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Tranexamic Acid Coated or Eluted Uterine Balloon and Co-Attached Cervical Shutter in Post Partum Haemorrhage. A New Combatant in the Armamentarium, Not Merely a Balloon but More

Abd El Aal Nasser Kamal

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Abstract

Described herein a Tranexamic Acid (TXA) - Coated or Eluted Uterine Balloon for use in an intra uterine location for primary management of postpartum haemorrhage (PPH). It enforces the tamponade effect of currently used non medicated uterine balloons with an additional inbuilt mechanism of local steady release of the antibrinolytic TXA into uterine cavity that has been evidenced to contribute to haemostasis in cases of PPH. The invention ushers a new era of utilizing the uterine balloon surface coat as a delivery vehicle for TXA. This can be achieved via different techniques including and not limited to matrix coating or eluting of nanoparticulate TXA in the outermost layer of the balloon .TXA coated or eluted balloon replenish non medicated balloons with a therapeutic modality of the TXA related - antifibrinolysis especially in hemorrhages known to be associated with coagulopathy. This potential for topical application of TXA rather than systemic administration of the drug avails the merit of avoiding TXA - related theoretical risk of thromboembolism.

***Index terms*—**

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I. Field of the Invention his invention relates to a functional development of currently used uterine balloons in cases of PPH, in the field of Obstetrics and modifying them to be a delivery vehicle for drugs known of their haemostatic action onto the bleeding site, i.e. uterine cavity. TXA coated or eluted uterine balloon will avail the non medicated uterine balloons in use nowadays for management of PPH with a dual

integrated pharmacomechanical mechanism, along with an innovative Author: Professor Emeritus of Obstetrics & Gynecology, Menoufia Faculty of Medicine, Egypt. e-mail: nasserkamal411@gmail.com mechanism, that is, the cervical shutter which safeguards against external fast escape of the medication from the uterine cavity, thus allowing drug retention inside the uterine cavity for a reasonable time so as to achieve its therapeutic effect. Utilization of outer coat of balloon as a polymer-based vehicle used for delivering tranexamic acid and other haemostatic agents can be brought about by the use of a drug coating or eluting matrices technology and a variety of different water soluble and lipid soluble specialized polymers. The latter will be selected according to which suits better the most efficient steady state of intra cavitary drug release.

1 II. Background of the Invention

The object of this invention is to enforce a dual pharmaco-mechanical effect of TXA medicated intrauterine balloon in the armamentarium of managing postpartum hemorrhage (PPH).

[0001]-Since PPH is one of the leading causes of maternal mortality worldwide, various strategies have been developed to prevent and control it. World Health Organization, the International Federation of Gynecology and Obstetrics, and the Royal College of Obstetricians and Gynaecologists all recommend a uterine balloon tamponade (UBT) if uterotonics and uterine massage fail to control bleeding. Intrauterine balloon tamponade has been suggested as an effective, easily administered minimally invasive treatment option to control uterine bleeding while and fertility sparing procedure [1,2,3].

[0002]-Multiple types of balloons are available, including Bakri balloon, BT-cath balloon tamponade catheter, Foley catheters, Rusch balloon, condom catheters and the Sengstaken-Blakemore tube. The Bakri postpartum balloon [4] and the BT -balloon tamponadecatheterare specifically designed for postpartum intrauterine tamponade, and they are the only such devices approved by the US Food and Drug Administration for this application [5] .

[0003]-It is believed that pressure greater than systemic arterial pressure applied to the uterine wall by the inflated balloon is the mechanism of controlling the hemorrhage. This pressure can be achieved by inflating different balloons by different volumes [6] .

[0004]-It has been also reported that TXA decreases postpartum blood loss after vaginal birth and after caesarean section **??**7][8] . A systematic review and metaanalysis indicate strong evidence that intravenous administration of tranexamic acid (TXA) reduces blood transfusion in surgery [9] .

[0005]-Although most of the randomized studies or the cohort studies have suggested no statistically significant increase of thrombo embolism with use of TXA, sporadic cases of pulmonary embolism have been reported [10] .

[0006]-The true risk of thromboembolism by TXA remains uncertain because those studies have not statistical powers enough to detect the risks of rare events as pulmonary embolism. However, It stays hitherto as theoretical risk.

[0007]-Recently, haemostatic effects of topical or intracavitary administration of TXA have been also shown in cardiothoracic or orthopedic surgery. Recent meta-analyses of several randomized controlled trials have shown that tranexamic acid reduces peri -and postoperative blood loss, blood transfusion requirements and reoperations caused by bleedings. **??**11][12] 13 https://www.hindawi.com/journals/criog/2015/195036/ -B14].

[0008]-Topical use may pose a reduced risk, if any, of thromboembolism because the serum concentration of TXA in topical use would be much lower than systemic use.

[0009]-Unlike in other fields of surgery, there has been no data on the topical or intra cavitary use of TXA in obstetrics, possibly due to technical difficulties in hollow organs with an opening like a uterus. In one study TXA has been added to a piece of gause wrapped around a ballon and it has been found in such way it was possible to deliver a high concentration of the TXA at bleeding spots inside the uterus ant to add effectively to cessation of PPH **??**14] .

[0010]-Moreover, TXA competitively inhibits activation of plasminogen, thereby reducing conversion of plasminogen to plasmin (fibrinolysin), an enzyme that degrades fibrin clots, fibrinogen, and other plasma proteins, including the procoagulant factors V and VIII. Tranexamic acid also directly inhibits plasmin activity, but higher doses are required than are needed to reduce plasmin formation **??**15] .

[0011]-In recent years the extensive trial comprising more than 20,000 patients in severe trauma with massive bleedings using tranexamic acid was presented i.e. CRASH-2 (Clinical Randomization of an Antifibrinolytic in Significant Haemorrhage). It showed that the survival was increased when tranexamic acid was given early after the accident compared to placebo **??**16] .

[0012]-Of utmost importance is the WOMAN (World Maternal Antifibrinolytic), a randomized, double-blind, placebo controlled trial among 15,000 with clinical diagnosis of postpartum haemorrhage that pointed out the efficacy of Tranexamic acid in reducing maternal mortality from post-partum haemorrhage with no adverse effects. The previous study has stressed upon that when used as a treatment for postpartum haemorrhage, tranexamic acid should be given as soon as possible after bleeding onset **??**17] .

[0013]-Over the past decade, a novel opportunity has been widely used in endovascular coronary ischaemic management, namely the surface coatings in surface mediated-drug delivery. In these applications, deposited polymer film act as both a coating to modulate surface properties and a reservoir for active therapeutic cargo and delivery vehicle (i.e. endovascular angioplasty with anti proliferative paclitaxel coated or eluted balloon catheter as to prevent re stenosis).

[0014]-The fore mentioned data led to the ideation of this invention with such conception of making use of the evidence based of safety and efficacy of local delivery of TXA in comparison to systemic route, maximizing the efficacy and functionality of currently used non medicated uterine balloons in postpartum haemorrhage through inbuilt medication with TXA utilizing the currently used surface coating or eluting techniques and slow release of nanoparticles of such drug from polymeric coat.

[0015]-This ideation represents a meeting point of evidence based research at the interface of chemistry, nanotechnology, clinical pharmacology and bio medicine to develop a safe and efficacious aid in managing PPH. It allows utilization of a dual pharmacomechanical effects to enforce the efficiency of the currently used non medicated uterine balloon via TXA topical intrauterine release from drug nano particles coated matrix in the balloon surface which is more safe than systemic administration as regards thromboembolic risk. Together with an innovative adaptive back up mechanism to retain the released drug in utero without being flushed out rapidly via the co attached cervical shutter or "Barricade", this generation of uterine medicated balloons would be an effective measure in the armamentarium of the treatment of PPH.

2 III. Description of the Invention

The present invention provides a basically and specifically medicated uterine balloon that comprises the dual grasp of both the mechanical compression of the classical uterine balloon, and a unique inbuilt design that can enable topical intrauterine release of TXA through its outer surface. So, it ushers a new era of currently used coated or eluted balloon with a different location (intrauterine), different indication (PPH) and a different medication (TXA, and other haemostatics).

Basically, the currently used balloons particularly B-T catheter balloon, a pear-shaped balloon tamponade catheter for controlling uterine postpartum hemorrhage. (Utah Medical products Inc. -patent US 8123773 B1) are blank or non medicated, so they offer solely a mechanical tamponade effect.

However, 2 achievements in the current invention that constitutes an additional dimension to these currently used balloons:-A-Basically, and specifically to this invention is first mention of utility of tranexamic acid (TXA)-coated or eluted uterine balloon in cases of PPH. The outer coat is functionally modified to act as a "cargo" or a delivery vehicle for TXA and possibly other haemostatics which will add a therapeutic dimension to the currently used plain uterine balloons especially in those cases of PPH co-associated with a coagulopathic defect .Examples for this drug delivery routes are many in the literature and some embodiments will be mentioned later. B-Cervical shutter, "Barricade": A back up mechanism to allow intra uterine residency of the released TXA. It is a cone shaped screw plug moving along the screw bar of the mid vaginal portion of the balloon catheter, the outer surface of which is modified as a screw bar allowing the Barricade to move towards the cervix shutting it at the cervico vaginal junction to halt the fast downward egress of the released drug, an additional mechanism for its longer topic residency inside the uterine cavity. Additional advantage of barricade screw are fixative and immobilizing influence on the balloon causing its strict apposition with endometrial surface and providing an extra counter pressure on the lower uterine segment which may be the site of bleeding in abnormally adherent placenta.

[0016]-In one embodiment, Thin film polymers can be used as a drug cargo in the TXA medicated uterine balloon by either surface coating and drug capturing via surface folding or eluting techniques may be methacrylic acid copolymers. The balloons which are coated while the balloon is inflated are preferred as it enables a coating procedure while the balloon is inflated and the sufficient drug adherence in the dry state allows for a subsequent folding without significant drug loss.

[0017]-In another embodiment, the polymers can be hydroxypropyl cellulose phthalate, hydroxypropyl methyl-cellulose phthalate, cellulose acetate phthalate, polyvinylacetate phthalate, polyvinylpyrrolidone phthalate, and the like. Coating morphology, coating thickness, drug-loss, drug-transfer to the uterine cavity, residual drug-concentration on the balloon surface and entire drug-load should be studied to choose most appropriate drug delivery mode with known biodegradability and biocompatiblity.

[0018]-In one embodiment,a coating technologyto deliver the TXA without the use of a permanent polymer carriercan be utilized . The ideal coating formulation should maximize the total dose that can deliver TXA onto the balloon surface at an efficient concentration may vary according to factors involved in the successful design of balloon-based delivery systems, including drug release kinetics, matrix coating transfer, trans cavitary drug partitioning, dissolution rate and release of unbound active drug . It is noteworthy, this system of TXA coated or eluted uterine balloon with close apposition of the balloon to uterine cavity because of immobilizing action and cervical shutter mechanism guarantees an efficient release of drug at a satisfactory concentration and for a duration lasting up to 24 hours.

[0019]-In another embodiment, Liposomes can be utilized as nanocarriers for targeted TXA delivery .They are defined as phospholipid vesicles consisting of one or more concentric lipid bilayers enclosing discrete aqueous spaces. The unique ability of liposomal systems to entrap both lipophilic and hydrophilic compounds enables a diverse range of drugs to be encapsulated by these vesicles. Liposomes present as an attractive delivery system due to their flexible physicochemical and biophysical properties, which allow easy manipulation to address different delivery considerations.

[0020]-In another embodiment a TXA coated balloon may be preferentially opted when put head to head with TXA eluted one as the potential advantages of drug coating technology compared to eluting process are

homogenous drug transfer , rapid drug release , and absence of remaining polymer implants which may be an appropriate option in case of PPH **??**18] .

[0021]-In one embodiment, Smart polymers can be the delivery vehicle. In particular, smart polymeric drug delivery systems have been explored as "intelligent" delivery systems able to release, at the appropriate time and site of action, entrapped drugs in response to specific physiological triggers. These polymers exhibit a non-linear response to a small stimulus leading to a macroscopic alteration in their structure/properties. The responses vary widely from swelling/contraction to disintegration. The most fascinating features of the smart polymers arise from their versatility and tunable sensitivity **??**19] .

[0022]-As wherein treating severe hemorrhage by external measures in open hollow organs like uterus is challenging because blood flow pushes hemostatic agents outward, reducing their efficacy. Accordingly, in one embodiment the self-propelling particles with its capability of autonomus movement with upstream orientation may be used for delivering therapeutics, such as coagulation factors deep into targeted location during hemorrhage in an upstream blood flow direction **??**20] .

[0023]-In any of the fore-mentioned embodiments, in this invention there is a modified balloon catheter shaft, where the external surface of balloon catheter at its intra vaginal portion presents a spiraled inclined plane on its external surface for a considerable length to cover a reasonable distance that allow screwing of the cervical shutter "Barricade". Such distance of the screw bar of the balloon catheter from mid vagina to the cervix measures 50mm and additional extra length of the screw bar from cervix to the lower uterine segment LUS that compensates for variations in lengths of uterine cavity (approximately 20mm-30mm) so as to allow an available screw bar for movement of screw plug distally to the required distance when the catheter is pulled downwards to stop short at cervico vaginal junction to offer a cervical shut effect. The latter allows a reasonable intrauterine residence of the medication. Noteworthy, the screw bar portion of the balloon catheter should be made harder in consistency than the remaining working length but still have a degree of flexibility. The target behind making this screw from a relatively harder polyurethane polymer is to allow some durability in the face of the moving screw plug.

[0024]-In the fore-mentioned embodiment, the co attached cervical shutter or "Barricade" is a cone shaped screw vaginal plug with its narrow proximal and distal wider portions is designated to work on the screw portion of balloon catheter. The screw plug weighs approximately 200-300 grams, measuring 40mm in length, 30mm in the distal widest diameter and tapering proximally through its length with the narrowest proximal outer diameter measuring 20mm Fig. (2). The "Barricade" screw plug should be made of material that guarantee resilience, inertness and non toxicity .It should have a smoothly surfaced outline to be easily manipulated (screwed) onto the screw bar of the external surface of the balloon and locked at the cervico-vaginal junction to serve as a cervical shutter.

[0025]-In reference to embodiments of [0023] & [0024], such modification does not only offer a cervical shutter but also provides the balloon with a self retaining capability without a need for attachment to the patient legging or attachment to an external weight which is the case in currently used balloons (Bakri B.T.). Moreover such embodiment enforces the balloon with extra counter compression especially on the adjacent lower uterine segment which in some cases may be the source of bleeding as in abnormally implanted and adherent placenta. & Excipients.

3 IV. Patent Citations

4 Claims

[0026]-Basically and specifically applicable to this invention and wherein said a TXA coated or eluted or medicated uterine balloon (an inflatable member with a proximal and distal ends and a working functional length ending in a stopcock and two way valve controlling the inflation and drainage ports) ,wherein said for use in post partumhaemorrhage (PPH), wherein, the outer layer of the balloon has been functionalized to serve to incorporate a matrix coating or eluting the antifibrinolytic, tranexamic acid particles or nano-particles for local release in the uterine cavity for that indication i.e. PPH. In this way, the currently used blank (non medicated or TXA uncoated) uterine balloons that are dependent solely on their tamponade effect could be replenished with adding the merits of topical application of anti fibrinolytic effect of tranexamic acid without the obligation of its systemic administration and its related theoretical risk of thromboembolism. Moreover, hereby, wherein said medicated or TXA coated or eluted uterine balloons, the medicament utilized is not restricted to tranexamic acid but is extended to include other haemostatic and coagulant medications like and not limited to thrombin, fibrinogen and activated recombinant factor seven (a FVll). Wherein said drug coating or eluting or other technologies utilized to functionalize balloons surface as delivery vehicle for a location (intra uterine), an indication (PPH) and a medication (TXA and other haemostatic) different from their currently used location, indication, and the released medications.

[0027]-As in claim 1, Wherein said drug coating or eluting utilized to functionalize balloons surface as delivery vehicle for a location (intra uterine), an indication (PPH) and a medication (TXA) different from their currently used location, indication, and the released medications. wherein said TXA coated or eluted or medicated uterine balloon for use in PPH, and the outer coat of the uterine balloon is functionalized as a delivery vehicle for TXA and other allied coagulants and wherein said a back up mechanism against the fast egress of the released of the fore mentioned medications in utero, the cervical shutter "Barricade" described thereof can be the innovative

serviceable back up mechanism. This cervical shutter is co attached with TXA coated or eluted uterine balloons so as to allow intrauterine retention of the drug and reasonable time for its action. The cervical shutter, "Barricade" is a specialized cone shaped (or any other shape that suits the vagina and can be easily manipulated intra vaginally) screw plug moving on the screw adapted intra vaginal portion of ball0on catheter to shut the cervix at the cervico-vaginal junction .The cervical shutter serves not only to shut the cervix for a longer intrauterine TXA residency but also it therapeutically exert an additional counter pressure at the lower uterine segment (LUS), which may be the main site of bleeding as in cases of placenta praevia and abnormally adherent placenta. [1] [2]

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[2] Tranexamic Acid Coated or Eluted Uterine Balloon and Co-Attached Cervical Shutter in Post Partum Haemorrhage. A New Combatant in the Armamentarium, Not Merely a Balloon but More

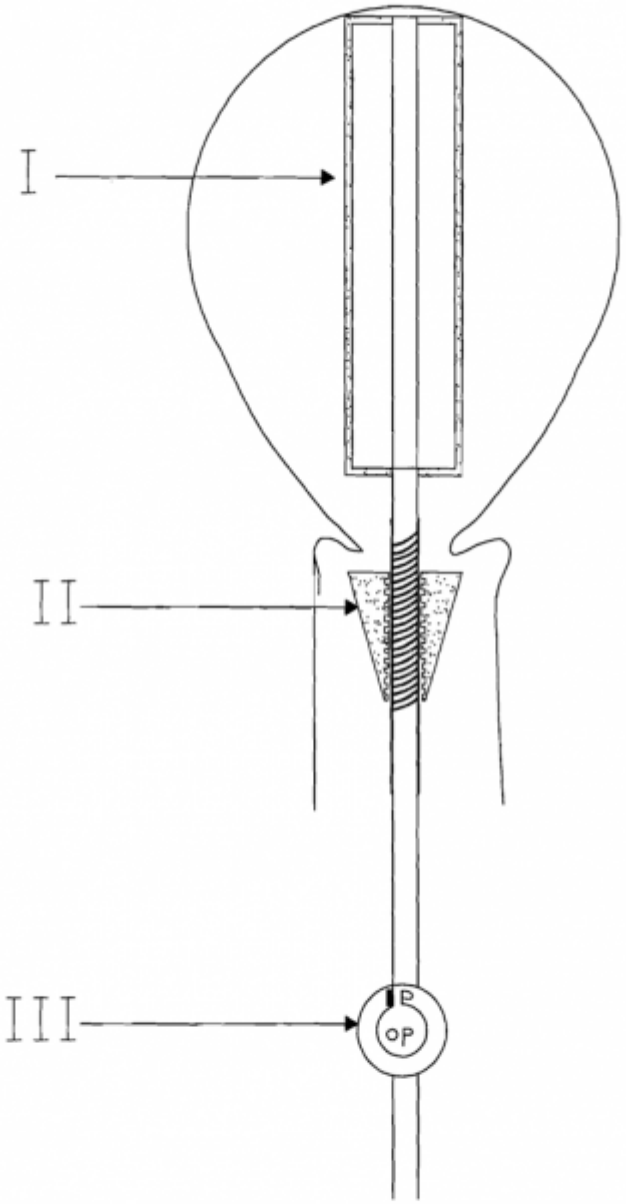

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Figure 1: Fig. 1 :Fig. 2 : 1 EFig. 3 :

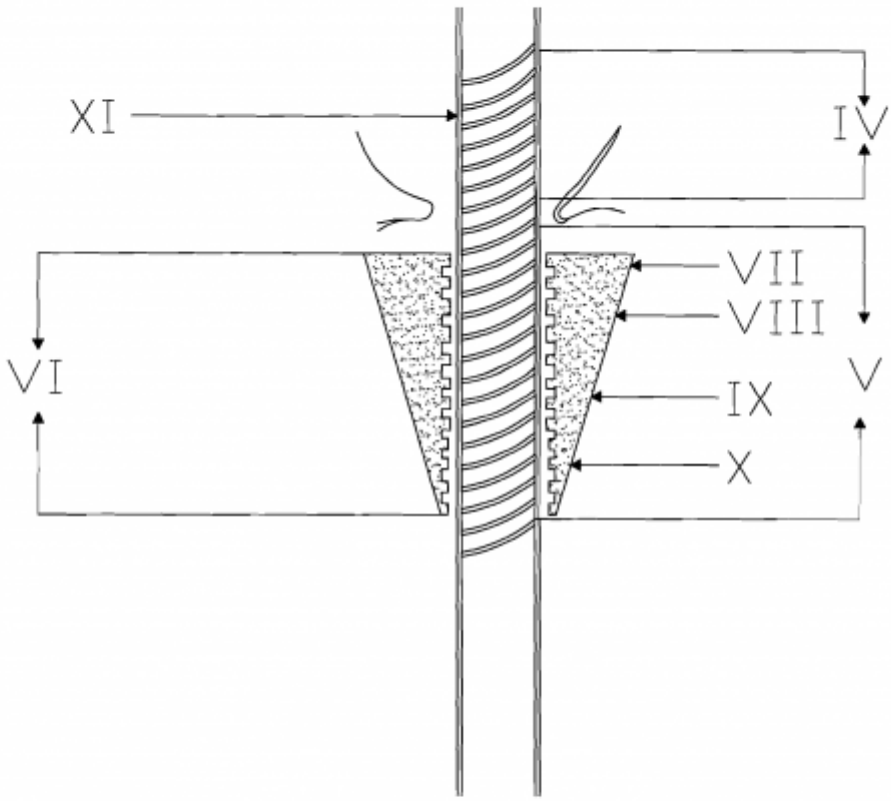

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Figure 2: Fig. 4 :

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Abstract-Described herein a Tranexamic Acid (TXA) -Coated

Figure 3:

[Bakri and Amri (2001)] 'Abdul Jabbar F. Tamponadeballoon for obstetrical bleeding'. Y N Bakri , A Amri . *Int. J. Gynaecol Obstet* 2001 Aug. 74 (2) p. .

[Peitsidis and Kadir ()] 'Antifibrinolytic therapy with tranexamic acid in pregnancy and postpartum'. P Peitsidis , R A Kadir . *Expert Opinion on Pharmacotherapy* 2011. 12 (4) p. .

[Fawzy et al. ()] 'Can local application of tranexamic acid reduce post-coronary bypass surgery blood loss? A randomized controlled trial'. H Fawzy , E Elmistekawy , D Bonneau , D Latter , L Errett . *Journal of Cardiothoracic Surgery* 2009. 4 p. 25.

[Dell'amore et al. ()] 'Can topical application of tranexamic acid reduce blood loss in thoracic surgery? A prospective randomised double blind investigation'. A Dell'amore , G Caroli , A Nizar . *Heart, Lung and Circulation* 2012. 21 (11) p. .

[Ker et al. ()] 'Effect of tranexamic acid on surgical bleeding: systematic review and cumulative metaanalysis'. K Ker , P Edwards , P Perel , H Shakur , I Roberts . ID e3054. *British Medical Journal* 2012. 344 (7858) .

[Shakur et al. ()] 'Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): A randomized, placebo-controlled trial'. H Shakur , I Roberts , R Bautista . *Lancet* 2010. 376 p. .

[Dildy and Clark ()] 'Postpartum hemorrhage'. G A Dildy , S L Clark . *Contemp Ob Gyn* 1993. 38 p. .

[Acog Practice Bulletin (2006)] 'postpartum hemorrhage'. Acog Practice Bulletin . *Clinical Management Guidelines for Obstetrician-Gynecologists Number* October 2006. 2006 Oct. 76 (4) p. . (Obstet Gynecol)

[Lalonde et al. (2006)] 'Postpartum hemorrhage today: ICM/FIGO initiative 2004-2006'. A Lalonde , B A Daviss , A Acosta , K Herschderfer . *Int J Gynaecol Obstet* 2006 Sep. 94 (3) p. .

[Condous et al. ()] 'The "tamponade test" in the management of massive postpartum hemorrhage'. G S Condous , S Arulkumaran , I Symonds , R Chapman , A Sinha , K Razvi . *Obstet Gynecol* 2003. 101 (4) p. .

[Chantrapitak et al. ()] 'The efficacy of lower uterine segment compression for prevention of early postpartum hemorrhage after vaginal delivery'. W Chantrapitak , K Srijuntuek , R Wattanaluangarun . *J Med Assoc Thai* 2011 Jun: 94. (6) p. .

[Khan et al. (2006)] 'WHO analysis of causes of maternal death: a systematic review'. K S Khan , D Wojdyla , Say L Gülmezoglu , A M Van Look , P . *Lancet* 2006 Apr 1. 367 (9516) p. .

[Wong et al.] J Wong , A Abrishami , El Beheiry , H . *Topical application of tranexamic acid reduces postoperative blood loss in total knee arthroplasty*,