A novel method of treating postpartum hemorrhage

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Description:

The present invention relates to implants and methods as novel treatment of postpartum hemorrhage.

BACKGROUND

Each year, roughly 14 million women worldwide suffer from postpartum hemorrhage, defined as blood loss exceeding 500 mL, making it one of the most common causes of morbidity and mortality following childbirth. Severe postpartum hemorrhage, involving blood loss in excess of 1000 mL, occurs in approximately 3% of all vaginal deliveries and a large number of caesarean deliveries. See e.g. Janice M. Anderson and Duncan Etches, Prevention and Management of Postpartum Hemorrhage, 75 μm. Family Physician 875-882 (Mar. 15, 2007). Complications may include infection, hypotension, anemia, fatigue, hemorrhagic shock and ultimately death. Id. There were, according to World Health Organization statistics, approximately 132,000 deaths worldwide due to postpartum hemorrhage in 2011 and, accordingly, there is an ongoing need for treatments that rapidly and effectively stanch uterine bleeding.

Common causes of postpartum hemorrhage include uterine atony, coagulopathy, retention of placental tissue, and genital tract trauma. Different treatments may be indicated for each of these causes—for example, uterine massage may be indicated for postpartum hemorrhage due to uterine atony, while closure of lacerations may be indicated for hemorrhage due to trauma—and the process of identifying a cause and selecting a suitable treatment therefore adds complexity and potentially delays the delivery of treatment. Moreover, in developing or rural environments, the availability of treatments for postpartum hemorrhage across the spectrum of causes may be limited. Accordingly, a need exists for systems and methods for treating postpartum hemorrhage that can be rapidly deployed and are useful in treating the condition across the full spectrum of its causes.

BRIEF DESCRIPTION OF THE INVENTION

The invention addresses the needs described above by providing, in one aspect, a uterine implant and delivery system for the treatment of hemorrhage including a pre-formed collapsible and/or expandable foam body that can be positioned within a uterus. , the implant optionally includes , a drug for delivery to the uterus. which degraded, resorbed or otherwise decomposed by normal physiological mechanisms .

In another aspect, the invention is a formulation or formulations that react to form a uterine implant when delivered to a uterus and

In another aspect, the invention is a method of treating postpartum hemorrhage., the method includes contacting a uterine wall with an implant comprising a biocompatible polymer foam. The implant may include multiple foam bodies which optionally have an edge portion and a thicker central portion. The polymer foam can have a compression force or it can apply a pressureon the uterus. The implant can, in various embodiments, have a volume of between 100% and 200% of the postpartum human uterus, and/or it can include one or more porous membranes or a drug that promotes blood clotting. The method may also include applying an agent to dissolve at least part of the implant following use. The thrombin foam may cause uterine contractions by applying pressure to the uterine wall, and the foam may be formed within the uterus of the patient . , The polymer foam can have a compression force . .

DETAILED DESCRIPTION

The invention includes a polyurethane foam implant and a delivery applicator. values at . The elastic properties of the foam allow it to expand from a compressed state and

conform to a site or sites of hemorrhage on the uterine wall which may be irregular or may have a variety of challenging morphologies. Foam implants of the invention are Foams used in implants of the invention can be closed-cell or open-cell. Foam implants of the invention preferably have recovery values between 80% and 100% and are made from bulk materials having high tensile strength so that foams of the invention can withstand the application, Additionally, foam implants of the invention are highly compliant, allowing them to expand to up to 50-100% or more of the volume of the uterus . Foams of the implant can also be resorbable, .

The Foam:

The foam comprising the implant is, in preferred embodiments, biocompatible and, in certain embodiments, resilient or viscoelastic. , the foam is at least partially resorbable, degradable or decomposable

Foams of the invention are preferably made of polyurethane, but can be of any suitable composition, including without limitation polyolefins (e.g. polyethylene, polypropylene, ethylene vinyl acetate copolymer, etc.), natural and synthetic latex, silicone, fluoropolymer (e.g. PTFE, etc.), polystyrene, epoxy, poly(vinyl chloride) (PVC), or phenolic polymers. Polyolefin foams, polystyrene, epoxy, PVC and phenolic foams can be flexible, but are generally more rigid than polyurethane foams, which may affect certain characteristics such as compression force deflection, and accordingly may affect their performance in achieving homeostasis via the mechanisms discussed in more detail below.

Although not wishing to be bound to any theory, the inventor believes that implants of the invention stop hemorrhage via three independent yet synergistic mechanisms: form morphology, tamponading and induction of uterine contraction.

With respect to foam morphology, the foam's pore structure, including size, morphology and tortuosity, can permit blood to enter the foam but resist blood flow. In cases of severe hemorrhage, a high flow rate or high blood velocity is thought to interfere with normal clotting by diluting activated clotting factors and disrupting fibrin clots before they have a chance to build. In addition, a large clot is required to close a large injury, and the time required for formation of a large clot is greater than for a small clot. By contrast, in smaller injuries, clotting is thought to occur more efficiently because the concentration of activated clotting factors is rapidly built up and sustained, and because the fibrin clots are able to grow rapidly to a size and strength sufficient to seal a small breach in a vessel wall. In certain embodiments, implants of the invention absorb hemorrhaged blood into small pores through which blood flows slowly and at relatively higher pressures, facilitating normal clotting and accelerating hemostasis. The foam also provides a large surface area for platelet and cell attachment and activation, and for

initiation of the coagulation cascade. . Without wishing to be bound to theory, low mass density foams with high pore densities are thought to be particularly well suited to slow rates of blood flow and to concentrate clotting factors, thereby promoting faster clotting. .

The foam includes polyurethanes or other polymers that promote clotting, as is discussed in more detail below. The use of polymers that improve or promote clotting may synergize with the effects of the morphology of the foam, and other factors discussed below, resulting in more efficient or faster clotting.

In certain related invention, the properties of the polyurethane used to make the foam are tailored to improve thrombogenicity, as discussed in U.S. patent application Ser. No. 12/862,362, ., the foam includes a pro-coagulant to promote clotting at the site of injury. Pro-coagulants useful in the invention include, without limitation, glucosamine-based materials, cellulose, collagen, gelatin, fibrinogen, thrombin, fibrin, biologics, hemostatic, kaolin, glass beads, anti-fibrinolytic drugs . Useful glucosamine-based materials include, without limitation, chitin, chitosan, and poly-N-acetyl glucosamine. Useful biologics include, without limitation, factor VII, factor XII, factor XI, factor VIII, factor IX or other coagulation factors from human or animal sources. Anti-fibrinolytic drugs including, without limitation, tranexamic acid and aminocaproic acid are used in certain embodiments of the invention. Some embodiments of the invention include vasoconstrictors such as epinephrine, norepinephrine, amphetamines, vasopressin, phenylephrine, pseudoephedrine, psilocybin and the like to induce constriction of major blood vessels.

In some embodiments, the foam includes silver nitrate ($AgNO_3$), which promotes clotting through a cautery action and has an antimicrobial effect.

Exogenous agents such as antibiotics, pro-coagulants or $AgNO_3$ can be incorporated throughout foams by adding them to bulk formulations used to make pre-formed or in-situ forming foam implants. Agents can also be applied to the outer surface of pre-formed foams and/or to the surfaces enveloping or partially enveloping foam implants of the invention by any suitable means known in the art.

In some embodiments, after the implant is deployed, portions of the foam that are in contact with blood preferentially absorb water from blood, decreasing the solvent concentration and thereby increasing the concentration of activated clotting factors, accelerating hemostasis. The foam matrix—the walls separating the pores—optionally

provides cell separation between cells and serum, and preferentially absorbs water or permits water to flow through the walls of pores, further concentrating clotting factors at the foam surface and contributing to hemostasis.

Another mechanism of action of implants of the invention is a tamponading effect on the uterus: in certain embodiments the foam expands to apply pressure to the uterine wall, compressing blood vessels, reducing blood flow and promoting clotting via the mechanisms discussed above. The foam implants preferably apply sufficient pressure to close small vessels held open by blood pressure. As a non-limiting example, in a patient with physiologically normal diastolic blood pressure, 80 mmHg, an implant of the invention, when deployed, can apply more than 80 mmHg (or approximately 1.5 PSI) of pressure to the uterine wall, promoting closure of open arterial blood vessels. Implants that apply tamponading pressure preferably, though not necessarily, include hydrophobic foam, to permit the application of pressure to the uterine wall while advantageously resisting the absorption of blood. To the extent that non-absorbed blood accumulates in the uterine space, the additional volume of blood adds to the pressure exerted by the implant on the uterine wall, enhancing the tamponading effect and reducing hemorrhage.

Another mechanism of action of implants of the invention is induction of uterine contraction: in certain embodiments, when the foam expands to apply pressure to the uterine wall, as discussed above, it stretches myometrial smooth muscle fibers within the uterine wall, stimulating contraction. As the smooth muscle fibers contract, the diameter of small uterine vessels is reduced, thereby reducing blood flow and promoting clotting as discussed above. Certain embodiments of the invention advantageously compress in response to normal uterine contraction forces, minimizing patient discomfort.. In certain embodiments, the invention includes a drug to induce uterine contraction, preferably one of oxytocin and misoprostol.

Because they can induce uterine contraction, embodiments of the invention can be useful in treating postpartum hemorrhage due to uterine atony. Embodiments of the invention may also be useful in treating postpartum hemorrhage due to coagulopathy, as the reduction of flow, high clotting surface area, and other aspects of the invention improve the conditions for clotting in cases where a patient has a clotting deficit. Implants of the invention can also be advantageous in treating postpartum hemorrhage in patients with abnormal uterine anatomy, such as uterine fibroids and uterine septum, as the induction of uterine contraction facilitates the establishment of conformal contact

between the implant and the uterine wall.

Infection is a potential complication of postpartum hemorrhage. In certain embodiments of the invention the risk of infection is reduced by incorporating AgNO3 and/or one or more anti-bacterial agents into the foam. As discussed above, the anti-bacterial agent is deposited on the surface of the foam implant after it is formed, incorporated into the bulk of the foam during formation, and/or incorporated into the membrane enveloping the foam. The anti-bacterial agent is optionally released from the foam and/or the membrane and delivered to the patient. Anti-bacterial agents useful with the invention include, without limitation, silver nitrate, silver sulfadiazine, gentamycin, penicillin, tetracycline, oxytetracycline, metacycline, doxycycline, minocycline, , erythromycin, and chloramphenicol.

The gel foam Implant:

The uterus typically resembles an inverted pear: the superior portion of the uterine cavity is relatively wide, while the inferior portion including the cervix is narrowed and slightly elongated. In the postpartum phase, the uterus has an irregular internal contour and can be variable in shape (long and narrow, or short and wide) but it generally retains its inverted pear-shaped proportions. The size of the postpartum uterus can vary from 5 to 13 cm in the antero-posterior direction, 14-25 cm in length and 7-14 cm in width (See, e.g. Mimi C. Berman and Harris L. Cohen, 1997, Diagnostic Medical Sonography: Obstetrics and Gynecology (1997)). The effective internal volume of the postpartum uterus is estimated at between 250 and 1,000 mL, based on fluid volumes reported in studies of Rusch balloon treatment for postpartum hemorrhage. See e.g. R. Keriakos and A. Mukhopadhyay, The use of the Rusch balloon for management of severe postpartum haemorrhage, 26 J. Obstetrics and Gynaecology 335-338 (May 2006). In preferred embodiments, implants of the invention are sized to be slightly larger than the uterine volume. Sizing the implant contributes to its ability to conformally contact the irregular uterine wall and apply pressure to induce uterine contraction and tamponading effect. The ability to conformally contact the uterine wall, whether due to oversizing, high compliance, or other factors, advantageously permits treatment of patients with abnormal uterine anatomy, including without limitation patients with uterine fibroids or a uterine septum.

Further Remarks:

The invention has been described with an emphasis on treatment of hemorrhage generally, and postpartum hemorrhage in particular. However, those skilled in the art will appreciate that implants, formulations and materials of the invention are adaptable to suit a wide variety of applications, particularly contraception, treatment of genital tract

infections, for example by replacing or supplementing portions of the invention disclosed above with agents useful for the selected applications, in particular spermicides, antibiotics, antimycotics, etc. and by modifying the scale of implants, the volume of material or formulation delivered to a patient, the hydrophilicity of the foam implant, etc. to suit the application of interest. The invention is also adaptable to function as an ordinary tampon, subject to modifications along the lines set forth above.

The aspects and embodiments of the invention disclosed above are not mutually exclusive, unless specified otherwise, and can be combined in any way that one skilled in the art might find useful or necessary.

The term “pore” is used throughout the application to refer to chambers within foams of the invention. The term “drug” is used to mean any bioactive agent, including without limitation pharmaceuticals, biomolecules, , and the like, as well as any suitable vector, excipient, adjuvant, salt, solvent, filler, substrate, buffer, filler or formulation necessary or useful to deliver the above to a patient.

While several embodiments of the present invention have been described and illustrated herein, those of ordinary skill in the art will readily envision a variety of other means and/or structures for performing the functions and/or obtaining the results and/or one or more of the advantages described herein, and each of such variations and/or modifications is deemed to be within the scope of the present invention. More generally, those skilled in the art will readily appreciate that all parameters, dimensions, materials, and configurations described herein are meant to be exemplary and that the actual parameters, dimensions, materials, and/or configurations will depend upon the specific application or applications for which the teachings of the present invention is/are used. Those skilled in the art will recognize, or be able to ascertain using this novel treatment.

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