

[54] **INTRAUTERINE CONTRACEPTIVE DEVICE
CONTAINING CERTAIN
PHARMACEUTICALLY ACCEPTABLE
STEROIDS**

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1971, abandoned, and Ser. No. 864,174, Oct. 6,
1969, abandoned.

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[51] **Int. Cl.** **A61m 31/00**

[58] **Field of Search** **128/260, 130, 131; 424/16,**
424/19-22, 238-243

[56] **References Cited**

OTHER PUBLICATIONS

Hohn J. Endocrin, 10:358-362, (1954), "Direct Pro-

gestational Action of Progesterone and Certain Re-
lated Steroids on the Endometrium of the Rhesus
Monkey."

Primary Examiner—Shep K. Rose

Attorney, Agent, or Firm—Paul L. Sabatine; Edward
L. Mandell

[57] **ABSTRACT**

An intrauterine delivery device for the administration
of anti-fertility steroid to a uterine cavity comprising a
body of non-toxic, biologically inert, polymeric release
rate controlling material containing therein a locally
contraceptively active steroid metabolite of progester-
one and permeable to the passage of the steroid as by
diffusion; and wherein the device, while in the uterus,
continuously meters the flow of a contraceptively ef-
fective amount of the steroid metabolite through the
material at a controlled and predetermined rate by dif-
fusion over a period of time to produce the anti-
fertility effect.

8 Claims, 4 Drawing Figures

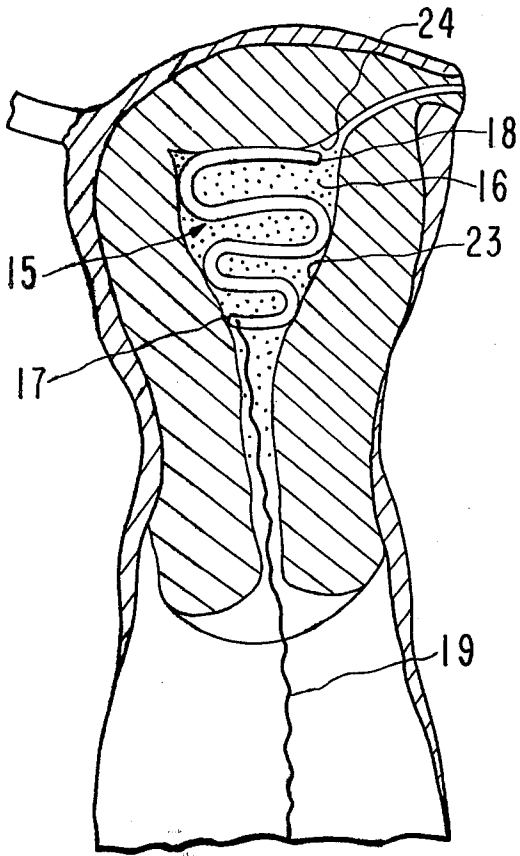


FIG. 1

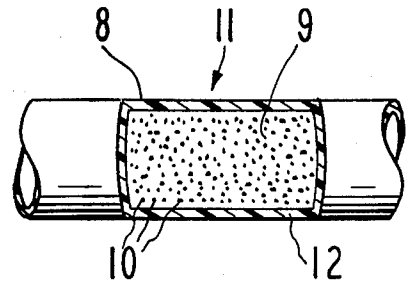


FIG. 2

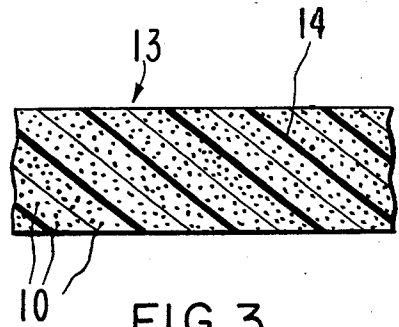


FIG. 3

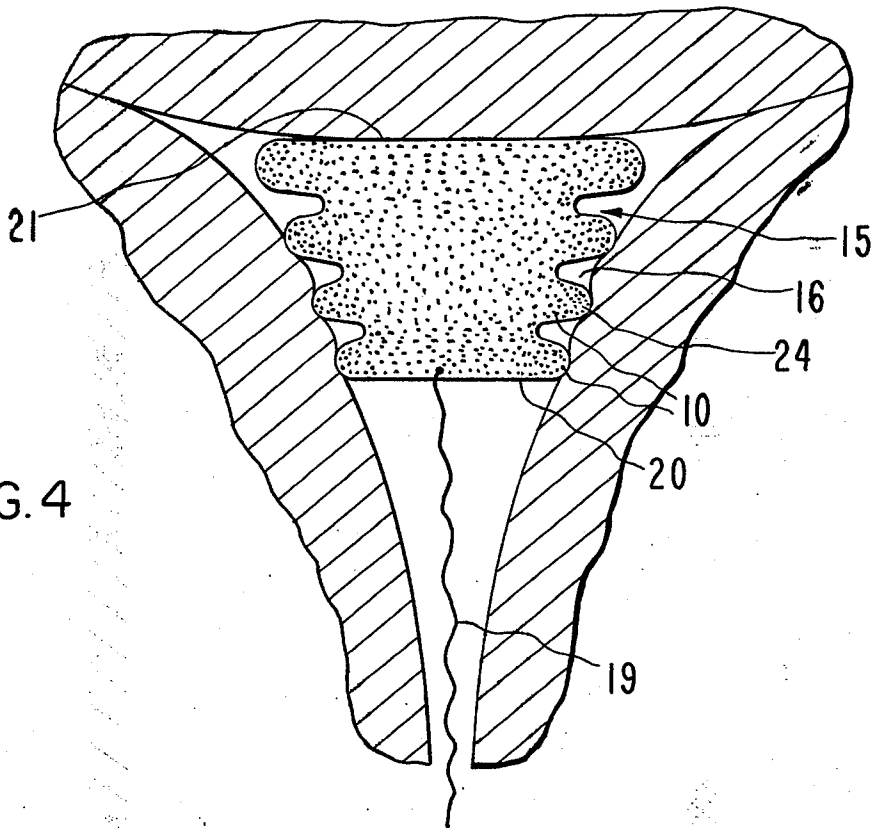


FIG. 4

INTRAUTERINE CONTRACEPTIVE DEVICE CONTAINING CERTAIN PHARMACEUTICALLY ACCEPTABLE STEROIDS

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation-in-part of U.S. Pat. application Ser. No. 201,055 filed on Nov. 22, 1971 and U.S. Pat. application Ser. No. 864,174 filed on Oct. 6, 1969. Both of these applications, both now abandoned, are assigned to the same assignee of this invention and these applications are incorporated into this application by reference.

BACKGROUND OF THE INVENTION

This invention relates to an intrauterine device and to a contraceptive method, and more particularly to a device and method for the predetermined controlled metering of the flow of a contraceptively effective amount of a locally contraceptively active pharmaceutically acceptable steroid metabolite of progesterone to the mammalian uterus over a prolonged and continuous period of time.

Intrauterine contraceptive devices of various configurations have become an increasingly popular means usable as a method of birth control. While generally reliable when in proper place, such devices are frequently expelled by the patient due to uterine contractions. This is a significant problem since the patient is often unaware that the device has been expelled. One approach to this problem has been to incorporate a progestational agent in the device in a manner such that a continuous low dose of the hormone is delivered to the uterus to reduce both the uterine contractility and expulsion of the devices. Reduction of uterine contractility also is helpful in reducing inflammation and uterine punctures which are sometimes attendant with the use of intrauterine devices. See Doyle et al., *Amer. J. Obstet. Gynecol.*, Vol. 101, pp. 564-568, 1968.

Other investigators have incorporated progestational agents in intrauterine devices with a view to controlling fertility by the hormonal effect of the progestational agent. Such work has been extended to other drug delivery systems including vaginal inserts and cervical rings, that is, progestogen releasing rings placed at the head of the cervix, and surgical implants, placed in the uterine area or elsewhere in the body.

In the main, progestational agents used in these prior studies have been the highly potent synthetic progestational agents such as chlormadinone acetate, megestrol acetate, melengestrol acetate, and medroxyprogesterone acetate. Such compounds have long half-lives in the body and are known to produce systemic progestogen effects. Even when applied to the uterus or vagina, it is not unreasonable to expect that continuous administration of these highly active compounds may produce some unwanted side reactions. One investigator has used progesterone as the progestational agent in such devices. See Scommegna et al., "Intrauterine Administration of Progesterone by a Slow Releasing Device," presented at annual meeting of the American Fertility Society, April, 1969.

Now, it has been found that many of the above disadvantages can be, overcome by using steroid metabolites of progesterone as anti-fertility agents for interfering with the female reproductive process. The use of steroid metabolites of progesterone for the purpose of

this invention, that is, as anti-fertility agents, is considered art unexpected since the metabolites of progesterone are reported to be devoid of progestational activity. See, *The Endocrinology of Reproduction*, by Velardo, Joseph T., pages 101 to 212, 1958, published by Oxford University Press, New York. Additionally, it has been unexpectedly found that steroid metabolites of progesterone can be incorporated into various and different intrauterine devices and released therefrom for interfering with the female reproductive process. These steroid metabolites, as used according to the mode and manner of the present invention have the additional advantage of acting locally, and if any is systemically absorbed unwanted side reactions are substantially avoided since the metabolite is present in a metabolized or essentially inactive form.

SUMMARY OF THE INVENTION

Accordingly, it is an immediate object of this invention to provide an improved birth control device which locally applies a locally contraceptively active metabolite of progesterone to the uterine walls.

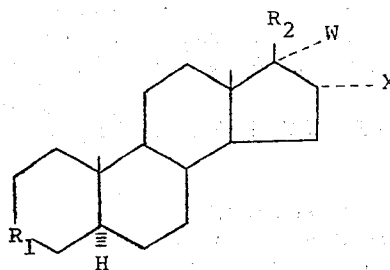
Still another object of the present invention is to provide an intrauterine device containing a biologically acceptable steroid metabolite of progesterone that is released by diffusion from the device in an amount effective for anti-fertility effects while simultaneously substantially avoiding the side effects generally known to the art.

Yet still another purpose of the invention is to provide an intrauterine device charged with a steroid metabolite useful for interfering with the female animal reproductive process at a local situ while simultaneously avoiding systemic effects.

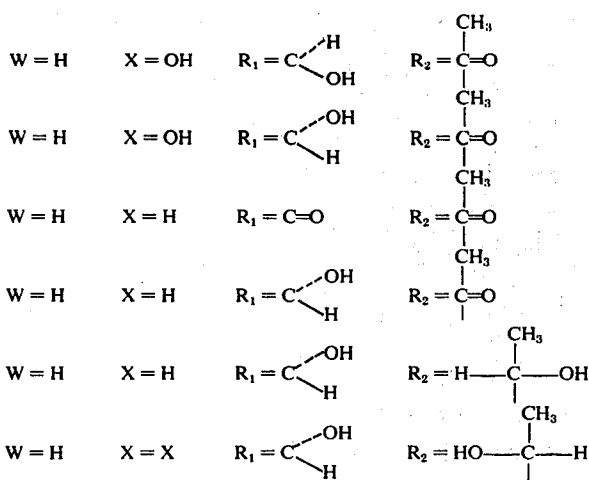
Another object of this invention is to provide a birth control device containing and gradually releasing a metabolite of progesterone having local fertility controlling activity but substantially no systemic progestational activity.

In attaining these objects, one aspect of this invention resides in an intrauterine device for the predetermined controlled metering of the flow of a locally contraceptively active steroid metabolite of progesterone to the uterus over a prolonged period of time, comprising a body of non-toxic biologically inert, polymeric release rate controlling material, permeable to the passage of the steroid metabolite by diffusion, which device is itself of a shape for insertion and for retention in a fertile uterus, or alternatively which is attached to a suitable shape for retention in the uterus containing therein a pharmaceutically acceptable steroid metabolite of progesterone having local fertility controlling activity.

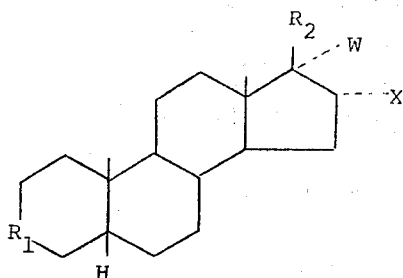
In further attaining the features, objects and other aspects of the invention, the pharmaceutically acceptable steroid metabolite is a member selected from the group consisting of 5α and 5β -preganes of the following general formula:



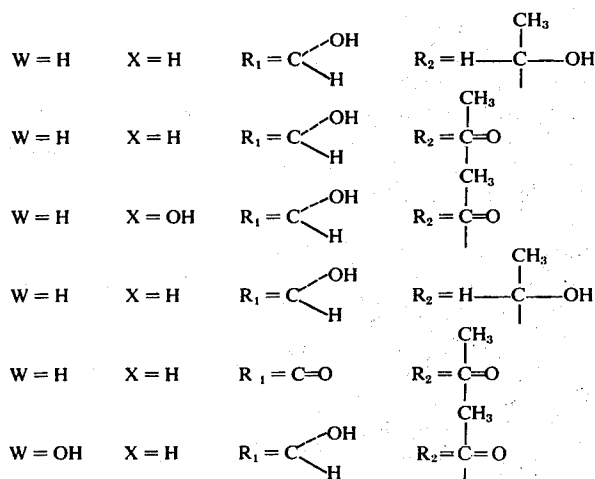
wherein:



and



wherein:



Other objects, features and advantages of this invention will become more apparent from the following description, drawing and accompanying claims.

BRIEF DESCRIPTION OF THE DRAWINGS

In the drawings, which are not drawn to scale, but rather are set forth to illustrate various embodiments of the invention, there appears as follows:

FIG. 1 is a side elevational view showing an intrauterine device of the "loop" type as disclosed in U.S. Pat. No. 3,250,271, in operative position within the animal uterus.

FIG. 2 is an enlarged perspective view of the bracketed segment of the intrauterine device of FIG. 1, illustrating according to this invention a locally contraceptively active steroid metabolite of progesterone confined in the lumen of the material of the device.

FIG. 3 is an enlarged perspective view of the bracketed segment of the intrauterine device of FIG. 1 illustrating according to this invention a locally contraceptively active 5 α or 5 β -pregnane steroid metabolite of progesterone charged throughout the release rate controlling polymeric material of the intrauterine delivery device.

FIG. 4 depicts an intrauterine drug release platform comprised of a release rate material having steroid metabolite integral therein.

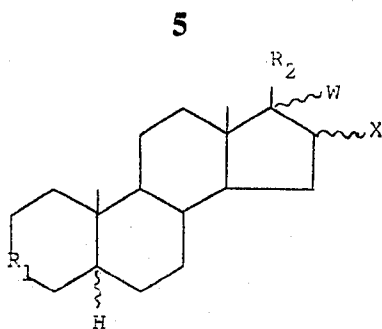
In the drawings and specification, like parts in related Figures are identified by like numbers. The terms appearing earlier in the specification and in the description of the drawings, as well as embodiments thereof, are further described elsewhere in the disclosure.

DETAILED DESCRIPTION OF THE INVENTION

In accordance with the present invention, there is provided an intrauterine device for the predetermined controlled and continuous metering of the flow of a contraceptively effective amount of a locally contraceptively active pharmaceutically acceptable steroid metabolite of progesterone to the mammalian uterus over a prolonged period of time. The intrauterine device or intrauterine platform is comprised of a body of non-toxic, biologically inert uterine acceptable polymeric release rate controlling material containing therein a locally contraceptively active steroid metabolite of progesterone and permeable to the passage of the steroid as by diffusion.

A locally contraceptively active steroid metabolite of progesterone is confined within an uterine acceptable polymeric material so that when inserted in the uterus of a fertile female capable of species reproduction, the material continuously meters the flow of an effective amount of the contraception steroid metabolite to the uterus by passage by diffusion of said metabolite through the polymeric material at a controlled rate. While the naturally occurring locally contraceptively active steroidal metabolites of progesterone exert contraceptive activity when applied locally to the uterus, the metabolites do not produce any significant unwanted systemic progestational activity. By locally delivering these metabolites from devices otherwise known as intrauterine devices or intrauterine platforms per se, an effective, reliable and safe means of birth control is provided.

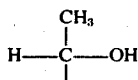
The presently preferred locally acting contraceptively active steroid metabolites of progesterone for use in this invention are embraced by the following formula:



wherein R₁ is a member selected from the group consisting of



and $>C=O$, R₂ is a member selected from the group consisting of



and



W is a member selected from the group consisting of H and OH and X is a member selected from the group consisting of H and OH.

Representative steroids suitable for the purpose of the invention include 5 β -pregnane-3 α ,20 α -diol, also known as pregnanediol; 5 β -pregnane-3 α -hydroxy-20-one, also known as pregnanolone; 5 α -pregnane-3 β ,16 α -dihydroxy-20-one; 5 α -pregnane-3 α ,16 α -dihydroxy-20-one; 5 β -pregnan-3 α ,16 α -dihydroxy-20-one; 5 β -pregnane-3 α ,20 β -diol; 5 α -pregnane-3,20-dione; 5 β -pregnane-3,20-dione; 5 α -pregnan-3 α -hydroxy-20-one; 5 α -pregnane-3 α ,20 α -diol; 5 α -pregnane-3 α ,20 β -diol; 5 β -pregnane-3 α ,17 α -dihydroxy-20-one, and the like. These steroids are commercially available and they can easily be prepared by processes fully described in U.S. Pat. Nos. 2,352,852; 2,160,719; 2,323,276; 2,229,818; 2,231,018; 2,223,377; 2,231,017; 2,156,275; and 2,108,646. Their preparation is also reported in *Biochem. J.*, Vol. 23, p. 1090, 1929; *Bev.*, Vol. 63, p. 659, 1930; *J. Biol. Chem.*, Vol. 143, p. 716, 1942; *J. Biol. Chem.*, Vol. 140, p. 797, 1941; *Bev.*, Vol. 68, p. 2094, 1935; *J. Am. Chem. Soc.*, Vol. 59, p. 1373, 1937; *J. Am. Chem. Soc.*, Vol. 59, p. 2291, 1937; and other standard references.

The above compounds can also be used in the pharmacologically acceptable derivatives thereof, such as the derivatives of their hydroxy or keto groups. Such derivatives should convert to the parent compounds upon release from the intrauterine platform by enzymatic transformation, pH assisted hydrolysis, and like body functions. They are used to enhance the release properties of the metabolite from the uterine device. Suitable derivatives include esters with pharmaceutically acceptable acids, such as the acetate, for example, cycloacetate, diethylamino acetate, propionate, butyrate, valerate, hexanoate, glucuronate, such as hemi- β , β -dimethylglutarate, heptanoate, maleate, citrate, succinate, tartrate, fumarate, malate, ascorbate,

benzoate, sulphate, phosphate, for example cyclohexylammonium benzylphosphate, and the like; ethers, especially lower alkyl ethers and ketals.

The polymeric release rate controlling material can be of suitable shape known to those skilled in the art to promote insertion and retention in the uterine cavity over short to prolonged periods of time. Alternatively, the polymeric release rate controlling material can be attached to an intrauterine device or intrauterine platform which is effective for the short to long term retention of said material in the uterine endometrium cavity. In general, suitable devices can be obtained by distributing the locally contraceptively active steroid progesterone metabolite in a solid or gel matrix of the polymeric rate controlling material; microencapsulating the agent and then distributing the microcapsules in the polymeric rate controlling material or confining the agent in a hollow container within the polymeric rate controlling material.

With regard to known shapes for promoting retention in the cavity, such devices can take various configurations, such as the conventional Lippes' "loop," as disclosed in U.S. Pat. No. 3,250,271; Marguiles' "spiral," as disclosed in U.S. Pat. No. 3,230,953; and the like, or matrix containing the agent suitably affixed to these conventional intrauterine devices. However, the particular configuration or shape of the device forms no part of the present invention. The main purpose of the device, in this invention, is to provide a depot or carrier for the continuous administration of locally contraceptively active steroidal progesterone metabolites to the uterus at a predetermined and controlled rate. Devices which in themselves are effective birth control means, such as the Lippes' loop, have their usefulness enhanced while other shapes are rendered effective in the first instance.

For ease of presentation the invention is described with reference to a specific intrauterine shape, which has arbitrarily been selected to be the loop disclosed by Lippes in U.S. Pat. No. 3,250,271. Another suitable intrauterine device is disclosed in copending application Ser. No. 61,141, filed Aug. 5, 1970, now U.S. Pat. No. 3,675,647, for an invention of Bruce B. Pharriss and Max Anliker. The disclosure of that copending application is relied upon and incorporated herein by reference. However, it will be appreciated that this is in no way to be construed as limiting the teaching of this invention. FIG. 1 generically depicts an intrauterine device 15 nested within a uterine cavity 16. Device 15 is made of a flexible material and has a memory for retaining its shape in the uterine cavity. The illustrated uterine cavity is of standard anatomy having sides 23 as well as fundus uterus 24. A thread 19 is attached to the trailing end 17, distant from lead end 18 of device 15 for manually removing device 15 from uterus 16. FIGS. 2 and 3 illustrate various embodiments detailing several structures for the loop shaped body.

FIG. 2 illustrates generally, by reference numeral 11 an enlarged segment of an intrauterine device 15 in the shape of a conventional loop. The body 8 of the loop 11 is structured in the form of a container with the locally contraceptively active steroid metabolite 10 confined in the lumen 9 of the material of the device. The release rate controlling walls or surface 12 of device 15 functions to control the rate of release of the steroid metabolite to the uterus. While walls 12 of such container can be of any convenient thickness, satisfactory

results can be obtained with thickness of 0.001 to 0.10 inches and more preferably between 0.005 and 0.05 inches. The diameter of the lumen 10 can be of any convenient size consistent with obtaining reasonable dimension for the overall diameter of the body of any device 15. Diameters from 0.05 to 0.2 inch are acceptable. The cross-section of the body 8 can be round or otherwise, with the former preferred for reasons of ease of fabrication. The intrauterine device 15 can be fabricated by molding a solid rod of the desired material and overall outside dimension having embedded therein a wire of same diameter as the desired dimensions of the lumen 10. After the molding operation, the wire can be removed resulting in the structure depicted in FIG. 2. The device can then be suitably filled with the desired locally contraceptively active metabolite and sealed to retain the steroid therein. The metabolite, when incorporated into devices of the type disclosed in FIG. 2, can be admixed in a suitable carrier, for example a silicon cured solid, and the like, if desired.

FIG. 3 illustrates by general reference number 13, an enlarged segment of an intrauterine device 15 in the shape of a loop wherein locally contraceptively active steroid metabolite of progesterone 10, illustrated as crystal dots, is distributed throughout the material forming the device. The material, when similar to the entire device 15, also serves as the matrix for the controlled rate of release of the steroid metabolite to the uterus. A device such as depicted in FIG. 3 can be fabricated by adding the metabolite to the matrix material in liquid form in a suitable mold and subsequently converting the matrix to a solid or gel by curing or cooling; or by immersing the solid matrix in the metabolite or a solution of the metabolite to effect diffusion of the metabolite into the matrix.

FIG. 4 illustrates an intrauterine device 15, or intrauterine platform within a normal, child-bearing woman's uterus 16. Device 15 is formed of a single piece of steroid release rate controlling material having a plurality of fingers 24 aligned along each side of device 15. Fingers 24 serve to both keep the device in uterus 16 and increase the area for releasing steroid 10 from device 15. A string 19 is fixed to the trailing end 20, opposite lead end 21, for removing device 15 from uterus 16.

Devices containing the steroid metabolite are formed at least in part of a material permeable to the steroid metabolite to permit passage of the steroid metabolite through the walls or body of the device at a relatively low rate by a process called diffusion. The rate of passage of the steroid metabolite through the wall or body is effected by the mechanisms of permeation and diffusion and it is therefore dependent on the porosity of the wall or body or the diffusivity and solubility of the steroid metabolite in the wall or body, as well as on the wall or body thickness. The mechanism by which diffusion is achieved may be explained on the basis of an activity or chemical potential gradient wherein the enclosed substance relieves its internal concentration within the device by spreading out into the adjacent medium. As the diffusing steroid metabolite is removed from the outer surface of the material of the device by body fluids, tissue absorption, and the like, the diffusive action continues through and from the device until the source of the metabolite has been substantially consumed. The steroid metabolite will have a definite and characteristic rate of passage through the body of the device which will in effect, establish the dosage rate

and amount of metabolite released from the surface during a given time interval. This means that selection of appropriate materials for fabricating the device will be dependent on the particular steroid progesterone metabolite to be used. By varying the composition, porosity, and thickness of the device wall or body, the release rate per area of device can be controlled; for the walls or body of the device act as solubility membranes or diffusion control systems to regulate or meter the flow of steroid metabolite from the device to the uterine walls. Thus, devices of the same surface area can provide different release rates and therefore daily dosages of the steroid metabolite by varying the characteristic of the device. The metabolite is metered through the walls or body of the device to the uterus of the female patient, with the rate controlled by the composition, porosity, and thickness of the walls or body of the device. In each instance, the device acts as a depot for the storage and continuous release of the steroid metabolite to the uterus.

The amount of useful steroid metabolite to be incorporated in the device to obtain the desired contraceptive effects or interference with the reproductive process, will vary depending upon the permeability or solubility of the particular steroid metabolite to be used, the material employed to fabricate the device and the length of time the device is to remain inserted in the uterus. Since this device is designed to control fertility for an extended period of time, such as 1 hour to 3 or more years, there is no critical upper limit on the amount of steroid metabolite incorporated into the device, as it meters a regulated amount from the device. Generally, the devices will contain from 250 nanograms to 5 grams or more of agent. The lower limit is determined by the fact that sufficient amounts of the steroid metabolite must remain in the uterine device to maintain the desired dosage. In order to achieve a contraceptive effect in a human adult female, the daily release dosage from the device should be in the range of between 1.0 and 1500 micrograms per day, and preferably between 10 micrograms to 1000 micrograms of, for example, pregnanediol per day. Thus, for example, using the steroid metabolite pregnanediol, as an example, and with an intrauterine device intended to remain in place for one year, and with a release rate of 1000 micrograms of pregnanediol per day, that is, for 24 hours, approximately 400 mg of pregnanediol would be incorporated in the device for a year supply. Other intrauterine devices, similar to these described, released about 20 to 60 micrograms per day, or up to 1500 micrograms per day, which rate of release is essentially free from unwanted side effects often associated with these steroids. Further, depending on the particular species of patient to be treated, such as mammals, female farm animals, such as cows, sheep and the like, the device of the invention releases a fertility suppressing amount of locally contraceptively active progesterone metabolite in the range of about 5 micrograms to 75 micrograms per kilogram of body weight per patient per day, up to 1500 micrograms per day.

The invention use of steroid metabolites for interfering with the reproductive process is achieved essentially without pyrogenic effects frequently associated with some of these metabolites. The pyrogenicity reported in *Chem. Abst.*, Vol. 57, page 5243h, 1962 for *Med. Klin.*, Vol. 57, pages 305 to 307, 1962; *Chem. Abst.*, Vol. 55, page 17910d, 1961 for *Symp. Deut. Ges.*

Endok., pages 69 to 75, 1959; *Chem. Abst.*, Vol. 55, page 12639c, 1961 for *Symp. Deut. Ges. Endok.*, Vol. 6, pages 69 to 75, 1959; *Chem. Abst.*, Vol. 56, page 9352g, 1962, for *Z. Geburt. u. Gynaek. Beilageheft.*, Vol. 157, pages 46 to 54, 1961; *Chem. Abst.*, Vol. 54, page 25136h, 1960, for *Trans. Assoc. Am. Phys.*, Vol. 72, pages 54 to 61, 1959; *Chem. Abst.*, Vol. 54, page 19951, 1960, for *A.M.A. Arch. Internal Med.*, Vol. 105, pages 701 to 708, 1960; and *Chem. Abst.*, Vol. 51, page 7589d, 1957, for *J. Clin. Endocrinol. and Metab.*, Vol. 17, pages 451 to 453, 1957; is attributed to single and multiple massive doses usually of 5 mg to 25 mg administered intramuscularly and intravenously with accompanying systemic effects. According to the mode and manner of the present invention, the pyrogenicity is avoided by a dose situ response relationship. The present invention slowly and locally releases the steroid in small amounts over a prolonged period of time to overcome the above reported disadvantages. The objects of this invention are achieved by releasing locally an effective amount of steroid for interfering with the reproductive process from 1 μ g to 1500 μ g over 24 hours. That is, the systemic pyrogenic effects that accompany the large doses by intramuscular and intravenous administration are beyond the scope of this invention.

Material having the ability to control the rate of release of steroid agent in the desired range is herein defined as a "release rate controlling material." These materials are those polymers which, in addition to being permeable to and compatible with the metabolite and uterine environment, are non-toxic, and biologically inert. Exemplary materials include hydrophobic polymers such as plasticized or unplasticized polyvinylchloride, plasticized nylon, plasticized soft nylon, plasticized polyethyleneterephthalate, natural rubber, C₂-C₄ olefins, e.g. polyethylene, polyisoprene, polyisobutylene, polybutadiene; silicone rubbers, especially the medical grade polydimethylsiloxanes, as described in U.S. Pat. No. 3,279,996, hydrophilic polymers such as the hydrophilic hydrogels of esters of acrylic and methacrylic acid (as described in U.S. Pat. Nos. 2,967,576 and 3,220,960, and Belgian Pat. No. 701,813), modified collagen, cross-linked polyvinylalcohol, and cross-linked partially hydrolyzed polyvinylacetate. Polymeric materials that tend to be irritating can be used but should be coated with a non-irritating polymeric coating. When plasticizers are used to impart flexibility to the polymer, various non-toxic plasticizers known to the art can be employed, such as long-chain fatty amides, higher alcohols, and high boiling esters such as di(isooctyl) sebacate or di(2-ethyl hexyl) phthalate, and the like.

The intrauterine device of the invention is easily fabricated as previously discussed in connection with the description of FIGS. 1 through 4. Using FIG. 3 as an example, steroid metabolite first is mixed with the matrix material, which can be in solid, semi-solid, or liquid form at the time, and distributed therethrough by ball-milling, calendaring, stirring, shaking, or like standard processing means. Where the metabolite is chemically compatible with monomers or prepolymers used to form the matrix, the metabolite particles can be added at this earlier stage and the matrix formed in situ. The matrix material, however made and having the metabolite distributed therethrough, can then be formed to a solid shape by molding, casting, pressing, extruding,

drawing, or like processes and conventional techniques. Depending on the material used to form the matrix, curing may be necessary at this stage. This ability to shape the matrix into devices of assorted shapes such as tubes, rods, disks, rings and other highly reproducible shapes of controllable composition, results in ready fabrication of devices with closely controlled characteristics.

Those skilled in the art can readily determine the rate of permeability of the steroid through a polymeric material or selected combinations of polymeric materials. One embodiment that has been found to be eminently well suited is to cast or hot press a film of the material to a thickness in the range of 2 to 60 mils. The film is used as a barrier between a rapidly stirred (e.g. 150 r.p.m.) saturated solution of the agent containing excess compound and a rapidly stirred solvent bath, both maintained at constant temperature (typically 37°C). Samples are periodically withdrawn from the solvent bath and analyzed for agent concentration. By plotting agent concentration in the solvent bath versus time, the permeability constant P of the membrane is determined by the Fick's First Law of Diffusion.

$$\text{Slope of plot} = \frac{Q_1 - Q_2}{t_1 - t_2} = P \frac{AC}{h}$$

wherein Q₁ = cumulative amount of agent in solvent in micrograms at t₁

Q₂ = cumulative amount of agent in solvent in micrograms at t₂

t₁ = elapsed time to first sample, i.e. Q₁

t₂ = elapsed time to second sample, i.e. Q₂

A = area of membrane in cm²

C = saturation concentration of agent in solution

h = thickness of membrane in cm.

By determining the slope of the plot, i.e.

$$\frac{Q_1 - Q_2}{t_1 - t_2}$$

and solving the equation using the known or measured values of A, C, and h, the permeability P constant in cm²/time of the material or membrane for a given compound is readily determined. Of course, this permeability constant is an inherent characteristic of the material for a given compound. Using the above technique, the permeability constant P for a select membrane and compound can be determined. These data can then be employed to design a device of the invention to release the metabolite to the uterus in the desired dosage range. Similarly, this experimental procedure or others known to those skilled in the art can be used to determine release rates for matrices and combinations of matrices and matrix with microcapsules of suitable polymeric materials as above disclosed in order to design intrauterine devices of this invention. These examples and like examples can be used to determine the rate of steroid release through different steroid release rate controlling materials are known to the art in *J. Pharm. Sci.*, Vol. 52, pages 1145 to 1149, 1963; *ibid.*, Vol. 53, pages 798 to 802, 1964; *ibid.*, Vol. 54, pages 1459 to 1464, 1965; *ibid.*, Vol. 55, pages 840 to 843 and 1224 to 1239, 1966; *Encyl. Polymer Sci. Technol.*,

Vol. 5 and Vol. 9, pages 65 to 82 and 794 to 807, 1968; the references cited therein and the like.

Alternatively, in certain cases equation II below can be employed to design the intrauterine device of this invention without the use of any experimental data by computations well known to those skilled in the art of polymer permeation. See for example, "Advances in Separation and Purification," Chapter 5, A. S. Michaels, entitled "Principles of Membrane Permeation Theory and Practice" (Interscience Publishers, N.Y., 1968). Initially, of course, it is necessary to select the specific shape and size and thereby establish the surface area of the device and, also, the metabolite and materials which are to be used.

For a compound having a molecular weight under ca. 900, e.g. pregnanediol, the diffusion coefficient in most nonglassy polymers will be in the range of 1×10^{-9} cm²/sec. to 5×10^{-9} cm²/sec. at mammalian body temperature of 37.5°C. In such cases the "specific permeation flux" of the compound is defined as the product of the permeation flux J , and the film thickness, t , through the polymer, and it is given by the equation:

$$Jt = C^* D$$

wherein J is the permeation flux; C^* is the concentration of the compound in the polymer when in saturation with the solid compound; D is the diffusivity of the compound in the polymer, and t is the film thickness of the polymer wall. The saturation concentration in a particular uterine acceptable polymer can be estimated with good accuracy if the solubility of the compound in an organic liquid of chemical constitution similar to that of the polymer is known. For example, the solubility of a particular compound in polyvinyl acetate will be nearly the same as its solubility in ethyl acetate; in polyethylene, nearly the same as in octane or cyclohexane, etc.

Thus, the solubility of pregnanediol in ethylene vinylacetate copolymer comprised of 9 percent vinylacetate at 37°C is estimated to be about 4 gm/100 gm. Hence, the specific permeation flux of pregnanediol through said copolymer can be calculated to be: $Jt = (4 \times 10^{-3} \text{ gm/gm}) (3 \times 10^{-9} \text{ cm}^2/\text{sec}) = 12 \times 10^{-12} \text{ cm}^2/\text{sec}$. wherein C^* is $4 \times 10^{-3} \text{ gm/gm}$; D is assumed to be $3 \times 10^{-9} \text{ cm}^2/\text{sec}$.

An intrauterine device designed to release 200 micrograms of pregnanediol per day, or 2×10^{-4} grams/day, which has an external surface area of 5 cm², if comprised of said ethylene vinylacetate copolymer, must therefore have an external membrane wall thickness of:

$$t = \frac{(12 \times 10^{-12})}{(2 \times 10^{-4})} \times \frac{(1)}{86,400} = 0.026 \text{ cm}$$

or 0.26 millimeters (10 mils)

wherein 86,400 is the number of seconds in a day; 2×10^{-4} is the grams of pregnanediol to be released per day and 5 cm² is the external surface area of the device. Thus, using this technique, it can be determined that an intrauterine device having a surface area 5 cm² and made of a polyethylene film 10 mils thick, will release 200 micrograms of pregnanediol per day. Ethylene vinylacetate copolymer as used for the fabrication of in-

trauterine devices does not constitute a part of this invention. Ethylene vinylacetate copolymer used for fabricating drug delivery devices including intrauterine devices is the invention disclosed and claimed in copending U.S. Pat. application Ser. No. 80,531, filed Oct. 14, 1970 now abandoned, and U.S. Pat. application Ser. No. 281,446, filed on Aug. 17, 1972. Both of these applications are assigned to the same assignee of this invention and they are incorporated herein by reference.

The following examples will serve to illustrate the invention without in any way being limiting thereon, as these examples and other examples thereof will become apparent to those versed in the art in the light of the present disclosure, drawing and the accompanying claims.

EXAMPLE 1

An intrauterine device is fabricated of ethylene vinylacetate copolymer comprised of 9 percent vinylacetate tubing of circular cross-section, measuring 7 cm in extended length and 3 mm outside diameter having a total external surface area of ca. 5 cm². The device has a shape of a hollow coil of total curvature of 480° and outside coil diameter of 2 cm having a bore of 2.5 mm diameter through its entire length. A 12 month supply of metabolite pregnanediol is inserted into the device. The amount is computed to be:

$$(200 \times 10^{-3} \text{ mg/day}) \times (365 \text{ days/yr}) = 73 \text{ milligrams}$$

Since the density of pregnanediol is of the order of 1.2 gm/cc, the volume occupied by the compound is 0.06 cc which can be easily inserted as a core in the above device. An amount in the order of 10 to 30 percent in excess of 73 milligrams can be used to insure adequate delivery during the time period.

The ends of the device are sealed using polytetrafluoroethylene plugs and cyanoacrylate adhesive, commercially available as Eastman 910 adhesive. The intrauterine device can be used for conception control by surgical insertion into each uterine horn of a 120 pound ewe. Each intrauterine device releases and supplied approximately 200 micrograms of pregnanediol per day for a period in excess of 1 year. It is highly preferred that the device be placed in both uterine horns in order to insure that conception is prevented.

EXAMPLE 2

One hundred milligrams of pregnanediol are inserted into a hollow tube of the ethylene vinylacetate copolymer of Example 1, 10 cm in length and having an inside diameter of 2.6 mm and an outside diameter of 3.0 mm. The tube is sealed in the same manner in Example 1 above. An IUD in the shape of a Lippes loop is then fabricated from ethylene vinylacetate copolymer comprised of 84 percent ethylene and 16 percent vinylacetate, by injection molding, having a total straightened length of 4.5 inches. The length of polyethylene tubing prepared above is secured to the body of the loop with cyanoacrylate adhesive, Eastman 910. This device can be used to control conception of a 150 pound ewe by insertion through the cervical os into the uterus. The device will release approximately 270 micrograms of pregnanediol per day for a period in excess of 1 year.

EXAMPLE 3

Uterine devices providing effective fertility suppression are prepared by repeating the procedure of Exam-

ples 1 and 2 with substitution of steroid pregnanediol by each of the following cyclopentanphenanthrene progesterone metabolites:

- 3 α -hydroxy-5 β -pregnan-20-one,
- 3 β ,16 α -dihydroxy-5 α -pregnan-20-one,
- 3 α ,16 α -dihydroxy-5 α -pregnan-20-one,
- 3 α ,16 α -dihydroxy-5 β -pregnan-20-one,
- 5 β -pregnane-3 α ,20 β -diol,
- 5 α -pregnane-3,20-dione,
- 5 β -pregnane-3,20-dione,
- 3 α -hydroxy-5 α -pregnan-20-one,
- 5 α -pregnane-3 α ,20 α -diol,
- 5 α -pregnane-3 α ,20 β -diol, and
- 3 α ,17 α -dihydroxy-5 β -pregnane-20-one.

This invention provides a reliable means of fertility control. By releasing selected locally pharmaceutically acceptable, contraceptively active ring saturated steroid metabolites of progesterone to the uterus, the desired local effect is achieved without obtaining unwanted and possibly toxic systemic progestational activity, and other side effects which is unexpected in the light of the prior art. And, while the invention has been described with reference to certain preferred embodiments thereof, wherein the improvement is described in details, those skilled in the art will appreciate that various modifications, changes, omissions and substitutions can be made without departing from the spirit of the invention. It is intended, therefore, that the invention be limited only by the scope of the following claims.

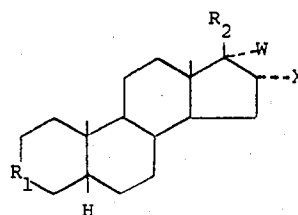
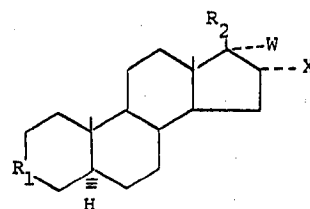
What is claimed is:

1. An intrauterine device adapted for insertion and placement in a uterus for the release of a pharmaceutically acceptable anti-fertility steroid metabolite comprising, a matrix formed of a nontoxic, biologically inert polymeric release rate controlling material containing a locally, contraceptively active saturated metabolite of progesterone and permeable to the passage of the metabolite by diffusion, and wherein the intrauterine device when placed in the uterus meters the flow of an effective amount of the metabolite up to 1500 micrograms per day for an antifertility effect through the material at a controlled and continuous rate over a prolonged period of time.

2. The intrauterine device of claim 1 wherein the device is adapted to release about 5 micrograms to about 50 micrograms of the locally, contraceptively active steroid metabolite per kilogram of body weight per day and wherein said metabolite is a member selected from the group: 5 β -pregnane-3 α -hydroxy-20-one, 5 α -pregnane-3 β ,16 α -dihydroxy-20-one, 5 α -pregnane-3 α ,16 α -dihydroxy-20-one, 5 β -pregnane-3 α ,20 β -diol, 5 α -pregnane-3,20-dione, 5 β -pregnane-3,20-dione, 5 α -pregnane-3 α -hydroxy-20-one, 5 α -pregnane-3 α ,20 α -diol, 5 α -pregnane-3 α ,20 β -diol, 5 β -pregnane-3 α ,17 α -dihydroxy-20-one, and mixtures thereof, essentially without systemic progestational effects.

3. An intrauterine device for the administration of a physiologically compatible steroid for interfering with the reproductive process to the uterine cavity comprising a matrix formed of nontoxic, biologically inert polymeric release rate controlling material containing therein 250 nanograms to 5 grams of a locally contraceptively active steroid metabolite of progesterone and permeable to the passage of the steroid by diffusion, and wherein the device when placed in the cavity meters the flow of an effective amount of the steroid up

to 1500 micrograms per day for an antifertility effect through the material at a controlled and continuous rate over a prolonged period of time with the steroid consisting of a member selected from the group of:



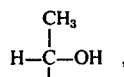
wherein R₁ is a member selected from the group consisting of C=O and



R₂ is a member selected from the group consisting of

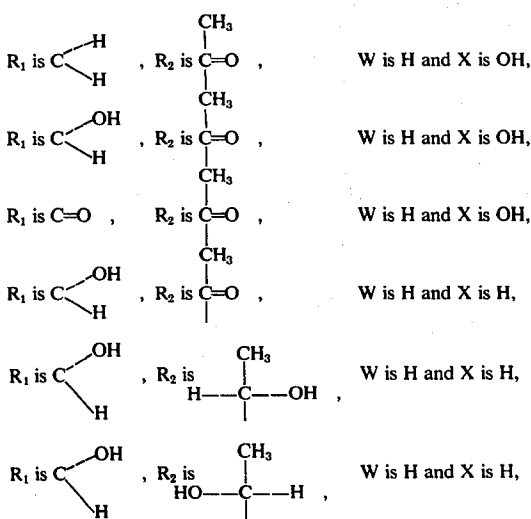


and



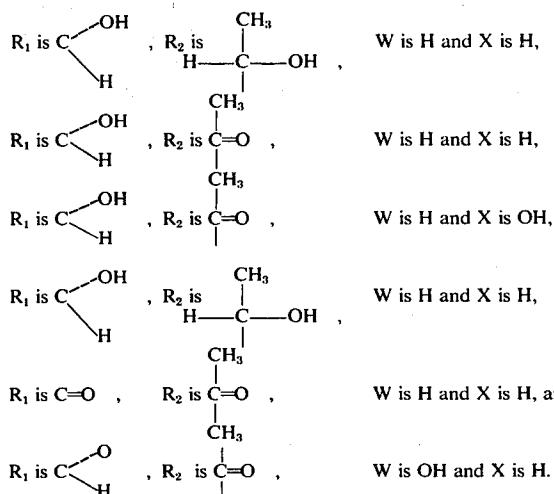
W is a member selected from the group consisting of H and OH, and X is a member selected from the group consisting of H and OH.

4. The intrauterine device of claim 3 when the steroid is 5 α , the groups R₁, R₂, W, and X are as follows:



when the steroid is 5 β , the groups R₁, R₂, W and X are as follows:

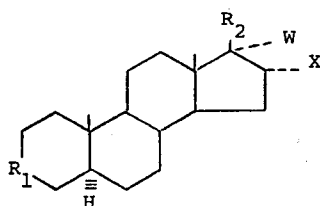
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5. An intrauterine device adapted for insertion and placement in a uterine cavity for the administration of a pharmaceutical antifertility steroid metabolite to the cavity comprising a reservoir surrounded by a wall formed of a nontoxic, biologically inert polymeric release rate controlling material containing therein a locally, contraceptively active saturated steroid metabolite of progesterone and permeable to the passage of the steroid by diffusion, and wherein the device when placed in the cavity meters the flow of an effective amount of the steroid up to 1500 micrograms per day for an antifertility effect through the material at a controlled and continuous rate over a prolonged period of time.

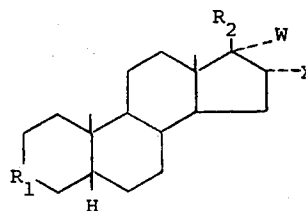
6. The intrauterine device of claim 5 wherein the device is adapted to release about 5 micrograms to about 50 micrograms of the locally, contraceptively active steroid metabolite per kilogram of body weight per day and wherein said steroid is a member selected from the group: 5 β -pregnane-3 α -hydroxy-20-one, 5 α -pregnane-3 β ,16 α -dihydroxy-20-one, 5 α -pregnane-3 α ,16 α -dihydroxy-20-one, 5 β -pregnane-3 α ,20 β -diol, 5 α -pregnane-3,20-dione, 5 β -pregnane-3,20-dione, 5 α -pregnane-3 α -hydroxy-20-one, 5 α -pregnane-3 α ,20 α -diol, 5 α -pregnane-3 α ,20 β -diol, 5 β -pregnane-3 α ,17 α -dihydroxy-20-one, and mixtures thereof, essentially without systemic progestational effects.

7. An intrauterine device for the administration of a physiologically compatible steroid for interfering with the reproductive process to a uterine cavity comprising a reservoir surrounded by a wall formed of nontoxic, biologically inert polymeric release rate controlling material containing 250 nanograms to 5 grams of a locally contraceptively active steroid metabolite of progesterone and permeable to the passage of the steroid by diffusion, and wherein the device when placed in the uterus meters the flow of an effective amount of the steroid up to 1500 micrograms per day for an antifertility effect through the material at a controlled and continuous rate over a prolonged period of time with the steroid consisting of a member selected from the group of:



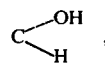
and

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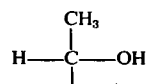
10 wherein R₁ is a member selected from the group consisting of C=O and



R₂ is a member selected from the group consisting of

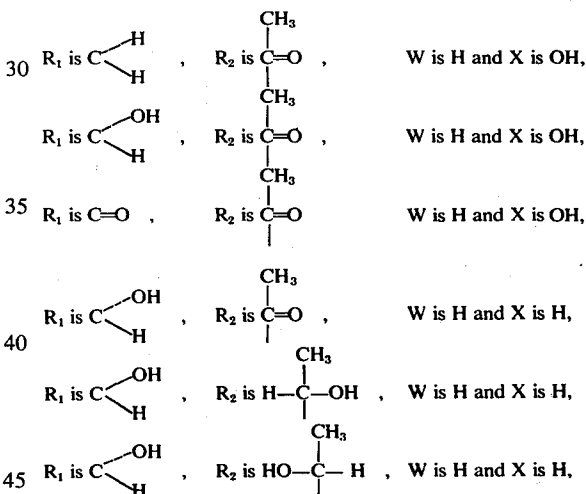


and

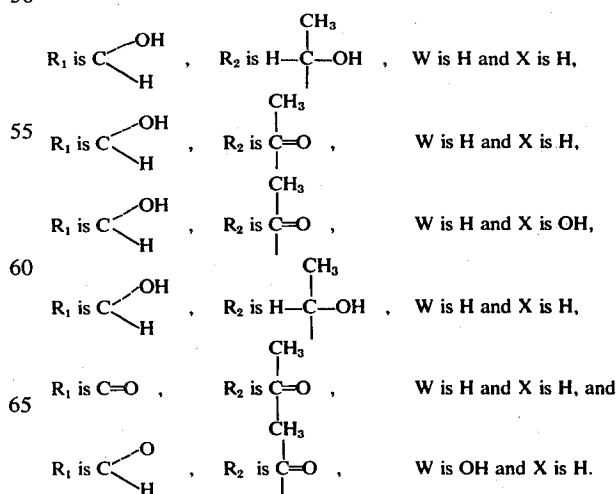


W is a member selected from the group consisting of H and OH, and X is a member selected from the group consisting of H and OH.

8. The intrauterine delivery device of claim 7 when the steroid is 5 α , the groups R₁, R₂, W, and X are as follows:



when the steroid is 5 β , the groups R₁, R₂, W and X are as follows:



* * * * *