmonary embolism during pregnancy treated with streptokinase. *Med J Aust* 1977; 1: 18–20.
29. Ludwig H and Genz H. Thrombolytic treatment during pregnancy. *Thromb Haemost* 1981; 46: 438–445.
30. Delclos GL and Davila F. Thrombolytic therapy for pulmonary embolism in pregnancy: a case report. *Am J Obstet Gynecol* 1986; 155: 375–376.
31. Fagher B, Ahlgren M and Astedt B. Acute massive pulmonary embolism treated with streptokinase during labor and the early puerperium. *Acta Obstet Gynecol Scand* 1990; 69: 659–661.
32. Baudo F, Caimi TM, Redaelli R, et al. Emergency treatment with recombinant tissue plasminogen activator of pulmonary embolism in a pregnant woman with antithrombin III deficiency. *Am J Obstet Gynecol* 1990; 163: 1274–1275.
33. Flossdorf T, Breulmann M and Hopf HB. Successful treatment of massive pulmonary embolism with recombinant tissue type plasminogen activator (rt-PA) in a pregnant woman with intact gravidity and preterm labour. *Intensive Care Med* 1990; 16: 454–456.
34. Seifried E, Gabelmann A, Ellbruck D, et al. Thrombolytic therapy of pulmonary artery embolism in early pregnancy with recombinant tissue-type plasminogen activator. *Geburtshilfe Frauenheilkd* 1991; 51: 655–658.
35. De Stefano V, Leone G, Teofili L, et al. Hepatic and portal veins thromboses in a pregnant woman with paroxysmal nocturnal hemoglobinuria and severe thrombocytopenia: efficacy of rt-PA in the treatment of the Budd-Chiari syndrome and successful outcome of pregnancy. [Abstract]. *Thromb Haemost* 1991; 65: 1188.
36. Mazeika PK and Oakley CM. Massive pulmonary embolism in pregnancy treated with streptokinase and percutaneous catheter fragmentation. *Eur Heart J* 1994; 15: 1281–1283.
37. Kramer WB, Belfort M, Saade GR, et al. Successful urokinase treatment of massive pulmonary embolism in pregnancy. *Obstet Gynecol* 1995; 86: 660–662.
38. La Valleur J, Molina E, Williams PP, et al. Use of urokinase in pregnancy. Two success stories. *Postgrad Med* 1996; 99: 269–270, 272–263.
39. Grand A, Ghadban W, Perret SP, et al. Ilio-femoral vein thrombosis treated with tissue plasminogen activator in a pregnant woman. *Ann Cardiol Angeiol (Paris)* 1996; 45: 517–522.
40. Saviotti M, Bongarzoni A and Casazza F. Massive pulmonary embolism during the third trimester of pregnancy: effectiveness of thrombolytic treatment with alteplase. *G Ital Cardiol* 1997; 27: 72–75.
41. Krishnamurthy P, Martin CB, Kay HH, et al. Catheter-directed thrombolysis for thromboembolic disease during pregnancy: a viable option. *J Matern Fetal Med* 1999; 8: 24–27.
42. Sofocleous CT, Hinrichs C, Bahramipour P, et al. Percutaneous management of life-threatening pulmonary embolism complicating early pregnancy. *J Vasc Interv Radiol* 2001; 12: 1355–1356.
43. Henrich W, Schmider A, Henrich M, et al. Acute iliac vein thrombosis in pregnancy treated successfully by streptokinase lysis: a case report. *J Perinat Med* 2001; 29: 155–157.
44. Ahearn GS, Hadjiliadis D, Govert JA, et al. Massive pulmonary embolism during pregnancy successfully treated with recombinant tissue plasminogen activator: a case report and review of treatment options. *Arch Intern Med* 2002; 162: 1221–1227.
45. Yap LB, Alp NJ and Forfar JC. Thrombolysis for acute massive pulmonary embolism during pregnancy. *Int J Cardiol* 2002; 82: 193–194.
46. Patel RK, Fasan O and Arya R. Thrombolysis in pregnancy. *Thromb Haemost* 2003; 90: 1216–1217.
47. Stefanovic BS, Vasiljevic Z, Mitrovic P, et al. Thrombolytic therapy for massive pulmonary embolism 12 hours after cesarean delivery despite contraindication? *Am J Emerg Med* 2006; 24: 502–504.
48. Trukhacheva E, Scharff M, Gardner M, et al. Massive pulmonary embolism in pregnancy treated with tissue plasminogen activator. *Obstet Gynecol* 2005; 106: 1156–1158.
49. Bechtel JJ, Mountford MC and Ellinwood WE. Massive pulmonary embolism in pregnancy treated with catheter fragmentation and local thrombolysis. *Obstet Gynecol* 2005; 106: 1158–1160.
50. te Raa GD, Ribbert LS, Snijder RJ, et al. Treatment options in massive pulmonary embolism during pregnancy; a case-report and review of literature. *Thromb Res* 2009; 124: 1–5.
51. Fasullo S, Maringhini G, Terrazzino G, et al. Thrombolysis for massive pulmonary embolism in pregnancy: a case report. *Int J Emerg Med* 2011; 4: 69.
52. Holden EL, Ranu H, Sheth A, et al. Thrombolysis for massive pulmonary embolism in pregnancy – a report of three cases and follow up over a two year period. *Thromb Res* 2011; 127: 58–59.
53. Lonjaret L, Lairez O, Galinier M, et al. Thrombolysis by recombinant tissue plasminogen activator during pregnancy: a case of massive pulmonary embolism. *Am J Emerg Med* 2011; 29: 694 e691–692.
54. Niwa J, Ohyama H, Matumura S, et al. Treatment of acute superior sagittal sinus thrombosis by t-PA infusion via venography – direct thrombolytic therapy in the acute phase. *Surg Neurol* 1998; 49: 425–429.
55. Elford K, Leader A, Wee R, et al. Stroke in ovarian hyperstimulation syndrome in early pregnancy treated with intra-arterial rt-PA. *Neurology* 2002; 59: 1270–1272.
56. Dapprich M and Boessenecker W. Fibrinolysis with alteplase in a pregnant woman with stroke. *Cerebrovasc Dis* 2002; 13: 290.
57. Weatherby SJ, Edwards NC, West R, et al. Good outcome in early pregnancy following direct thrombolysis for cerebral venous sinus thrombosis. *J Neurol* 2003; 250: 1372–1373.
58. Johnson DM, Kramer DC, Cohen E, et al. Thrombolytic therapy for acute stroke in late pregnancy with intra-arterial recombinant tissue plasminogen activator. *Stroke* 2005; 36: e53–55.
59. Murugappan A, Coplin WM, Al-Sadat AN, et al. Thrombolytic therapy of acute ischemic stroke during pregnancy. *Neurology* 2006; 66: 768–770.
60. Wiese KM, Talkad A, Mathews M, et al. Intravenous recombinant tissue plasminogen activator in a pregnant woman with cardioembolic stroke. *Stroke* 2006; 37: 2168–2169.
61. Leonhardt G, Gaul C, Nietsch HH, et al. Thrombolytic therapy in pregnancy. *J Thromb Thrombolysis* 2006; 21: 271–276.
62. Yamaguchi Y, Kondo T, Ihara M, et al. Intravenous recombinant tissue plasminogen activator in an 18-week pregnant woman with embolic stroke. *Rinsho Shinkeigaku* 2010; 50: 315–319.
63. Li Y, Margraf J, Kluck B, et al. Thrombolytic therapy for ischemic stroke secondary to paradoxical embolism in pregnancy: a case report and literature review. *Neurologist* 2012; 18: 44–48.
64. Tassi R, Acampa M, Marotta G, et al. Systemic thrombolysis for stroke in pregnancy. *Am J Emerg Med* 2013; 31: 448.e1–3.
65. Witchitz S, Veyrat C, Moisson P, et al. Fibrinolytic treatment of thrombus on prosthetic heart valves. *Br Heart J* 1980; 44: 545–554.
66. Ramamurthy S, Talwar KK, Saxena A, et al. Prosthetic mitral valve thrombosis in pregnancy successfully treated with streptokinase. *Am Heart J* 1994; 127: 446–448.
67. Azzano O, French P, Robin J, et al. Thrombolytic therapy with rt-PA for thrombosis of tricuspid valve prosthesis during pregnancy. *Arch Mal Coeur Vaiss* 1995; 88: 267–270.
68. Schumacher B, Belfort MA and Card RJ. Successful treatment of acute myocardial infarction during pregnancy with tissue plasminogen activator. *Am J Obstet Gynecol* 1997; 176: 716–719.
69. Fleyfel M, Bourzoufi K, Huin G, et al. Recombinant tissue type plasminogen activator treatment of thrombosed mitral valve prosthesis during pregnancy. *Can J Anaesth* 1997; 44: 735–738.

70. Rinaldi JP, Yassine M, Aboujaoude F, et al. Successful thrombolysis on an aortic valve prosthesis by plasminogen tissue activator during pregnancy. *Arch Mal Coeur Vaiss* 1999; 92: 427–430.
71. Abbadi H. Successful thrombolysis of mitral valve prosthesis by streptokinase during pregnancy. *East Mediterr Health J* 2001; 7: 283–286.
72. Anbarasan C, Kumar VS, Latchumanadhas K, et al. Successful thrombolysis of prosthetic mitral valve thrombosis in early pregnancy. *J Heart Valve Dis* 2001; 10: 393–395.
73. Nanas JN, Kontoyannis SA, Mitsibounas DN, et al. Thrombolytic treatment for thrombosis of a mitral valve prosthesis during pregnancy. *Intensive Care Med* 2001; 27: 1668–1669.
74. Behrendt P, Schwartzkopff B, Perings S, et al. Successful thrombolysis of st. Jude medical aortic prosthesis with tissue-type plasminogen activator in a pregnant woman: a case report. *Cardiol Rev* 2002; 10: 349–353.
75. Nassar AH, Abdallah ME, Moukarbel GV, et al. Sequential use of thrombolytic agents for thrombosed mitral valve prosthesis during pregnancy. *J Perinat Med* 2003; 31: 257–260.
76. Sahnoun-Trabelsi I, Jimenez M, Choussat A, et al. Prosthetic valve thrombosis in pregnancy. A single-center study of 12 cases. *Arch Mal Coeur Vaiss* 2004; 97: 305–310.
77. Wei A, Alison J, Goldstein J, et al. Prosthetic pulmonary valve thrombosis in pregnancy successfully treated with thrombolysis. *Intern Med J* 2008; 38: 142–143.
78. Kaya EB, Kocabas U, Aksoy H, et al. Successful fibrinolytic treatment in a pregnant woman with acute mitral prosthetic valve thrombosis. *Clin Cardiol* 2010; 33: E101–103.
79. Ozer O, Davutoglu V, Soydinc HE, et al. Fibrinolytic therapy of prosthetic mitral valve thrombosis during pregnancy: three case reports and review of the literature. *Clin Appl Thromb Hemost* 2010; 16: 406–413.
80. Srinivas BC, Moorthy N, Kuldeep A, et al. Thrombolytic therapy in prosthetic valve thrombosis during early pregnancy. *Indian Heart J* 2012; 64: 74–76.
81. Kanter DS, Mikkola KM, Patel SR, et al. Thrombolytic therapy for pulmonary embolism. Frequency of intracranial hemorrhage and associated risk factors. *Chest* 1997; 111: 1241–1245.
82. Loscalzo J and Braunwald E. Tissue plasminogen activator. *N Engl J Med* 1988; 319: 925–931.